Therapeutic and toxic effects of *Cinnamomum cassia* bark in rabbits: a biochemical, haematological and histopathological study

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Abstract

Phytomedicines have potentially used for the treatment of hyperlipidemia and other metabolic disorders. Herbal safety is very crucial especially of their chronic use in any problem. This study was conducted to investigate the effective and safe dose of *Cinnamomum cassia* bark. Thirty healthy male rabbits were divided into three groups; 2 test groups and control group C. Powder of *C. cassia* bark was mixed in distilled water and administered to the test groups 1 and 2 at the dose of 25 mg/Kg and 50 mg/Kg respectively for three months, whereas control group (n=10) received distilled water. At the end of dosing, blood samples were obtained to determine biochemical and hematological parameters such as liver enzymes, cardiac enzymes, complete blood count (CBC), blood glucose HbA1c, kidney function test, electrolytes and lipid profile. Histopathological examination of heart, kidney, stomach and liver tissues were performed to find its toxic effects. The dose of 50 mg/kg of *C. cassia* bark powder caused 45.39 % and 55.4% increase in the level of serum glutamic pyruvic transaminase (SGPT) alkaline phosphatase (ALP) respectively. Bilirubin levels, CBC, electrolytes and hematological indices (hemoglobin (Hb), red blood cell RBC, hematocrit (HCT), mean corpuscular hemoglobin (MCH), Leukocyte and Platelet count) were in normal range. HbA1c reading of the treated animal with 25 mg/kg of C. cinnamon showed 5.9 ± 0.08% decrease as compared with control as 7.5 ± 0.21%. Test group 2 showed significantly increased the level of LDH value as 284.7 % than the control. Test group 1 and 2 showed significantly higher urea level as 87.16% and 63.39% respectively than the control and creatinine level showed in normal range. Doses of 25 mg/kg and 50 mg/kg of cinnamon bark

exhibited significant reduction in the cholesterol HDL ratio i.e. 22.5% and 14.14 % respectively as compared to control. Test group 2 produced significant reduction in cholesterol and triglycerides level as 27% and 12.06%. The level of LDL was reduced by cinnamon bark at the doses of 25 mg/kg and 50 mg/kg as 18.72% and 23.28%. Histopathological analysis showed noticeable changes in the tissues of animal of test group 2 showed such as Photomicrograph from heart, kidney and liver tissues showed conjugated architecture of cardiac muscles, shrinkage in renal tubule and swallowed hepatocytes respectively. This study generates the evidence to substantiate the traditional use of *C. cassia* bark in the treatment of hyperlipidemia and regulation of blood sugar. The dose of 25 mg/kg of *C. cassia* bark showed more safe in prolonged use. Further future studies are recommended to focus the toxicity related with its each phytoconstituent.

Keyword: *Cinnamomum cassia*, hepatic enzymes, lipid profile, cardiac enzymes, electrolytes

Introduction

Hyperlipidemia is one of the major cause of high mortality rate. Lipid profile is correlated with the incidence of heart diseases (Dong *et al*., 2021). Number of causative factors of dyslipidemia such as age, life style, eating habits, medicines, heredity and different hormonal problems (Opoku *et al*., 2019). Different synthetic drugs are used for their anti-hyperlipidemic potential. The conventional drugs are used alone or in combination but produced lot of side effects. Muscle pain, stomach problem, constipation, memory loss and drug resistance are the most common adverse effects by the used of anti-hyperlipidemic medicines. Interactions are also reported between the number of prescription medicines and dietary supplements with lipid lowering drug. (Rauf *et al*., 2022).

Cinnamomum cassia belongs to family Lauraceae. Bark of *C. cassia* have intense aromatic and sweet taste. It is frequently used as spice in number of dishes (Zaidi *et al*., 2015). *C. cassia* is a common traditional Chinese medicine and used as an alternative medicine in many Asian countries. *C. cassia* to treat various diseases, such as cardiovascular disease, chronic gastrointestinal disease, gynecological disorders and inflammatory diseases. Pharmacological and phytochemical studies have been done on *C. cassia* and 160 phytochemicals have been separated and identified. *C. cassia* possess a wide range of medicinal effects as confirmed in many studies. *C. cassia*, *C. verum*, and *C. tamala* are extensively used in local and traditional medicine for the treatment of a multitude of disorders (Hong *et al*., 2012; Kwon *et al*., 2006; Zhang *et al*., 2019).

Herbal use was increase gradually in the treatment and prevention of different problems. Toxic effects were occurred different cases of herbal practice by their chronic treatment, improper dosage, interaction with medicines, food and other herbs (Vega *et al*., 2017). The current study was carried out to demonstrate the effects of *Cinnamomum cassia* on hepatic enzymes, cardiac enzymes, kidney function, blood count, blood glucose, electrolytes and lipid profile in experimental animals after dosing of 3 months. Furthermore, the histopathological examination

of liver, stomach, kidney and heart were conducted to investigate any abnormal change in the tissues.

Methodology

Plant material and Preparation of extract

The bark of *Cinnamomum cassia* was purchased from local herbal supplier, identified from herbarium by Department of Pharmacognosy, FUUAST Karachi, Pakistan and provide voucher specimen No CCB-08-19.

The material of plant was grinded into fine powder with the help of grinder. Doses of 25 mg/kg and 50 mg/kg were mixed in minimum amount of water for oral administration in test groups of rabbits.

Animal selection

White, healthy male rabbits, weighing 1000-1500 grams were housed in well-ventilated and spacious cages to conduct animal studies. They were housed under standard lighting (12 hours light/dark cycle), environmentally controlled, provided normal diet (fresh hay grass) and water ad libitum (Esteves *et al*., 2017).

Ethical consideration

Experimental protocol to evaluate the effects of *Cinnamomum cassia* bark powder in water, on hepatic enzymes and blood lipids in rabbits after dosing of 90 days was approved by Institutional Ethical Committee of FUUAST Karachi, Pakistan and issued Ref letter No. FUUAST/Pharm/Ethic/01-2020.

Dosing

Rabbits were divided into three groups; control and test groups 1 and 2. Each group was comprised of 10 rabbits. Group C served as untreated group or control, each rabbit received diet and water. Additionally, the rabbits in test group 1, and 2 received water mixture of *cinnamon cassia* bark powder at the doses of 25 mg/Kg and 50 mg/Kg respectively. The doses were administered once a day on every morning through an oral route by using gastric gavage for the duration of three months. All rabbits were acclimatized for a period of 10 days before the administration of doses.

Collection of blood

After 90 days of dosing, blood samples were collected for haematological and biochemical analysis.

Biochemical tests

Blood plasma were obtained from the blood samples by centrifugation at 3000 r.p.m. for 15 min by Humax 14 K (Germany) and stored at −20 °C for biochemical analysis to find different parameters.

Auto chemistry analyzer was used to determine the liver enzymes by including gamma-glutamyl Transferase (γ-GT), serum glutamic pyruvic transaminase (SGPT) alkaline phosphatase (ALP)

from the collected plasma. Other parameters were also detected such as direct bilirubin (DBR), indirect bilirubin and total bilirubin (TBR) levels. Kidney function test assessed by the measuring of Urea and creatinine level. Cardiac enzymes such as Lactate dehydrogenase (LDH), Creatine phosphokinase (CPK), Creatine phosphokinase-MB (CPK-MB), serum glutamic-oxaloacetic transaminase (SGOT) were determined. Different electrolytes such as Sodium, Potassium, Chloride and Bicarbonate were also determined.

lipid profile was determined by measuring the total cholesterol, triglycerides, LDL, VLDL and HDL levels by the enzymatic colorimetric (CHOD-PAP) method using an automated biochemistry analyzer (Konelab 20, Thermo Fisher Scientific, Helsinki, Finland). Low density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula (Friedewald *et al*., 1972).

Haematological tests and Histopathological examination

Different Parameters of blood were determined by using an hematology analyzer ((Mazumder *et al*., 1999). HbA1c (glycosylated hemoglobin) test is used to evaluate the blood sugar level. Histopathological examinations were performed to measure any morphological change in different organs by modified method of Olayode *et al*, 2020.

Statistical analysis

One-way analysis of variance (ANOVA) followed by Turkey's post-hoc test (GraphPad Software, La Jolla, California, USA).

Results

Liver enzymes and bilirubin level

The effect of 25 mg/kg and 50 mg/kg doses of *C. cassia* bark powder on hepatic enzymes were presented in table 1. *C. cassia* bark at the dose of 25 mg/kg produced slight increase in the levels of SGPT as 71.33 ± 2. U/L and 50 mg/kg produced significant increase in the levels of SGPT as 84.33 ± 5.31 U/L as compared with control as 58 ± 0.81 U/L. The level of alkaline phosphatase, at the dose of 25 mg/kg of *C. cassia* bark powder was within the normal range as 90.33 ± 4.64 U/L compared with control reading as 79 ± 0.81 U/L. 50 mg/kg of *C. cassia* bark powder showed the significantly elevated level of alkaline phosphatase that was 122.0 ± 4.54 U/L. Both doses of cinnamon bark 25 mg/kg and 50 mg/kg slightly decrease the level of GGT, that were 12 ± 2.16 and 13 ± 0.81 U/L respectively as compared with control reading as 16.66 ± 0.94 U/L.

The dose of 25 mg/kg of cinnamon bark exhibited slightly lower in the level of direct bilirubin i.e. 0.09 ± 0.09 mg/dl and 50 mg/kg of cinnamon bark showed similar level of direct bilirubin as control (0.1 ± 0.009 mg/dl). The dose of 25 mg/kg cinnamon bark extract exhibited significant reduction in the level of indirect bilirubin as 0.12 ± 0.02 mg/dl than the control as 0.16 ± 0.032 mg/dl. Total bilirubin of the Test group 1 is lower as 0.21 ± 0.023 mg/dl than the control as 0.27 ± 0.023 mg/dl (Table 1).

Table 1 Effect of *C. cassia* bark powder on hepatic enzymes and bilirubin level

Test	Parameter	**C** (control) **0.5ml water**	Test group 1 **25 mg/kg *C. cassia***	Test group 2 **50 mg/kg *C. cassia***
Hepatic enzymes	SGPT(U/L)	58 ± 0.81	71.33 ± 2.4	84.33 ± 5.31**
	% increase/decrease	-	22.98↑	45.39↓
	ALP(U/L)	79 ± 0.81	90.33 ± 4.64**	122 ± 4.54
	% increase/decrease	-	14.3↑	55.4↑
	GGT (U/L)	16.66 ± 0.94*	12 ± 2.16*	13 ± 0.81*
	% increase/decrease		27.97↓	21.96↓
Bilirubin level	Direct Bilirubin level (mg/dl)	0.1 ± 0.009	0.09 ± 0.009	0.1 ± 0.004
	% increase/decrease	-	10↓	-
	Indirect Bilirubin level (mg/dl)	0.16 ± 0.032*	0.12 ± 0.02*	0.15 ± 0.012
	% increase/decrease	-	25↓	6.25↓
	Total Bilirubin	0.27 ± 0.023	0.21 ± 0.023	0.26 ± 0.016
	% increase/decrease(mg/dl)	-	22.2↓	3.7↓

Data presented as mean ± standard error of the mean; $p < 0.05$ were considered statistically significant

Complete Blood Count and HbA1c

Apart from the observed changes in platelets, HCT and MCV, in general, other hematological indices did not show any significant changes in all tested doses when compared to control. Hematological indices like hemoglobin (Hg), red blood cell RBC, hematocrit (HCT), mean corpuscular hemoglobin (MCH), Leukocyte and Platelet count were in normal range. Mean corpuscular volume (MCV) of test group 1 showed slightly higher value than that of the normal range and MCH of control was higher than normal range but reduced in animals in test groups. HBA1c readings of Test group 1 showed better control on blood glucose level 5.9 ± 0.08%. whereas control and test 2 indicated diabetic as 7.5 ± 0.21 and 6.93 ± 0.63 respectively (Table 2).

Table 2 Effect of *C. cassia* bark powder on Complete Blood Count and HbA1c ↑↓

Complete Blood Count	**C (control)** 0.5 ml water	**Test group 1** 25 mg/kg *C. cassia*	% increase/ decrease	**Test group 2** 50 mg/kg *C. cassia*	% increase/decrease
Hemoglobin (g/dl)	11.4 ± 0.4	10.7 ± 0.21	6.1↓	11.96 ± 0.36	4.9↑
RBC (million/µl)	5.52 ± 0.12	5.06 ± 0.2	8.3↓	5.8 ± 0.08	**5**↑
Hematocrit %	35.6 ± 1.8	40.2 ± 3.88	12.9↑	41.13 ± 1.87	15.5↑
MCV (mm^3)	64.53 ± 4.35	79.28 ± 6.08	22.8↑	70.88 ± 2.24	9.8↑
MCH (pg/cell)	20.66 ± 1.19	21.17 ± 1.29	2.4↑	20.62 ± 0.34	0.1↓
MCHC %	32.07 ± 1.48	26.87 ± 2.7	16.2↓	29.11 ± 0.43	9.2↓

Total Leukocyte/µl	5.53 $x10^3$± 0.26	3.93 $x10^3$± 0.28	28.9↓	5.43 $x10^3$± 0.65	1.8↓
Platelet count (/L)	365.33×10^9 ± 8.21	257×10^9 ± 11.57	29.6↓	381.33×10^9 ± 4.02	4.3↑
Blood Glucose HbA1c (%)	7.5 ± 0.21	5.9 ± 0.08	21.3↓	6.93 ± 0.63	7.6↓

Data presented as mean ± standard error of the mean; $p < 0.05$ were considered statistically significant

Cardiac Enzymes, Electrolytes and Kidney Function

Cardiac enzymes such as Lactate dehydrogenase (LDH), Creatine phosphokinase (CPK), Creatine phosphokinase-MB (CPK-MB), serum glutamic-oxaloacetic transaminase (SGOT) were analyzed for the assessment of cardiac effect of *C. cassia* bark. LDH value of the Test group 1 181.33 ± 2.86 U/L is more higher than control while Test group 2 significantly increased the level of LDH value as396.33 ± 3.68 than the control103 ± 0.81 U/L. CPK value of the Test group 1 is slightly higher than the control as 377.66 ± 7.03 U/L while Test group 2 showed more higher value as 579.33 ± 6.12 U/L. Test group 1 showed significantly lower CK-MB value as 208 ± 2.94 U/L than the control 457.66 ± 0.94 U/L and Test group 2 showed slightly higher value as 579.33 ± 6.12 U/L

Test group 1 showed higher value of SGOT level as 52 ± 3.74 U/L than the control 33 ± 0.81 U/L while Test group 2 showed higher value as 70 ± 4.32 U/L.

Electrolytes **(**Sodium, Chloride, Potassium and bicarbonate) were not altered significantly and found in the normal range. Kidney Function was assessed by the measurement of urea and creatinine level.Test group 1 and 2 showed significantly higher urea level as 63 ± 3.55 mg/dl and 55 ± 4.89 mg/dl respectively than the control 33.66 ± 4.18 mg/dl. Test group 1 showed slightly lower creatinine level as 1 ± 0.16 mg/dl while Test group 2 showed higher Creatinine level as 1.2 ± 0.14 mg/dl than the control as 1.14 ± 0.04 mg/dl (Table 3).

Table 3: Effect of *C. cassia* bark powder on Cardiac Enzymes, Electrolytes and Kidney Function

Test	**Parameter**	**C (control)** 0.5 ml water	**Test group 1** 25 mg/kg *C. cassia*	**Test group 2** 50 mg/kg *C. cassia*
Cardiac Enzymes	LDH (U/L)	103 ± 0.81	181.33 ± 2.86	396.33 ± 3.68
	% increase/decrease	-	43.1↑	284.7↑
	CPK (U/L)	345.66 ± 3.29	377.66 ± 7.03	579.33 ± 6.12
	% increase/decrease	-	9.25↑	67.6↑
	CK-MB (U/L)	457.66 ± 0.94	208 ± 2.94	470.33 ± 9.97
	% increase/decrease	-	54.55↓	2.76↑
	SGOT (U/L)	33 ± 0.81	52 ± 3.74	70 ± 4.32
	% increase/decrease	-	57.5↑	112.1↑
Electr olytes	Sodium mmol/l	145.66 ± 0.47	143.33 ± 0.47	146 ± 0.81
	% increase/decrease	-	0.016↓	0.2↑
	Potassium mg/dl	6.56 ± 0.16	4.86 ± 0.18	5.4 ± 0.14

	% increase/decrease	-	25.9↓	17.6↓
	Chloride mmol/l	97.66 ± 0.47	105.33 ± 1.69	102 ± 1.63
	% increase/decrease	-	7.85↑	4.4↑
	Bicarbonate mmol/l	22.33 ± 1.69	23 ± 0.81	22 ± 2.16
	% increase/decrease	-	3.0↑	1.4↓
Kidney Function	Urea (mg/dl)	33.66 ± 4.18	63 ± 3.55	55 ± 4.89
	% increase/decrease	-	87.16↑	63.39↑
	Creatinine (mg/dl)	1.14 ± 0.04	1 ± 0.16	1.2 ± 0.14
	% increase/decrease	-	12.2↓	5.2↑

Data presented as mean ± standard error of the mean; $p < 0.05$ were considered statistically significant

Lipid profile

C. cassia bark on lipid profile is shown in table 4. Doses of 25 mg/kg and 50 mg/kg of cinnamon bark exhibited significant reduction in the cholesterol HDL ratio i.e. 1.75 ± 0.31 and 1.98 ± 0.22 respectively, in comparison to control as 2.26 ± 0.18. Test group 2 produced significant reduction in cholesterol level as 18.0 ± 6.97 mg/dl than the control 24.66 ± 0.94 mg/dl. The level of triglycerides was reduced in highly significant manner at 50 mg/kg as 58.33 ± 6.01 mg/dl. Cinnamon bark produced highly significant reductions in the levels of HDL at the 50 mg/kg, the reading was 9.0 ± 2.94 mg/dl compared to control as 11 ± 1.41mg/dl. The level of LDL was reduced by cinnamon bark at the doses of 25 mg/kg and 50 mg/kg as 22 ± 5.03 mg/dl and 20.66 ± 3.24 mg/dl respectively as compared to control as 26.93 ± 0.67 mg/dl. The variations have been observed in the level of VLDL at different doses of cinnamon bark, at dose of 25 mg/kg the VLDL level slightly increased as 14.2 ± 1.97 mg/dl and at the dose of 50 mg/kg the VLDL level significantly reduced as 11.46 ± 1.03 mg/dl in comparison to control as 13.13 ± 0.09 mg/dl (Table 4).

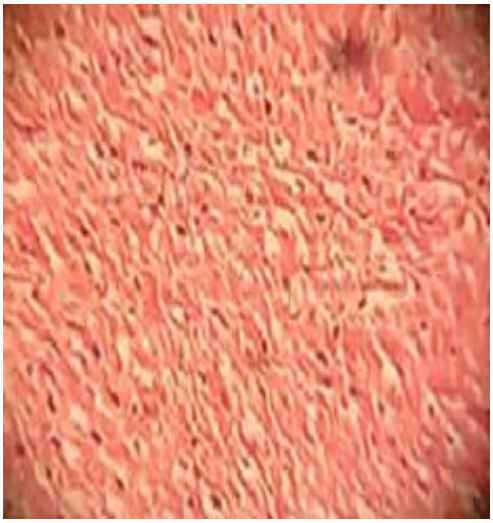
Table 4: Effect of aqueous extract of *C. cassia* bark on lipid profile

Lipid Profile	**C (control)** 0.5 ml water	**Test group 1** 25 mg/kg *C. cassia*	% increase/ decrease	**Test group 2** 50 mg/kg *C. cassia*	% increase/ decrease
Cholesterol HDL ratio	2.26 ± 0.18	1.75 ± 0.31**	22.5	1.98 ± 0.22**	14.14
Cholesterol (mg/dl)	24.66 ± 0.94	20.33 ± 2.86**	17.5	18 ± 6.97**	27
Triglycerides (mg/dl)	66.33 ± 1.24	66.66 ± 8.65**	0.49	58.33 ± 6.01**	12.06
HDL (mg/dl)	11 ± 1.41	11.66 ± 0.47**	6	9 ± 2.94**	27.2
LDL (mg/dl)	26.93 ± 0.67	22 ± 5.03**	18.72	20.66 ± 3.24**	23.28
VLDL (mg/dl)	13.13 ± 0.09	14.2 ± 1.97**	8.14	11.46 ± 1.03**	12.7

Data presented as mean ± standard error of the mean; $p < 0.05$ were considered statistically significant

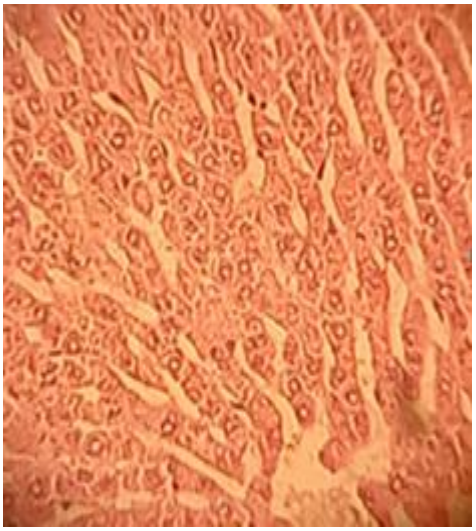
Histopathological examination

heart



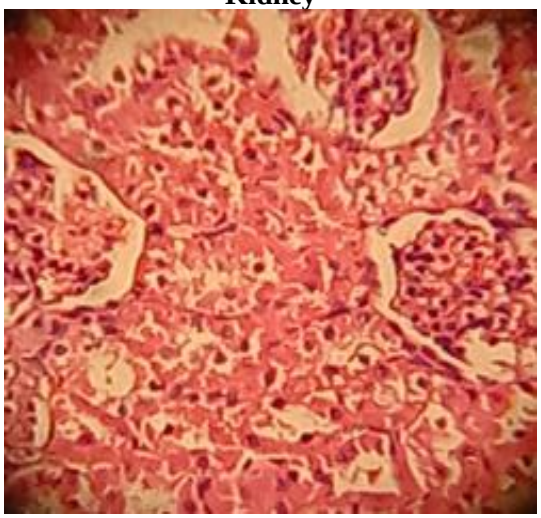
This photomicrograph shows a specimen obtained from the heart of Cinnamon bark 25mg and stained with H&E stain X400. The examination of the frozen section revealed it to be normal with intact endocardium, mayocardium, and pericardium. No sign of inflammation seen through the wall, and no fibrosis is seen.

liver



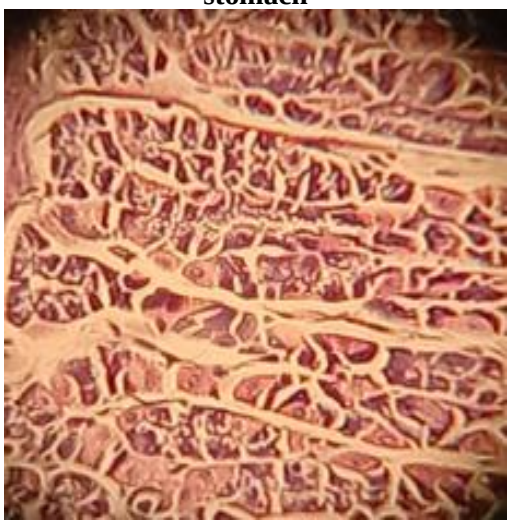
This photomicrograph shows a specimen obtain from the liver of Cinnamon bark 25mg and stained with H&E stain X 400. Hepatocytes are swallow but no convencing micro vesicular steatosis are present., dilation of portal tract were present moderate inflammation is seen. No fatty alteration found. No fibrosis and necrosis was seen.

Kidney



This photomicrograph shows a specimen obtained from the kidney of Cinnamon bark 25mg subject and stained with H&E stain X100. The examination of the frozen section revealed it to have shrinkage in renal tubule. No infiltration of immune infiltrate is seen. Variable size glomeruli present.

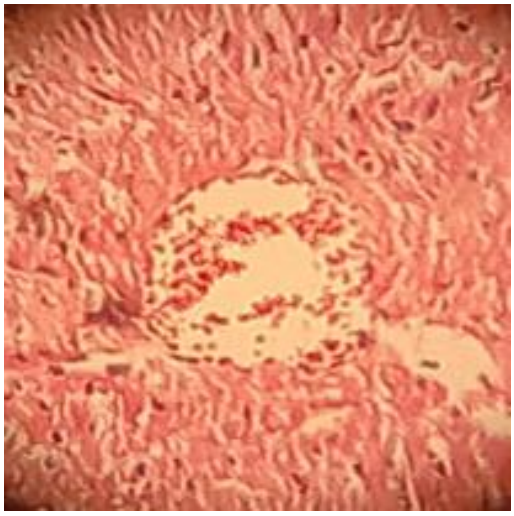
stomach



This photomicrograph shows a specimen obtained from the stomach of Cinnamon bark 25mg and stained with H&E stain X100. The examination of the frozen section revealed to have intact glandular architecture, gland lined by intact epithelium. No infiltration is seen, Lamina propia is intact.

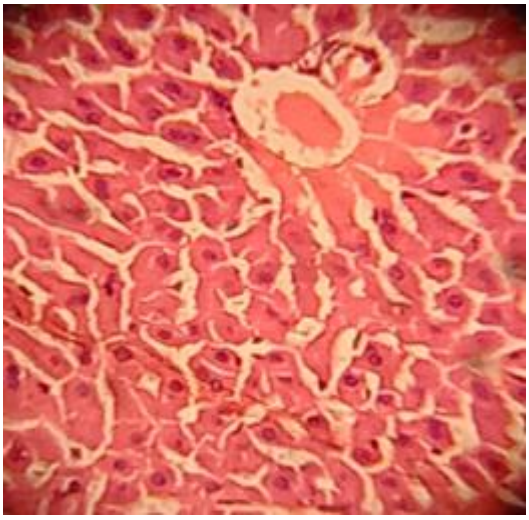
Figure 1 Photomicrograph of a specimen obtained from the liver, heart, Kidney and stomach of a rabbit treated with *Cinnamon cassia* bark at dose of 25 mg/Kg

heart



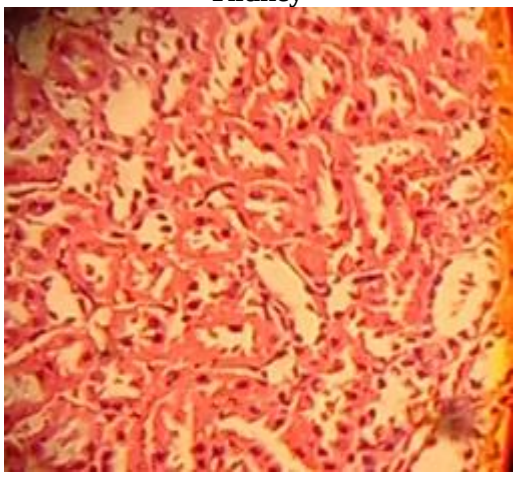
This photomicrograph shows a specimen obtained from the heart of Cinnamon bark 50mg and stained with H&E stain X400. The examination of frozen section showed conjugated architecture of cardiac muscles, infiltration of blood found, no edema in pericardial lining.

liver



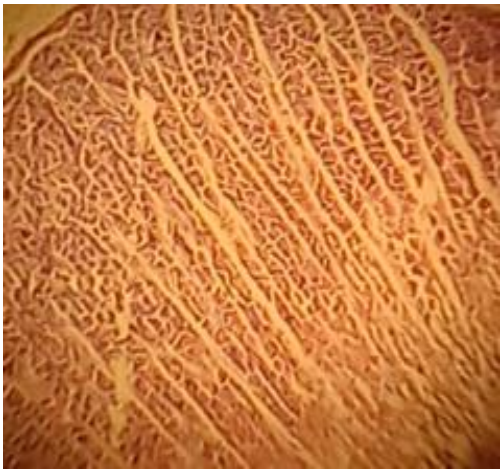
This photomicrograph shows a specimen obtain from the liver of Cinnamon bark 50mg and stained with H&E stain X 400. Hepatocytes are swallow 10% micro vesicular steatosis are present, dilation of portal tract were present moderate inflammation were present. Mild fibrotic change is found.

Kidney



This photomicrograph shows a specimen obtained from the kidney of Cinnamon bark 50mg subject and stained with H&E stain X100. The examination of the frozen section revealed it to have shrinkage in renal tubule. mild infiltration of immune infiltrate is seen. Mild tubulitis was found.

stomach



This photomicrograph shows a specimen obtained from the stomach of Cinnamon bark 50mg and stained with H&E stain X100. The examination of the frozen section revealed to have intact glandular architecture, gland lined by intact epithelium. No infiltration is seen, Lamina propia is intact.

Figure 2 Photomicrograph of a specimen obtained from the liver, heart, Kidney and stomach of a rabbit treated with *Cinnamon cassia* bark at dose of 50 mg/Kg

Discussion

Doses of *C. cassia* bark powder were administered at 25 mg/kg and 50 mg/kg in the form of water mixture over the period of three months showed an increase in the levels of hepatic enzymes such as serum glutamic pyruvic transaminase (SGPT) alkaline phosphatase (ALP). The dose of 50 mg/kg of *C. cassia* bark powder produced 45.39 % and 55.4% increase in the level of serum glutamic pyruvic transaminase (SGPT) alkaline phosphatase (ALP) respectively which indicated the hepatoxicity of *C. cassia* bark. SGPT is a key enzyme known to be associated with liver parenchymal cells and when there is hepatic injury, the enzymes leak into the blood stream. The greater the degree of the liver damage, the higher the activity of the enzyme (Brennan *et al*., 2022). However, level of gamma-GT were decrease at 25 mg/kg and 50 mg/kg doses of *C. cassia* bark powder which indicated the biliary obstruction. Different parameters of bilirubin level showed no hepatic injury in the treated animals. Complete blood count of the animals including hemoglobin (Hg), red blood cell RBC, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), Leukocyte and Platelet count were in normal range. HbA1c of animals taken the 25 mg/kg of C. cinnamon showed test group 1 showed better control on blood glucose as compared with HbA1c readings of control and test group 2. The dose of 25 mg/kg of C. cinnamon bark powder mixed in water effectively regulated the carbohydrate metabolism as compared with supplements.

Cardiac enzymes were assessed for the safe use of *C. cassia* bark. LDH value of the Test group 1 is higher as 181.33 ± 2.86 U/L and Test group 2 is significantly higher as 396.33 ± 3.68 U/L than control as 103 ± 0.81 U/L. CPK value of the Test group showed more higher value as 579.33 ± 6.12 U/L than the control as 345.66 ± 3.29U/L. Test group 1 showed higher value of SGOT level as 52 ± 3.74 U/L than the control 33 ± 0.81 U/L while Test group 2 showed higher value as 70 ± 4.32 U/L. Dose dependant increase in the level of cardiac enzymes showed degeneration of cardiac tissues. Urea and creatinine level were used to assessed the effect of *C. cassia* bark on Kidney function. Test group 1 and 2 showed significantly higher urea level as 63 ± 3.55 mg/dl and 55 ± 4.89 mg/dl respectively than the control 33.66 ± 4.18 mg/dl indicated the improper kidney function but normal creatinine levels were in normal range which Test group 1 showed slightly lower creatinine level as 1 ± 0.16 mg/dl while Test group 2 showed higher Creatinine level as 1.2 ± 0.14 mg/dl than the control as 1.14 ± 0.04 mg/dl.
C. cassia bark powder administered over period of three months reduced the cholesterol HDL ratio in comparison to control. Similarly, the serum cholesterol, triglycerides, LDL, and VLDL level also decreased significantly in a dose dependent fashion as compared to control group.

The histopathological examination of tissues revealed toxic effects at the dose of 50mg/kg of *C. cassia* bark. Photomicrograph of heart from the animal of test group 2 showed conjugated architecture of cardiac muscles and infiltration of blood. Shrinkage in renal tubule, mild infiltration and mild tubulitis were observed in the photomicrograph of kidney tissues while Photomicrograph of liver from the animal of test group 2 showed moderate inflammation and mild fibrotic change (Figure 3).

Cinnamon has been considered as a safe flavoring agent in food for thousands of years (Balasubramanian *et al*., 2016; Für Risikobewertung, 2006). Significant decrease in the cholesterol, triglycerides, LDL and VLDL levels were measured in treated animals with *C. cassia* extract powder at both doses of 25 mg/g and 50 mg/kg as compared to those in the untreated group. Hypolipidemic effect was seen with administration of *C. cassia* enriched diet over period of 2-months (Aldalou, 2021). *C. cassia* could be in preventing the synthesis of cholesterol or facilitating the excretion of cholesterol (Khan *et al*., 2003) Alternatively, there is evidence that cinnamon improves the hepatic bile acid synthesis and increases the degeneration of cholesterol to fecal bile acid and neutral sterol. Moreover, it has been reported that the cinnamon has strong lipolytic action. Therefore, the *C. cassia* extract reduces the serum level of triglycerides by impeding the synthesis of triglycerides by the fat hydrolysis, which may lower down the serum levels of triglycerides (Lichtinghagen *et al.*, 2006; Kannappan *et al*., 2006). The anti-hyperlipidemic effect of C. cassia could be attributable to the presence cinnamaldehyde (Dugoua *et al*., 2007). It is reported previously, the treatment with the cinnamon caused an increased in HDL levels. This effect may be due to the decreased conversion of HDL to VLDL in the liver and intestine, or it can be due to its ability to hydrolyze the fats that, in turn, leads to the increase in HDL level in blood (Khan *et al*., 2003). In contrary, our study findings revealed highly significant reductions in the levels of HDL (9.0 ± 2.94) at dose of 50 mg in comparison to control (11 ± 1.41). *C. cassia* contains up to 1% coumarin, and a tolerable daily intake of 0.1 mg/kg/day (Iwata *et al.*, 2016). It is one of the known hepatotoxic and caused allergic reactions. Prolonged oral exposure to coumarin could be cause of oxidative stress (Ihanus, 2021) may be a reason of its hepatotoxic and cardiac toxic potential.

Conclusion

In conclusion, the results of the present study revealed that, *Cinnamomum cassia* have potential to exhibit hypolipidemic effect in safe doses. Thus, *Cinnamomum cassia* can be utilized as an adjunctive therapy for the treatment of hyperlipidemia and hyperglycemia. This work can be extended to understand the mechanisms of hepatotoxic and cardiac toxic effects at higher doses as well as the investigation of the causative constituents.

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