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# HEPATOPROTECTIVE EVALUATION OF *ZIZIPHUS MAURITIANA* BARK EXTRACT ON EXPERIMENTAL ANIMALS

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## ABSTRACT

The present investigation entitled "Hepatoprotective Evaluation of Ziziphus Mauritiana Bark Extract on Experimental Animals has been carried out and presented in the thesis. The present investigation is concerned with the widely distributed indigenous plants Ziziphus Mauritiana. From the survey of literature of this plant, it is observed that this plant is well known. In order to do a systematic study on a lead molecule discovery and optimization, we have gone in for a treatment of a set of ailments by diverse plants species from different family. Ziziphus Mauritiana belongs to the family of Rhammaceae was reported to possess anti-inflammatory, anti-covulsant, skin infection, antioxidant activity. It is a medium to large trees, 12 m in hight, bark dark brown, found in villeges forest on wastelands throughout India. The work involves extraction, GC-MS, pharmacological screening of the extracts, isolation and characterization of constituents by using modern analytical techniques. Keeping in view of the various medicinal uses of the plant mentioned in the literature pharmacological evaluation was carried out to substantiate folklore claim. Toxicity studied result revealed that both EE an aqueous extract on oral route was safe to administer at high dose of 2000mg/kg.

**Keywords:** *Ziziphus mauritiana*; Antioxidant; Anti-inflammatory; Hepatoprotective.

## INTRODUCTION

The liver's highly specialized tissue consisting of mostly hepatocytes regulates a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions.

The liver is a gland and plays a major role in metabolism with numerous functions in the human body, including regulation of glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification.

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(REF 23-28)Alcohol and its toxic metabolites can damage key liver cells (primarily hepatocytes and parenchymal cells) through the excessive generation of molecules called free radicals. Particularly important are the actions of oxygen containing free radicals known as reactive oxygen species (ROS).

*Ziziphus mauritiana* grows wild in forest and also on wastelands throughout India. In India it is commonly known as Ber and in English it is known as Indian Berry. Berconsists of 45 genera and 550 species which are widely distributed in tropical and subtropical climates in the world.

Almost all the parts of the plant have medicinal value. The methanolic extracts of ZM fruits is also reported to possess hepatoprotective activity against paracetamol and thioacetamide induced liver damage[46]. The aims and objective of this study was to Hepatoprotective evaluation of *Ziziphus mauritiana* bark extract on experimental animals.

## MATERIALS AND METHODS

### Plant preparation

This includes Plant parts of *Ziziphus mauritiana* was collected from Bagawas local area of Jaipur District. Authentification done by Department of Botany University of Rajasthan and registration number given is as **RUBL 211604.** Ash is the remaining following ignition of medicinal plant material. The material was evenly spread and ignited by gradually increasing temp to 500-600˚C, until it is white, indicating absence of carbon. It was then cooled in desicator and weighed content of total ash in mg/gm of air dried material was calculated.

### Experimental Design

Wistar albino rats either sex weighing between 180 g and 200 g will be selected for the hepatoprotective activity. The animals will be stabilized for 1 week. They will maintain in standard conditions at room temperature, 60 ± 5% relative humidity and 12 hrs light dark cycle. For assessment of hepatoprotective activity Standard drug Silymarin 200 mg/kg p.o.and both test drug, ZMBE 200 mg/kg and 400 mg/kg oral were administered by oral route for 14 days for the evaluation of hepatotoxicity activity in experimental animals. All the animals were divided into five groups of five animals of approximately same weight range (180-200 g) and same and same age (12-13 weeks) in each group.

Group I - Positive Control ( Paracetamol and 2% v/v Tween 80 for 10 days).Group II- Negative Control (2% v/v Tween 80 for 10 days). Group III - Standard drug ( Paracetamol 2g/kg and Silymarin 200 mg/kg) .Group IV - Test group-I ( Paracetamol and ZMBE 200 mg/kg). Group V- Test group-II (Paracetamol 2g/kg and ZMBE 400 mg/kg).

### Biochemical Estimation

At the end of the study (On 14$^{th}$ day) period, rats were anaesthesized by using anesthetic ether, and then blood samples will be collected for different biochemical analysis. The rats were sacrificed by the cervical dislocation.

### Histological Estimation

Small fragments of the liver was washed in ice-cold saline, fixed in 10% formalin solution for 24 h, dehydrated with ethanol (50%), embedded in praffin and the fixative was removed by washing through running tap water over night. The sections were stained with eosin- haemotoxylin dye for photo microscopic observation of necrosis, steatosis and fatty change of hepatic cells. After dehydration and cleaning the sections were mounted and observed under lightmicroscope for details.

## RESULTS

### Extraction

After extraction dried mass were collected and % yield was found to be-

***Ziziphus* Bark % Yield** = 9.42%

***Ziziphus Mauritina* Bark:**

**ASH VALUES:** Ash values of *ziziphus Mauritiana* bark was found to be as Total ash 10.8% w/w,acid Insoluble ash 4.1 % w/w and Water soluble ash was found to be 4.8 % w/w.

**Table 1: Ash values of *Ziziphus Mauritiana* bark**

| Type of Ash | | Value in % (w/w) |
|---|---|---|
| 1. | Total ash | 10.8 |
| 2. | Acid insoluble ash | 4.1 |
| 3. | Water soluble ash | 4.8 |

## Loss on Drying

Loss on drying of ziziphus maurutiana bark was found to be 8.79 % w/w.

**Table 2: Value of loss on drying of *ziziphus mauritiana* bark:**

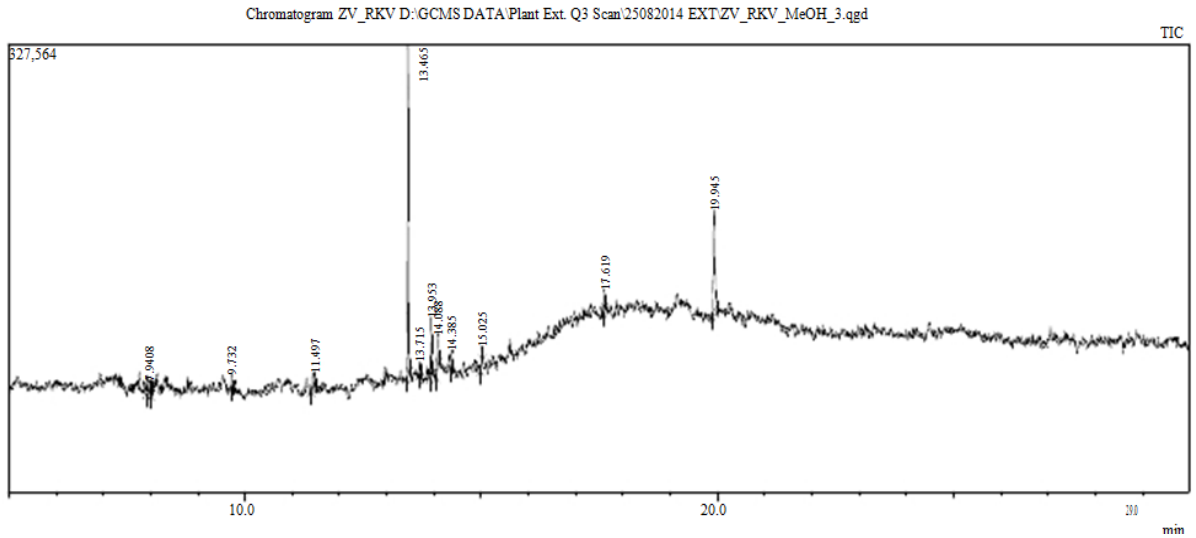
| S.No. | Plant | Weight of disc + drug before drying (A) | Weight of disc + weight of drug after drying(B) | (A-B) | Loss on drying in % (A-B) w/w |
|---|---|---|---|---|---|
| 1. | Ziziphus mauritiana | 69.6147 | 68.7351 | 0.8796 | 8.79 |

## GC-MS data Identification

Data were evaluated and matched with the inbuilt NIST library. All the peaks were identified with their comparative area and area % MS library identified the compound on the basis of mass.

## GC-MS of Ziziphus Mauritiana Bark Extract

The major constituent of *Ziziphus Mauritiana* Bark was found to be Dibutyl phthalate with highest peak area 306118 and highest area % 39.95




.**Figure1 :** *Ziziphus Mauritiana* Bark Chromatogram:

**Table 3:** Retention time and Area Percentage of *Ziziphus Mauritiana* Bark

| Peak No. | R.Time | Area | Area % | Name |
|---|---|---|---|---|
| 1. | 7.940 | 38240 | 4.99 | |
| 2. | 8.030 | 13108 | 1.71 | |
| 3. | 9.732 | 14710 | 1.92 | 1-Undecanol |
| 4. | 11.497 | 41969 | 5.48 | Tridecane |
| 5. | 13.465 | 306118 | 39.95 | Dibutyl phthalate |
| 6. | 13.715 | 11047 | 1.44 | Undecane |
| 7. | 13.953 | 57229 | 7.47 | Benzenepropanoic acid,3,5-bis(1,1-Dimethylethyl)-4-hydroxy-,methylester |
| 8. | 14.088 | 36548 | 4.77 | n-Hexadecanoic acid |
| 9. | 14.385 | 17680 | 2.31 | Eicosane |
| 10 | 15.025 | 14217 | 1.86 | Octacosane |
| 11. | 17.619 | 26586 | 3.47 | Bis(2-ethylhexyl)phthalate |
| 12. | 19.945 | 188713 | 24.63 | Squalene |
| | | 766165 | 100.00 | |

## Hepatoprotective activity

Rats treated with Paracetamol (2 g/kg, p.o.) developed significant hepatic damage as observed from levels of the hepatospecific enzymes as well as severe alterations of different liver parameters. Activities of SGOT, SGPT and ALP were significantly increased in paracetamol treated animals (Group 2). Serum bilirubin level was also significantly enhanced upon paracetamol treatment. The levels of total proteins and albumins were decreased in rats treated with paracetamol when compared with control rats (Group 1). Histopathological changes confirmed the hepatic damage when compared to the normal animals liver tissue (fig 2a). Paracetamol treatment showed extensive centriolobular necrosis. There was a mild chronic inflammatory cell infiltrate in the portal tracts.(fig2b).

Oral administration of *ziziphus mauritiana* bark ethanolic extract,test group 1 (200mg/kg,dose) significantly ($P < 0.001$) decreased the levels of SGOT, 71.23 ± 6.43IU/L), SGPT(63.01 ± 3.33IU/L), ALP (164.68 ± 14.65 IU/L) and Bilirubin (2.9 ± 0.25 mg/dl) when compared to group II 133.66 ± 11.03, 104.42 ± 10.09, 453.96 ± 18.98 IU/L and 3.52 ± 064 mg/dl respectively. In fact the elevated level of ALP from 453.96 ± 18.98 to 164.68 ± 14.65 IU/L by EE and standard drug silymarin (215.06 ± 18.44 IU/L). It reveals that EE has got more power to reduce the elevated level of ALP than the standard drug silymarin. The increased bilirubin value (3.52 ± 0.64 mg/dl) was reduced to ( 2.9 ± 0.25 mg/dl) by oral administration of EE, which is below the control value (2.95 ± 0.39 mg/dl). The total protein and albumin levels were increased (10.99 ± 0.29 g/dl ,7.71 ± 0.14 g/dl ) respectively; in EE treated animals when compared to Paracetamol treated rats. The activity exhibited by standard drug silymarin was much more higher than the EE treated rats in case of total protein and albumin. The increase in total protein and albumin level in EE treated provides for the protective effect of EE on live

**Table 4:** Effect of Ziziphus Mauritiana Bark Extract on serum biochemical parameters in rats with paracetamol-induced liver damage

| Groups | Treatment | Dose | SGOT IU/L | SGPT IU/L | ALP IU/L | Bilirubin Mg/dl | Total protein Gm/dl | Albumin Gm/dl | Globulin Gm/dl | A/G ratio |
|---|---|---|---|---|---|---|---|---|---|---|
| **Group-I** | Negative Control | 2% v/v | 49.81± 1.31 | 40.50± 2.13 | 111.28± 11.59 | 2.95± 0.39 | 10.47± 0.10 | 7.66± 0.07 | 2.81± 0.04 | 2.72± 0.09 |
| **Group-II** | Positive Control | Paracetamol and 2% v/v | 133.66± 1.03 | 102.42 ± 10.09 | 453.96± 18.98 | 3.52± 0.64 | 10.01± 0.44 | 7.0± 0.13 | 3.01± 0.08 | 2.32± 0.14 |
| **Group-III** | Standard drug | Paracetamol 2g/kg and Silymarin 200 mg/kg | 57.65± 1.95a | 51.40± 5.38b | 215.06± 18.44 | 2.68± 0.16a | 11.35± 0.41 | 7.72± 0.09 | 3.36± 0.15 | 2.13± 0.11 |
| **Group-IV** | Test group-I | Paracetamol and ZMBE 200 mg/kg | 71.23± 6.43a | 63.01± 3.33a | 164.68± 14.65a | 2.90± 0.25 | 10.99± 0.29 | 7.71± 0.14 | 3.28± 0.12 | 2.35± 0.09 |
| **Group-V** | Test group-II | Paracetamol 2g/kg and ZMBE 400 mg/kg | 106.55± 4.45a | 84.38± 8.00 | 293.62± 9.93b | 2.90± 019 | 10.18± 0.77 | 7.60± 0.11 | 2.58± 0.17 | 2.94± 0.14 |

+Values are given as mean ± S.E.M for five rats in each group.
aP < 0.001; bP < compared to control.

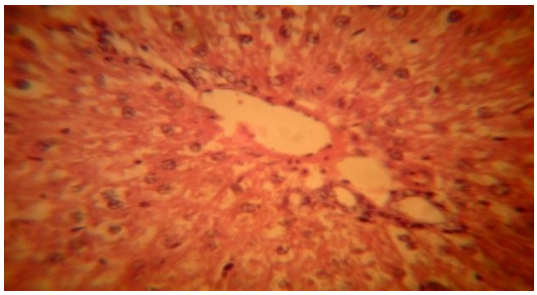


Fig 2a: Liver section of a normal rat showing normal hepatic cell architecture.

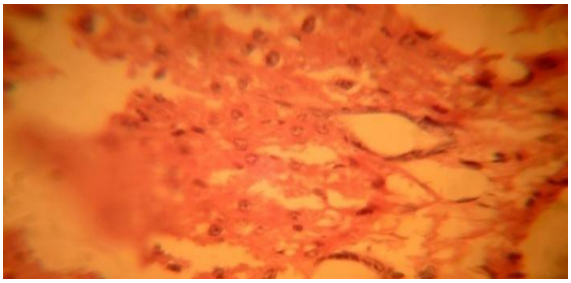


Fig 2b: Liver section of rat with paracetamol induces hepatotoxicity showing severe

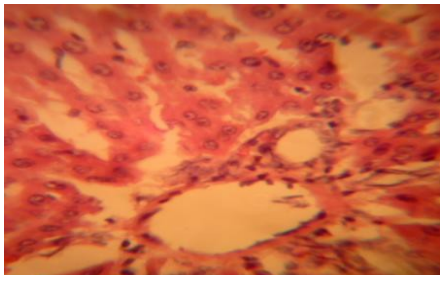


Fig 2c: Liver section of rat induce with paracetamol + standard drug silymarin showing almost normal hepatic cell architecture.

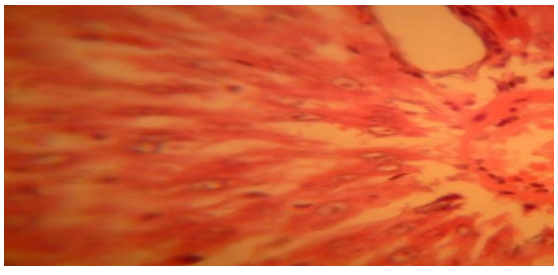


Fig 2d: Liver section of a rat induce with paracetamol + EE (test group 1) treated group showing almost normal hepatic cell architecture.

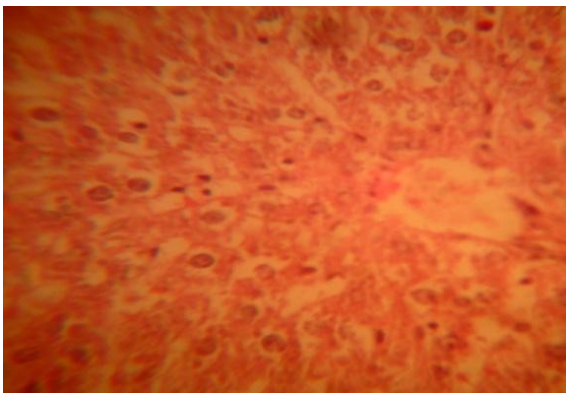


Fig 2 e Liver section of rat induce with paracetamol + EE(test group 2) treated group showing mild focal necrosis.

The test group-2(EE) reduced the elevated marker enzyme levels only to certain extent and bilirubin level has reduced to the normal value. Test group-2(EE) has increased the total protein content and albumin level remarkably. Both EE and test group-2(EE) were compared with the standard herbal drug silymarin with a dose of 200mg/kg, body weight, p.o. silymarin has provided a better inhibition, of the elevated level of SGOT, SGPT,ALP and serum bilirubin and also increased the total protein content and albumin level. Overall the activity exhibited by EE was comparable with that of the standard drug silymarin.

The findings described above were supported by the histopathological study where an oral administration of either standard drug silymarin (fig 2c) or EE improved the histopathological picture of the liver. The histopathological pattern of the livers of the rats treated with the EE showed a normal lobular pattern with a mild degree of fatty change,necrosis and inflammation (fig 2d).where as silymarin treated group shown a normal hepatic cell architecture(fig 2c)

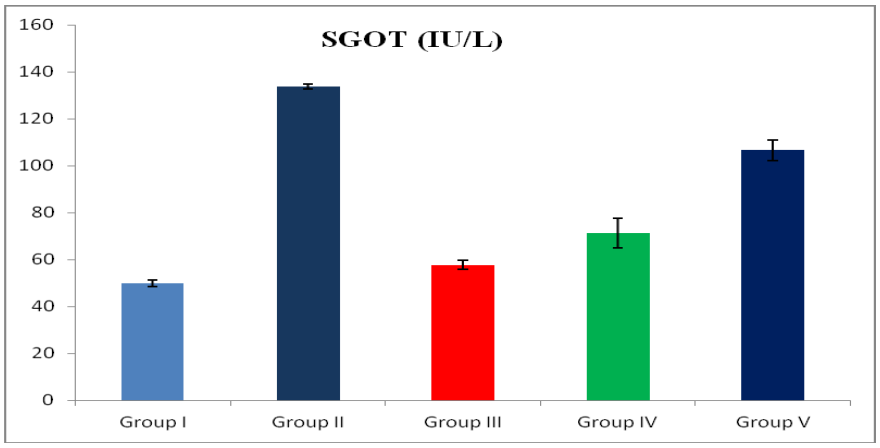



Fig 3a: SGOT value v/s different treatment groups.

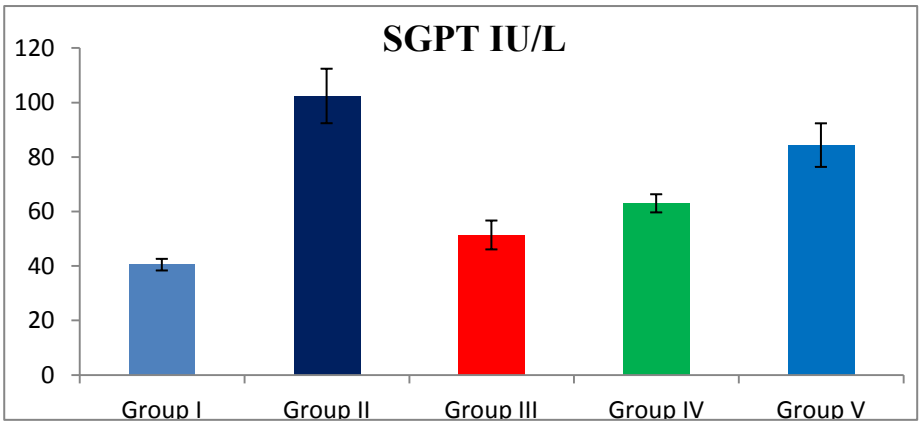



Fig 3b: SGPT value v/s different treatment groups

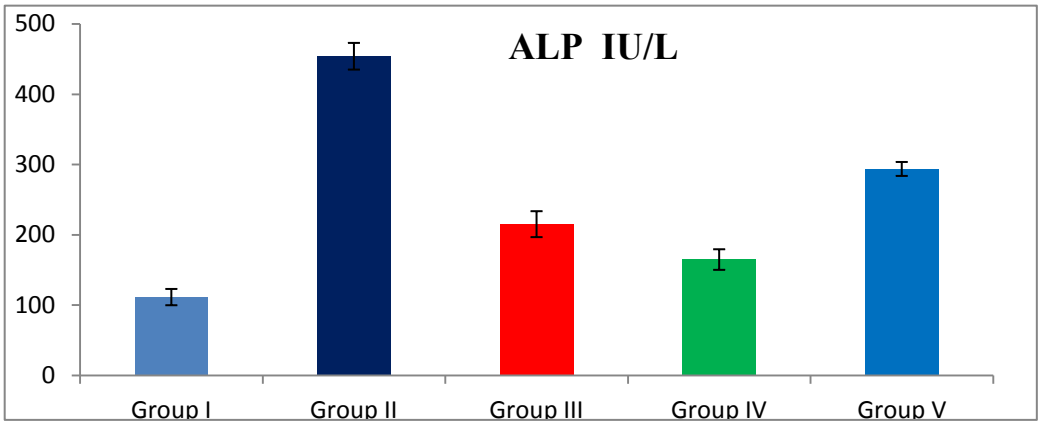



Fig 3C: ALP value v/s different treatment groups

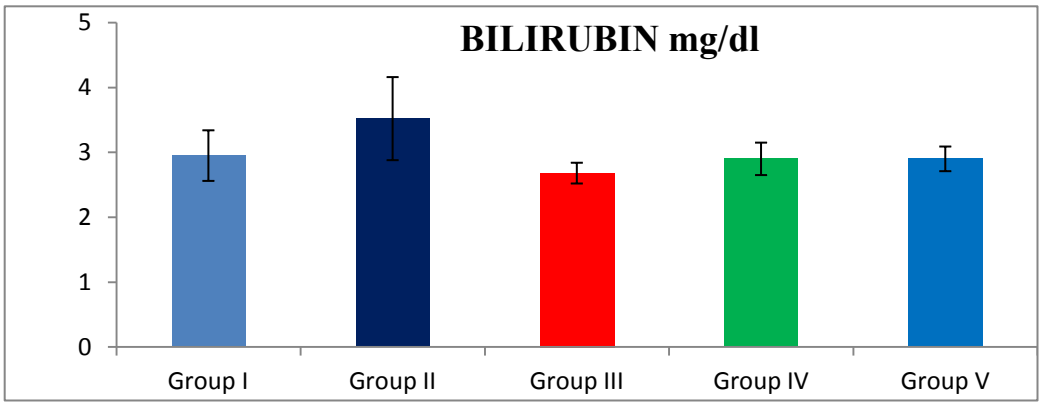



Fig 3D: BILIRUBIN value v/s different treatment groups

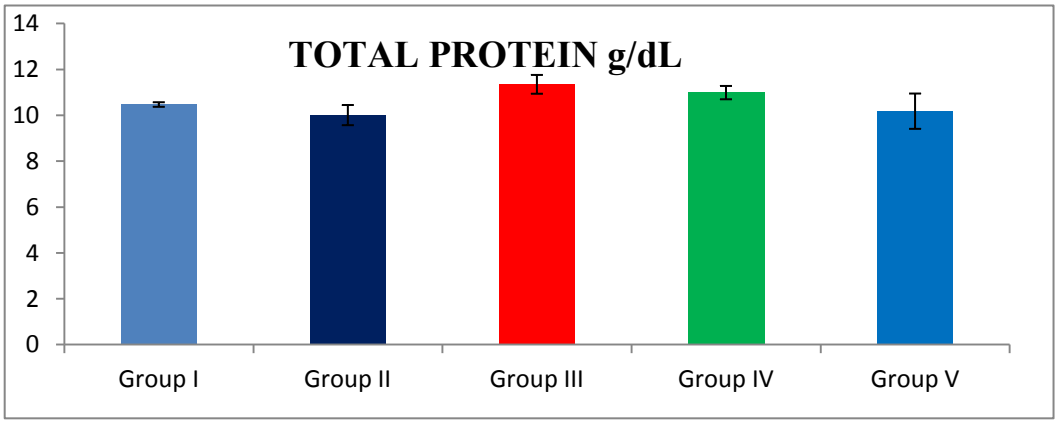



Fig 3E: Total protein value v/s different treatment groups

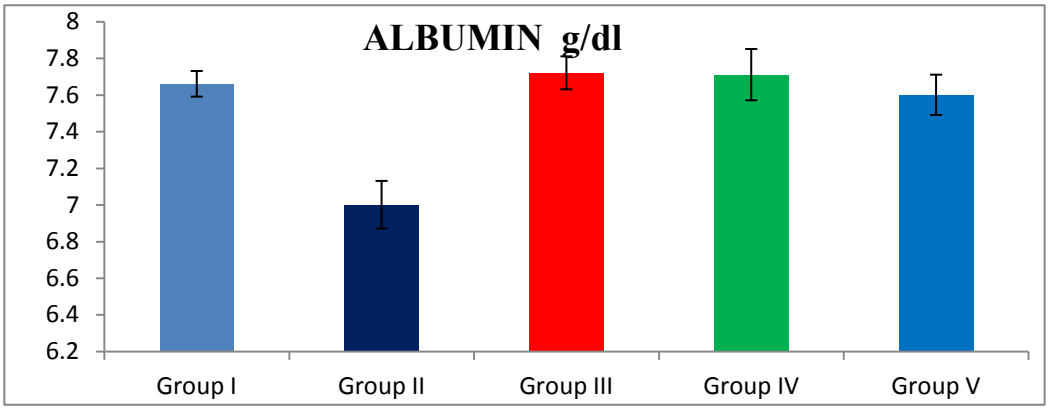



Fig 3F: Albumin value v/s different treatment groups

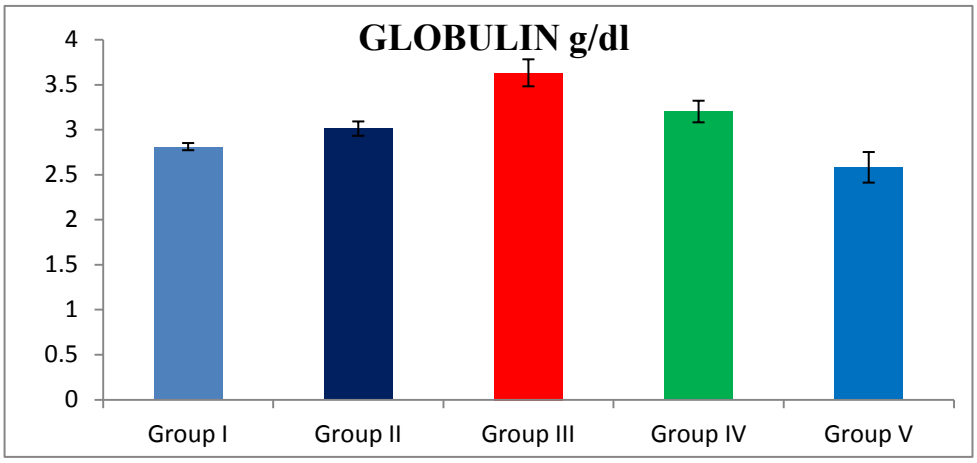



Fig 3G: Globulin value v/s different treatment groups

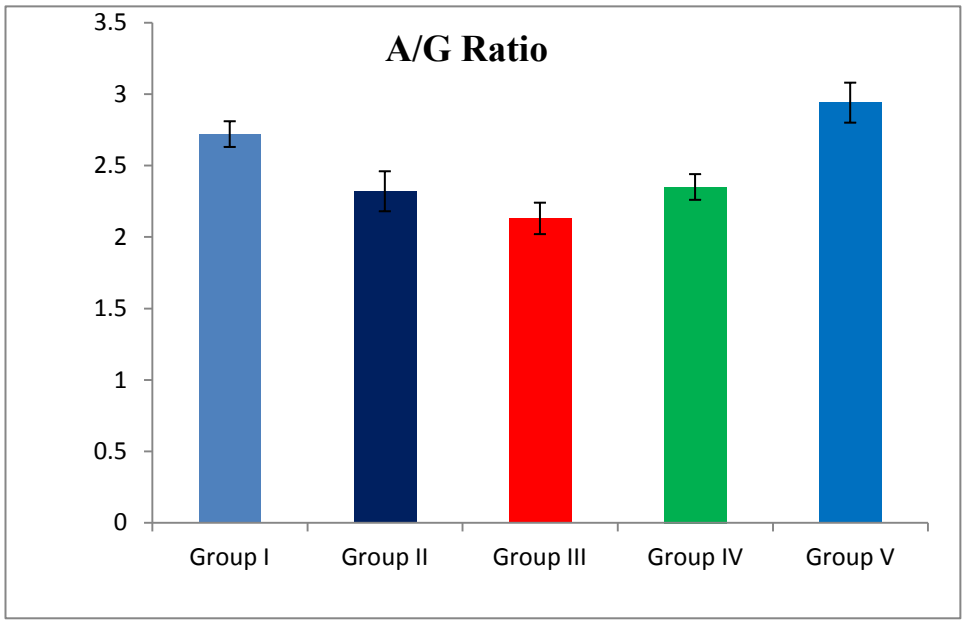



Fig 3H: A/G ratio value v/s different treatment groups

## DISCUSSION

Ziziphus Mauritiana is a widely traditionally used and potent medicinal plant amongst all the thousands of medicinal plants. The pharmacological activities reported in the present review confirm that the therapeutic value of Ziziphus Mauritiana is much more. It is an important source of compounds with theirs chemical structures as well as pharmacological properties. The presence of phytochemical constituents and pharmacological activities proved that the plant has a leading capacity for the development of new good efficacy drugs in future. Thus, a detailed and systematic medicinal study is required for identification, cataloguing and documentation of plants, which may provide a meaningful way for the promotion of the traditional knowledge of the herbal medicinal plants. Damage to the structural integrity of liver is reflected by an increase in the level of serum transaminases because these are cytoplasmic in location and are released into circulation after cellular damage. In this study a similar rise in the level of SGOT, SGPT, and ALP in paracetamol treated rats were observed. The oral administration of EE of barks of *Ziziphus mauritiana* in the present study seems to offer protection to the structural integrity of hepatocellular membrane. This in evident from the significant reduction in serum SGOT, SGPT and ALP levels, and thus offers protection against paracetamol-induced liver toxicity in rats. Decreased bilirubin level observed after the administration of EE could be a further evidence for the protection against paracetamol-induced

hepatotoxicity.Toxic dose of paracetamol, a widely used over the counter analgesic and antipyretic, produces hepatic necrosis when ingested in very large doses. It is metabolized in the liver primarily to glucuronide and sulphate conjugates. Paracetamol toxicity is due to the formation of toxic metabolites when a part of it is metabolized by cytochrome $P_{450.}$ Induction of cytochrome $P_{450}$ or depletion of hepatic glutathione is a prerequisite for paracetamol-induced hepatotoxicity. Therefore the anti-hepatotoxic activity of the drug may be due to, inhibition of cytochrome $P_{450,}$ promotion of glucuronidation, stimulation of hepatic regeneration, activation of the function of the reticuloendothelial systems or inhibition of protein biosynthesis.

## CONCLUSION

Thus this study confirms the protective action of the EE *Ziziphus mauritiana* Bark against experimentally induced liver damage in rats, which was comparable to that of a standard hepatoprotective drug silymarin. SGOT, SGPT, ALP and serum bilirubin are the most sensitive test employed in the diagnosis of hepatic diseases. The elevated levels of these parameters were reduced by the treatment with *Ziziphus mauritiana* Bark extract. This hepatoprotective activity may be due to the presence of active principle Dibutyl phthalate that was reported to possess heptoprotectant activity.

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*21* "If a person stops consuming the vitamin, the body's stores of this vitamin usually take about 3 to 5 years to exhaust"

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