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Evaluation of the Protective Role of Vitamin C and Pomegranate Juice Against the Physiological Effects of Carbamazepine on Certain Biochemical Variables in White Rats

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Abstract:

Carbamazepine (CBZ) is one of the main anti-epileptic drugs (AEDs) used to treat epilepsy, neuralgia, alcohol withdrawal syndrome, schizophrenia, and bipolar disorder. Studies have shown that long-term use of carbamazepine may cause various side effects such as hepatotoxicity, testicular dysfunction, and metabolic disorders. This study was conducted on 60 female rats with an average weight of 200–250 grams and ages ranging from 4–6 weeks. The rats were divided into 12 groups, each consisting of 5 animals. The results showed an increase in antioxidant levels (glutathione GSH and malondialdehyde MAD), as well as elevated levels of liver enzymes (AST and ALT) and immune markers (CRP and HCY) in the group treated with carbamazepine at therapeutic, double, and excessive doses compared to the control group. On the other hand, the group treated with pomegranate juice and vitamin C alongside carbamazepine at various doses showed a significant decrease in antioxidant levels, liver enzymes, and immune markers. The current study aims to understand the effects of carbamazepine on experimental animals, specifically its impact on antioxidant levels (GSH and MAD), liver enzymes (ALT and AST), C-reactive protein (CRP), and homocysteine (HCY). Additionally, the study sought to investigate the role of vitamin C and pomegranate juice in countering the harmful effects of the drug.

Keywords: Carbamazepine, Vitamin C, Pomegranate Juice, Oxidative Stress, Glutathione, Liver Enzymes, C-Reactive Protein, Homocysteine.

تقييم الدور الوقائي لفيتامين C وعصير الرمان المضاد للتأثيرات الفسيولوجية لعقار الكاربامازيبين Carbamazepine في بعض المتغيرات الكيموحيوية في الجرذان البيض

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مستخلص:

كاربامازيبين (CBZ) هو أحد الأدوية الرئيسية المضادة للصرع (AEDs) المستخدمة في علاج الصرع، وآلام الأعصاب، ومتلازمة انسحاب الكحول، والفصام، والاضطراب ثنائي القطب. وقد أظهرت الدراسات أن الاستخدام طويل الأمد للكاربامازيبين قد يسبب آثارًا جانبية مختلفة مثل سمية الكبد، واختلال وظائف الخصيتين، والاضطرابات الأيضية. اجريت هذه الدراسة على 60 جرذا من الاناث بمتوسط وزن 250–200 جراماً واعمار من 6–4 اسابيع والتي تم تقسيمها الى 12 مجموعة كل مجموعة تضمنت 5 حيوانات. واظهرت نتائج زيادة في مستويات مضادات الاكسدة GSH و MAD وكذلك زيادة مستوى انزيمات الكبد AST , ALT والمناعية CRP و HCY في المجموعة المعاملة بعقار الكاربامازيبين بالجرعة العلاجية والمضاعفة والمفرطة مقارنة مع مجموعة السيطرة في المقابل اظهرت المجموعة المعالجة بعصير الرمان وفيتامين C مع عقار الكاربامازيبين وبجرع مختلفة انخفاضاً كبيراً في مستويات مضادات الأكسدة وانزيمات الكبد و المناعية. تهدف الدراسة الحالية إلى فهم آثار عقار الكاربامازيبين على حيوانات التجارب وتأثيرهُ على مستويات مضادات الاكسدة الكلوتاثيون (GSH) والمالوندهايد(MAD) وكذلك تأثيرهُ على إنزيمات الكبد (ALT) و(AST) وبروتين C التفاعلي (CRP) والهوموسستين (HCY) بالإضافة الى ذلك سعت الدراسة الى التحقق في دور فيتامين C وعصير الرمان ضد تأثيرات العقار الضارة

الكلمات المفتاحية : الكاربامازيبين، فيتامين C ، عصير الرمان، الإجهاد التأكسدي، الكلوتاثيون، إنزيمات الكبد، بروتين سي التفاعلي ، الهوموسستين .

Introduction:

Carbamazepine (CBZ) is among the most commonly used drugs for the treatment of epilepsy and is also utilized in managing several other conditions, including nerve pain, schizophrenia, and manic depression (Osuntokun et al., 2020). It is classified as a sedative agent; however, its frequent use without medical supervision poses a significant risk, potentially leading to drug dependence, similar to the misuse of narcotics such as tramadol, which adversely affects brain function and behavior. Other notable antiepileptic drugs (AEDs) include phenytoin, levetiracetam, and valproate (Demirci et al., 2021).

The prolonged use of medications is often associated with toxic side effects, which manifest in various tissues and organs of the body. Several studies have highlighted the adverse impacts of CBZ; for instance, one study demonstrated its teratogenic effects, showing that exposure during pregnancy resulted in halted fetal growth, malformations, and reduced fetal weight (Jose et al., 2017). Concerning its neurotoxic effects, a study by Demirci et al. (2021) reported the presence of edema between nerve cells and neuroglial cells, indicative of central nervous system damage. Moreover, renal toxicity was observed, characterized by hypertrophy of epithelial cells lining the renal tubules and an overall enlargement of the kidneys (Elif et al., 2021).

Additionally, CBZ has been shown to contribute to oxidative stress alongside its therapeutic effects, as its metabolite, arene oxide, is implicated in cellular damage (Eghbal et al., 2013). CBZ and its active metabolite disrupt intracellular antioxidant defense systems, leading to oxidative injury and cellular dysfunction. Furthermore, CBZ has been associated with reproductive toxicity, causing tissue damage that results in reproductive disorders (Akorede et al., 2020).

In recent years, research efforts have focused on developing novel therapeutic approaches with antioxidant properties to mitigate oxidative stress and neuronal damage in epilepsy. Pomegranate (Punica granatum) has emerged as a promising candidate due to its high content of secondary me-

tabolites, such as polyphenols, which possess potent antioxidant activities. These compounds may enhance epilepsy management by reducing oxidative damage, restoring mitochondrial function, and protecting the brain from hyperexcitability and neurodegeneration associated with epilepsy (Sarmast et al., 2020).

Vitamin C (ascorbic acid) is recognized as a potent antioxidant, anti-inflammatory agent, and immunomodulator. It functions as a cofactor for essential monooxygenase and dioxygenase enzymes, thereby exerting diverse physiological effects (Carita et al., 2020). Various studies have confirmed the hepatoprotective properties of Vitamin C, attributing its effects to its robust antioxidant capacity. Both in vitro and in vivo studies have demonstrated that Vitamin C normalizes levels of key biomarkers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and malondialdehyde (MDA), following liver injury (He et al., 2018).

Materials and Methods:

Experimental Animals

A total of 60 healthy female albino rats, aged between 4 to 6 weeks and weighing between 200–250 grams, were used in this experiment. The animals were obtained from the Animal House, College of Veterinary Medicine, University of Tikrit. The animals were housed and maintained under standard laboratory conditions (proper ventilation and controlled temperature) for a period of 2 months. All animals were confirmed to be free from any clinical diseases, fed standard pellet diets, and provided water ad libitum.

Experimental Design

The animals were randomly divided into 12 groups, with 5 rats in each group, as shown in the table below:

No.	Group	Treatment
1	Control Group	Distilled water only
2	Pomegranate Juice Group	1 ml
3	Vitamin C Group	1 ml
4	Therapeutic Dose of Carbamazepine	1 ml
5	Double Dose of Carbamazepine	2 ml
6	Overdose of Carbamazepine	4 ml
7	Therapeutic Dose of Carbamazepine + Pomegranate Juice	1 ml + 1 ml
8	Double Dose of Carbamazepine + Pomegranate Juice	2 ml + 1 ml
9	Overdose of Carbamazepine + Pomegranate Juice	4 ml + 1 ml
10	Therapeutic Dose of Carbamazepine + Vitamin C	1 ml + 1 ml
11	Double Dose of Carbamazepine + Vitamin C	2 ml + 1 ml
12	Overdose of Carbamazepine + Vitamin C	4 ml + 1 ml

Determination of Treatment Doses

The effective doses used in this study were calculated based on the method described by Nair and Jacob (2016), adjusting the human equivalent oral dose (200 mg) for rats. One carbamazepine tablet was dissolved in 67 ml of distilled water, with the following doses administered:

• 1 ml per rat for the therapeutic dose.

• 2 ml for the double dose.

• 4 ml for the overdose.

Pomegranate juice was prepared by cleaning the pomegranate fruits, separating the seeds from the peels, and blending them using a manual mixer. The fresh juice was immediately administered orally. The effective dose (1 ml per rat) was determined based on the findings of Al-Hadidi et al. (2014).

Vitamin C was prepared according to Hussein (2009) at a concentration of 250 mg/kg body weight. It was dissolved in 5 ml of distilled water, and 1 ml was administered per rat. Vitamin C was supplied by Arwa Medical Supplies (ACS Chemicals, India).

Blood Sample Collection

At the end of the 60-day experimental period, rats were fasted for 24 hours, weighed, and anesthetized using chloroform. Blood samples were collected via cardiac puncture using a 5 ml syringe, drawing approximately 4–5 ml of blood per animal.

Biochemical Assays

• Glutathione (GSH) levels in serum were determined using Ellman's reagent method (Ellman, 1959).

• Malondialdehyde (MDA) levels were measured using a modified thiobarbituric acid reactive substances (TBARS) assay as described by Guidet and Shah (1989).

• The activities of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by the colorimetric method using Biolabo (France) commercial diagnostic kits, following Tietz (1999).

• Serum levels of C-reactive protein (CRP) and homocysteine (HCY) were assessed using the sandwich ELISA technique.

Statistical Analysis

The data obtained from biochemical analyses were subjected to analysis of variance (ANOVA) using SPSS software version 10.0 (SPSS Inc., Chicago, USA). Mean comparisons between groups were performed using Duncan's multiple range test, with statistical significance considered at $P < 0.05$.

Results:

The results presented in Table 2 show a significant increase ($P \leq 0.05$) in antioxidant markers (GSH and MDA), liver enzymes (AST and ALT), and immune markers (CRP and HCY) in the groups treated with carbamazepine at therapeutic, double, and overdose levels compared to the control group. However, the groups co-treated with pomegranate juice or vitamin C alongside carbamazepine (at various doses) demonstrated a significant reduction in the levels of antioxidants, liver enzymes (ALT and AST), and immune markers (CRP and HCY).

The study findings indicate that the co-administration of pomegranate juice and vitamin C effectively alleviated the carbamazepine-induced increases in oxidative stress, liver damage, and immune response markers. This protective effect is attributed to the antioxidant properties of pomegranate juice and vitamin C.

Table 2: Effect of Pomegranate Juice, Vitamin C, Carbamazepine (at therapeutic, double, and overdose levels), and their combinations on the studied serum parameters in female albino rats.

Treatment Group	GSH (µmol/L)	MDA (nmol/L)	ALT (U/L)	AST (U/L)	CRP (mg/L)	HCY (µmol/L)
Control	22.650 ± 0.992 bc	3212 ± 44537 b	42.91 ± 8.20 d	32.95 ± 5.16 d	4.84 ± 0.812 d	17.62 ± 4.620 cd
Pomegranate Juice	23.555 ± 0.745 ab	47895 ± 4213 a	64.11 ± 7.76 b	80.92 ± 5.41 a	5.85 ± 2.19 d	15.44 ± 1.849 de
Vitamin C	23.088 ± 0.717 ab	38460 ± 31154 c	53.49 ± 1.923 c	81.24 ± 10.70 a	10.41 ± 2.860 ab	16.43 ± 2.510 d
CBZ Therapeutic Dose	23.035 ± 0.773 ab	30680 ± 4888 f	81.70 ± 7.72 a	69.79 ± 6.650 b	8.48 ± 2.170 c	13.85 ± 3.140 e
CBZ Double Dose	23.079 ± 0.699 ab	39656 ± 579 c	80.30 ± 2.78 a	45.90 ± 10.30 c	9.47 ± 3.400 bc	16.32 ± 2.290 d
CBZ Overdose	22.760 ± 0.244 bc	32912 ± 412 ef	77.29 ± 8.05 a	52.65 ± 10.59 c	9.33 ± 2.880 bc	15.47 ± 3.200 de
CBZ Therapeutic + Pomegranate Juice	19.180 ± 1.055 ef	32760 ± 2341 ef	60.57 ± 5.78 b	51.15 ± 4.72 c	10.06 ± 1.307 abc	19.14 ± 1.222 bc
CBZ Double Dose + Pomegranate Juice	18.868 ± 0.785 f	35364 ± 1022 d	77.03 ± 5.68 a	51.11 ± 6.05 c	8.32 ± 2.230 c	21.58 ± 1.445 ab
CBZ Overdose + Pomegranate Juice	18.555 ± 0.633 f	34398 ± 959 de	55.66 ± 8.17 c	62.69 ± 8.12 b	12.17 ± 3.510 a	15.26 ± 3.950 de
CBZ Therapeutic + Vitamin C	20.020 ± 3.390 de	29877 ± 1028 f	76.20 ± 7.64 a	80.43 ± 4.75 a	9.48 ± 0.695 bc	17.28 ± 1.950 cd
CBZ Double Dose + Vitamin C	21.359 ± 2.043 cd	32367 ± 834 ef	64.52 ± 6.49 b	67.25 ± 12.95 b	12.34 ± 1.820 a	23.13 ± 4.000 a
CBZ Overdose + Vitamin C	24.363 ± 0.215 a	32454 ± 835 ef	43.33 ± 8.15 d	69.59 ± 6.79 b	11.44 ± 1.028 ab	20.26 ± 1.022 b

- Values are expressed as mean ± standard deviation (SD).
- Different superscript letters (a, b, c, etc.) indicate significant differences at $P < 0.05$.
- Number of rats per group: 5.

Discussion:

The results of this study are consistent with previous research by Osuntokun et al. (2021) and Sabr (2023), which showed that the administration of carbamazepine leads to a significant increase in antioxidant markers (GSH and MDA). This increase may be attributed to elevated levels of lipid peroxide in the plasma as a result of secondary metabolic processes triggered by carbamazepine. Carbamazepine stimulates the production of large amounts of free radicals. In the absence of an effective defense mechanism, free radicals oxidize unsaturated fatty acids, leading to the formation of peroxyl radicals. These radicals can extract a hydrogen ion (H^+) from another fatty acid, perpetuating the chain reaction and thus raising lipid peroxide levels (Santharani, 2012; Aliu et al., 2017).

The notable efficacy of pomegranate juice in reducing oxidative stress markers in plasma could be due to its phenolic compounds that inhibit oxidation. Pomegranate juice contains anthocyanins, which enhance the antioxidant capacity (increasing GSH and reducing MDA), thereby preserving hepatic cell function and preventing leakage of these enzymes into the bloodstream (Surai et al., 2019).

The study also showed a decrease in GSH levels in the groups treated with carbamazepine (therapeutic and double doses) combined with Vitamin C, compared to the groups treated with carbamazepine alone. As illustrated in Figure 2, Vitamin C plays a crucial role in scavenging free radicals by inhibiting lipid peroxidation and providing a protective role against oxidative stress by suppressing oxidation activities (Masheswari et al., 2015).

Carbamazepine treatment also induced biochemical changes at the hepatic level, as evidenced by the significant elevations of liver enzymes AST and ALT compared to the control group. These findings align with Akorede et al. (2023), suggesting that carbamazepine-induced hepatotoxicity may result from the production of reactive oxygen species (ROS), which attack DNA and generate hydrogen peroxides and highly reactive hydroxyl radicals (OH^-), causing cellular damage due to

decreased antioxidant defenses.

The severity of hepatotoxicity due to carbamazepine varies depending on the dose and duration of administration. Elevated AST and ALT levels could be attributed to hepatocellular injury caused by the accumulation of toxic metabolites within hepatic cells, leading to direct or indirect cellular damage (Chrismawan et al., 2020). The rise in serum AST levels could reflect damage to liver tissue, as also observed in the current study. It has been reported that daily consumption of pomegranate juice can reduce liver enzyme levels, lower lipid peroxide levels, and increase antioxidant enzyme activity in the liver (such as GSH), thereby protecting against liver damage, improving mitochondrial function, and mitigating oxidative stress (Hossein et al., 2024).

Regarding the groups treated with carbamazepine and Vitamin C, Vitamin C appeared to alleviate the changes in AST activity caused by carbamazepine, particularly in the overdose group. This protective effect is likely due to Vitamin C's ability to guard against hepatic, muscular, and intestinal tissue injuries induced by carbamazepine (Akorede et al., 2023). Similarly, Hadzagic et al. (2017) demonstrated that co-administration of Vitamin C with carbamazepine prevented the rise in liver enzymes, supporting its hepatoprotective effect attributed to its antioxidant properties.

The current study also showed a significant increase in C-reactive protein (CRP) levels in the serum of rats treated with carbamazepine at therapeutic, double, and overdose doses, consistent with findings by Dkv (2018). This increase may be due to the drug's impact on the liver and immune system, potentially triggering a transient inflammatory response or affecting liver CYP450 enzymes, leading to mild inflammation.

C-reactive protein (CRP) is a well-established inflammatory marker used to assess inflammation levels in the body. A significant elevation in CRP during carbamazepine use could suggest inflammation or an immune reaction, such as the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), which can be serious. The rise in CRP may also reflect

hepatitis or other side effects like vasculitis (Ishikawa et al., 2025), which attributed the increase in CRP to the contribution of inflammatory pathways in epileptogenic tissue, leading to neurodegeneration and refractory epilepsy.

Furthermore, the results demonstrated that pomegranate juice and Vitamin C helped reduce CRP and HCY levels, likely due to their content of bioactive compounds with immunomodulatory and anti-inflammatory properties (Petel et al., 2022).

Conclusions:

This study showed that carbamazepine treatment at various doses caused significant oxidative stress, liver damage, and inflammation in rats. Co-administration of pomegranate juice or Vitamin C effectively reduced these harmful effects by lowering oxidative markers, liver enzymes, and inflammatory proteins. These results highlight the protective role of natural antioxidants in reducing carbamazepine-induced toxicity. Further research is recommended to confirm these findings and explore their clinical applications.

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