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Hepatoprotective Effects of *Glycyrrhiza glabra* and *Cichorium intybus* in Paracetamol-Induced Toxicity in Rattus norvegicus

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ABSTRACT:

Aims and Objectives: The present study was aimed to determine hepatoprotective role of two plants *Glycyrrhiza glabra* and Cicorium intybus against paracetamol (acetaminophen) exposure hepatotoxicity in albino rats (Rattus norvegicus). It has been demonstrated that *G. glabra* and *C.intybus* extract has biological capabilities of anti-oxidation, detoxification and anti-infection.

Methodology: So, to evaluate the effects of *G. glabra* and *C.intyubs* administration on the liver's histology and some biochemical parameters were investigated. Rattus norvegicus male rats (n= 48) were randomly distributed into four groups. Experimental groups were given acetaminophen with 2.5mg/kg BW /day for 5 days respectively to induce hepatotoxicity, then aqueous extract of *G. glabra* (Roots) and *C.intybus* (Seeds) at 200 mg/kg/day was given for a period of 10, 20 and 30 days. After the completion of experiment, tissues were taken and blood was collected in order to evaluate histopathological changes, and for studies of biochemical parameters separately. The obtained results showed hepatic necrosis and centrilobular hepatic congestion with a decrease in hepatocytes diameter, and increase in sinusoidal spaces was also observed in the liver of treated rats.

Results: Liver enzymes ALP, AST and ALT and other biochemical factors Albumin, Bilirubin showed a significant increase in 200 mg/kg extract received rats in comparison with control ($P<0.05$) and ($P<0.01$). *G.glabra* and *C.intybus* have shown a remarkable and effective impact on RLW which was statistically significant ($P<0.05$), percentage increase and decrease showed that both plants have good effective on the recovery of body weight, affected by the paracetamol (acetaminophen) toxicity.Some harmful effects of *C.intybus* were seen on integrity of liver in 30 days consumption of this plant.

Keywords: Hepatoprotective effects, Glycyrrhiza glabra, Cichorium intybus, paracetamol-induced toxicity, Rattus norvegicus, liver dysfunction, medicinal plants, antioxidative properties, detoxification, anti-inflammatory, liver tonic.

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INTRODUCTION

In the human body, the liver is the largest organ with a weight of approximately 1500 g, located in the upper right corner of the abdomen. The liver performs more than 500 crucial metabolic functions [1]. Hepatotoxicity is the dysfunction or damage of the liver due to excessive exposure to xenobiotics or drugs [2]. The chemicals responsible for liver dysfunction are known as hepatotoxins. These include exogenous compounds such as medicinal drugs, industrial waste and chemicals, herbal

remedies, dietary supplements, and natural toxins such as microcystins [3,4].

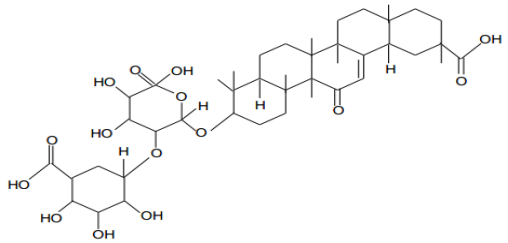
Acetaminophen, paracetamol, or N-acetyl-p-aminophenol (APAP) is a frequently used antipyretic and analgesic drug [5]. Overdose, whether in therapeutic misuse or suicidal cases, can induce severe hepatotoxicity [6]. Approximately 50% of acute liver failure cases are due to APAP toxicity and are associated with nearly 30% mortality [7]. Davidson and Eastham were the first to report acetaminophen-induced hepatotoxicity in overdose [8].

Acetaminophen occurs as a white crystalline powder with an odorless smell and a bitter taste when administered orally. It has a melting point of 169–172°C and is non-flammable with a specific gravity of 1.293. The compound is prepared at a pH of about 5.5–6.5 and is miscible with water, methanol, and ethanol [9].

Metabolic Action of Acetaminophen

Extensive studies have been conducted on the metabolism of acetaminophen, and its pathways are well established [10]. The liver plays a key role in its metabolism. Three major pathways are involved, accounting for approximately 55–60% of metabolism. Sulfation accounts for about 20–30%, while glutathione conjugation and N-hydroxylation account for less than 15%.

The major enzyme involved is hepatic cytochrome P450, which leads to the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), an alkylating compound. CYP2E1 and CYP3A are the key isoenzymes involved in this process [10].



GLYCYRRHIZIN

Hepatoprotective Plants: In current study we have used two plants “Glycyrrhiza glabra” and “ Cicorium intybus”.

Glycyrrhiza Glabra: *Glycyrrhiza glabra* L. belongs to the family Fabaceae (Leguminosae) and is a well-known medicinal plant [11]. Ali Louei Monfared reported that *Glycyrrhiza glabra* extract possesses various biological activities, including anti-infective, antioxidant, and detoxification properties; however, limited data are available regarding its potential side effects on liver integrity [12].

Cichorium intybus is a perennial herbal plant belonging to the family Asteraceae [13]. This plant contains several medicinally important compounds such as sesquiterpene lactones, inulin, coumarins, vitamins, and flavonoids. It is used for its anti-hepatotoxic, anti-inflammatory, and hepatoprotective effects, and also acts as a liver tonic, cholagogue, depurative, diuretic, emmenagogue, and alexeteric agent, with additional anticancer and therapeutic uses [14].

Body Condition and Body Weight: Following treatment, the rats were observed over a 12-hour period and no mortality was recorded over that period. Rats administered with acetaminophen at doses of 2.5mg/ kg body weight/day after 2-3 days were sick and less active as compared to normal rats group,they also had a rough coat and poor appetite. While the control rats, and those treated with C.intybus and G.glabra were alert and active, had glossy coat, and were showing good appetite.

Animals: Forty-eight albino rats (Rattus norvegicus) of 200-300 g body weight were used in the current study. The rats were given free access to water and food. They were allowed to acclimatize for one week. They were maintained at 12 hours light, and 12 hours dark cycle during experiment. The animals were collected from the animal house of University of Lahore

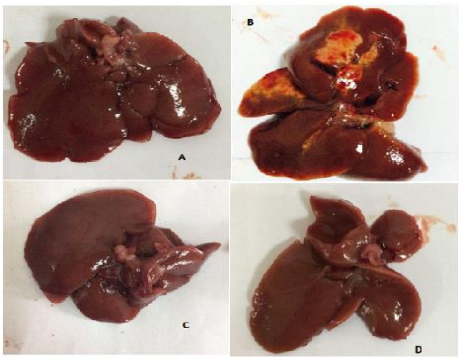


Figure 2: Morphological characteristics of rat livers: (A) Control group (Alert and glossy) (B) Acetaminophine 2.5mg/kg body weight (Less active and sick) (C) Cicorium intybus 200mg/kg treated (Active) (D) Glycyrrhiza glabra 200mg/kg treated (Active).

Group-1 (Control): This group was used as control rats and were given free access to food and water. Number of rats (n=4) were used in control group

Group-2 (Paracetamol): It contain four animals (n=4) which were given 2.5mg to induced hepatotoxicity in animals. Rats received it for a period of 5 days

Group-3 (Paracetamol+G.glabra): 200mg of G.glabra given orally to the four animals (n=4) that was dissolved in the water. According to the experimental design the treatment was given accordingly 10, 20 and 30 days.

Group-4 (Paracetamol+C.intybus): An dosage of 200mg was used for four (n=4) that was dissolved in water. The plants were administrated after the five days application of acetaminophen. The hepatoprotective effects were checked after respectively 10,20 and then 30 days.

Biochemical Analysis: The samples were processed and analyzed for the estimation of aspartate aminotransferase (AST), alkaline phosphate (ALP), alanine aminotransferase (ALT), bilirubin total (BILT), total protein (TP). For the quantitative determination of above

enzymes in plasma or serum Cobas c 111 systems has been used. %increase(+) or decrease (-) in Body weight gain following G.glabra and C.intybus to acetaminophen exposed rats.

Table-1: Groups treatement for 5,10,15,20,25,and 30 days.

Group/ Treatment	5 Days	10 Days	15 Days	20 Days	25 Days	30 Days
Control	3.7	8.6	21.7	37.0	57.5	76.3
P+ C.intybus	-7.9	8.1	14.0	23.6	31.6	42.6
P+ G. glabra	-11.4	12.0	24.0	40.4	66.7	76.0

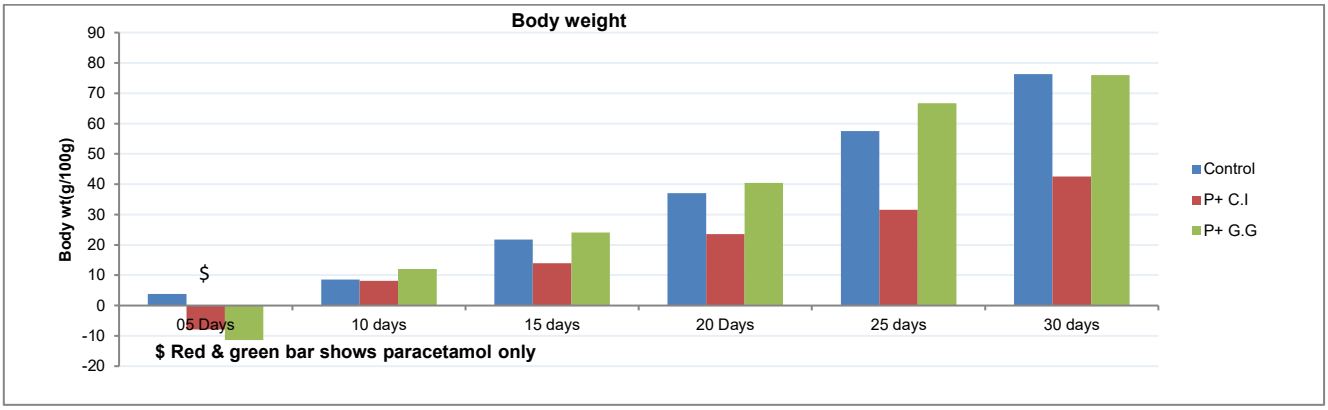


Figure 2: Administration of G.glabra and C.intybus to paracetamol exposed rats:Percent increase(+) or decresae (-) in body weight gain following administration of G.glabra and C.intybus to paracetamol exposed rats.

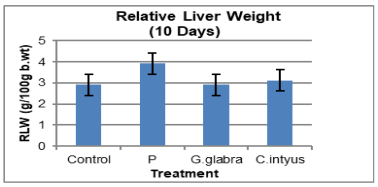
20 days showed that, G.glabra treated group and Control group are has almost near values i.e 40.4±14.1 and 37.0±3.8, indicating the clear effective role of G.glabra against the paracetmol induced decrease in body weight of rats, and was statistically significant p<0.05. 25 days experimental work showed that, G.glabra has an small elevation in value as compared to the control group, which was 66.7± 12 while in the case of control group it was 57.5±9.7, But at 30 days treatment the G.glabra treated group and Control group had the same value that was 76±14.3 and 76.3±3.3 which gave absolutely good result of G.glabra as good body weight gainer and it showed an excellent recovery in body weight of rats. G.glabra value within 25, 30 days was observed as statistically significant P<0.05.

Relative Liver Weight (RLW): It was observed that, the relative liver weight (RLW) in the case of paracetamol induced toxicity rats was increased 3.9±0.16 in 10 days as compared to control group that was observed as 2.9±0.03, G.glabra has shown a value of 2.9±0.03 thaw was almost equal to the control group suggesting potential role of it in the organ weight. While C.intybus has shown an value of 3.1±0.12 which wasn't near to control group. Statistically significant value p<0.05 of RLW was observed in the 10 days. In 20 days experiment, an increased value of 3.7±0.16 as compared to control group i.e 2.8±0.02, declare abnormality in liver of rats. After administration of G.glabra (3±0.06) and C.intybus (2.9±0.08) remarkable recovery in liver size was observed, which showed their role in the improvement of liver size. Statistically significant value of RLW i.e P<0.05 was found in 20 days. In the case of result of 30 days experiments, paracetamol treated group give a raising value of 4±0.18 as compared to control group 2.7±0.15, this elevation is due to aberration of liver. This abnormal size of liver is potentially recovered back to control group with values of 2.6±0.02 in the case of G.glabra and 2.7±0.20 in the case of C.intybus . Within the 30 days statistically significant value p<0.05 was observed.

Table-2: Treatement of Groups in 10,20,and 30days

Group/ Treatment	10 Days	20 Days	30 Days
Control	2.9±0.12	2.8±0.02	2.7±0.15
Paracetamol	3.9±0.16*	3.7±0.16**	4±0.18**
G. glabra	2.9±0.03*	3±0.06**	2.6±0.20**
C. intybus	3.1±0.12*	2.9±0.08**	2.7±0.20**

Fig-3:Relative liver Weight of treatement in 10days



Relative Liver Weight (RLW) of 10 days treatment of G.glabra and C.intybus following 5 days acetaminophen expose rats

Fig-4: Relative Liver Weight ofTreatement in 20 days

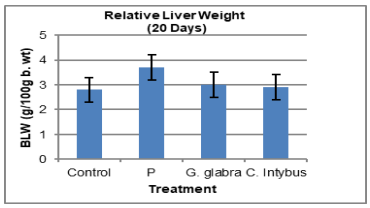


Fig-5:Relative liver Weight of treatement in 30days

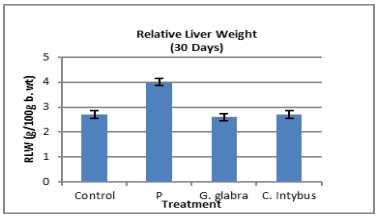
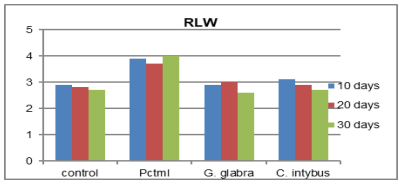


Fig-6:administration of G.glabra and C.intybus exposed rats in 10, 20 and 30 days .



RLW following administration of G.glabra and C.intybus exposed rats in 10, 20 and 30 days .

In 10 days experimental work, graphically it can be clearly evaluated that, paracetamol treated group has shown an increase in the relative liver weight, and its increase from the control group bar shows an abnormality. Administration of G.glabra and C.intybus has shown an notable recovery of relative liver weight (RLW) back to the control group bar as shown above. It is clearly evident from graph bar of Fig 9 that, RLW of paracetamol treated group is crossing the control group bar indicating unusual result, while treated groups bars G. glabra and C intybus are showing a marked improvement in the RLW. 30 days treatment group shows that RLW of paracetamol was increased from the normal range (control group) showing clearly the adverse effect of acetaminophen on organ weight, while graph bar of both administrated plants shows that their values of 2.6±0.20 and 2.7±0.20.

Biochemical Analysis of 10 Days Experiment: Results in the above Table 5 showed the hepato-protective effect of Glycyrrhiza glabra and Cicorium intybus administration following hepatic damage induced by Acetaminophen (paracetamol),

Alanine Aminotransferase (ALT): The liver function enzyme, ALT activity in the 10 days control group was (53.2± 4.8) IU/L, which has been increased in the case of paracetamol (84.0± 17.8) which shows marked increase from the normal group. Percentage comparison difference between Control and Paracetamol was 58%.The marked alleviation in ALT level was also observed in C.intybus (66.6± and G.glabra administrated groups, showing hepato-protective role. Statistically significant value (P<0.05) was observed in C.intybus and G.glabra groups, respectively.

Aspartate Transaminase (AST): AST in the table showed that, in normal group (73.5±6.25) in the case of paracetamol it was found (74.6± 1.20) with slight elevation, Glycyrrhiza administration in 10 days rats showed the marked recovery (72.3±2.60) while Cicorium showed an value of (80.0 ± 12.1). The AST in the 10 days was statistically moderately significant (P<0.01). During % comparison a 2% decreased was observed which showed paracetamol hepatotoxicity.

Alkaline Phosphatase (ALP): ALP has shown a value of (211±37.1), while the paracetamol showed a decreased value of (94.3±19.5) which indicate the injury in the liver, and % comparison difference between both of these was 55%. Cicorium intybus showed a hepato-protective effect with an value of (222±36.8)

Bilirubin (BIL): Bilirubin content of the of blood remained almost same from Control 0.057±0.14 to Paracetamol and G.glabra (0.053±0.080 and 0.040±0.01) except C.intybus (0.086±0.01) Paracetamol showed percentage decrease of 7% when compared with the control group. Comparison of Control with C.intybus and G.glabra showed a percentage of 2% and 6%

Total Protein (TP): In the case of Total Protein, statistically significant activity was observed after the administration of hepato-protective plants, Glycyrrhiza and Cicorium P≤0.05 (5.60±0.23 and 5.16±0.14), while control showed a value of (5.50±0.1). Percentage % comparison between normal and paracetamol group showed a difference of 26% which indicate the hepato injury by paracetamol in rats.

Albumin: Albumin activity was observed statistically significant P≤0.05 among the 10 days groups, normal group has shown an value of (4.07±0.13) while paracetamol group's value decreased (2.43±0.06), with a percentage difference of -40.2% which signify liver dysfunction. Hepato-protective role of Cichorium and Glycyrrhiza was clearly found (4.26±0.11 and 5.16±0.14)

Biochemical Analysis of 20 Days Experiment

Alanine Aminotransferase (ALT): ALT activity in 20 days table has shown a value of 53.2±4.8 in control group,

Paracetamol group has shown an exalted value of 67.7±14.6 which declared deliberately the damage by liver tissues, values alleviate back towards the normal after the administration of both hepato-protective plants, 46.0±9.0 and 44.2±5.1, respectively. Values showed that they are statistically moderately significant P<0.01.Percentage comparison exhibited 27% in the case of Control and paracetamol, C.intybus and G.glabra had showed 13% and 16% comparison with control group. .

Aspartate Transaminase (AST): AST content observed was 73.5±12.5, while no noticeable results were found for C.intybus and G.glabra.

Alkaline Phosphatase (ALP): ALP value in Paracetamol 278.2±26.92 had increased from normal group 211.0±74.3 that showed liver tissues injury, a percentage difference of 31% was observed. while in the case of G.glabra its value was 224.2±36.1 and C.intybus didn't showered any marked recovery.

Bilirubin: Bilirubin content in G.glabra and C.intybus had not shown prominent recovery after the paracetamol hepatotoxicity which was extended as 0.097±0.71 from normal group 0.057±0.028 with a percentage % of 70%. In the case of G.glabra it was just 8%.

Total Protein: Total protein content was found insignificant throughout the days, Control has shown a value of 5.50±0.1 while its value slightly increased due to toxicity induced by paracetamol, C.intyus and G.glabar had showed the same value of 5.07±0.36. If the % comparison was observed Control and paracetamol 9% , both plants showed a same % which was 7.81%.

Albumin: Albumin content of the 20 days experiment showed statistically significant values through groups and days (P≤0.05) as shown in the table. Its extended in the paracetamol 4.45±0.08, G.glabra didn't showed marked recovery 4.60±0.2 as compared to the C.intybus which has a value of 4.10±0.38.

Biochemical Analysis of 30 Days Experiment

Alanine Aminotransferase (ALT): ALT was observed as statistically moderately significant P<0.01 in 30 days, Control goup has shown a value of 44.8±4.11, when paracetamol value was compared with Control it was clearly reported the abnormality in the liver, C.Intybus and G.glabra (43.6±5.78 and 43.2±4.32) had showed a good recovery and values reaches back towards the normal group. Control and paracetamol group had showed a % difference of 27%, while C and G had given 13.5 and 16.9% difference.

Aspartate Transaminase (AST): AST activity in 30 days was also found as statistically moderately significant P<0.01, paracetamol (107±20.6) didn't showed marked elevation from normal group so hepatotoxicity wasn't observed in the case of acetaminophen. G.glabra (170±22.7) showed notable heaptoprotective effect as compared to the C.intybus (131±12.7).A prominent percentage difference of 67% was perceived between normal and paracetamol group. While C.intybus has given a 92% and G.glabra 77%.

Alkaline Phosphatase (ALP): 30 days data of ALP showed a control value of 181±23.4, paracetamol value was lower as compared to the normal group 153±13.7, in the case of G.glabra the obtained value was 213±12.8 which was higher than control value indicating the abnormality may be due to long period administration of G.glabra and C.intybus had shown a value of 168±31.0 and no marked recovery was observe in the case of both plants. ALP was found statistically significant P<0.05 in 30 days, while insignificant in the case of groups.

Bilirubin (BIL): Bilirubin was observed as statistically significant P<0.05, normal group has shown a value of 0.66±0.35,while value of this parameter has been decreased prominently in the case of paracetamol 0.16±0.06,which indicate the abnormality of liver function regarding to this parameter. A notable change of 0.75±0.01 was seen in Bilirubin content after G.glabra application but no noteworthy hepatoprotectve effect of C. Intybus was observed with an lesser value of 0.36±0.01 as compared to control value.

Total protein (TP): Total protein content was found insignificant throughout the days, control has shown a value of 5.50±0.1 while its value slightly increased due to toxicity induced by paracetamol, C.intyus and G.glabra had showed the same value of 5.07±0.36. If the % comparison was observed Control and paracetamol 9% , both plants showed a same % which was 7.81%.

Histopathology Control: Tissues of liver of normal rats preserved by Hematoxylin and Eosin (H&E).Control group showed sinusoidal spaces and normal hepatic architecture with discrete liver cells (Fig 23,A).The hepatocytes were in proper arrangement of cuboidal hepatocytes separated from each other by blood sinusoids lined. The hepatocytes appeared polyhedral in shape with large rounded vesicular nuclei. It was observed that, hepatocytes were in proper arrangement and of separated from each other by blood sinusoidal lines. There was no malignancy, atypia or pathological changes. (Figure A)

Table-3: Comparative Analysis of Hepatic Function Biomarkers Across Different Treatment Groups Over Time: Unveiling the Impact of Pctml, C. Intybus, and G. Glabra on Liver Health

Group/ Treatment	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Bilirubin (mg/dL)	Total Protein (mg/dL)	Albumin (g/dL)
Control						
10 days	53.2 ± 4.8	73.5±6.25	211±74.3	0.057±0.028	5.50±0.14	4.07±0.13
20 days	53.2±9.6	73.5±12.5	211±74.3	0.057±0.028	5.50±0.29	4.07±0.26
30 days	44.8±4.11	172±12.2	181±23.4	0.66±0.35	5.36±0.27	3.90±0.26
Pctml						
10 days	84.0±17.8^{a**}	74.6±1.20**	94.3±19*	0.053±0.08^{a*}	4.03±0.11^{a}	2.43±0.06^{a*}
20 days	67.7±14.6^{a**}	123±27.2**	278.2±26.92*	0.097±0.71^{a*}	5.97±0.095^{a}	4.45±0.115^{a*}
30 days	50.6±5.89^{a**}	107±20.6**	153±13.7*	0.16±0.06^{a*}	4.53±0.37^{a}	4.23±0.02^{a*}
C. Intybus						
10 days	66.6±7.97^{b**}	80.0±12.10**	222±36.8*	0.086±0.01^{b*}	5.60±0.23^{b}	4.26±0.11^{b*}
20 days	46.0±9.0^{b**}	141±37.5**	164.0±79.3*	0.147±0.041^{b*}	5.07±0.72^{b}	4.10±0.77^{b*}
30 days	43.6±5.78^{b**}	131±12.7**	168±31.0*	0.36±0.01^{b*}	5.60±0.31^{b}	3.73±0.28^{b*}
G. glabra						
10 days	64.3±6.35^{c**}	72.3±2.60**	65.0±5.8*	0.040±0.01^{c*}	5.16±0.14^{c}	5.16±0.14^{c*}
20 days	44.2±5.1^{c**}	130±18.0**	224.2±36.1*	0.160±0.43^{c*}	5.07±0.72^{c}	4.60±0.40c*
30 days	43.2±4.32^{c**}	170±22.7**	213±12.8*	0.75±0.01^{c*}	5.47±0.15^{c}	4.10±0.21^{c*}

*= P<0.05 **= P<0.01, ± show SEM (Standard Error),a= significant difference between para and ctrl, b= significant difference between para and C. Intybus, c= significant difference between para and G.glabra

Paracetamol: Acetaminophen treated rat revealed markedly disturbed parenchymal architecture of the hepatocytes in the form of cytoplasmic vacuolation, degeneration, and acute necrosis of hepatocytes. Microabscess was observed that involve few necrotic debris and inflammatory cells. Other histopathological changes such as extensive accumulation of connective tissue that results in the formation of the continuous fibrosis septa. Steatosis was also observed that leads to the liver cirrhosis and finally to the liver fibrosis, and accumulation of hepatic tissue fibrosis septa around cental vein with areas of hemorrhages in blood vessels and steatosis.

Glycyrrhiza Glabra: Liver histopathology of Glycyrrhiza glabra treated rats was observed at different magnification of microsope to elucidate any marked change by this hepato-protective plan. Portal triade (PT), sinusoids are also visible clearly(X200). There was small congestion and dilation of sinusoidal spaces at some places of liver tissue.

Cicorium Intybus: Different magnification power of microscope was used to evaluate the any hepatoprotective histopathological changes caused after the administration of Cicorium intybus

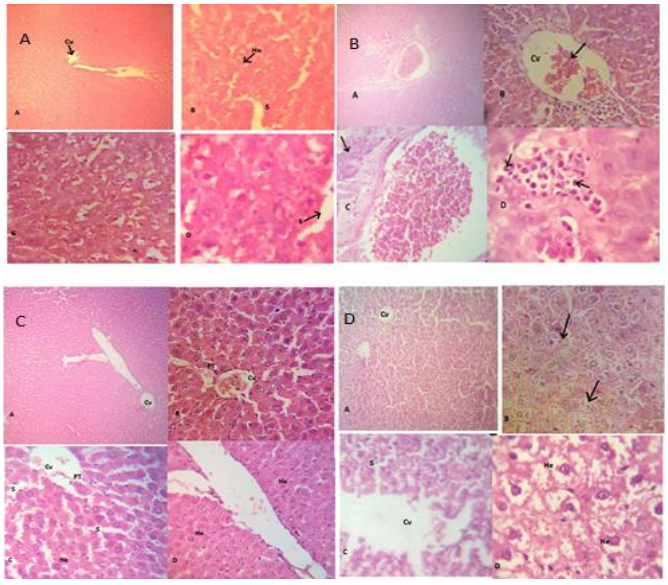


Fig-7: A.Histopathology of rat liver (control group). B.Histopathology of acetaminophen treated rat C. Histopathology of G. glabra treated. D. Histopathology of C.intybus rat.

DISCUSSION

Recent studies have shown that acetaminophen overuse in mice and rats can cause extensive centrilobular hepatic necrosis and elevated serum ALT and AST levels [15].

Acetaminophen toxicity primarily affects the central regions of liver lobules, leading to hepatocyte necrosis. Species variations exist in sensitivity to paracetamol; in most rat strains, acetaminophen is primarily hepatotoxic, while in others such as Fischer 344, nephrotoxic effects are also observed [16,17].

Cell death mechanisms due to APAP toxicity in humans and mice are initiated by the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), generated by cytochrome P450 enzymes CYP2E1 and CYP1A2. NAPQI is normally detoxified by conjugation with glutathione (GSH), but GSH reserves become depleted in cases of overdose [18]. Studies further indicate that APAP-induced liver injury involves oxidative stress, mitochondrial dysfunction, activation of c-Jun N-terminal kinase (JNK), and nuclear DNA fragmentation. However, mechanisms of injury differ in rats, where cell death predominantly occurs via apoptosis [11].

In the present study, alanine aminotransferase (ALT) levels were significantly elevated following acetaminophen overdose compared to controls ($p < 0.01$). Leakage of ALT into serum indicates damage to hepatocyte endoplasmic membranes [14]. ALT is a specific biomarker for liver injury and reflects hepatocellular integrity. It has been reported that free radical-mediated cellular damage contributes to hepatocyte necrosis induced by acetaminophen [16].

Aspartate aminotransferase (AST) activity was also significantly elevated ($p < 0.01$) in rats treated with acetaminophen (2.5 mg/kg), further confirming hepatotoxicity. Elevated AST levels indicate hepatocyte membrane damage. Previous studies demonstrated that acetaminophen at 400 mg/kg significantly increased AST activity within 4–6 hours post-administration [12–14], whereas lower doses (16–66 mg/kg) caused minimal changes [15].

In the present study, alkaline phosphatase (ALP) levels were significantly elevated ($p < 0.05$), which is associated with cholestatic liver disease and hepatocellular damage [16,18]. Total bilirubin levels were significantly elevated in the acetaminophen-treated group ($p < 0.05$), indicating hepatotoxicity. Liver damage leads to increased conjugated and unconjugated bilirubin levels and may be associated with drug toxicity, infections, and metabolic disturbances [17].

Albumin levels are typically elevated in conditions such as dehydration or increased hepatic synthesis [18]. Liver dysfunction may also alter protein synthesis as a compensatory mechanism [9]. Additionally, corticosteroids and thyroid hormones influence albumin production [2]. The presence of bioactive compounds such as flavonoids, triterpenes, and steroids may contribute to improved liver regeneration and increased albumin levels.

The present study aimed to evaluate the hepatoprotective activity of *Glycyrrhiza glabra* and *Cichorium intybus* against acetaminophen-induced hepatotoxicity in albino rats. It is well established that acute toxicity effects occur within 24 hours of drug administration [12-15].

Caspase-1 and Akt-1 are key molecular targets associated with hepatotoxicity. Overexpression of Akt-1 is linked to tumorigenesis and inhibition of apoptosis [3]. Caspase-1 mediates apoptosis via death receptor pathways. Compounds such as methyl 4-hydroxyphenylacetate and 4-hydroxyphenylacetic acid exhibit hepatoprotective effects by inhibiting caspase-1 and downregulating Akt-1 expression, thereby reducing liver damage and tumor formation [3-13].

Histopathological findings in *G. glabra*-treated rats showed increased sinusoidal spaces, reduced hepatocyte diameter, centrilobular congestion, and focal necrosis. These alterations may result from hepatic metabolism of plant extracts [13]. Increased metabolic activity may lead to changes in hepatocyte morphology, while excessive detoxification processes can result in focal necrosis [14].

Glycyrrhizin metabolism involves intestinal bacteria producing glycyrrhetinic acid via β-D-glucuronidase activity [15]. When administered intravenously, glycyrrhizin is metabolized in the liver to 3-monoglucuronide glycyrrhetinic acid, which undergoes enterohepatic circulation [16]. Glycyrrhizin has demonstrated protective effects against gentamicin-induced renal damage [17], while glabridin exhibits anti-nephritic effects in experimental models [18].

CONCLUSION

Evaluation of G.glabra and C.intybus for the prevention of paracetamol-induced hepatotoxicity was successfully performed in rats. Both plants hasshown the ability to protect the liver against hepatic injury when a toxicdose of paracetamol was administered to rats. Hepatotoxicity always remained the prime concern for scientists, doctors and drug developmental agencies. On the basis of body weight it was observed that the G.glabra has shown an prominent recovery as compared to C. intybus. Relative body weight (RLW) of paracetamol treated rat was increased as compared to control rat, the administration of both plants has played crucial recovery of RLW. Futhermore, biochemical and histopathological study, it is evaluated that, both G.glabra and C. intybus have good efficacy in the prevention of hepatic injury caused by paracetamol (acetaminophen) at a dosage of 200mg/kg. It is concluded that after treatment with G,glabra and C.intybus hepatic enzymes and body weight has recovered, and level of biochemical parameters ALT, AST, ALP, Bilirubin, Albumin, Total protein were improved towards normal, which was disturbed by toxification and metabolic activation of acetaminophen can be altered by using different medicinal plants or herbs. For future prospect additional plant and herbs extracts can screened and the isolation of different hepatoprotective phytochemicals from these plant extract can decrease the possibility of hepatotoxicity and liver necrosis.

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