

Effects and Interactions of Ginger and Propranolol in Pre-Hepatic Portal Hypertensive Rats

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ABSTRACT

AIM: Portal hypertension (PHT) is a frequent sequel of liver fibrosis and cirrhosis. Propranolol is commonly used for lowering portal pressure and preventing variceal bleeding. The hepatoprotective effect of ginger has been reported. The aim of this study is to assess the effects and interactions of ginger and propranolol in pre-hepatic PHT in male albino rats.

MATERIALS AND METHODS: Adult male albino rats were divided into 3 main groups. The first group: control rats. The second group: sham-operated rats and third group: pre-hepatic portal hypertensive rats induced by partial portal vein ligation (PPVL). The third group is subdivided into: subgroup (1): untreated-PPVL group and subgroups 2-6 were treated with propranolol 75mg/Kg; ginger 90 mg/kg; 180mg/Kg; ginger 90 mg/kg plus propranolol

75 mg/kg, and ginger 180 mg/kg plus propranolol 75 mg/kg respectively. The portal pressure was measured in all groups then rats were sacrificed and blood samples were collected for estimation of alanine aminotransferase (ALT) and alkaline phosphatase (AP) levels then hepatic as well as gastro-intestinal tissues were obtained for histopathological examination.

RESULTS: Ginger, propranolol and in combinations significantly decreased the elevated portal pressure and histopathological scores in the liver and esophagus in relation to PPVL group. Ginger, and in combination with propranolol significantly decreased the histopathological scores in stomach and intestine as well as the ALT level, while AP level was reduced only by administration of ginger in a dose 90mg/kg alone and in combination with propranolol in relation to PPVL group. Propranolol produced non-significant reductions in the gastrointestinal histopathological score and ALT as well as AP levels in relation to PPVL group.

CONCLUSION: In PPVL rats, ginger and propranolol decreased portal pressure, histopathological changes in liver and esophagus while, those of stomach and intestine as well as ALT and AP levels were improved by ginger and ginger-propranolol combinations.

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Key words: Ginger; Propranolol; Portal hypertension; Portal vein ligation

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INTRODUCTION

Portal hypertension (PHT) plays an important role in the natural history of cirrhosis, and is associated with several clinical consequences^[1]. It is an increase in pressure in portal vein and its tributaries and patients with portal pressure above 12mmHg are prone to the development of complications^[2]. Partial portal vein ligation (PPVL) is one of the most commonly used methods in induction of pre-hepatic PHT. Portal vein ligation induces marked elevation of alanine aminotransferase (ALT) level^[3]. The increase in serum alkaline phosphatase (AP) is associated with liver disease and refers to intra or extra hepatic cholestasis and some destruction of hepatic cell membrane^[4].

Propranolol is a competitive non-selective β blocker; it is used in treatment of PHT and showed a beneficial effect in prevention of variceal bleeding and rebleeding^[5]. Propranolol decreases portal pressure by decreasing cardiac output (β_1 blocking action) and prevent splanchnic vasodilatation (β_2 blocking effect)^[6].

Ginger had been traditionally used in treatment of nausea and vomiting, inflammatory conditions and to support circulatory and immune system^[7]. Sahebkar^[8] reported that, due to anti-inflammatory and anti-oxidant effects of ginger, it showed promising results in non-alcoholic fatty liver disease.

The aim of this work is to assess the prophylactic effect of ginger on PHT and its interactions with propranolol on the experimentally-induced PHT in adult male albino rats.

METHODS

Drugs and chemicals

Ginger (*Zingiber officinale*), powder, MEPACO-Egypt, Enchas Al-raml, Al-sharkeiya, Egypt, Propranolol hydrochloride, powder, Sigma St. Louis, MO. USA, Ethyl carbamate (Urethane), crystals, Prolabo, Paris, France, Ketamine Hydrochloride, vial Troikaa Pharmaceuticals LTd Gujarat, India, Normal saline, 0.9%, Elmottahedoon CO, Tenth of Ramadan City, Egypt, Haematoxlin and eosin (Sigma St. Louis, MO. USA).

Animals

Adult male albino rats weighing 180-200 gm were obtained from faculty of veterinary medicine animal house, Egypt. These animals were housed under hygienic and standard environmental conditions (22±1°C) and 12h light-dark cycle. They were allowed free access to food and water ad-libitum. The animals were deprived of food but allowed free access to tap water for 24 h prior to the experiment.

Induction of pre-hepatic portal hypertension

Partial portal vein ligation (PPVL) model has been performed in this study as described by Castaneda *et al.*^[9] Rats were anesthetized with ketamine hydrochloride (75-100 mg/kg, IM). Portal vein trunk is freed from the surrounding tissues after midline abdominal incision was made, and a ligature of 4-0 silk was placed around the vein. A 20-gauge, blunt-end needle was placed alongside the vein and the ligature tied incompletely to the needle and vein. The subsequent removal of the needle was establishing a calibrated stenosis of the portal vein that had the diameter of the needle. Then the abdominal incision was closed in two layers by using 2-0 silk ligature. Sham rats underwent an identical procedure except that portal vein was isolated but not stenosed. Each rat was injected with 0.5 mL of benzyl-penicillin (diluted in 4 mL distilled water) for 3 days to avoid infection. Hence formation of collaterals occurs as early as 12

days after portal vein obstruction and the average time to formation is approximately 5 weeks^[10], the portal pressure measurements, biochemical analysis and histopathological specimens were done after 6 weeks after ligation of portal vein.

Portal pressure measurement

Six weeks after PPVL, the rats were anesthetized with urethane (1.3 gm/kg IP as 25% freshly prepared solution)^[11]. A midline abdominal incision was made then the ileocolic vein was cannulated with polyethylene tubing (PE-50) to measure portal venous pressure through pressure transducer "PT400" that was attached to FC137 strain gauge coupler of oscillograph 400 MD 4C (Palmar-Bioscience).

Biochemical tests

Blood was collected by direct cardiac puncture. Blood samples were kept at room temperature for 30 min and underwent 15 min of centrifugation at 1,500×g, then serum was separated and transferred to sterile polypropylene tubes and frozen at -40°C until levels of alanine aminotransferase (ALT) and alkaline phosphatase (AP) were estimated. AP was measured by colorimetric kinetic method^[13] and ALT by colorimetric method^[14].

Histopathological examination

Tissues from the involved animals including liver, lower third of esophagus, fundus of the stomach and suspected lesions of the intestine were taken and fixed in buffer formalin (10%) which stabilizes the tissues to prevent decay. The formalin fixed tissues were paraffin embedded, and prepared as 5- μ m-thick sections. For light microscopic examination, all tissues were stained with H&E and the specimens were evaluated for the presence of inflammatory cell infiltrate, hepatocyte death and necrosis by the method of Batts and Ludwid^[15].

Grading system for liver pathology:^[16]

Grade	Portal/periportal activity	Lobular activity
0	None	None
1	Portal inflammation	Inflammation but no necrosis
2	Mild piecemeal necrosis	Focal necrosis or acidophil bodies
3	Moderate piecemeal necrosis	Severe focal cell damage
4	Severe piecemeal necrosis	Damage includes bridging necrosis

Grading system for gastroenteropathy:^[17]

Grade	Description
1	Minimal (cellular infiltration).
2	Mild (inflammatory cellular infiltration, dilated vessels).
3	Moderate (lymphocytic cell infiltration, congested blood vessels, cherry red spots)
4	Marked (cellular infiltration, congested tortuous blood vessels in mucosa and sub-mucosa with edema, erosion).

Experimental Design

Propranolol and gingers were freshly prepared in distilled water to be administered at a volume of 1mL/100gm rat orally once daily. After 1 week of acclimatization, rats were randomized and separated into 3 main groups: (1) Control rats ($n=6$); (2) Sham operated rats ($n=6$); and (3) Pre-hepatic portal hypertensive rats induced by regulated pre-hepatic PVL ($n=48$) as described above. The third group was subdivided into 6 equal subgroups. Subgroup (1): received distilled water (untreated PPVL-group); Subgroup (2) received propranolol, 75 mg/kg^[18], Subgroup (3) received ginger, 90mg/kg; Subgroup (4) received ginger, 180 mg/kg; Subgroup (5) received ginger, 90 mg

plus propranolol, 75 mg/kg; Subgroup (6) received ginger, 180 mg/kg plus propranolol, 75 mg/kg.

Propranolol administration was started one day before PPVL^[19]. Ginger doses were given for 30 days before PVL^[20]. After PPVL propranolol and ginger administration were continued for 6 weeks.

Statistical analysis

Results were expressed as mean \pm SE. Statistical evaluation was done using one-way analysis of variance (ANOVA), and least significant difference "LSD" multiple comparison test using SPSS software version 14, SPSS Science, Chicago, IL, USA. Values of $p < 0.05$ were considered significant^[21].

All experimental procedures were approved by the local authorities at the Faculty of Medicine, Zagazig University, Egypt (Ethical Committee for Animal Handling at Zagazig University, ECAHZU).

RESULTS

The portal pressure and serum levels of ALT and AP were significantly increased in PPVL-untreated group compared with control and sham-operated groups. The latter group didn't have significant changes in the previous parameters compared with control group. Administration of propranolol, ginger or ginger-propranolol combinations significantly decreased the portal pressure ($P < 0.05$) in relation to PVL-untreated group. There were no significant differences between propranolol, ginger and the combination groups. (Table 1)

Regarding ALT, its level was significantly decreased after administration of ginger and ginger-propranolol combinations ($P < 0.05$) in relation to PPVL-untreated and propranolol-treated groups. Ginger in a dose of 90mg/kg alone and in combination with propranolol significantly reduced the serum level of AP ($P < 0.05$) in relation to PPVL-untreated, propranolol, ginger 180mg/kg and ginger 180mg/kg-propranolol treated groups. Administration of propranolol alone produced non-significant decrease in ALT and AP levels in relation to PPVL-untreated group. (Table 1)

The mean values of liver and gastrointestinal histopathological score were increased in PPVL-untreated rats in relation to control and sham-operated groups. There was no significant difference between sham and control groups. In the liver, and esophagus the histopathological scores were significantly decreased after administration of propranolol, ginger and ginger-propranolol combinations ($P < 0.05$) in relation to PPVL-untreated group. There were no significant differences between propranolol, ginger and the combination groups. (Table 2 and figure 1, 2)

In the stomach, and intestine the histopathological scores were significantly decreased after administration of ginger and ginger-propranolol combinations ($P < 0.05$) in relation to PVL-untreated group. Propranolol alone produced non-significant decrease in the gastrointestinal histopathological scores in relation PPVL-untreated group. There was a significant difference between ginger 90mg/kg-propranolol combination and propranolol-treated groups. (Table 2 and figures 3, 4).

DISCUSSION

Partial-PVL (PPVL) model has been widely used in the study of the pathophysiology of PHT^[22]. This model was utilized in this study to investigate the effect of ginger and its interaction with propranolol which is commonly used in PHT treatment. The PPVL-untreated group showed significant elevation in the portal venous pressure which could be explained by mechanical obstruction of the portal

Table 1 Effect of oral administration of ginger, propranolol or both on portal pressure and liver enzymes levels in portal vein-ligated rats (N=6).

Parameters	Portal pressure (mmHg)	Serum ALT (U/mL)	Serum AP (IU/L)
Control	16.34 \pm 1.09	23.5 \pm 2.9	98.2 \pm 14.4
Sham	17.08 \pm 1.16	23.5 \pm 2.9	98.2 \pm 14.4
PPVL-untreated	30.4 \pm 0.84 ¹	43.8 \pm 4.9 ¹	164.8 \pm 46.5 ¹
Propranolol	21.1 \pm 1.23 ²	37 \pm 5.3 ¹	150.3 \pm 13 ¹
Ginger (90 mg/kg)	22.6 \pm 1.72 ²	27.8 \pm 1.5 ³	80 \pm 12.4 ⁴
Ginger (180 mg/kg)	22.9 \pm 1.19 ²	29.7 \pm 2.9 ³	151.6 \pm 15.2 ¹
Ginger (90 mg/kg) + Propranolol	18.08 \pm 0.84 ²	28.5 \pm 2.6 ³	100 \pm 4.4 ⁴
Ginger (180 mg/kg) + Propranolol	20.17 \pm 0.75 ²	30.5 \pm 3 ³	142 \pm 33.6 ¹

ALT: Alanine aminotransferase, AP: alkaline phosphatase, PPVL: partial portal vein ligated. Results are presented as the mean \pm S.E.M. N: Number of animals in each group.

¹Significantly different from the corresponding mean value of control and sham group at $p < 0.05$;

²Significantly different from the corresponding mean value of PPVL-untreated group at $p < 0.05$;

³Significantly different from the corresponding mean value of propranolol-treated and PPVL-untreated groups at $p < 0.05$;

⁴Significantly different from the corresponding mean value of PPVL-untreated, propranolol, ginger 180 mg/kg and ginger 180mg/kg-propranolol treated groups at $p < 0.05$.

Table 2 Effect of oral administration of ginger, propranolol or both on histopathological score in the liver, esophagus, stomach and intestine in PVL rats (N=6)

Organ	Liver	Esophagus	Stomach	Intestine
Control	0.54 \pm 0.08	0.63 \pm 0.12	0.68 \pm 0.09	0.52 \pm 0.11
Sham	0.67 \pm 0.13	0.67 \pm 0.13	0.67 \pm 0.13	0.67 \pm 0.13
PPVL-untreated	3.17 \pm 0.22 ¹	3 \pm 0 ¹	3 \pm 0 ¹	3 \pm 0 ¹
Propranolol (75mg/kg)	2 \pm 0.17 ²	2 \pm 0.17 ²	2.33 \pm 0.21 ¹	2.33 \pm 0.2 ¹
Ginger(90 mg/kg)	2.33 \pm 0.21 ²	2 \pm 0.17 ²	1.5 \pm 0.22 ²	1.5 \pm 0.22 ²
Ginger(180 mg/kg)	2.33 \pm 0.31 ²	2 \pm 0 ²	2 \pm 0.17 ²	2 \pm 0.17 ²
Ginger (90 mg/kg) + Propranolol	2 \pm 0.17 ²	1.5 \pm 0.22 ²	1.33 \pm 0.21 ³	1.33 \pm 0.21 ³
Ginger (180 mg/kg) + Propranolol	2 \pm 0.21 ²	1.33 \pm 0.21 ²	2 \pm 0.17 ²	2 \pm 0.17 ²

PPVL: Partial portal vein ligated. Results are presented as the mean \pm S.E.M. N: Number of animals in each group.

¹Significantly different from the corresponding mean value of control and sham group at $p < 0.05$.

²Significantly different from the corresponding mean value of PPVL-untreated group at $p < 0.05$.

³Significantly different from the corresponding mean value of PPVL-untreated and propranolol-treated groups at $p < 0.05$.

flow^[23].

Pre-hepatic PHT and its complications could be considered as a consequence of inflammatory and metabolic disorder^[24]. Pro- and anti-inflammatory mediators like nitric oxide (NO) and tumor necrosis factor α (TNF- α), are released from the gut and the liver in PHT^[25]. NO and its possible interaction with prostaglandin I₂ (PGI₂) is responsible for splanchnic vasodilatation and the maintenance of hyperdynamic circulation^[26,27]. Moreover, the changes in the type and amount of intestinal microflora predispose to liver cirrhosis and hepatic encephalopathy^[28].

In the present study, propranolol produced significant reduction in portal pressure. The mechanistic explanation of this effect could be attributed to both β_1 and β_2 blocking action with subsequent decrease in cardiac output and reduction of splanchnic blood flow due to splanchnic vasoconstriction respectively^[29]. Pérez-Paramo *et al.*^[30] suggested that propranolol could also decrease portal pressure by its ability to attenuate the bacterial translocation.

As regarding the effect of ginger on portal pressure, the results of present work showed that, the utilized doses significantly reduced the

portal pressure. This effect might be attributed to reduction of NO and PG production within the splanchnic circulation^[31]. Moreover, ginger could decrease the inflammatory mediators like TNF- α , interleukin-1 β (IL-1 β), carbon monoxide (CO) and IL-10^[25]. In the same context, the potential antimicrobial effect of ginger^[32] as well as inhibition of angiogenesis^[33] could share in the reduction of portal pressure.

In this study, co-administration of ginger with propranolol decreased the portal pressure. The latter effect was non-significantly different from that obtained with propranolol alone. This effect means that ginger mechanisms of lowering the elevated portal pressure did not synergize propranolol effect on the portal pressure.

The histological examination of liver of pre-hepatic portal hypertensive rats showed cellular infiltration, congested sinusoids and occasionally extended to areas of focal damage and necrosis. The exact mechanisms of liver histopathological changes in portal hypertension are not fully understood but there are some possible explanations; reduced portal blood flow causing hypoxia that induces mitochondrial dysfunction in the extra-hepatic portal obstruction in rats^[34] and the increased level of TNF- α , IL1 β and NO in the liver in pre-hepatic portal hypertensive rats^[35]. The disturbance in liver function tests in the PPVL-untreated group supports the results of histological examination.

The current study demonstrated that propranolol significantly reduced liver pathological changes in comparison to PPVL-untreated group. These results are in agreement with Sigala *et al.*^[36] who reported that sympathetic nervous system (SNS) signaling regulates hepatic fibrogenesis through effects on hepatic stellate cells (HSC), in which

SNS activation accelerates progression of NAFLD. PHT in rat shows persistent splanchnic alterations related to the elevated pressure and produces changes in the metabolism of lipids and carbohydrates that could be involved in the development of liver steatosis^[25].

Ginger significantly reduced liver pathological and biochemical changes in relation to PPVL-untreated group. These results are in parallel with that reported by Habib *et al.*^[37] who reported that the 6-gingerol and 6-paradol (ingredients of ginger) showed a strong anti-inflammatory activity and ability to suppress the TNF- α production in rats. Sahebkar^[8] reported that ginger has been suggested to prevent NAFLD or suppress its progression not only through down-regulation of pro-inflammatory cytokines but also by sensitizing insulin effects, promoting antioxidant effects and reducing hepatic triglyceride content which can prevent steatosis.

In the present study, ginger but not propranolol administration significantly decreased the elevated ALT levels. The AP level was decreased after administration of ginger 90 mg/kg only or in combination of propranolol but not with either ginger 180 mg/kg or propranolol alone. These results explored that ginger has hepatoprotective effect, more at the lower dose. The difference between ginger and propranolol effect on ALT & AP levels could reside in the strong anti-inflammatory activity of ginger and its ability to suppress the TNF- α production^[37], the pro-inflammatory cytokines as well as promoting antioxidant effects^[8]. Decline in these effects with increasing the dose of ginger and their absence with propranolol administration could explain why ginger, especially the small dose, decreased ALT and AP enzymes.

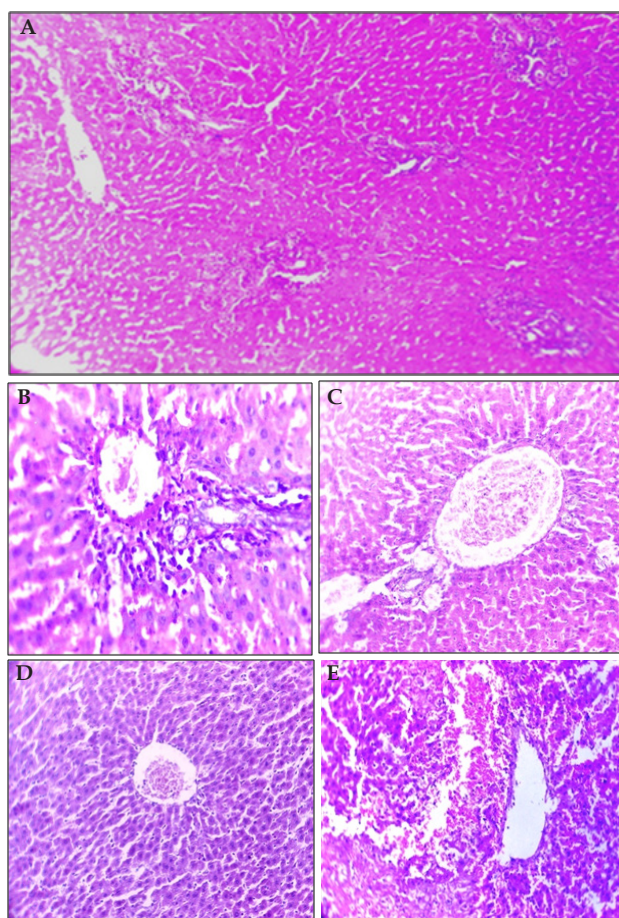


Figure 1 Photomicrographs for the hepatic pathological results: (A) normal hepatic tissue, (B) score-1, (C) score-2, (D) score-3, (E) score-4 (H&E $\times 400$).

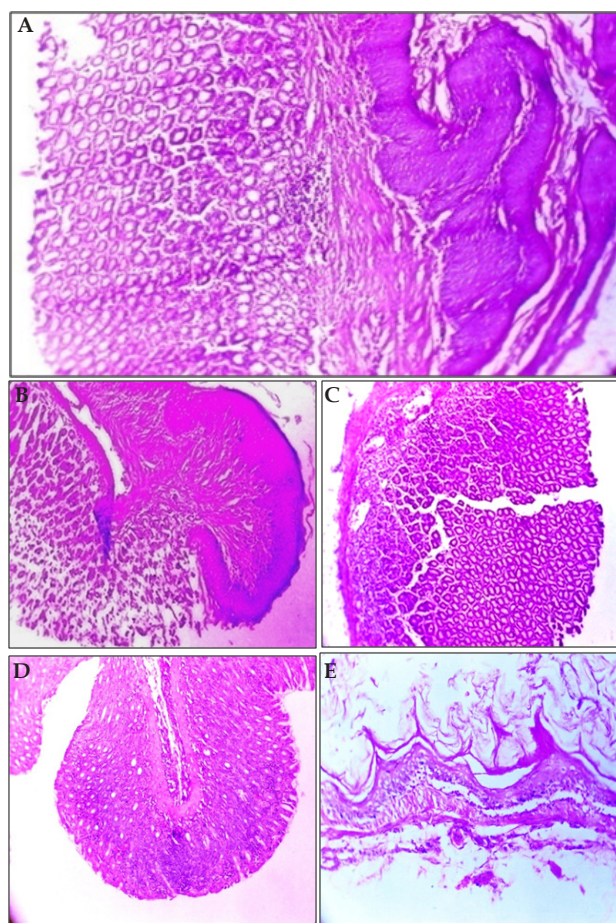


Figure 2 Photomicrographs for the esophageal histopathological results: (A) normal esophageal tissue, (B) score-1, (C) score-2, (D) score-3, (E) score-4 (H&E $\times 400$).

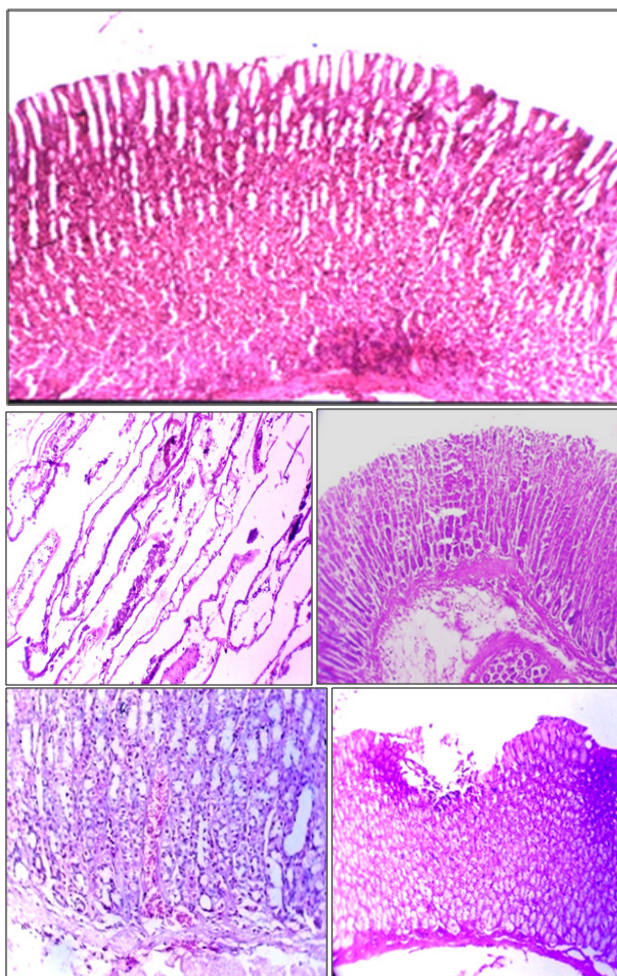


Figure 3 Photomicrographs for the gastric histopathological results: (A) normal gastric tissue, (B) score-1, (C) score-2, (D) score-3, (E) score-4 (H&E ×400).

In the present investigations, the histological examination of esophagus, stomach and intestine in pre-hepatic portal hypertensive rats, revealed lymphocytic cellular infiltration, edematous mucosa, erosions with dilated tortuous vessels. The possible causes of these changes include ischemia/reperfusion with subsequent production of oxidative and nitrosative stress factors^[38], and locally released mediators cause vasodilatation as well as angiogenesis^[39].

The results of the present study showed that, ginger administration significantly reduced the histopathological changes in the esophagus, stomach and intestine while; propranolol reduced these changes in the esophagus only in relation to PPVL-untreated group

The protective effect of propranolol on portal hypertensive enteropathy is a matter of controversy. Rafailidis *et al*^[40] reported that early propranolol administration at a dose of 30 mg/kg/ day prevents portal hypertensive vasculopathy in rats and explained this by its ability to decrease portal pressure gradient and inhibit angiogenesis. On the other hand, study by Fizzano *et al*^[41] showed that long-term administration of propranolol (75 mg/Kg/day) is model dependent; reducing portal pressure and improved hemodynamic changes in carbon tetrachloride model while in bile duct-ligated model the reduction was insignificant. Their explanation to this model dependent effect related to the difference in the incidence of bacterial translocation between these models.

This controversy may explain the significant reduction in esophageal changes which related mainly to the ability of propranolol to decrease portal pressure, while in stomach and intestine there were

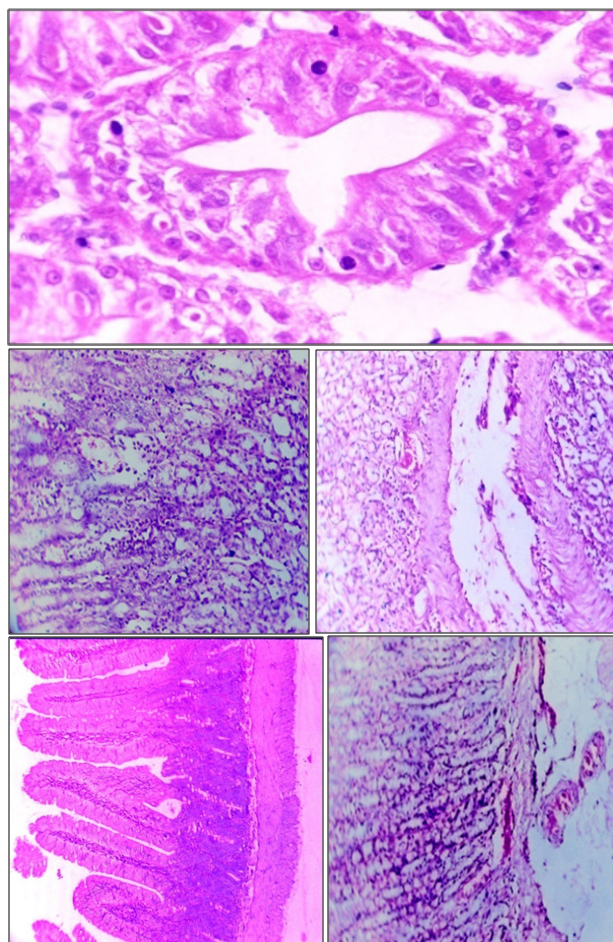


Figure 4 Photomicrographs for the intestinal histopathological results: (A) normal intestinal tissue, (B) score-1, (C) score-2, (D) score-3, (E) score-4 (H&E ×400).

higher density of bacterial translocation.

In case portal hypertensive gastroenteropathy, protective effect of ginger could be attributed to its anti-inflammatory effect as well as, the antimicrobial activity that antagonize bacterial translocation^[31].

Co-administration of propranolol with ginger 90 mg/Kg showed significant reduction of gastrointestinal histopathological changes in comparison to propranolol group indicating the potential value of its co-administration with propranolol in portal hypertensive enteropathy. The greater value of combination of propranolol with the smaller dose (90 mg/Kg/day) of ginger might refer to its better anti-inflammatory effect as well as antimicrobial activity than the higher dose.

CONCLUSION

In PPVL rats, ginger and propranolol decreased portal pressure and the related histopathological changes in the liver and esophagus while, those of stomach and intestine as well as biochemical tests were improved by ginger and ginger-propranolol combinations.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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