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Hepatoprotective and antioxidant potential of Cuscuta Reflexa Roxb in CCl_4 induced mice

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Abstract: *Cuscuta Reflexa Roxb.* belongs to the family Convolvulaceae is found in Indomalaysia, Srilanka, indigenous to Chattishgarh, Bangal, Karnataka and Rajasthan in India. The main active principle present in the plant is cuscutin, Cuscutalin and reducing sugar. Amarvelin, resin oil (3%), reducing sugars, fatty acid and phytosterol are all present in the seeds. Cuscutin, dulcitol, luteolin, quercetin and luteolin glycoside are all present in the stem. It is described as an expectorant, an anti-inflammatory, a blood purifier and a pain reliever in Indian traditional medicine. Hepatoprotective action may be caused by flavonoid content. On the other hand, there is no information accessible regarding Cuscuta Reflexa Roxb activity against in-vivo antioxidant activities and CCl_4 induced hepatotoxicity tests. Therefore, the current effort has been conducted to evaluate the ethanolic extract of Cuscuta Reflexa Roxb's hepatoprotective and antioxidant properties. on swiss albino mice activity produced by CCl_4 . In-vitro hydroxyl, nitric oxide, lipid peroxidation and DPPH scanning activities further support this.

Key words: *Cuscuta Reflexa Roxb.* Hepatoprotective, Anti-oxidant, CCl_4, and Hepatic injury

Abbrevations: SOD(Super oxide dismutase), CAT(Catalase), NO(Nitric oxide)

1. Introduction:

The liver is an extremely significant organ since it controls a wide range of other bodily processes. It is crucial to several functions, including secretion, metabolism and storage. It is able to develop useful principles, which gives it the ability to regulate the chemical composition of its own body in a very effective manner. It possesses the ability to do this. Carbon tetrachloride (CCl_4), paracetamol, nitrosamine, polycyclic aromatic hydrocarbons and drinking an excessive amount of alcohol are all examples of substances that are harmful to the liver[1].The liver generates a wide variety of enzymes that can eliminate free radicals. Such enzymes include catalase, glutathione peroxidase and superoxide dismutase. Any oxidative waste products produced by cells might be removed by these enzymes[2]. Additionally, reactive oxygen species (ROS) have been linked to the ageing process (ROS). Liver disease is a well-known global health issue. Sometimes, conventional and synthetic therapies for liver illness are insufficient, if not harmful. There are several common household goods that are harmful to the liver including CCl_4, paracetamol, nitrosamines, and polycyclic aromatic hydrocarbons[3,4].The liver's cytochrome P450 enzymes metabolically activate these compounds, turning them into reactive & poisonous molecules that harm the livers of both experimental animals and people. These enzymes have the potential to set off the production

of a certain class of hepatotoxicant known as polycyclic aromatic hydrocarbons[5]. During the biotransformation of CCl4, which is carried out by the hepatic microsomal cytochrome P450 & hepatotoxic chemicals such as trichloromethyl free radicals are produced[6].

2.PLANT PROFILE :-

Fig:1 *Cuscuta Reflexa* Roxb

Scientific Name : *Cuscuta Reflexa* Roxb,

Family : Convolvulaceae

Chemical constituents: cuscutalin & cuscutin flavonoids

Medicinal uses: Hepatic Injury, liver indurations and jaundice

3.MATERIALS AND METHODS:

EXPERIMENTAL ANIMALS:

Swiss albino mice, both male and female, weighing between 25 and 30 grammes apiece, were used in the study. For the purpose of performing study on them, The Bilwal Medchem and Research Laboratory Pvt.Ltd provide animal facility to their needs. The temperature was set at 23°C, the humidity at 50%, and the light and dark cycles were repeated every 12 hours to protect the animals' health. Before the experiment began, the animals were all allowed a week to become accustomed to their new surroundings. After being randomly allocated to an experimental or control group, the mice were housed individually in sterile polypropylene cages with sterile rice husk as bedding. Consistent pellets served as their primary food supply and water was available without restriction. To lessen the effects of stress not directly related to the experiment, we gave the animals 48 hours to acclimate to the lab before beginning the treatment. Bilwal medchem and research laboratory Pvt.Ltd. has an approval of IAEC (Institutional Animal Ethical Committee). The use of animals in research was authorised by (REG.No.-2005/PO/RcBT/S/18/CPCSEA). The Committee for the Purpose of Control and Supervision of Experiments on Animals of the Government of India was the entity responsible for drafting these regulations (CPCSEA).

PLANT MATERIAL

Plant materials :

The whole plant of **Cuscuta Reflexa Roxb.** was authenticated by the scientist-E&Head of office Vinod Maina from BSI, Jodhpur (Rajasthan) and the reference number is (BSI/AZRC/1.12012/Tech./2021-22(PI.Id.)/155.

Methods

Plant collection and extract preparation:

- Approximately 3 kilogrammes (3 kg) of plant material was gathered from the area around Dausa, District, Rajasthan (India), and allowed to dry at room temperature for about two months.
- Preparation of the extracts: After proper drying of the plant, the plant was coarsely powdered for extraction process.
- The coarsely powdered plant Cuscuta Reflexa Roxb. was extracted with 90% ethanol solution in soxhlet extractor batchwise till discolouration of the powdered drug appears.
- After the extraction of the whole coarsely powdered drug, it was filtered and further carried out for distillation process by using distillator to remove liquid present in the extract.
- After distillation process, the extract was concentrated on hot plate to remove moisture.
- Then the extract was stored in the desiccator to protect from moisture and contamination for preliminary qualitative phytochemical investigation and pharmacological investigation.
- The yield of the corrosive extracts was determined as a percentage. The colour and consistency of ethanolic extract was noted which has been summarized in table

Percentage extractives and physical characteristic of ethanolic extract of Cuscuta Reflexa Roxb

Table:1

Solvent	Plant	Colour and consistency	% yield(W/W)
Ethanol	Cuscuta Reflexa Roxb	Dark grayish & sticky	6.80

4.PHARMACOLOGICAL EVALUATION

Acute Toxicity Study[7]:

According to the OECD's requirements 15-day acute toxicity study using Swiss albino mice of both sexes and weighing 25–30 g was conducted to examine the effects of Cuscuta Reflexa Roxb. The animals spent the full night without food or water before taking part in the experiment. When evaluating acute toxicity, the up-and-down approach was used. As part of acute toxicity studies, Cuscuta Reflexa Roxb ethanolic extract was administered to animals, but neither toxicity symptoms nor animal deaths were observed. This led researchers to conclude that even at the greatest dose of 2,000 milligrammes per kilogramme of body weight, the substance was not lethal. The extract's hepatoprotective and antioxidant activities were evaluated at doses of 200 mg/kg and 100 mg/kg body weight, or 1/10th and 1/20th of the whole dose respectively.

EXPERIMENTAL DESIGN FOR SCREENING MODEL CCl_4 :

Group-1: Normal Control mice treated with 0.9% NaCl [2 ml/kg day]

Group-2: Mice treated with (CCl_4 20µl/kg i.p in olive oil)

Group-3: Mice treated with *Silymarin* (50 mg/ kg p.o) + CCl_4.

Group-4: Mice treated with *Cuscuta Reflexa* alone (200mg/kg p.o)

Group-5: Mice treated with *Cuscuta Reflexa* (100mg/kg p.o) + CCl_4

Group-6: Mice treated with *Cuscuta Reflexa* (200mg/kg p.o) + CCl_4

PROCEDURE[8,9]

Animals were as shown above grouped and treated for a period of 21 days. On 17th day, CCl_4 in olive oil (20µl/kg i.p) was administered to all groups other than group I and IV. Group III received standard drug silymarin 50 mg/kg p.o. once in a day and CCl_4 as mentioned above. Where as group IV, V and VI were treated with test extract dose of (200,100, 200 mg/kg p.o.) respectively. During this period of treatment the mice were maintained under normal diet and water. All the animals were sacrificed 72 hrs, after the administration of CCl_4 i.e. on 21st day. Blood was collected by retro orbital bleeding under mild ether anesthesia. Blood was allowed to clot at room temperature for 30 min, subjected to centrifugation (3000 rpm for 15 min.) and subjected to biochemical parameters.

Liver was dissected out and subjected for morphological study such as wet liver weight of each animal. Further the liver was placed in 10% formalin solution for histopathological study. Then the 10% of liver homogenate was subjected for in-vivo antioxidant estimation.

ESTIMATION OF BIOCHEMICAL PARAMETERS:

ESTIMATION OF SERUM SGPT/ALT, SGOT/AST, SERUM ALKALINE PHOSPHATE (ALP) AND BILIRUBIN

ANTIOXIDANT ESTIMATION:

ESTIMATION OF TOTAL PROTEIN (TP), *GLUTATHIONE (GSH)*, TOTAL THIOLS, *LIPID PEROXIDATION*, CATALASE AND SOD

STUDIES ON IN-VITRO STEADY-STATE FREE RADICAL SCAVENGING (CCl_4)

Reaction with DPPH radical, hydroxyl radical, Lipid peroxidation (Lpx) assay and Nitric oxide

5.RESULT:

Researchers investigated the phytochemical and pharmacological qualities of an extract made from the entire plant of Cuscuta Reflexa Roxb for the purpose of this study. The following details are derived from the ongoing inquiry that's being carried out.

Phytochemical investigation:

Preparation of extract and properties:

The use of ethanol as a solvent in the soxhelt extraction method led to a significant increase in the percentage of powdered whole-plant extract that was obtained. The yield was 6.80 percent and the colour of the ethanolic extract was a dark greyish brown.

Preliminary Phytochemical Studies:

The results of a qualitative chemical analysis done on an ethanolic extract of the whole plant of Cuscuta Reflexa Roxb are presented in Table 5.1. This analysis was carried out for the presence of components. Based on this information, we may infer that the extract has the following components: flavonoids, glycosides, protein, triterpinoid, alkaloid, steroids and saponins.

ASSESSMENT OF HEPATOPROTECTIVE EFFECTS

Table :2

Effect of Cuscuta Reflexa Roxb. ethanolic extract on elevated liver enzymes (alanine aminotransferase, alanine phosphotransferase, alkaline phosphatase and bilirubin (total and direct)) in CCl_4-induced hepatotoxicity.

Treatment	Liver weight in g	AST.IU/L	ALT.IU/L.	ALP.IU/L.	Total Bilirubin mg/dl.	Direct Bilirubin mg/dl.
Normal	1.835±0.183	82.31±3.35***	47.71±0.65***	106.45±3.05***	1.101±0.021***	0.250±0.042**
CCl_4	2.120±0.2048	242.53 ±5.53	206.45±4.04	190.8±5.45	4.721±0.006	1.890±0.742
Silymarin+CCl_4	1.687±0.168	93.13±0.53***	57.45±1.06***	128.4±1.02***	1.374±0.020***	0.622±0.034*
EtOH-200 alone	1.843±0.1145	85.46±2.16***	47.87±0.86***	109.75±2.47***	1.085±0.004***	0.316±0.011**
EtOH-100+CCl_4	1.573±0.1355	103.43±2.22***	65.31±2.31***	139.54±1.02***	1.690±0.004***	0.750±0.076
EtOH-200+CCl_4	1.442±0.0889	97.21±1.08***	60.05±0.87***	130.36±2.04***	1.442±0.032***	0.654±0.021*
df=5	n=6	n=6	n=6	n=6	n=6	n=6
Confidence level	99%	99%	99%	99%	99%	99%

Each value represents Mean ± SEM. *P<0.01; **p<0.001; ***p<0.0001compared to CCl_4 group. One way ANOVA followed by Dunnett.'s multiple comparison test

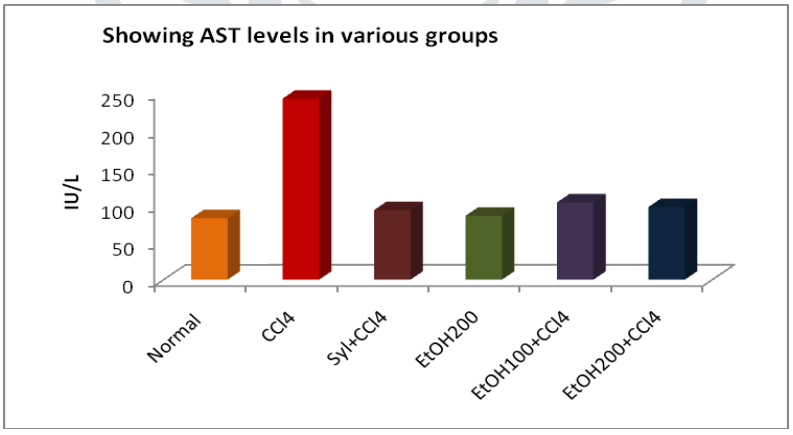


Fig. 2: AST levels in various groups

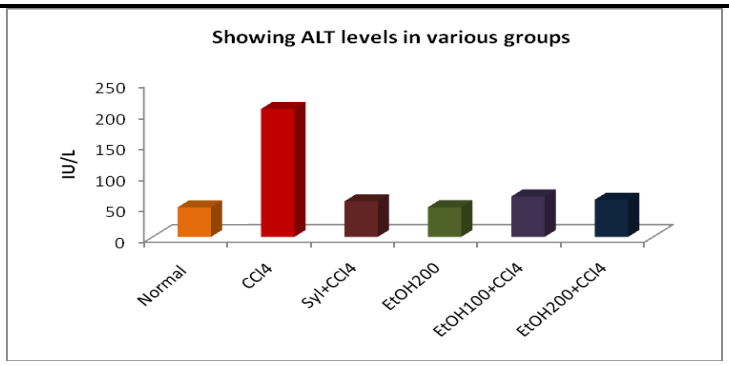


Fig.3: ALT levels in various groups

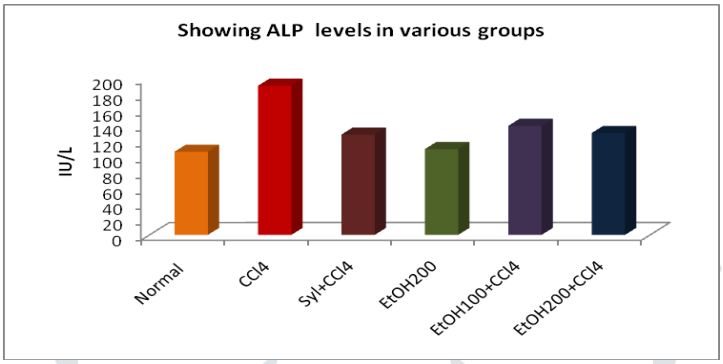


Fig.4: ALP levels in various groups

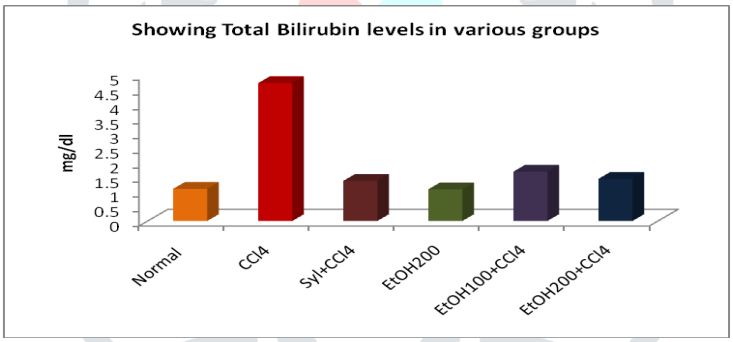


Fig.5 Total Bilirubin levels in various groups

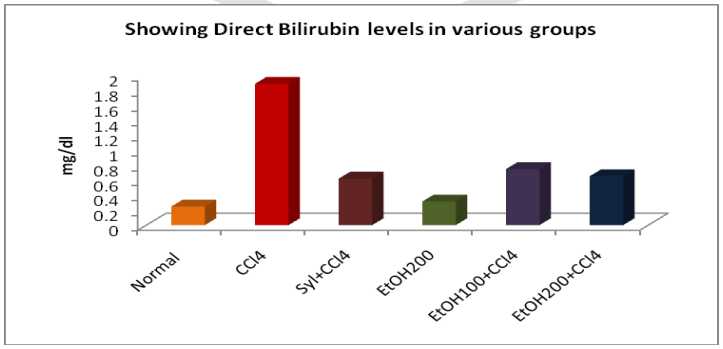


Fig.6 Direct Bilirubin levels in various groups

Assessing Antioxidant Action:

Table:3

Cuscuta Reflexa Roxb. ethanolic extract has antioxidative properties on its own on tissue Total protein, GSH, Total thiol, Catalase, LPO and SOD in CCl_4 induced hepatotoxicity.

Treatment	Total Protein mg/100mg of wet tissue	GSH nmol/mg of protein	Total Thiol nmol/mg of protein	CAT unit/mg protein	LPO unit/mg protein	SOD unit/mg of protein
Normal	45.64±0.9498****	27.54±0.9459****	86.99±0.6972****	196.6±0.9335****	3.358±0.3231****	45.65±0.9642****
CCl_4	12.5±0.9628	12.64±0.9769	44.63±0.9994	55.63±0.9618	59.65±1.022	13.51±0.9801
Syl+CCl_4	39.51±1.019*****	24.68±0.9904****	79.37±1.01*****	152.5±0.9588****	8.51±0..2857****	41.42±0.9649****
EtOH200 alone	43.47±0.9382*****	28.65±0.9724****	80.65±1.04*****	190.6±1.041*****	5.24±0.1507*****	43.56±1.022*****
EtOH100 +CCl_4	27.44±1.031*****	20.48±1.002*****	70.59±0.899*****	111.6±0.982*****	10.18±0.6222*****	33.63±0.9992****
EtOH200 +CCl_4	35.26±1.136*****	25.5±0.9103*****	78.81±0.969*****	147.7±0.9786****	9.675±1.186*****	39.4±0.9847*****
df=5	n=6	n=6	n=6	n=6	n=6	n=6
Confidence level	99%	99%	99%	99%	99%	99%

The values show the Mean ±SEM. For each group, *P<0.01, **P<0.001, and ***P<0.0001 versus the CCl_4 group. Dunnett's multiple comparison test after a one-way analysis of variance.

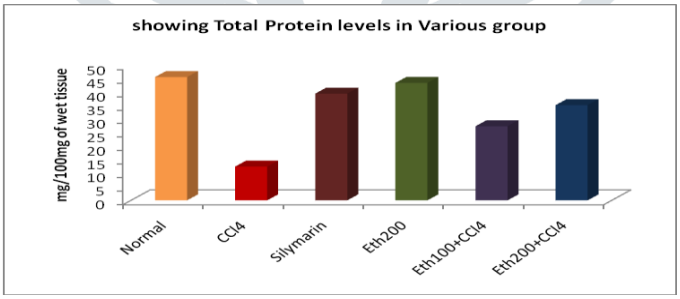


Fig.7 Total Protein levels in various groups

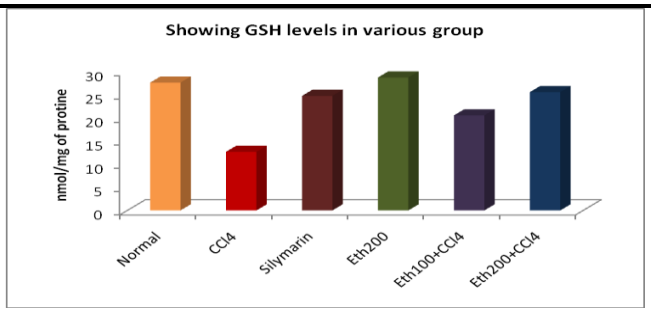


Fig.8 GSH levels in various groups

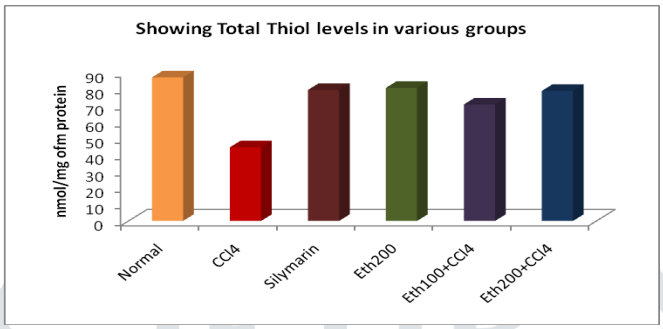


Fig.9 Total Thiol levels in various groups

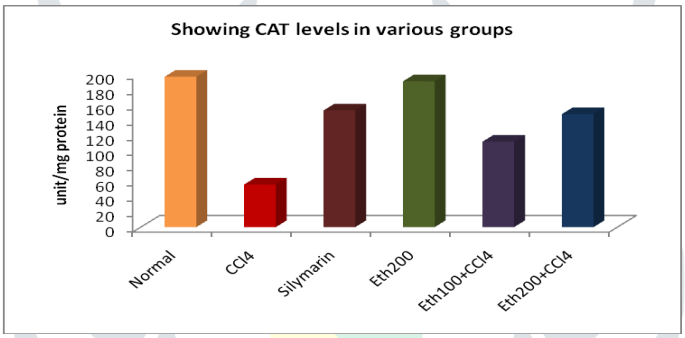


Fig.10 CAT levels in various groups

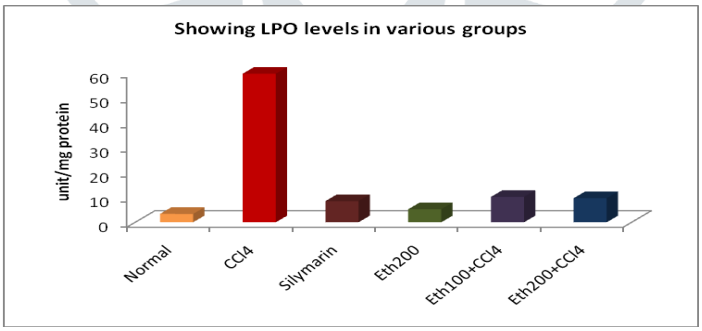


Fig.11 LPO levels in various groups

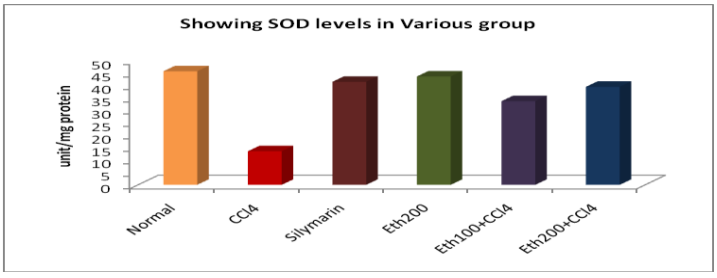


Fig.12 SOD levels in various groups

Antioxidant Activity Tests Conducted on a Petri Dish (CCl_4):

Table 4

The effect of Cuscuta reflexa Roxb ethanol extract on liver defence (OH^-) redical scavenging activity against CCl_4-induced oxidative stress.

Groups	Absorbance	% inhibition in activity	IC_{50} value
Control	0.630	0.00	66.7µg/ml
Control+6.25 µg	0.405	36.40	
Control+12.5 µg	0.371	42.80	
Control+25 µg	0.325	50.02	
Control+50 µg	0.278	55.87	
Control+75 µg	0.242	62.25	
Control+100 µg	0.205	67.81	
Control+200 µg	0.165	74.80	
Control+300 µg	0.125	80.15	
Control+400 µg	0.093	84.85	

$Y = 38.99-0.1412\ X$, $r^2= 0.6058$

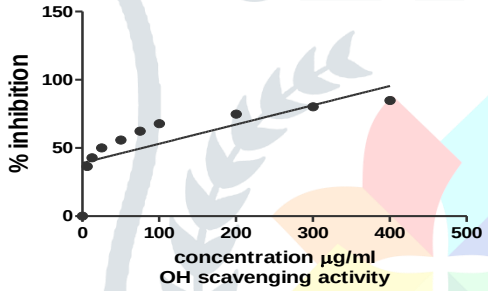


Fig. **13**

Table:5

Effect of Cuscuta Reflexa Roxb ethanolic extract on lipid peroxidation scavenging activities in CCl_4-induced liver damage

Groups	Absorbance	% inhibition in activity	IC_{50} value
Control	0.868	0.00	68µg/ml
Control+1.25 µg	0.744	14.28	
Control+2.5 µg	0.631	27.30	
Control+5 µg	0.575	33.75	
Control+10 µg	0.503	42.05	
Control+20 µg	0.446	48.61	
Control+40 µg	0.375	56.79	
Control+60 µg	0.340	60.82	
Control+80 µg	0.275	68.48	
Control+100 µg	0.201	76.31	
Control+200 µg	0.175	79.83	
Control+300 µg	0.111	87.21	

$Y=33.92-0.2306X$

$r^2=0.6309$

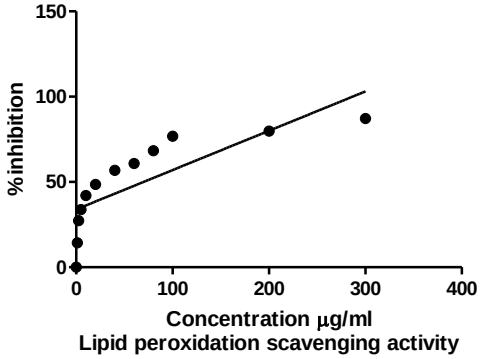


Fig. 14

Table :6

Effect of Cuscuta Reflexa Roxb's ethanolic extract on nitric oxide-scavenging capacity in CCl_4-induced hepatotoxicity

Groups	Absorbance	% inhibition in activity	IC_{50} Value
Control	0.787	0.00	
Control+25 µg	0.732	6.98	
Control+50 µg	0.711	9.65	
Control+100µg	0.697	11.43	
Control+125µg	0.651	17.28	
Control+175µg	0.636	19.18	
Control+200µg	0.602	23.50	378µg/ml
Control+250µg	0.535	32.02	
Control+300µg	0.456	42.05	
Control+350µg	0.398	49.42	
Control+400 µg	0.354	55.01	
Control+450µg	0.325	58.70	
Control+500µg	0.301	61.75	

Y=0.9127-0.1282X

r^2=0.9843

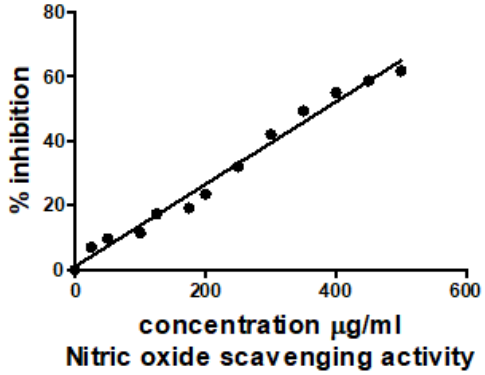


Fig. 15

Table :7

Effect of Cuscuta Reflexa Roxb ethanolic extract on DPPH Scavenging activities in CCl_4-induced liver damage

Groups	Absorbance	% inhibition in activity	IC_{50} Value
Control	0.652	0.00	125µg/ml
Control+1.25 µg	0.635	2.60	
Control+2.5 µg	0.597	8.43	
Control+5 µg	0.561	13.95	
Control+10 µg	0.513	21.31	
Control+20 µg	0.445	31.71	
Control+40 µg	0.322	50.61	
Control+60 µg	0.301	53.83	
Control+80 µg	0.277	57.51	
Control+100 µg	0.251	61.50	
Control+200 µg	0.244	62.57	
Control+300 µg	0.226	65.33	

Y=25.07-0.1875X

r^2=0.5621

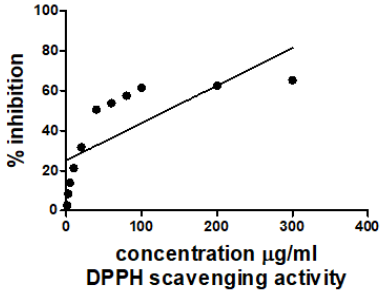
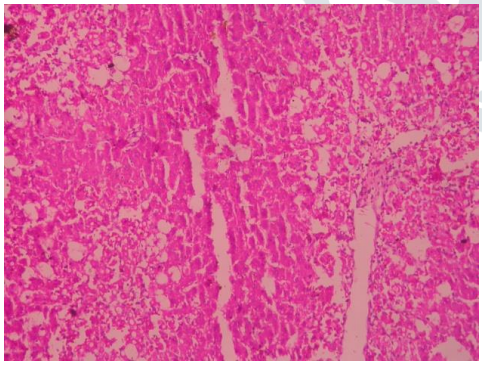
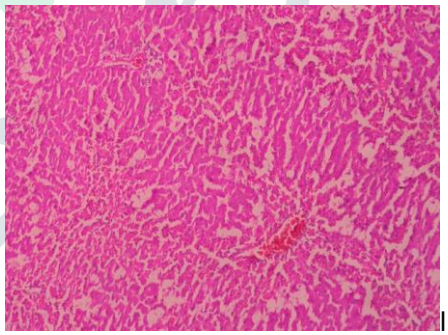


Fig. 16

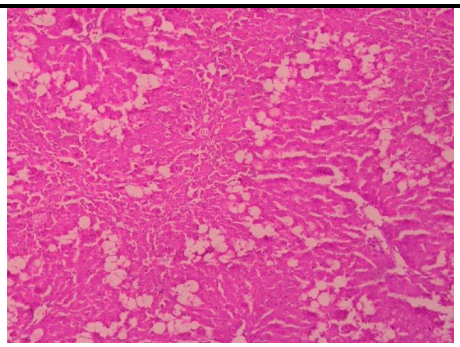
Photograph of liver biopsy in CCl_4 induced hepatotoxicity in mices



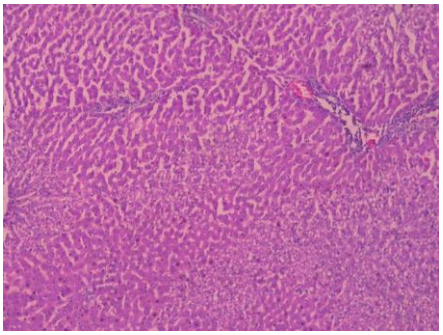
Silymarine+CCl_4 treated group
Fig. 17



CCl_4 treated group
Fig 18



EtoH-100+CCl_4 treated group
Fig. 19



EtoH-200+CCl_4 treated group
Fig. 20

6.Discussion

In this study, we investigated how an ethanolic extract of Cuscuta Reflexa Roxb produces its effect on albino mice's livers that had been poisoned by CCl_4 Specifically, we looked at how the extract helped to the recovery process.

The ethanolic extract that was created, put through a phytochemical test and the findings showed that alkaloids, sugars, glycosides, flavonoids and steroids were present.

According to the OECD's recommendations, research on the ethanolic extract's acute toxicity were conducted (Up and Down method). This was decided to be the upper limit because there were no fatalities at the dosage of 2000 mg/kg and dosages of 100 mg/kg and 200 mg/kg respectively were thought to be useful for evaluating hepatoprotective and antioxidant properties.

The activity of direct bilirubin (DIB), total bilirubin (TB), alanine phosphotransferase (ALP) and alanine aminotransferase (AST) & alanine transaminase(ALT) in the serum were raised in mice treated with CCl_4 indicating liver damage and oxidative stress. The condition that develops when the liver's cell membranes are so severely damaged that they are no longer able to operate normally is known as hepatic encephalopathy. As the underlying cause of this illness, liver dysfunction can be identified[10].Following administration of the ethanolic extract, It was demonstrated that the increased levels of biochemical markers such AST, ALT, ALP and Total and Direct Bilirubin had decreased. According to the findings of the histopathological investigation, there were discernible improvements in the hepatic globular architecture, a reduction in lymphatic infiltration, and Kuffer cell proliferation that appeared normal. It would suggest from these findings that the ethanolic extract of Cuscuta Reflexa Roxb. offers some degree of protection to the liver against the toxicity caused by CCl_4 .In light of early phytochemical studies that suggested the extract contained phenolic and flavonoid components, both of which are known for their antioxidant and hepatoprotective actions. It is important to note that these components are not present in large quantities. In order to determine the level of antioxidant activity that an ethanolic extract of Cuscuta Reflexa Roxb possessed, living organisms were used in the study. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH), lysozyme (LPO), total protein (TP), and total thiol are significant elements of this defence (TT) Which convert active oxygen molecules to non toxic. The concentrations of total protein, glutathione peroxidase,super oxidedismutase, catalase and malondialdehyde were measured to assess the level of in vivo antioxidant activity.It is believed that the production of lipid peroxides by free radical derivatives of CCl_4 plays a significant role in the liver damage brought on by this chemical (such as CCl_3).

Therefore, either antioxidant activity or the inhibition of free radical production is substantially correlated with protection against CCl_4-induced hepatotoxicity.It is likely that the CCl_4-induced hepatotoxicity, which results in oxidative stress and ultimately liver necrosis, alters the equilibrium between ROS formation and these antioxidant defences. A decrease in the activity of the enzymes glutathione, catalase and superoxide dismutase (SOD) was utilised to show that the liver damage brought on by the treatment of CCl_4 to mice was irreversible. In this study, those exposed to either CCl_4 had lower levels of the antioxidants glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT). Following pretreatment with an ethanolic extract of Cuscuta Reflexa Roxb, the levels of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in the liver were all restored. Mice given CCl_4 showed an increase in hepatic lipid peroxidation. Additionally, pretreatment with an ethanolic extract of Cuscuta Reflexa Roxb prevented the liver's MDA levels from rising, which is a symptom of accelerated lipid peroxidation[11].

Additional support for the aforementioned finding was supplied by studies of the plant extract's ability to scavenge free radicals, which were conducted independently. We discover that the ethanolic extract has substantial free radical scavenging activity against Lpx, OH and nitric oxide free radicals when we use DPPH as a measure of free radicals. This is the case when we compare the extract to these radicals.

In a similar manner, the liver weights of the animals were measured and it was discovered that the group that was treated with CCl_4 had an increase in their liver weight. Therefore, as compared to the control groups that were given CCl_4, the groups who were given Cuscuta Reflexa Roxb. ethanolic extract had a significant reduction in the amount of weight of livers.Liver cytochrome P_{450} enzymes are required for the synthesis of reactive and toxic metabolites from hepatotoxicants such as carbon tetrachloride. These metabolites are subsequently accountable for inducing liver damage in experimental animals.Free radicals are known to harm cells and tissues by forming covalent connections with them and oxidising lipids among other actions. By removing "free radicals," which are lone oxygen molecules that have become out of balance, antioxidants stop oxidative damage to cells. Plasma contains several well-known enzymes that perform antioxidative functions by converting reactive oxygen and nitrogen species into stable molecules and scavenging additional free radicals including superoxide dismutase (SOD), catalase (CAT) & glutathione (GSH). These enzymes include superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH). Since the biochemical and tissue abrasion caused by CCl4 could be reversed with treatment using an ethanolic extract of Cuscuta Reflexa Roxb, the hepatoprotective effect against CCl_4 challenge is most likely brought on by its ability to scavenge free radicals and prevent lipid peroxidation.

7.Conclusion

This suggests that the Cuscuta Reflexa Roxb. extract's antioxidant activity may be to blame for the plant's hepatoprotective qualities. It's possible that the presence of flavonoids and phenolic chemicals shows treatment of liver damage and antioxidantactivity. Extract of Cuscuta Reflexa Roxb. has been shown to possess both hepatoprotective and antioxidant effects, as determined by biochemical and histological testing.For the purpose of screening, I used a mouse model of toxicity caused by CCl_4. Using this model, I noticed that the ethanolic extract of Cuscuta Reflexa Roxb had the highest concentration of flavonoids and consequently the greatest hepatoprotective properties (cuscutin).

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