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Potential Curative Effects of Taurine and Curcumin on Rats Liver with Pre-eclampsia Induced by Doxorubicin

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Abstract:

This study was conducted to investigate the effects of taurine or/and curcumin supplementations on the liver of pre-eclamptic rats. Pre-eclampsia was induced in pregnant rats by 10mg adriamycin /kg. b.wt. intraperitoneal (tri-weekly) for 2 weeks. The pregnant rats were dissected on the 20th day of gestation. The rats were examined for morphological changes, biochemical analysis and DNA damage evaluation. Significant alterations were recorded in the number of implantation and resorption sites, live fetuses, activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl-transferase (GGT) as well as concentrations of albumin and total protein associated with disturbance in the levels of haptoglobin (HPG), liver-fatty acid binding protein (L-FABP), Total antioxidant status (TAS) and total oxidant status (TOS) in pre-eclampsia groups compared with their corresponding control ones. Also, external morphological examination of fetuses exhibited malformed and resorbed fetuses in toxemic group. Comet assay from liver tissues of all pregnant mother rats were measured which showed high percentage of DNA damage 58.48, 36.27, 52.05 and 25.14% in V, VI, VII and VIII toxemic rat groups respectively than control group 5.93, 5, 3.77, 4.53% in I, II, III and IV rat groups respectively. Remarkable corrections had occurred in all previously studied parameters after being treated orally with 500mg taurine /kg. b.wt/day and/or 500mg curcumin /kg. b.wt/day for 2 weeks. Co-administration of taurine and curcumin to the pre-eclamptic rats' group caused the maximum correction effects on all studied parameters due to modulation of free radical scavenger as well as cell membrane stabilizer through reduction of lipid peroxidation production and enhancement of cellular antioxidant enzymes system".

Keywords : *Pre-eclampsia, Adriamycin, Taurine, Curcumin, Rats, liver disease.*

1. Introduction:

Preeclampsia is a pregnancy-associated condition characterized by high blood pressure. It causes damage to vital organs such as the liver, kidneys and heart. It is a serious health trouble for pregnant women and can be fatal if left untreated. Also, it might lead to placental disturbance, intrauterine growth restriction and stillbirth **[1].**

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Preeclampsia pathophysiology in rat models involves abnormal placentation, inflammation and oxidative stress associated with angiogenic imbalance. These factors contribute to the development of systemic endothelial and multi-organ dysfunction, including hepatic disease **[2]**.

Hepatic manifestations often include hepatocellular injury, impaired liver function and histological changes indicative of liver damage. **[3]** noted alterations in hepatic gene expression, dysregulation of lipid metabolism and elevation in the oxidative stress of rat's liver with preeclampsia symptoms.

The development of hepatic disorders in preeclampsia rat models is associated with pronouncing oxidative stress. The increment of reactive oxygen species formation and elevation in pro-inflammatory cytokines led to hepatocellular damage and dysfunction. However, dysregulation of antioxidant defense mechanisms may impair liver oxidative stress during preeclampsia **[4]**.

Taurine (sulfur-containing amino acid) is circulated throughout the body, especially in the liver, the heart, leukocytes, retina, platelets and brain. It may be generated endogenously from methionine and cysteine. It does not encode for protein. Taurine has several physiological actions such as bile salt synthesis, anti-inflammation, calcium homeostasis, osmoregulation, antioxidation and central nervous system function **[5]**.

In the liver, taurine has a chief function which is to conjugate bile acids for excretion of bile. Also, taurine plays a variety of physiological and pharmacological effects in the liver and other tissues, such as osmoregulation, cellular plasma membrane stabilization, antioxidant effects and detoxification **[6]**. Taurine is also known to enhance lipids profile and protect the liver from various liver injuries **[7,8]**.

Curcumin decreases oxidative stress by increasing the activity of antioxidants like superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT) **[9]**. Curcumin, the most important active ingredient in turmeric, which is a polyphenol molecule and is produced from the rhizomes of *Curcuma longa L*. Curcumin has been scientifically proven to exhibit antioxidant, anticancer, antihyperlipidemic, antiviral, anticoagulant, anti-inflammatory, anti-apoptotic and immunosuppressive activities in several investigations **[10]**. Curcumin has been also established to have anti-inflammatory properties in a variety of inflammatory and autoimmune disorders. Its anti-inflammatory activity is mostly because of its polyphenolic ingredients. Curcumin interacts with various pro-inflammatory chemicals and reduces inflammation by directly scavenging their molecular targets **[11].**

The current study was carried out to investigate the alteration in the levels of innovative biomarkers in pre-eclampsia induced with adriamycin in rats. Also, this study illustrates the possible prospective therapeutic roles of taurine and curcumin against toxic effects of adriamycin in pregnant rats.

2. Materials and methods

2.1. Chemicals:

Doxorubicin was procured under trade name Adriamycin from local pharmacy (PHARMACIA Co., Sweden). Taurine was purchased from Sigma-Aldrich (St. Louis, MO, USA). Curcumin was bought from EVA-Pharma Company, Giza, Egypt.

2.2. Animals:

64 female virgin Albino rats (*Rattus norvegicus*) weighting 180-200g, 10-12 weeks of age were used in this study and 16 male albino rats weighting 200-220g, age 10-12 weeks were used for mating only. Animals were obtained from the Animal House of Faculty of Medicine, Ain Shams University, Research Institute (MASRI), Cairo, Egypt. All animals were kept under hygiene and control conditions in metallic cages (relative humidity of 50-55%, temperature 22±2°C and with natural light/day cycle). They fed standard laboratory animal diet according to NRC (1995). Food and fresh tap water was available and replenished daily. They were acclimatized for one week before the experiment.

2.3. Ethical Approval:

This investigation was approved by the Ethics Committee of the animals that were kept in accordance with the Animal House of Faculty of Medicine, Ain Shams University, Research Institute (MASRI) guidelines on the use and care of animals in research with Ethical approval No.: RE (188) 22.

2.4. Experimental design:

Females showing pro-estrus stage were used for mating. Every 4 virgin female rats were placed with one male rat late afternoon for copulation overnight. Early next morning, vaginal smears were performed for the evidence of mating. To ensure successful mating, spermatozoa were clearly seen together with the cornfield cells. The day on which spermatozoa was observed; this day was considered as the 1^{st} day of gestation.

Pregnant female rats were equally divided into 8 groups (eight rats in each one). All pregnant females were treated according to the relevant treatment from the 7^{th} day till the 19^{th} day of gestation and then dissected at the 20^{th} day of gestation.

Group (I) or (Control): Control group, pregnant females received 0.5 ml dist. water daily orally by using of orogastric tube.

Group (II) or (T): Taurine positive control group, female rats were treated with 500mg taurine /kg. b.wt/day orally by using of orogastric tube **[12].**

Group (III) or (Cr): Curcumin positive control group, female rats were treated with 500mg curcumin /kg. b.wt /day orally by using of orogastric tube **[13].**

Group (IV) or (Mix): Mixture positive control group, female rats were treated with both taurine and curcumin as described in groups (II)and (III).

Group (V) or (ADR): The toxemic group, pregnant females were administrated 10mg adriamycin /kg. b.wt. intraperitoneal (tri-weekly) for 2 weeks **[14].**

Group (VI) or (ADR+T): The toxemic pregnant rats were administrated adriamycin as previous animals' group (V) and treated with taurine as previously described in group (II).

Group (VII) or (ADR +Cr): The toxemic pregnant rats were administrated adriamycin as the previous animals' group (V) and treated with curcumin as previously described in group (III)

Group (VIII): (ADR+ Mix): The toxemic pregnant rats were administrated adriamycin as the previous animals' group (V) and treated with both taurine and curcumin as described in group (IV).

2.5. Pregnant females and fetus parameters:

The weight of the pregnant females of the control and experimental groups were recorded weekly by using GR analytical balance. Increment in the weekly body weights were recorded as pregnancy associated with appearance of nipples of the mammary glands.

At the 20^{th} day of gestation, pregnant female rats were anesthetized by inhalation of isoflurane before blood samples collection by orbital plexus bleeding technique according to **[15].** Within an hour of the blood sample collection, sera were collected by centrifuging the blood at 3000rpm for 10 minutes at room temperature. Sera was then divided into small aliquots and stored in Eppendorf's at −20°C for further biochemical analyses.

After blood collection, female rats were investigated; the uterus was examined for the total implantation sites, no. of fetuses, resorption sites and abortion sites. Livers were washed with cool saline solution (0.9% NaCl). Then, they were stored at −20°C for biochemical analyses and comet assay.

2.6. Fetus parameters

Fetuses were morphologically examined for any abnormalities. The dead and live fetuses were recorded and photographed for any anomalies.

2.7. Biochemical analysis:

2.7.1. Liver function profile:

Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl-transferase (GGT) as well as serum concentrations of total protein and albumin were determined according to **[16,17,18,19,20]** respectively by using commercial kits**.** These kits were purchased from CliniChem Ltd, Budafoki Street, H-1117 Budapest, Hungary and approving the manufacturer's instructions.

Serum rat levels of haptoglobin (HPG) and liver-fatty acid binding protein (L-FABP) were estimated according to **[21,22]** respectively using a solid phase enzyme linked immunosorbent assay (ELISA) and following the manufacturer instructions. The rat HG and rat L-FABP kits were procured from Kamiya Biomedical Company, Gateway Drive, Seattle, USA.

2.7.2. Determination of liver total oxidative/antioxidant status (TAC and TOS):

Total antioxidant status (TAS) was assayed in liver tissues according to **[23].** However, total oxidant status (TOS) was measured in liver tissues according to **[24].** The TAS and TOS kits were bought from Labor Diagnostika Nord GmbH & Co., Nordhorn, Germany.

2.8. Comet assay:

Comet assay is performed in Animal Reproduction Research Institute – ARRI, Giza, Egypt. According to **[25]**, all comet assay stages were completed with the least amount of illumination possible, and the slides were coded. After being submerged in lysis solution (which contained 2.5M NaCl, 100mM EDTA, 10mM Tris, pH 10; 10% DMSO and 1% Triton 100-X were added right before usage), slides were cleaned. After 20 minutes, DNA unwinding time and in an alkaline (pH >13) environment, electrophoresis was carried out at 4°C for 30 minutes at 0.7 V/cm and 300mA. After neutralizing for 15 minutes (0.4M Tris at pH 7.5), the slides were fixed in absolute ethanol, air dried and kept at 4 °C. After applying ethidium bromide stain to the slides, they were examined right after utilizing fluorescence microscope connected to a computer-based analysis system **[26].** For each animal, a hundred randomly chosen nucleoids were assessed. The tail moment, tail length, and tail intensity (% tail DNA) were used to represent the results. Equations for measuring tail length and tail moment according to **[27].**

Tail length (µm) = the distance between center of the nucleus and the end of tail

Tail moment = tail length (µm) × % tail DNA

2.9. Statistical analysis:

Version 16.0 of the statistical processing system support (SPSS) for Windows program was used to analyze all the data. A-Analysis of differences One-way ANOVA followed by a T-test. B- Two-way ANOVA of variance followed by Duncan's multiple range tests were used to look for any noteworthy variations between the independent sample and the groups. To determine statistical significance between control and treated groups the univariable was employed. The means ± standard

deviation was reported for the various groups' acquired findings. For all statistical tests, the significance threshold was set at $p<0.05$.

3. Results:

3.1. Effect on pregnant rats and fetuses:

The females' weights and mortality rates were recorded. On the 20th day of gestation, their uteri were investigated to record the numbers of the implantation sites and no. of viable fetuses as well as the percentages of resorption and abortion.

3.1.1. Change in maternal body weights:

In this study, the average maternal body weights were recorded on 1st, 7th, 14thand20th day of gestation and presented in **Table (1).** The percentage of change in maternal body weights showed an increase in the body weights during the first week of gestation in control and treated groups. The average body weights on the 7th day of gestation increased by 6.7 in group (I), 10.7, 7.1, 10.4, 11.5, 3.7, 5.2 and 7.3% in II, III, IV, V, VII and VIII rat groups respectively. The highest percentage of change was perceived in group (V), and the lowest percentage of change was varified in group (VI).

The percentage change in maternal body weights on the 14th day of gestation amplified by11.6in group I, 18.38, 12.1, 18.4, 0.22, 0.41, 0.53 and0.74 in II, III, IV, V, VI, VII and VIII rat groups respectively. The extreme percentage of change was noted in group (IV), and the least percentage of change was noticed in group (V).

The average maternal body weights on the 20th day of gestation increased by 30in group I, 30.6, 28, 36.69, 0.71, 4.29, 3.58 and5.51% in II, III, IV, V, VI, VII and VIII rat groups respectively. Where the maximum percentage of change was found in group (IV), and the minimum percentage of change was recorded in group (V).

Table (1): showing average weight of pregnant females in control and treated groups in 1st, 7th, 14thand 20th days of gestation.

Groups/days	1st day	7th day	14th day	20th day
Group I (Control)	192.8±9.583^{aB}	205.2±8.35^{bB}	215.2±9.65^{cB}	250.8±27.77^{dB}
Group II (T)	190.4±9.63^{aC}	210.8±16.86^{bA}	225.4±31.59^{cA}	248.8±36.33^{dC}
Group III (Cr)	192.2±5.59^{aB}	206±9.27^{bB}	215.4±6.27^{cB}	246.2±29.63^{dC}
Group IV (Mix)	190.2±8.07^{aC}	210±14.58^{bA}	225.2±24.12^{cA}	260±17.18^{dA}
Group V (AD)	180.8±9.44^{aE}	201.6±6.66^{dD}	181.2± 7^{bE}	182.2±16.36^{cE}
Group VI (AD+T)	195.6±2.07^{aA}	203±7.58^{dC}	196.4±13.89^{bD}	204±5.36^{cD}
Group VII (AD+ Cr)	190.2±6.28^{aC}	200± 4.12^{dD}	191.6±18.42^{bD}	197±12.76^{cD}
Group VIII (AD+ Mix)	188.8±8.35^{aD}	202.6±6.99^{dC}	196.4±14.35^{bC}	199.2±4.14^{cD}

- Data are expressed as mean ± SD for 8 rats/ groups.
- Means bearing superscript (A, B, C, D, E) within the same interval are significantly different at $p < 0.05$.
  Where **A** is the highest value, **B** is significantly different from A, C is significantly different from **A** and **B**, **D** is significantly different from **A**, **B** and **C**, **E** is significantly different from **A**, **B**, **C**, **D**. If two groups differ numerically but not differ significantly, they take the same letter.
- Means bearing superscript (a, b, c, d) within the same group during different intervals are significantly different at $p < 0.05$.
  Where **a** is the lowest value, **b** is significantly different from **a**, **c** is significantly different from **a** and **b**, **d** is significantly different from **a, b, c**.

3.1.2. Abortion rates %:

The percentage of abortions was recorded in **Table (2).** Abortion in treated groups occurred after the 7th day of gestation. A large drop in maternal body weight is a sign of abortion and showing an empty uterus when dissected. The control group was shown in **Figure (1A)**, abortion was illustrated in **Figure (1B)**. On the 20th day of gestation, no abortion was recorded in the control group and positive control groups. Complete abortions were observed in female rats presenting 50 of pregnant rats, 25, 25 and 12.5% recorded in V, VI, VII and VIII rat groups respectively. With the highest rate in group (V)and the lowest rate in group (VIII).

3.1.3. Resorption rates %:

Resorption rates that present the total implantation sites and percentages of resorbed fetuses among control, positive control and treated groups. On the 20th day of gestation, the number of resorbed fetuses were observed in the uteri of the dissected mothers. Partial and complete resorption sites were recorded in **Table (2)** and **Figures (1C and 1D)** showing growth retardation in the uterus. no partial and complete resorption were recorded in control group and positive control groups, but One case of complete resorption was observed in group 5 **Figure (1E).** The percentage of partial resorbed fetuses among the groups was recorded by 50, 33,60 and 21 V, VI, VII and VIII among groups fetuses respectively. With the uppermost in group (V) and the lowermost in group (VIII).

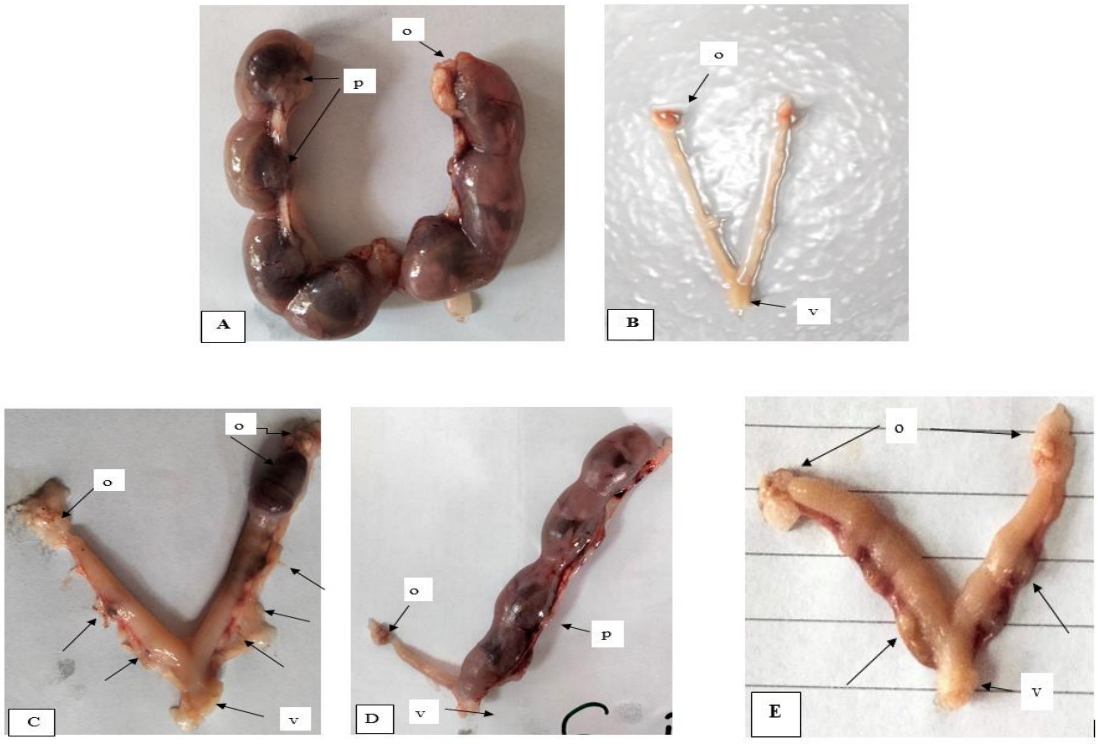

Figure (1): photographs of the female rat uteri dissected on the 20th day of gestation with magnification power of 12.5X:

(A) uterus with symmetric distribution of fetuses in the two uterine horns and normal physiological appearance of pregnancy from group I. control group.
(B) uterus with complete abortion from group V.
(C) uterus with complete abortion with notable resorption sites (arrows) and intensive bleeding in the two uterine horns from group V.
(D) asymmetrical distribution of fetuses in the two horns from group VIII.
(E) uterus with complete resorption in both horns with notable resorption sites (arrows) from group VII.
O ovaries; p: placenta; v: vagina.

3.1.4. External morphology of fetuses:

Table (2) shows the total number of fetuses and the average number of fetuses per mother. No abnormal fetuses were observed in control and positive control groups, but abnormal fetuses are observed representing 37.5, 23.8, 20 and 14% of the total number of fetuses in V, VI, VII and VIII rat groups respectively. Compared to fetuses from control group **Figure (2a),** the external morphology examination of the fetuses illustrated that adriamycin causes growth retardation of the fetuses as in **Figure (2b)**. Other abnormalities observed in the fetuses are brachdactylism (shortness of fore and hind limbs) **Figure (2c)**, paralysis of hind limbs **Figure (2d)** and paralysis of fore limb **Figure (2e).** Growth retardation is indicated by reduction in body length compared with control. The growth retardation is also observed in V, VI, VII and VIII rat groups as illustrated in **Figure (3).**

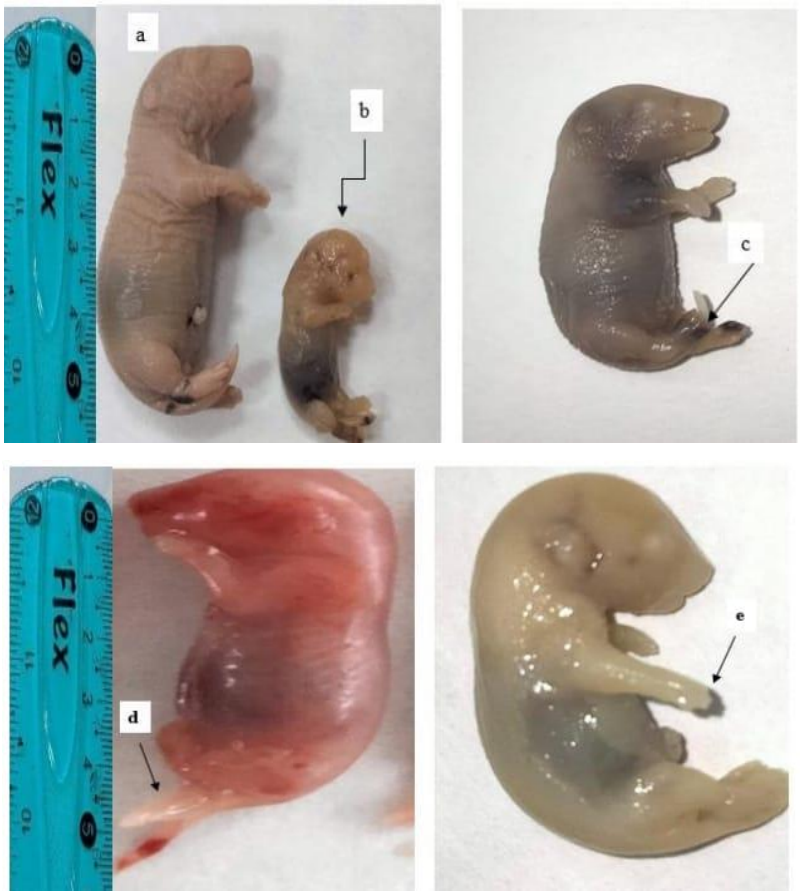

Figure (2): photographs of the female rat fetuses on the 20th day of gestation with magnification power of 12.5X:

(a) fetus with normal appearance with no abnormalities from group I.
(b) abnormal fetus with growth retardation, shorter in length and smaller in size from group VIII.
(c) abnormal fetus with brachydactylic (shortness of digits) compared to normal fetus (arrow) from group V.
(d) abnormal fetus with paralysis in hind limb(arrow) from group VI.
(e) abnormal fetus with paralysis in fore limb (arrow) from group VII.

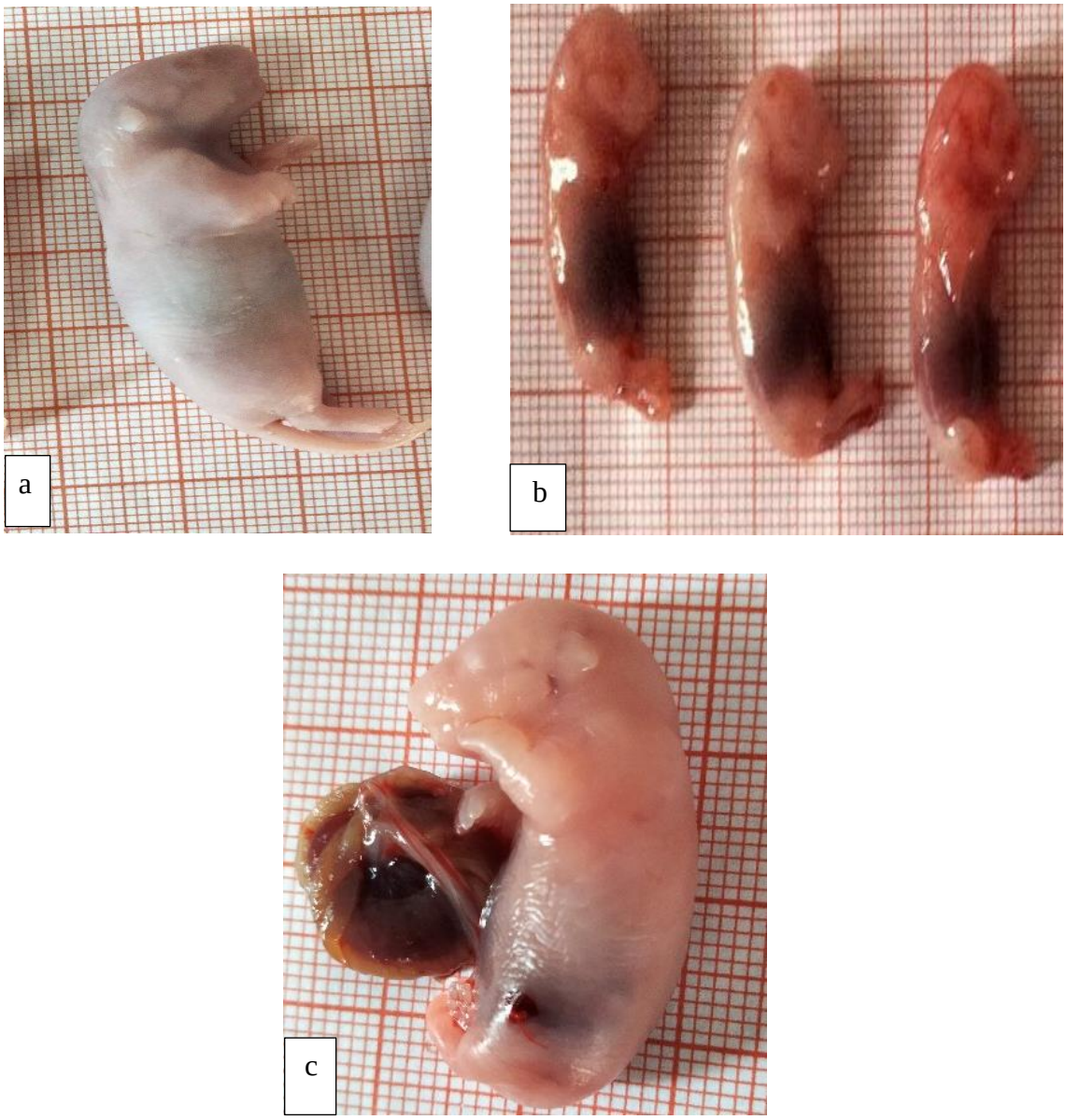

Figure (3): photographs of the female rat fetuses on the 20th day of gestation:
(a) image of fetus with normal length from group (I).
(b) image of fetuses from group (V) with growth retardation compared to control.
(c) Image of fetus with medium length from group VIII.

Table (2): Values of morphological examination of fetuses in pre-eclampsia rat groups treated with taurine or/and curcumin.

No. of group	No.of pregnant mothers	Total Implantation sites	fetuses/ mother	No.of live fetuses	% of resorped fetuses	No.of aborted mothers	% of Malformed fetuses
Group I (Control)	8	76	9.5	76	0	0	0
GroupII (T)	8	64	8	64	0	0	0
GroupIII (Cr)	8	68	8.5	68	0	0	0
Group IV (Mix)	8	72	9	72	0	0	0
Group V (ADR)	8	8	2	4	50%	50%	37.5%
GroupVI (ADR+ T)	8	21	3.5	14	33.3%	25%	23.8%
GroupVII (ADR+Cr)	8	15	2.5	6	60%	25%	20%
GroupVIII (ADR+Mix)	8	28	4	22	21%	12.5%	14%

- Data is illustrated as mean ± SD for 8 rats/ groups.

3.2. Biochemical parameters:

3.2.1. Liver function profile results:

As Given in **Table (3),** There was a noteworthy increment in the serum activities of ALT, AST and GGT accompanied with remarkable reductions in total protein and albumin levels as a result of administration of 10mg adriamycin /kg. b.wt and pronouncing of toxicity in pregnant rats. The percentage of elevations in serum ALT activities were reached to 161.23, 103.48, 135.33 and 71.55 in V, VI, VII and VIII rat groups respectively. The percentage of serum AST activities was achieved to 144, 71, 100 and 35 in V, VI, VII and VIII rat groups respectively. The percentage of escalation in serum GGT activities were attained to 505, 169, 304and 80 in V, VI, VII and VIII rat groups respectively.

On the other hand, the percent of reductions in the levels of total protein and albumin were achieved to 21, 14, 17 and 7 for total protein and 31.3, 17, 24 and 8 for albumin in V, VI, VII and VIII rat groups respectively. A considerable correction was occurred in the previous parameters after toxemic rats group were treated with 500mg taurine /kg. b.wt/day or with 500mg curcumin /kg. b.wt/day. However, the improvement in toxemic rats' group which was treated with taurine was better than that was treated with curcumin.

The best ameliorative effects were recorded after treatment with both antioxidants (taurine and curcumin) compared with their corresponding normal control rats' group.

Table (3): The curative role of taurine or curcumin and their mixtures on serum liver function tests in toxemic pregnant rats.

Groups/ parameters	ALT (U/l)	AST (U/l)	GGT (U/l)	T. protein (g/dL)	Albumin (g/dL)
Group I (Control)	23.55±0.49^{E}	90.44±1.35^{E}	32.43±1.37^{E}	6.19±0.02^{A}	4.22±0.01^{A}
Group II (T)	23.39±0.61^{E}	89.752±1.59^{E}	30.91±0.61^{E}	6.2±0.01^{A}	4.23±0.01^{A}
Group III (Cr)	23.54±0.32^{E}	90.71±1.71^{E}	31.75±0.75^{E}	6.17±0.03^{A}	4.2±0.01^{A}
Group IV (Mix)	22.96±0.66^{E}	89.25±1.6^{E}	30.77±0.54^{E}	6.27±0.04^{A}	4.27±0.05^{A}
Group V (ADR)	61.52±0.71^{A}	221.22±6.8^{A}	196.04±5.68^{A}	4.92±0.04^{E}	2.92±0.05^{E}
Group VI (ADR+ T)	47.92±0.76^{C}	155.34±1.81^{C}	87.194±2.3^{C}	5.32±0.04^{C}	3.47±0.03^{C}
Group VII (ADR+ Cr)	55.42±1.1^{B}	181±3.62^{B}	131.14±2.66^{B}	5.08±0.05^{D}	3.18±0.07^{D}
GroupVIII (ADR+ Mix)	40.41±1.59^{D}	122.77±1.16^{D}	51.34±1.22^{D}	5.65±0.12^{B}	3.87±0.07^{B}

- Data is illustrated as mean ± SD for 8 rats/ groups.
- Mean bearing variant superscript (A, B, C, D, E) in each parameter differ significantly at ($p<0.05$).

  Where **A** is the highest value, **B** is significantly different from A, C is significantly different from **A** and **B**, **D** is significantly different from **A**, **B** and **C**, **E** is significantly different from **A**, **B**, **C**, **D**. If two groups differ numerically but not differ significantly, they take the same letter.

3.2.2. Serum level of HPG and L-FABP (ng/ml):

Induction of preeclampsia as a result of adriamycin administration led to significant ($p<0.05$) amplification happened in the serum levels of HPG, L-FABP **(Table 4)**. The percentage of inflation in serum level of HPG stretched to 164, 90, 127 and 53 in V, VI, VII and VIII rat groups respectively. The percentage of escalation in serum level of L-FABP accomplished to 164, 90, 127 and 53 in V, VI, VII and VIII rat groups respectively. Treated toxemic rat groups with 500mg taurine /kg. b.wt/day or 500mg curcumin /kg. b.wt/day cause extraordinary enhancement effects on both HPG and L-FABP levels. The maximum modification was verified after toxemic animals' group was treated with both taurine and curcumin compared to their matching control group as shown in **Table (4)**.

3.2.3. levels of liver total oxidative/antioxidant status (TAC and TOS):

The data acquired in **Table (4)** clarified a significant ($p<0.05$) drop in the level of TAS in toxemic rats which was recorded as 45, 24, 35 and 6% in groups V, VI, VII and VIII rat groups respectively. However, the induction of preeclampsia in the rats group caused a marked increment in the level of TOS, which was noted as 97, 51, 67 and 27% in groups V, VI, VII and VIII rat groups respectively. Treated toxemic rat groups led to notable modulation effects on TAS and TOS levels. The most rectification was noticed in toxemic animals group treated with a mixture of taurine and curcumin as shown in **Table (4).**

Table (4): The curative role of taurine or curcumin and their mixtures on levels of (L-FABP, HPG, TAS and TOS) in toxemic pregnant rats.

Groups/ parameters	L-FAB (g/dL)	HPG (g/dL)	TAS (mmol/g)	TOS (mmol/g)
Group I (Control)	68.07 ± 0.7^{E}	7.19 ± 0.02^{E}	1.81 ± 0.03^{A}	0.43 ± 0.11^{E}
Group II (T)	65.32 ± 1.67^{E}	7.19 ± 0.012^{E}	1.84 ± 0.02^{A}	0.43 ± 0.01^{E}
Group III (Cr)	67.05 ± 1.21^{E}	7.21 ± 0.01^{E}	1.85 ± 0.05^{A}	0.45 ± 0.01^{E}
Group IV (Mix)	66.24 ± 1.91^{E}	7.22 ± 0.03^{E}	1.83 ± 0.02^{A}	0.45 ± 0.01^{E}
Group V (AD)	126.04 ± 2.13^{A}	19.03 ± 0.44^{A}	0.98 ± 0.01^{E}	0.85 ± 0.01^{A}
Group VI (AD+ T)	94.77 ± 0.63^{C}	13.73 ± 0.19^{C}	1.37 ± 0.01^{C}	0.65 ± 0.01^{C}
Group VII (AD+ Cr)	102.14 ± 1.12^{B}	16.24 ± 0.53^{B}	1.16 ± 0.01^{D}	0.72 ± 0.01^{B}
Group VIII (AD+ Mix)	82.71 ± 1.7^{D}	11.06 ± 0.18^{D}	1.69 ± 0.01^{B}	$0.55\pm.01^{D}$

- Data are illustrated as mean ± SD for 8 rats/ groups.
- Mean bearing common superscript (A, B, C, D, E) in each parameter differ significantly at ($p<0.05$).

  Where **A** is the highest value, **B** is significantly different from A, C is significantly different from **A** and **B**, **D** is significantly different from **A**, **B** and **C**, **E** is significantly different from **A**, **B**, **C**, **D**. If two groups differ numerically but not differ significantly, they take the same letter.

3.3. Comet assay:

Detection of DNA damage in liver tissue nuclei of maternal rats caused by adriamycin drug and DNA repair after treatment using antioxidants taurine and curcumin carried out by comet assay. Comet was prepared from eight groups, a total of 200 comets were recorded for each group.

The results were recorded in **Table (5)** for the different three parameters of comet assay: tail length, tail moment and DNA% in tail respectively. The plate **Figure (4)** showed pictures of comet assay of samples from different groups.

3.3.1. Tail length, tail moment and percentage of DNA in tail of comet assay:

On measuring values of tail length among control and treated groups, the control and the positive control groups showed insignificant changes in tail length, tail moment and percentage of DNA in tail.

Significant amplifications in tail moment reached to 219.9±65, 67.63±37, 107.8±59 and 99.2±58.6 in V, VI, VII and VIII rat groups respectively. Also, remarkable elevations in tail length were observed as 376±182.2, 187.2±103.2, 207±121.7 and 99.2±58.6 in V, VI, VII and VIII animals' groups respectively.

Moreover, the percentage of DNA in a tail reflects the degree of DNA damage. Significant ($p<0.05$) elevations in the percentage of DNA in tail were recorded as 58.48, 36.27, 52.05 and 25.14% in V, VI, VII and VIII rat groups respectively.

Table (5): The curative role of taurine or curcumin and their mixtures on levels of tail moment, tail length and % of tail DNA in toxemic pregnant rats.

Groups/ parameters	Tail moment	Tail length (µm)	% of DNA in tail
Group I control	.95±0.89^{E}	16±2.24^{E}	5.93±1.92^{E}
Group II T	.87±0.8^{E}	17.4±2.07^{E}	5±1.89^{E}
Group III Cr	.80±0.38^{E}	21.2±4.15^{E}	3.77±2.37^{E}
Group IV Mix	.96±.7^{E}	21.2±11.82^{E}	4.53±1.56^{E}
Group V ADR	219.9±65^{A}	376±182.2^{A}	58.48±10.5^{A}
Group VI ADR+ T	67.63±37^{C}	187.2±103.2^{C}	36.27±1^{C}
Group VII ADR+ Cr	107.75±59^{B}	207±121.7^{B}	52.05±6.25^{B}
Group VIII ADR+ Mix	24.94±12^{D}	99.2±58.6^{D}	25.14±9.44^{D}

- Data are illustrated as mean ± SD for 8 rats/ groups.
- Mean bearing variant superscript (A, B, C, D, E) in each parameter differ significantly at ($p<0.05$).

Where **A** is the highest value, **B** is significantly different from A, C is significantly different from **A** and **B**, **D** is significantly different from **A**, **B** and **C**, **E** is significantly different from **A**, **B**, **C**, **D**. If two groups differ numerically but not differ significantly, they take the same letter.

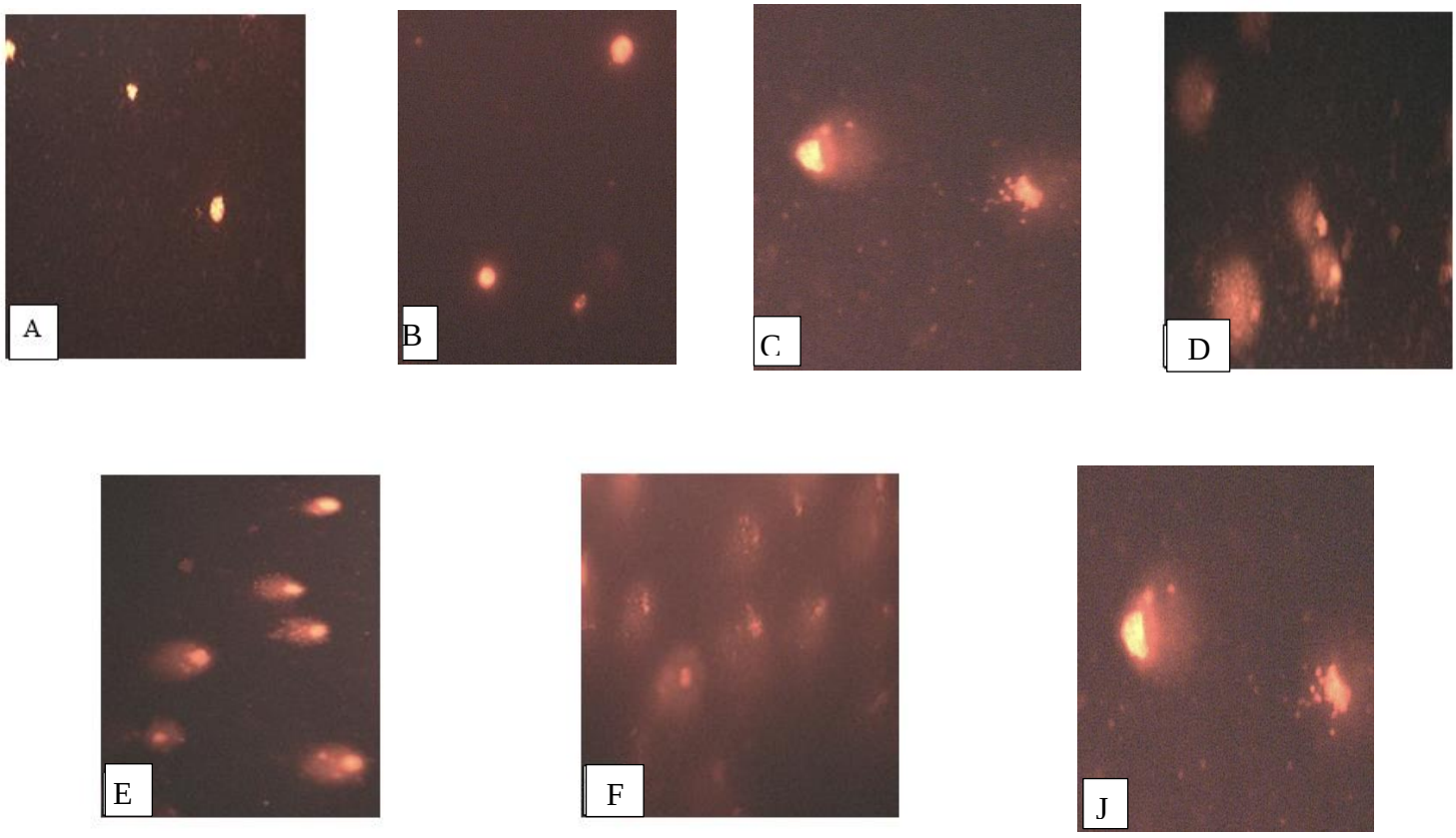

Figure (4): photographs for comet assay analysis of liver tissue nuclei with magnification power of X400 showing:

A: control group Shows G0; B: taurine group shows G0; C: curcumin group shows G1; D: Adriamycin group shows G4; E: Adriamycin-taurine group shows G2; F: Adriamycin-curcumin group shows G3 and G4; J: Adriamycin-mix group shows G1.

Where: G0 means no damage of DNA, G1 means 15% of DNA is damaged, G2 means 15%- 32% of DNA is damaged, G3 means 32%-60% of DNA is damaged, G4 means 100% of DNA is damaged.

4. Discussion

Toxemia during pregnancy is called eclampsia and leads to serious problems in both mothers and their infants **[28]**. Pre-eclamptic women face several risks including abruption, hypertension, diabetes mellitus, nephropathy and cardiovascular disease **[29,30]**.

Doxorubicin (DOX) is a common chemotherapeutic antibiotic and widely used for the treatment of numerous cancers such as sarcomas, thyroid carcinoma, gastric carcinoma, bronchogenic carcinoma,

breast cancer, multiple myeloma and acute lymphocytic leukemia **[31]**. It is administered intravenously in dosage regimens specific to the type of cancer and progression **[32]**.

During doxorubicin metabolism, free radicals release and react with hepatocyte lipids, proteins and nuclei acids causing mitochondrial dysfunction and lipid peroxidation which induces apoptosis and cell death because of reduction in the activity of topoisomerase-II and thus inhibiting cell division **[33].**

DOX is metabolized by liver cytoplasmic and microsomal reductase enzymes, resulting in the accumulation of toxic and immunogenic intermediates that led to the pronouncing of liver damage **[34]**. DOX works by causing DNA damage in cancer cells, preventing them from proliferating **[35]**. DOX toxicity is caused by several actions. It may initiate oxidative stress and impair mitochondrial activity by building up ROS in noncancerous cells **[36,37]**.

In recent work, pregnant rats were used as an animal model for induction of pre-eclampsia by adriamycin administration *via* intraperitoneal injection with cumulative dose of DOX (10mg/Kg B.wt.), which divided into 6 equal injections over a period of two weeks according to the method of **[14]**. Loss of appetite, fatigue and weakness were pronounced in the toxemic rats' group as a result of DOX administration compared with the control animals' group. Also, a remarkable reduction in the body weight in the toxemic rats' group was observed compared with control animals' group. These data may be due to the loss of appetite, the decreasing of food intake and appearance of peripheral gastroenteritis and stomatitis (disturbance in trigger zone or/and vomiting center). These data are in harmony with that obtained by **[38,39,40,41].**

In this investigation, the number of fetuses declined considerably in pre-eclamptic rats' group because of DOX administration as well as marked increment in the rate of abortion rate with partial or complete resorption rate in the uteri of the toxemic rat mothers associated with serious malformations in the fetus included brachdactylism (shortness of fore and hind limbs), reduction in the finger digits and paralysis in limbs. These results agree with several authors **[39,42]**. They related these results to the appearance of placental ischemia, declining nutrients and diminishing oxygen consumption associated with cardiac dysfunction.

As a side effect of DOX administration, serious toxicities to non-tumor tissues can occur **[43]**. Hence, hepatotoxicity is one of the side effects of DOX-treatment in cancer patients **[44,45]**. Carbonyl reductases and cytochrome P_{450} are used to metabolize DOX occurring in the liver. DOX metabolism in the liver leads to ROS production causing oxidative stress, mitochondrial dysfunction and inflammation. This is thought to be the mechanism how DOX-induced hepatotoxicity, leakage of hepatic enzymes into the circulation and hepatocyte death **[46]**.

In the current study, the serum activities of ALT, AST and GGT and the serum levels of haptoglobin and L-FABP concentrations as well as liver TOC levels were increased ($P<0.05$) significantly associated with considerable decline in the serum concentrations of total protein and albumin and liver TAC levels in the toxemic rats' group because of DOX administration compared with control animals' group. These conclusions come in agreement with several previous observations on DOX hepatotoxicity in the liver of patients or animals because of deficiency in the immune system,

mitochondrial dysfunction, elevation of redox status and increment de novo lipogenesis in hepatic tissues as well as pronouncing fragility and permeability in cell membrane [**47,48**]. The last authors attributed these data to abilities of DOX to stimulate oxidative stress by disruption of cellular redox homeostasis (changes in the antioxidant and oxidative status) as well as disturbance in the hepatic expression of HO^{-1} (regulates phase II enzymes in production of various antioxidant intermediates and heme metabolism). Similar findings are in the same line with **[49,50]**.

Numerous authors revealed that a marked elevation in lipid peroxidation production and hepatic MDA correlated with a considerable reduction in content of hepatic glutathione because of DOX administration **[48,51]**. Similar findings are in the same line with **[49,50,52]** showed remarkable elevation in the level of L-FABP in the circulation and decreased in the liver of toxemic animals' group due to maternal hypoperfusion which led to insufficient oxygen delivery to the brain as well as over-expression of hypoxia-inducible factor-1α (HlP-lα) which upregulates the expression of FABP in ischemia-induced hepatic damage. Also, **[53]** noted extensive increment in the levels of FABP in sera, livers and hearts in pre-eclamptic mice with hepatic or cardiac ischemia. In addition, the last authors showed rising L-FABP levels in both amniotic fluid and placenta of pre-eclamptic mice.

Taurine has been essential for mitochondrial tRNAs. Currently, mitochondrial encephalomyopathies are caused by lacking two taurine-containing modified uridines, (5-taurinomethyluridine and 5-taurinomethyl-2-thiouridine). Taurine biosynthesis is controlled by cysteine sulfonic acid decarboxylase which is low in most mammalian tissues. So, dietary taurine uptake via the taurine transporter Taut is the major route for taurine in most cell types **[54]**. Moreover, experimental evidence also suggests that taurine may be used as a direct antioxidant **[55]**. Also, the antioxidant effect of taurine may be due to its scavenging ability to hydroxyl radical **[56]**. As well as some substantial evidence indicates that taurine works against oxidative damage by interfering with reactive oxygen species activity and decreasing the formation of reactive oxygen species **[54]**. Taurine is also implicated in immunomodulation, protein stabilization, stress response, antioxidant defense and cell volume homeostasis **[57].**

In this work, the toxemic rats group as a result of DOX administration was treated with 500mg taurine/kg.b.wt/day (Group VI) led to remarkable enhancements in appetite, food intake, body weight, survival number of fetuses and the rate of abortion as well as reduction in the appearance of brachdactylism associated with marked corrections in all physiological studied parameters when compared to their corresponding non treated pre-eclamptic rats group (Group V). These investigations may be due to defensive consequences of taurine through decline in the free radicals' formation and pro-oxidants production. As well as amelioration in mitochondrial function. Also, elevation of ATP synthesis which led to improving the respiratory chain. It also results in modification in the endoplasmic reticulum and corrections in PI3K/Akt/mTOR signaling pathway and pro-inflammatory cytokines. These data are in accordance with numerous authors **[58,59,60,61].**

The protective effects of curcumin against chemically induced hepatotoxicity have been attributed to its intrinsic antioxidant properties **[62]**. In addition, curcumin has led to increase expression of antioxidant enzymes, such as glutathione reductase, glutathione S-transferase, quinone

oxidoreductase and NADPH in both liver and kidney of mice **[63]**. Thus, curcumin was used to hinder lipid peroxidation and inhibit induced oxidative stress **[64]**.

In this investigation, pre-eclamptic rats group (Group VII) which treated with 500mg curcumin/kg.b.wt/day led to substantial corrections in the morphological features and number of fetuses and considerable enhancements in all physiological and biochemical parameters investigated when compared to their subsequent non treated pre-eclamptic rats group (Group V). These data may be attributed to the antioxidants activity of curcumin which combat the negative impacts of oxidative stress either by directly working as antioxidants or by activating/persuading cellular antioxidant enzyme mechanisms through decline ROS production and act as immunomodulator agent. The data obtained in this investigation are in harmony with several research **[9,10,11,65]**.

5. Conclusion:

From the above cited data, it can be concluded that the administration of DOX induced pre-eclampsia in rats with hepatic toxicity led to liver dysfunction with elevation of serum liver markers (haptoglobin and L-FABP) as well as increment of oxidative damage, evidenced by elevation of hepatic TOS levels in accordance with reduction of hepatic TAC levels due to progression in the formation of reactive oxygen species (ROS). Co-administration of taurine and curcumin to the pre-eclamptic rats' group caused the maximum correction effects on all studied embryological, biochemical and molecular parameters due to modulation of free radical scavenger as well as cell membrane stabilizer through reduction of lipid peroxidation production and enhancement of cellular antioxidant enzymes system.

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8. Conflicts of Interest

The authors declare no conflict of interest.

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الملخص العربى

التاثيرات العلاجية المحتملة للتورين والكركمين على كبد الجرذان المصابة بتسمم الحمل الناجم عن عقار الدوكسوروبيسين

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الملخص العربى:

تم اجراء هذه الدراسة للتحقق من تاثير مكملات التورين والكركمين على كبد الجرذان المصابة بتسمم الحمل. تم حقن الجرذان الحوامل بواسطة ١٠ مللى جرام من عقار الدوكسوروبيسين لمدة اسبوعين داخل تجويف البطن من اليوم السابع الى اليوم التاسع عشر من الحمل. وبعد تشريح الجرذان الحوامل فى اليوم العشرين من الحمل و فحصها بحثا عن التغيرات المورفولوجية والتغيرات الكيميائية الحيوية وتحديد نسبة تلف الحمض النووى.وبعد ذلك تم تسجيل مواقع تواجد الاجنة وتحديد اعداد الاجنة المصابة والاجنة الحية والميتة ، و تم قياس مستويات انزيمات الكبد مثل: ناقلات امين الالانين وناقلات الاسبارتات وناقلة الببتيد غاما بالاضافة الى تركيزات الالبيومين والبروتين الكلى. تم ملاحظة اختلال فى مستويات الهبتوجلوبين و مستويات بروتين الكبد المسئوول عن ربط الاحماض الدهنية ومستويات مضادات الاكسدة الكلية و مستويات عوامل الاكسدة الكلية فى مجموعات تسمم الحمل مقارنة بالمجموعات العادية المقابلة لها. كما تم اجراء فحص خارجى للاجنة للتحقق من وجود اى تشوهات. تم اجراء تحليل فحص المذنبات فى كبد جميع الجرذان الحوامل لتحديد نسبة تلف الحمض النووى و اللتى سجلت نسبة عالية فى مجموعة الجرذان المصابة بتسمم الحمل بنسبة ٥٨٪ وعند مقارنتها بالمجموعة العادية المقابلة لها لوحظ التلف بنسبة ٥٪ فقط . كما لوحظ حدوث تحسن فى المعايير التى تم ذكرها سابقا بعد معالجة الجرذان المصابة بتسمم الحمل ب٥٠٠مللى جرام من التورين اوالكركمين عن طريق الفم لمدة اسبوعين.

الاستنتاج: ادى اعطاء التورين والكركمين معا لمجموعة الجرذان المصابة بتسمم الحمل الي افضل النتائج التصحيحية لجميع المعايير التى تم ذكرها سابقا؛ ويرجع ذلك الى تعزيز نشاط الانزيمات المضادة للاكسدة الخلوية وتقليل انتاج الدهون المؤكسدة.

الكلمات الدالة: تسمم الحمل – الدوكسوروبيسين – التورين – الكركمين.