EFFECT OF GINGER AND PROPRANOLOL ON EXPERIMENTALLY INDUCED PORTAL HYPERTENSION IN ADULT MALE ALBINO RATS

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ABSTRACT

Background: The incidence and prevalence of portal hypertension in Egypt is very high. Propranolol is one of the most commonly used drugs for lowering portal pressure and preventing variceal bleeding. Ginger was reported to have anti-inflammatory and hepatoprotective effect. **Objectives**: The aim of this study is to evaluate the effects of ginger and its co-administration with propranolol in prehepatic portal hypertension in male albino rats. **Design**: One hundred fifty six adult male albino rats weighting 140- 220 gm were divided into 7 groups. **Group1** (**Sham group**), the remaining groups were subjected to partial portal vein ligation (PPVL). **Group2 (control group)**: received orally distilled water. **Group 3** (propranolol 75mg/Kg/ day). **Group 4** (ginger 90mg/Kg/ day). **Group 5** (ginger 180mg/Kg/ day). **Group 6 ginger** (90mg/kg/day) plus propranolol (75mg/kg/day). **Group 7** ginger (180mg/kg/day) plus propranolol (75mg/kg/day). Propranolol was given orally one day before portal vein ligation (PVL) while ginger powder was given orally 30 days before PVL. These medications were given maximally for 90days after PVL. The following parameters were measured in all previous groups after PVL either at 14, 45 or 90 days: mean arterial blood pressure (MABP), heart rate, portal pressure, then rats were sacrificed and blood samples were collected to assess liver function tests and hepatic and gastro-intestinal tissues were obtained for histopathological examination. **Results: Group (2)** showed significant increase in portal pressure, heart rate, liver functions as well as pathological changes in liver, esophagus, stomach and intestine while MABP was reduced. The other groups from the 3rd group to the 7th group showed significant reduction in portal pressure and in the mean values of the pathological changes.

Conclusion: Ginger especially in a dose of 90mg/kg/day has a protective effect against portal hypertension induced in adult male albino rats. In addition, co-administration with propranolol enhances its protective effect especially hepatic and gastro-intestinal lesions however ginger at a dose of 180mg/kg/day carries risk of drug-herb interaction.

Recommendations: Further clinical studies on ginger extracts are needed to evaluate the effect of ginger on portal hypertension.

Key words: Ginger, Propranolol, portal hypertension, Portal vein ligation.

INTRODUCTION

The incidence and prevalence of portal hypertension (PH) in Egypt is very high due to bilharizial peri-portal fibrosis and/or liver cirrhosis induced by hepatitis C virus (HCV) **(Zakaria et al., 2011).** Portal hypertension 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 **(D'Amico et al., 2006).** Partial portal vein ligation (PVL) one of the most commonly used methods in induction of prehepatic portal hypertension. **Propranolol** is a competitive non-selective β blocker; it is used in treatment of portal hypertension and showed a beneficial effect in prevention of variceal bleeding and rebleeding **(Baik et al., 2003).** Propranolol decreases portal pressure by decreasing cardiac output (β1 blocking action) and prevent splanchnic vasodilatation (β2 blocking effect) (**Wang et al., 2010**). **Ginger** (*Zingiber officinale*) is a perennial plant in tropical areas. It has been used for centuries both as herb and culinary spice **(El-menshawy et al., 1999).** Ginger had been traditionally used in treatment of nausea and vomiting, inflammatory conditions and to support circulatory and immune system **(White, 2007). Sahebkar (2011)** 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 investigate the possible prophylactic effect of ginger on portal hypertension and its interaction

with propranolol on the experimentally induced portal hypertension in adult male albino rats.

MATERIALS AND METHODS

Drugs and chemicals:*Drugs and chemicals:*

1- Ginger, powder (MEPACO-Egypt, Enchas Al- raml, Al-sharkeiya governorate, Egypt). Weighed and freshly prepared in distilled water.
2- Propranolol HCL, powder (Sigma, St. Louis, MO., USA), dissolved in distilled water.
3- Normal saline, 0.9% (Elmottahedoon CO, 10th of Ramadan City, Egypt).
4- Ketamine HCL, (Troikaa Pharmacuticals LTd. Gujarat, India), 50mg, vial (10ml)
5- Ethyl carbamate (Urethane), crystals (Prolabo, Paris), dissolved in distilled water.
6- Haematoxlin and Eosin (Sigma, St. Louis, MO., USA).
7- Formalin 10% (Al-Gomhoria CO, Zagazig, Al-sharkeiya governorate, Egypt).

Animals:

One hundred fifty six adult male albino rats weighing 140-220 gm were obtained from Faculty of Veterinary Medicine Zagazig university- Animal Unit. All experiments in this study were performed in accordance with the guidelines for animal research from National Research Center, Cairo, Egypt. The study protocol was approved by the ethical committee at Faculty of Medicine Zagazig University. Animals received a standard diet and water, ad libitum, and were housed in Faculty of Medicine Zagazig University Animal House with 12 hours light/dark cycle. Animals were kept for one week before starting the study to accommodate the environment in the animal house.

Methods:

Induction of portal hypertension:

Partial portal vein ligation model has been made in this study as described by **Castaneda et al. (2000).** Rats were anesthetized with ketamine hydrochloride (75-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. Since formation of collaterals occurs as early as 12 days after portal vein obstruction and the average time to formation is approximately 5 weeks (**De Franchis and Primignani, 2001**), the portal pressure was measured after 2 weeks, 6 weeks and 12 weeks after ligation of portal vein.

Measurement of portal pressure:

After had being fast for 12 h, with free access only to water, rats were anesthetized with urethane (1.3gm/kg intraperitonial as 25% freshly prepared solution) (**Rafailidis et al., 2008**). A midline abdominal incision was made, and then the portal pressure was measured by inserting a normal saline filled 20-gauge needle into the portal vein. The needle was joined to a PE-50 tube which is connected to a pressure recorder. The pressure reading (cm/water) was considered satisfactory when a stable recording was produced and respiratory variations were observed on the recording scale. The external zero reference point was placed at the midpoint of the animal, 1cm above the operating table (**Mendez-Lopez et al., 2007**).

Method of blood pressure and ECG measurement:

The arterial blood pressure was measured by invasive technique in which an arterial cannula was introduced into one carotid artery which was attached to PT400 blood pressure tranceducer and connected to one channel of 4-channel oscillograph (**Bioscience, London**)(**Kramer and Remie**, **2005**).

Lead II ECG was recorded by using ECG limb cable that was attached to FC123 strain gauge of oscillograph. HR/min was calculated from the recorded ECG pattern on the paper speed of 25mm/sec (**Subramani and Ramasamy, 2012**).

Biochemical tests:

Blood samples which were collected underwent to 15 min of centrifugation at 1,500×g, and then serum was separated and transferred to sterile polypropylene tubes. This

serum was then frozen at -40◦C until alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase(AP), bilirubin and protein were estimated by biochemical testing methods .***Histopathological examination:*** Tissues from the involved animals including liver tissue, 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-µm-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 Ludwig (1995).**

Table (1): Grade system of liver pathology (Scheuer, 1991)

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

Table (2): Grading system for gastro-enteropathy (Stewart and Sanyal, 2003)

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 protocol:

I-Induction of portal hypertension: (as described above).

II- **Oral administration of ginger and propranolol powder:**

Ginger and propranolol powder were dissolved in distilled water and administered orally using a smooth stainless steel tube, connected to an ordinary 5 ml syringe. The tube was introduced into the esophagus during administration to ensure adequate drug delivery and to avoid regurgitation. Doses were selected based on a pilot experiment and previous studies **(El-menshawy et al, 1999).** The concentrations of the drugs were freshly prepared to be administered at volume of 1ml/100gm rat orally.

III- Animals: one hundred fifty six adult male albino rats weighting between 140-220 gm were used.

Rats were divided into the following main groups:

1.Sham operated group (**n= 20 rats**): a midline abdominal incision was made without PVL and then the abdomen is closed in two layers.

2. Control portal hypertension group (**n=24 rats**): a PVL as described above was made. Rats in both groups (1and 2) received orally distilled water throughout the duration of the experiment.

3. ***Propranolol (*75mg/kg*) group*** (**n=22 rats**): Rats received propranolol in a dose of 75mg/kg/day orally (**Lin et al., 1991).**

4. Ginger (90mg/kg) group (**n=22 rats**): received ginger in a dose of 90mg/kg/day orally.

5. Ginger (180mg/kg) group (**n=22 rats**): received ginger in a dose of 180mg/kg/day orally**.**

6. Ginger (90mg/kg) and propranolol (*75mg/kg*) group (**n=22 rats**): received both

ginger in a dose of 90mg/kg/day and propranolol in a dose of 75mg/kg/day orally.

***7. Ginger (180mg/kg) and propranolol (75mg/kg) group* (n=24 rats**): received both ginger in a dose of 180mg/kg/day and propranolol in a dose of 75mg/kg/day orally.

The propranolol administration started one day before PVL **(Huang et al., 1998)** while ginger started 30days before ligation **(El-menshawy et al, 1999)** and both continued through the duration of experiment. All rats were observed daily for detection of any bleeding disorders and recording number of died rats in each group.

**** Mortality rate:**

Two deaths in sham group, six in group (2 and 7) and four in every remaining group.

The remaining number of rats in each group was subdivided into 3 subgroups:

Subgroup (**a**) (n=6): were subjected to portal pressure, blood pressure and heart rate assessment and then scarified after 14 days after PVL.

Subgroup (b) and **Subgroup** (**c**): as subgroup (a) but scarified at 45 and 90 days after PVL respectively.

The following parameters were measured in all previous groups after PVL at 14, 45 (**Said et al., 2006)** and 90 days **(Mendez-Lopez et al., 2007**): MABP (mmHg), heart rate (beat/min), portal pressure (cm/H2O). Rats were sacrificed by decapitation and blood samples were collected for biochemical parameters, then tissues were obtained for histopathological examination.

Statistical analysis

Data were expressed as (means ± SE). Statistical comparison between different groups was done using one way analysis of variance (**ANOVA**), followed by **Post-Hoc** (least significant difference "**LSD**") tests as described by **Levesque, (2007)** using SPSS 14 Evaluation Version computer program (**SPSS Inc., Chicago, IL**). Statistical significance was established at P< 0.05.

RESULTS

Effect on portal pressure:

Control portal group showed significant ($p<0.05$) increase in portal pressure in comparison with sham group at 14, 45 and 90 days after PVL. The portal pressure was significantly ($p<0.05$) decreased in all groups in comparison with the control portal group at 14, 45 and 90 days after PVL (the reduction in group 4 started at 45days) (**Table 3**).

Effect on heart rate and mean arterial blood pressure:

The MABP in the control portal vein ligated rats was significantly ($p<0.05$) decreased in comparison with sham group at 14, 45 and 90 days after PVL**.** No significant changes in MABP between all portal vein ligated groups (**Table 4**).

As regard HR the control portal vein ligated rats was significantly ($p<0.05$) increased in comparison with sham group at 45 and 90 days after PVL**.** All portal vein ligated groups showed significant ($p<0.05$) decrease in HR in comparison with the control portal group except group (4) at 45 and 90days and group (5) at 90days after PVL (**Table 5**).

Histopathological and biochemical results:

As regard hepatic histopathological and biochemical results the pathological changes in control portal group showed cellular infiltration, dilated blood sinusoids with focal hemorrhage, the mean value were significantly ($p<0.05$) higher in comparison to sham group, these pathological changes are significantly ($p<0.05$) decrease in groups from (3) to (7) at 14, 45 and 90 days after PVL in comparison to control portal group (the reduction in group (4) started at 45 days)**(Tables 6, 7 and 8, photo 1A,B,C,D and E).**

In **control portal** group the serum levels of **ALT**, and **AP** (at **45** days) and **AST** and **bilirubin** (at **90days**) were significantly($p<0.05$) elevated, while total plasma **proteins** (at **90days**) were significantly($p<0.05$) decreased in comparison to sham group (**Tables 7 and 8**). **At 14 days**, serum **ALT** levels in groups (**4, 5 and 6**), **AST** in groups (**4 and 6**), and **bilirubin** in groups (**4 and 5**) showed significant reduction in comparison to control portal group (**Table 6).**

At 45 days, serum **ALT** levels in groups (**4, 5, 6 and 7**), **AP** in groups (**4 and 6**) and **bilirubin** in groups (**5 and 7**) showed significant reduction in comparison to control portal group, the reduction in **AP** was also significant in comparison to **propranolol** group (**Table 7**). **At 90 days**, serum **ALT** levels in groups (**3, 4 and 6**), **AST** in groups (**4 and 6**), **AP** in group (**4**) and **bilirubin** in groups (**3 and 4**) showed ($p<0.05$) significant reduction in comparison to control portal group (**Table 8**).

As regard esophageal**,** gastric and intestinal pathological changes in control portal group showed inflammatory cell infiltration, interstitial edema, thickened mucosa and sub-mucosa, congested tortuous vessels with areas of hemorrhage, the mean values of these changes were significantly ($p<0.05$) higher in comparison to sham group **(Photo 2D,E, 3D, 3E and 4D, 4E)**. As regard esophageal pathological changes, the groups from **(3) to (7)** showed significant ($p<0.05$) decrease in comparison to control portal group at 14, 45 and 90 days except group (**4**) and (**5**) at 14 days after PVL (**Tables 9, 10 and11, Photo 2 B and 2C**). Concerning gastric and intestinal pathological changes, comparing to control portal group there were significant ($p<0.05$) decrease in group from **(4)to (7)** at **45 and 90** days after PVL, while at 14 days, only group (**5**) and(**7**) were significantly ($p<0.05$) decreased (**Tables 9, 10 and11, Photo 3B, 3C, 4B and 4C**)

Table (3): Effect of pre-administration of ginger (90, 180 mg/kg), propranolol (75mg/kg) and combination of both on the portal pressure in portal vein ligated rats at 14, 45 and 90 days after PVL

Parameter / Groups	Portal Pressure (cmH_2O) 14 days	45days	90 days
1-Sham	$15.66^{A} \pm 1.05$ a	$17.08^{A} \pm 1.16$ ab	$17.58^{A} \pm 0.72$ b
2- Control portal	$26.5^{B} \pm 0.91$ a	$30.42^{B} \pm 0.84$ b	$28.08^{B} \pm 0.39$ ab
3- Propranolol	$21.42^{C} \pm 1.04$ a	$26.17^{CD} \pm 1.23$ b	$25.83^{C} \pm 0.48$ b
4-Ginger(90mg)	$24.52^{B} \pm 0.73$ ab	$26.6^{C} \pm 1.72$ a	$24.17^{C} \pm 1.01$ b
5-Ginger(180mg)	$22.5^{C} \pm 0.52$ a	$24.92^{CD} \pm 1.19$ b	$24.08^{C} \pm 0.86$ ab
6- Ginger(90mg) +Propranolol	$22^{C} \pm 0.53$ a	$26.08^{CD} \pm 0.84$ b	$25^{C} \pm 0.97$ b
7-Ginger(180mg) +Propranolol	$22.5^{C} \pm 0.52$ a	$24.17^{D} \pm 0.75$ ab	$25.5^{C} \pm 0.77$ b

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Values in the same raw with different subscript small letters are significantly ($p<0.05$) different.

Table (4): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on the mean arterial blood pressure (MABP) in portal vein ligated rats at 14, 45 and 90 days after PVL

Parameter / Groups	Mean Arterial Blood Pressure (mmHg)		
	14days	45days	90 days
1-Sham	109^{A} ± 9.29 a	100^{A} ± 7.03 a	101.4^{A} ± 6.79 a
2- Control portal	85^{B} ± 3.86 a	82^{B} ± 6.71 a	83.3^{B} ± 6.73 a
3- Propranolol	78.5^{B} ± 4.09 a	80.67^{B} ± 7.35 a	82.83^{B} ± 6.22 a
4-Ginger(90mg)	81^{B} ± 4.93 a	85^{B} ± 7.84 a	85^{B} ± 3.27 a
5-Ginger(180mg)	78^{B} ± 6.73 a	82^{B} ± 7.51 a	82^{B} ± 7.2 a
6- Ginger(90mg) +Propranolol	80^{B} ± 10.4 a	77^{B} ± 6.43 a	80^{B} ± 7.4 b
7-Ginger(180mg) +Propranolol	77^{B} ± 2.6 a	75^{B} ± 9. 5 a	78.33^{B} ± 7.25 a

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Values in the same raw with different subscript small letters are significantly ($p<0.05$) different.

Table (5): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on the heart rate in portal vein ligated rats at 14, 45 and 90 days after PVL

Parameter / Groups	Heart rate (beats\min)		
	14 days	45days	90 days
1-Sham	286.5^{A} ± 24.1 a	247.5^{AC} ± 16.6 b	263.5^{A} ± 32.3 ab
2- Control portal	325^{B} ± 19.6 a	296^{B} ± 28.4 b	280^{A} ± 22.1 b
3- Propranolol	242.5^{CD} ± 9.2 a	230.5^{AD} ± 23.6 a	233.5^{B} ± 16.3 a
4-Ginger(90mg)	262.5^{AC} ± 4.4 a	270^{BC} ± 12.4 a	273.5^{A} ± 22.8 a
5-Ginger(180mg)	255^{C} ± 21.3 a	260^{C} ± 8.5 a	265^{A} ± 18.9 a
6- Ginger(90mg) +Propranolol	226.5^{DE} ± 16.7 a	218^{D} ± 25.3 a	230.5^{B} ± 30.7 a
7-Ginger(180mg) +Propranolol	217.5^{E} ± 12.9 a	215^{D} ± 36. 4 a	220.5^{B} ± 18.5 a

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Values in the same raw with different subscript small letters are significantly ($p<0.05$) different.

Table (6): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on liver histopathological changes and function tests in portal vein ligated rats at 14 days after PVL

parameters	liver histopathological changes and function tests					
	14 days after PVL					
Groups	Liver pathologic changes	Serum ALT (U/ml)	Serum AST (U/ml)	Serum AP (IU/L)	Serum Bilirubin (mg/dl)	Total Serum Proteins (g/dl)
sham	$0.67^{A} \pm 0.13$	$20.6^{AB} \pm 6.9$	$52.3^{A} \pm 12.9$	$86.8^{A} \pm 10.4$	$0.74^{AB} \pm 0.19$	$3.5^{A} \pm 0.19$
Control portal	$2.67^{B} \pm 0.31$	$32.2^{A} \pm 7$	$75.2^{A} \pm 7$	$114.6^{A} \pm 16.7$	$1^{A} \pm 0.2$	$3.5^{A} \pm 0.57$
Propranolol	$1.67^{C} \pm 0.33$	$23.5^{AB} \pm 5.8$	$52.2^{A} \pm 10.2$	$101.5^{A} \pm 7.4$	$0.86^{AB} \pm 0.19$	$3.17^{A} \pm 0.14$
Ginger (90mg/kg)	$2.67^{B} \pm 0.21$	$14^{B} \pm 0.5$	$24.7^{B} \pm 2.6$	$107.5^{A} \pm 19.3$	$0.3^{B} \pm 0.04$	$3.7^{A} \pm 0.27$
Ginger (180mg/kg)	$1.67^{C} \pm 0.33$	$19^{B} \pm 3.9$	$61.5^{A} \pm 2.2$	$105^{A} \pm 10.9$	$0.4^{B} \pm 0.12$	$3.4^{A} \pm 0.52$
Propranolol+ Ginger (90mg/kg)	$1.83^{C} \pm 0.21$	$16.6^{B} \pm 0.56$	$31.2^{B} \pm 0.7$	$101.8^{A} \pm 11.1$	$0.85^{AB} \pm 0.2$	$3.3^{A} \pm 0.31$
Propranolol+ Ginger (180mg/kg)	$1.67^{C} \pm 0.31$	$20.5^{AB} \pm 5$	$55.2^{A} \pm 5$	$105.8^{A} \pm 21.7$	$0.5^{AB} \pm 0.1$	$3.15^{A} \pm 0.37$

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Alanine aminotransferase (**ALT**), Aspatate aminotransferase (**AST**) Alkaline phosphatase (**AP**)

Table (7) Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on liver histopathological changes and function tests in portal vein ligated rats at 45 days after PVL

parameters	liver histopathological changes and function tests					
	45 days after PVL					
Groups	**Liver pathological changes**	**Serum ALT (U/ml)**	**Serum AST (U/ml)**	**Serum AP (IU/L)**	**Serum Bilirubin (mg/dl)**	**Total Serum Proteins (g/dl)**
sham	0.67^{A} ± 0.13	23.5^{A}± 2.9	92.8^{A}± 9.3	98.2^{A} ± 14.4	0.5^{A} ± 0.09	3.7^{A}± 0.17
Control portal	3.17^{B} ±0.22	43.8^{B} ± 4. 9	97.2^{A} ±9.7	164.8^{B} ± 46.5	1.3^{B} ±0.03	3.3^{A} ±0.42
Propranolol	2^{C} ± 0. 17	37^{AB} ±5.3	87.3^{A} ± 6. 7	150.3^{B} ±13	0.9^{AB} ± 0. 3	3.7^{A} ± 0.73
Ginger (90mg/kg)	2.33^{C} ± 0.21	27.8^{A} ± 1.5	93.5^{A} ± 7.4	80^{A}± 12.4	0.9^{AB} ± 0.1	3.9^{A} ± 0.19
Ginger (180mg/kg)	2.33^{C} ± 0.31	29.7^{A} ± 2.9	91.3^{A} ± 6.7	151.6^{B} ± 15.2	0.5^{A} ± 0.09	3.6^{A} ± 0.35
Propranolol+ Ginger (90mg/kg)	2^{C} ± 0. 17	28.5^{A} ± 2.6	86.7^{A} ± 5.04	100^{A} ± 4.4	1^{AB} ± 0.1	3.7^{A} ± 0.24
Propranolol+ Ginger (180mg/kg)	2^{C} ± 0. 17	30.5^{A} ± 3	94.3^{A} ± 10.4	142.3^{AB} ± 33.6	0.5^{A} ± 0.09	3.6^{A} ± 0.3

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Alanine aminotransferase (**ALT**), Aspatate aminotransferase (**AST**) Alkaline phosphatase (**AP**)

Table (8): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on liver histopathological changes and function tests in portal vein ligated rats at 90 days after PVL

parameters	liver histopathological changes and function tests					
	90 days after PVL					
Groups	Liver pathological changes	Serum ALT (U/ml)	Serum AST (U/ml)	Serum AP (IU/L)	Serum Bilirubin (mg/dl)	Total Serum Proteins (g/dl)
sham	$0.67^{A} \pm 0.13$	$23^{A} \pm 1.4$	$80^{A} \pm 5$	$81.8^{A} \pm 6.6$	$0.8^{A} \pm 0.2$	$4.4^{A} \pm 0.17$
Control portal	$3.67^{B} \pm 0.22$	$35.5^{B} \pm 4.8$	$122^{B} \pm 12.5$	$103.8^{A} \pm 10.6$	$1.4^{B} \pm 0.16$	$3.4^{B} \pm 0.36$
Propranolol	$2.67^{C} \pm 0.21$	$24.5^{A} \pm 2.9$	$107.5^{AB} \pm 8.6$	$96.5^{A} \pm 7.1$	$0.8^{A} \pm 0.2$	$3.5^{B} \pm 0.2$
Ginger (90mg/kg)	$2.67^{C} \pm 0.21$	$20.5^{A} \pm 1$	$82.2^{A} \pm 5.7$	$61^{B} \pm 5.8$	$0.8^{A} \pm 0.2$	$4^{AB} \pm 0.19$
Ginger (180mg/kg)	$2.67^{C} \pm 0.33$	$27^{AB} \pm 4.6$	$109.3^{AB} \pm 8.2$	$96.6^{A} \pm 12.9$	$0.86^{AB} \pm 0.19$	$3.9^{AB} \pm 0.19$
Propranolol+ Ginger (90mg/kg)	$2.67^{C} \pm 0.21$	$20.2^{A} \pm 1.8$	$80^{A} \pm 5.6$	$87.5^{A} \pm 8.8$	$0.9^{AB} \pm 0.1$	$3.7^{AB} \pm 0.2$
Propranolol+ Ginger (180mg/kg)	$2.67^{C} \pm 0.21$	$28^{AB} \pm 2$	$106.8^{AB} \pm 14.8$	$92.3^{A} \pm 4.8$	$0.9^{AB} \pm 0.3$	$3.5^{B} \pm 0.21$

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.
- Values in the same raw with different subscript small letters are significantly ($p<0.05$) different.
- Alanine aminotransferase (**ALT**), Aspatate aminotransferase (**AST**) Alkaline phosphatase (**AP**)

Table (9): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on the esophageal, gastric and intestinal histopathological changes at 14 days after PVL

organs	The esophageal, gastric and intestinal histopathological changes		
	14 days after PVL		
groups	esophagus	stomach	intestine
sham	$0.5^{A} \pm 0.12$	$0.5^{A} \pm 0.12$	$0.5^{A} \pm 0.12$
Control portal	$1.83^{B} \pm 0.17$	$1.67^{B} \pm 0.21$	$1.67^{B} \pm 0.21$
Propranolol	$1^{AC} \pm 0.3$	$1.17^{AB} \pm 0.3$	$1.17^{AB} \pm 0.3$
Ginger (90mg/kg)	$1.5^{BC} \pm 0.22$	$1.5^{BC} \pm 0.22$	$1.5^{BC} \pm 0.22$
Ginger (180mg/kg)	$1.33^{BC} \pm 0.42$	$0.83^{AC} \pm 0.17$	$0.83^{AC} \pm 0.17$
Propranolol+ Ginger (90mg/kg)	$1^{AC} \pm 0.3$	$1.33^{BC} \pm 0.21$	$1.17^{AB} \pm 0.17$
Propranolol+ Ginger (180mg/kg)	$1^{AC} \pm 0.3$	$0.83^{AC} \pm 0.17$	$0.83^{AC} \pm 0.17$

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.

Table (10): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on the esophageal, gastric and intestinal histopathological changes at 45 days after PVL

organs	The esophageal, gastric and intestinal histopathological changes		
	45 days after PVL		
groups	esophagus	stomach	intestine
sham	$0.67^{A} \pm 0.13$	$0.67^{A} \pm 0.13$	$0.67^{A} \pm 0.13$
Control portal	$3^{B} \pm 0$	$3^{B} \pm 0$	$3^{B} \pm 0$
Propranolol	$2^{C} \pm 0.17$	$2.33^{BC} \pm 0.21$	$2.33^{BC} \pm 0.21$
Ginger (90mg/kg)	$2^{C} \pm 0.17$	$1.5^{CD} \pm 0.22$	$1.5^{CD} \pm 0.22$
Ginger (180mg/kg)	$2^{C} \pm 0$	$2^{CD} \pm 0.17$	$2^{CD} \pm 0.17$
Propranolol+ Ginger (90mg/kg)	$1.5^{C} \pm 0.22$	$1.33^{D} \pm 0.21$	$1.33^{D} \pm 0.21$
Propranolol+ Ginger (180mg/kg)	$1.33^{C} \pm 0.21$	$2^{CD} \pm 0.17$	$2^{C} \pm 0.17$

Values represent as means ± SE. Number of rats in each group = 6

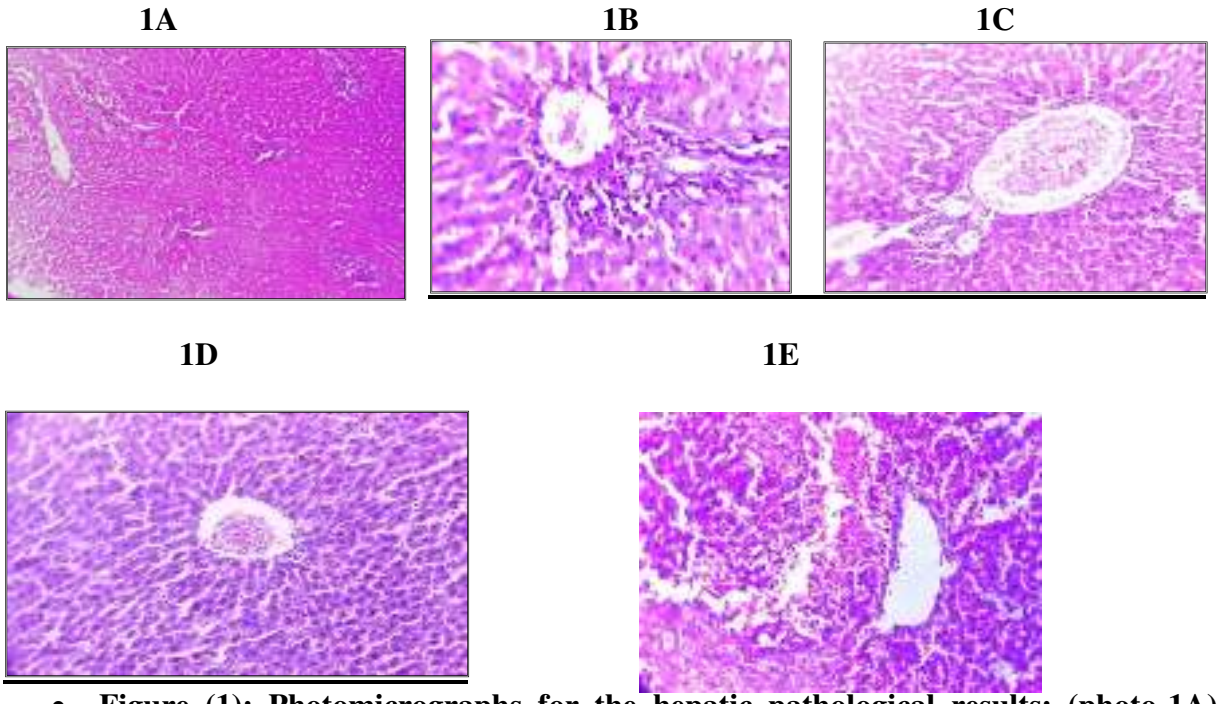
- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.

Table (11): Effect of pre-administration of ginger (90, 180mg/kg), propranolol (75mg/kg) and combination of both on the esophageal, gastric and intestinal histopathological changes at 90 days after PVL (n=6):

Organs	The esophageal, gastric and intestinal histopathological changes		
	90 days after PVL		
groups	esophagus	stomach	intestine
sham	$1^{A} \pm 0$	$1^{A} \pm 0.17$	$1^{A} \pm 0.3$
Control portal	$3.67^{B} \pm 0.22$	$3^{B} \pm 0$	$3^{B} \pm 0$
Propranolol	$2.33^{C} \pm 0.21$	$2.33^{BC} \pm 0.21$	$2.33^{BC} \pm 0.21$
Ginger (90mg/kg)	$2.67^{C} \pm 0.21$	$1.5^{CD} \pm 0.22$	$1.5^{CD} \pm 0.22$
Ginger (180mg/kg)	$2.33^{C} \pm 0.21$	$2^{CD} \pm 0.17$	$2^{CD} \pm 0.17$
Propranolol+ Ginger (90mg/kg)	$1.83^{C} \pm 0.3$	$1.33^{D} \pm 0.21$	$1.33^{D} \pm 0.21$
Propranolol+ Ginger (180mg/kg)	$1.83^{C} \pm 0.3$	$2^{CD} \pm 0.17$	$2^{C} \pm 0.17$

Values represent as means ± SE. Number of rats in each group = 6

- Values in the same column with different superscript capital letters are significantly ($p<0.05$) different.



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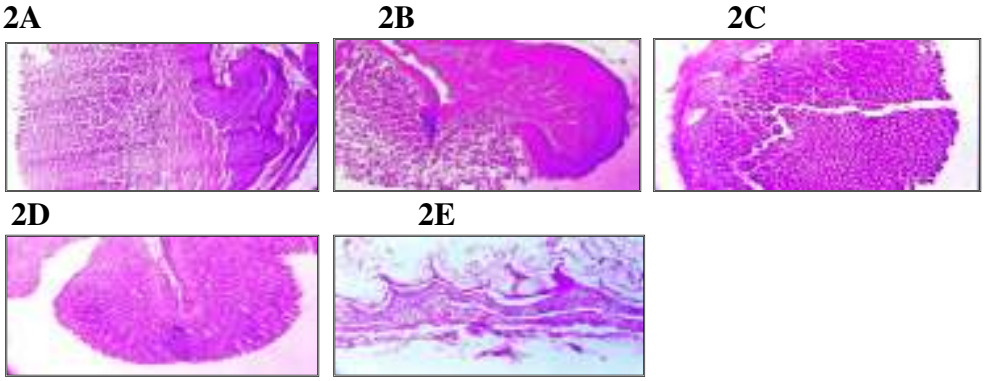

Figure (2): Photomicrographs for the esophageal histopathological results: (photo2A) normal esophageal tissue, (2B) score-1, (2C) score-2, (2D) score-3, (2E) score-4 (H&E ×400).

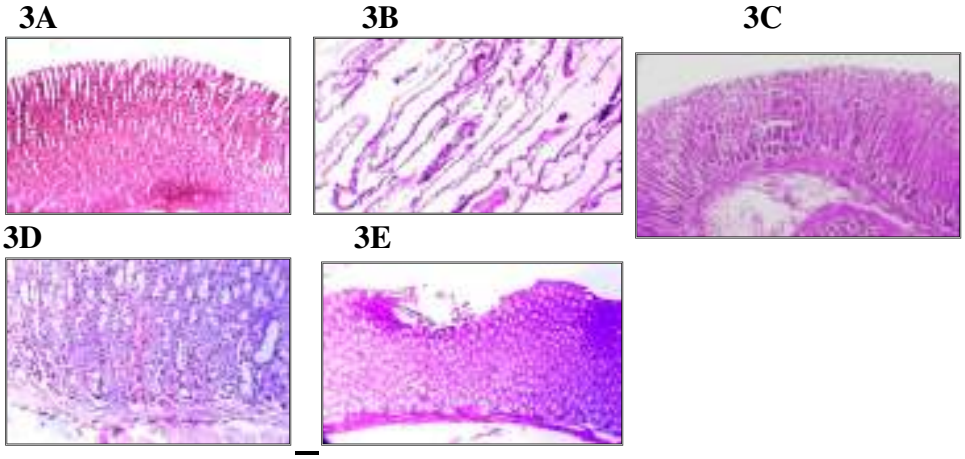

Figure (3): Photomicrographs for the gastric histopathological results: (photo3A) normal gastric tissue, (3B) score-1, (3C) score-2, (3D) score-3, (3E) score-4 (H&E ×400).

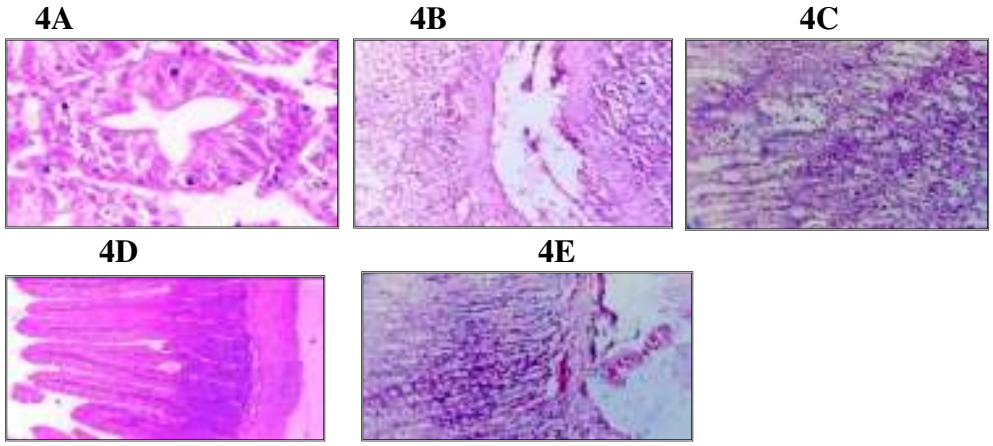

Figure (4): Photomicrographs for the intestinal histopathological results: (photo4A) normal intestinal tissue, (4B) score-1, (4C) score-2, (4D) score-3, (4E) score-4 (H&E ×400).

DISCUSSION

Egyptian ministry of health estimated the prevalence of HCV in Egypt by 14.7% of general population **(El-Zanaty and Way, 2009 and Mohamed et al., 2013)**. Due to this high prevalence rate of HCV and also the endemicity of bilharizial peri-portal fibrosis, the incidence and prevalence of portal hypertension in Egypt reached record level **(Zakaria et al., 2011).** There are no reports analyzing the effect of ginger on portal hypertension and its possible interaction with, propranolol which is widely used in these cases. In this study, in order to induce prehepatic portal hypertension, a model of PPVL was made to adult male albino rats and portal pressure was measured either at 14, 45 or 90 days after PVL, this PPVL showed significant elevation in the portal venous pressure which could be explained by mechanical obstruction of the portal flow (**Abraldes et al., 2006).** the aim of this work was to investigate the role of ginger in portal hypertension as there are different studies considered prehepatic portal hypertension and its complications as inflammatory and metabolic disorder, and described some changes such as: ischemia reperfusion, inflammatory cellular infiltration, translocation of intestinal bacteria and angiogensis as consequences of its induction **(Aller et al., 2007 & Sánchez-Patán et al., 2008)**. **Aller et al. (2005)** reported that 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 portal hypertension. **Martell et al. (2010)** and **Xu et al. (2008)** reported that, NO and its possible interaction with prostaglandin I_2 (PGI_2) is responsible for splanchinc vasodilatation and the maintenance of hyperdynamic circulation. Moreover, **Fooladi et al. (2013)** reported that, the changes in the type and amount of intestinal microflora predispose to liver cirrhosis and hepatic encephalopathy.

In the present study, pretreatment with propranolol produced significant reduction in portal pressure. These results are in agreement with the work of **Vorobioff et al. (1993)** who suggested that the portal pressure lowering effect of propranolol is due to both β1 and β2 blocking action with subsequent decrease in cardiac output and reduction of splanchnic blood flow due to splanchnic vasoconstriction. **Pérez-Paramo et al. (2000)** suggested that propranolol could also decrease portal pressure by its ability to attenuate the bacterial translocation.

Concerning the effect of ginger on the portal hypertension, it was found that pretreatment with ginger (by the previous doses) significantly reduced portal pressure. The effect of ginger on portal hypertension might be attributed to its effect on NO and PG production within the splanchnic circulation reducing them. This assumption agrees with that published by **Hsieh et al. (2008)** who reported that *shogaol* (one of ginger ingredients) reduces NO and PG production. Another possible mechanism is the ability of ginger to decrease the inflammatory mediators like TNF-α, interlukin-1β (IL-1β), carbon monoxide (CO) and IL-10**(Aller et al., 2005).** This explanation agrees with that published by **Habib et al. (2008).** The potential antimicrobial effect of ginger which was reported by **Nicoll and Henein (2009)** could be considered as a possible mechanism of action in the explanation of portal pressure lowering ability of ginger. The ability of ginger to inhibit angiogenesis is another possible potential mechanism in the reduction of portal pressure (**Rhode et al., 2007**).

The co-administration of propranolol with ginger in this study showed significant decrease in portal pressure when compared to control portal hypertension group. It seemed that co-administration of ginger with propranolol did not disturb its portal pressure lowering effect.

As regard (MABP) and (HR) changes in portal hypertensive rats, MABP is significantly reduced while HR is significantly increased in comparison to sham group. These results are in agreement with that reported by **Iwakiri and Groszmann (2006)** explaining their finding by systemic vasodilatation with subsequent reflex tachycardia. In the present study pretreatment

with propranolol reduced the heart rate significantly in comparison to control portal hypertension group. Propranolol blocks β1 receptors in cardiac muscles with subsequent reduction in heart rate **(Klarenbach et al., 2010).** These results are in agreement with the work of **Dib et al (2006)** who reported that propranolol decreased MABP and heart rate in rats with pre-hepatic portal hypertension. Ginger showed significant reduction in HR in comparison to control portal group at 14 and 45days after PVL. The possible explanation is the dual muscarinic and Ca^{++} channels blocking effects of ginger as mentioned by **Ghayur et al. (2005)**. The co-administration of only ginger 180mg/kg/day plus propranolol showed significant reduction on HR in comparison to propranolol at 14 days after PVL which may be due to additive effect of both substances.

As regard the **histological examination of** hepatocytes of portal hypertensive rats in this study there were pathological changes in the form of cellular infiltration and congested sinusoids which coincide with that reported by **Aller et al. (2007)** who explained these changes by the development of hepatic steatosis, the most common form of nonalcoholic fatty liver disease (NAFLD)**.** The exact mechanisms of liver steatosis in portal hypertension are not fully understood but there are some possible explanations; reduced portal blood flow causing hypoxia and anoxia induce mitochondrial dysfunction in the extrahepatic portal obstruction in rats (**Wakabayashi, 2002)** and the increased level of TNF-α, IL1β and NO in the liver in prehepatic portal hypertensive rats (**Prieto et al., 2005).** The disturbances in liver function tests in control portal group supports the results of histological examination. The current study demonstrated that pretreatment with propranolol significantly reduced liver pathological changes and decrease the ALT and bilirubin levels in comparison to control portal group. These results are in agreement with that reported by **Sigala et al. (2013)** that sympathetic nervous system (SNS) signaling regulates murine hepatic fibrogenesis through effects on hepatic stellate cells (HSC), in which SNS activation accelerates progression of NAFLD.

As regard the effect of ginger, in this study pretreatment with ginger reduced significantly liver pathological and biochemical changes in comparison to control group. These results are in parallel with that reported by **Habib et al. (2008)** 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 (2011)** reported that ginger has been suggested to prevent NAFLD or suppress its progression not only though down-regulation of pro-inflammatory cytokines but also by sensitizing insulin effects, promoting antioxidant effects and reducing hepatic triglyceride content which can prevent steatosis.

The co-administration of propranolol with ginger significantly improved hepatic pathological and biochemical changes. This combination did not disturb the beneficial effect of propranolol group even it increased the hepatoprotective effect of propranolol as showed by significant reduction in serum AST at 14 days and AP levels at 45 days after PVL in ginger 90mg/kg/day plus propranolol group when compared to propranolol group alone.

As regard the pathological changes in the esophagus, stomach and intestine in portal hypertensive rats in this study, the histological examination of these organs revealed lymphocytic cellular infiltration, edematous mucosa, erosions with dilated tortuous vessels. These results are in agreement with that reported by **Aller et al. (2007)**. The possible causes of these changes include ischemia/reperfusion with subsequent production of oxidative and nitrosative stress factors (**Blikslager et al., 2007**), locally released mediators cause vasodilatation (**Aller et al., 2007)** and angiogenesis induced by growth factors (VEGF) and cytokines (TNF-α and NO) accelerate angiogenesis **(Mendez-Lopez et al., 2007**). In the present work pretreatment with propranolol showed significant reduction in pathological changes in the esophagus in comparison to control portal

group, while the reduction in gastric and intestinal changes was non- significant. The protective effect of propranolol on portal hypertensive enteropathy is a matter of controversy. **Rafailidis et al. (2009)** 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 **Fizanne et al. (2008)** showed that long-term administration of propranolol (75mg/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 higher density of bacterial translocation.

In this study pretreatment with ginger reduced significantly esophageal, gastric and intestinal changes. These results could be attributed to anti-inflammatory effect of ginger beside its antimicrobial activity antagonizing bacterial translocation. These assumptions are in agree with what reported by **Nicoll and Henein (2009).** Co-administration of propranolol with ginger 90mg/Kg/day showed significant reduction of gastric and intestinal pathological changes in comparison to propranolol group indicating the potential value of its co-administrated with propranolol in portal hypertensive enteropathy.

As regard mortality rate, the highest rate (25%) were present in both control portal and (propranolol 75mg/Kg plus ginger 180mg/Kg) groups, while the other 4 ligated groups showed the same mortality rate equal to 18% indicating possible drug-herb interactions in large doses. **Kim et al. (2012)** showed that ginger extract inhibits CYP2C9-mediated drug metabolism in a concentration-dependent manner, as propranolol is metabolized by this iso-enzyme so co-administration of both substances could potentiate propranolol effect especially on cardiovascular system (marked bradycardia). On the other hand, the elimination of ginger is mainly hepatic (**Wang et al., 2009**) so its co-administration with propranolol (hepatic microsomal enzyme inhibitor) could potentiate its anticoagulant effects which may produce bleeding tendency; in the results of this experiment autopsy showed severe congestion of the mesenteric and splenic veins, as well as hyperemia, friable intestine and focal hemorrhage in liver, gut and kidney.

CONCLUSION

From the aforementioned results **it was concluded** that ginger has a prophylactic effect on the portal hypertension by decreasing portal pressure and reducing its complications. Ginger dose affects its potential protective effects, where the dose of 90mg\kg\day showed better liver function tests results. Ginger co-administration with propranolol (especially ginger 90mg\kg\ day) showed a synergistic effect mainly as regard gastro-intestinal pathological results and some liver function tests results. On the other hand, this combination carries the risk of drug-herb interaction especially with higher dose of ginger (ginger 180mg\kg\day).

RECOMMENDATIONS

1- Health education and counseling about potential benefits and hazards of commonly used herbs like ginger is required.

2- Ginger administration could produce drug interactions with propranolol which seems to be beneficial in small doses but carries some hazards in large dose.

3- The multiplicity of action of herbs like ginger related to its high contents of active ingredients so further experimental as well as clinical studies on ginger extracts are needed to evaluate the effect of ginger on portal hypertension.

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تأثير الزنجبيل ودواء البروبرانولول على ارتفاع ضغط الدم في الوريد البابي المحدث تجريبيا في ذكران الجرذان البيضاء البالغة

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يعد معدل ارتفاع ضغط الدم في الوريد البابي في جمهورية مصر العربية من اعلى المعدلات في العالم. ولذلك فان العلاج الدوائي لهذا المرض يظل دائما في دائرة اهتمام الباحثين.و يعتبر الزنجبيل احدى النباتات الموسمية وتستخدم جذور هذا النبات في كثير من الاغراض الطبية.بينما مايزال البروبرانولول محل خلاف في مدي جدوي استخدامه في تلك الحالات. وتهدف هذه الدراسة الى معرفة التأثير المحتمل لنبات الزنجبيل على ارتفاع ضغط الدم في الوريد البابي و مدى امكانية حدوث تفاعل دوائي مع عقار البروبرانولول. ولقد تم استخدام 156من ذكران الجرذان البيضاء في هذه الدراسة تم وضعهم جميعا في ظروف مطابقة للمواصفات المعملية القياسية. تم تخصيص 20 منهم لعمل المجموعة الخادعة (لم تتعرض لعملية الربط) بينما تعرضت باقي الجرذان لعملية ربط جزئي للوريد البابي ترتب عليها ارتفاع ضغط الدم داخل هذا الوريد ثم قسمت الجرذان للمجموعات التالية: المجموعة الضابطة (لم تتناول سوي ماء مقطر) ومجموعة تناولت البروبرانولول بجرعة 75مجم/ كجم / يوم عن طريق الفم ومجموعتين تناولتا الزنجبيل بجرعة 90 او 180مجم / كجم / يوم عن طريق الفم ومجموعتين تناولتا كلا من البروبرانولول بجرعة 75مجم/ كجم / يوم و الزنجبيل بجرعة 90 او 180مجم / كجم / يوم عن طريق الفم. ولقد كان تناول هذه المواد لمده لم تتجاوز 90يوم . وقد تم قياس كل من ضغط الدم وعدد نبضات القلب و ضغط دم الوريد البابي و بعض وظائف الكبد والتغيرات الباثولوجية لانسجة الجهاز الهضمي و الكبد بعد 14 و 45 و 90 يوم من عملية الربط.**وقد اظهرت النتائج** حدوث ارتفاع في ضغط الدم في الوريد البابي- انخفاض في ضغط الدم مع سرعة في ضربات القلب مع خلل بوظائف الكبد وحدوث تغيرات باثولوجية في المجموعة القياسية مع تحسن لهذة التغيرات بنسبة متفاوتة في باقي المجموعات.

من هذه النتائج يمكن ان نستخلص ان للزنجبيل تأثير وقائي ضد ارتفاع ضغط الدم في الوريد البابي بالاضافة لقدرته على تقليل المضاعفات الناجمة عن هذا الارتفاع . كذلك وضح ان تفاعل الزنجبيل مع دواء البروبرانولول هو تفاعل ايجابي خصوصا مع استخدام جرعة **90مجم/ كجم / يوم** من الزنجبيل بينما اظهرت النتائج ان التفاعل بين الزنجبيل بجرعة 180**مجم/ كجم / يوم** مع البروبرانولول يحمل خطورة التفاعلات الدوائية . لذا نوصي بمزيد من الابحاث المعملية والاكلينيكية على مستخلصات الزنجبيل لتقييم اثرها على ارتفاع ضغط الدم في الوريد البابي .