Hepatoprotective Effect of Cinnamon (Cinnamomumzeylanicum) on Paracetamol Induced Liver Damage in Long-Evans Male Rats

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Abstract

Background: Liver is a vital organ in the body is primarily responsible for the metabolism of endogenous and exogenous agents. It can be damaged by poisonous effects of chemicals, toxins, prolonged and uncontrolled use of drugs. Cinnamon is an evergreen tree. The inner bark of the tree has been used as spice and flavoring for food which may have hepatoprotective effect.

Objective: To observe the effect of cinnamon (*Cinnamomumzeylanicum)* on paracetamol induced liver damage in Long-Evansmale rats.

Method: This study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka from 1st July 2019 to 30th June 2020. A total number of thirty (30) apparently healthy Long-Evansmale rats were taken for the study. They were divided into two groups, control group (Group A) and experimental group (Group B –cinnamon pretreated and paracetamol treated group). Control group was subdivided into group A_1 (baseline control) and group A_2 (paracetamol treated control group). Each of this group consisted of ten (10) rats.

Result: The mean serum total bilirubin, ALT, AST levels were significantly higher in paracetamol treated control group and cinnamon pretreated and paracetamol treated group in comparison to those of baseline control group. Again, the mean serum total bilirubin, ALT, AST levels were significantly lower in cinnamon pretreated and paracetamol treated group in comparison to those ofparacetamol treated control group. Again, the mean malondialdehyde (MDA) concentration in liver was significantly higher in paracetamol treated control group and cinnamon pretreated and paracetamol treated group in comparison to that of baseline control group.Again the mean malondialdehyde (MDA) concentration in liver was significantly lower incinnamon pretreated and paracetamol treated group in comparison to that ofparacetamol treated control group. Moreover, abnormal histological findings of liver were observed in 0% of rats in baseline control group, 100% of rats inparacetamol treated control group, 30% of rats in cinnamon pretreated and paracetamol treated group.

Conclusion: The present study reveals that cinnamon has hepatoprotective effect against paracetamol induced liver damage in Long-Evans male.

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Introduction

Liver is the largest and essential gland in the body. It conducts a vast array of biochemical and metabolic functions.[1] There are many causes of liver disease such as virus, alcohol, gallstone, drugs etc. leads to inflammation and necrosis.[2] Several classes of chemical agents produce acute as well as chronic liver injury. Acetaminophen represents the most prevalent cause of acute liver failure.[3] In Bangladesh, about 13.2% patients visiting Department of Hepatology are suffering from liver diseases[3] and 73.1% of death is due to fulminant hepatic failure.[4] Conventional hepato-protective drugs used for the treatment of such adverse reactions are often inadequate and it is needed to de-challenge the offending drug. Therefore, it is important to explore hepatoprotective effect of natural products.[5] Cinnamon the evergreen tree belongs to the Lauracea family. It is used as a spice for thousands of years.[4] Phytochemical analysis of bark extract of cinnamon demonstrates the presence of flavonoids, tannins, saponins, alkaloids, terpenoidsand phenols.[6] Many previous journals documented many beneficial effects of cinnamon extract against alcohol-induced and CCL_4-induced liver injury.[6] Cinnamon also has preventive action on paracetamol induced hepatotoxicity in rats.[7]

Objective

To observe the effect of cinnamon (*Cinnamomumzeylanicum)* on paracetamol induced liver damage in Long-Evansmale rats.

Methods

All rats were purchased from animal house of Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University (BSMMU). They were kept in the animal house of Institution of Nutrition and Food Science, University of Dhaka, where the experiment was carried out. The aqueous extract of cinnamon was prepared according to.[7,12] All the animals were acclimatized for 14 days prior to intervention at 27-28º C room temperature.[15]They were kept under 12 hours light/ 12 hours dark cycle. During this period the animals had free access to standard rat food pellets and allowed to drink water as desired. After acclimatization the total study period was twenty eight (28) days. At the beginning of study period (day 1)initial body weight of all the rats were measured and at the end of study period their final body weight was also measured. Blood samples were collected on day 1 from the tail vein of all rats to assess the liver function. All the rats received basal diet. In addition to basal diet, rats of baseline control group received normal saline (20 ml/ kg body weight) orally daily. Hepatotoxicity was induced by administration of single daily morning dose of paracetamol (1.5g/kg body weight) orally by gastric gavage on day 26, 27 and 28 after overnight fasting except baseline control group. Cinnamon extract (400 mg/kg/ day dissolved in 1 ml distilled water) were given to experimental group (group B) orally in morning between 9:00 AM to 10:00 AM for 28 consecutive days.At the end of the study period all the rats were sacrificed on day 29 (after 24 hours of last dose of paracetamol administration on day 28). Then blood samples (3ml) were collected from heart. After that supernatant serum was preserved in the refrigerator. The liver was removed from each rat and weighed. Serum levels of total bilirubin, ALT, AST were measured by standard laboratory procedure in the Department of Physiology in SSMC, by semi-automated analyzer machine. Assessment of malondialdehyde (MDA) content of liver tissue homogenate was done by using standard laboratory kits in the laboratory of Department of Biochemistry and Molecular Biology, Jahangirnagar University, Savar, Dhaka. Histological slides were prepared and observed under microscope and

photomicrograph were taken by using standard laboratory procedure in the Department of Pathology, SSMC.

Results:

Data were expressed as mean±SD (standard deviation). The statistical analysis was done by using statistical package for social science (SPSS) for windows version 22. One way ANOVA test was performed for comparison among the groups and then post hoc-Bonferroni test was done to compare between groups. Fisher's exact test, paired sample ' t ' test was done as applicable. p value ≤ 0.05 was considered as level of significance.

Table I: Body weight and Liver weight in different groups of rats (N=30)

Group	Body weight (gm)		% change of body weight [(F-I)/Ix100]	Liver Weight (gm)	
	Initial (I)	Final (F)			
A_1 (n=10)	176.30 ± (167 - 187)	7.50183.80 ± (172 - 195)	7.834.26 ± (2.70 - 5.56)	0.933.18 ± (3.02 - 3.30)	0.09
:A_2 (n=10)	177.70 ± (168 - 200)	9.75172.80 ± (164 - 192)	8.79-2.74 ± (-4.00 – [-1.73])	0.644.51 ± (4.10 - 5.35)	0.52
B (n=10)	178.80 ± (167 - 190)	6.68184.00 ± (175 - 196)	6.272.92 ± (2.20 - 4.79)	0.773.65 ± (3.15 - 4.42)	0.36

Multiplecomparisons

	Initial body weight	Final body weight	% change of body weight	Liver weight
	p value	p value	p value	p value
A_1 vs A_2vs B	0.788^{ns}	0.004^{**}	$<0.001^{***}$	$<0.001^{***}$
A_1 vs A_2	1.000^{ns}	0.011^{*}	$<0.001^{***}$	$<0.001^{***}$
A_1 vs B	1.000^{ns}	1.000^{ns}	0.002^{**}	0.025^{*}
A_2 vs B	1.000^{ns}	0.009^{**}	$<0.001^{***}$	$<0.001^{***}$

Liver weight was significantly lower ($p<0.001$) in cinnamon pretreated and paracetamol treated group than that of paracetamol treated control group.

Table II: Mean Serum total bilirubin, ALT, AST and mean MDA levels in different groups

Group	Serum total bilirubin (mg/dL)	Serum ALT (U/L)	Serum AST (U/L)	MDA (nmol/mg protein)
A_1 (n=10)	0.61 ± 0.21 (0.28 - 0.92)	35.60 ± 6.74 (26.00 - 42.00)	36.80 ± 5.61 (28.00 - 42.00)	8.33 ± 1.82 (5.74 - 11.03)
A_2 (n=10)	2.43 ± 0.57 (1.80 - 3.30)	95.90 ± 20.51 (65.00 - 130.00)	96.10 ± 20.01 (66.00 - 128.00)	17.74 ± 2.74 (14.58 - 22.23)
B (n=10)	1.00 ± 0.11 (0.82 - 1.12)	47.50 ± 6.24 (40.00 - 60.00)	48.00 ± 6.29 (40.00 - 63.00)	11.30 ± 2.53 (8.89 - 15.23)

Multiple comparisons

	Serum total bilirubin	Serum ALT	Serum AST	MDA
	P value	P value	P value	P value
A_1 vs A_2 vs B	<0.001***	<0.001***	<0.001***	<0.001***
A_1 vs A_2	<0.001***	<0.001***	<0.001***	<0.001***
A_1 vs B	0.066^{ns}	0.150^{ns}	0.168^{ns}	0.030
A_2 vs B	<0.001***	<0.001***	<0.001***	<0.001***

In this study, serum total bilirubin, ALT, AST,mean MDA levels were significantly higher in paracetamol treated control group andcinnamon pretreated and paracetmol treated group($p<0.001$) in comparison to that of baseline control group. Again, serum total bilirubin, ALT, AST, mean MDA levels of cinnamon pretreated and paracetamol treated group was significantly ($p<0.001$) lower in comparison to that of paracetamol treated control group.

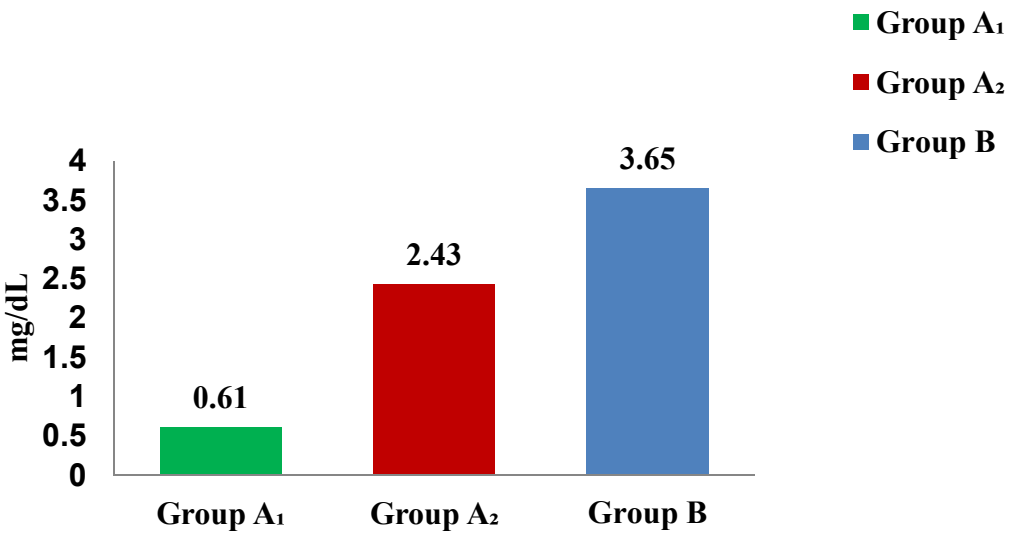

Figure 1. Mean serum bilirubin level in different groups of rats

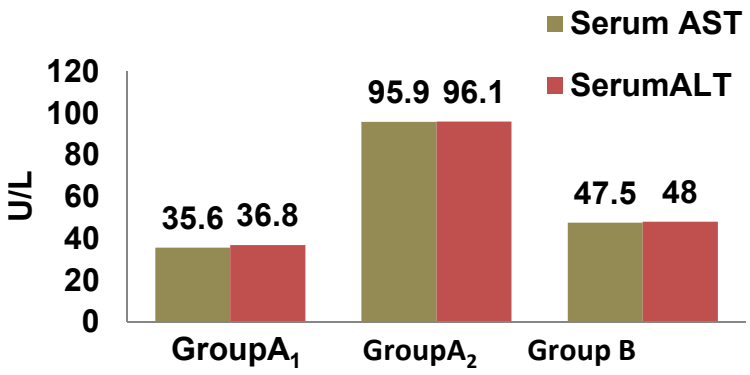

Figure 2. Mean serum ALT, AST level in different groups of rats

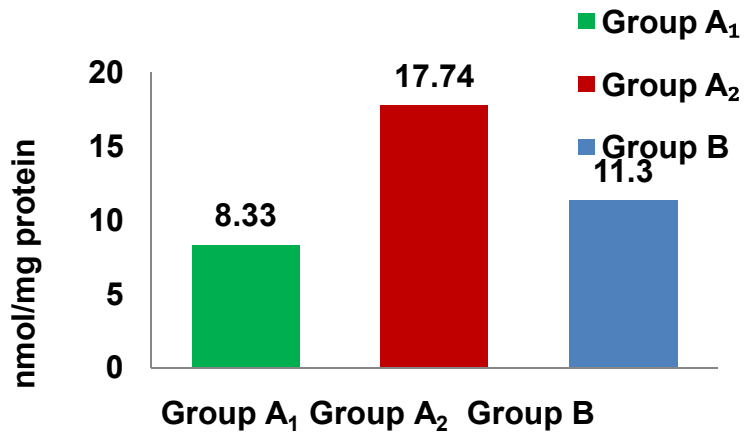

Figure 3. Mean MDA level in different groups of rats

Table III: Histopathological observation of liver in different groups of rats (N=30)& findings

Group	Observation	Result/Findings
Group A_1 (n=10) (Baseline control group)	Architecture of hepatic lobule, central vein. Structure of hepatocyte, portal tract. Orientation of hepatic sinusoids.	Normal hepatic structure in all 10 rats
Group A_2 (n=10) (Paracetamol treated control group)	Presence of centrilobular necrosis. Disorganization of hepatic sinusoids. Infiltration of lymphocytes and kuffer cells infiltration. Presence of fatty change. Balloning degeneration.	Moderate histological changes in all 10 rats
Group B (n=10) (Cinnamon pretreated and paracetamol treated group)	Almost normal architecture of hepatic lobule and central vein. Almost normal structure of hepatocyte and portal tract. Less/absence of lymphocyte and kuffer cells infiltration. Less/absence of centrilobular necrosis.	Almost normal histological finding in 7 rats and mild histological changes in 3 rats

Normal	Mild change	Moderate change
Normal architecture of hepatic lobule, central vein. Normal structure of hepatocyte, portal tract. Normal orientation of hepatic sinusoids.	Less/absence of lymphocyte and kuffer cells infiltration. Less/absence of centrilobular necrosis.	Presence of centrilobular necrosis. Disorganization of hepatic sinusoids. Infiltration of lymphocytes and kuffer cells infiltration. Presence of fatty change. Balloning degeneration.

Table IV: Distribution of rats by the histopathological changes in liver

Histoiogical findings		
Group	**Normal**	**Abnormal**
Group A_1	10(100.0)	0(0.0)
GroupA_2	0(0.0)	10(100.0)
Group B	7 (70)	3(30.0)

	P value
A_1 vs A_2	$<0.001^{***}$
A_1 vs B	0.210^{ns}
A_2 vs B	0.003^{**}

Only minimal histological changes of liver were observed in 30% rats of cinnamon pretreated and paracetamol treated rats.

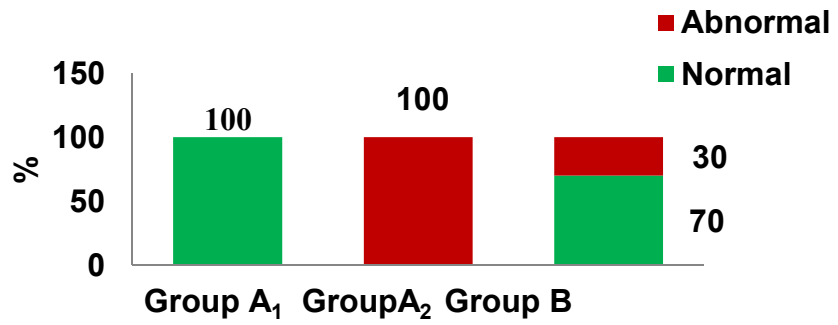

Figure 4. Histological findings in different groups of rats

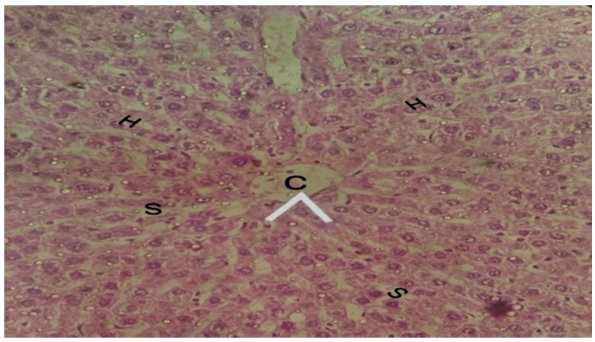

Figure 5. Photomicrograph: Architecture of liver of baseline control rats (here C, S, H represent central vein, sinusoid and hepatocyte respectively in X 400).

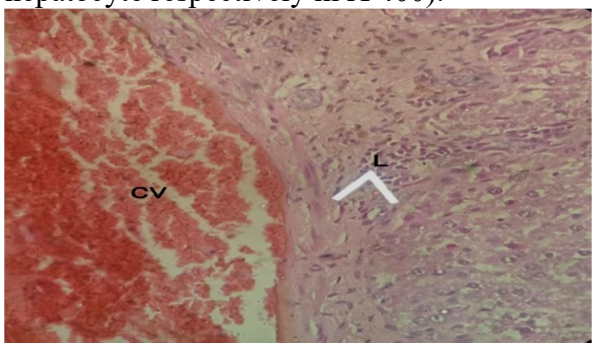

Figure 6. Photomicrograph: Architecture of liver of paracetamol treated control rats (here CV, L represent, congested central vein, lymphocyte infiltration respectively in X 100).

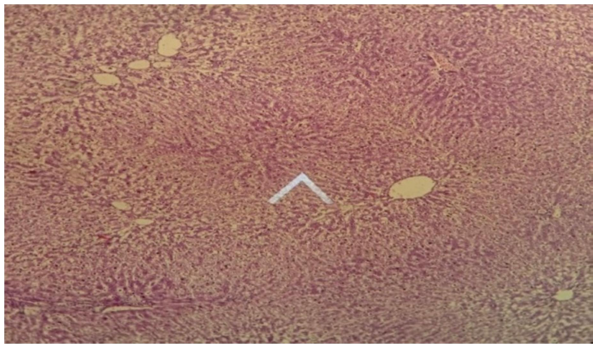

Figure 7. Photomicrograph: Architecture of liver of cinnamon pretreated and paracetamol treated rats in X 100.

Discussion

The present study was carried out to evaluate the hepatoprotective effect of cinnamon on paracetamol induced hepatotoxic rats. For the purpose of the study serum levels of total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), malondialdehyde (MDA) in liver homogenate were measured to assess liver function. Moreover, histological examination of liver was also done to observe the microscopical findings of the liver.

In the present study, thirty (30) Long-Evans male rats, 90-120 days old, weighing between 150-200g were taken. After acclimatization for 14 days, they were randomly divided into three groups, such as baseline control group (A_1), paracetamol treated control group (A_2), cinnamon pretreated and paracetamol treated group (B). All groups of rats received basal diet for 28 days. To produce hepatotoxicity,

paracetamol treated control group (A_2) and cinnamon pretreated and paracetamol treated group (B) received paracetamol orally (1.5g/kg/day) for last 3 days (26^{th} to 28^{th} days) of study period. In addition to this cinnamon pretreated and paracetamol treated group (B) also received aqueous extract of cinnamon orally (400mg/kg/day) for 28 days (day 1 to day 28).

In the present study, final body weight of paracetamol treated controlgroup wassignificantly ($p<0.05$) lower in paracetamol treated control group in comparison to that of baseline control group. Again, final body weight of cinnamon pretreated and paracetamol treated group and baseline control group were almost similar and the difference was not statistically significant. In this study, liver weight was significantly higher in both paracetamol treated control group ($p<0.001$) and cinnamon pretreated and paracetamol treated group ($p<0.05$) in comparison to that of baseline control group. Again, liver weight was significantly lower ($p<0.001$) in cinnamon pretreated and paracetamol treated group than that of paracetamol treated control group. Almost similar findings were observed by Esha BR et al.[8]

In this study, serum total bilirubin, ALT, AST levels were significantly higher in paracetamol treated control group ($p<0.001$) in comparison to that of baseline control group. Again serum total bilirubin, ALT, AST levels of cinnamon pretreated and paracetamol treated group was significantly ($p<0.001$) lower in cinnamon pretreated and paracetamol treated group in comparison to that of paracetamol treated control group and the difference was not statistically significant. Similar finding was also observed by Fadil HAE et al.[9]

In this study, MDA concentration in liver tissue homogenate was significantly ($p<0.001$) higher in paracetamol treated control group in comparison to that of baseline control group. Again, serum total bilirubin, ALT, AST levels of cinnamon pretreated and paracetamol treated group was significantly ($p<0.001$) lower in comparison to that of paracetamol treated control group. Similar finding was also observed Ghany MG et al.[10] Moderate histological changes such as presence of centrilobular necrosis, disorganization of hepatic sinusoids, infiltration of lymphocytes and kuffer cells, presence of fatty change and ballooning degeneration were observed in this study in paracetamol treated control group.

On the other hand, only minimal histological changes of liver were observed in 30% rats of cinnamon pretreated and paracetamol treated rats. These findings were also in agreement with those of different researchers of other countries.[11, 12]

In the present study, paracetamol induced liver damage was observed in Long evans male rats as evidenced by their measured increased serum levels of total bilirubin, ALT,AST and MDA concentration in liver. These changes may be due to increased production of free radicals which initiates lipid peroxidation and subsequent cellular damage which is evidenced by increase MDA level in liver homogenate. Disruption of normal histological structure of liver tissue in paracetamol treated control rats in favor of this statement. But this cannot be elucidated from the study as concentrations of free radicals were not measured.

Again, serum levels of total bilirubin, ALT, AST and MDA concentration in liver were lowered in cinnamon pretreated and paracetamol treated rats than those of paracetamol treated control rats which

suggested the possibility of the cinnamon extract to give protection against paracetamol induced liver injury. Furthermore, histopathological changes found in cinnamon pretreated and paracetamol treated group were less than those of paracetamol treated group, which provide direct evidence of hepatoprotective effect of the extract of cinnamon. This protective effect might be due to free radical scavenging activity of cinnamon.

Conclusion

From this study it may be concluded that cinnamon has hepatoprotective effect on paracetamol induced liver damage in Long-Evans male rats.

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