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Pharmacological Evaluation of Capsicum Chinense leaves extract on Carbon tetra-chloride induced Hepatotoxicity in Mice

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Abstract

The term "toxicity" refers to the harmful effects of a drug on a living thing as a whole, including bacteria, plants, and animals, as well as the underlying structures of living things, such as cells (cytotoxicity), organs (organotoxicity), and livers (hepatotoxicity). The most prevalent manifestation of hepatotoxicity is liver dysfunction or damage brought on by taking too many medications or xenobiotics. Exogenous substances with clinical significance are known as hepatotoxicants like CCl4. The objectives ofPharmacological evaluation of hepatoprotective effect of leaves extract of Capsicum Chinense in CCl4 induced hepatotoxicity in Swiss albino mice.For hepatotoxicity studies, reduced dose of Capsicum Chinense (50mg/kg), (100mg/kg) was administered daily for 21days. Total bilirubin, Total protein, Albumin, Globulin, SGOT, SGPT, ALP and liver weight were estimated in serum. CCl4 dose (2ml/kg i.p) with olive oil in the ratio of 1:1 v/v twice in a week is given to mice for induced hepatotoxicity during 21 days studies. Induction of CCl4 dose (2ml/kg i.p) with olive oil in the ratio of 1:1 v/v increased the biochemical marker of Total bilirubin, SGOT, SGPT, ALP,and Total protein, albumin and globulin were decreased. The improving effect of Capsicum chinense in hepatotoxicity is investigated in this study.

Key words: Hepatotoxicity, Capsicum Chinense, Silymarin, Oxidative stress, Reactive oxygen species.

INTRODUCTION

The term "toxicity" refers to the harmful effects of a drug on a living thing as a whole, including bacteria,plants, and animals, as well as the underlying structures of living things, such as cells (cytotoxicity), organs (organotoxicity), and livers (hepatotoxicity)**[1].**"Hepar," the Greek word meaning liver, additionally occurs to refer hepato- hepatocyte, & hepatic conditions. **[2]**The majority of the time, oxidative strain is the cause of liver dysfunction, which progresses through stenosis to persistent

hepatitis, cirrhosis, inflammation of the liver, and cancer of the hepatic cells. In US, liver problems affect approximately fifty percent of people. **[3]**The specific processes behind the development of cirrhosis of the liver remain poorly known, while peroxides from lipids and free electrons have received a lot of interest. **[4]**The oxidation of lipids and ECM formation can be brought on by CCl4, which can lead to liver damage.**[5]** The most prevalent manifestation of hepatotoxicity is liver dysfunction or damage brought on by taking too many medications and foreign substances. **[6]**Exogenous substances with clinical significance are known as hepatotoxicants. These substances can cause liver injury when overdosed on medications such as chemicals used in industry like alcoholic beverages, CCl_4, B-galactosamine, Thio-acetamide or Anti-tubercular medications such as rifampin, ethambutol and so forth. **[7]**Healthy tissue will always react severely to damage of any form with inflammatory. It's a multifaceted process that is often linked to pain and includes things like higher permeability of the arteries, enhanced decomposition of proteins, and changes to membranes. **[8,9]**It has recently been established that agricultural products are organic suppliers of a variety of bioactive chemicals. **[10]**.Peppers are one of these vegetables, the genus Capsicum includes peppers. **[11]** Capsicum Chinense which is commonly known as Habanero pepper, king chilli or bhut jolokia can be utilized as a painkiller and to cure inflammation-related disorders like osteoarthritis, rheumatic persistent discomfort in the stomach, and other conditions. Experimental on plants that are purportedly used in folklore as anti-inflammatory properties and painkillers might thus be seen as a useful and rational methodology in the quest for novel analgesics and anti-inflammatory medications. **[12]**

MATERIAL AND METHODS

Identification and Collection of the Plant

The leaves part of the Capsicum chinense plant has been collected from the local area of Mazbat, Assam, India and were air dried in the shade.

Extraction method of the plant

Dried leaves of Capsicum chinense were collected and then grinded into coarse powder using mortar and pestle and stored in an air-tight container to protect from the moisture. Hydromethanolic method was used in the study for the extraction of the plant. The plant extract was prepared by maceration process where 100gm crude drug powder was soaked in 75% methanol in beaker for 72 hrs. at room temperature with occasional stirring. After 72 hrs. the liquid phase stained, filtered using filter paper and evaporated to dryness in hot air oven as a result the extract was obtained and weighed.**[13]**

Figure.No.1

Figure No. 2

Experimental Animals

Swiss albino male mice weighing 30-40 g approximately of 9- 11 weeks of age were used for the experiment which have been obtained from Lala Lajpat Rai University of Veterinary and Animal

Sciences, Hisar, Haryana, India. They were housed in laboratory environment with regular housing conditions (temperature- 25C under 12 hrs. light and 12 hrs. dark cycle) with a standard pellet feed. All animal procedures were performed according with regulations specified by the institutional animal ethics committee CPCSEA.

Animal Grouping

Mice are divided into 5 groups (6 animals each in a group) and classified as following:

Group 1 (Normal Control Group): Normal saline water and food were given to mice for 21 days.

Group 2 (Diseased Control Group): Weekly twice, mice were injected with(2ml/kg CCl_4in olive oilby (1:1 ratio, v/v) through intraperitoneal route.

Group 3 (Test Group, 50mg/kg): Weekly twice, mice were injected 2ml/kg CCl_4 in olive oil (1:1 ratio, v/v) through IP with 50mg/kg leaves extract of Capsicum chinense, daily via orally for 21 days.

Group 4 (Test Group, 100mg/kg): Weekly twice, mice were injected 2ml/kg CCl_4 in olive oil (1:1 ratio, v/v) through intraperitoneal route with 100 mg/kg leaves extract of Capsicum chinense, daily via orally for 21 days.

Group 5 (Standard Group): Weekly twice, mice were injected 2ml/kg CCl_4 in olive oil (1:1 ratio, v/v) through intraperitoneal route with 100 mg/kg of Silymarin, daily via orally for 21 days.

On 22^{th} day, to lessen suffering, all of the animals were sacrificed following the last dosage while undergoing appropriate anaesthetics. The blood sample to be collected and tinted fluid examined liver enzyme markers in vivo using this method. By severing the falciform and coronary tendons, the liver's tissue was isolated of the ribcage. The livers were washed and then stored for histological examination in a ten percent formaldehyde mixture.

RESULTS

Statistical analysis

Results were expressed as mean ± SEM, (n=6). Statistical analysis was performed with one way analysis of variance (ANOVA) followed by Tukey test. P value less than <0.05 was considered to be statistically significant. *P<0.05, **<0.01 and ***<0.001.

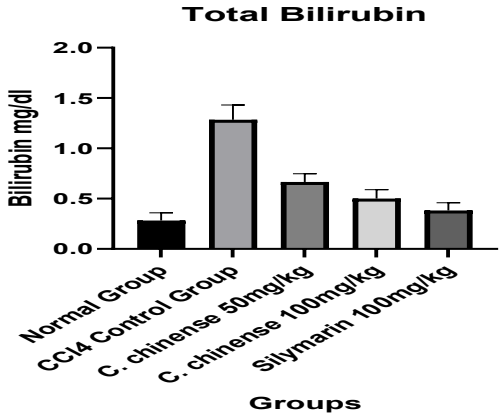
TABLE.NO. 1 Shows: Effect of various pharmacological interventions on level of Total Bilirubin. (mg/dl)

Sl. No	Group Name	Total Bilirubin Level
1.	Normal Control	0.283± 0.075
2.	Disease control	1.283± 0.147
3.	Treatment group (Capsicum Chinense) 50mg/kg	0.666± 0.081
4.	Treatment group (Capsicum Chinense) 100mg/kg	0.500± 0.089
5.	CCl4 + Silymarin (Standard group)	0.383± 0.075

Values are expressed as mean± SEM, (N=6)

TABLE.NO. 2 shows: Multiple comparison of total bilirubin level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	-1.0	-1.166 to -0.834	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	0.616	0.4511 to 0.782	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	0.783	0.6178 to 0.948	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	0.900	0.734 to 1.066	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	0.166	0.0011 to 0.3322	Yes	.048
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	0.116	-0.0488 to 0.2822	No	.264



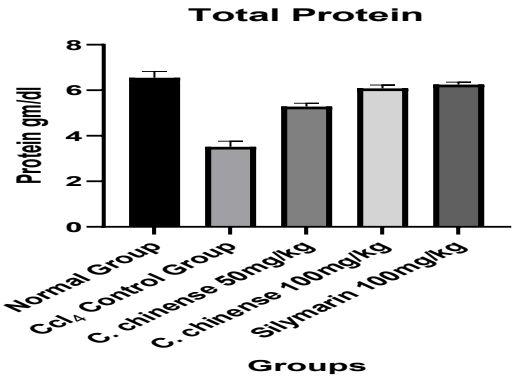
Graph.no.1: Effect of C. Chinense with CCl4 on Total Bilirubin level.

Table.no. 3 shows: Effect of various pharmacological interventions on level of Total Protein. (gm/dl)

Sl. No	Group Name	Total Protein Level
1.	Normal Control	6.550± 0.2739
2.	Disease control	3.517± 0.2483
3.	Treatment group (Capsicum Chinense) 50mg/kg	5.283± 0.1472
4.	Treatment group (Capsicum Chinense) 100mg/kg	6.083± 0.1472
5.	CCl4 + Silymarin (Standard group)	6.250± 0.1049

TABLE.NO.4 shows the multiple comparison of total protien level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	3.033	2.702 to 3.365	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	-1.767	-2.098 to -1.435	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	-2.567	-2.898 to -2.235	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	-2.733	-3.065 to -2.402	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	-0.800	-1.131 to – 0.4686	Yes	<.001
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	-0.1667	-0.4981 to 0.1647	No	.586



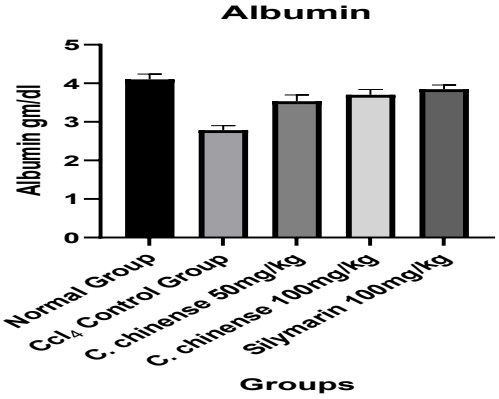
Graph.no.2: Effect of C. Chinense with CCl4 on Total Protein level.

Table.no.5. Shows: Effect of various pharmacological interventions on level of Albumin (gm/dl)

Sl. No	Group Name	Total Albumin Level
1.	Normal Control	4.100 ± 0.1414
2.	Disease control	2.783 ± 0.1169
3.	Treatment group (Capsicum Chinense) 50mg/kg	3.533 ± 0.1633
4.	Treatment group (Capsicum Chinense) 100mg/kg	3.700 ± 0.1414
5.	CCl4 + Silymarin (Standard group)	3.850 ± 0.1049

Table.no.6 shows. shows the multiple comparison of albumin level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	1.317	1.087 to 1.546	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	-0.750	-0.9792 to -0.5208	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	-0.916	-1.146 to -0.6875	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	-1.067	-1.296 to -0.8375	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	-0.1667	-0.395 to –0.0625	No	.237
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	-0.1500	-0.3792 to 0.0791	No	.332



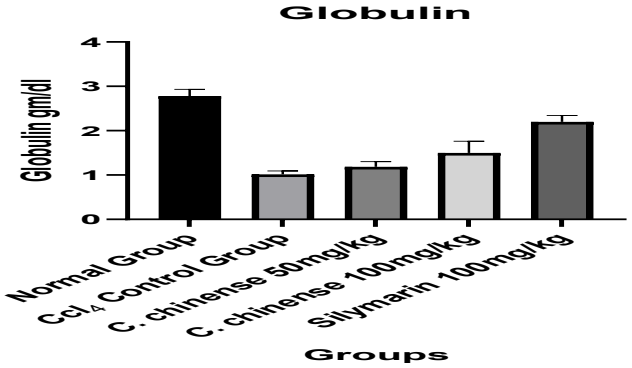
Graph.no. 3: Effect of C. Chinense with CCl4 on Albumin level.

Table.no. 7. Shows: Effect of various pharmacological interventions on level of Globulin (gm/dl)

Sl. No	Group Name	Globulin Level
1.	Normal Control	2.783 ± 0.1472
2.	Disease control	1.017 ± 0.0752
3.	Treatment group (Capsicum Chinense) 50mg/kg	1.183 ± 0.1169
4.	Treatment group (Capsicum Chinense) 100mg/kg	1.500 ± 0.2608
5.	CCl4 + Silymarin (Standard group)	2.200 ± 0.1414

Table.no. 8 shows: shows the multiple comparison of globulin level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	1.767	1.494 to 2.039	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	-0.1667	-0.439 to -0.1057	No	.397
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	-0.4833	-0.7557 to -0.2110	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	-1.183	-1.456 to -0.9110	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	-0.3167	-0.5890 to –0.04431	Yes	.017
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	-0.7000	-0.9724 to-0.4276	Yes	<.001



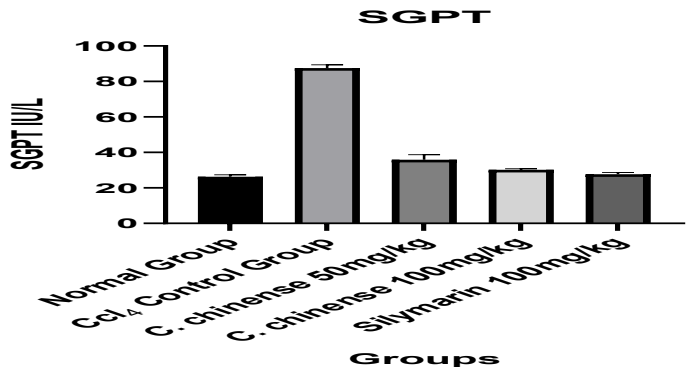
Graph.no. 4 shows: Effect of C. Chinense with CCl4 on Globulin level.

Table.no. 9. **Shows**: **Effect of various pharmacological interventions on level of SGPT (IU/L)**

Sl. No	Group Name	SGPT Level
1.	Normal Control	26.27 ± 1.124
2.	Disease control	87.50 ± 1.871
3.	Treatment group (Capsicum Chinense) 50mg/kg	35.83 ± 2.858
4.	Treatment group (Capsicum Chinense) 100mg/kg	30.20 ± 0.632
5.	CCl4 + Silymarin (Standard group)	27.67 ± 1.033

Table.no. 10 shows: shows the multiple comparison of SGPT level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	-61.23	-64.11 to -58.36	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	51.67	48.79 to 54.54	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	57.30	54.42 to 60.18	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	59.83	56.96 to 62.71	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	5.633	2.756 to 8.510	Yes	<.001
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	2.533	-0.3438 to 5.410	No	.104



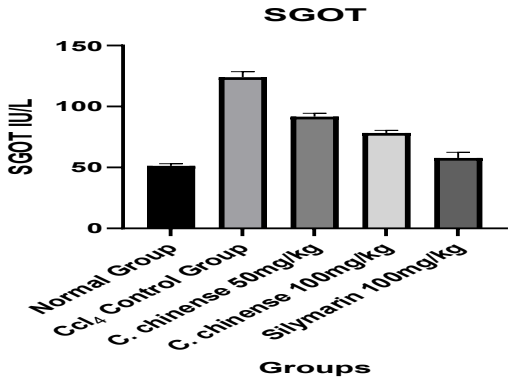
Graph.no. 5 shows: Effect of C. Chinense with CCl4 on SGPT level

Table.no. 11 shows:Effect of various pharmacological interventions on level of SGOT (IU/L)

Sl. No	Group Name	SGOT Level
1.	Normal Control	51.33 ± 1.751
2.	Disease control	124.0 ± 4.517
3.	Treatment group (Capsicum Chinense) 50mg/kg	91.67 ± 2.805
4.	Treatment group (Capsicum Chinense) 100mg/kg	78.33 ± 2.160
5.	CCl4 + Silymarin (Standard group)	57.83 ± 4.622

Table.no. 12 shows: shows the multiple comparison of SGOT level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	-72.67	-78.41 to -66.92	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	32.33	26.59 to 38.08	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	45.67	39.92 to 51.41	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	66.17	60.42 to 71.91	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	13.33	7.590 to 19.08	Yes	<.001
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	20.50	10.76 to 26.24	Yes	<.001



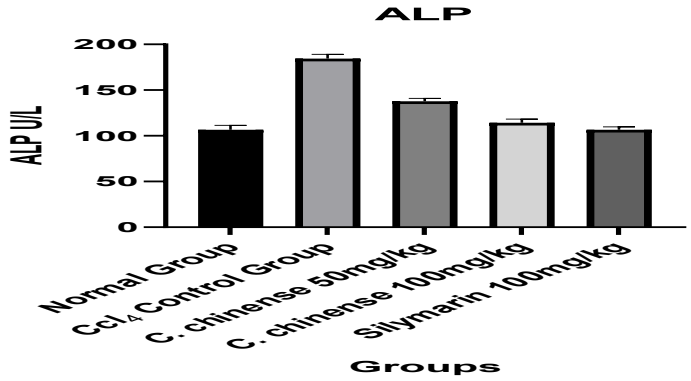
Graph.no. 6 shows: Effect of C. Chinense with CCl4 on SGOT level.

Table.no. 13 shows: Effect of various pharmacological interventions on level of ALP (U/L)

Sl. No	Group Name	ALP Level
1.	Normal Control	106.5 ± 4.970
2.	Disease control (CCl4)	184 ± 4.761
3.	Treatment group (Capsicum Chinense) 50mg/kg	137.7 ± 3.266
4.	Treatment group (Capsicum Chinense) 100mg/kg	114.2 ± 4.021
5.	CCl4 + Silymarin (Standard group)	106.5 ± 3.271

Table.no. 14 shows: shows the multiple comparison of ALP level in different groups.

Sl.No	Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Adjusted P Value
1.	Normal vs. Disease	-77.83	-84.82 to -70.85	Yes	<.001
2.	Disease vs. Treatment(Capsicum Chinense) 50mg/kg	46.67	39.68 to 53.65	Yes	<.001
3.	Disease vs. Treatment(Capsicum Chinense) 100 mg/kg	70.17	63.18 to 77.15	Yes	<.001
4.	Disease vs. Standard (Silymarin 100mg/kg)	77.83	70.85 to 84.82	Yes	<.001
5.	Treatment 50 mg/kg vs Treatment 100mg/ kg	23.50	16.51 to 30.49	Yes	<.001
6.	Treatment 100mg/kg vs Silymarin 100mg/kg	7.667	0.6796 to 14.65	Yes	.026



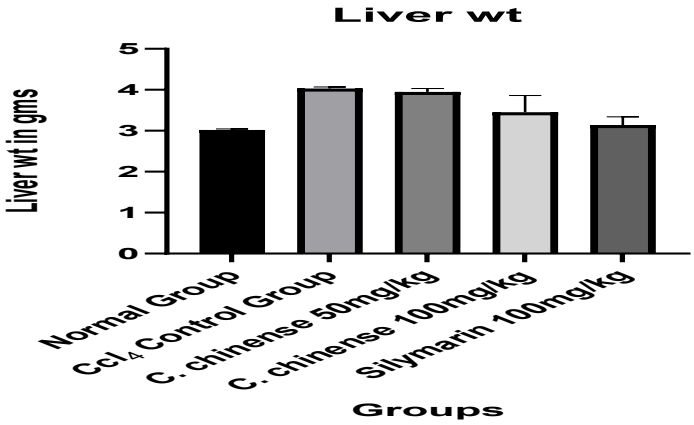
Graph.no. 7 shows: Effect of C. Chinense with CCl4 on ALP level.

Table.no. 20shows:Effect of various pharmacological interventions on level of Liver weight (gm)

Sl. No	Group Name	Liver wt.
1.	Normal Control	3.017 ± 0.02582
2.	Disease control (CCl4)	4.032 ± 0.03656
3.	Treatment group (Capsicum Chinense) 50mg/kg	3.948 ± 0.08400
4.	Treatment group (Capsicum Chinense) 100mg/kg	3.453 ± 0.4078
5.	CCl4 + Silymarin (Standard group)	3.40 ± 0.1995

TABLE.NO. 20 shows: the multiple comparison of Liver wt. in different groups.

No	key's multiple comparisons test	an Diff.	00% CI of di	nificant?	justed P Value
	mal vs. Disease	015	67 to -0.6633		01
	ease vs. Treatment(Capsicum Chine ng/kg	333	684 to 0.4351		6
	ease vs. Treatment(Capsicum Chine mg/kg	783	266 to 0.9301		01
	ease vs. Standard (Silymarin 100mg/k	917	399 to 1.243		01
	atment 50 mg/kg vs Treatment 100	950	433 to 0.8467		3
	atment 100mg/kg vs Silymarin 100mg	133	3841 to 0.665		3



Graph.no. 8 shows: Effect of C. Chinense with CCl4 on liver wt.

Histopathology of Mice Liver

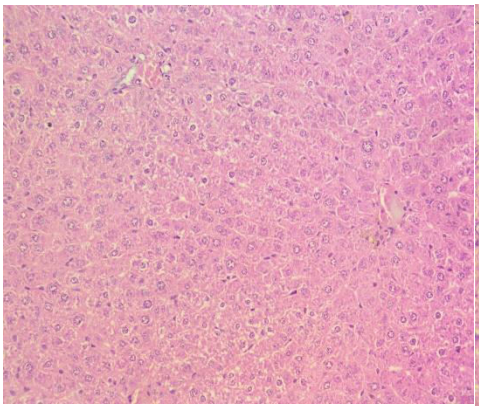


Fig.no.3- (a) Normal Control

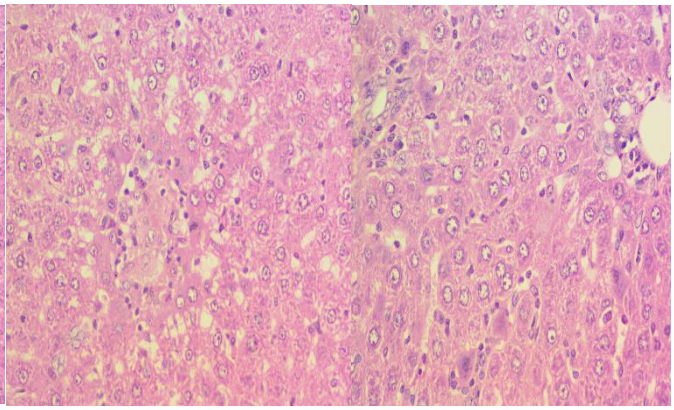


Fig.no.3- (b) Disease Control

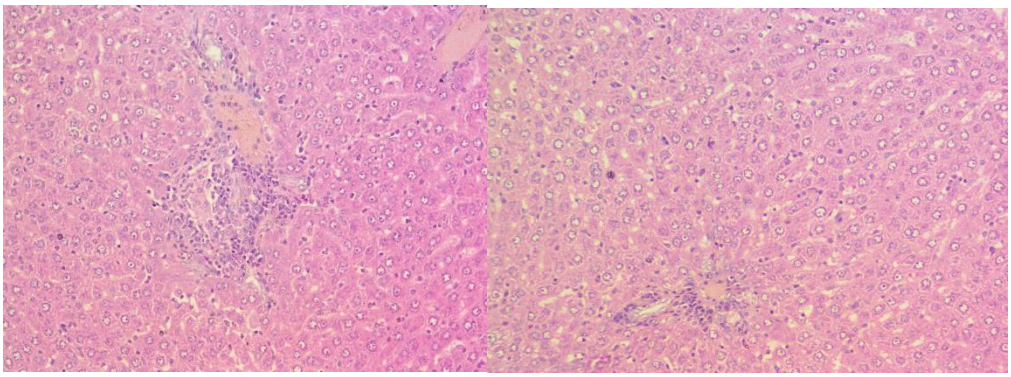


Fig.no.3- (c) C. Chinense 50mg/kg **Fig.no.3- (d) C. Chinense 100mg/kg**

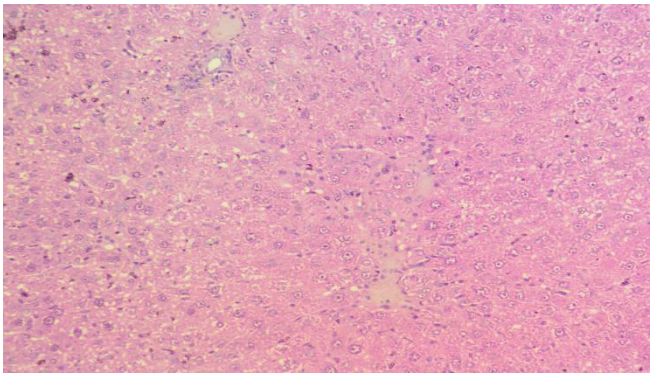


Fig.no.3-(e) Silymarin 100mg/kg

Figure, Photomicrograph (original magnification 45x) of histopathological studies of mice liver of various groups. **(Fig. a)** Liver sections showing normal appearing portal are. Areas around hepatic vein appear normal. **(Fig. b)** Liver sections showing moderate hepatocytic degeneration with drop out necrosis, ballooning degeneration mainly in periportal area and occasional around hepatic vein. Prominent fatty changes also noted. Congestion along with mononuclear cells infiltration noted. Marked choleastasis noted. **(Fig. c)** Liver sections showing mild to moderate hepatocytic degeneration with vesicular degeneration mainly in periportal area and occasional around hepatic vein. Prominent fatty changes also noted. Drop out necrosis, hemorrhage, congestion, steatosis along with mononuclear cells infiltration noted. **(Fig. d)** Liver sections showing minimal hepatocytic degeneration with moderate Kupffer cells hyperplasia. Mild fatty liver changes noted. Scanty hemorrhage, congestion, mild steatosis along with minimal mononuclear cells infiltration noted. **(Fig e)** Liver sections showing occasional hepatocytic degeneration with regenerative changes exhibiting prominent Kupffer cell hyperplasia. Mild to moderate fatty changes also noted around periportal region. Scanty hemorrhage, congestion, mild steatosis along with minimal mononuclear cells infiltration noted.

Discussion

In the present study, CCl4 induced hepatotoxicity is clearly evidenced by the marked elevation biochemical markers are total bilirubin, SGOT, SGPT, ALP and decreased biochemical markers are total protein, Albumin, Globulin. These biochemical parameters are used as a specific hepatic marker during diagnosis in the early detection of hepatic toxicity. In this study the Total bilirubin, SGPT, SGOT, ALP level isincreased in CCl4 control group when compared to normal control group in 21 days study. This suggest that after administration of Capsicum Chinense at reduced dose at (50mg/kg), (100mg/kg) and the total bilirubin, SGPT, SGOT, ALP level is decreased in group 3 and group 4 when compared with

CCl4 control group, which indicates that Capsicum Chinense shows its beneficial effects on liver. After administration of Silymarin (100mg/kg p.o) the level of total bilirubin, SGPT, SGOT, ALPis decreased in group 5 when compare with CCl4 control group.

In present study, the level of Total protein, albumin and globulin aredecreased in CCl4 control group when compared with normal control group. After administration of Capsicum Chinense at reduced doses at 50mg/kg and 100 mg/kg the level of Total protein, albumin and globulin areincreased and improving ingroup 3 and 4 when compare to the CCl4 control group. Which indicates that Capsicum Chinese shows protective effect on liver. After administration of Silymarin (100mg/kg p.o) the level of Total protein, albumin and globulin are increased and much improving in group 5 when compared with CCl4 control group.

And the liver weight of the mice shows increased in CCl4 control group when compare with normal control group. After treatment with C. Chinense extract and silymarin, the change in liver weight is similar to normal control group.

Conclusion

Data from the study suggest that Capsicum Chinense can 'posses' hepatoprotective and beneficial action on the Lier. Capsicum Chinese at reduced dose (50mg/kg) and (100mg/kg), decreases the biochemical markers which is elevated in hepatotoxicity. This will open new perspectives that Capsicum Chinense is a hepatoprotective compounds to prevent and treat the occurrence of hepatotoxicity.

Abbreviation

SGOT- Serum glutamic oxaloacetic transaminase
SGPT- Serum glutamic pyruvic transaminase
ALP- Alkaline phosphatase
CCL4- Carbon tetra chloride
C. Chinense- Capsicum Chinense
i.p- Intraperitoneal

Conflict of Interest

The author has no conflict of interest.

Acknowledgement

The author is thankful to Dr. Sanjay Singh (Principal) and Guide (Mrs. Priti Khanduri) and Co-guide (Mr. Rahul Singh Dhariyal) for his Scientific advice and provide every facility during the research protocol.

Author Contribution

WRD- Writing original Draft
RSD- Original concept
PK- Supervision
SS- Supervision

Ethical Approval

The research study was conducted at Siddhartha institute of pharmacy, Near IT park, Dehradun 248001. The animal house is CPCSEA approval. And the registration no. of the animal house – 1435/PO/RE/S/11/CPCSEA

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