

Effect of dried ginger water extract on hypertriglyceridemia induced acute pancreatitis in rats

Abstract

Background/objectives: Acute pancreatitis (AP) is characterized by tissue edema, acinar necrosis, hemorrhage, and fat necrosis, as well as inflammation and perivascular infiltration in the pancreas. Serum triglyceride levels more than 1000 mg/dl are accountable for AP. Ginger extract has been reported to reduce the triglyceride level in diabetic rats. This study is aimed to determine the effect of ginger water extract on AP in rats.

Methods: Hypertriglyceridemic-AP was induced by poloxamer 407 (0.7 gm/kg) in Wistar rats. The treatment of ginger water extract was given in two groups with doses of 200 and 400 mg/kg in the rats. The effect of ginger water extract on serum blood glucose, triglyceride, and lipoprotein profile was estimated to access its lipid-lowering properties. The effect of ginger water extract on lipid peroxidation, superoxide dismutase, catalase, and glutathione was also studied.

Results: Ginger extract showed significantly reduced blood glucose, triglyceride, total cholesterol, α -amylase, and increased good cholesterol levels compared to the disease control group that indicated beneficial lipid-lowering properties. Furthermore, ginger water extract was also significantly reduced lipid peroxidation and enhanced superoxide dismutase, catalase, and glutathione levels as compared with the disease control group.

Conclusion: In conclusion, the ameliorative effect of ginger extract against poloxamer 407 induced HTG-AP. Demonstrated lipid-lowering and antioxidant properties of ginger extract. The present study, showed protective effect of ginger against Acute Pancreatitis in rats.

Keywords: acute pancreatitis, hypertriglyceridemia, poloxamer-407, ginger extract

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Introduction

Acute pancreatitis (AP) is an acute inflammation of the pancreas characterized by auto-digestion of the pancreatic parenchyma, interstitial fat necrosis, and necrotizing vasculitis resulted from inappropriate intracellular activation of proteolytic pancreatic enzymes.¹ The inflammation may be limited to the pancreas, spread to surrounding tissues, or even involve the remote organs, ensuing in multi-organ failure or occasional death occurs in some patients.² AP is identified by inflammation of the pancreas with the release of cytokines and pro-inflammatory mediators in the pancreas.³

The occurrence of AP is very high in the USA, Finland, and Scotland 49.3, 46.6, and 41.9 per 100,000 populations, respectively. A study has been also reported that 3.6-13.2 cases of acute pancreatitis per 100,000 pediatric individuals per year and the mortality rate are approximately 4-10%.⁴ The ginger has been reported for its antiulcer activity.⁵ The anti-inflammatory action is due to enhancement in gastric juice mucin secretion and decrease in cell shedding.⁶ The anti-inflammatory effect of water extract of ginger (*Zingiber officinale*) on prostaglandin-E2 (PGE2) production has been also reported in rats.⁷ A high level of triglyceride (hypertriglyceridemia) plays a vital role in the pathogenesis of acute pancreatitis.⁷ Water extract of ginger has been also reported to decrease triglyceride levels.⁸ So, this study aims to determine the effect of extracted ginger against hypertriglyceridemic acute pancreatitis.

Method

Preparation of ginger extract

Ginger powder and water were mixed and inserted into a rotary shaker overnight (120 rpm and 70 °C for 24 hours) and filtered properly and collected the filtrate. Add water into the remaining residue and the same process was carried out three times. Water from the collected filtrate was evaporated by rotary shaker evaporator and dried ginger extract was collected for the study.³⁰

Animals and experimental protocols

The experiment protocol was approved by the Institutional Animal Ethics Committee (IAEC) [Protocol no. IAES/DPS/SU/1702] as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment, Forest and Climate Change, Government of India, New Delhi. Five month old Wistar female rats were divided into the following groups: (1) normal control (CON) (n=6); (2) disease control (DC) treated with poloxamer-407 dose 0.7 gm/kg/day, i.p. (Sigma Aldrich Ltd., USA) (n=6); (3) low dose treated (Ginger Extract-200 mg/kg/day, PO)(n=6); (4) high dose-treated (Ginger Extract- 400 mg/kg/day, PO),³² (n=6). The Ginger extract was administered to the rats orally and also poloxamer 407 was administered to the rat's i.p., for a period of 30 days. Rats were housed in standard environmental conditions and had free access to standard chow and water ad libitum.

All animals were monitored routinely for alteration in weight of animal and mortality all over the course of the study.³¹

Blood sample collection and serum analysis

At the end of the month, rats were fasted for 12 h., and blood samples were collected from the retro-orbital plexuses under light ether anesthesia. Serum was separated and analyzed for total cholesterol, triglyceride (TG), glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and amylase, spectrophotometrically (Shimadzu UV-1601, Japan) by using available biochemical diagnostic kits (H.K. Corporation Pvt. Ltd., India).

Statistical analysis

Statistical analyses were carried out using Graph Pad Prism 5.0 (Graph Pad Software, San Diego, CA, USA). All the data are presented as mean±S.E.M. (n=6). The significance of the difference of different parameters was determined by One-way Analysis of Variance (ANOVA) followed by Tukey's test. As the value of p<0.05 was considered statistically significant.

Results and discussion

Effect of ginger on blood sugar levels in rats

At the end of the study, as per the Table 1 the disease control group showed a major (p<0.001) increase in plasma glucose compared to the control group and ginger extract (200 mg/kg & 400 mg/kg) produced a significant (p<0.001) decrease in plasma glucose compared to the disease control group. The aggravation of acute pancreatitis by hyperglycemia was observed by increasing the concentration of advanced glycation end products (AGEs) or other receptors for advanced glycation end products ligands (RAGE).⁹ Also, pancreatic

glucagon-like peptide-1 (GLP-1) is crucial for glucose-regulation, and GLP-1 is produced by the beta cell within the pancreas which is vital for insulin secretion and normal glucose tolerance.¹⁰ Increased blood sugar and increased rate of metabolic acidosis during the course of AP.¹¹ Ginger extract was reported to the reduced blood glucose level in alloxan-induced diabetes rats.¹² Akhiani et al.,¹³ also found that ginger extract significantly decreased the blood glucose within the streptozotocin-induced diabetic rats. In our study, ginger extract (200 mg/kg and 400 mg/kg) both doses were able to reduce blood glucose as previously described. Our results are in line with the earlier reports that showed the protective effect of ginger in BG regulation.

Estimation of triglycerides

The disease control group was shown a significant (p<0.001) increased in plasma triglyceride compared to the control group and ginger extract (200 mg/kg & 400 mg/kg) produced a significant (p<0.001) decreased in plasma triglyceride levels compared to the disease control group. Chylomicrons are triglyceride (TG) rich lipoprotein particles. TG are present within the circulation when TG is >900 mg/dl, they are large enough to occlude the pancreatic capillaries resulting in ischemia and acinar structural alteration, along with the discharge of pancreatic lipase. Enhanced lipolysis results in an increased concentration of free fatty acids (FFA) which ends up within the release of inflammatory mediators and free radicals.¹⁴ In our study, both doses of ginger extract (200 mg/kg and 400 mg/kg) reduced TG compared to the disease control group. Gao et al.,⁸ who found that the alcoholic extract of ginger (50 mg/kg) over 5 weeks reversed liquid fructose-induced increased plasma TG and hepatic TG content in rats. The ginger extract also significantly decreased plasma concentration of TG in fructose-induced kidney injury through suppression of renal overexpression of pro-inflammatory cytokines in rats.¹⁵ Our result's according to the above findings.

Table 1 Effect of ginger extract on blood parameters

Gr. No	Treatment	Blood glucose (mg/dl)	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	Amylase U/L
I	Normal	101.5±7.371	110±12.33	51.55±0.5737	40.55±3.626 ^{####}	65.45±4.011	49.26±1.461
II	Disease control	305.3±33.63 ^{***}	1219±28.53 ^{***}	428.8±16.27 ^{***}	21.17±1.283 ^{***}	40.30±5.680*	342.1±28.47 ^{***}
III	GE (200 mg/kg)	150±18.29 ^{###}	758.2±46.02 ^{###}	56.56±3.950 ^{###}	66.36±11.19 [#]	45.82±6.514	80.46±29.29 ^{###}
IV	GE (400 mg/kg)	123.5±10.06 ^{###}	402.5±78.66 ^{###}	40.55±3.626 ^{###}	43.07±5.063	48.37±6.997	107.3±28.19 ^{###}

Values are expressed as mean±SEM, statistical analysis was performed by One-way Analysis of Variance (ANOVA) followed by turkey's multiple comparison test, n = 6, ^{***}p < 0.001 vs. DC, ^{**}p < 0.01 vs. DC, ^{*}p < 0.05 vs. DC, ^{###}p < 0.001 vs. GE (200 mg/kg), ^{**}p < 0.01 vs. GE (400 mg/kg), ^{*}p < 0.05 vs. GE, GE: Ginger extract, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol

Table 2 Effect of ginger extract on antioxidant parameter

Gr. No	Treatment	LPO (nM/mg of protein)	SOD (U/mg of protein)	Catalase (U/mg of protein)	GSH (nM/mg of protein)
I	Normal	6.549±1.356	61.52±3.812	0.08384±0.01881	12.42±1.328
II	Disease control	64.30±10.68 ^{***}	29.39±0.8870*	0.01107±0.008731*	4.226±0.6672 ^{***}
III	GE (200 mg/kg)	37.50±4.147 [#]	63.95±5.010 [#]	0.08378±0.01538 [#]	10.19±0.7493 ^{###}
IV	GE (400 mg/kg)	13.43±0.6344 ^{###}	81.86±12.48 ^{###}	0.09292±0.09292 [#]	11.94±1.431 ^{###}

Values are expressed as mean±SEM, statistical analysis was performed by One-way Analysis of Variance (ANOVA) followed by tukey's multiple comparison test, N=6, ^{***}p < 0.001 vs. DC, ^{**}p < 0.01 vs. DC, ^{*}p < 0.05 vs. DC, ^{###}p < 0.001 vs. GE, ^{**}p < 0.01 vs. GE (200 mg/kg), ^{*}p < 0.05 vs. GE (400 mg/kg), GE: Ginger extract, LPO: lipid peroxidation, SOD: Superoxide dismutase, GSH: Reduced Glutathione

Estimation of total cholesterol (TC)

At the end of the study, the disease control group showed a big (p<0.05) increased in plasma total cholesterol compared to the control

group and after 30 days of treatment, ginger extract (200 mg/kg & 400 mg/kg) produced a significant (p<0.05) decrease in plasma total cholesterol compared to the disease control group.

Estimation of HDL cholesterol (HDL-C) and LDL cholesterol (LDL-C)

The disease control group showed a major ($p < 0.001$) decreased in plasma HDL cholesterol compared to the control group and after 30 days (200 mg/kg & 400 mg/kg) treatment with ginger extract produced a big ($p < 0.01$) increased in plasma HDL cholesterol levels compared to the disease control group. At the top of the study, the disease control group showed a big ($p < 0.05$) decreased in plasma LDL cholesterol compared to the control group. After 30 days (200 mg/kg & 400 mg/kg) treatment with ginger extract doesn't produced a major ($p < 0.05$) decreased in plasma LDL cholesterol compared to disease control group.

Hypercholesterolemia and hyperlipidemia are commonly identified in AP.¹⁶ Hyperlipidemia may be a rare but known and established risk factor for pancreatitis or early diagnosis of pancreatitis is vital to stop its recurrence and complications. The parameters of lipid profile namely TC, LDL-C, are higher and HDL-C is lower in pancreatitis.¹⁷ The protein composition of HDL Apolipoprotein A1 (APO-A1) depleted which is that the major protein component of HDL. it's also liable for cholesterol homeostasis by transporting excessive cholesterol from tissue to the liver and more emphasis placed upon its anti-inflammatory effect.¹⁷ In our study, we found that increased TC Level and decreased HDL-C within the disease control group compared with the control group. Ginger extract (200 mg/kg and 400 mg/kg) both doses are reduced TC and increased 'GOOD CHOLESTEROL' (HDL-C) but it doesn't have a big effect on LDL-C level. A big reduction of serum TC, LDL-C, and improvement of HDL-C levels was observed in ginger extract treated rats.¹⁸ Another study also reported a big reduction of serum TC, LDL-C, and improvement of HDL-C significantly by aqueous ginger infusion in hypercholesterolemic rats.¹⁹ Our findings are under the sooner studies done by others, where treatment with ginger decrease TC and increase HDL-C.

Estimation of alpha-amylase

At the end of the study, the disease control group showed a major ($p < 0.001$) increased in plasma amylase compared to the control group, and ginger extract (200 mg/kg & 400 mg/kg) produced a big ($p < 0.001$) decreased in plasma amylase level compared to the disease control group. Since it's become well recognized that an elevated serum amylase may be a valid diagnosis of AP. The pancreas produced amylase enzyme and inflammation of the pancreas liable for the high level of amylase within the bloodstream. In our study, ginger extract (200 mg/kg and 400 mg/kg) both doses significantly reduced amylase compared to the disease control group. The ginger is additionally reported for the great potential for amylase inhibition related to type 2 diabetes management.²⁰ Also in vitro study reported that ginger has strong anti-amylase activity.²¹ As per our findings, treatment with GE resulted in significant depletion of amylase level which is in agreement with the above investigations.

Lipid peroxidation (LPO)

At the end of the study, the disease control group showed a significant ($p < 0.001$) increased in lipid peroxidase compared to the control group. At the end of 30 days treatment, ginger extract (200 mg/kg & 400 mg/kg) produced a significant ($p < 0.05$ and $p < 0.001$) reduction in lipid peroxidase level compared to disease control group. Lipid peroxidation is an oxidative deterioration of lipid products. Their formation occurs in enzymatic or non-enzymatic reaction reactions involving activated chemical species known as reactive

oxygen species (ROS) which are responsible for toxic effects in the body via tissue damage. Level of lipid peroxidation raised in acute pancreatitis.²¹ In our study, ginger extract (200 mg/kg and 400 mg/kg) both doses are reduced LPO level compared to a disease control group. A study reported, oral administration of aqueous ginger extract significantly ameliorates paraben induced lipid peroxidation in mice by increasing the anti-oxidative defense mechanism in cells.²² Ginger also decreased lipid peroxidation level in 1, 2-dimethyl hydrazine induced colon carcinogenesis.²³ The findings of the present study are following earlier studies which demonstrated that the protective effect of ginger against LPO activity.

Reduced glutathione

At the end of the study, the disease control group showed a significant ($p < 0.001$) decreased in glutathione level compared to the control group and both doses of ginger extract (200 mg/kg & 400 mg/kg) produced a significant ($p < 0.01$ and $p < 0.001$) increased in glutathione level compared to the disease control group. Glutathione plays a role in acinar stimulus secretion and maintenance of the cytoskeleton thus depletion of intracellular glutathione may contribute to impairment and premature activation of pancreatic proenzyme. Depletion of glutathione is responsible for oxidative stress and tissue damaged in pancreatitis.²⁴ In our study, ginger extract (200 mg/kg and 400 mg/kg) both doses are significantly increased glutathione level compared to the disease control group. Ginger increased significantly glutathione levels in diabetic rat tissue.²⁵ Also, ginger was reported for increased glutathione against acetic acid-induced ulcerative colitis in rats.²⁶ Glutathione level decreased in AP. So, the result is in harmony with the above study, and ginger extract increased glutathione level.

Superoxide dismutase (SOD)

At the end of the study, the disease control group showed a significant ($p < 0.05$) decreased in SOD level compared to the control group and treatment with ginger extract (200 mg/kg & 400 mg/kg) produced a significant ($p < 0.05$ and $p < 0.001$) increased in SOD level compared to the disease control group. SOD is regarded as the primary defense against the harmful effect of oxyradicals in the cells, which catalyzes the transfer of superoxide radicals to H_2O_2 (Freeman and Crapo 1982). SOD is a group of the enzyme that catalyze the dismutation of superoxide radicals (O_2^-) molecular oxygen (O_2) and hydrogen peroxide (H_2O_2) and provide cellular defense against reactive oxygen species (ROS). In our study, we found that ginger extract (200 mg/kg and 400 mg/kg) both doses are significantly increased SOD level compared to a disease control group. The ginger extract significantly increased the SOD level in rats and shows a curative effect in ulcerative colitis.²⁶ Ginger has been also showing the dose-dependent effect on the antioxidant activity and elevated SOD in diabetic rabbits.²⁸ SOD level decreased in AP, and improvement in SOD level showed a significant reduction of ROS generation. So, the result is consistent with the above study, and ginger extract increased SOD level.

Catalase

At the end of the study, the disease control group showed a significant ($p < 0.05$) decreased in catalase level compared to the control group, and the treated group with ginger extract (200 mg/kg & 400 mg/kg), produced a significant ($p < 0.05$) increased in catalase level compared to a disease control group. Catalase is a common enzyme found in all living organisms and it catalyzes the decomposition of H_2O_2 to water & oxygen and increased anti-oxidant capacity.²⁹ In our study, ginger extract (200 mg/kg and 400 mg/kg)

both doses are significantly increased catalase level compared to the disease control group. The ginger extract significantly increased the catalase level in rats and shows the curative effect in ulcerative colitis.²⁶ Ginger has been also showing the dose-dependent effect on the antioxidant activity and elevated catalase in diabetic rabbits.²⁸ Our finding illustrated the significantly increased catalase with treatment.

Histopathological studies

Fig. demonstrated the effect of ginger treatments on the histopathology of the pancreas. Figure 1A demonstrates the control group pancreas. As compared to the control group (Figure 1B) disease control group showed progressively damaged, fatty necrosis, acinar cell necrosis, and fibroblastic cell proliferation in the pancreas. Treatment of ginger reduced damage compared to the disease control group (Figure 1C&1D).

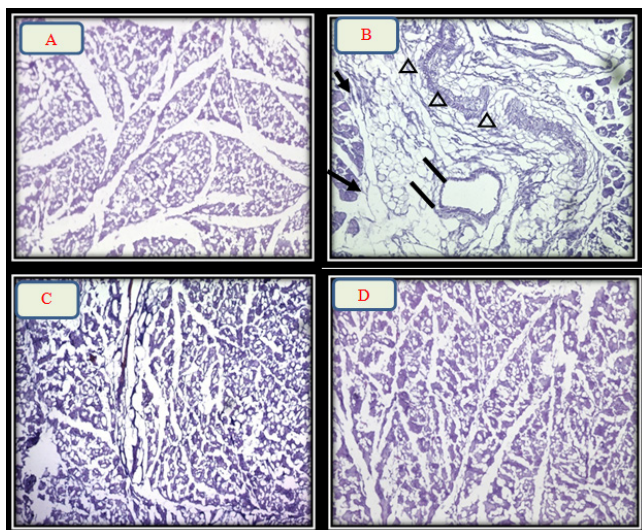


Figure 1 Representative photomicrographs of Hematoxylin and Eosin (H&E) stained pancreas from each studied group. Magnification: 10x.

A: Control group;

B: disease control group (poloxamer 407),

➔ Shows pancreatic damage by fatty necrosis,

△ Portion shows acivnar cell necrosis,

— Indicate fibroblastic cell proliferation.

Figure C & D treated with Ginger 200 mg/kg and 400 mg/kg doses, reduced the pancreatic damage. As per our results of histopathology of the pancreas indicated that the treatment group significantly reduced pancreatic damage.

Conclusion

In conclusion, the present study, for the first time, shows potential anti-inflammatory as well as antilipemic action of dried ginger water extract against hypertriglyceridemia induced acute pancreatitis in experimental animals. This study has justified the traditional claim for using ginger extract in the treatment of hypertriglyceridemic acute pancreatitis. Further studies are required to explore the full therapeutic potential of the ginger and to identify an interesting lead compound along with their molecular mechanism of action.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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