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EVALUATION OF THE HEPATOPROTECTIVE POTENTIAL OF AQUEOUS EXTRACT OF *CINNAMOMUM TAMALA* AGAINST CARBON TETRACHLORIDE (CCL_4)-INDUCED HEPATOTOXICITY IN ALBINO RATS.

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Abstract

Background: The liver, a complex organ with numerous functions, is highly susceptible to diseases that can result in liver failure, severe health complications, and can be fatal in later stages. Although modern medicine has made significant progress, current hepatoprotective treatments are inefficient and carry risks of complications. *Cinnamomum tamala*, a herbal plant commonly used as a spice in Indian households, has been suggested to have hepatoprotective properties. The present study was conducted to evaluate the protective effect of the aqueous extract of *Cinnamomum tamala* (AECT) against Carbon tetrachloride (CCl_4) induced hepatotoxicity in albino Wistar rats.

Methods: The present experimental study was conducted with Albino Wistar rats of either sex (150-200 gms) after obtaining approval from the Institutional Animal Ethical committee. To evaluate the hepatoprotective potential of AECT against CCl_4 induced hepatotoxicity, animals were divided into five groups of six animals each. Group I was given normal saline (1ml/kg/day) per orally (p.o.) for 21 days, Group II was administered CCl_4 (1ml/kg) intraperitoneally (i.p.) only once on the 21st day, Group III was given Liv-52 (1ml/kg/day) p.o. for 21 days, Group IV and V were treated with AECT in graded dose (200 mg/kg and 400 mg/kg) p.o. respectively for 21 days. Injection of CCl_4 (1ml/kg) i.p. was administered once on the 21st day to Groups III, IV, and V. The rats were sacrificed under anaesthesia - Ketamine (75 mg/kg) given i.p. after 24 hours. Blood samples (vol. ~ 5 ml) for performing biochemical tests i.e., Alanine transaminase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), serum albumin, and bilirubin were collected from abdominal aorta. Consequently, animals were sacrificed and the liver was dissected out for histopathological examination. The data obtained was evaluated and analyzed by ANOVA followed by a post hoc test.

Results: Pre-treated groups of aqueous extract of *Cinnamomum tamala* exhibited a significant ($p>0.001$) dose-dependent limitation in the rise of ALT, AST, ALP, and serum bilirubin. AECT (400 mg/kg per oral) demonstrated greater protective effect. Histopathological observations further supported the biochemical findings.

Conclusion: The aqueous extract of *Cinnamomum tamala* possesses hepatoprotective potential against carbon tetrachloride induced- hepatotoxicity in a dose-dependent manner.

Keywords: *Cinnamomum tamala*, Hepatotoxicity, Carbon tetrachloride, Albino rats.

INTRODUCTION

Diseases related to the liver are among major ailments and also one of the prime causes of morbidity and mortality despite appropriate management. These diseases are classified into different categories namely hepatosis (noninflammatory), acute or chronic hepatitis (inflammatory), and cirrhosis (degenerative). Liver diseases encompass a range of conditions, including those caused by viruses such as Hepatitis A, Hepatitis B, and Hepatitis C. Excessive alcohol consumption can lead to conditions like Fatty liver and Cirrhosis. Inherited disorders like Wilson's disease and Hemochromatosis, as well as autoimmune hepatitis and Primary biliary cirrhosis, are also major examples of hepatic diseases.

Medicines derived from natural sources, known as nutraceuticals, can provide micronutrients and non-nutritive phytochemicals that offer potential health benefits. Many indigenous plants are known to possess hepatoprotective properties and have been used in Ayurvedic medicine for centuries. Some formulations have been proven to be effective hepatoprotective agents in both experimental and clinical studies. For instance, LIV-52, a product from the Himalaya Drug Company, has demonstrated hepatoprotective effects [1].

Cinnamomum tamala, commonly known as Tejpat or Bay Leaf is an important traditional medicinal plant in India, found in various regions of the country. It is valued for its aromatic leaves, which are rich in bioactive compounds with therapeutic, culinary, and medicinal uses. The plant contains cinnamaldehyde, cinnamic acid, cinnamate, and several other components known for their therapeutic effects against cancer, inflammation, cardiovascular diseases, and neurological disorders. The leaves of *Cinnamomum tamala* have a profound impact on biological systems such as the immune system, gastrointestinal tract, and liver [2].

Cinnamomum tamala has been claimed to possess hepatoprotective activity [3], but their hepatoprotective potential has not yet been established scientifically, and no convincing literature is available presently. So this study was designed to explore the hepatoprotective potential of ***Cinnamomum tamala.***

MATERIALS AND METHODS

Experimental animals

Healthy albino Wistar rats, weighing between 150-200g and of either sex, were obtained from the rat rearing unit of the Central Animal House of the institute. The animals were housed in polypropylene cages in CCSEA-approved Central Animal House at LLRM Medical College, maintained under standard laboratory conditions. These conditions included alternating periods of light and darkness of 12 hours each, a controlled temperature of 25±2ºC, and relative humidity maintained between 45% to 55%. The rats had free access to a standard rat pellet diet and tap water *ad libitum*. After one week of acclimatization, the animals were considered suitable for the study, excluding pregnant female rats.

This prospective randomized experimental study was conducted in the Department of Pharmacology, L.L.R.M. Medical College, Meerut (U.P.) from May 2023 to July 2023 for 3 months. The study was initiated after obtaining approval (Approval no. IAEC/2023/01 dated

17/04/2023) from the Institutional Animal Ethical Committee of Lala Lajpat Rai Medical College, Meerut, U.P., India, registered under CCSEA (Registration No. 819/Po/Re/S/04/CPCSEA).

Method of preparation of extract

The leaves of ***Cinnamomum tamala*** were collected from local market. The leaves were thoroughly washed with distilled water to remove the adhering impurities and dried in a shaded area. The dried leaves were powdered. The dried powder of *Cinnamomum tamala* leaves was first defatted using petroleum ether (60-80 ºC) and then extracted with distilled water using the hot maceration method. After complete removal of the solvent by drying, an aqueous extract of *Cinnamomum tamala* leaves was obtained. The extract was stored in a sealed container at 4 ºC until needed. A fresh solution of *Cinnamomum tamala* extract was prepared in distilled water for the current study when needed [4].

Materials

The commercially available injectable preparation of Carbon tetrachloride (CCl_4) (Central Drug House Pvt. Ltd., Delhi) was used. Sources of drugs and chemicals used in the present study were: LIV 52 (Himalaya Drug Company) and Ketamine (Kawality Pharmaceuticals). Biochemical parameters were estimated spectrophotometrically.

Experimental Study design

The animals were randomly divided into five groups of six animals each.

Group-1: Control group animals were administered normal saline (1ml/kg) orally once every morning for test duration of 21 days.

Group-2: In addition to rat pellet diet and tap water *ad libitum*, this group was given CCl_4 (1ml/kg) i.p. once on 21st day.

Group-3: This group was administered Liv-52 (1ml/kg) orally once every morning as a single dose for 21 days followed by an injection of CCl_4 (1 ml/kg) i.p. on 21st day.

Group-4: This group was administered aqueous extract of ***Cinnamomum tamala*** (200mg/kg) orally once daily every morning for 21 days followed by injection CCl_4 (1ml/kg) i.p. on 21st day.

Group-5: This group was administered aqueous extract of ***Cinnamomum tamala*** (400mg/kg) orally once daily every morning for 21 days followed by injection CCl_4 (1ml/kg) i.p. on 21st day.

Liv.52 and the test compound *Cinnamomum tamala* were administered by gavage method, and animals were fasted 3-4 hours prior to and 1 hour after administration of drugs to ensure proper absorption. After administration of carbon tetrachloride (CCl_4), animals of all the groups were fasted for 24 hours. Thereafter, animals were euthanized under Ketamine (75 mg/kg) and Xylazine (10 mg/kg) anaesthesia given intraperitoneally (i.p.).

Blood samples were collected from the abdominal aorta (5 ml) for performing liver function tests, which included total Bilirubin, Aspartate aminotransferase, Alanine transaminase,

Alkaline phosphatase and albumin. Also, the liver was then dissected out for histopathological studies.

Estimation of biochemical parameters

The blood collected was left to stand for half an hour before being centrifuged at approximately 2000 rpm for 10 minutes. The resulting serum was used to analyze (ALT), (ALP), (AST), total bilirubin, and albumin levels for the intended biochemical study.

Histopathological examination

The liver was removed from the animal and rinsed with normal saline. A one-centimeter piece was cut and immersed in 10% neutral formalin for 12-24 hours. It was then dehydrated, cleared with ethanol and xylene, and embedded in paraffin wax to prepare blocks. Sections of 5µ thickness were cut from the blocks using a microtome, processed in an alcohol-xylene series, stained with Harris hematoxylin and eosin stain, and subjected to histopathological examination.

Statistical analysis

Mean ± SD was calculated for each group to observe the general trend of the group. ANOVA test was applied to test the significance of the results. P values < 0.05 were considered significant. P-values were estimated by referring to appropriate tables.

RESULTS

It was observed that aqueous extract of *Cinnamomum tamala* offered dose dependant hepatoprotection as reflected by significant improvement in biochemical parameters. In the dose of 400 mg/kg for 21 days, the hepatoprotective potential of aqueous extract of *Cinnamomum tamala* was found to be comparable to the response offered by LIV 52.

Effect on total Serum Bilirubin

The total bilirubin level in the normal saline administered group was 0.46 ± 0.03 mg/dl. Following the administration of CCl_4, it significantly increased to 2.56 ± 0.12 mg/dl ($p < 0.001$). Pretreatment with the known hepatoprotective preparation Liv 52 significantly limited the rise in total bilirubin levels after CCl_4 administration to 1.53 ± 0.06 mg/dl ($p < 0.001$).

Treatment with *Cinnamomum tamala* demonstrated a dose-dependent limitation of the total bilirubin rise after CCl_4 administration. While the dose of 200 mg/kg for 21 days significantly limited total bilirubin rise (2 ± 0.05 mg/dl) compared to the CCl_4 - treated group ($p< 0.01$), it did not match the efficacy of the Liv 52 treated group. However, at a dose of 400 mg/kg for 21 days, *Cinnamomum tamala* extract exhibited higher efficacy in limiting the total bilirubin rise after CCl_4 administration to 1.9 ± 0.05 mg/dl, which was significant ($p < 0.001$).

Effect on Aspartate Aminotransferase (AST)

The mean Aspartate Aminotransferase (AST) level in normal saline administered group was 37.66±0.88 IU/L while the administration of CCl_4 resulted in highly significant rise in AST levels to 530.33±15.16 IU/L ($p<0.001$).

Administration of known hepatoprotective preparation Liv 52 notably ($p<0.001$) limited the rise in total bilirubin levels after CCl_4 administration to 309.33±10.47 IU/L.

A significant limitation of Aspartate Aminotransferase (AST) is seen with the dose of 200mg/kg of *Cinnamomum tamala* for 21 days (450.66±4.80 IU/L) when compared to CCl_4

treated group ($p<0.01$). However, in dose of 400mg/kg for 21 days the *Cinnamomum tamala* extract had much higher efficacy in limiting the total AST rise after CCl_4 adminstration to 337.33±2.90 IU/L ($p<0.001$).

Effects on Alanine Aminotransferase (ALT)

The ALT level in the normal saline administered group was 39.33 ± 2.66 IU/L. Following the administration of CCl_4, it significantly increased to 508.33 ± 14.40 IU/L ($p<0.001$).

Pretreatment with hepatoprotective preparation Liv 52 significantly limited the rise in ALT levels after CCl_4 administration to 333.33 ± 3.52 IU/L ($p<0.001$).

Administration of *Cinnamomum tamala* in the dose of 200 mg/kg exhibited a considerable limitation of ALT rise (416.33 ± 3.52 IU/L) compared to the CCl_4-treated group (Toxic group) ($p<0.01$). At the dose of 400 mg/kg, the aqueous extract of *Cinnamomum tamala* exhibited much higher efficacy in limiting the ALT rise after CCl_4 administration to 370 ± 1.15 IU/L ($p<0.001$).

Effects on Alkaline Phosphatase (ALP)

ALP level in normal saline treated group was 239.06±5.79 IU/L. The levels were found to be raised with CCl_4 administration to 619±15.15 IU/L ($p<0.001$). Pre-treatment with Liv 52 significantly limited the rise in ALP levels after CCl_4 administration to 426.86±3.53 IU/L ($p<0.001$).

Pre- treatment with *Cinnamomum tamala* restricted the rise of ALP levels in all doses in comparison to CCl_4 treated group (Toxic Group). Although the dose of 200 mg/kg did not match the efficacy of Liv 52 treated group, it demonstrated a notable limitation of ALP rise (547.56 ± 3.35 IU/L) ($p<0.01$). However, at a dose of 400 mg/kg, it showed much higher efficacy in limiting the ALP to 488.86 ± 3.60 IU/L ($p<0.001$).

Effect on Albumin

There was no appreciable difference in serum Albumin levels of any of the groups and all the measurements recorded were in normal range. The Albumin levels varied from 3.2 gm/dl to 4.1 gm/dl. No significant difference was observed in serum albumin levels in different groups when compared to the normal saline group ($p>0.05$).

Table 1: Effect of Liv 52, Aqueous extracts of *Cinnamomum tamala* in its respective doses on Carbon tetrachloride (CCl_4) induced changes in various biochemical parameters (n=6).

Group	Treatment	Total Bilirubin (mg/dl) (mean±SE)	Aspartate Aminotransferase (AST) (IU/L) (mean±SE)	Alanine Aminotransferase (ALT) (IU/L) (mean±SE)	Alkaline Phosphatase (ALP) (IU/L) (mean±SE)	Albumin (gm/dl) (mean±SE)
1.	Normal saline (1ml/kg p.o)	0.46±0.03	37.66±0.88	39.33±2.66	239.06±5.79	3.66±0.16
2.	CCl_4 (1ml/kg i.p)	$2.56±0.12^{\gamma}$	$530.33±15.16^{\gamma}$	$508.33±14.40^{\gamma}$	$619±15.15^{\gamma}$	$3.63±0.13^{\delta}$
3.	Liv 52 (1ml/kg p.o)	$1.53±0.06^{\alpha}$	$309.33±10.47^{\alpha}$	$333.33±3.52^{\alpha}$	$426.86±3.53^{\alpha}$	$3.46±0.08^{\delta}$
4.	*Cinnamomum tamala* (200 mg/kg p.o)	$2.0±0.05^{\beta}$	$450.66±4.80^{\beta}$	$416.33±3.52^{\beta}$	$547.56±3.35^{\beta}$	$3.66±0.23^{\delta}$
5.	*Cinnamomum tamala* (400 mg/kg p.o)	$1.9±0.05^{\alpha}$	$337.33±2.90^{\alpha}$	$370±1.15^{\alpha}$	$488.86±3.60^{\alpha}$	$3.76±0.24^{\delta}$

$^{\alpha}P > 0.001$ as compared to CCl_4 treated group.

$^{\beta}P > 0.01$ as compared to CCl_4 treated group.

$^{\gamma}P > 0.001$ as compared to normal saline treated group.

$^{\delta}P > 0.05$ as compared to normal saline treated group.

Fig 1: Effect of liv-52, Aqueous extract of *Cinnamomum tamala* in its respective doses on Carbon tetrachloride (CCl_4) induced changes in AST, ALT and ALP levels.

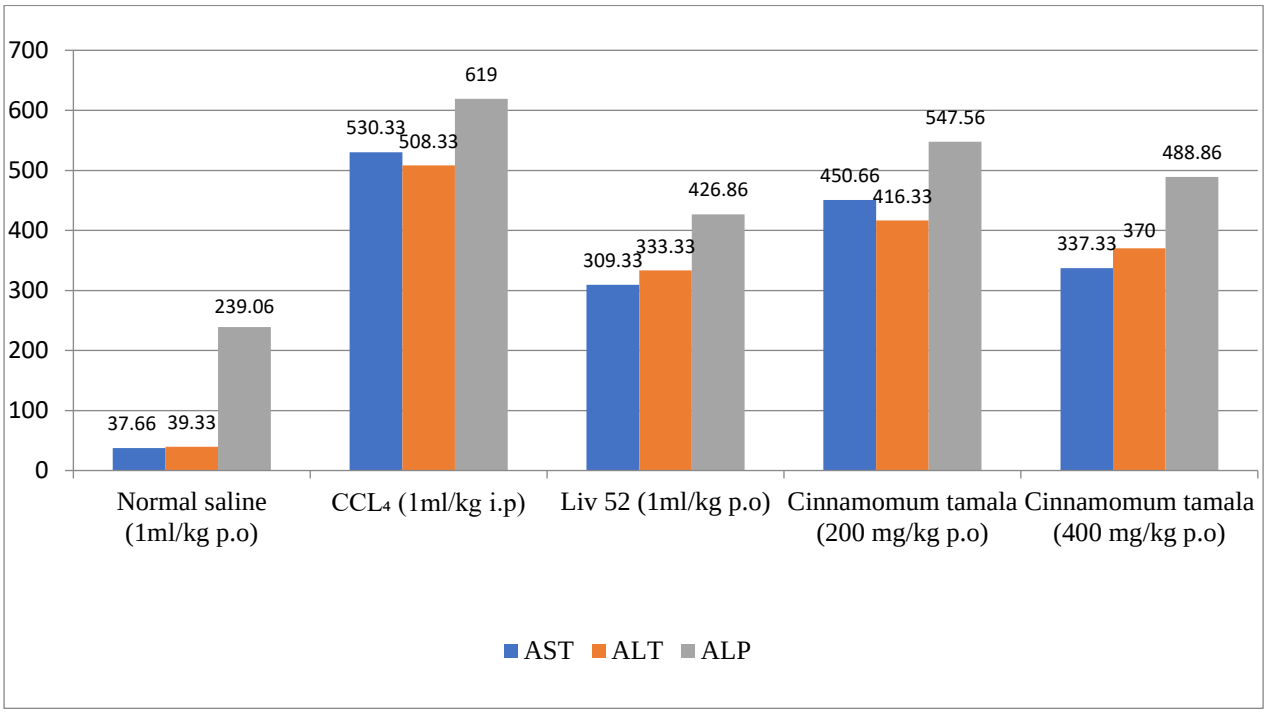
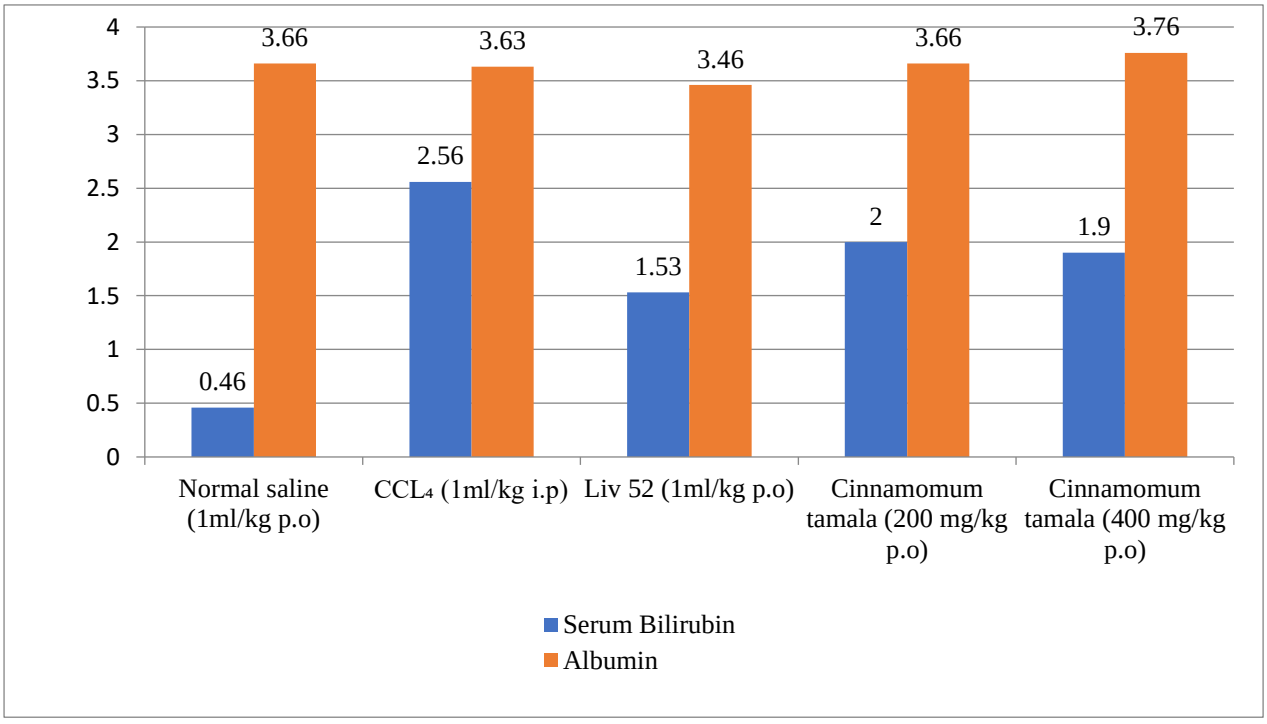


Fig 2: Effect of liv-52, Aqueous extract of *Cinnamomum tamala* in its respective doses on Carbon tetrachloride (CCl_4) induced changes in total bilirubin and serum albumin levels.



Histopathological changes

Histology of livers of normal saline treated group exhibited normal liver architecture. The hepatic cords and the sinusoids were well visible (Fig 3).

Marked necrosis, cytoplasmic vacuolations and steatotic changes was seen in the CCl_4 treated group. Congestion of central vein was seen (Fig 4).

Liv 52 treated group revealed very mild signs of liver injury. Only difference from the normal saline treated group was the presence of inflammatory cells and hydropic changes in Centrilobular hepatocytes (Fig 5).

Group treated with aqueous extract of *Cinnamomum tamala* (AECT) in dose 200mg/kg exhibited marked hydropic changes in Centrilobular hepatocytes with the presence of inflammation and congestion (Fig 6); however at dose 400mg/kg AECT demonstrated mild inflammation in centrilobular area with normal hepatocytes. Focal hepatocytes, however, showed hydropic changes (Fig 7).

Fig 3: Microscopic features of the liver stained with (Hematoxylin & Eosin stain) (10x) of the group treated with normal saline (1ml/kg/day) p.o. for 21 days.

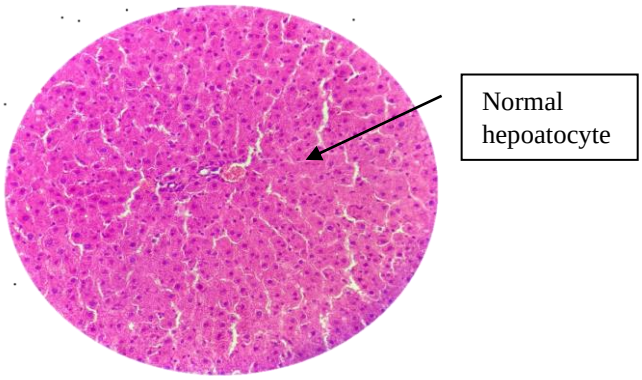


Fig 4: Microscopic features of the liver stained with H&E (40x) of the group treated with CCl_4 (1ml/kg) i.p. on 21st day.

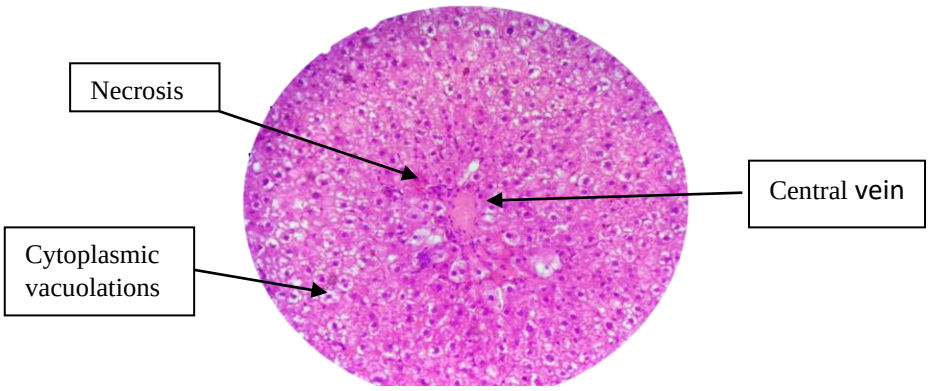


Fig 5: Microscopic features of the liver stained H&E (40x) of the group treated with Liv-52 (1ml/kg/day) p.o. for 21 days with CCl_4 (1ml/kg) i.p. on 21st day.

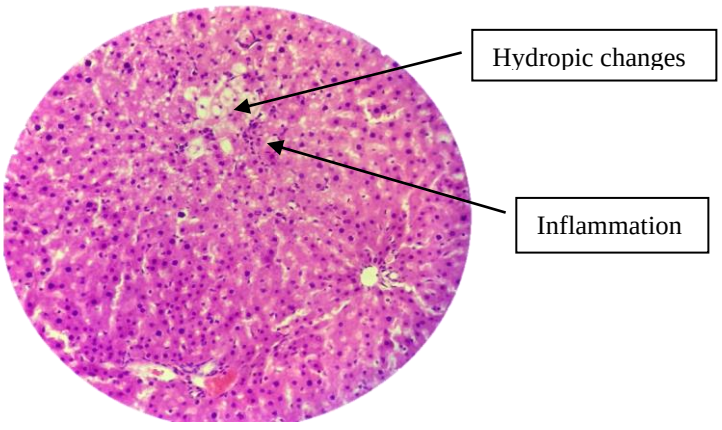


Fig 6: Microscopic features of the liver stained with H&E (10x) of the group treated with *Cinnamomum tamala* (200mg/kg/day) p.o. for 21 days with CCl_4 (1ml/kg) i.p. on 21st day.

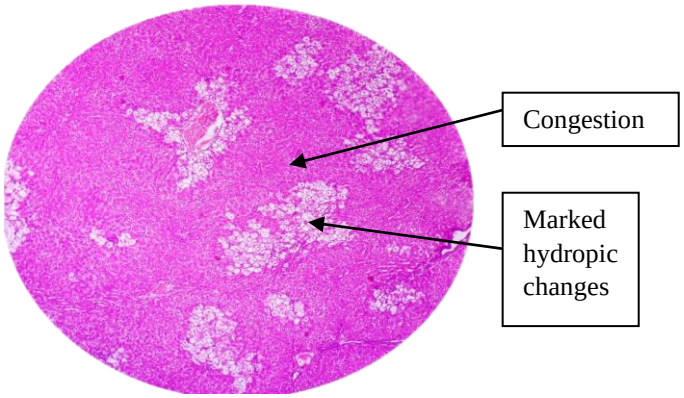
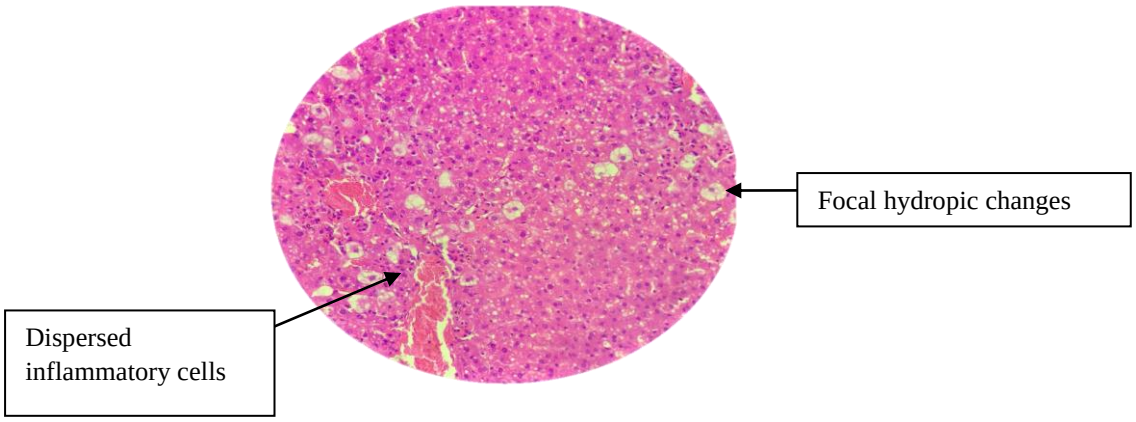


Fig 7: Microscopic features of the liver stained with H&E (40x) of the group treated with *Cinnamomum tamala* (400mg/kg/day) p.o. for 21 days with CCl_4 (1ml/kg) i.p. on 21st day.



DISCUSSION

Despite extensive research in medicine, there are still very few drugs that effectively stimulate liver functions, protect the liver from damage, or aid in the regeneration of hepatic cells. Consequently, numerous studies have focused on evaluating the hepatoprotective effects of natural plant preparations, aiming to develop phytochemical agents capable of inhibiting oxidative damage. Various herbal formulations are used to treat a wide range of clinical diseases, although their modes of action are not fully understood. This study explores the hepatoprotective activity of aqueous extract of *Cinnamomum tamala* and compares it with a scientifically established Ayurvedic preparation, Liv-52, against CCl_4-induced hepatotoxicity in Albino Wistar rats.

In this study, liver damage was induced by carbon tetrachloride (CCl_4), a commonly used model for screening hepatoprotective drugs [5]. The increase in serum levels of alanine transaminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST), is attributable to the compromised structural integrity of liver. These enzymes are cytoplasmic in location and are released into circulation following cellular damage [6]. CCl_4 induces hepatotoxicity through metabolic activation, selectively affecting liver cells and altering their metabolic functions. CCl_4 is metabolically activated by the cytochrome P-450 dependent mixed oxidase system in the endoplasmic reticulum, forming the trichloromethyl free radical (CCl_3). This radical combines with cellular lipids and proteins in the presence of oxygen, leading to lipid peroxidation [7]. This process results in structural changes in the endoplasmic reticulum and other membranes, loss of metabolic enzyme activation, liver injury, and elevated levels of ALT, ALP, AST, and total bilirubin. Additionally, histopathological analysis done in this study confirmed CCl_4-induced hepatotoxicity, showing severe centrilobular necrosis, hepatocyte necrosis, portal inflammation, inflammatory cell infiltration, and both macrovesicular and microvesicular steatosis [8].

Liv-52, a well known hepatoprotective agent contains *Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, Achillea millefolium, Tamarix gallica, and Mandur basma*. It serves as a hepatotonic and has been traditionally used to treat various liver disorders. Experimental studies have shown that Liv-52 provides significant protection against hepatic damage caused by carbon tetrachloride, alcohol, and beryllium [9]. Liv-52 restores liver functional efficiency by protecting the hepatic parenchyma and promoting hepatocellular regeneration. Its antiperoxidative activity preserves the functional integrity of cell membranes, maintains cytochrome P-450 levels, accelerates the recovery period, and ensures the restoration of hepatic functions. Additionally, Liv-52 acts as a free radical scavenger and antioxidant. It inhibits lipid peroxidation and limits the generation of free radicals following CCl_4-induced hepatotoxicity, thereby preventing the rise in serum enzyme levels. Previous clinical studies also indicate that Liv-52 has a protective effect on the liver against alcohol-induced hepatic damage and hepatitis B virus infection, with no reported side effects [10].

The aqueous extract of *Cinnamomum tamala* exhibited dose dependent hepatoprotection that was confirmed by changes in biochemical parameters as well as histologically. The exact hepatoprotective mechanism of the aqueous extract of *Cinnamomum tamala* has not been well established as yet, but it is likely attributable to their phytochemical constituents with antioxidant properties.

Cinnamomum tamala extract when administered in higher dose (400 mg/kg) for 21 days provided more significant results as compared to *Cinnamomum tamala* extract in lower dose

(200 mg/kg) for 21 days but fall short as compared to protection provided by Liv-52. No significant change in albumin level was observed.

Cinnamomum tamala is traditionally used to alleviate pain and reduce inflammation in patients suffering from arthritic rheumatism. The plant contains cinnamaldehyde, cinnamic acid, cinnamate, and various other components that exhibit strong therapeutic effects against cancer, inflammatory conditions, cardiovascular, and neurological disorders. Polyphenols in *Cinnamomum tamala* demonstrate significant antioxidant, anti-inflammatory, antidiabetic, antimicrobial, and anticancer properties. *Cinnamomum tamala* leaves exert strong effect on biological systems such as immune system, gastro-intestinal tract, and liver [11]. Eswaran MB et al., (2010) [12] reported that *Cinnamomum tamala* leaves demonstrated gastro-protective effects in experimental animals, probably because of free radical scavenging properties. Nephroprotective effect is also exhibited in a similar study done on rabbits to investigate the reno-protective properties of *Cinnamomum tamala* against gentamicin induced nephrotoxicity; the nephroprotective effect is most likely due to the high phenolic content of *Cinnamomum tamala* which exhibited concentration-dependent anti oxidant action inhibiting oxidative damage and protection against gentamicin-induced renal toxicity [13].

The exact hepatoprotective mechanism of aqueous extract of *Cinnamomum tamala* has not been evaluated in the present study but it can be postulated to be due to the presence of phytochemical constituents with antioxidant potential. However, comprehensive and extensive research, conducted over a longer duration and with a larger sample size is needed to explore the pharmacokinetic and pharmacodynamic profile of this extract, which will provide the foundation for future clinical trials.

CONCLUSION

The present study concludes that aqueous extract of *Cinnamomum tamala* possess hepatoprotective effect. In the group treated with carbon tetrachloride (CCl_4), significant disturbances in hepatocyte architecture and a disrupted liver profile were observed. However, pretreatment with aqueous extract of *Cinnamomum tamala* limited functional hepatic derangement and preserved cyto-architecture.

The experimental data demonstrated that pretreatment with aqueous extract of *Cinnamomum tamala* not only limited the rise in alanine transaminase, alkaline phosphatase, aspartate aminotransferase and serum bilirubin but also provided significant histopathological protection following CCl_4 administration which indicates hepatoprotective action.

The dosage form of *Cinnamomum tamala* can be altered to enhance effectiveness. The safety profile of AECT has been promising in this study. Future research should focus on identifying the phytochemicals or bioactive compounds in these plants responsible for their hepatoprotective effects.

Cinnamomum tamala is commonly used as a household spice and traditional medicinal herb, it also holds significant potential as a source of compounds for clinical trials that require further evaluation for their efficacy and disease prevention capabilities.

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