Ethanolic Leaf Extract Effects of *Carica papaya* on Acetaminophen- Induced Hepatotoxicity in Adult Wistar Rats

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Abstract- Carica papaya is used in traditional system of medicine to treat various hepatic disorders and it has recently been used to treat paracetamol stimulated liver damage in rats in India. This present work was to examine the activities of ethanolic extract of Carica papaya leaves in preventing liver damage caused by acetaminophen (the major active ingredients) triggered liver injury in rats. Oxidative stress was induced in wistar strain albino rats by administration of a single dose of acetaminophen 2.0g/kg before the administration of the extract and this causes an increase in the activity of marker enzymes, total protein and bilirubin and was significantly restored by the leaf extract. At (200-500) mg/kg, there was a reduction in serum enzyme levels when compared with toxicant group. But the ethanol extract at an oral dose of 200mg/kg exhibited a significant protection against acetaminophen induced liver damage. Vitamin E was used as a standard reference which exhibited significant hepatoprotective activity. The histopathological examination of liver provided supportive evidence. Conclusively, the work provided an acceptable explanation of Carica papaya in the treatment of disease-related liver damage.

Index Terms- Acetaminophen, Carica papaya, Hepatotoxicity, Hepatoprotective activity

I. INTRODUCTION

Carica papaya is a tropical, herbaceous plant more commonly known as pawpaw whose original home is South America where other closely related species such as *carica candamarcensis*, *carica monoica* and *carica cauliflora.*It reaches about 4 -5 m tall and generally produces only one unbranched, soft fibrous stem supporting a crown of large-lobed leaves on long pentiole [1].
Due to high demand for therapeutic drugs from natural products, greater attention has been shifted to pawpaw plants containing health protective constituents, which are essential in preventing diseases and maintaining a state of well-being [2].
In recent years, there has been a particular interest in the antioxidants and health benefits of phytochemicals in pawpaw leaves and seeds. Pawpaw leaves and seeds have been known for a large range of purposes including nutrition, medicine, beverages and industrial use.
Carica papaya plants produce natural compounds (annonaceous acetogenins) in leaf bark and twig tissues that possess both highly anti-tumor and pesticidal properties. It was suggested that a potentially lucrative industry based simply on production of plant biomass could develop for production of anti-cancer drugs [3].
Carica papaya leaf tea or extract has a reputation as a tumor-destroying agent [4]. The papaya fruit, as well as all other parts of the plant, contain a milky juice in which an active principle known as papain is present. Aside from its value as a remedy in dyspepsia and kindred ailments, it has been utilized for the clarification of beer. The juice has been in use on meat to make it tender [5].
Fresh, green pawpaw leaf is an antiseptic, whilst the brown, dried pawpaw leaf is the best as a tonic and blood purifier [6]. Chewing the seeds of unripe pawpaw fruit also helps to clear nasal congestion [7]. The green unripe pawpaw has a therapeutic value due to its quality. The tea prepared with the green papaya leaf, promotes digestion and aids in the treatment of ailments such as chronic indigestion, overweight and obesity, arteriosclerosis, high blood pressure and weakening of the heart [8].
Paracetamol (called acetaminophen in the USA) is one of the most commonly used non-narcotic analgesic and antipyretic agents. It has relatively weak anti-inflammatory activity. Paracetamol is reported to be selective inhibitor of Cox 3 (cyclooxygenase). Although some reported evidence show that paracetamol has significant anti-inflammatory action [9]. Paracetamol toxicity is one of the most common causes of poisoning worldwide. Paracetamol was the fourth most common cause of death following self-poisoning in the United Kingdom in 1989; [10], yet it is still one of the most common analgesic and antipyretic drugs often used around the world to treat pains and mild feverish conditions.
As far as this is true, it is also one of the major cause of liver damage such as liver necrosis. Toxic doses of paracetamol cause a serious potentially fatal hepatotoxicity. These toxic effects occur when the liver enzymes catalyzing the normal conjugation reactions are saturated, causing the drug to be metabolized by the mixed function oxidases. The resulting toxic metabolized, N-acetyl-P-

benzoquinone imine (NAPQI), is inactivated by conjugation with glutathione, but when glutathione is depleted, the toxic intermediate accumulates and reacts with nucleophilic constituents in the cell. This causes necrosis in the liver and also in the kidney tubules. This work examined the protective activity of pawpaw leaf extract, against acetaminophen-induced liver damage in adult Wistar rats.

II. MATERIALS AND METHODS

A total of forty adult rats with an average weight of 200 g were used for the experiment. They were acclimatized to laboratory conditions for 2 weeks and were fed with a standard pellet and drinking water. The rats were divided into eight groups of five rats each and were given the following treatment.

Group I: Control .
Group II: Induced with Acetaminophen standard only (2g/kg body weight, orally).
Group III: Carica papaya ethanolic leaf extract only (200mg/kg body weight, orally).
Group IV: Induced with 2g/kg acetaminophen standard and treated with 200mg/kg vitamin E standard
Group V: Induced with 2g/kg acetaminophen standard and treated with 200mg/kg ethanolic leaf extract.
Group VI: Induced with 2g/kg acetaminophen standard and treated with 300mg/kg ethanolic leaf extract.
Group VII: Induced with 2g/kg acetaminophen standard and treated with 400mg/kg ethanolic leaf extract.
Group VIII: Induced with 2g/kg acetaminophen standard and treated with 500mg/kg ethanolic leaf extract.

A. Administration of Extract and Acetaminophen

The normal control (Group I) received only distilled water daily for 7 days. Group II were induced with Acetaminophen standard only (2g/kg body weight, orally). Test groups animals (Groups V-VIII) were given an oral doses of 200mg/kg, 300mg/kg, 400mg/kg and 500mg/kg of the ethanolic extract, respectively, for 7 days. These test group animals (Groups V-VIII) were first administered acetaminophen (2g/kg body weight, orally) before the administration of the extract. Group IV received standard drug vitamin E (200mg/kg) for 7 days. Group III received only the extract at 200mg/kg b.w, orally for 7 days.
Animals were sacrificed 24 hours following the last treatment, blood was collected, allowed to clot and was separated at 2500 rpm for 15 minutes and biochemical investigations were carried out both in the serum and liver. Liver was analyzed and histopathological studies were carried out.

B. Enzyme Assay

The levels of Alanine aminotransaminase(ALT), Alkaline phosphatase(ALP), Aspartate aminotransaminase (AST), Albumin and Bilirubin in the serum were determined by colorimetric method (21) using Randox diagnostic kits (USA). Pyruvate solutions of varied millimolar concentrations were used to prepare a standard curve from which AST activities were computed as described by [11]. Alanine aminotransaminase (ALT) assay was carried out as described for AST except that 200Mm DL-Alanine replaced L-Aspartate in the procedures.

C. Histological Studies

The liver tissues were analyzed by fixing in 10% formalin, dehydrated in gradual ethanol 80% and cleared in xylene and embedded in paraffin. Sections were prepared and then stained with hematoxylin and eosin dye for photomicroscopic observation.

D. Statistical Analysis

All data were presented as Mean ± standard deviation. One-way analysis of variance (ANOVA) and Duncan test was carried out to test any significant differences between their means. P values equals .05 (P=.05) were considered statistically significant.

III. RESULTS

The results in Table 1 shows a significant increase (P=.05) in the serum levels of the hepatic enzymes of group II acetaminophen treated rats compared with control (Group I) and other Groups III-VIII which received *Carica papaya* ethanolic leaf extract and vitamin E standard. Hepatic damage induced by acetaminophen was observed from this study (Figure 2). There was a significant increase (P=.05) in the marker enzymes; ALP, ALT, AST also in Albumin, Bilirubin in acetaminophen treated rats (Table 1).

IV. DISCUSSION OF RESULTS

Table 1: Effects of ethanolic leaf extract concentrations of *Carica papaya* on Serum, ALT, AST, ALP, Protein and Bilirubin levels on intoxicated rats given 2g/kg acetaminophen

Group	Treatment	Protein (g/dl)	BLB (mg/dl)	ALP (U/L)	ALT (U/L)	AST (U/L)
1	Control	$10.50^{b}\pm0.65$	$0.00^{b}\pm0.00$	$101.25^{abc}\pm3.54$	$21.75^{a}\pm3.71$	$55.00^{a}\pm7.05$
2	Toxicant	$11.00^{b}\pm1.00$	$0.75^{c}\pm0.05$	$135.50^{d}\pm3.50$	$39.00^{c}\pm6.00$	$77.00^{b}\pm4.00$
3	Leaf extract only (200mg/kg)	$10.67^{b}\pm0.67$	$0.23^{b}\pm0.03$	$83.33^{ab}\pm3.18$	$21.00^{a}\pm1.53$	$60.33^{ab}\pm2.40$
4	Toxicant+Vit.E (200mg/kg)	$11.00^{b}\pm0.71$	$0.23^{b}\pm0.03$	$118.25^{cd}\pm7.51$	$26.00^{ab}\pm1.47$	$69.50^{ab}\pm5.78$
5	Toxicant+ 200mg/kg leaf extract	$9.00^{ab}\pm0.58$	$0.20^{b}\pm0.06$	$75.33^{a}\pm7.86$	$27.67^{ab}\pm1.20$	$51.33^{a}\pm4.67$
6	Toxicant+ 300mg/kg leaf extract	$9.25^{ab}\pm0.75$	$0.25^{b}\pm0.06$	$96.00^{abc}\pm9.97$	$34.75^{a}\pm2.29$	$67.00^{ab}\pm1.96$
7	Toxicant+ 400mg/kg leaf extract	$8.00^{a}\pm0.41$	$0.25^{b}\pm0.06$	$117.00^{cd}\pm12.07$	$26.75^{ab}\pm5.04$	$62.50^{ab}\pm3.48$
8	Toxicant+ 500mg/kg leaf extract	$9.75^{ab}\pm0.25$	$0.35^{b}\pm0.06$	$110.00^{bcd}\pm7.35$	$41.75^{c}\pm4.11$	$56.25^{a}\pm7.47$

Values are expressed as $\overline{x} \pm SD$, n=5. Means followed different superscripts are significantly different (P=.05) from one another.

Table 2: Effects of various leaf extract concentrations of *Carica papaya* on Liver, ALT, AST, ALP, Protein and Bilirubin levels on intoxicated rats given 2g/kg acetaminophen.

Group	Treatment	Protein (g/dl)	BLB (mg/dl)	ALP (U/L)	ALT (U/L)	AST (U/L)
1	Control	$4.13^{ab}\pm0.43$	$0.003^{a}\pm0.003$	$25.00^{ab}\pm3.51$	$13.75^{bc}\pm2.39$	$15.25^{a}\pm2.25$
2	Toxicant	$3.25^{a}\pm0.25$	$0.03^{a}\pm0.01$	$36.50^{b}\pm3.50$	$11.00^{abc}\pm1.00$	$8.00^{a}\pm2.00$
3	Leaf extract only (200mg/kg)	$4.57^{ab}\pm1.16$	$0.01^{a}\pm0.003$	$25.00^{ab}\pm8.66$	$7.00^{a}\pm1.53$	$13.67^{a}\pm1.86$
4	Toxicant+Vit.E (200mg/kg)	$4.60^{b}\pm0.87$	$0.02^{a}\pm0.003$	$27.50^{ab}\pm3.23$	$6.25^{a}\pm1.32$	$10.50^{a}\pm0.50$
5	Toxicant+ 200mg/kg leaf extract	$4.73^{ab}\pm1.10$	$0.01^{a}\pm0.003$	$33.33^{b}\pm3.33$	$9.00^{ab}\pm1.00$	$11.67^{a}\pm1.67$
6	Toxicant+ 300mg/kg leaf extract	$6.30^{b}\pm0.17$	$0.02^{a}\pm0.003$	$17.50^{a}\pm3.23$	$13.25^{bc}\pm1.38$	$13.00^{a}\pm1.78$
7	Toxicant+ 400mg/kg leaf extract	$5.65^{b}\pm0.20$	$0.008^{a}\pm0.003$	$25.25^{ab}\pm3.68$	$11.75^{abc}\pm1.03$	$9.50^{a}\pm0.29$
8	Toxicant+ 500mg/kg leaf extract	$5.45^{b}\pm0.58$	$0.02^{a}\pm0.005$	$27.00^{ab}\pm3.63$	$15.75^{c}\pm2.17$	$14.25^{a}\pm2.14$

Values are expressed as $\overline{x} \pm SD$, n=5. Means followed different superscripts are significantly different (P=.05) from one another.

Table 2 shows a significant reduction (P=.05) in the levels of these hepatic enzymes in the liver of group II acetaminophen treated rats compared with control and other groups (III-VIII). Treatment with extract (200mg/kg b.wt to 500mg/kg b.wt), after experimental liver damage resulted with marked reduction of marker enzymes levels in the blood circulation and a significant elevation in the liver

compared with group II acetaminophen treated rats. Administration of acetaminophen led to degeneration of liver vitality, fibrosis and necrosis on histological observation of the liver of acetaminophen –treated rats (Figure2). The treatment of the rats in groups V-VIII with ethanolic leaf extract of *Carica papaya* after acetaminophen exposure restored the damaged features of the liver by obviously reducing the levels of hepatic enzyme markers in the serum and reversing histopathological changes of degeneration with evidence of revitalization (Figure V-VIII). The administration of *Carica papaya* ethanolic leaf extract in group V-VIII rats after acetaminophen exposure significantly restored all the chemical processes and histological changes produced as a result of acetaminophen exposure. It can be deduced from this study that group V rats treated with 200mg/kg *Carica papaya* ethanolic leaf extract was more effective than other groups. It also shown that this 200mg/kg *Carica papaya* ethanolic leaf extract was more effective than vitamin E standard which was used as a standard reference and known to exhibit significant hepatoprotective activity.

The structure of the liver was well preserved in group III rats following exposure to ethanolic leaf extract of *Carica papaya* only (Figure 3). The features and the structures of the liver section on histological observation in group III that is; *Carica papaya* treated rats only appeared to correspond to the group I (control). Similarly, the values of marker enzymes in group III were also found to be normal compared with the values obtained from the group I (Table 1 and 2). There was no significant disparity between group I (control) and group III (*Carica papaya* extract only) as shown in (Figure 3, Table 1 and 2).

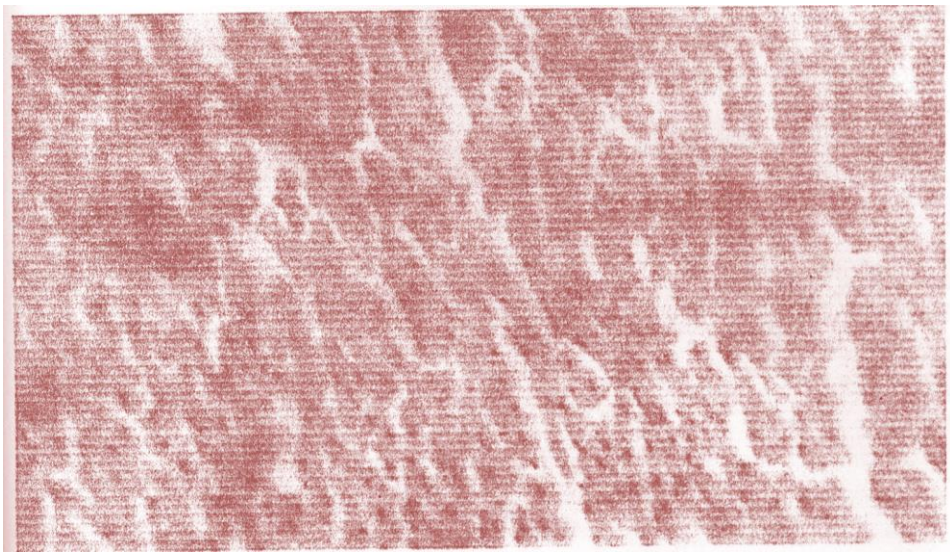

Fig. 1: Control

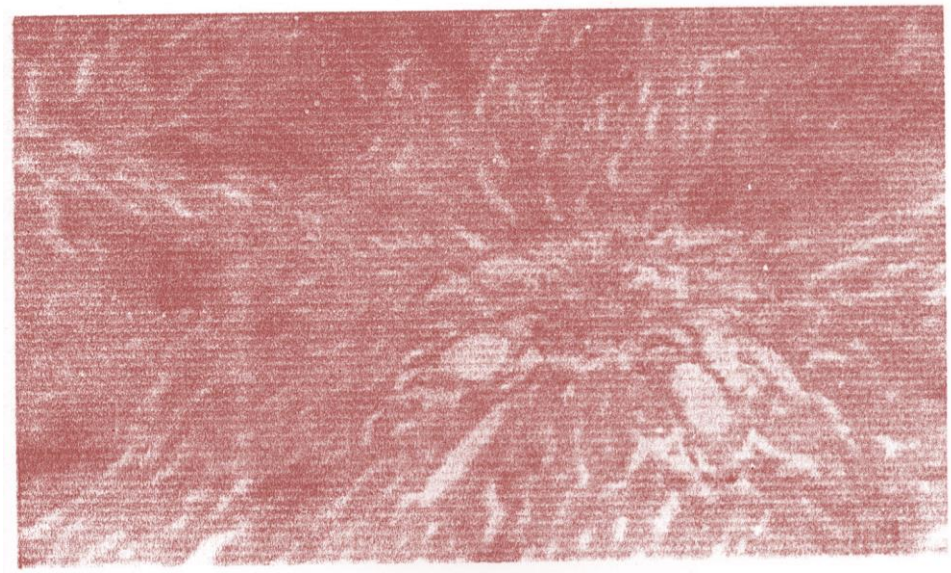

Fig. 2: Liver cells of rat given 2g/kg acetamminophen

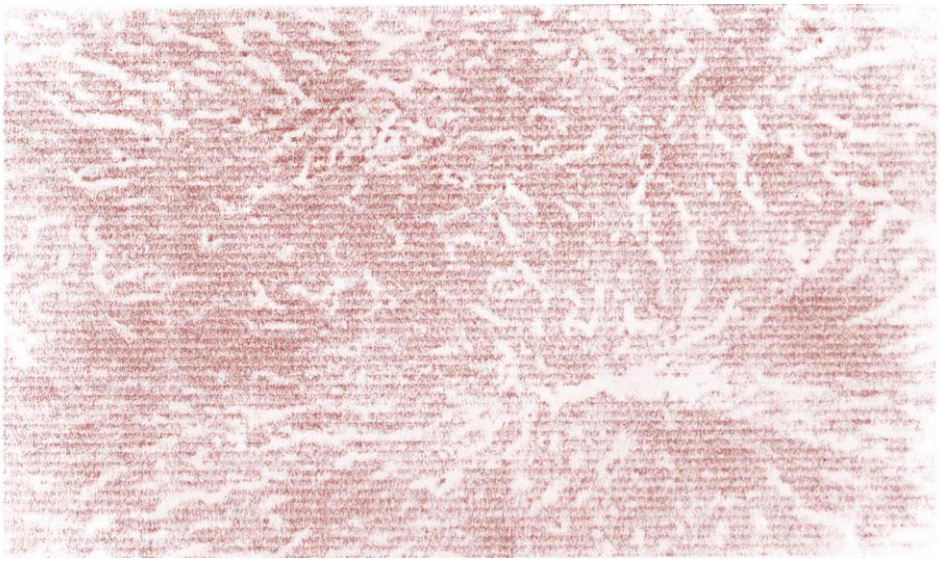

Fig. 3: Liver cells of rats given 200mg/kg Carica papaya leaf extract (Plant only)

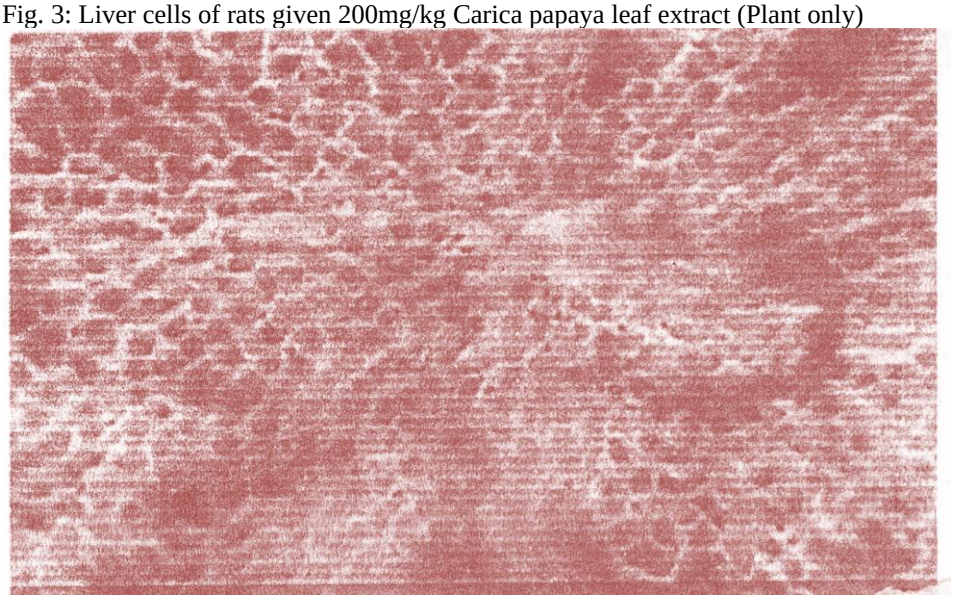

Fig. 4: Liver cells of rat given 2g/kg acetamminophen treated with 200mg/kg vitamin E

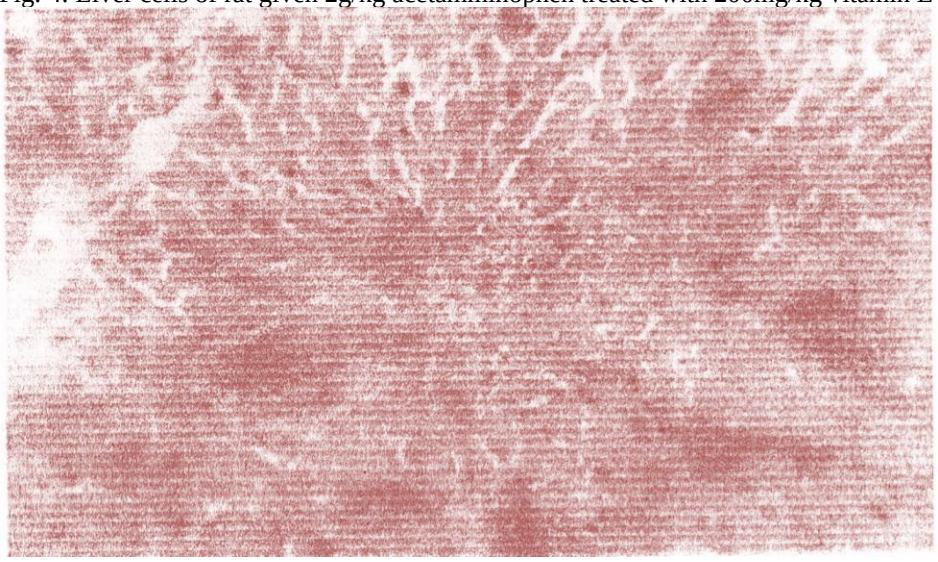

Fig. 5: Liver cells of rats given 2g/kg acetaminophen treated with 200mg/kg Carica papaya leaf extract

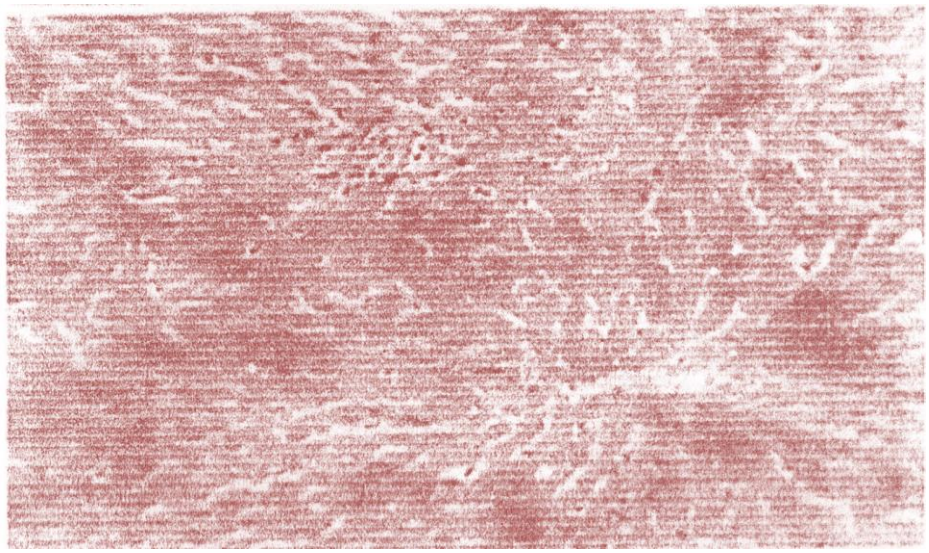

Fig. 6: Liver cells of rats given 2g/kg acetaminophen treated with 300mg/kg Carica papaya leaf extract

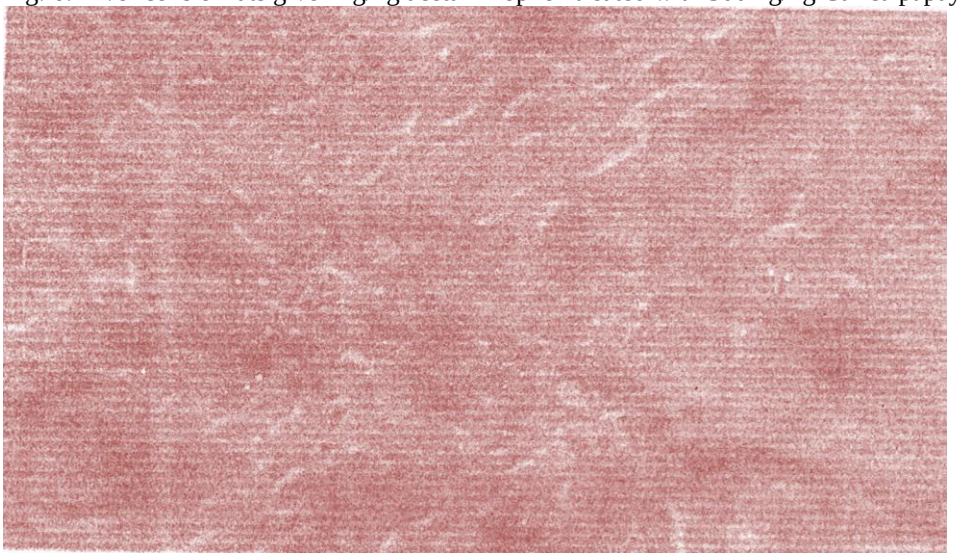

Fig. 7: Liver cells of rats given 2g/kg acetaminophen treated with 400mg/kg Carica papaya leaf extract

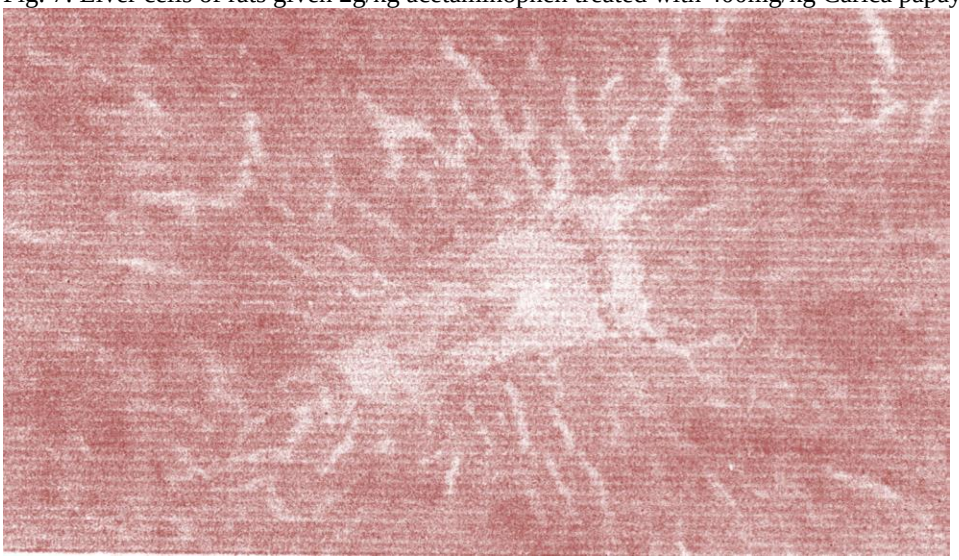

Fig. 8: Liver cells of rats given 2g/kg acetaminophen treated with 500mg/kg Carica papaya leaf extract

During the past years, the scientists have been engaged in the development of hepatoprotective agents from medicinal plants which perform a significant part in the management and treatment of liver disorders. *Carica papaya* leaf extract has a reputation as a tumour-destroying agent [4] and has also known to exhibits both anti tumour activity and immunomodulatory effects [12]. The quantitative phytochemical analysis of leaf extract of *Carica papaya* revealed the presence of some bioactive compounds such as flavonoids, alkaloids, saponin, total phenolics and tannins [13]. However, the hepatoprotective, anti-inflammatory, medicinal effects of *Carica papaya*,are as a results of the phytochemicals present.

The increase in the enzyme activity serum signifies damages to the liver enzymes. Nevertheless, damage to the liver cells makes the liver cells (hepatocytes) membrane water-permeable allowing some of the enzymes to leak out into the blood circulation. Generally, any impairment to the liver will cause elevations in blood of transaminases. However, the presence of elevated transaminases, (ALT and AST) indicates liver damage [14]. Different studies showed previously that overdose of acetaminophen in mice and rats can cause severe and extensive necrosis cell in the centralobular area in the liver and increased serum enzymes levels in rats which is in line with the outcome of the present work [15,16]. Necrosis or liver injury discharges the enzyme into blood circulation, raising the levels of serum enzymes and hence can be measured in the serum. ALP is a marker enzyme for the plasma membrane and endoplasmic reticulum [17], it is occasionally employed to assess the integrity of plasma membrane of liver [18].The significant increase in ALP activity (Table 1) after administration of extract may be due to disruption of liver plasma membrane. Increased in the levels of serum enzymes indicates cellular leakage and loss of functional integrity of cell membrane in liver [19].

[20] reported that the mechanism of hepatotoxicity of paracetamol has been studied extensively. The toxicity occurs because of its reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI exerts its toxicity mainly through its oxidative effects on cellular proteins sulfhydryl compounds are among the most important endogenous antioxidants. Glutathione (GSH) is the main intracellular non protein sulfhydryl and it plays an important role in the maintenance of cellular proteins and lipids in their functional states. NAPQI binds to GSH, forming a conjugate which results in conversion of GSH to GSSG (oxidized form of glutathione). When GSH is lowered, the toxic effects of oxidative insult are well pronounced, resulting in increased membrane and cell damage. At this point, others protein and non-protein sulfhydryl groups present in the cell provide an important alternate protection [21].

In this study, acute liver damage was instigated by administration of acetaminophen at an orally dose of 2.0g/kg. Administration of acetaminophen led to a significant ($p<0.05$) increase of hepatic enzymes in the serum when compared to group I (control). There was a significant ($p<0.05$) regeneration of these enzyme levels in the liver on administration of the leaf extract in a dose dependent manner and also by vitamin E at a dose of 200mg/kg (Table 1 and 2). The high levels of hepatic enzymes in the serum of acetaminophen-induced hepatic injury became significantly reduced by the extract due to its membrane stabilizing activity and its antioxidant property. Thus, the leakage of intracellular enzymes was prevented. This agrees with the fact that serum levels of transaminases return to normal with the healing hepatic parenchyma and the regeneration of hepatocytes [22].

The findings from the work were further confirmed by histopathological study of the liver. The histopathological examination clearly reveals that the liver sections from the group III given only 200mg/kg *Carica papaya* ethanolic extract (Figure 3) showed no significant morphological change when compared to the group 1(control) (Figure 1). Liver section from the group I showed normal lobular structures with a normal hepatic cells and a well- preserved nucleus. It also showed neither portal inflammation nor any morphological changes.

Liver sections from the rats given acetaminophen only (Figure 2) showed chronic inflammation, hepatocellular necrosis, massive fatty changes, nuclear form of enlargement and cytoplasmic inclusion fibrosis, compared to control group (Figure 1) and all other groups (Figures 4-8). Treatment with 200mg/kg *Carica papaya* extract only, 200mg/kg Vitamin E, and (200-500) mg/kg doses of *Carica papaya* leaf extract revealed that the hepatic cells from these groups have no significant differences when compared to control group, showing maximum hepatoprotective and therapeutic effects. Furthermore, the results showed that the group III (200mg/kg *Carica papaya* extract only) and group V (2g/kg acetaminophen +200mg/kg *Carica papaya* extract) were more effective than other doses of the extract and Vitamin E standard.
These morphological changes in the liver cells of rats given only acetaminophen might be due to oxidative stress resulting from toxicity of acetaminophen on the hepatic cells. The reversal and restoration of all the biochemical enzymatic assays and histological alterations caused by acetaminophen which was restored by the administration of *Carica papaya* leaf extract. This might be due to antioxidant property of the extract which healed and preserved the hepatic tissue from possible acetaminophen-induced oxidative stress which could lead to hepatic damage as observed in Figure 2.

V. CONCLUSION

Thus, in conclusion, *Carica papaya* ethanolic leaf extract can be regarded to be an effective hepatoprotective and therapeutic agent that brings remedy or restores the damage caused by acetaminophen (the major active ingredient in paracetamol) to the liver function. Hence the extract can be used in drug formulations and to provide a synergistic effect with other hepatoprotective drugs and thereby preventing the hepatocellular diseases.

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