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## EXAMINING *CARICA PAPAYA* LEAF EXTRACT'S POTENTIAL FOR TREATING RATS' HEPATOTOXICITY AND NEPHROTOXICITY CAUSED BY PARACETAMOL.

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### ABSTRACT

*Carica papaya* is an important economic plant that has many nutritional advantages and, remarkable medicinal purposes including treatment of a wide range of illnesses. Thus, the purpose of this study was to determine how well *carica papaya* leaf extract mitigates the effects of paracetamol on blood biochemical markers and oxidative damage of rats. Six groups each group consists of six male albino rats, weighing  $150 \pm 15$  g, were created. Group one consisted of a healthy group; Group two consisted of rats given an ethanol papaya extract (100 mg/kg body weight); Group three consisted of rats given an ethanol papaya extract (200 mg/kg body weight). Rats in group four were given paracetamol (2g/kg b.wt). Rats in group five received a pretreatment of *carica papaya* extract (100 mg/kg body weight) and a 30-minute paracetamol treatment. Rats in group six received 200 mg/kg body weight of *carica papaya* extract as a pretreatment before receiving paracetamol. The experiment continued for two months. The group receiving paracetamol showed a significant increase in blood markers, including urea, creatinine, AST, ALT, and ALP. As a result of these findings, preventing oxidative stress caused by paracetamol was achieved through pretreatment with *carica papaya* extract which improved antioxidant enzymes (CAT and SOD). According to these results, paracetamol-induced liver and kidney damage can be prevented by the hepato-protective and nephroprotective actions of *Carica papaya* leaf extract. lowering oxidative stress, boosting antioxidant defenses, encouraging liver cell regeneration, and regaining normal liver and kidney function, helps in mitigating liver and kidney damage.

**Keywords:** *carica papaya*, paracetamol, SOD, CAT, oxidative stress.

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## INTRODUCTION:

Papaya, scientifically referred to as *Carica papaya*, is an indigenous tropical fruit tree species from Central and South America (Da Silva *et al.*, 2007). The potential therapeutic properties of *Carica papaya* leaves have been widely acknowledged and they have been employed in traditional medicine to treat a multitude of afflictions. The medicinal properties of the leaves are attributed to a variety of bioactive compounds, such as flavonoids, phenolic compounds, and alkaloids (Sharma *et al.*, 2022). The leaves of *Carica papaya* have garnered significant interest in scientific investigations owing to their possible therapeutic attributes. Enzymes such as papain and bioactive compounds including flavonoids, alkaloids, and phenolic compounds are abundant in them. The leaves of *Carica papaya* contain these compounds, which are responsible for their antioxidant, anti-inflammatory, immunomodulatory, and hepatoprotective properties (Heena and Sunil, 2019). *Carica papaya* leaf extract has been ascribed its hepatoprotective properties to its capacity to eliminate free radicals, impede lipid peroxidation, strengthen antioxidant defense mechanisms, and modulate inflammatory pathways. Additionally, the presence of papain, an enzyme with proteolytic activity, is believed to aid in liver cell regeneration and tissue repair (Kong *et al.*, 2021). The putative hepatoprotective effects of *Carica papaya* leaf extract in animal models, including rats, have been the subject of numerous studies (Shaban *et al.*, 2021). The hepatoprotective properties of *Carica papaya* leaf extract

are ascribed to its anti-inflammatory, regenerative, and antioxidant attributes (Sharma *et al.*, 2022). These attributes aid in mitigating oxidative stress, minimizing inflammation, and facilitating the regeneration of liver cells. Over-the-counter Paracetamol, often known as acetaminophen, is a widely used medication for pain relief and fever reduction (Ayoub, 2021). It is generally considered safe when used within the recommended dosage. However, excessive or prolonged use of paracetamol can lead to hepatotoxicity, primarily due to the production of toxic metabolites through the cytochrome P450 pathway (Offor *et al.*, 2022). However, it can cause hepatotoxicity, which is characterized by liver damage and dysfunction at high doses or with prolonged use (Rotundo and Pysopoulos, 2020). Rats are commonly used as animal models to study paracetamol-induced hepatotoxicity due to their physiological and genetic similarities to humans (Xu *et al.*, 2021). These studies have demonstrated promising results, suggesting that *Carica papaya* leaf extract possesses hepatoprotective properties that may help mitigate paracetamol-induced liver damage.

## MATERIALS AND METHODS:

### Source of *Carica papaya* leaves

*Carica Papaya* leaves were obtained from a farm. The faculty of agriculture at Minia University Abdou, M.A.H. Professor of Ornamental Plants, Horticulture Department, Faculty of Agriculture, Minia University, Egypt who identified the plant. For extraction, the leaves were washed, dried naturally,

and subsequently powdered into a fine powder.

#### Chemicals:

Assay tablets of paracetamol were purchased from a local pharmacy in Minia city. From Bio Diagnostic Chemical Company, kits were obtained to measure serum protein, albumin, AST, ALT, urea, creatinine, uric acid, glutathione reduced, catalase, and SOD. All other solvents and chemicals utilized were of the highest quality available in the market.

#### Preparation of plant extract :

Molecular target compounds were isolated from papaya leaves utilizing a combination of polar and non-polar solvents, including ethyl acetate, acetone, and ethanol. The ethanol, acetone, and ethyl acetate extracts of *Carica papaya* leaves were prepared with minor modifications to the method described by Abdullah *et al.* (2014).

#### Estimation of total phenolic and flavonoid contents:

The determination of total flavonoid content (TFC) and total phenolic content (TPC) was conducted utilizing colorimetric and Folin-Ciocalteu photometric assays, respectively (Yoo *et al.*, 2008).

#### Treatment was started then continued for two month as follow.

| Groups    | Treatment   |
|-----------|---|
| Group (1) | Control   |
| Group( 2) | C.P (100 mg/kg b.w) the extract was suspended in 2ml of 2% w/v carboxy methyl cellulose (walia <i>et al.</i> , 2011).for 60 days  |
| Group( 3) | C.P (200 mg/kg b.w) the extract was suspended in 2ml of 2% w/v carboxy methyl cellulose (walia <i>et al.</i> , 2011).for 60 days. |
| Group (4) | Paracetamol (2g/kg b.w daily) given orally by stomach according to Senthilkumar <i>et al.</i> , (2014).                           |
| Group (5) | C.P (100 mg/kg b.w) in the same of group 2+ Paracetamol (2g/kg b.w daily).  |
| Group (6) | C.P (200 mg/kg b.w) in the same of group 3+ Paracetamol (2g/kg b.w daily).  |

#### Experimental animals and Design:

The Sprague-Dawley strain albino rats, consisting of 36 males and weighing approximately  $150 \pm 15$  g each, were obtained from Nahda University and housed in the Biological Laboratory of the Department of Biological Chemistry at Minia University's Faculty of Agriculture. Every experiment was conducted in adherence to the protocols established by the Agriculture Chemistry department of the Faculty of Agriculture in Minia, Egypt, in accordance with the guidelines for animal research provided by the Ethics Committee Approval No. (MU/FA 022/ 12/22). The research was carried out in adherence to the regulations set forth by the institution and local legislation. Rats were housed in plastic cages within a chamber with  $25 \pm 2$  air conditioning (alternating light and dark periods every 12 hours). A two-week supply of commercially balanced meals and unrestricted potable water were provided prior to the commencement of the trial. Weight was recorded for each rodent at the beginning of the experiment and then weekly until its conclusion. In order to evaluate the effects of *carica papaya* leaf extract on normal rats, six groups of six rodents each were established after the acclimation phase.

Rats were given an overnight fast and then anesthesia to obtain blood samples from the retro-orbital plexus at the conclusion of the 60-day period (Schermer 1967). After allowing the blood to coagulate at room temperature, it was centrifuged for 15 minutes at 40 °C at 3000 rpm. For use in various biochemical parameters, including serum protein (Gornall *et al.*, 1949), albumin (Dumas *et al.*, 1971), urea (Fawcett and Soctt, 1960), creatinine (Murray, 1984), uric acid (Barham and Tinder, 1972), glutathione reduced (Beutler *et al.* 1963), catalase (Aebi, 1984), and SOD (Nishikimi *et al.*, 1972).

#### Histopathological Examinations:

Autopsy samples from rats in various groups' livers and kidney were obtained, and the slides made according to Bancroft *et al.*, (1996).

#### Statistical analysis:

Utilizing the means and standard deviations of six parallel measurements, the experimental data were statistically analyzed. Methods of analysis of variance (ANOVA) were implemented. To perform the statistical computations, the GraphPad Prism® software (GraphPad Software, San Diego, CA, USA) was utilized (Motulsky, 1999)

## RESULTS AND DISCUSSION:

### Quantitative screening of phytochemicals:

The total phenolic contents of the *carica papaya* extract are displayed in Table (1), where the highest values, approximately 33.75 and 30.50 mg/m total phenolic contents, are found in the ethanol and acetone extracts. Ethyl acetate extract, on the other hand, showed a value of 28.83 mg/m. The acetone extract has the highest flavonoid content in the same table, with values of around 28.75 and 25.75 mg/m, followed by the ethyl acetate extract at 25.00 mg/m. Plant phenolic extracts consist of various kinds of phenols that are soluble in various solvents. According to Zohra (2011), alcohol yields positive results for the extraction procedure. The most effective solvent for removing polyphenols from *carica papaya* leaves is alcohol solutions (Victor *et al.*, 2018). According to Omidiwura (2018), the yield of phenols produced by ethanol solvent was higher than that of other solvents while remaining constant.

**Table 1. Total phenolic compounds and total flavonoids of *Carica papaya* extracts**

| Extracts                     | Total phenolic compounds (mg/g) <sup>a</sup> | Total flavonoids (mg/g) <sup>b</sup> |
|------------------------------|--|--------------------------------------|
| <b>Ethanol extract</b>       | 33.75± 4.6                                   | 25.00 ±3.30                          |
| <b>Acetone extract</b>       | 30.50± 3.5                                   | 28.75± 0.90                          |
| <b>Ethyl acetate extract</b> | 28.83 ±4.21                                  | 25.75 ± 1.00                         |

a: milligrams of gallic acid equivalent per gram of dry leaf extract; b: milligrams of quercetin equivalent per gram of dry leaf extract. Each number is represented as the mean plus or minus the standard deviation, with a sample size of 6.

**-Body Weight Gain and daily feed intake in Tested Animals:**

Changes in body weight increase and daily feed consumption in animals subjected to testing are displayed in Table 2. After two months of paracetamol treatment, rats' daily feed intake and body weight increase were marginally lower than those of the

normal control group. While daily feed intake and body weight growth were still lower than normal control, the treatment groups, which received *Carica papaya* at two doses (100 mg, 200 mg) in addition to paracetamol exhibited an increase in these areas when compared to paracetamol alone.

**Table 2 Effect *Carica papaya* Extracts (100, 200 mg/kg b. wt.) and paracetamol on Body Weight of Rats**

| Groups          | Mean Final body weight(g) | Mean Body weight gain(g) | Daily feed intake(g) |
|-----------------|---------------------------|--------------------------|----------------------|
| Control         | 327±13.6                  | 171±8.2                  | 18                   |
| Cp1             | 280±29.1                  | 118.3±2.5                | 20.6                 |
| Cp2             | 285±14                    | 136.3±1.1                | 20.2                 |
| Paracetamol     | 224±24.4 <sup>a</sup>     | 56±28.6 <sup>a</sup>     | 12.91                |
| Cp1 paracetamol | 248±37 <sup>a</sup>       | 86±26.9 <sup>ab</sup>    | 17.43                |
| Cp2 paracetamol | 228±13.5 <sup>a</sup>     | 74.33±8.1 <sup>ab</sup>  | 15.91                |

The mean ± standard deviation of observations was calculated for six rodents. <sup>a</sup>Notably distinct from the control group ( $P < 0.05$ ); <sup>b</sup>Notably distinct from the group administered paracetamol ( $P < 0.05$ ). CP1 and CP2 contain 100 and 200 mg/kg b. wt., respectively, of *carica papaya* extract.

**Impact of paracetamol and carica papaya extract (100, 200 mg/kg b.w.) on a few biochemical parameters in the serum of test rats.**

**-Liver functions:**

Serum variations in AST, ALT, ALP, and total protein albumin are displayed in (Table 3). Rats given paracetamol for two months had lower blood levels of albumin and total protein than the normal control group. In contrast, the treated groups that received *Carica papaya* at two doses (100 mg and 200 mg) in addition to paracetamol showed an increase in total protein and albumin, though these values were still lower than those of the normal control group. Serum ALT, AST, and ALP activity were also decreased. Sensitive indicators for evaluating liver injury included serum ALT and AST activity (Li *et al.*, 2018). It's also important to remember that the enzyme alkaline phosphatase (ALP), being found in both the liver and the bones, is essential for the removal of phosphate groups. The present results are consistent with those of El Menyiy *et al.* (2018) and Naggayi *et al.* (2015), who found that, paracetamol significantly, decreased serum total protein and albumin and elevated aspartate and alanine aminotransferase activities when compared with the control. Additionally, Koshak *et al.* (2023) found that administering a sub-lethal dosage of paracetamol (2 g/kg) resulted in liver damage in the rats, as evidenced by a marked rise in the blood levels of alkaline phosphatase (ALP) and transaminases (AST and ALT).

**Table 3. Effects of C.P1 and C.P2 on Liver function in Serum of Albino Rats.**

| Groups          | Total Protein(g/dl)     | Albumin(g/dl)             | AST(u/ml)                | ALT(u/ml)                 | ALP(u/ml)                |
|-----------------|-------------------------|---------------------------|--------------------------|---------------------------|--------------------------|
| Control         | 5.3±0.057               | 2.867 ±0.5774             | 38.30±1.10               | 31.10±1.73                | 2.77±0.251               |
| Cp1             | 4.2±0.208 <sup>a</sup>  | 2.18±0.05 <sup>a</sup>    | 42.30± 1.61              | 41.47±1.78                | 9.33±0.153               |
| Cp2             | 4.7±0.10                | 2.533 ±0.05               | 49.40±0.76               | 37.27±3.47                | 7.17±0.838               |
| Paractamol      | 1.7±0.10 <sup>a</sup>   | 1.17±0.15 <sup>a</sup>    | 111.5±1.57 <sup>ab</sup> | 82.90±5.23 <sup>a</sup>   | 22.60±1.05 <sup>a</sup>  |
| Cp1+paractamol  | 2.9±0.10 <sup>ab</sup>  | 1.40±0.10 <sup>ab</sup>   | 86.65±3.85 <sup>a</sup>  | 59.23±4.33 <sup>ab</sup>  | 21.00±0.700 <sup>a</sup> |
| Cp2+ paractamol | 3.9±0.458 <sup>ab</sup> | 2.07±0.1528 <sup>ab</sup> | 78.77±3.29 <sup>ab</sup> | 46.40± 3.20 <sup>ab</sup> | 15.23±1.71 <sup>ab</sup> |

The mean ± standard deviation of observations was calculated for six rodents. <sup>a</sup>Notably distinct from the control group (P < 0.05); <sup>b</sup>Notably distinct from the group administered paracetamol (P < 0.05). Cp1 and Cp2 contain 100 and 200 mg/kg b. wt., respectively, of carica papaya extract.

Rats' liver enzyme levels rose when given paracetamol. Increased hepatic dysfunction or pathology, such as blocked bile ducts or particular skeletal deformities, may be indicated by elevated alkaline phosphatase values. Depleted glutathione, high reactive oxygen species, and cytochrome P450 isoforms were recognized to contribute to the pathophysiology of paracetamol-induced liver injury. It's interesting to note that *carica papaya* extract inhibited different isoforms of cytochrome 450. This suggests that inhibition of cytochrome P450, reduces the formation of N-acetyl-p-benzoquinone imines and maintains the glutathione pathway active. Subsequently, *carica papaya* extract may mitigate the negative effects of paracetamol toxicity. The results of other research (Ojo *et al.*, 2006; Jiang *et al.*, 2017) are consistent with the elevation of liver enzymes caused by high dose of paracetamol. Since the liver is where albumin is mostly generated, a fall in serum albumin and total protein

caused by an overdose of paracetamol is another sign of liver damage. Proteinuria brought on by a large dose of paracetamol may be the cause of this effect on serum albumin and total protein (Sugimoto *et al.*, 2011).

#### **Kidney function:**

Changes in serum renal function levels are displayed in (Table 4). Rats given paracetamol for two months had higher serum levels of urea and creatinine while uric acid was lower than the normal control group. In another hand the treated groups with *Carica papaya* at two doses (100 mg, 200 mg) in combination with paracetamol showed decrease of urea, creation and increase uric acid compared to paracetamol alone . The present result are in the same line as those by El Menyiy *et al.*(2018) and Naggayi *et al.* (2015) who found that paracetamol considerably raised blood creatinine and blood urea nitrogen, but it dramatically decreased serum uric acid.

**Table 4. Effects of C.P1 and C.P2 on kidney function Level m(g/dl) in Serum of Albino Rats.**

| Groups          | Urea (mg/dl)            | Creatinine (mg/dl)        | Uric acid (mg/dl)         |
|-----------------|-------------------------|---------------------------|---------------------------|
| control         | 9.60±1.015              | 0.66±0.577                | 5.20 ±0.346               |
| Cp1             | 10.33± 0.152            | 0. 86±0.577               | 4.20 ±0.6 <sup>a</sup>    |
| Cp2             | 11.50±0.200             | 1.00±0.100                | 4. 43 ±1.21               |
| Paracetamol     | 13.73±1.29 <sup>a</sup> | 3.13±0.057 <sup>a</sup>   | 2.50 ±0.200 <sup>a</sup>  |
| Cp1 paracetamol | 11.87±2.76 <sup>b</sup> | 1.40 ±0.100 <sup>ab</sup> | 3.20±0.100 <sup>ab</sup>  |
| Cp2 paracetamol | 11.7±1.484 <sup>b</sup> | 1.13 ±0.208 <sup>ab</sup> | 3.56 ±0.550 <sup>ab</sup> |

The mean ± standard deviation of observations was calculated for six rodents. <sup>a</sup>Notably distinct from the control group (P < 0.05); <sup>b</sup>Notably distinct from the group administered paracetamol (P < 0.05). Cp1 and Cp2 contain 100 and 200 mg/kg b. wt., respectively, of carica papaya extract.

Additionally, Hegazy *et al.*'s study in 2021 found that administering paracetamol to the group receiving treatment caused a discernible decline in the biochemical alterations found in that group. Prolonged increases in serum urea and creatinine concentrations were observed in response to the biological modifications. The results are consistent with those of Jaz *et al.* (2016), who discovered that the administration of paracetamol significantly increased serum concentrations of urea and creatinine (P < 0.05) , when comparison to the control group.

#### Oxidative Enzymes

Table (5) displays the hepatic and renal GSH, CAT, and SOD activity. Changes in the blood levels of SOD, GSH, and catalase for the kidney and liver are displayed in Table 9. Rats given paracetamol for two months had lower serum levels of SOD, GSH, and catalase for the kidney and liver than the normal control group. While SOD, GSH, and catalase levels in the kidney and liver were higher in the treated groups given *carica papaya* at two doses (100 mg, 200 mg) in addition to paracetamol than the corresponding levels on giving the paracetamol alone, Both treatments were remained lower than in the normal control group.

**Table 5. Effects of carica papaya leaves extract at two doses and paracetamol on hepatic and renal SOD, GSH and CAT in rats of Albino Rats.**

| Groups           | SOD Liver (U/ml)           | SOD Kidney (U/ml)         | Catalase Liver (U/g protein) | Catalase kidney(U/g protein) | GSH Liver ( mg/g)        | GSH Kidney ( mg/g)       |
|------------------|----------------------------|---------------------------|------------------------------|------------------------------|--------------------------|--------------------------|
| Control          | 355.7 ± 4.7                | 368.3±6.3                 | 165±1.73a                    | 81.7±4.04                    | 3.30±0.100               | 4.26±0.321               |
| Cp1              | 330.3±3.5                  | 344 ± 6.3                 | 163±5.00                     | 100±0.577                    | 2.80±0.100 <sup>a</sup>  | 3.30±0.173 <sup>a</sup>  |
| Cp2              | 336 ±3.65                  | 364.7 ± 8.3               | 164±1.15                     | 115±3.22                     | 2.83±0.115 <sup>a</sup>  | 3.50±0.360 <sup>a</sup>  |
| Paracetamol      | 164 ± 8.00 <sup>a</sup>    | 114.3 ±3.5 <sup>a</sup>   | 84±2.98 <sup>a</sup>         | 203.3±1.53 <sup>a</sup>      | 1.46±0.159 <sup>a</sup>  | 1.33±0.321 <sup>a</sup>  |
| Cp1+ paracetamol | 222 ±3.7.0 <sup>ab</sup>   | 242.3 ± 4.8 <sup>ab</sup> | 87.33±3.05 <sup>a</sup>      | 145±7.57 <sup>ab</sup>       | 1.60±0.115 <sup>a</sup>  | 2.26±0.115 <sup>ab</sup> |
| Cp2+ paracetamol | 283.3± 54.12 <sup>ab</sup> | 276 ± 5.6 <sup>ab</sup>   | 149±2.51 <sup>ab</sup>       | 129±3.00 <sup>ab</sup>       | 2.30±0.057 <sup>ab</sup> | 2.13±0.321 <sup>ab</sup> |

The mean ± standard deviation of observations was calculated for six rodents. <sup>a</sup>Notably distinct from the control group ( $P < 0.05$ ); <sup>b</sup>Notably distinct from the group administered paracetamol ( $P < 0.05$ ). Cp1 and Cp2 contain 100 and 200 mg/kg b. wt., respectively, of carica papaya extract.

Enzymatic antioxidants are essential because they shield cells from oxidative damage. The present findings are consistent with those of Kandemir *et al.* (2017) and, Aboshama *et al.* (2024), Whose found that paracetamol dramatically decreased the antioxidant activity of SOD and CAT in the liver renal tissue when compared to the control group. Additionally, Okokon *et al.* (2017) demonstrated that paracetamol administration resulted in significant decreases in the activities of SOD, catalase, and GSH level in liver tissue when compared with the control group. Conversely, Raffaelli *et al.* (2015) assessed the antioxidative potential of goods made from *C. papaya* yeast fermentation. Subsequently SOD

activity significantly increased. Sadek (2012) looked into how *C. papaya* extracts shielded rats' liver and kidney enzymes from acrylamide-induced damage.

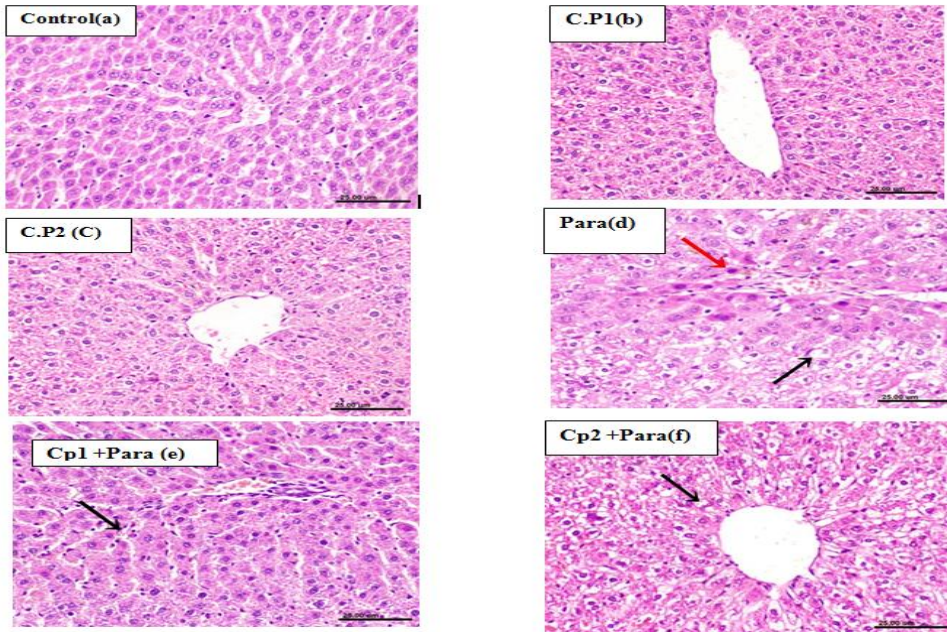
#### Histopathological examination of liver:

The livers of rats in the control group exhibited normal histoarchitecture of hepatic tissue when observed microscopically (Fig 1. a). Furthermore, liver of rats from groups given *carica papaya* extract (100, 200mg /kg) exhibited no histopathological lesions (Fig 1. b, c). On contrary, liver of rats from group paracetamol described necrosis of sporadic hepatocytes (Fig 1. d), ballooning degeneration of



hepatocytes congestion of hepato portal blood vessel vacuolar degeneration of hepatocytes and focal hepatocellular necrosis. Meanwhile, liver from group given *carica papaya* extract (100mg) with paracetamol revealed Kupffer cells activation (Fig 1. e), slight hydropic

degeneration of hepatocytes and congestion Furthermore, sections from group given *carica papaya* extract (200mg) with paracetamol exhibited only slight hydropic degeneration of hepatocytes (Fig 1. f).



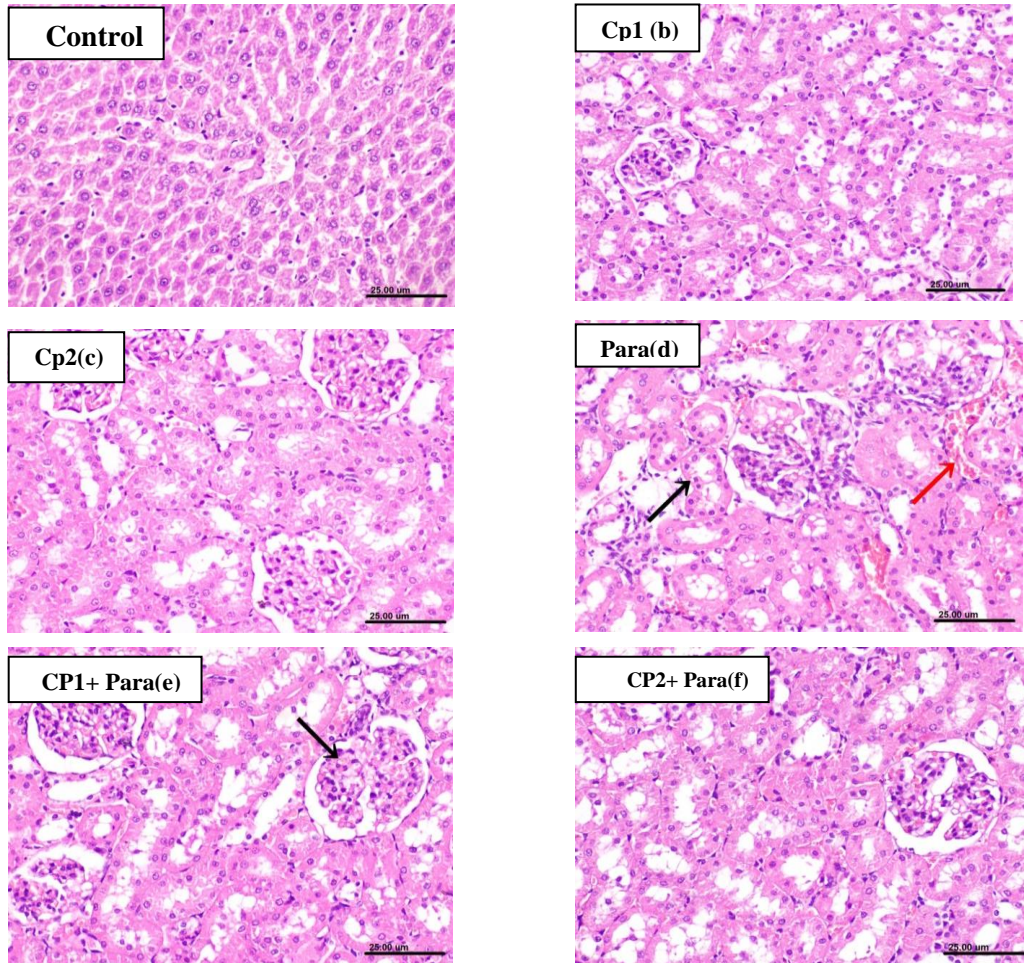
**Fig 1. Histopathological examination of liver** :(a): Photomicrograph of liver of rat from group control showing the normal histoarchitecture of hepatic tissue (H & E X 400, scale bar 25µm). (b): Photomicrograph of liver of rat from group c.p1 showing no histopathological lesions (H & E X 400, scale bar 25µm). (c): Photomicrograph of liver of rat from group carica papaya (200mg kg<sup>-1</sup>) showing no histopathological lesions (H & E X 400, scale bar 25µm). (d): Photomicrograph of liver of rat from group paracetamol showing necrosis of sporadic hepatocytes (red arrow) and ballooning degeneration of hepatocytes (black arrow) (H & E X 400, scale bar 25µm). (e): Photomicrograph of liver of rat from group c.p1 + para showing Kupffer cells activation (black arrow) (H & E X 400, scale bar 25µm). (f): Photomicrograph of liver of rat from group c.p2+ para showing slight hydropic degeneration of hepatocytes (arrow) (H & E X 400, scale bar 25µm).

The results of our study align with the observations made by Okokon *et al.* (2017), which indicated that rodents administered paracetamol exhibited a disorderly appearance of healthy hepatic cells, hyperplasia, centrilobular necrosis, vascular and cellular degeneration, polymorphonuclear aggregation, inflammation, and fatty degeneration.

**Histopathological analysis of the kidneys:**

The kidneys of rats from groups Cp1, Cp2, and control exhibited a normal histological structure of renal parenchyma when viewed microscopically. (Fig 2.a, b, c). In addition, renal tubule epithelial lining vacuolar degeneration was observed in the kidneys of rats in the paracetamol group (Fig 2.d). Conversely, glomerular tuft congestion was marginal in sections from the Cp1 para group (Fig 2.e).

Nevertheless, certain sections from group Cp2 para did not exhibit any discernible histopathological changes (Fig 2.f). These findings are consistent with those of Hegazy *et al.* (2021), who demonstrated that paracetamol induced distinct histopathological alterations in the medulla and renal cortex. The results of Ahmed *et al.* (2015) indicate that a high dose of paracetamol can lead to an increase in permeability of renal blood vessels. This, in turn, can cause interstitial edema and severe congestion in the glomerular tufts and renal blood capillaries. These findings align with the observed hypertrophy, hyper cellularity, and congestion of glomerular capillaries in the current study. Moreover, hyper cellular glomeruli are present in the renal cortex as a consequence of the mesangial cells' enhanced proliferation (Aziz *et al.*, 2013).



**Figure 2. Histopathological examination of kidneys** (a): Group control showing the normal histological structure of renal parenchyma (H & E X 400, scale bar 25μm). (b): Group c.p1 showing the normal histological structure of renal parenchyma (H & E X 400, scale bar 25μm). (c): Group c.p2 showing the normal histological structure of renal parenchyma (H & E X 400, scale bar 25μm). (d): Group para showing marked vacuolar degeneration of epithelial lining renal tubules (black arrow) and congestion of intertubular renal blood vessel (red arrow) (H & E X 400, scale bar 25μm). (e): Group c.p1 para showing slight congestion of glomerular tuft (arrow) (H & E X 400, scale bar 25μm). (f): Group c.p2 para showing no histopathological alterations (H & E X 400, scale bar 25μm).

Conversely, a subset of the renal glomeruli examined in this investigation exhibited glomerular atrophy. The observed phenomena can be explained by a reduction in the glomerular filtration of the drug due to capillary constriction. Renal tubules exhibited tubular dilatation, necrosis of tubular cells, sloughing of necrotic tubular epithelial cells into the lumens of tubules, substantial cytoplasmic vacuolization, tubular cell enlargement, and darkly stained nuclei. In accordance with the findings documented by Kirbas *et al.* (2015), substantial deformation was observed in the epithelial cell structures of both the proximal and distal

tubules. Cellular shedding of the epithelium of the distal tubules was induced by lumen dilation and edematous fluid, whereas the proximal tubules' distended epithelial cells caused extensive degeneration of structures.

**CONCLUSION:**

According to the present study's findings, oxidative damage and blood biochemical indicators can be lessened by paracetamol when given in doses of 200 mg / kg of *carica papaya* extract. The efficacy of *carica papaya* extract in reducing the toxicity of paracetamol may be attributed to its antioxidant characteristics.

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دراسة قدرة مستخلص أوراق الباباظ لعلاج التسمم الكبدي والكلوي لدى الجرذان الناجم عن الباراسيتامول.

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يعتبر الباباظ من النباتات الاقتصادية الهامة التي لها فوائد غذائية كثيرة، وأعراض طبية رائعة، وتستخدم لإنتاج المواد المستخدمة في علاج مجموعة واسعة من الأمراض. ولذا، كان الغرض من هذه الدراسة تحديد مدى نجاح مستخلص أوراق الباباظ في تخفيف آثار الباراسيتامول على العلامات البيوكيميائية في الدم والأضرار التأكسدية فيما يتعلق بالفئران أجريت التجارب في قسم الكيمياء الزراعيه – كلية الزراعة – جامعة المنيا وفيها تم تقسيم ذكور الجرذان الي ست مجموعات كل مجموعة مكونة من ستة فئران ألبينو ، بوزن  $150 \pm 15$  جم. المجموعة الأولى تتكون من مجموعة صحية؛ تتألف المجموعة الثانية من فئران أعطيت مستخلص الباباظ الإيثانولي (100 ملجم/كجم من وزن الجسم؛ المجموعة الثالثة تتكون من فئران أعطيت مستخلص الباباظ الإيثانولي (200 ملجم/كجم من وزن الجسم)؛ أعطيت الفئران في المجموعة الرابعة باراسيتامول (2 جرام/كجم من وزن الجسم). تلقت الفئران في المجموعة الخامسة معاملة مسبقة بمستخلص الباباظ (100 ملجم / كجم من وزن الجسم) مع الباراسيتامول ، تلقت الفئران في المجموعة السادسة معاملة مسبقة بمستخلص الباباظ (200 ملجم / كجم من الجسم مع الباراسيتامول وتم انتهاء تجربته بعد شهرين ، حيث أظهرت المجموعة التي تناولت الباراسيتامول زيادة ملحوظة في المؤشرات الحيوية، بما في ذلك اليوريا والكرياتينين وAST وALT وALP. نتيجة لهذه النتائج، تم تحقيق منع الإجهاد التأكسدي الناجم عن الباراسيتامول من خلال المعاملة المسبقة بمستخلص الباباظ الذي يحسن الإنزيمات المضادة للأكسدة (CAT وSOD)، ويمكن الوقاية من تلف الكبد والكلى الناجم عن الباراسيتامول باستخدام مستخلص أوراق الباباظ. من خلال خفض الإجهاد التأكسدي، وتعزيز الدفاعات المضادة للأكسدة، وتشجيع تجديد خلايا الكبد، واستعادة وظائف الكبد والكلى الطبيعية، وكذلك المساعدة على تخفيف تلف الكبد والكلى .