Hematological Studies on the Effect of Grape Seed Extract and L-Carnitine Against Doxorubicin-Induced Toxicity in Rats

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Abstract:

The study aimed to investigate the protective effect of grape seed extract (GSE) and L-carnitine (L-CA) in reducing toxicity caused by doxorubicin (DOX) in rats. Six groups of male albino rats were used in the experiment. Group I: The Control group received a normal saline solution throughout the 35-day experimental period. Group II: Given GSE (100 mg/kg b.wt., daily). Group III: Given L-CA (150 mg/kg b.wt., twice a week). Group IV: Administered DOX (10 mg/kg b.wt.) on day 28 of the experiment to induce toxicity. Group V: Received a combination of GSE (100 mg/kg b.wt.) and DOX (10 mg/kg b.wt., on day 28). Group VI: Received a combination of L-CA (150 mg/kg b.wt.) and DOX (10 mg/kg b.wt., on day 28). The results showed that the rats injected with DOX had reduced body weight, as well as signs of microcytic hypochromic anemia, leukopenia, neutropenia, lymphopenia, monocytopenia, and thrombocytopenia. However, the groups pretreated with GSE and L-CA showed improvement in these parameters compared to the DOX group. This suggested that GSE and L-CA have a protective effect against DOX-induced toxicity.

Keywords: Doxorubicin, hematology, grape seed extract, L-carnitine, rats.

Introduction:

Doxorubicin (DOX), a cytotoxic antibiotic from the anthracyclines family ***(Rawat et al., 2021)***, is effective against solid tumors like lymphomas, Hodgkin's disease, Kaposi's sarcoma, acute lymphoblastic leukemia, and juvenile and metastatic cancers ***(Wenningmann et al., 2019)***. However, its clinical usage is limited due to dose-limiting adverse effects on non-neoplastic cells, such as cardiotoxicity, myelotoxicity, and hematological toxicity ***(Al-Sowayan, 2014)***.

Co-administering DOX with chemoprotective medications can reduce toxicity to healthy tissues and enhance therapeutic effectiveness

(Moutabian et al., 2022). Grape seed extract (GSE) is a complex mixture of polyphenols collectively known as Proanthocyanidin (PAs) with stronger antioxidant effects than vitamins C and E ***(Shavandi et al., 2018).***

L-CA is an amino acid crucial for cells that need a lot of energy, like the cardiac system, transporting long-chain fatty acids through the mitochondrial membrane, generating ATP during β-oxidation, and possessing anti-inflammatory, anti-apoptotic, and antioxidant properties ***(Abd El-Motelp, 2022)***.

The present study aims to investigate the protective effect of grape seed extract and L-carnitine against DOX-induced toxicity in male albino rats.

Material and methods

Animals

Sixty albino male rats weighing 300–400 g were purchased from the National Research Center in Giza. They were housed in controlled conditions with human care and a one-week acclimatization period before the experiment. The animals were housed at 20-25°C and 50% humidity, with a 12-hour light/dark cycle, and had free access to feed and water.

Drugs and Chemicals:

Grape seed extract was obtained from Shaanxi Jintai Biological Engineering Co., Ltd., while Doxorubicin (Adriadox) was obtained from RMPL Pharma LLP. L-carnitine was obtained from Martinez Nieto, S.A., and carboxymethyl cellulose sodium salt (CMC) from Techno PharmChem in India.

Grape seed extract preparation:

1- Water extract of grape seed was dissolved in CMC.

2-In this study 100 mg of grape seed extract powder dissolved in 2.3 ml CMC.

3- Rats were given grape seed extract orally by oral gavage at a dose of 100 mg/kg per day for 35 days, according to ***Adıyaman et al. (2021)***.

Experimental Design and Grouping of Rats:

At the beginning of the study, the animals were weighed and randomly divided into 6 groups as follows:

Group (1): Served as a normal control group and received saline for 35 days.

Group (2): grape seed treated group; rats received 100 mg/kg b.wt. by oral gavage daily for 35 days according to **Adıyaman et al., (2021)**.

Group (3): L-carnitine treated group; rats received 150 mg /kg b.wt. by oral gavage twice per week for 35 days according to **Tousson et al., (2016)**.

Group (4): Served as a cardio-intoxicated group; induced by i.p. injection of 10 mg /kg b.wt. of DOX on day 28 of the experiment according to **Adıyaman et al., (2021)**.

Group (5) grape seed treated group; rats received 100 mg/kg b.wt. by oral gavage daily for 35 days with i.p. injection of 10 mg /kg b.wt. of DOX on day 28 of the experiment.

Group (6): L-carnitine treated group; rats received 150 mg /kg b.wt. by oral gavage twice per week for 35 days with i.p. injection of 10 mg /kg b.wt. of DOX on day 28 of the experiment.

Sampling

Rats were sacrificed twice: first on day 29 (after 24 hours following the induction of toxicity) for half of each group, and once on day 35 (at the end of the experiment) (the other half).

Blood samples were collected from rats' retro-orbital venous plexus under Tetrahydrofuran inhalation anesthesia for hematological evaluation.

Hematological parameters evaluation:

Included erythrocytes count, Hb concentration, PCV %, MCV (fl), MCH (pg), MCHC (g/dl), total and differential leukocytic count, and platelets count were performed according to ***Feldman et al. (2000)***.

Statistical Analysis:

The study used one-way ANOVA and Duncan's multiple range tests to analyze data, with results considered significant at a ($P \leq 0.05$) probability level. Data were analyzed using SPSS 25 for Windows.

Results

Effect of doxorubicin and protective agents (grape seed extract and l-carnitine) on body weight.

As seen in **Table (1)**, oral administration of GSE and L-CA alone had no statistically significant effect on body weight on the 29th day of the experiment. There was a significant decrease in the DOX, GSE, and L-CA pretreatment groups as compared with the control.

On the 35th day of the experiment, GSE and L-CA administration alone revealed non-significant variation when compared to normal control. However, there was a significant reduction in the DOX and GSE pretreated groups when compared with the control group. Moreover, the L-CA pretreated group showed a significant increase when compared with the DOX group.

Effect of doxorubicin and protective agents (grape seed extract and l-carnitine) on hematological parameters.

Erythrogram

As shown in **Table (2)**, there was no significant change between all experimental groups on the 29th day of the experiment.

Oral treatment with GSE and L-CA showed a non-significant variation in the erythrogram when compared to normal control on the 35th day of the experiment. The group injected with DOX showed a significant reduction in erythrogram when compared with the control group, reflecting microcytic hypochromic anemia. Furthermore, the pretreated group with GSE and L-CA showed a significant improvement in erythrogram when compared with the DOX group. The pretreated group with L-CA showed a significant increase when compared to the pretreated group with GSE.

Leukogram and platelets

As demonstrated in **Table (3)**, a non-significant variation in leukogram and platelets count was detected across all groups on the 29th day of the experiment.

On day 35, the groups that gastric intubated with GSE and L-CA reported a non-significant variation in leukogram and platelets count when compared to the control. DOX injection showed a significant reduction in WBCs, neutrophils, lymphocytes, monocytes, and platelets count with non-significant variation in eosinophils when compared with the control group. On the other hand, the groups pretreated with GSE and L-CA showed a significant increase in WBCs, neutrophils, lymphocytes, monocytes, and platelets count when compared with the DOX group. The pretreated group with L-CA showed a significant increase in WBCs, neutrophils, lymphocytes, and platelets count when compared with the pretreated group with GSE.

Table 1: The effects of doxorubicin cardiotoxicity as well as the protective effects of grape seed and l-carnitine on body weight after 29 and 35 days.

Parameters Treatment	Body weight (g)
At day 29	
Control	363.00 ^{a} ± 1.00
GSE	361.00 ^{a} ± 1.00
L-CA	365.00^{a} ± 2.89
DOX	341.33 ^{b} ± 5.93
GSE + DOX	340.00 ^{b} ± 5.77
L-CA + DOX	334.00 ^{b} ± 1.53
At day 35	
Control	372.00 ^{a} ± 6.93
GSE	360.67 ^{a} ± 6.36
L-CA	359.67 ^{a} ± 6.07
DOX	275.00 ^{c} ± 5.20
GSE + DOX	286.00 ^{bc} ± 3.00
L-CA + DOX	308.00 ^{b} ± 9.17

Values are expressed as mean (means ± SE).

Means with the same letter in the same column are non-significant at ($p \leq 0.05$).

GSE: grape seed extract, L-CA: L-carnitine, DOX: doxorubicin.

Table 2: *The effects of doxorubicin cardiotoxicity as well as the protective effects of grape seed and l-carnitine on erythrogram after 29 and 35 days.*

Parameters / Treatment	RBCs count ($l0^6$/µl)	Hemoglobin (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (%)
At day 29						
Control	8.38 [a] ± 0.13	12.73 [a] ± 0.12	45.53 [a] ± 0.12	54.38 [a] ± 0.70	15.21 [a] ± 0.35	27.97 [a] ± 0.31
GSE	8.64 [a] ± 0.18	12.30 [a] ± 0.15	45.23 [a] ± 0.23	52.42 [a] ± 1.06	14.26 [a] ± 0.46	27.19 [a] ± 0.32
L-CA	8.71 [a] ± 0.04	12.60 [a] ± 0.31	45.40 [a] ± 0.10	52.17 [a] ± 1.24	14.49 [a] ± 0.66	27.75 [a] ± 0.66
DOX	8.35 [a] ± 0.05	12.27 [a] ± 0.13	45.37 [a] ± 0.23	54.31 [a] ± 0.27	14.68 [a] ± 0.19	27.04 [a] ± 0.20
GSE + DOX	8.38 [a] ± 0.28	12.77 [a] ± 0.09	46.20 [a] ± 0.82	55.18 [a] ± 1.05	15.26 [a] ± 0.45	27.65 [a] ± 0.33
L-CA + DOX	8.38 [a] ± 0.20	12.50 [a] ± 0.09	45.37 [a] ± 0.19	54.20 [a] ± 1.36	14.93 [a] ± 0.33	27.55 [a] ± 0.23
At day 35						
Control	8.44 [a] ± 0.11	12.97 [a] ± 0.12	45.47 [a] ± 0.13	53.87 [a] ± 0.83	15.36 [a] ± 0.24	28.52 [a] ± 0.22
GSE	8.45 [a] ± 0.20	12.80 [a] ± 0.21	45.20 [a] ± 0.23	53.48 [a] ± 0.58	15.15 [a] ± 0.36	28.32 [a] ± 0.38
L-CA	8.37 [a] ± 0.09	12.80 [a] ± 0.25	45.17 [a] ± 0.09	53.99 [a] ± 0.57	15.30 [a] ± 0.23	28.34 [a] ± 0.51
DOX	6.80 [d] ± 0.06	7.03 [d] ± 0.09	29.20 [d] ± 0.15	42.94 [d] ± 0.39	10.34 [d] ± 0.05	24.09 [d] ± 0.33
GSE + DOX	7.30 [c] ± 0.06	8.47 [c] ± 0.09	33.43 [c] ± 0.23	45.80 [c] ± 0.06	11.60 [c] ± 0.03	25.32 [c] ± 0.09
L-CA + DOX	7.90 [b] ± 0.06	10.17 [b] ± 0.09	38.23 [b] ± 0.15	48.40 [b] ± 0.46	12.87 [b] ± 0.17	26.59 [b] ± 0.31

Values are expressed as mean (means ± SE).

Means with the same letter in the same column are non-significant at ($p \leq 0.05$).

GSE: grape seed extract, L-CA: L-carnitine, DOX: doxorubicin.

Table 3: *The effects of doxorubicin cardiotoxicity as well as the protective effects of grape seed and l-carnitine on leukogram and platelets after 29 and 35 days.*

Parameters / Treatment	WBCs (10^3/µl)	Neutrophil (10^3/µl)	Lymphocyte (10^3/µl)	Monocyte (10^3/µl)	Eosinophil (10^3/µl)	Platelet count (10^3/µl)
At day 29						
Control	12.40 ^{a} ± 0.31	4.49 ^{a} ± 0.03	6.46 ^{a} ± 0.17	1.33 ^{a} ± 0.03	0.12 ^{a} ± 0.01	650.83 ^{a} ± 0.60
GSE	12.37 ^{a} ± 0.19	4.48 ^{a} ± 0.03	6.44 ^{a} ± 0.10	.32 ^{a} ± 0.02	0.13 ^{a} ± 0.00	51.30 ^{a} ± 0.35
L-CA	12.37 ^{a} ± 0.18	4.48 ^{a} ± 0.04	6.46 ^{a} ± 0.11	1.30 ^{a} ± 0.02	0.13 ^{a} ± 0.01	651.37 ^{a} ± 0.38
DOX	12.53 ^{a} ± 0.15	4.54 ^{a} ± 0.03	6.54 ^{a} ± 0.09	1.32 ^{a} ± 0.01	0.13 ^{a} ± 0.00	651.07 ^{a} ± 0.52
GSE + DOX	12.33 ^{a} ± 0.18	4.47 ^{a} ± 0.05	6.45 ^{a} ± 0.10	1.29 ^{a} ± 0.02	0.12 ^{a} ± 0.00	651.23 ^{a} ± 0.38
L-CA + DOX	12.40 ^{a} ± 0.06	4.48 ^{a} ± 0.10	6.45 ^{a} ± 0.04	1.35 ^{a} ± 0.01	0.12 ^{a} ± 0.01	651.07 ^{a} ± 0.52
At day 35						
ontrol	12.33 ^{a} ± 0.09	4.46 ^{a} ± 0.25	6.36 ^{a} ± 0.06	1.38 ^{a} ± 0.02	0.14 ^{a} ± 0.01	650.67 ^{a} ± 0.73
GSE	13.53 ^{a} ± 0.09	4.52 ^{a} ± 0.14	6.50 ^{a} ± 0.06	1.39 ^{a} ± 0.01	0.13 ^{a} ± 0.00	650.19 ^{a} ± 0.04
L-CA	12.40 ^{a} ± 0.12	4.47 ^{a} ± 0.17	6.41 ^{a} ± 0.08	1.39 ^{a} ± 0. 01	0.12 ^{a} ± 0.01	650.17 ^{a} ± 0.09
DOX	7.47 ^{d} ± 0.09	2.21 ^{d} ± 0.06	3.93 ^{d} ± 0.05	1.17 ^{b} ± 0.01	0.13 ^{a} ± 0.02	396.20 ^{d} ± 0.12
GSE + DOX	9.80 ^{c} ± 0.12	3.12 ^{c} ± 0.04	5.16 ^{c} ± 0.06	1.37 ^{a} ± 0.05	0.14 ^{a} ± 0.01	482.27 ^{c} ± 0.15
L-CA + DOX	10.90 ^{b} ± 0.10	3.76 ^{b} ± 0.03	5.66 ^{b} ± 0.04	1.34 ^{a} ± 0. 04	0.14 ^{a} ± 0.00	582.28 ^{b} ± 0.14

Values are expressed as mean (means ± SE).
Means with the same letter in the same column are non-significant at ($p \leq 0.05$).
GSE: grape seed extract, L-CA: L-carnitine, DOX: doxorubicin.

Discussion

Doxorubicin (DOX) has substantial antitumor activity, making it an antineoplastic treatment for solid and hematological cancers. Nevertheless, its limited therapeutic value stems from its myelosuppressive effects, irreversible cardiotoxicity, and cancer cell resistance ***(Jaćević et al., 2018)***. Therefore, we examined the protective properties of GSE and L-CA in protecting albino rats from doxorubicin-induced toxicity.

As shown in our study, oral administration of grape seed and l-carnitine did not affect body weight at days 29 and 35, consistent with ***Yousef et al. (2009)*** for grape seed extract and ***Gökçe et al. (2023)*** for l-carnitine.

After 24 hours of DOX infusion, all groups that received DOX experienced a significant drop in

body weight. On day 35 a significant decrease was noted. This is in agreement with ***Babaei et al., (2020)*** and ***Eisvand et al., (2022). Jaćević et al. (2018)*** revealed that the drop in body weight was due to a lack of appetite and severe lesions in the GIT's epithelium, inhibiting food consumption.

In our study, pretreatment with GSE resulted in a non-significant change in body weight as compared to the control group on day 29 of the experiment. On day 35 of the trial, there was a significantly higher body weight as compared to the DOX group. Similar results were reported by ***Razmaraii et al. (2016). Abu Hafsa et al. (2018)*** revealed that GS's phenolic substances have antioxidant properties, potentially reducing peristaltic activity, and protecting intestinal mucosa from oxidative damage. This was demonstrated by increased food consumption and an increase in body weight.

Pretreatment with L-CA shows a significant increase in body weight on day 35 of the experiment as compared to GSE+DOX. This result agrees with ***Alabi et al. (2018). Dokmeci et al. (2005)*** revealed that L-CA prevents mucosal lesions by preventing lipid peroxidation and promoting gastroprotection through free radical scavenging and cytoprotecting. This positively influences body weight and food intake.

Regarding our result on the hemogram, it is worth noting that GSE and L-CA had no negative impact. These were consistent with those of ***Çetin et al. (2008)*** for Grape seed extract and similar to ***Uluisik et al. (2014)*** for l-carnitine.

On day 29 of the experiment there was a non-significant change in the erythrogram in DOX-intoxicated rats than in the control. Similar results were obtained by ***Torres et al. (2010).*** On day 35 of the experiment a reduction was noted as compared to the control, reflecting microcytic hypochromic anemia. Similar results were reported by ***Khanmohammadi et al. (2018); Afsar et al. (2017); Boussada et al., (2017)***. ***Farag et al. (2021)*** reported that oxidative stress targets RBCs, leading to heme production inhibition, erythropoiesis loss, and hemopoietic system loss, potentially causing anemia.

Our study found no significant variation in leukogram and platelet levels on day 29, but a significant reduction in WBCs, neutrophils, lymphocytes, monocytes, and platelets on day 35, indicating immunity changes. As myelotoxicity is common with DOX therapy. Similar to the results by ***Botelho et al. (2020); Ifeanacho et al. (2020); Sergazy et al (2020)***. According to ***Botelho et al., (2020),*** DOX exposure led to a significant decline in white cell and platelet counts, causing hematological toxicity and potentially fatal cytopenia, necessitating medication cessation.

The grape seed pretreated group showed a curable effect, with an increase in hematological

parameters than the DOX group. but it was still lower than the control. Similar to ***Hasona and Morsi (2019). Nazima et al. (2016)*** demonstrated that GS restored hematological parameters to near normal levels in Cd-treated rats, due to the presence of the 3- and 5-hydroxyl groups with 4-oxo group functions acting as electron donors and protecting heme from oxidative stress.

L-CA pretreated group showed increased hemogram compared to the DOX group and the group pretreated with grape seed. These results were in line with those of ***Alabi et al. (2018)***. ***Malaguarnera et al. (2011)*** showed that L-CA protected red blood cells from oxidative stress and stabilized their membranes, The protective effects of L-CA on anemia may be due to a decrease in lipid peroxidation, which raises erythrocytes. The increase in white blood cell count in our study could be attributed, According to ***Mate et al. (2010),*** to the role of L-CA counteracting impaired immune responses by reducing oxidative stress and lipid peroxidation and increasing the levels of antioxidant enzymes. Also, ***Strasser et al. (2007)*** reported a significant β-oxidation activity in WBC, suggesting that carnitine-dependent energy production from fatty acids plays a role in the effects of L-CA on immune cells.

Conclusion

We hypothesized that the GSE and L-CA protected against DOX-induced toxicity.

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دراسات دموية على تأثير مستخلص بذور العنب وإلكارنيتين ضد السمية المحدثة بالدوكسوروبيسين في الجرذان

الملخص العربي

استهدفت هذه الرسالة دراسة تأثير إعطاء بذور العنب ومادة الكارنيتين لمدة 35 يوم على الجرذان المسممة بالدوكسوروبسين وقد أجريت هذه الدراسة على 60 جرذ وتم تقسيمهم الى 6 مجموعات متساوية إشتملت كل مجموعة على 10 جرذان

لم تظهر المجموعات التي تلقت مستخلص بذور العنب ومادة إلكارنيتين منفردين أي تغيرات معنوية في جميع مؤشرات التحاليل. بينما انخفض وزن الجسم لدي الجرذان المسممة بالدوكسوروبيسين كما أظهرت المجموعات المعالجة مسبقًا بمستخلص بذور العنب ومادة إلكارنيتين تحسن في اوزان الجسم مقارنة بالمجموعة الدوكسوروبيسين .كما أظهرت صورة الدم إصابة الجرذان المسممة بالدوكسوروبيسين بفقر الدم من النوع الصغير الخلايا منخفض الصبغة مع نقص كرات الدم البيضاء ونقصان في الصفائح الدموية في المجموعة المسممة وهذا مقارنة بالمجموعة الضابطة. بينما أظهرت المجموعات المعالجة مسبقا تحسن في صورة الدم.