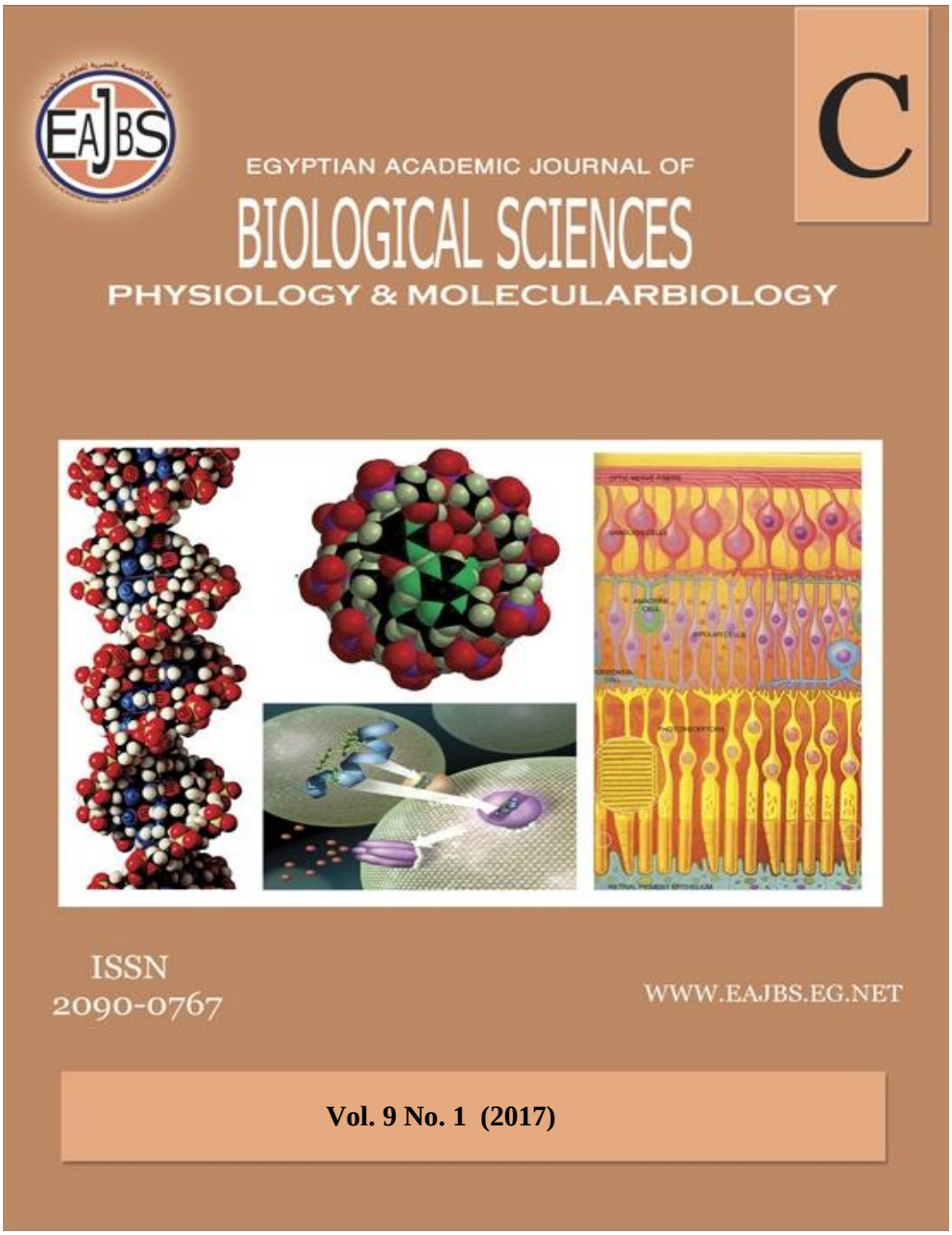


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# Effect of Fullerene $C_{60}$ (NPs) on Cyclophosphamide-Induced Hepato and Cardiac Toxicity in Male Albino Rats.

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Cyclophosphamide (CP), Fullerene C60, Toxicity nanoparticles (NPs), in vivo and Albino Rats

## ABSTRACT

**Background:** Toxicity due to drugs used for neoplastic disorders is documented in previous studies. Cyclophosphamide (CP) is a widely used as anticancer drug, which could cause toxicity of normal cells through its toxic metabolites. The fullerene family, especially Fullerene $C_{60}$ nanoparticles (NPs) can be utilized in many and different biological fields. We evaluated the protective role of Fullerene $C_{60}$ (NPs) in the toxicity induced by cyclophosphamide.

**Methods:** The activities of serum Liver marker enzymes; alanin amino transferase (ALT) and aspartate amino transeferase (AST), alkaline phosphatase (ALP). T. protein, Albumin, serum heart marker enzymes; Lactate dehydrogenase (LDH) and creatinine phosphokinase (CK) were determined.

**Results:** Toxicity of the organs like heart, and liver was proved from increases of ALT, AST, ALP, LDH and CK values and a decrease in T. protein and Albumin in cyclophosphamide (200 mg/kg a single dose) administered rats, Fullerene $C_{60}$NPsdissolved in olive oil (0.8 mg/ml) oral treatment will show enhancement against toxicity induced by (CP)at a dose of 4 mg/kg body weight daily for 10 days.

**Conclusion**: In this study, we wish to report that, the *in vivo* treatment of Fullerene $C_{60}$ (NPs) was improved the biochemical changes caused by cyclophosphamide-induced toxicities. These results have importance in the fields of medicine. This may open the way for the biomedical applications of $C_{60}$in treatment of cancer, neurodegenerative disorders, and ageing.

## INTRODUCTION

Among these nanoscale chemical structures, fullerenes represent an important source of the biocompatible molecules because of their capacity to be in contact with cells and biological tissues without altering their behaviour (yang *et al.*, 2007). The fullerene family, and especially $C_{60}$, has very appealing photo-electro-chemical and physical properties, which can be exploited in many and different biological fields (Bosi *et al.*, 2003).

$C_{60}$ is soluble in lipid droplets inside living cells (Garbi *et al.*, 2005) as well as in fats in general. Moreover, $C_{60}$ can freely cross membrane barriers as observed experimentally and recently modelled by computer simulations (Wong-Ekkabut *et al.*, 2008).

Cyclophosphamide (CP) is one of the most effective alkylating agents which used to treat several cancers. A broad range of organ systems may be adversely affected, with dose-limiting toxicity. The mechanisms by which antitumour agents damage or kill both tumour and normal cells are still poorly understood. They may include the effects of reactive species such as organoplatinum compounds (Reed *et al.*, 1987). There are attempts to develop cytoprotective strategies.

The activated CP metabolites are transported via the bloodstream to both tumor and healthy tissues, where DNA and protein damage occurs. Several authors have shown that CP induces damage to mitochondrial membranes, proteins, nucleic acids, and lysosomal membrane (Al-Nasser, 1998 and Sudharsan *et al.*, 2006).

Hepatic Biotransformation of CP to phosphoramide mustard and acrolein leads to the formation of high level of free radicals, and serum levels of ALT, AST and ALP are the most commonly used clinical markers of hepatocellular toxicity (Shokrzadeh *et al.*, 2014), Serum T. protein and albumin levels serve as a marker of the degree of chronic hepatic failure, therefore the influence of CP metabolism on the liver and heart function enzymes was assessed in this study. Abu-Sinna *et al*. (2005) reported that injection of a bradykinin potentiating factor in sub-lethally-irradiated and non-irradiated growing Guinea pigs accelerated the generation of thymus and spleen cellularity. It is worthy to mention that, (Salman, 2009) reported that BPF enhanced total protein and albumin in irradiated Guinea pigs. Moreover, they found that the bradykinin was stimulated the release of several cytokines important in proliferation and differentiation of various blood cell progenitors (Bekheet *et al.*, 2013 and Salman *et al.*, 2016). These cytokines include interlukin-1(IL-1), (IL-3), (IL-6), tumor necrosis factor α (TNFα), interferon-γ and granulocyte-macrophage-colony stimulating factor (GM-CSF) that are known to affect recovery from radiation-induced hemopoietic injury. These cytokines have been shown to accelerate hematopoiesis recovery after a sub-lethal dose of whole-body irradiation (Salman *et al.*, 2017).

Finally, this study is initiated to investigate the possible treatment of Fullerene $C_{60}$ against side effects of CP-induced liver and heart disorders in rats based on some of biochemical parameters of some marker enzymes.

## MATERIALS AND METHODS

### Animals:

Adult male albino rats of approximate age and weight (2 months and about 200 ± 50 g.) were selected from the animal house of the Egyptian Organization for Biological Products and Vaccines (VACSERA), Helwan, Cairo, Egypt. The animals were housed in the animal house of the faculty of science, South valley University, Qena, Egypt, for two weeks under normal condition with a balanced diet and water *ad libitum*.

### Drugs and chemicals:

**Fullerene $C_{60}$** (purity 99.9%) was obtained from Lydow Group Limited Research Corporation (China) and used without further purification.

**CP** (Cyclophosphamide) was supplied as vials from Baxter Oncology, Germany.

**Virgin olive oil** is obtained from a Colavita Extra Virgin Olive Oil Company which extracted from Olives harvested and pressed in Itally.

Kits of liver functions and heart enzymes were obtained from Spectrum company for biotechnology, Cairo, Egypt.

### C60-olive oil solution preparation:

After sourcing the high purity $C_{60}$, we prepared $C_{60}$-olive oil solution according to Batti *et al.*, (2012). Fifty mg of $C_{60}$ were dissolved in 10 ml of olive

oil by stirring for 2 weeks at ambient temperature in the dark. The resulting mixture was centrifuged at 5.000 g. for 1h. and the supernatant was filtered through a Millipore filter with 0.25 mm porosity.

**Experimental design:**

Adult male albino rats of approximate age and weight (2 months and about 200±50gm) were divided into three groups:

**Group 1**: Each animal of this group were intraperitoneally injected (i.p.) daily with 0.9% isotonic saline solution at a dose (1 ml/kg body weight) for 10 days and served as a normal group.

**Group II**: Each animal of which was injected intraperitonially with a single dose of CP (200 mg/kg b. w.) and served as a positive control and left out treatment.

**Group III**: This group was injected with a single dose of CP (200 mg/kg b. w.) and treated orally by Fullerene $C_{60}$ (4 mg /kg b. w.) per day for 10 days.

The serum blood was collected for biochemical analysis (ALT, AST, ALP, T.protein, albumin, LDH and CK activities).

## RESULTS

### Effect of fullerene $C_{60}$ on the level of liver marker enzymes

As illustrated in Figs. 1, 2 & 3 respectively, the positive control group showed a highly significant increase ($p<0.01$) in ALT, AST and ALP in comparison with normal animals. While, after 10 days of $C_{60}$-olive oil treatment after a single dose of CP, there were a significant decrease ($p<0.05$) in AST and ALP when compared with control.

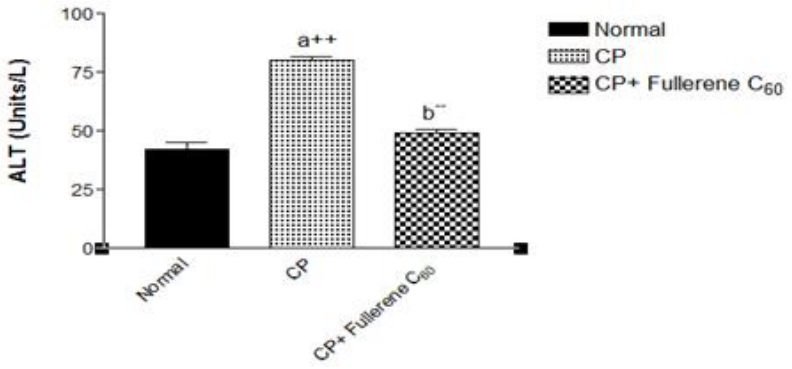


Fig. 1: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on serum ALT (Units /L) in blood of male Albino rats.

a+ = significant increased compared to normal at $p<0.05$.

++a = highly significant increased compared to normal at $p<0.01$.

-a = significantly decreased compared to normal at $p<0.05$.

- -a = highly significant decreased compared to normal at $p<0.01$.

+b = significant increased compared to control at $p<0.05$.

++b = highly significant increased compared to control at $p<0.01$.

-b= significant decreased compared to control at $p<0.05$.

- -b = highly significant decreased compared to control at $p<0.01$.

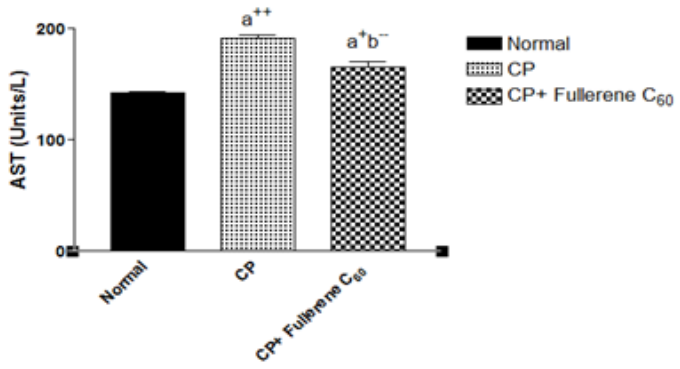


Fig. 2: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on serum AST (Units /L) in blood of male Albino rats.
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

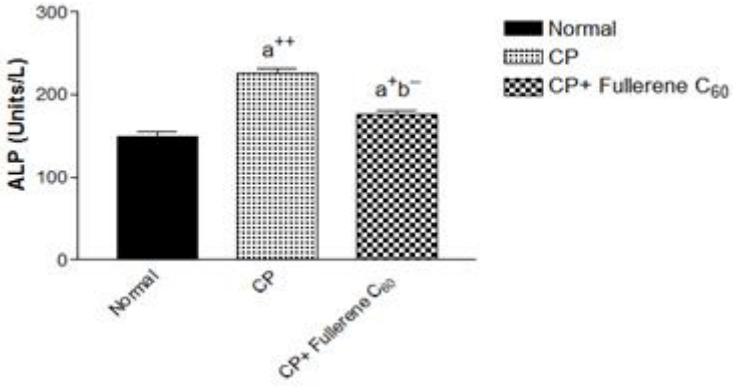


Fig. 3: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on serum ALP (Units/L) in blood of male Albino rats.
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

On the other hand, the control group showed a highly significant decrease (p<0.01) in T. protein and Albumin in comparison with normal animals., While, after 10 days of $C_{60}$-olive oil treatment after a single dose of CP, there were a significant increase (p<0.05) in T. protein and Albumin compared to control animals, but not abroach to normal animals (Figs. 4 & 5.).

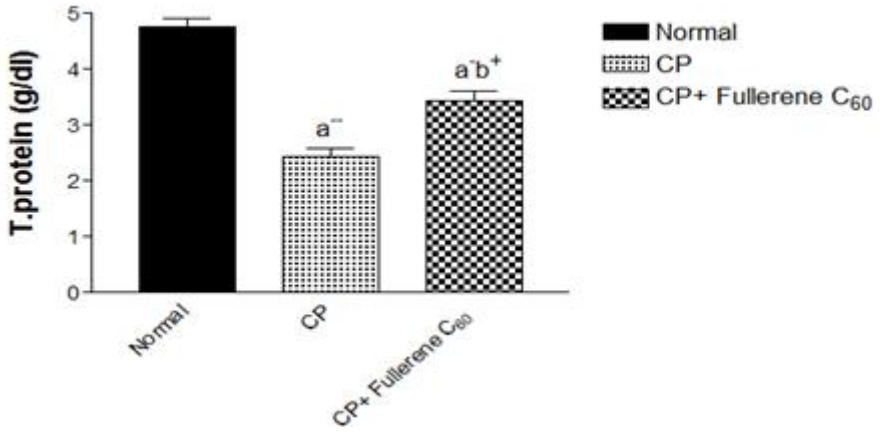


Fig. 4: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on serum T.protein (g/dl) of male Albino rats:
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

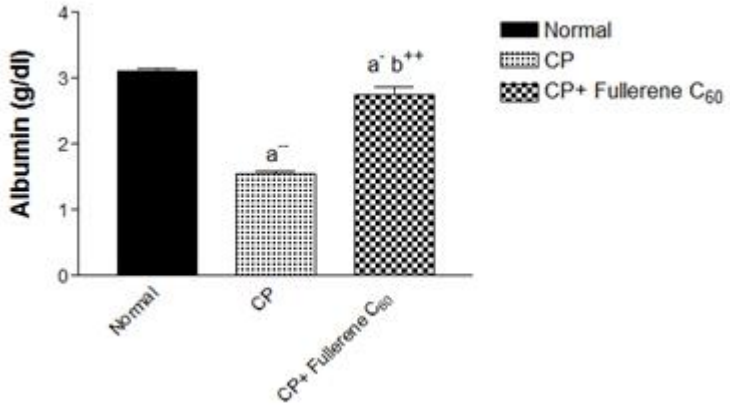


Fig. 5: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on serum Albumin (g/dl) of male Albino rats:
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

## Effect of fullerene $C_{60}$ on the level of heart marker enzymes

As illustrated in Figs. 6 & 7 respectively, the control group showed a highly significant increase (p<0.01) in LDH and CK in comparison with normal animals, while in the group which administrated with $C_{60}$-olive oil for 10 days only showed a significant decrease (p<0.05) value in LDH and CK compared with control animals

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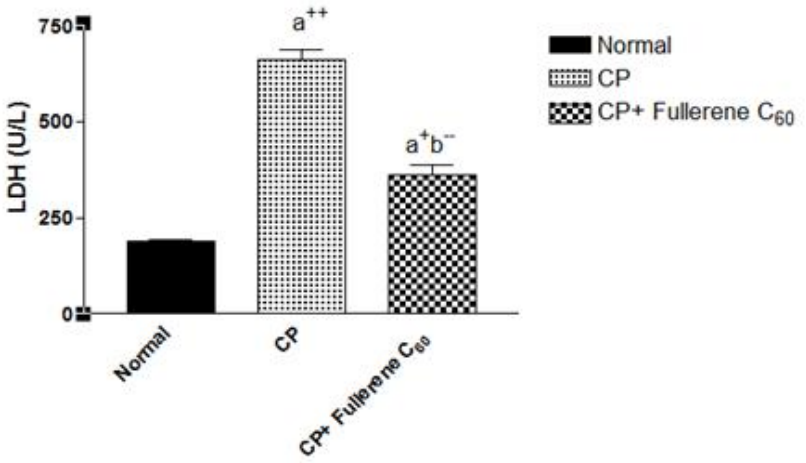


Fig. 6: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on LDH (U/L) in blood of male Albino rats.
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

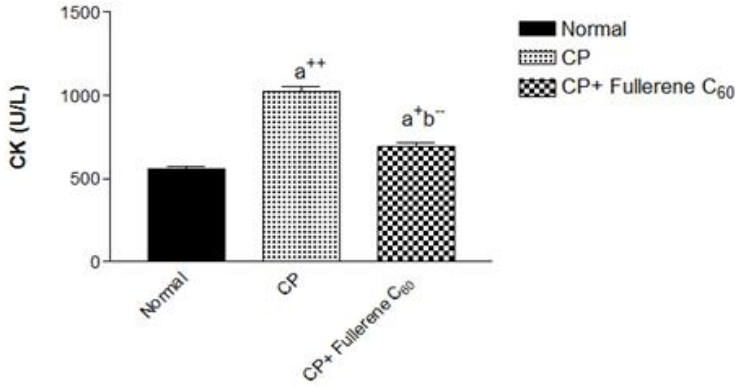


Fig. 7: Effect of orally administration of $C_{60}$-olive oil treatment (4 mg/kg b. w) daily for 10 days after a single dose of CP (200 mg/kg b. w.) on CK (U/L) in blood of male Albino rats.
a+ = significant increased compared to normal at p<0.05.
++a = highly significant increased compared to normal at p<0.01.
-a = significantly decreased compared to normal at p<0.05.
- -a = highly significant decreased compared to normal at p<0.01.
+b = significant increased compared to control at p<0.05.
++b = highly significant increased compared to control at p<0.01.
-b= significant decreased compared to control at p<0.05.
- -b = highly significant decreased compared to control at p<0.01.

## DISCUSSION

CP is a prodrug metabolized by hepatic cytochrome P450 (CYP450) system to both active and inactive compounds (Rooney *et al.,* 2004), Serum levels of ALT and AST are elevated, which is due to release of these enzymes to serum from damaged hepatic tissue (Ghosh *et al.*,1999).

In addition, the increase in the ALP in serum may be due to some alteration in lysosomal enzyme activities by CP in the liver (metabolic organ). This elevation is due to release of the enzyme from the tissue into the serum (DAS and Dasgupta, 1997).

The obtained data indicated a significant improving effect of fullerene $C_{60}$ on the serum activities of ALT, AST, and ALP induced by CP, this is in agreement with Batti *et al*., (2012) who reported that improving effect of fullerene $C_{60}$ on the altered activities of liver enzymes which induced by $CCl_4$-intoxication.

It was also found that the rats injected with CP showed a significant decrease in the T. Protein and albumin post injection. The present results are in accordance with other studies (Mano *et al.,* 2006). Liver dysfunction was observed, including disturbances in the synthesis of selected proteins (Mohamed, 2014). In addition, Senthilkumar *et al.,* (2006) found that hypo-proteinemia was observed in rats injected with CP for two days and they attributed that to the CP exerts a direct impact on plasma cells.

In the present study Fullerene C60 treated animals showed a pronounced increase in T. protein and albumin compared to CP i.p. injected animals, indicating that Fullerene C60 tended to prevent the damage and suppressed the leakage of enzymes through cellular membranes. This result is in accordance with Batti et al. (2012), that was an indication of stabilization of plasma membrane as well as repairmen of hepatic tissue damage that can be considered as an expression of the functional improvement of the hepatocytes (Azevedo Costa *et al*., 2012).

Furthermore, CP metabolites attack soluble cell components as well as membranes eventually leading to impairment of cell functioning and cytolysis (Fransen *et al.,* 2001). CP also provoked a marked decrease in the activities of cardiac mitochondrial function (Sudharsan *et al.,*2006). So that, the elevation of LDH and CK in the serum is accompanied by heart disorders as adverse effect of CP injection.

In the present study, the Fullerene $C_{60}$ NPs decrease the elevation of Heart enzymes LDH and CK in serum. Furthermore, Fullerene $C_{60}$ can prevent local tissue hypoxia syndromes which resulted from chemotherapy (ShetabBoushehri *et al.,* 2010). The mechanism which explain the enhancement in cardiac function by fullerene is depends mainly on its anti-oxidative powerful capacity.

The mechanism of production of ROS takes place when cyclophosphamide metabolized by CYP3A4 in the liver into the reactive aldehydes chloroacetaldehyde and dichloroethylcyclophosphamide (Huitema *et al.,* 2000 and wahlang *et al.,* 2015). On the other hand, Stankiewicz *et al*. (2002) shown that, CP causes changes in the antioxidant status. The reduction in their activities after CP administration is probably connected with damage to the structures of these enzymes, which is caused by ROS that oxidatively modify the proteins' structures (Davies and Goldberg, 1987).

Fullerene $C_{60}$ can scavenge large numbers of free radicals (Andrievsky *et al.,* 2009), $C_{60}$ can act as a decomposition catalyst for $O_2^{-\bullet}$ and $H_2O_2$, and may be working as a cytochrome P450 inhibitor (Gharbi *et al.,* 2005). Besides that, it can inactivate Kupffer cells (liver resident macrophages) through accumulation and

overloading with a large number of $C_{60}$ aggregates (Bolskar *et al.*, 2003).

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## ARABIC SUMMARY

### تاثير فوليرين الكربون الستيني على عقار سيكلوفوسفاميد الذي يسبب سمية الكبد والقلب في الذكور الجرذان البيضاء

**عبد الرحيم على الشاطر- محمد محمود على سالمان – اسماء سيد محمد**
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مما لا مرية فيه أن عقار السيكلوفوسفاميد (الاندوكسان) أحد العقاقير الشائعة الاستعمال في علاج عديد من الأورام الخبيثة كما أنه أحد المثبطات المناعية الفعالة المستخدمة في علاج بعض الأمراض كالروماتويد. ومن ثم فقد أصبح واجبا إلقاء بعض الضوء حول الآثار الجانبية الضارة لهذا العقار على بعض العمليات البيوكيميائية لبعض أعضاء ذكور الجرذان البيضاء البالغة وتشمل الكبد والقلب باعتبارها من الأعضاء التي تتأثر من جراء استخدام هذا العقار.

يعد فلورين الكربون الستيني واحدا من أهم المواد النانومترية الكربونية الجيدة لما تتميز به من خصائص بيولوجية فريدة من حيث القدرة على النفاذ واختراق الموانع والحواجز البيولوجية عبرالأغشية البلازمية للخلايا وكذلك الأوعية الدموية المختافة والجدير بالذكر أن عنصر الكربون يدخل في تكوين ١٩% من أوزان أجسامنا فهو يدخل في تركيب البروتينات و الكربوهيدرات والدهون والأحماض النووية كما يتميز بتنوع خصائصه وتباين سماته.

ومن ثم فقد تم تقسيم ذكور الجرذان البيضاء إلى ثلاث مجموعات:-

**المجموعة الأولى** :- هي المجموعة الضابطة تم حقنها بمحلول فسيولوجي Na Cl( 0.9% ) بمقدار ١ مل/كجم

**المجموعة الثانية :-** فقد تم علاجها بعقار السيكلوفوسفاميد فقط و بجرعة مقدارها (٢٠٠مجم/كجم)

**المجموعة الثالثة** :- فقد تم علاجها بعقار السيكلوفوسفاميد،بجرعة (٢٠٠مجم/كجم) ايضا و ثم تم حقنها بفلورين الكربون الستيني بجرعة مقدارها (٤ مجم/كجم).

ولقد اظهرت نتائج تلك الدراسة ازديادا معنويا في مستوى وظائف الكبد والقلب في المجموعة الثانية حيث لوحظ ازديادا معنويا في مستوى الالانين امينو ترانسيفيريز (ALT)، اسبارتيت امينو ترانسفيريز(AST)، الكالين فوسفاتيز(ALP)، لاكتيت ديهيدروجينيز(LDH)، كرياتينين فوسفوكينيز(CK) وانخفاضاً معنويا ملحوظاً في مستوى البروتين الكلى (T.protein) و الالبيومين (Albumin) في الدم كما كان هناك انخفاضاً معنويا في مستوى وظائف الكبد والقلب

ومما جذب الانتباه أن نتائج المجموعة الثالثة والتي تم معالجتها بعقار ($Fullerene\ C_{60}$) وحقنها بالفلورين والكربون الستيني فقد أظهرت نتائج تلك المجموعة بجلاء انخفاضاً معنويا ملحوظاً في مستوى الالانين امينو ترانسيفيريز (ALT)، اسبارتيت امينو ترانسفيريز(AST)، الكالين فوسفاتيز(ALP)، لاكتيت ديهيدروجينيز (LDH)، كرياتينين فوسفوكينيز (CK) وازدياداً ملحوظاً في مستوى البروتين الكلى (T. protein) والالبيومين (Albumin) في الدم.

نستنتج من هذه الدراسة أن تعاطي فلورين الكربون الستيني يسبب تحسناً في مستوى وظائف الكبد والقلب للجرذان المعالجة بعقار السيكلوفوسفاميد والذي يستعمل في علاج الكثير من الأمراض المزمنة.