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Research Article

PROTECTIVE EFFECT OF ETHANOLIC EXTRACT AND ITS ETHYLACETATE AND n-BUTANOL FRACTIONS OF *SECHIUM EDULE* FRUITS AGAINST CARBON TETRACHLORIDE INDUCED HEPATIC INJURY IN RATS

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ABSTRACT

Ethanolic extract of fruits of *Sechium edule* and its different fractions (100, 200 mg/kg, p.o) showed significant hepatoprotective activity against CCl_4 induced hepatotoxicity in rats by reducing the levels of AST, ALT, ALP, total billirubin and hepatic lipid peroxidation and increasing the levels of antioxidants markers like hepatic glutathione (GSH), catalase (CAT), super oxide dismutase (SOD) and total protein in a dose dependent manner, which was confirmed by histopathological examination. Thus, the ethanolic extract of fruits of *Sechium edule* could protect the liver cells from CCl_4 induced liver damages, by its antioxidative effect on hepatocytes.

Keywords: *Sechium edule*, CCl_4, Hepatoprotective activity, Hepatotoxicity, Antioxidative

INTRODUCTION

Sechium edule is an edible plant that belongs to the family Cucurbitaceae also known as sayote, choko, chocho, chow-chow, and vegetable pear. The chayote is a herbaceous, perennial, monoecious, vigorous creeper or climbing plant. The fruits grow either individually or in pairs on a shared peduncle. They are fleshy or fleshy-fibrous, may have longitudinal ridges or furrows, and come in many different shapes (globose, ovoid, subovoid, pyriform) and colours (dark or light green) [1]. The fruits and the seed especially, are rich in several important amino acids [2]. A lectin from the exudate of *Sechium edule* was purified [3]. Eight flavonoids, including three *C*-glycosyl and five *O*-glycosyl flavones, were detected [4]. Twenty known Gibberellins' have been identified in extracts of the seeds of *Sechium edule* [5]. The leaves and fruits have diuretic, cardiovascular and anti-inflammatory properties, the leaves has been used in the treatment of arteriosclerosis and hypertension, and to dissolve kidney stones [6, 7]. It has been reported that the ethanolic extracts of dried leaves and water extracts of seeds were found to possess higher radical-scavenging, reducing power and antioxidant activities by the mechanism of inhibition of lipid peroxidation, free radical scavenging activity [8]. Literature reviews indicated hepatoprotective activity of this plant has not been evaluated so far. In view of this, the present study was aimed to evaluating the hepatoprotective activity of ethanolic extract and its ethylacetate, n-butanol fractions of *Sechium edule* fruits.

MATERIALS AND METHODS

Plant Material

Fruits of *Sechium edule* were collected from Reliance Fresh, Secunderabad and also from Bangalore. The fruit material was taxonomically identified and authenticated by Dr. Shiddamallayya N at Regional Research Institute (Ay.), Bangalore, where the voucher specimen is conserved under the reference number (RRCBI/MCW/7/2008). The fruits of *Sechium edule* were isolated, chopped into small pieces, dried under shade at room temperature for seven days and powdered. The powder was defatted with petroleum ether (60-80 GR) for 72 h and then the dried powder was extracted with ethyl alcohol to get a yield of 12.1 % w/w. Dried extract dissolved in distilled water was used for the study. The ethanolic extract was dispersed in distilled water and partitioned with ethyl acetate in a separating funnel till the colourless ethyl acetate fraction is obtained. Then the aqueous part is then partitioned with n-butanol to get the butanol fraction. Ethyl acetate and butanol fraction so obtained was concentrated by keeping in boiling water bath to get the solid residue. The dried extracts were stored in airtight container and placed in refrigerator.

Phytochemical screening

Preliminary phytochemical screening of ethanolic extract of *Sechium edule* fruits and its ethyl acetate and n-butanol fractions were performed for the presence of alkaloids, phenolics, flavonoids, saponins, carotenoids, carbohydrates and glycosides [9].

Drugs and chemicals

Carbontetrachloride was procured from E. Merck chemicals pvt. Ltd, Mumbai, India, silymarin were obtained from Micro Labs, Bangalore, India. ALT, AST, ALP, Total bilirubin, Totlal protein and Creatinine kits were obtained from Span Diagnostics, Surath, India. All other chemicals used in this study were obtained commercially and were of analytical grade.

Experimental animals

In-bred wistar rats weighing 150-200g maintained under controlled conditions of temperature (23± 2°C) and humidity (50 ± 5%) and a 12-hour light–dark cycle, were used for the experiment. They were housed in sanitised polypropylene cages containing sterile paddy husk as bedding. They had free access to standard rat pellet diet and water *ad libitum*. The animals were given a week's time to get acclimatized with the laboratory conditions. All the experimental procedures were performed according to the committee for the purpose of control and supervision of experiments on animals (CPCSEA), ministry of social justice and empowerment Government of India, norms and approved by the Institutional Animal Ethics Committee (IAEC).

Acute toxicity studies

Rats were kept overnight fasting prior to drug administration. animals were received a single oral dose (2000 mg/kg, b.w.) of ethanolic extract of *Sechium edule* fruits and its ethyl acetate and n-butanol fractions. After the administration of *Sechium edule* fruit extract and its different fractions food was withheld for further 3–4 h. Animals were observed individually at least once during the first 30 min after dosing, periodically during the first 24 h (with special attention during the first 4 h) and daily thereafter for a period of 14 days. Once daily cage side observations included changes in skin and fur, eyes and mucous membrane (nasal) and also respiratory rate, circulatory (heart rate and blood pressure), autonomic (salivation, lacrimation, perspiration, piloerection, urinary incontinence, and defecation) and central nervous system (ptosis, drowsiness, gait, tremors and convulsion) changes. Mortality, if any, was determined over a period of 2 weeks [10].

Selection of dose of the extract and its fractions

LD_{50} was done as per OECD guidelines for fixing the dose for biological evaluation. The LD_{50} of *Sechium edule* fruit extract and its different fractions as per OECD guidelines falls under class four values with no signs of acute toxicity at 2000 mg/kg. The biological evaluation was carried out at doses of 100 and 200 mg/kg body weight.

Carbon tetrachloride induced hepatotoxicity in rats[11, 12]

Rats were divided into nine groups containing six rats in each groups.

Group I (control) animals were administered a single dose of water (1 ml/kg, p.o.) daily for 5 days and received liquid paraffin (1 ml/kg, s.c.) on day 2and 3.

Group II (CCl_4) received water (1ml/kg body wt., p.o.) once daily for 5 days and received CCl_4: liquid paraffin (1:1, 2 ml/kg bodyweight, s.c.) on day 2 and 3.

Group III received standard drug Silymarin (50 mg/kg, p.o.) once daily for 5 days.

Group IV received ethanolic extract of *Sechium edule* (200mg/kg, p.o.).

Group V received ethanolic extract of *Sechium edule* (100mg/kg, p.o.).

Group VI received ethyl acetate fraction of *Sechium edule* ethanolic extract (200mg/kg, p.o.).

Group VII received ethyl acetate fraction of *Sechium edule* ethanolic extract (100mg/kg,p.o.).

Group VIII received butanol fraction of Sechium *edule* ethanolic extract (200mg/kg, p.o.).

Group IX received butanol fraction of *Sechium edule* ethanolic extract (100mg/kg, p.o.).

Test group animals (Groups IV-IX) were administered orally ethanolic extracts and other fractions, respectively, once daily for 5 days and were administered simultaneously CCl_4: liquid paraffin (1:1, 2 ml/kg body weight, s.c.) on day 2 and 3 after 30 min of administration of the silymarin or ethanolic extracts and its fractions.

Assessment of hepatoprotective activity

Animals were sacrificed 24 h after the last treatment. Blood was collected by retero orbital sinus puncture, under mild ether anaesthesia.and serum was separated by centrifugation 2500 rpm for 15 min and biochemical investigations were carried out. Liver was dissected out rinsed clean in saline and preserved in 10% formalin for histopathological study.

I. Serum biochemical estimations

The serum was used to estimate the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were assayed using standard kits (SPAN India Ltd, Surat). The results were expressed as units/liter (IU/L).The levels of total protein and total billirubin were estimated in the serum using standard commercial kits from (SPAN India Ltd, Surat, India).

II. Histopathological studies[13]

Portions of the liver from all the experimental groups were fixed in 10% formalin, dehydrated in alcohol and then embedded in paraffin. Microtome sections (5µm thick) were prepatred from each liver sample and stained with haemtoxylin- eosin (H&E) dye. The sections were examined for the pathological findings of hepatotoxicity.

Measurement of antioxidant activity

From all the experimental groups, the portions of the liver was collected and rinsed with 0.15 Tris –HCl (pH 7.4). A 10% w/v of liver homogenate was prepared in 0.15 M Tris- HCl buffer and processed for the estimation of lipid peroxidation in the form of malonidialdehyde (MDA) in liver by measuring the thiobarbituric acid reactive substance (TBARS) [14]. From the part of the homogenate, after precipitating proteins with 20% trichloro acetic acid (TCA) containing 1 Mm EDTA, the supernatant was used for reduced glutathione (GSH) estimation[15]. The rest of the homogenate was centrifuged at 2000m rpm for 10 min at 4°C. The cell free supernatant thus obtained was used for the estimation of super oxide dismutase (SOD) [16] and catalase (CAT)[17] activity.

Statistical Analysis

Data for hepatoprotective activity were expressed as Mean ± SEM from six rats in each group. Hepatoprotective activity were analysed statistically using one way analysis of variance (ANOVA), followed by Dunnett's t-test with the help of graph pad prism 4.0 soft ware. P value of < 0.05 was considered as statistically significant.

RESULT

Phytochemical screening

Phytochemical screening of the ethanolic extract of *Sechium edule* fruits showed the presence of carbohydrate, flavanoids, saponin glycosides, tannins and proteins. Whereas the ethyl acetate and n-butanol fractions showed the presence of flavanoids and saponin glycosides respectively.

Acute toxicity studies

In LD_{50} studies, it was found that the animals were safe up to a maximum dose of 2000 mg/kg body weight. There were no changes in normal behaviour pattern and no signs and symptoms of toxicity and mortality were observed. The biological evaluation was carried out at doses of 100 and 200 mg/kg body weight.

Effect of extract of *Sechium edule* and its fractions on Serum biochemical parameters

In CCl_4 induced hepatotoxicity the activities of serum hepatic marker enzymes namely aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and total billirubin level showed a significant ($p<0.01$) increase in CCl_4 treated animals as compared to control group and the total serum protein concentration was significantly ($p<0.01$) lower in CCl_4 treated group (Table 1). Administering *Sechium edule* and its fractions significantly reduced the levels of AST, ALT, ALP and total billirubin level in CCl_4 treated rats as compared to the animals treated with CCl_4 alone and the total serum protein concentration was significantly increased.

The level of serum creatinine showed significant ($p<0.01$) increase in CCl_4 treated animals as compared with normal control group. Treatment with *Sechium edule* and its fractions or silymarin in CCl_4 treated rats showed significant decrease in serum creatinine level (Table 1).

Effect of extract of *Sechium edule* and its fractions on antioxidant activity

There was a significant increase in MDA content and reduction in GSH, SOD and CAT activities of CCl_4 intoxicated animals (Table 2). Treatment with silymarin (50mg/kg. po) and extracts and its fractions significantly ($p< 0.05$) prevented increase in MDA levels and brought them near to normal level, where as GSH, SOD, CAT levels were significantly ($p<0.05$) raised, thus providing protection against CCl_4 toxicities.

Histopathology of liver

Figure 1(A-I) shows effect of silymarin, *Sechium edule* fruits ethanolic extract and its ethyl acetate and n – butanol fractions on CCl_4 induced hepatotoxicity in rats. Control group (A) animals showed a normal hepatic architecture. In CCl_4 treated group (B), severe hepatotoxicity was evidenced by kupffer cell hyperplasia, inflammatory cells, apoptosis, microvascular fatty changes and centrilobular necrosis. Treatment with silymarin (C) showed normal architecture with less fatty changes. ethanolic extract of *Sechium edule* fruits (D, F, H) and its ethyl acetate and n-bulanol fractions at the dose of 200mg/kg, p.o. to carbon tetrachloride treated rats exhibited almost normal architecture with reduced inflammation, necrosis.

Table 1: Effect of extract of *Sechium edule* and its fractions on biochemical parameters asparate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein (TP), Total bilirubin (TB) and serum creatinine in CCl_4 induced hepatotoxicity in rats

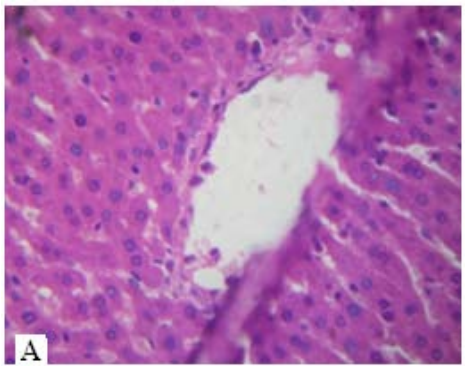
Groups	AST(IU/l)	ALT(IU/l)	ALP(KA)	TP(g/dl)	TB(mg/dl)	Creatinine(mg/100ml)
Normal control	60± 0.707	69.03±0.236	5.19±0.397	6.667±0.600	1.48±0.189	2.09±0.161
CCl_4 + liquid paraffin	252 ± 1.22##	545.5 ± 3.32##	11.9 ± 0.360##	2.27 ± 0.013##	8.055± 0.055##	5.9 ±0.211##
Silymarin (50mg/Kg)	129.8 ±0.85**	153.6 ± 0.83**	4.79 ± 0.060**	6.543± 0.072**	4.58± 0.015**	3.0 ±0.173**
Ethanolic extract of S.E (200mg/Kg)	197.5 ±1.19**	219.8 ±1.63**	3.69 ±0.125**	7.021±0.336**	5.659±0.134**	3.4 ±0.194**
Ethanolic extract of S.E (100mg/Kg)	210.5 ± 2.10**	300.3 ± 0.86**	9.98 ± 0.21**	5.697 ± 0.13**	7.07 ± 0.096**	5.16 ±0.056**
Ethyl acetate fraction of S.E (200mg/Kg)	189.8 ±1.79**	194.9 ± 2.00**	5.005 ± 0.21**	6.813 ± 0.11**	4.96 ± 0.092**	4.36 ±0.133**
Ethyl acetate fraction of S.E (100mg/Kg)	205.5 ± 2.10**	290.7 ± 1.04**	7.17 ± 0.10**	3.82± 0.08**	5.84 ± 0.130**	5.16 ±0.079**
n- Butanol fraction of S.E (200mg/Kg)	152 ± 1.47**	251.2 ± 1.27**	8.372 ±0.076**	6.366 ± 0.095**	2.95 ± 0.09**	4.04 ±0.201**
n- Butanol fraction of S.E (100mg/Kg)	204 ±1.58**	347.2 ± 6.13**	9.285 ± 0.11**	4.9 ± 0.348**	5.217 ± 0.184**	5.16 ±0.132**

Values are expressed as mean ± SEM, n=6; ## P<0.01 considered statistically significant as compared to normal control group; ** P< 0.01 considered statistically significant as compared to carbon tetrachloride treated group.

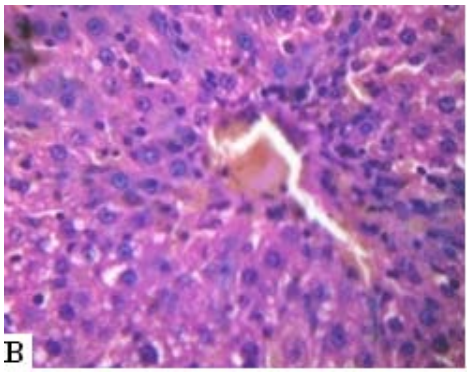
Table 2: Effect of ethanol extract and its fractions of *Sechium edule* fruits on malonidialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) in CCl_4 induced hepatic damage in rats.

Groups	MDA (nM MDA/mgprotein)	GSH (µg/mgprotein)	SOD(U/mg protein)	CAT(U/mg protein)
Normal control	7.780±0.5656	19.75 ±0.8145	15.35±0.6894	175.3±2.617
CCl_4 + liquid paraffin	23.13±0.5376##	9.372 ±0.7356##	7.825±0.4123##	75.01±2.383##
Silymarin (50mg/Kg)	12.95±0.5273**	17.46 ±0.6837**	12.94±0.3535**	143.8±2.497**
Ethanolic extract of S.E (200mg/Kg)	16.07±0.7923**	15.72 ±0.4553**	12.31±0.4077**	123.4±2.160**
Ethanolic extract of S.E (100mg/Kg)	20.04±0.3808*	11.14 ±0.5359 ns	9.568±0.4481*	99.56±2.483**
Ethyl acetate fraction of S.E (200mg/Kg)	14.10±0.6536**	16.82 ±0.4737**	12.38±0.3279**	137.5±1.392**
Ethyl acetate fraction of S.E (100mg/Kg)	19.74±0.6894**	12.66 ±0.4523**	9.023±0.3909 ns	103.4±1.200**
n- Butanol fraction of S.E (200mg/Kg)	16.72±1.252**	14.71 ±0.6150**	11.32±0.2963**	115.7±2.105**
n- Butanol fraction of S.E (100mg/Kg)	21.02±0.6751ns	11.31 ±0.5627 ns	8.392±0.4802 ns	88.56±2.318**

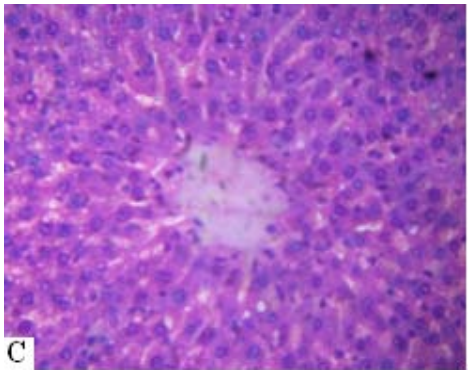
Values are expressed as mean ± SEM, n=6; ## P<0.05 considered statistically significant as compared to normal control group; * P <0.01, ** P < 0.05 considered statistically significant, ns non significan, as compared to carbon tetrachloride treated group.



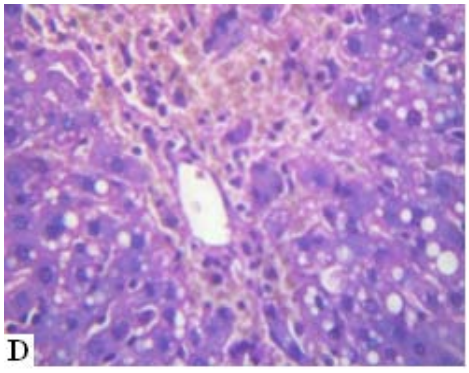
Group I (Normal control)



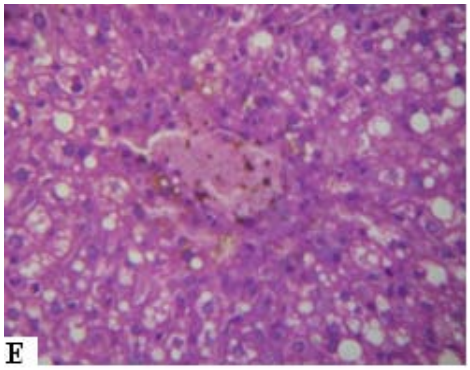
Group II (CCl_4 + liquid paraffin)



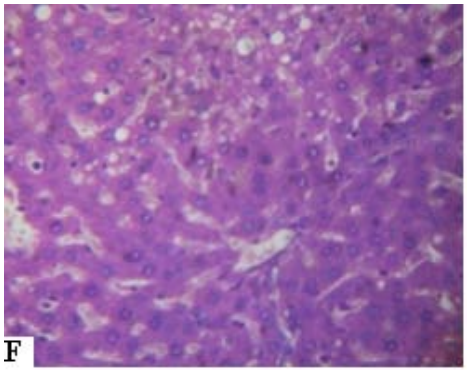
Group III (Silymarin , 50mg/Kg)



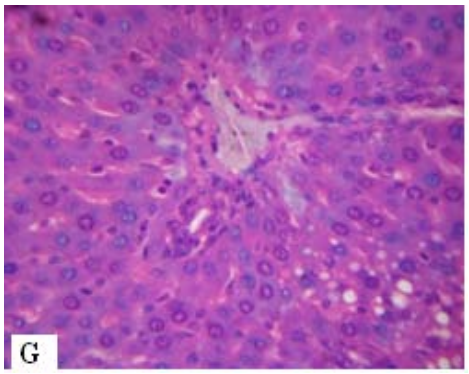
Group IV (Ethanolic extract of S.E, 200mg/Kg, p.o.)



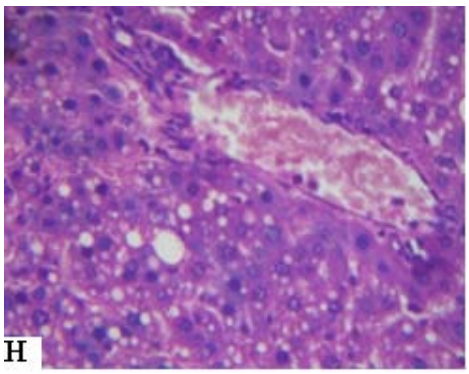
Group V (Ethanolic extract of S.E, 100mg/Kg, p.o.)



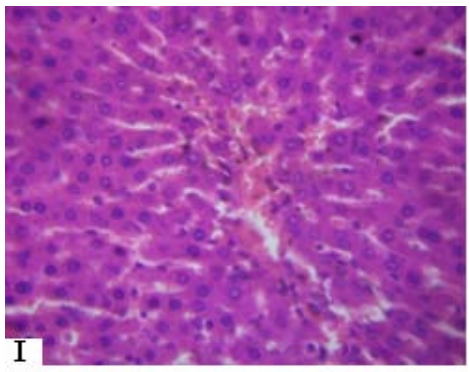
Group VI (Ethyl acetate fraction of S.E, 200mg/Kg, p.o.)



Group VII (Ethyl acetate fraction of S.E, 100mg/Kg)



Group VIII (n- Butanol fraction of S.E, 200mg/Kg, p.o.)



Group IX (n- Butanol fraction of S.E,100mg/Kg, p.o.)

DISCUSSION

Carbon tetrachloride it induces hepatotoxicity by metabolic activation, therefore, it selectively causes toxicity in liver cells maintaining semi-normal metabolic function[12]. Carbon tetrachloride is accumulated in hepatic parenchyma cells and metabolically activated by the cytochrome P-450 dependent mixed oxidase in the endoplasmic reticulum to form trichloromethyl free radical ($^{\bullet}CCl_3$) which combined with cellular lipids and proteins in the presence of oxygen to induce lipid peroxidation[18,19] . These result in changes of structures of the endoplasmic reticulum and other membrane [11], loss of metabolic enzyme activation such as, elevated levels of serum marker enzymes like AST, ALT, ALP, depletion of GSH, reduction of protein synthesis, increased lipid peroxidation, destruction of Ca^{2+} homeostasis[20] and loss of glucose-6-phosphatase activation; consequently, the functional integrity of hepatic mitochondria is altered, ultimately leading to liver injury[21].

The disturbance in the transport function of the hepatocytes as a result of hepatic injury by CCl_4 causes the leakage of enzymes from cells due to altered permeability of membrane, results in decreased levels of AST, ALT and ALP in the hepatic cells and a raised level in serum. For the assessment of liver damage by CCl_4 hepatotoxin, the determination of enzyme levels such as AST and ALT is largely used. AST can be found in the liver, cardiac muscle, kidney, brain, pancreas, lungs, skeletal muscle, leukocytes and erythrocytes (in decreasing concentrations), whereas the highest concentration of ALT is found in the liver[22]. Necrosis or membrane damage releases the enzyme into circulation. Therefore, it can be measured in serum. High levels of AST indicate liver damage, such as that due to viral hepatitis as well as cardiac infarction and muscle injury. ALT catalyses the conversion of alanine to pyruvate and glutamate, and is released in a similar manner. In tissues, ALT occurs in two locations, the cytosol and mitochondria. Therefore, ALT is more specific to the liver, and is thus a better parameter for detecting liver injury. Serum ALP and bilirubin levels on the other hand, are related to the function of hepatic cell. Increase in serum level of ALP is due to increased synthesis, in presence of increasing biliary pressure. Bilirubin is one of the most useful clinical clue for the severity of necrosis and its accumulation is a measure of binding, conjugation and excretory capacity of hepatocyte[23]. A reduction in total serum protein (TSP) observed in the CCl_4 treated animals may be associated with the decrease in the number of hepatocytes which in turn may result into decreased hepatic capacity to synthesize protein [24]. Hence decline in total protein content can be deemed as a

useful index of the severity of cellular dysfunction in chronic liver diseases which indicates hepatopathy.

In CCl_4-induced hepatotoxicity in rats, our results suggest that the treatment with *Sechium edule* ethanolic extract and its different fractions significantly reduced the enhanced level of serum ALT, AST which seem to offer the protection and maintain the functional integrity of hepatic cells. Effective control of bilirubin level and alkaline phosphatase activity by different doses of the extract and its fractions points towards an early improvement in the secretory mechanism of the hepatic cell. The significant raise in protein levels suggests the stabilization of endoplasmic reticulum leading to protein synthesis[25]. These results indicate that the *Sechium edule* ethanolic extract and its different fractions preserved structural integrity of the hepatocellular membrane and showed dose dependant protective effect.

Lipid peroxidation has been postulated to be the destructive process in liver injury due to CCl_4 administration, which in turn yields products like MDA [26, 27]. In the present study elevation of MDA levels was observed in liver of animals treated with CCl_4, it indicates the enhanced lipid peroxidation leading to tissue damage and also free radical generation exceeding the cellular radicals scavenging capacity i.e, failure of antioxidant defence mechanism. Treatment with ethanolic extract and its different fractions of *Sechium edule* fruits significantly reduced the levels of lipid peroxidation. Hence, it may be possible that mechanism of hepatoprotection of *Sechium edule* fruits is due to its antioxidant activity.

Glutathione (GSH) is one of the most abundant tripetide, non enzymatic biological [28] antioxidant present in the liver. GSH is helpful for the removal of free radicals such as H_2O_2 and superoxide radicals, alkoxy radicals, detoxification of foreign chemicals and biotransformation of drugs [29]. In the present study, CCl_4 treatment decreased the GSH content in the liver due to enhanced level of lipid peroxidation, where as treatment with ethanolic extract and its different fractions of *Sechium edule* fruits, silymarin significantly increased the GSH levels.

SOD and CAT are key defense enzymes in liver injury caused by ROS and oxidative stress. Catalase (CAT) is a haemoprotein; that protects the cells from accumulation of H_2O_2 by dismutating it to form H_2O and O_2[30]. There by reduction in this enzymes indicate the toxic effects of reactive oxygen species. Sod is one of the most abundant intracellular antioxidant enzymes present in all aerobic cells and it has antitoxic effect against reactive oxygen species [31]. In the present study, it was observed that treatment with ethanolic extract and its different fractions of *Sechium edule* fruits, silymarin significantly increased hepatic sod, cat activities. This suggest that *Sechium edule* fruits extract and its fractions reduce ROS that may decrease the oxidative damage to the hepatocytes and improves the activities of the liver antioxidant enzymes.

Thus, administration of ethanolic extract and its different fractions of *Sechium edule* fruits revealed hepatoprotective activity against the toxic effects of $CC1_4$ by significantly reducing the enhanced level of serum ALT, AST, alkaline phosphatase and bilirubin to the near normal levels, there was significant increase in total protein levels and significant decrease in serum creatinine levels when compared to $CC1_4$ group. Treatment with silymarin or ethanolic extract of *Sechium edule* fruits (200mg/kg, p.o.) and its different fractions (200mg/kg, p.o.) to carbon tetrachloride treated rats exhibited almost normal architecture of liver by decreasing the changes like kupffer cell hyperplasia, inflammatory cells, apoptosis, microvascular fatty changes and centrilobular necrosis that were evidenced by CCl_4 treated group.

The preliminary phytochemical analysis of the extracts has shown the presence of flavonoids and saponins which have been known for its antioxidant and hepatoprotective activities which was also supported by the literature review (eg, silymarin, rutin, apigenin, catechin, quercetin, naringenin) [32-36].

There by the results reveal that the ethanolic extract and its fractions of *Sechium edule* fruit has significant hepatoprotective and antioxidant activities on CCl_4 induced hepatic damage in rats. Histoarchitectural improvement further supported by biochemical changes in liver, reduction in serum marker enzymes (AST, ALT, ALP, and TB), and augmentation of endogenous antioxidants supports its hepatoprotective and antioxidant activity. This hepatoprotective activity of the extracts and its fractions of *Sechium edule* may be due to its potent antioxidant activity /or by scavenging free radicals and inhibiting lipid peroxidation which may be due to the presence of flavanoids.

CONCLUSION

The results of our study demonstrate the hepatoprotective activity of ethanolic extract and its different fractions of *Sechium edule* fruits. The probable mechanism for its hepatoprotection may be due to its antioxidant activity.

The ethanolic extract and its different fractions also found to show reduction of the serum creatinine level.

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