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Original Article

Hepatoprotective Effect of Whole Plant Powder *Leucas aspera* Spreng

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ABSTRACT

Background: In recent years plant origin drugs have gained more popularity as hepatoprotective agents owing to their safety, low-cost and efficacy and thus for safe hepatoprotective agents will be having an ever-increasing demand. **Materials and Methods:** Hepatoprotective activity of *Leucas aspera* Spreng *(Dronapushpi panchanga)* powder was conducted using albino Wistar rats in hepatotoxicity model triggered by paracetamol. The test drugs and reference standard were given through oral route and toxicant was given through intramuscular route. The degree of protection was determined on the basis of reversal or attenuation of toxicant induced modification to the biochemical parameters and changes in histopathology. **Results:** Serum transaminase, total bilirubin, ALP, and other test results are significantly altered when paracetamol is administered. Hepatoprotection ranges from fair to good to be demonstrated by the reversal of key biochemical variables' values, such as total bilirubin and SGPT, in both the test and reference compounds. Liver sections from the reference compound and test drug groups that were pre-treated and that received paracetamol injections showed mild to moderate disturbance, relatively less degenerative changes and necrosis than the toxicant control group, and nearly normal cytoarchitecture, indicating very good hepatoprotection, according to a histopathological study. **Conclusion:** Principal biochemical indicators such as total bilirubin and SGPT are reversed in both reference and test medicines, indicating moderate to good hepatoprotection. Similar findings are also observed in histopathological analysis.

Keywords: Biochemical Parameters, *Dronapushpi*, Hepatoprotective, Histopathological Investigation, Paracetamol.

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INTRODUCTION

Leucas aspera is seen as weed throughout India from Himalayan region to Sri Lanka and is commonly known as *Thumbai.* Traditionally the plant is used for many ailments[1,2] and we come across it's usage for *Kamala* (jaundice) condition in various *Nighantus* (lexicon) like *Kaiyadeva, Madanapala, Cakradutta* and *Madhava dravyaguna.*[3-7]

The Liver is the vital organ plays a supreme role in supporting all the vital functions of our body like metabolism, excretion of metabolites, even regulates the homeostasis of the body and also helps to combat against disease, has role in energy production and detoxifies the extrinsic substance and also eliminates them. Because of this, the liver will be vulnerable to different factors which injure it and making it most constantly affected organ.[8]

Chemicals and drugs causing hepatotoxicity is the most common kind of iatrogenic afflictions being the most prevalent serious health problem having only symptomatic treatment through some immunosuppressive and corticosteroid agents.[9]

Liver disorders are the cause for about 20000 deaths every year. The herbal drugs have shown promising results in maintenance of normal functions of the liver. About 80% of populations in the world are dependent on herbal origin traditional medicine.[10]

In recent years plant origin drugs have gained more popularity as hepatoprotective agents owing to their safety, low-cost and efficacy and thus for safe hepatoprotective agents will be having an ever-increasing demand.[11]

The hepatoprotective activity of three different doses of *Dronapushpi panchanga* (*Leucas aspera* Spreng) powder-Therapeutic (TED), half-dose (TED×1/2), and double-dose (TED×2)-was tested in this study against hepatic injury induced by paracetamol. The results were compared to standard hepatoprotective agents for rats intoxicated with paracetamol, silymarin.

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MATERIALS AND METHODS

Collection and preparation of test drug

The test medication *Dronapushpi panchanga* was collected from the natural environment of the Hassan district of Karnataka and a sample specimen of the plant (No. 230.13032101) was deposited at the SDM centre for Research in Ayurveda and Allied Science, Udupi.[12] The standard procedure was followed at SDMCAH, Hassan, Karnatak's *Rasashastra* and *Bhaishajya Kalpana* Department to prepare the *Churna* (powder).[13] Before powdering the plant material was shade dried.

Standard hepatoprotective drug

Silymarin is the reference standard medication used to evaluate hepatoprotective properties. Silybon-70 mg, Batch no- SIAD0033, Mfd-June 2012, Exp-May 2015, manufactured by Micro Labs Limited, HB-211, village Katha, P.O Boddi, tehsil, Nalagarh Dist, Solan-173205 (H.P.).

Toxicants

The toxicant utilized to cause hepatic damage in the relevant procedure is as follows: Paracetamol-Injection. (Brand name: FEVASTIN.), Batch No. TAB 2029, MFG.-October 2012, EXP.-September 2016. Manufactured in India by Tablets (India) Limited, 179, T.H Road, Chennai.

Chemicals

All of the chemicals and reagents utilized in the experimental study were obtained from conventional and reputable companies and are of analytical grade, which is often used in laboratories. Biochemical and enzymatic kits for biochemical examinations were acquired from ERBA Diagnostic Mannheim and Transasia Biochemicals Ltd., Daman.

Animals

Wistar rats were used for the study. The animals used for the current study were obtained from the S.D.M. Centre for Research in Ayurveda and Allied Sciences, Udupi, Karnataka, animal house. With the approval of the Institutional Animal Ethics Committee (IAEC) and as per SDMCAU, IAEC, 2012-13-HSN 06. The animals were allowed access to the regular day-night cycles and ideal humidity and temperature were maintained. Pranav Agro industries, Pune's, Amrut brand rat pellets were used to feed rats and tap water were given *ad libitum*.

Evaluation of hepatoprotective activity

Groups were formed from thirty-six albinos of either sex, weighing between 160 and 270 g. The female and male rats were isolated to check the chances of pregnancy. The chosen rats were split up into six groups of six rats each and each group received treatment for nine days. In the current study, a hepatotoxicity model produced by paracetamol was used to test the hepatoprotective properties of *Leucas aspera* Spreng (*Dronapushpi panchanga*) powder in rats. By suspending in 0.5% gum Acacia, the test drugs and reference standard were given through oral route between 8 to 10 am utilizing rat feeding tube attached to the syringe and toxicant was given through intramuscular route using insulin syringe 1 hr after the drug administration. By calculating the therapeutic dosage of human to rat dosage based on surface area ratio, the dosage of the medicines, vehicle, and toxicants were assessed using the Pages and Barnes 1969 table.[14]

In Water control group rats received tap the water for 9 days. Paracetamol control (disease control) group received distilled water and 0.5% gum Acacia for first 7 days rats and on the 7th day toxicant paracetamol 1 g/kg body weight was administered to induce hepatic injury via intramuscular route.[15] Standard drug treated rats group received Silymarin 50 mg/ kg for first 7 days and on the 7th day toxicant paracetamol 1g/kg body weight was given to induce hepatic injury via intramuscular route. TED, TED×1/2 and TED×2 rats group received 1.08 g/kg body weight, 0.54 g/kg body weight and 2.16 g/kg body weight respectively for first 7 days and on the 7th day toxicant paracetamol 1 g/kg body weight was given to induce hepatic injury via intramuscular route. The blood collected from orbital plexuses in tubes was sent for biochemical analysis following the 48 hr of paracetamol intoxication through IM route. By cervical dislocation the rats were sacrificed, the liver was carefully excised out cleansed to separate extraneous tissues, blotted to take out the blood stain and noted the weight. For further histopathological procedure a part of liver was conserved in 10% formalin. The liver sections from different groups were examined microscopically for histopathological changes. The microscopic sections from paracetamol given test drugs and reference standard pre-treated groups were compared with paracetamol control group sections.

Estimation of Serum Biochemical Parameters

By carotid bleeding the blood samples were collected in to sterilized centrifuge tubes and coagulated for 30 min at 37°C. At 2500 rpm for 10 min the clear serum was separated. To assess the liver function, bio-chemical investigations like Serum transaminase, ALP, direct bilirubin, serum cholesterol, total protein, serum triglycerides, serum urea, blood sugar and serum creatinine were carried out.[16]

Histopathological examination of liver tissue

In 10% buffered neutral formalin, the materials were fixed for 48 hr and then for bouin solution, paraffin sections were taken at 5 µm in thickness were obtained, later processed in alcohol-xylene series and followed by staining with alum haematoxylin and eosin. The slides were examined for histopathological alterations using a binocular research Carl Zeiss microscope (Germany).[17]

Statistical analysis

The data were presented as Mean±SEM. Using one-way Analysis of Variance (ANOVA) followed by post hoc Dunnett's "*t*" test, for determining the degree of significance of the observed effects. Statistical significance was defined as a '*p*' value of less than 0.05. The analysis was done employing Graph Pad version 3.

RESULTS

Effect of test drug on changes in body weight

A little rise in body weight was observed in the control group. When compared to the PC group, the TED dose test medication group showed a reversal of the weight loss produced by paracetamol intoxication. The reference standard administered group and the remaining two test medicines did not exhibit reversal (Table 1).

Effect of test drug on percentage changes in liver weight

When compared to a normal control, paracetamol intoxication slightly increased liver weight, but the difference was not statistically significant. Comparing the pre-treated reference standard paracetamol-injected rats to the PC group, a little but non-significant rise was seen. Comparing the test drug administered groups to the PC group; a similar marginal to moderate non-significant rise was seen (Table 2).

Effect of test drug on Serum Biochemical Parameters

When compared to the normal control group, paracetamol intoxication led to a statistically significant increase in SGOT activity that was more than five times higher. The toxicant-induced elevation was dramatically reduced in the reference standard group. The decrease was moderate and minor in the TED, half-TED, and TEDx2 dosage groups, respectively. Both observed results were statistically non-significant (Table 3). When compared to the normal control group, paracetamol intoxication resulted in a five-fold statistically highly significant increase in SGPT activity. This toxicant elevation was significantly reduced in the reference standard and all three-test drug administered groups, and the effect was found to be dose dependent (Table 3). Statistically insignificant yet moderate depression in ALPase activity was seen on administration of paracetamol. When comparing the administered test and reference standard groups to the toxicant control group, an apparent increase in ALPase activity was observed in both groups; however, the statistical significance was only observed in the reference standard group (Table 3).

Serum total protein decreased in a mild and statistically non-significant way in response to paracetamol intoxication. The reference standard demonstrated a marginally statistically non-significant rise in contrast to the toxicant control, while the TEDx2 dosage group demonstrated a marginally statistically non-significant drop. Due to variance in the collected data, a considerable rise was noticed in half of the TED group; nevertheless, this observation was found to be statistically non-significant (Table 4). When compared to the normal control group, the paracetamol-intoxicated group showed a notably elevated serum urea level. This induced rise was found to be significantly reversed in the reference standard and TED dosage test medication, while only a moderate reversal was observed in the other two groups. Because of data variation, the mentioned changes were found to be statistically non-significant (Table 3). When compared to the normal control group, paracetamol intoxication led to a striking nearly two-fold increase in serum creatinine levels. The reference standard and TED dose test medication administered groups were shown to significantly reverse this toxicant-induced increase; however, changes were statistically non-significant because of data variation. In compared to the toxicant control group, a marginal and statistically non-significant rise was seen in the half TED and TEDx2 dosage treated group (Table 3). When compared to the normal control group, the administration of paracetamol led to a statistically significant increase in the serum total cholesterol level. There was a slight reversal of this rise that was statistically non-significant for both the reference standard and TEDx2 dose test medication groups. Comparing the half TED group to the toxicant control, a marginal and statistically non-significant rise was observed and a marginal decrease in the TED group (Table 4). Serum triglyceride

Table 1: Impact of experimental medication on alterations in body weight in rats given paracetamol.

Groups	Prior to therapy, body weight(g) Mean±SEM	Following therapy, body weight (g) Mean±SEM	% change
W.C.	186.66±7.03	190.16±8.05	-
P.C.	232.33±16.50	222.83±16.56	4.08 NQSD
RS+PC	200±13.90	197.83±15.96	1.08 NSD
TED+PC	236.16±13.03	240.33±14.0	1.76 NSI
TED×1/2+PC	250.4±7.11	237.8±5.90	5.03 SD
TED×2+PC	263.83±5.34	253.33±7.09	3.97 SD

Data: Mean±SEM (*n*= 6).

levels appeared to rise by 54.49% due to paracetamol intoxication compared to the normal control group. However, there was no statistically significant elevation. The administered groups of the TEDx2 dose test medication and reference standard revealed a modest but statistically non-significant decrease as compared to the toxicant control group. There were considerable and marginal statistically non-significant declines in the TED and half-TED groups (Table 4). When compared to the normal control group, there was an apparent 19.64 percent drop in serum sugar levels due to paracetamol intoxication. It was determined that this decline was not statistically significant. An increase that was modest to moderate and statistically not significant was noted in the reference standard TED and TEDx2 dose provided groups. Despite a 20.53% drop in the half-TED dosage group, it was also determined that this result was statistically not-significant (Table 3). When compared to rats in the normal control group, the paracetamol administration caused a greater than two-fold increase in the blood total bilirubin concentration. Both the reference and test drug treated groups showed a significant decrease in this toxicant-induced increase. A startling maximum decline of 68.61% was noted in the group that received half of the TED dosage test medication. The reduction was 50.98% in the group that received the TED dose and 45.09% in the group that received the TEDx2 dose (Table 4). The direct bilirubin level did not alter after paracetamol was administered. The administration of a test medication at TED dose standard reference also produced no results. Table 4 indicates that the slight rise in TEDx2 dose given group and the moderate increase in half TED dose given group were not statistically significant.

Effect of test drug on liver histopathological examinations:

Microscopic analysis of the animals in the control group revealed normal cytoarchitecture in the sections (Figure 1a). In comparison to liver slices from a normal control group, the liver cytoarchitecture of the group that took paracetamol was shown to be considerably disrupted. A number of abnormalities were noted, such as necrosis, leukocyte infiltration, balloon cell formation, micro and macro fatty alterations, sinusoidal dilatation, and restoration regions (Figure 1b). Liver sections from the group receiving paracetamol injection and the reference standard (Silymarin) pre-treated showed modest to moderate disruption and nearly normal cytoarchitecture, indicating excellent hepatoprotection (Figure 1c). The degenerative alterations were minor in majority of the parts scanned in the test drug half-TED dosage administered group. There were only a few areas of substantial fatty changes, mild cell infiltration, and necrosis (Figure 1d). The degenerative alterations in the test drug TED dosage managed group were classified as modest to severe (Figure 1e). Comparatively speaking, the test drug TEDx2 dosage administered group experienced fewer necrosis and degenerative alterations than the toxicant control group. This group showed

Table 2: Impact of experimental medication on liver weight in rats given paracetamol.

Groups	Comparative weight of the liver (g/100g body weight) Mean±SEM	% Change
W.C.	7.27±0.44	-
P.C.	7.44±0.32	2.33 NSI #
RS + PC	7.49±0.34	0.672 NSI @
TED+ PC	8.41±0.37	13.03 NSI @
TED×1/2+PC	7.61±0.20	2.28 NSI @
TED×2+PC	7.99±0.23	7.39 NSI @

Data: Mean±SEM (*n*=6); @ compared with positive control, # compared with normal control.

Table 3: Impact of experimental medication on serum transaminase, alkaline phosphatase, sugar, urea, creatinin activities: in paracetamol treated rats.

Groups	SGOT (IU/L) Mean±SEM	SGPT (IU/L) Mean±SEM	ALP (IU/dL) Mean±SEM	Serum Sugar (mg/dL) Mean±SEM
W.C.	155.16±20.02	77.16±19.99	389.83±68.55	140.0±4.11
P.C.	955.08±87.43**#(ESI)	505±65.93**# (ESI)	287.83±26.96# (NSD)	112.0±8.01# (NSD)
RS+PC	452.78±93.18*@ (ESD)	250±27.18**@ (ESD)	535.23±76.67@ (NQSI)	126.5±8.84@ (NQSI)
TED+ PC	821.3±23.79 @ (NSD)	229.5±44.35**@(ESD)	414.01±46.03@ (NQSI)	131.8±4.77@ (NQSI)
TED×1/2 + PC	756.52±64.92@ (NSD)	175.6±18.72**@(ESD)	422.32±97.02@ (NQSI)	089.4±25.02@ (NQSD)
TED×2 + PC	921.5±80.13@ (NSD)	188.83±18.79**@(ESD)	413.33±55.01@ (NQSI)	118.33±7.92@ (NQSI)

Data: Mean±SEM (*n*=6); ** $p<0.01$, * $p<0.05$, @ compared with positive control, # compared with normal control.

Table 4: Impact of experimental medication on serum total protein, cholesterol, triglycerides, total bilirubin, direct bilirubin activities: in rats given paracetamol.

Groups	Total Protein (g/dL) Mean± SEM	Serum Cholesterol (mg/dL) Mean±SEM	Serum Triglycerides (mg/dL) Mean±SEM	Total Bilirubin (mg/dL) Mean±SEM	Direct Bilirubin (mg/dL) Mean±SEM
W.C.	6.46±0.20	49.83±3.20	87.16±14.18	0.15±0.02	0.09±0.005
P.C.	5.47±0.25 # (NSD)	81.60±6.69*# (VSI)	134.66±21.18# (NSI)	0.51±0.09**# (ESI)	0.10±0.00# (NSI)
RS + PC	6.06±0.15 @ (NSI)	57.83±8.42@ (NSD)	101.50±20.4@ (NSD)	0.18±0.01**@ (ESD)	0.10±0.01 @ (NSI)
TED+ PC	5.09±0.09 @ (NSD)	79.5±6.38 @ (NSD)	155.66±39.9@ (NSI)	0.25±0.03**@ (ESD)	0.10 ±0.00 @ (NSI)
TED×1/2+PC	12.10±6.05@ (NSI)	90.4±13.77@ (NSI)	124.4±19.67@ (NSD)	0.16±0.02**@ (ESD)	0.14±0.02 @ (NSI)
TED×2 + PC	5.43±0.16 @ (NSD)	70.33±5.72@ (NSD)	96.00±08.7 @ (NSD)	0.28±0.03**@ (ESD)	0.11±0.02 @ (NSI)

Data: Mean±SEM (n=6); **p<0.01, * p<0.05, @ compared with positive control, # compared with normal control.

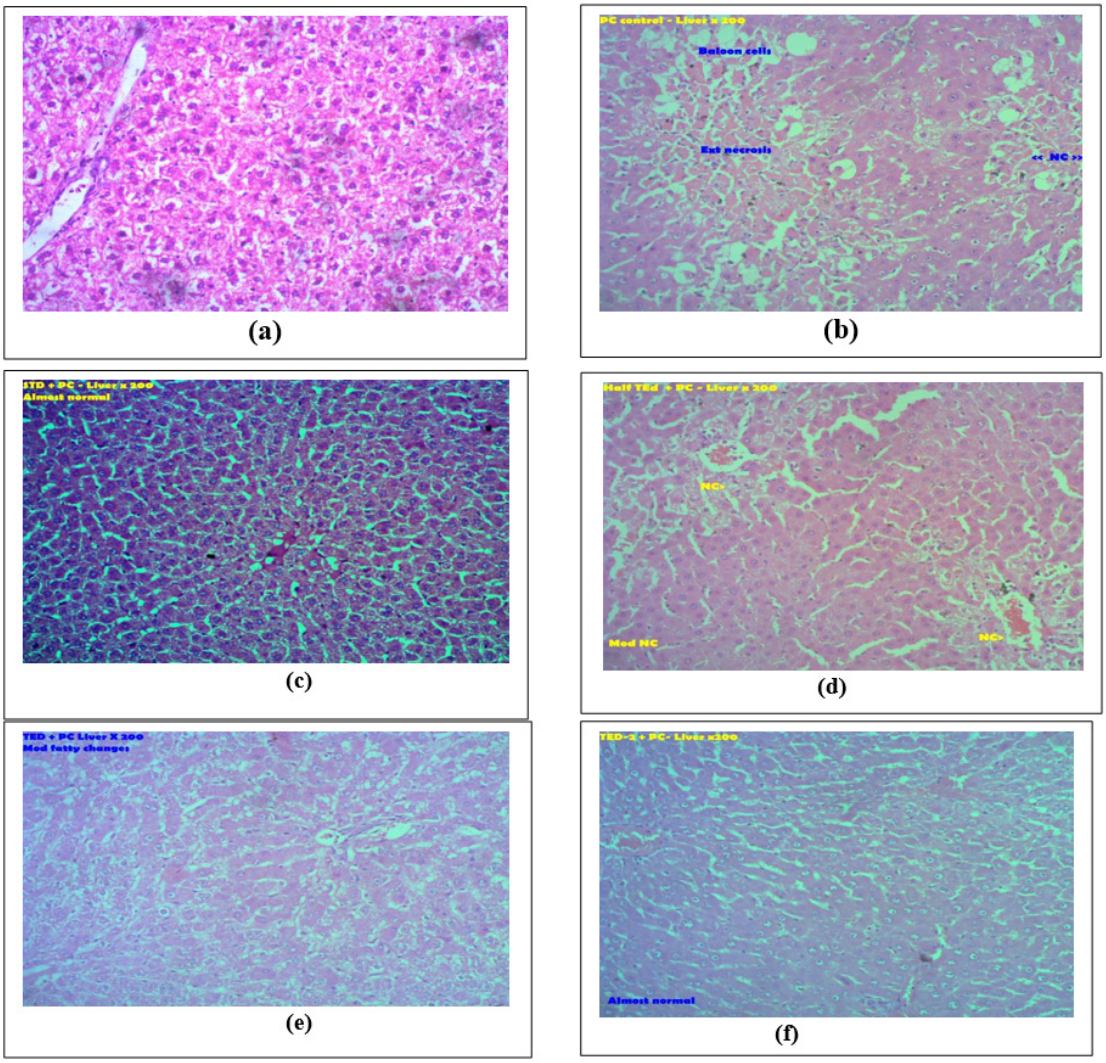

Figure 1: Histopathological study of liver in rats exposed to paracetamol developed hepatotoxicity (a) WC; (b) PC; (c) RS+PC; (d) TEDx1/2+PC; (e) TED+PC; (f) TEDX2+PC.

mild micro fatty alterations with nearly normal cytoarchitecture (Figure 1f).

DISCUSSION

Chemicals and drugs induced hepatotoxicity is the most common kind of iatrogenic afflictions and is among the most prevalent serious health problem.[18] In the present study, paracetamol intoxication in rats caused marked liver injury. Ponderal changes were seen for two parameters. They are the weight of the liver and the body. The gain in the body was seen in both therapeutic and water control group, whereas in paracetamol administration group, half and double dose test drug group, reference standard silymarin group moderate decrease was observed. Body weight decrease and changes in the specific organ in focus are the sensitive markers for indicating toxicity and tissue degeneration. The results indicate that there is no significant effect of the test formulation at any of the three dose levels on the alterations caused by the toxicants mentioned above.

The weight of the liver was the second parameter. Here, the administration of paracetamol causes weight gain. None of the groups that were tested were able to appreciably reverse this growth. Rather, there was a slight increase that was noted. The rise might indicate hepatic induction rather than drug-induced damage.

Toxicant paracetamol administration led to marked changes in serum transaminase, total bilirubin, ALP, serum triglycerides, direct bilirubin, seruncreatinin, total protein, blood sugar, serum urea and serum cholesterol levels.

Estimation of SGOT and SGPT is most regularly done to assess liver cell necrosis. Damage to the tissues producing SGOT and SGPT will increase their level in serum. It is well known that serum transaminase levels rise in hepatotoxicity caused by paracetamol. In the current study also, significant increase was noticed. This elevation of SGOT was significantly reduced by the reference standard silymarin administration but the test drug did not produce statistically significant reduction. Since the elevation of this SGOT is seen in injury to various organs where test drug might not have protective activity.

SGPT specified for liver tissue is a cytosolic enzyme. Hence analysis of the same in liver cell injury will have tremendous predictive value.[19] In the current study remarkable increase was noticed. When test medication was administered at therapeutic, half, double, or reference standard silymarin, the toxicant-induced rise of SGPT was considerably inhibited. The highest magnitude of reversal was observed in silymarin group, it being 94.89%, in test drug at therapeutic dose group 54.62%, half dose group 65.28% and double dose group 62.66%. This can be considered as suggestive of significant hepatoprotection along with the observations of histopathological examination.

Elevations in glucose can occasionally be noticed in hepatic diseases.[20] Serum blood sugar was not affected to significant extent and the test formulation did not have any significant influence. This indicates that this parameter may not have predictive value.

Following paracetamol, there was a notable rise in serum cholesterol and a mild rise in serum triglyceride levels. Total serum cholesterol, triglyceride is regularly evaluated in liver disease because they are synthesized in the liver.[21]

In this study, there was a significant increase in serum total cholesterol and a notable elevation in triglyceride levels. This could be a sign of cholestasis caused by a toxicant. Nevertheless, neither the test medication nor the reference standard significantly reduced this increase in the serum total cholesterol level. Rather, a slight rise was observed in the half-dosage group, a considerable decline in the test medication at the therapeutic dose and a double dose group compared to the reference standard group. Similarly, elevation observed in the serum triglycerides level was not significantly reversed by the test drug groups and reference standard group. Rather, the test drug at half and double dose group, the reference standard group, and the test drug at therapeutic dose group all showed signs of moderate depression. Therefore, measuring changes in serum triglycerides and cholesterol did not aid in identifying the hepatoprotective effect. This can be interpreted by suggesting that the test drug and reference standard though could decrease injury to the hepatocytes could not influence the toxicant induced cholestasis to significant extent.

Increase in serum alkaline phosphatase can be seen in hepatobiliary disease, in obstruction of biliary tract and parenchymal liver disease like cirrhosis, metastatic liver disease and hepatitis.[22]

In the current investigation, paracetamol intoxication was associated with a non-significant decrease in alkaline phosphatase activity rather than an elevation. None of the test medication groups or the reference standard was able to appreciably reverse this decline. Rather, the test drug groups at therapeutic, half and double dose groups showed non-significant elevation, while the reference standard group showed a substantial increase. Reversal of ALPase depression can be considered as a sign of hepatoprotection. Since this parameter is sensitive to cholestasis non reversal of the observed changes indicates that the test formulation and even reference standards have no significant influence over cholestasis.

Decrease in Total serum protein can be seen cirrhosis of liver.[23] In the current investigation, administering paracetamol at toxic levels resulted in a non-significant decrease in total protein. Neither the reference standard group nor the test drug groups had any appreciable changes. As a result, the hepatoprotective activity was not determined by this measure.

The level of bilirubin rises in diseases that affect the hepatocytes, haemolysis, and liver deficiencies that prevent the liver from processing bilirubin, such as Gilbert's disease. The bilirubin is found in the blood in two forms: conjugated (direct), soluble in water, which the kidneys can excrete, and unconjugated (indirect), soluble in water that is bound to albumin in the blood. Indirect fraction bilirubin rise is hardly because of liver disease but principally increase seen in haemolytic and number of genetic disorders. Because of hepatocellular damage, the control group using paracetamol had an extraordinarily substantial increase in total bilirubin in the current study. The test and reference standard at different dose levels dramatically and greatly reduced this rise. This decline can indicate that the test medication has a strong hepatoprotective effect.

A rise in conjugated bilirubin is always indicative of hepatic or biliary tract dysfunction.[24] In the current investigation, the injection of paracetamol resulted in a moderate rise of direct bilirubin. Test drug groups and also reference standard group did not induce any significant change. This may indicate that test formulation has no significant effect on direct bilirubin changes.

Thus, remarkable changes in the majority of the serum biochemical variables can be seen after the administration of toxicant paracetamol. The overall activity profile indicated a reversal of key variables, including total bilirubin and SGPT, and suggested that the test formulation included moderate to good hepatoprotection.

Analysing the histopathological changes in this study shows that paracetamol causes a significant amount of liver damage. These changes are significantly reversed in the test formulation administered group, matching the protection seen in the reference standard. This can be regarded as definitive proof that the test formulation contains a significant amount of hepatoprotection.

Phytochemical investigation of the test drug disclosed the existence of notable number of phenols, flavonoids, glycoside, coumarin, steroids, and tannins.[25] Polyphenols, flavonoids, glucosides, saponins, unsaturated fatty acids, tannins and alkaloids are the plant derived phytochemicals found to be helpful in the management of liver disorders.[26] Silymarin which is used to treat hepatitis, toxin induced liver dysfunctions and liver cirrhosis is also one of the potent flavonoids.[27] Flavonoids are the chief phenolic content having strong antioxidant and anti-inflammatory activities.[28]

The hepato-protective activity which is seen in many plants where polyphenol content has been held responsible and this result has been credited to powerful antioxidant activity of polyphenol fractions.[29] It has been observed that rats will develop an inflammatory reaction in the liver when treated with N-acetyl-p-aminophenol.[30] And this response is assumed to be because of release of chemotactic elements from the hepatocytes.[31] There will be reduction of the antioxidant enzymes comprising Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GSH-Px) in paracetamol therapy. In paracetamol toxicity, it is also observed that there is a reduction of GSH-Px.[32] This GSH-Px is a chief enzyme for protection against GSH depletion in tissues. Hepatotoxicity caused by the Paracetamol may be due to the cumulation of reactive oxygen species, pro-inflammatory cytokines or by direct effect and through either protein damage after the initial lesions. Also been seen that noticeable increase in nitric oxide level following the paracetamol treatment. It can be supposed that the oxidative injury because of that toxicant would be reduced because of the antioxidant activity of the polyphenols present in the test drug. From these findings, it can be assumed that observed hepatoprotection is possibly through inhibiting the production of the damaging free radical surge, oxidant radical release and reduction of resultant of pro-inflammatory activity.[33,34]

CONCLUSION

Principal variables such as total bilirubin and SGPT are reversed in both reference standard and test compounds, indicating moderate to good hepatoprotection in serum biochemical analysis. Reversal of the harmful effects developed by paracetamol intoxication is also observed in histopathological investigation, indicating good cytoprotection in both reference standard and test drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALP: Alkaline phosphatase; **SGPT:** Serum glutamic-pyruvic transaminase; **SGOT:** Serum glutamic-oxaloacetic transaminase; **TED:** Therapeutically Effective Dose; **TED×1/2:** Half Therapeutically Effective Dose; **TEDx2:** Double Therapeutically Effective Dose; **SOD:** Superoxide dismutase; **CAT:** Analyses of catalase; **GSH-Px:** Glutathione peroxidase; **W.C.:** Water control; **P.C:** Paracetamol control; **RS:** Reference Silymarin; **mg:** Milligram **g:** Gram; **Kg:** Kilogram; **IM:** Intra Muscular; **IU/L:** International units per liter; **dl:** Deciliter; **NQSD:** Non quite significant decrease; **NQSI:** Non quite significant increase; **NSD:**

Non-significant decrease; **NSI:** Non-significant increase; **SD:** Significant decrease; **SI:** Significant increase; **ESD:** Extremely significant decrease; **ESI:** Extremely significant increase.

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