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Biochemical Assessment of the Hepatoprotective Role of β-Amino Butyric Acid in Carbon Tetrachloride–Induced Liver Injury in Male Sprague-Dawley Rats

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ABSTRACT

Liver damage is a serious disease that has a close relationship with toxic compounds such as carbon tetrachloride (CCl_4). This study was conducted to determine the possible protective and therapeutic effect of beta amino butyric acid (BABA), a non-protein amino acid, on this damage in male rats. Thirty adult mice were randomly divided into six groups (the experiment lasted 30 days). The negative control group received only saline, the positive control group received CCl_4 (0.08 of body weight) , and the remaining four groups (A, B, C, and D) received CCl_4 for liver damage and were subsequently treated with increased doses (50, 100, 150, and 200 mg/kg) of BABA (both substances were injected into the peritoneum). After laboratory tests of biochemical indicators, including measurement of plasminogen-1 activator inhibitor (PAI-1) and Protein phosphatase (PP) in serum using (ELISA), the results showed a significant reduction ($P \leq 0.01$) in these biochemical markers (PAI-1 and PP) in the group injected with CCl_4 only, indicating liver dysfunction, compared to the negative control. In contrast, the groups injected with low doses of BABA (50 and 100 mg/kg) showed significant improvement in these markers, suggesting that these doses can reduce this damage and restore liver function, while larger doses (150 and 200 mg/kg) showed partial improvement. These findings open a wider scope for research into the use of BABA as a potential treatment for liver damage, suggesting it could be a promising treatment to reduce liver disease caused by toxic compounds by reducing inflammation, regulating blood clotting.

Keywords: Liver damage, CCl_4, Liver functions, BABA, PAI-1, PP

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Introduction:

The liver is the main organ that plays an important role in many functions that enable the body to maintain physiological balance, as it works to filter and purify the blood from toxins, drugs, alcohol and harmful chemical compounds and convert them into harmless compounds by excreting them through waste products [1,2]. Many toxic substances can cause liver damage, including carbon tetrachloride (CCl_4) [3]. It is a toxic chemical compound, colorless and non-flammable liquid with a characteristic chloroform-like odor [4]. It is widely used in research to induce hepatotoxicity [5]. Toxicity occurs in the liver when cytochrome P450 (especially CYP2E1) converts CCl_4 into free radicals CCl_3•, which binds to lipids, proteins and nucleic acids, disrupting lipid metabolism and causing hepatic steatosis, when it interacts with oxygen, the most reactive free radicals CCl_3OO• are formed, which leads to lipid oxidation and damage to cell membranes. Thus, it leads to increased levels of liver enzymes ALT, AST and ALP, collagen deposition, and hepatic structure deformation., elevated bilirubin and bile acid levels, indicating impaired bile drainage [6]. CCl_4 also disrupts the liver's ability to detox, increasing the risk of liver damage and metabolic disorders [7].Therefore, there is a need to look for more effective therapeutic substances and fewer side effects, especially those that are bioactive, for example, beta-aminobutyric acid (BABA) is a non-protein amino acid, classified as a free compound that is rare in nature but found in plants. One study showed that it can stimulate systemic resistance acquired in a wide range of plants[8], Another study also showed its protective role in activating the body's immunity and strengthening its defenses against infection[9]. On the other hand, one study conducted on male mice infected with Staphylococcus aureus proved that the treatment of animals with the amino acid (BABA) led to a significant increase in the percentage of lymphocytes in the blood, which indicates the activation of the body's immunity against infection [10]. In addition, a recent study in male mice revealed a clear association between high levels of ALT enzymes and AST in high-dose CCl_4 exposures as these elevated enzymes are a vital marker of liver damage, while BABA treatment reduced these levels, reflecting its role in protecting liver function,[11]. In this study, some biochemical markers that show the effect of physiological changes in the model of liver damage and treatment with beta-amino acids were measured, including, plasminogen-1 activator inhibitor (PAI-1): is the main physiological inhibitor of plasminogen activators (PAs), is an important

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inhibitor of the plasminogen/plasmin system [12]. Being a fast-acting inhibitor of histological plasminogen activators (tPA), it fundamentally impairs fibrinolysis by inhibiting urokinase-type plasminogen activator (uPA) and its interaction with biological bonds such as fibronectin and cell surface receptors, PAI-1's function extends to pericellular protein lysis, tissue remodeling, and other processes [13]. PAI-1 regulates liver fat metabolism. RNA sequencing revealed that PAI-1 directly regulates gene expression of several genes involved in mammalian lipid balance, including fibroblast growth factor (FGF21) and Proprotein Convertase Subtilisin/ kexin type 9 (PCSK9) [14]. An enzyme has also been measured Protein phosphatase (PP): It is an enzyme responsible for removing phosphate groups from phosphorylated amino acid residues such as serine (Ser), threonine (Thr) or tyrosine (Tyr)[15]. This process complements the action of protein kinases that add phosphate and provide an essential regulatory mechanism to activate or disrupt the functions of proteins, thus controlling a wide range of different processes such as cellular signal transduction, cell division, oxidative stress response and regulation of inflammatory pathways[16,17].This balance between phosphorylation and dephosphorylation maintains hepatic astrocyte regeneration, and that any imbalance in the functioning of PP leads to a disruption in the functioning of hepatic astrocytes, which enhances the inflammatory response and directs the liver towards fibrosis[18]. This study aims to evaluate the therapeutic role of beta-aminobutyric acid (BABA) in reducing carbon tetrachloride liver damage (CCl_4) in male rats. This was achieved by measuring several of biochemical indicators, including PAI-1 and PP to illustrate the potential effects of BABA in restoring liver function and reducing damage caused by CCl_4.

Materials and Methods

Animals

Thirty pure white Sprague Dawley rats were obtained from the National Centre for Drug Control, aged 6-8 weeks, weighing between 150-180 grams, were used. They were placed in plastic cages covered with a metal clip cover for ventilation with dimensions (45 cm long, 27 cm wide and 18 cm high). The experiment was carried out in the house of the Faculty of Veterinary Medicine - University of Fallujah, and after creating the appropriate environmental conditions for the animal of moderate temperature, good ventilation and a suitable light period they were fed with feed Specific proportions (130 grams per cage per day) and 12 days of adaptation to the

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surrounding environment prior to the start of the experiment. After a period of acclimatization, the mice were given three doses of CCl_4 from Sigma-Aldrich (Germany) by injection into the peritoneal cavity (CCl_4 solution was prepared by dissolving 50 mL of pure olive oil with 4 ml of CCl_4 to become the desired concentration of 0.08 body weight, and it was administered every three days), Five therapeutic doses of BABA were then administered by Sigma Aldrich (Germany) (BABA solution was prepared by dissolving the required weight according to body weight in 10 mL of distilled water and it was administered every three days).The doses were given according to the specific concentration and volume as follows.

Control (-): This collection was injected with a volume of 2 mL of ordinary saline solution

Control (+): This collection was injected with 2 mL CCl_4 at a concentration of 0.08 body weight

Group A :This collection was injected with 2 mL of CCl_4 at a concentration of 0.08 body weight, followed by 2 mL of BABA at a dose of 50 mg / kg body weight.

Group B: This collection was injected with 2 mL of CCl_4 at a concentration of 0.08 body weight, followed by 2 mL of BABA at a dose of 100 mg / kg body weight.

Group C: This collection was injected with 2 mL of CCl_4 at a concentration of 0.08 body weight, followed by 2 mL of BABA at a dose of 150 mg / kg body weight.

Group D: This collection was injected with 2 mL of CCl_4 at a concentration of 0.08 body weight, followed by 2 mL of BABA at a dose of 200 mg / kg body weight.

Ethical Approval:

The experimental protocol and animal use procedures (Protocol No. 260, dated 26/12/2024) were approved by the Institutional Ethics Committee, and all procedures were conducted in strict compliance with the ethical standards of the University of Anbar.

Blood Sample Collection:

At the end of the 30-day trial period, mice were anesthetized using a chloroform solution (0.5 mL) from Thomas Baker (Ambionath, India). Blood samples were collected by direct heart piercing using sterile syringes and transferred to gel tubes for subsequent biochemical analysis. Prior to the ELISA test, the serum was separated from the blood samples, by placing the samples in clean, anticoagulant-free tubes, and then leaving the samples at room temperature for 20-30 minutes for it to coagulate Blood. The centrifuge was then performed at 3000 rpm for 10

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minutes, after which the pure serum was carefully separated and placed in clean microtubules, then kept at -20 degrees° for the time of the test.

ELISA Test:

The enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum concentrations of PAI-1 and PP using commercial ELISA kits provided by Shanghai Coon Koon Biotech Co., Ltd (China). The examination was performed as follows:

1. All reagents were prepared before inspection, and the standards and samples were added in duplicates to the micro-ELSA tape plate.

2.The wells were allocated for the standards and samples, with 50 µL of the standard added to the respective wells.

3. 10 µL of the test specimen was added to the specimen well, followed by 40 µL of dilution solution. Nothing was added to the empty well.

4. 100 µL of HRP conjugated detector was added to all wells, and the plate was closed and incubated at 37°C for 60 minutes.

5. The washing solution was prepared by diluting the concentrated solution 1:20 with distilled or deionized water.

6. After incubation, the cap was carefully removed, the liquid was drained, each well was washed with the washing solution for five times, and for the automatic device 350 microliters were used for each well.

7. 50 µL of chromogen A was added to each well, followed by 50 µL of chromogen B. The dish was gently shaken and incubated for 15 minutes at 37°C in the dark.

8. 50 µL of stop solution was added to each well to finish the reaction, turning the color from blue to yellow, and the plate was gently stirred to uniformize the color when needed

9. The empty well was used as zero, and the optical density (OD) of each well was measured at 450 nm within 15 minutes of adding the stop solution.

Statistical Analysis:

The Statistical Packages of Social Sciences(SPSS, version 26, IBM Corp Armonk, NY, USA) [19], was used to detect the effect of difference groups in study parameters. LSD-Least significant difference was used to significant compare between means at a significance level of $P \leq 0.01$.

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Results:

The results of the statistical analysis as shown in Figure (1) showed that there were significant differences (P≤0.01), where the mean positive control treatment was 22.47 pg/mL ±0.08 c)) compared to the negative control treatment (±0.39 a, 51.92 pg/mL) under the probability level of 0.0018 at the significance level of 12.172**±.(35.62 pg/mL ±5.56 b) and (D) (29.59 pg/mL ±3.61 BC) and mean positive control treatment 22.47 pg/mL ±0.08 c)) compared to the negative control treatment (±0.39 a 51.92 pg/mL) under a probability level of 0.0018 at a significance level of 12.172**. No significant differences were shown between the mean treatment (C) of 23.20 pg/mL±0.67 c)) and the mean positive control treatment 22.47pg/mL ±0.08 c)) below the probability level of 0.0018 at a significance level of 12.172**.

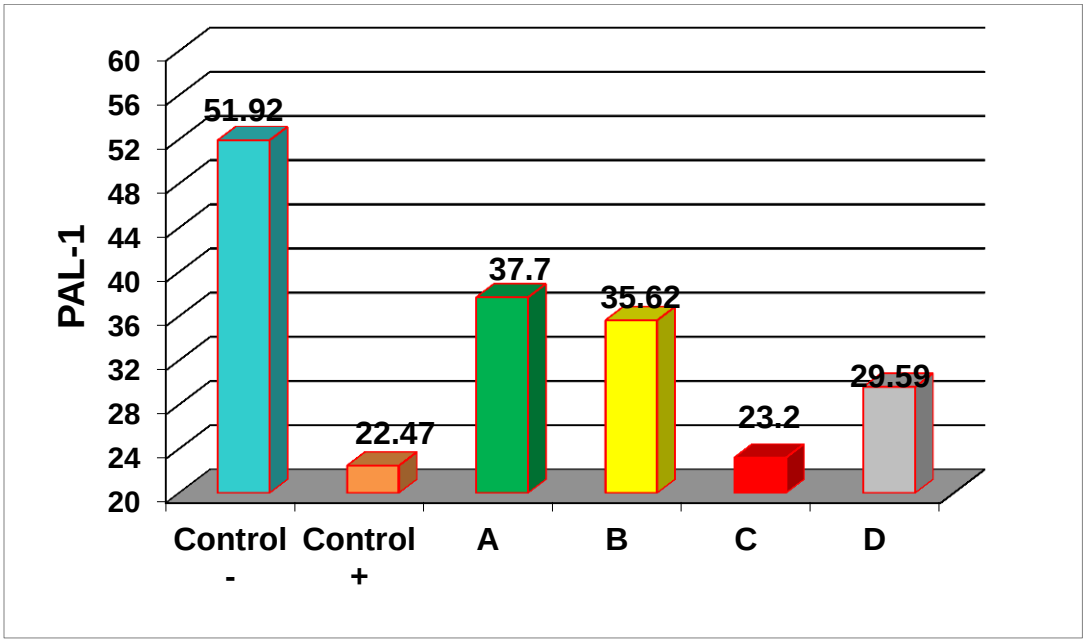

Figure 1: PAI-1 level in the BABA and CCl_4 treated groups

The results of the statistical analysis as shown in Figure (2) also confirmed the existence of significant differences (P≤0.01), where the average positive control treatment was 1.353 pg/mL ±0.16)) compared to the negative control treatment (2.213 pg/mL ±0.05) under the probability level of 0.0283 at a significance level of 0.596*. Significant differences were also observed between the mean coefficients A (1.723 pg/mL±0.21) and treatment B (1.766 pg/mL ±0.28)), treatment C (1.600 pg/mL ±0.26) and the mean positive control treatment of 1.353

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pg/mL ±0.16)) compared to the negative control treatment (2.213 pg/mL ±0.05) below the probability level of 0.0283 at a significance level of 0.596. There were no significant differences between the mean treatment D (1.123 pg/mL ±0.04) and the mean positive control treatment (1.353 pg/mL±0.16)) compared to the negative control treatment (2.213 pg/mL ±0.05) under a probability level of 0.0283 at a significance level of 0.596*.

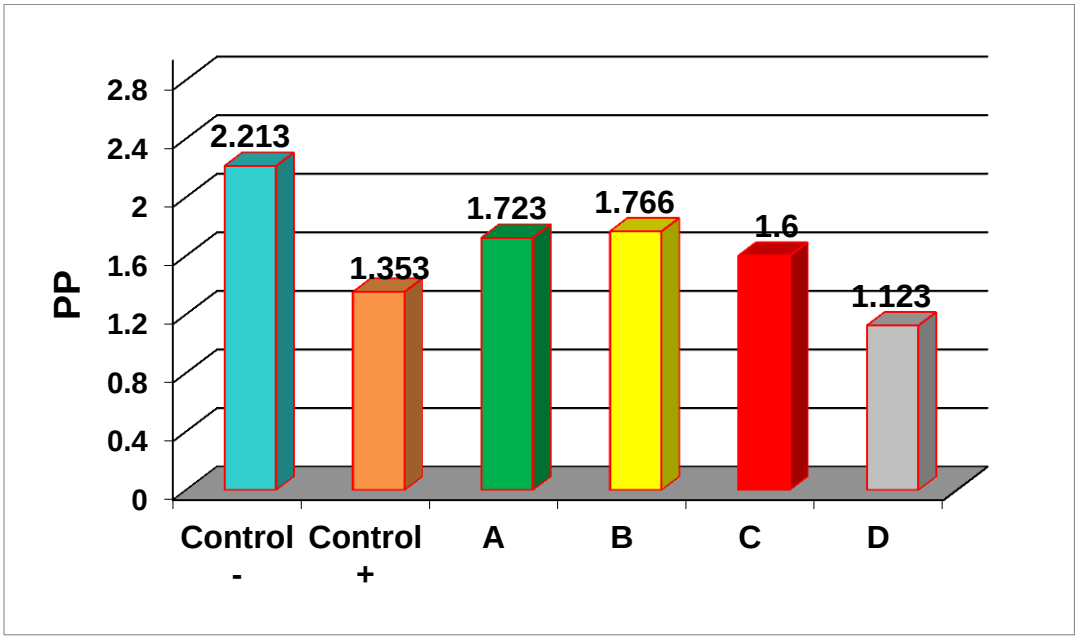

Figure 2: PP level in the BABA and CCl_4 treated groups

Discussion:

The results of the current study as shown in Figure (1) showed that carbon tetrachloride (CCl_4) causes liver damage through a mechanism based on metabolic activation by CYP450 enzymes and this is consistent with this study [20]. The level of PAI-1 was significantly lower in the positive control group, a biomarker of liver damage, compared to the negative control group whose level reflected the normal physiological state of the liver, although its elevated levels were associated with chronic cirrhosis [21,22]. However, there are cases in which excessive degradation of fibrin occurs so that tPA rises in the blood due to inflammation and this rise is associated with PAI-1 and with it forms the t-PAIC compound, which leads to the consumption of PAI-1 and its low level in serum as in the case of sepsis, a serious pathological condition that occurs as a result

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of the body's exposure to bacteria, fungal or viral infections that damage organs, including the liver [23]. It is therefore possible that a low level of PAI-1 has something to do with the acute toxicity caused by CCl_4, which causes damage to liver cells and a decreased ability to synthesize proteins, including PAI-1. When dealing with BABA, for groups A, B, C, and D), 50 mg/kg and 100 mg/kg, respectively, the best concentrations were in restoring the enzyme to its normal level, demonstrating the effectiveness of these concentrations in reducing the toxic effect of CCl_4, while the concentration of 150 mg/kg did not show a significant improvement, on the contrary, it showed a decrease in the level of PAI-1, and the concentration of 200 mg/ kg showed only partial improvement, suggesting a reduction in therapeutic efficacy at high concentrations of BABA .For the PP protein, its level was normal in the negative control group, in contrast, its level decreased in the positive control group as shown in Figure (2), indicating hepatitis [24], and according to a study that showed that low levels of PPP6C in the liver accelerate MASH disease [25]. One study also indicated that low PP2A-Ca is a direct cause of hepatic fat associated with parenteral nutrition [26].Oxidative stress-causing free radicals also inactivate both the phosphatase and tansin homologous deleted on chromosome 10 (PTEN) and the T cell tyrosine phosphatase protein (TCPTP) [27]. when treated with BABA, for groups (A, B, C, D) The 100 mg/kg concentration and the 50 mg/kg concentration, respectively, showed a significant improvement in the level of PP, suggesting that these concentrations contributed to the restoration of part of cellular homeostasis, in contrast to the concentration of 150 mg/kg showed less effectiveness in restoring the normal level of PP, while the higher concentration (200 mg/kg) showed the lowest level of PP, suggesting that higher concentrations of BABA had a negative effect on the PP level, it should also be taken into account that the best concentration of processing varies depending on the type of biochemical index. The results of this study proved that the amino acid (BABA) showed therapeutic efficacy against liver damage and oxidative stress, and this is consistent with one of the recent studies conducted on a model of *Sprague dawley* mice that caused liver damage using CCl_4, then treated with BABA, and the levels of some biomarkers were measured, including MicroRNA-34a (miR-34a). MicroRNA-210 (miR-210), MicroRNA-146a(miR-146a), Cluster of Differentiation4 (CD4) and Cluster of Differentiation 8 (CD8) were elevated when liver was damaged, and when BABA was given in

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different concentrations, it showed a decrease in the levels of these biomarkers, indicating that BABA has a protective effect against liver damage [28].

Conclusion

The results of this study showed beta-aminobutyric acid (BABA) as a remarkably effective treatment against liver damage caused by exposure to carbon tetrachloride (CCl_4). The use of BABA helped regulate levels of biochemical indicators of inflammation and oxidative stress in the liver. Concentrations lower than 50 mg/kg and 100 mg/kg showed a better observed response in liver improvement, while higher concentrations of 150 mg/kg and 200 mg/kg showed partial or no improvement. Therefore, it can be concluded that beta-aminobutyric acid (BABA) represents a promising treatment for liver diseases in the future.

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