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HEPATOPROTECTIVE EFFECT OF TAMARINDUS INDICA L. LEAF EXTRACT AGAINST PARACETAMOL INDUCED HEPATOTOXICITY IN ALBINO RATS

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ABSTRACT

The objective of the present study was to evaluate the long term toxicity of paracetamol infusion in male albino wister rat. The protective effects of aqueous extract of Tamarindus indica Linn in comparison to Hepamerz were studied on paracetamol induced hepatotoxicity. Different groups of animals were administered with the paracetamol, hepamerz and Tamarind leaf extract for 40 days. Biochemical estimation like SGPT, SGOT, total bilirubin count and serum total protein were done along with hematological study such as total RBC count and Hb%. Also histo-pathological studies of liver tissue were observed. On treatment with paracetamol a significant increase in SGPT, SGOT, total bilirubin, serum total protein and significant decrease in total RBC count, Hb% were observed. Moderate hepato-protective effect as well as significant decrease in the level of SGPT, SGOT and increase in total RBC count was observed after application of the aqueous extract of Tamarindus indica leaf. These results were almost same as hepamerz effect. Histopathological impairment after paracetamol application, was also improved by supplementation of Tamarind leaf extract and hepamerz.

KEYWORDS: Tamarindus indica Linn., hepamerz, paracetamol, necrosis, hepatotoxicity, bilirubin.

INTRODUCTION

Liver diseases are one of the major health concerns. Liver disorders still lack its prognosis due to effective preventive measures. Among these liver disorders, liver cirrhosis is a major public health problem. Based on autopsy studies, its prevalence is 4.5%–9.5% in the general population, which means that hundreds of millions of people are affected worldwide.[1-2] Though remarkable advances in the field of modern medicine have been made, liver disorders remain as problematic as before; thus, the search for new effective measure is still under experiment.

Paracetamol belongs to a class of drugs which is able to reduce pain and body temperature. However, this is the most common cause of drug-induced liver disorders and acute liver failure in humans and experimental animals. As a result of the high rate of abuse, paracetamol overdose is the common cause of drug-induced liver failure.

The pharmacological investigations revealed that the Tamarindus indica pulp extract is antifungal, hypoglycemic, cholesterolemic, cytotoxic, anti-inflammatory, gastrointestinal and hypolipomic in its activities.[3-5] There are various components present in different parts of Tamarind indica L. such as citric acid, pipecolic acid nicotinic acid, 1-malic acid, volatile oils (geraniol, limonene),[6] pipecolic acid, lupanone, lupeol,[7] orientin, isoorientin,[8] vitamin B3, vitamin C, vitexin, isovitexin,[9] Furan derivatives, carboxylic acid,[10] Phlorotannins, apple acid, grape acid,[11] succinic acid, citric acid, tartaric acid, pectin, invert sugar,[12-13] β-amyrin, β-sitosterol, palmitic acid, oleic acid, linoleic acid, eicosanoic acid,[14] β-sinosterol, (+)-pinitol, octacosanyl ferulate and 21- oxobehenic acid.[15] The chemical structure of few components has been given below.[16]

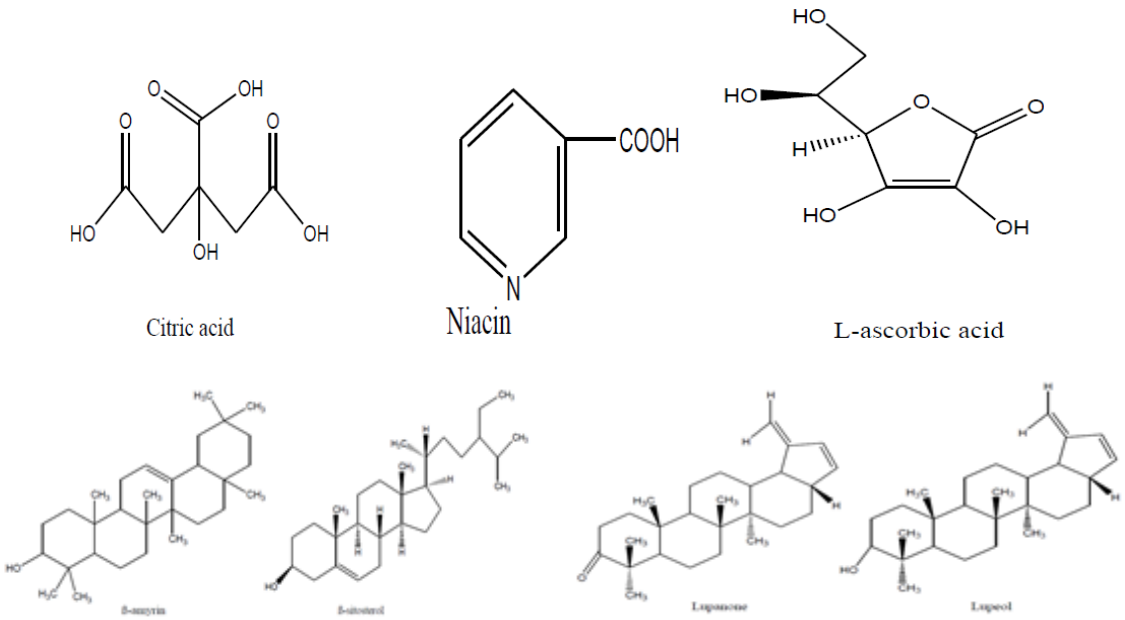

Fig 1: Chemical structure of few components of Tamarindus indica L.

It is well established fact that aqueous extract of different parts of Tamarindus indica. Linn plants (Caesalpinaeciae) has positive effect on hepatotoxicity in rats. Significant hepato-regenerative effect of aquous extract of Tamarindus indica leaves in paracetamol induced rat was observed earlier.[17] It was also suggested earlier that, leaf powder of Tamarindus indica. Linn showed good result in liver functioning by inhibiting production of reactive oxygen species (ROS) thereby maintaining redox balance.[18] It is also established that supplement of Tamarindus indica leaf powder (10g%) for 4 weeks decreased plasma glucose ,lipid levels, lipid peroxidation, increased hepatic glycogen content, hexokinase activity and cholesterol excretion with simultaneous improvement in antioxidant profile of both hepatic and renal tissue.[19] Tamarind pulp extract has been proved effective to mediate the recovery after fluoride induced reproductive toxicity in male rats.[20] The present study is an attempt to justify the hepatoprotective role of aqueous extract of Tamarindus indica leaf in paracetamol induced hepatotoxicity in male albino rats.

MATERIALS AND METHOD

Collection of plant materials

Leaves of Tamarindus indica were collected from Berhampore, Murshidabad, West Bengal, India. The flora of Murshidabad, West Bengal was used for identification and authentication of the plant. Collected materials was washed thoroughly in running water, rinsed in distilled water and dried in open air and grinded into powder.

Plant extract preparation

Leaves were shade dried and coarsely powdered .The powder was soaked separately in distilled water for overnight. Next day, mixture was centrifuged for 30 minutes in 5000 rpm. Then the supernatant fluid was filtered by filter paper and vacuum dried at 40-50°C to get a dry powder, which was dissolved in double distilled water for final use.

Animals of experiment

Adult male albino rats weighing between 100-150 gm of initial body weight were selected and kept in polypropylene cages in the animal house. They were housed under standard laboratory conditions with a 12 hour daylight cycle and had free access to food and water. They were acclimatized to laboratory condition for two weeks prior to the commencement of experiment.

Animal grouping and treatment

Twenty four animals were randomly divided into four groups with each group consisting of six rats. The four groups of rats were subjected to the following oral treatment once a day for 40 days.

Group I: Rats received 1ml of distilled water as the control group.

Group II: Rats received 250mg/kg body weight of paracetamol.

Group III: Rats received 250mg/kg body weight of paracetamol followed by 150 mg/kg body weight of Hepamerz, a hepatoprotective drug.

Group IV: Rats received 250mg/kg body weight of paracetamol followed by aqueous extract of 500mg/kg body weight of Tamarindus indica Linn. Leaf extract.

Animal sacrifice and measurement of parameters

At the end of the treatment, body weights of all the animals were taken by electronic balance. Overnight fasted animals were then anaesthetized one after another by anesthetic ether followed by cervical dislocation. Blood was taken from hepatic portal vein and was allowed to coagulate. Haemoglobin was measured in all experimental groups of animals by Ranganathan and Gunasekaran.[21] RBC was also counted in all

experimental as well as control animals by Neubauer Haemocytometer.[22] Serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) were measured of all the control and experimental animals by the supplied standard kit ("COGENT," Clinical Chemistry division of Span Diagnostics Ltd.). Serum bilirubin was estimated by Malloy and Evelyn method.[23] The total serum protein was estimated by the Lowry method with a standard curve of BSA.[24] Liver of each rat was dissected out and weights were taken with the help of electronic balance. Liver from each experimental animal was processed for histopathological examination and 5µ thick sections were taken and stained with hematoxylin and eosin,[25] for further observation.

Statistical analysis

The statistical analysis was carried out by Student's "*t*" test.[26] to generalize the results of various hematological, biochemical and histopathological parameters of experimental groups in comparison to their respective control group and P<0.05 was considered as a significant result.

RESULT

Body weight

Treatment of rat for 40 days with 250 mg/kg body weight of paracetamol caused no significant changes in body weight relative to control. There is also no significant change found in the Hepamarz,and aqueous extract of Tamarindus indica leaf (TI) treated rats, as shown in Table 1.

Table 1: Results of body weight gain % of different experimental groups including the control group. Values are mean±SEM (g%, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
22.96±0.93	22.95±1.03	22.95±0.77	22.96±0.96

P: Paracetamol, TI: Tamarindus indica

Percentage of haemoglobin (Hb)

Hb% has been reduced significantly (p<0.05) in paracetamol treated group of animals in comparison to their respective control. Significant increment in Hb% has also been noticed after administration of both the hepamerz and Tamarindus indica leaf extract along with paracetamol in comparison with only paracetamol treated group of animals, as shown in table 2.

Table 2: Results of haemoglobin % of different experimental groups including the control group. Values are mean±SEM (g/dl, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
12.20±0.95	10.60±1.01	11.90±0.79	11.80±0.89

P: Paracetamol, TI: Tamarindus indica

Total count of RBC

RBC count has also been changed in similar fashion as it has taken place in case of Hb%. Paracetamol treated animals showed significant (p<0.05) reduction than control animals. Significant increment in RBC count has also been observed in both hepamerz and Tamarindus indica treated animals group along with paracetamol in comparison with only paracetamol treated group, as shown in table 3.

Table 3: Results of RBC count of different experimental groups including the control group. Values are mean±SEM (x10^6/µl, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
6.45±1.04	5.55±1.23	5.86±0.97	5.68±1.16

P: Paracetamol, TI: Tamarindus indica

SGOT

In rats treated with paracetamol, SGOT increased significantly as compared to the control group. On the other hand, significant decrease (P<0.05) in serum SGOT was observed following the administration of Tamarindus indica leaf extract. The rate of decline in

serum enzymes level following this administration was the same as that of hepamerz, as shown in Table 4.

Table 4: Results of SGOT level of different experimental groups including the control group. Values are mean±SEM (IU/L, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
57.85±1.48	102.24±1.87	91.36±2.47	87.79±1.83

P: Paracetamol, TI: Tamarindus indica

SGPT

In rats treated with paracetamol, SGPT level increased significantly as compared to the control group. On the other hand, a significant decrease (P<0.05) in serum SGPT was observed following the administration of Tamarindus indica leaf extract. The rate of decline in serum enzymes level following administration of Tamarindus indica leaf extract was the same as that of hepamerz, as shown in Table 5.

Table 5: Results of SGPT level of different experimental groups including the control group. Values are mean±SEM (IU/L, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
69.62±2.15	131.93±2.81	93.04±1.92	90.27±2.33

P: Paracetamol, TI: Tamarindus indica

Total bilirubin

Paracetamol treated group showed significant (P<0.05) increase in bilirubin level compare to the control group. After treatment with Tamarindus indica leaf extract the level of bilirubin decreased significantly than paracetamol treated group same as hepamerz treated group along with paracetamol compare to only paracetamol treated group, as shown in table 6.

Table 6: Results of total bilirubin level of different experimental groups including the control group. Values are mean±SEM (mg/dl, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
0.45±0.021	1.06±0.049	0.52±0.038	0.65±0.031

P: Paracetamol, TI: Tamarindus indica

Total protein

In rats treated with paracetamol, total protein decreased significantly as compared to the control group. On the other hand, a significant increase (P<0.05) in total serum protein was observed following the administration of Tamarindus indica leaf extract. The rate of increase in serum enzymes level following administration of this herbal extract was the same as that of hepamerz, as shown in Table 7.

Table 7: Results of serum total protein level of different experimental groups including the control group. Values are mean±SEM (g/dl, *n*=6) followed by two-tail *t*-test.

Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
6.79±0.41	5.80±0.39	7.15±0.49	6.98±0.37

P: Paracetamol, TI: Tamarindus indica

Histopathological effect

Section of liver of paracetamol treated animals showed massive necrotic changes as compared to normal liver structure. Architectural changes along with other degenerative changes have also been observed in paracetamol treated rats. Significant recovery has been noticed after administration of Tamarindus indica leaf extract to the experimental animals along with paracetamol. This recovery is similar to the hepamerz treated animal group, as shown in table 8.

Table 8: Results of the histopathological study of liver of various microscopic observation of different experimental animal groups including the control group.

Microscopic observation	Gr-I (Control)	Gr-II (P)	Gr-III (P+Hepamerz)	Gr-IV (P+TI)
Necrosis	–	+++	+	++
Central venule dilation (CV)	normal	++	–	+
Sinusoidal dilation (SD)	normal	+++	+	+
Pyknotic cell (PK)	–	+++	–	+

P: Paracetamol, TI: Tamarindus indica

DISCUSSION

Paracetamol (acetaminophen), an over-the-counter drug, is widely used for the treatment of mild pain and pyrexia. Because of its over-the-counter status, cases of both accidental and intentional paracetamol overdose are numerous. As a result of this high rate of abuse, paracetamol has been described as the most common cause of drug induced liver failure in the United States.[27] The analgesic effect of paracetamol is probably dependent on the rate and amount of active drug reaching the CNS which is believed to cross Blood Brain Barrier. It is believed that selective inhibition of the enzyme COX-3 (cyclooxygenase-3 which is similar to COX1 and COX2) causes reduction in body temperature (fever) and pain sensation by blocking the production of prostaglandins (PGE2) as COX plays key regulatory role in thromboxane and PGs formation.[28] Toxicity from paracetamol (acetaminophen) is not from the drug itself but from its metabolites; *N*-acetyl-*p*-benzoquinone imine (N acetylimidoquinone/NAPQ1). Paracetamol biotransformation depicted below in Fig 2.[29]

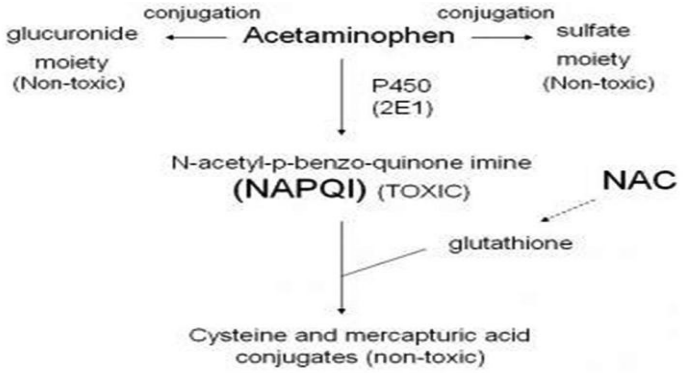

Figure 2: Acetaminophen (paracetamol) metabolism.

Hepamerz is a detoxicant hepatoprotector which is combination drug of L-ornithine and L-aspartate.[30] This drug generally protects liver from non alcoholic fatty liver disease.[31] The main and most important distinctness of this drug from other medicine for treatment of liver is in fact, it not just neutralizes toxins and arrests them to clear from the body as detoxicating agent but also actively helps in restoration of cell and natural function of liver. Hepatoprotective effect is ensured by decreasing toxic load on liver, as well as metabolic support of hepatic cells by two amino acids which are ornithine and aspartate included in this drug content.

Besides insignificant changes in body weight gain percentage in all experimental animals, the nature of paracetamol has been well reflected in present study. Paracetamol deteriorated the hematological parameters including Hb% and total RBC count in experimrntal animals in comparison with the control animals. This drug also affected the biochemical parameters like bilirubin, SGPT, SGOT and serum total protein significantly. Except these hematological and biochemical parameters paracetamol also hampered the histological properties of liver in several ways.

Tamarind leaf extract improved the level of Hb% as well as total RBC count in exposed animals compared to the reduced level of these two hematological indices in paracetamol treated animals. SGPT is thought to be related with the integrity of the mitochondria.[32] and it is also sufficient in amount in liver and functional as a marker of metabolic function.[33] Paracetamol-induced significant change in SGPT reveals metabolic impairment. Significant improvement mechanism has been observed after Hepamerz and Tamarind leaf extract administration in the present study. SGOT has integrity related to lysosomes.[34] and adrenal corticoids stimulates SGOT activity.[35] Paracetamol supplementation showed a significant increase in serum SGOT level indicating metabolic impairment. Administration of Hepamerz and Tamarind leaf extracts in the experimental groups counteracted the effect of paracetamol significantly in the present study. Serum bilirubin concentration was also

improved significantly after Tamarind leaf extract administration compared to the paracetamol induced decrease in bilirubin level. This effect is as same as hepamerz action observed in treated animals. Previous experiment was also in support declaring its (Tamarindus indica) use against jaundice.[36-37] Administration of Hepamerz and Tamarind leaf extract has restored the serum total protein level in the present study in significant way. Hence, it is obvious that, besides Hepamerz, the herbal product, Tamarind leaf extract also helps in normal functioning of the protein after restoring its level in serum.[17]

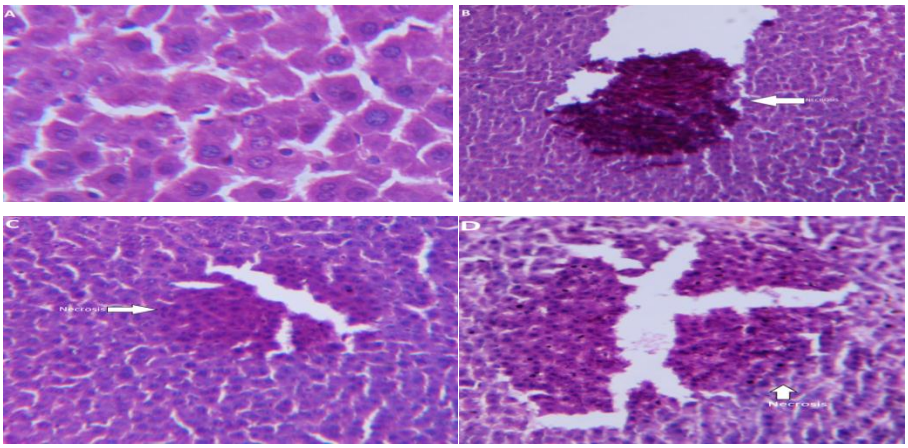

Fig. 3: Necrosis in liver cells: (A) Normal liver section of Control (B) Paracetamol induced liver section (C) Hepamerz treated liver section and (D) Tamarindus indica treated liver section.

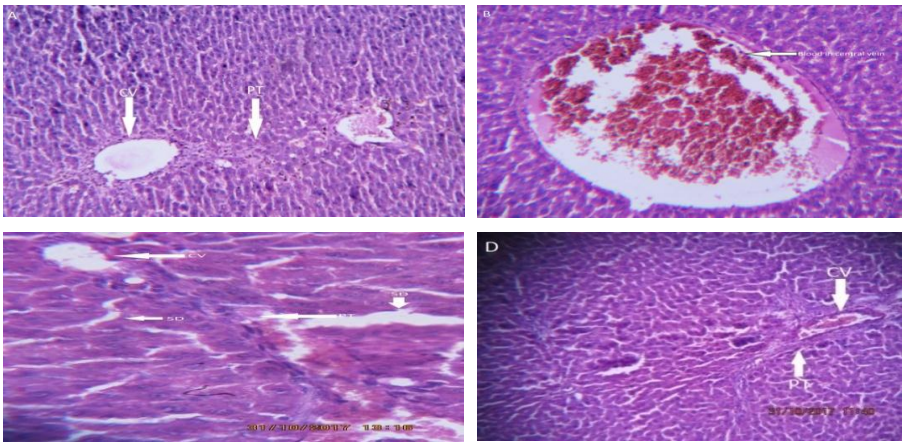

Fig. 4: Central venule dilation in liver section: (A) Normal liver section of Control group (B) Paracetamol induced liver section (C) Hepamerz treated liver section (D) Tamarindus indica treated liver section.

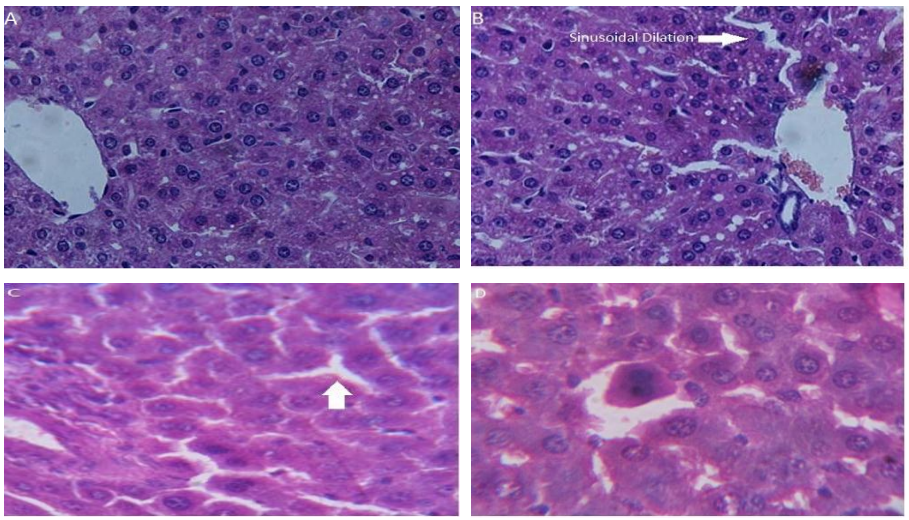

Fig. 5: Sinusoidal dilation: (A) Normal liver section of Control group (B) Paracetamol induced liver section (C) Hepamerz treated liver section (D) Tamarindus indica treated liver section.

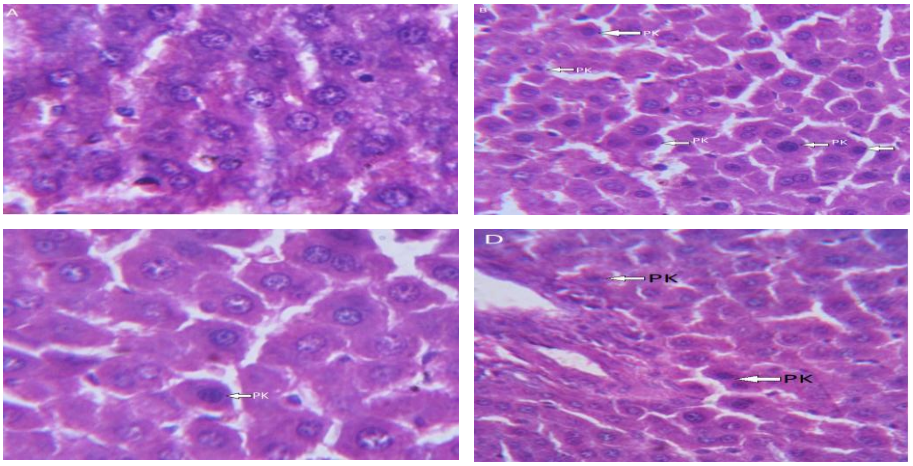

Fig. 6: Pyknotic cells in liver section: (A) Normal liver section of Control group (B) Paracetamol induced liver section (C) Hepamerz treated liver section (D) Tamarindus indica treated liver section.

As the histopathological observation is concerned, all the effects and recoveries after administration of paracetamol, hepamerz and Tamarind leaf extract have been compared with the liver section of control group of animals. The necrotic effect (Fig: 3A-3D) has been found after paracetamol administration which has been repaired by Hepamerz and Tamarind leaf extract supplementation. Central venule dilation (Fig: 4A-4D) and sinusoidal dilation (Fig: 5A-5D) were also remarkable on paracetamol application. This damage was effectively repaired by Hepamerz and Tamarind leaf extract supplementation along with paracetamol in the present study. Pyknotic cells (Fig: 6A-6D) were also found in paracetamol treated liver section which has been significantly reduced in number in Tamarind leaf extract treated group and hepamerz treated group accordingly. Assessment of liver damage especially necrosis, may usually be determined by the alteration of hepatic enzymes. Serum level of such enzymes is key indicator and decisive factors for damage of liver structure. ALT catalyses the conversion of alanine and is more specific to liver. Thus it is taken as better parameter to assess the liver damage.[38] Number of scientific reports indicated that, flavonoids, β carotin, ascorbic acid present in experimental drug have protective effect on liver due to their antioxidant properties.[39-40] From overall observation, it has been justified that, Tamarind leaf extract has hepatoprotective action as per the parameters are concerned in this present study.

CONCLUSION

Our observations have suggested that Tamarind leaf extract, has an influencial role in therapeutic properties against chemically induced acute liver disorders in male albino rats. These findings confirmed that aqueous extract of this experimental drug is useful in eliminating paracetamol induced acute liver toxicity and are approachable to Hepamerz. Although hepamerz is an expensive medicine and is not affordable to everyone in our society. However, Tamarind leaf extract is easily feasible and not expensive. Hence, in the near future, after further detailed observation, this herbal product may be used for hepatic toxicity management.

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