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Research Paper

Role of *Moringa oleifera* Lam. seed or leaf supplemented diet on serum oxidative stress marker and intestinal motility alterations in acute pancreatic rats

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Abstract

This study aimed to determine the effects of *Moringa oleifera* Lam (MO) on gastrointestinal motility alterations in L-arginine induced acute pancreatitis (AP) rats. A total of 55 rats were used for this study and divided into seven groups. Rats were fed with normal rat chow (control, AP and magnesium+AP groups) or with *Moringa oleifera* Lam *seed* (5 or 15%) or *Moringa oleifera* Lam *leaf* (5 or15%) supplemented diet for 4 weeks prior to acute pancreatitis induction. Magnesium (500mg/kg bw) was administered 1 hour before AP induction and continued for 3 days. Acute pancreatitis was induced by the administration of double dose of l-arginine (ip, 320g/100g bw) at 1-hour interval. Intestinal transit time and gastric emptying using charcoal meal as well as serum lipase concentration, malondialdehyde level, myeloperoxidase activity and superoxide dismutase level were assessed. Animals were sacrificed prior to induction and 72 hours after induction. *Moringa oleifera* Lam leaf at 15% showed a significant $p<0.05$ decreased in intestinal transit time and gastric emptying prior to induction of AP. The induction of AP resulted in significant decrease in gastric and intestinal motility which were improved in *Moringa oleifera* Lam seed and leaf especially at 15% seed and 5% leaf groups. Acute pancreatitis equally caused an increase in serum lipase concentration, MDA and MPO activities and a significant decreased in SOD activity. *Moringa oleifera* Lam seed and leaf significantly reverse these effects therefore can be said to have a good effect on gastrointestinal motility alterations associated with acute pancreatitis.

Keywords: acute pancreatitis, serum lipase, L-arginine, oxidative stress, gastrointestinal motility, *Moringa oleifera* Lam.

Introduction

Acute pancreatitis (AP) is an acute inflammation of the pancreas affecting mainly the exocrine pancreas and may also involve the entire pancreas as well as various organs of the body[1]. It is a life-threatening illness with substantial morbidity and mortality rate of about 15% especially in severe cases with widespread pancreatic necrosis[2]. It is characterized by abnormal activation of intra-acinar pancreatic enzymes which then leaked into the interstitium of the pancreas, triggering auto-digestion of the pancreatic tissue[3,4]. The inflammatory response may be restricted to the pancreatic gland with oedema or necrosis, or may include the surrounding tissues as well as distant organs hence, the symptoms vary from moderate abdominal pain to very severe complication[5]. Acute pancreatitis is mainly caused by alcohol abuse and gallstones with long-term alcoholism emerging as the most diagnosed cause[6]. However, drug associated pancreatitis has been reported in some cases, in which case early detection and stoppage of suspected drug makes it possible to treat drug-induced acute

pancreatitis faster[7]. Acute pancreatitis is usually associated with persistent organ failure which is the most determinant factor resulting in mortality[8]. Gastrointestinal motility is usually altered during acute pancreatitis both at the early phase due to systematic inflammatory response and at the late phase due to infectious complications[9-11]. It is also believed that motility disorders of the gastrointestinal tract could be a contributing factor to abdominal discomfort along other factors such as outflow obstruction of pancreatic secretions and inflammation to neural structures experienced during AP. Therefore, inhibiting inflammatory response may help improve gastrointestinal dysmotility and also improve AP[5]. Delayed gastric emptying is very common and it is usually a complication especially after pancreatectomy resulting in increased hospital length of stay, readmission and high cost post-operatively[12-14].There are few experimental studies that have addressed the effect of AP on gastrointestinal function. There is also no effective treatment for inflammatory response during AP and gastrointestinal motility inhibition observed during the course of the disease, hence the need for alternative treatment.

Moringa Oleifera (*M. oleifera*) Lam is a genus of 13 species of the flowering plant in the family of *Moringaceae*. It has the ability to grow fast and can attain a height of 3 meters just 10 months of cultivation and about 10-12 m when fully grown[15]. *Moringa oleifera* Lam has been widely reported to possess antimicrobial, antioxidant, antiulcer, cyto-protective, antidiabetic, anticancer, neuroprotective and anti-inflammatory properties[16-18].The leaves and seeds are well eaten as nutritional supplements[19]. *Moringa oleifera* Lam contains numerous bioactive compounds such as phenols, phytochemicals, caffeoylquinic acid, β-sitosterol, quercetin, kaempferol, vitamins, and minerals, especially essential amino acids and β-carotene, possessing anti-inflammatory properties which might explain some of its pharmacological properties[20-22]. However, the potential effect of *Moringa oleifera* Lamon gastrointestinal motility alterations in acute pancreatitis is yet to be explored. This research therefore looked at the effect of *Moringa oleifera* Lamon *in vivo* gastrointestinal (gastric and small intestine) motility and serum oxidative stress markers in AP.

Figure 1: A picture of Moringa *oleifera* Lam tree where the plant was obtained and used in this study

Materials and methods

This research received the consent approval from the Federal University of Technology Akure Ethical Committee and the experiment was carried out according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science (NAS)[23]. Animals were kept under standard laboratory conditions with a 12 hours light/ 12 hours dark cycle and allowed free access to water and food. *Moringa oleifera* Lam seeds and leaves were collected from the Federal University of Technology Akure (FUTA) environment and were authenticated at FUTA herbarium (voucher specimen number, 0219) by Omomoh B.E. They were air dried, ground into powder and incorporated into standard rat diet as represented in table 1.

Table 1: The composition of the feed

Feed composition	Control feed (kg)	5% *Moringa oleifera* Lam. (kg)	15% *Moringa oleifera* Lam. (kg)
Groundnut cake	2.08	2.08	2.08
Soya meal	6.40	6.40	6.40
Fish meal	3.20	3.20	3.20
Palm kernel cake	1.60	1.60	1.60
Wheat offal	4.80	4.80	4.80
D-methionine	0.08	0.08	0.08
Bone meal	1.60	1.60	1.60
Broiler premix	0.08	0.08	0.08
Salt	0.08	0.08	0.08
Lysine	0.08	0.08	0.08
Corn starch	20.00	18.00	14.00
Moringa oleifera Lam	-	2.00	6.00
TOTAL	40.00	40.00	40.00

Experimental protocols

A total of 55 Male Wistar rats randomly divided into the following groups; Control (5 animals), Acute pancreatitis (AP- 5 animals), *Moringa oleifera* Lam 5% seed (10 animals), *Moringa oleifera* Lam15% seed (10 animals), *Moringa oleifera* Lam5% leaf (10 animals), *Moringa oleifera* Lam 15% leaf (10 animals) and Magnesium (500mg/kg- 5 animals).*Moringa oleifera* Lam seeds or leaves were incorporated into the diet and fed to the animals for 4 weeks prior to induction of AP and continued for 3 days after induction. Magnesium was administered 1 hour before induction of AP and continued once daily for 3 days.

Induction of acute pancreatitis

Powdered L-arginine (LOBA Chemie PVT Ltd, India) was dissolved in normal saline and the pH adjusted to 7. Acute pancreatitis was induced according to the method described by Cikman*et al*., [24]. Double doses of L-arginine 320mg/100g was administered intraperitoneally at 1-hour interval. Animals were sacrificed 72 hours after L-arginine administration. Blood was obtained from the heart via cardiac puncture and transferred into a plain bottle. The blood samples were then centrifuge at 4000g for 10 minutes to obtain the serum which was immediately frozen until used for serum lipase levels and oxidative stress markers.

Serum lipase assay

Serum lipase levels were determined at 37^0C by commercially available kit (Agappe Diagnostics Switzerland GmbH) with spectrophotometer according to the manufacturer's instructions.

Gastric emptying and small intestinal transit

The rats were fasted for 24 h and gastric emptying with slight modification as stated below and intestinal transit time were carried out using charcoal meal. Charcoal meal (1 mL) prepared using 10% charcoal and 5% acacia gum suspended in distilled water and made up to 100ml of solution, was administered orally. The animals were sacrificed 30 minutes after by giving ketamine followed by cervical dislocation. The stomach was clamped with a string at the lower oesophageal end and at the pylorus end to prevent leakage and then resected. The whole stomach weight was taken and thereafter opened up to empty its content and properly rinsed in saline solution. The stomach was blotted and the empty stomach weight was then taken. The difference between the full stomach weight and the empty stomach weight represents the quantity of content left over in the stomach[25]. As such, an increase in gastric content indicates decrease in gastric emptying and vice versa. The small intestine was removed carefully and the leading length representing the most distal point of migration of charcoal meal was measured and expressed as percentage propulsion of charcoal meal compared to the total length of the small intestine[26].

$$\% \text{ intestinal propulsion} = \frac{\text{Distance travelled by charcoal meal}}{\text{Length of small intestine}} \times 100$$

$$\% \text{ inhibition of propulsion} = \frac{\text{Length of the small intestine-distance travelled by charcoal}}{\text{Length of small intestine}} \times 100$$

Serum Malondialdehyde (MDA), Myeloperoxidase (MPO) and Superoxide dismutase (SOD) assays

Malondialdehyde (MDA) as a marker of lipid peroxidation was determined by measuring the thiobarbituric reactive substances (TBARS) produced during lipid peroxidation according to the method of Varshney and Kale[27]. This method is based on the reaction between 2-thiobarbituric acid and MDA resulting in a pink solution which can be read at an absorbance of 532 nm.Myeloperoxidase (MPO) activity was determined according to the method of Xia and Zweier[28]. O-dianisidine is oxidized by MPO in the presence of hydrogen peroxide and can be measured at 460nm.Superoxide dismutase (SOD) inhibits the autooxidation of epinephrine at a pH of 10.2. According to the method of Misra and Fridovich[29] SOD activity was determined using epinephrine and 0.05M Carbonate buffer (pH 10.2) at a wavelength of 480nm.

Statistical Analysis

One-way ANOVA followed by Turkey's multiple comparison tests was used for the statistical analysis. The variables are expressed as mean and standard error of mean with p value of less than 0.05 considered to be significant.

Results and Discussion

Effect of *Moringa oleifera* Lam on serum lipase concentration and oxidative stress markers (MDA, MPO and SOD) following induction of acute pancreatitis

As shown in Table 2, when compared with control group, AP induction resulted in significant increase in serum lipase concentration, MDA and MPO activities while, significantly decrease SOD activity ($p<0.0001$). This is consistent with previous reports as enzyme activation and release is a consequence of increased reactive oxygen species and free radicals which destroys the membrane of the pancreas making it highly permeable[30,31]. Elevated levels of MPO in circulation are usually associated with systemic inflammation and oxidative stress[32]. Pre-treatment with *Moringa oleifera* Lam seed or leaf contained in diet as well as with magnesium resulted in substantial increase in serum SOD and decrease in lipase, MDA and MPO thereby ameliorating oxidative stress due to AP. Previous studies have established that *Moringa oleifera* Lam is capable of chelating free radicals[33,34].

Table 2: Effect of *Moringa oleifera* Lam on serum lipase and oxidative stress markers (MDA, MPO and SOD)

Groups	Lipase (U/L)	MDA (nmol/ml)	MPO (µmol/ml)	SOD (U/mgprot)
Control	3,10±0.44#	0.25±0.03#	0.14±0.01#	215.20±20.83#
AP	28.15±5.03*	0.88±0.12*	0.63±0.07*	157.20±7.61*
5% *M. oleifera* Lam seed + AP	7.44±2.01#	0.29±0.04#	0.24±0.06#	207.20±4.79#
15% *M. oleifera* Lam seed + AP	3.72±0.76#	0.48±0.03*#	0.79±0.05*	194.18±4.79#
5% *M. oleifera* Lam leaf + AP	3.10±0.44#	0.19±0.02#	0.17±0.05#	203.00±1.39#
15% *M. oleifera* Lam leaf + AP	3.70±0.72#	0.19±0.01#	0.23±0.06#	201.4±6.19#
Magnesium + AP	6.82±1.58#	0.41±0.08#	0.19±0.04#	217.70±4.03#

Results are expressed as mean ± SEM.

* Significant when compared to control, # significant when compared to AP

Effect of *Moringa oleifera* Lam on gastric emptying and small intestinal transit prior to the induction of acute pancreatitis

The result did show a significant ($p<0.0001$) inhibitory effect of only *Moringa oleifera* Lam leaf at 15% on gastric emptying and intestinal transit compared to control. Other *Moringa oleifera* Lam groups (leaf- 5%, seed- 5 and 15%) and magnesium group had no significant changes compared to the control group as represented in figure 2c, a and b. This is in agreement with the report of Lakshminarayana *et al*.,[35], stating that leaf extract of *Moringa oleifera* Lam demonstrated antidiarrheal

activity. The mechanism of action of *Moringa oleifera* Lam was attributed to its anti-propulsive and antisecretory effects as the leaf extract of *Moringa oleifera* Lam also significantly inhibit intestinal motility by decreasing the mean movement of charcoal meal.

Effect of *Moringa oleifera* Lam on gastric emptying and small intestinal transit following induction of acute pancreatitis

Gastric emptying (figure 3c) was delayed in AP group compared to control group. *Moringa oleifera* Lamseed (15%) and leaf (5%) significantly ($p<0.01$) reveres the effect of AP. However, *Moringa oleifera* Lam seed (5%) and leaf (15%) as well as magnesium showed no significant difference compared to AP group. Intestinal transit (figure 3a and b) of charcoal meal was significantly inhibited in AP group compared to control group. All *Moringa oleifera* Lam groups significantly ($p<0.05$) increased intestinal transit compared to AP group. The observed inhibition of gastric and intestinal motility following the induction of AP is in line with earlier reports[10,11,36-38].

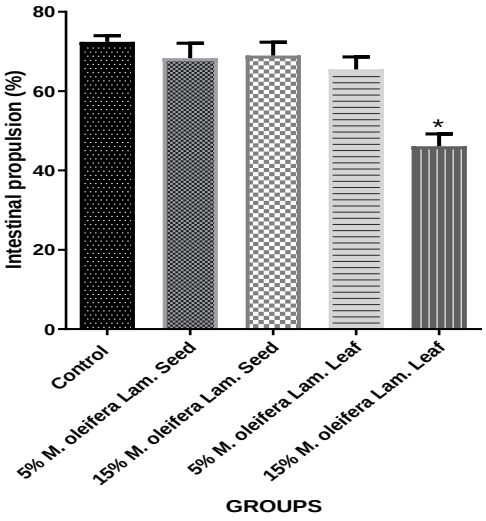

Figure 2a: Small intestinal propulsion

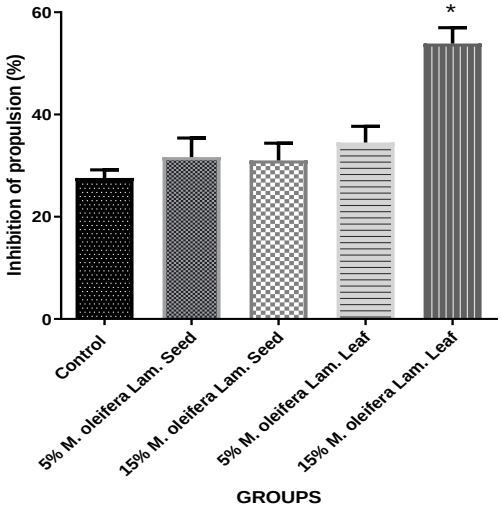

Figure 2b: Inhibition of small intestinal propulsion

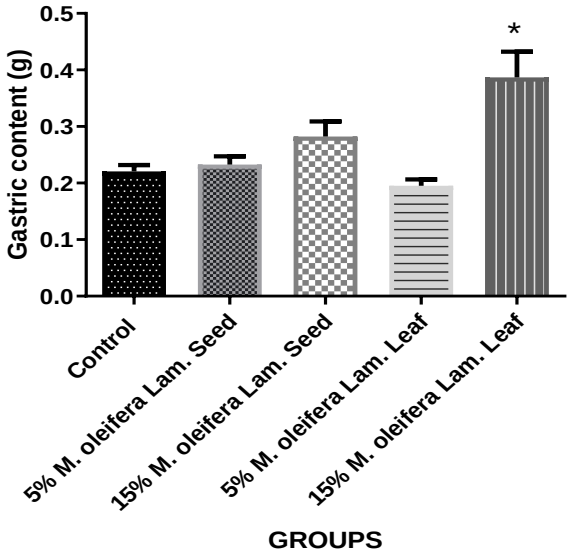

Figure 2c: Gastric emptying

Figure 2: Effect of *Moringa oleifera* Lam on gastrointestinal motility prior to acute pancreatitis induction. All results are expressed as mean ± SEM. * significant when compared to control

Effect of *Moringa oleifera* Lam on gastrointestinal motility 72 hours following induction of acute pancreatitis. All results are expressed as mean ± SEM. * and # significant when compared to control and AP respectively

Acute pancreatitis has also been reported to disrupt the migrating motor complex and intestinal contractility *in vitro*[39,40]. Gastrointestinal dysmotility in AP has been related to systemic inflammation resulting from increase in inflammatory mediators such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), during acute pancreatitis. This leads to decrease smooth muscle electrical activity and eventual paralysis of the intestine[35,36]. *Moringa oleifera* Lam significantly improve gastric motility as well as intestinal motility, however, the mechanism of action is yet to be elucidated. Its anti-inflammatory effects have been widely reported in various diseases[15,41,42] and was also observed from this study via its action on myeloperoxidase enzyme which could be a possible mechanism of action since systemic inflammation greatly affects intestinal motility.

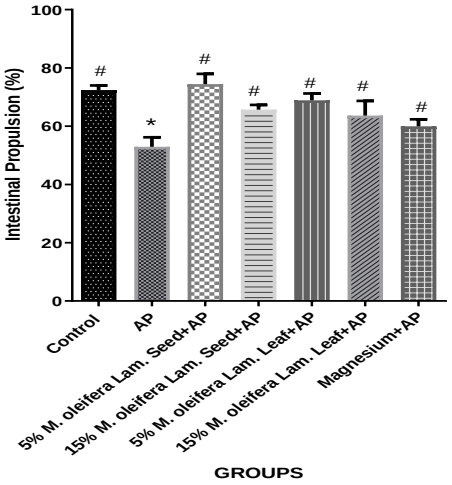

Figure 3a: Small intestinal propulsion

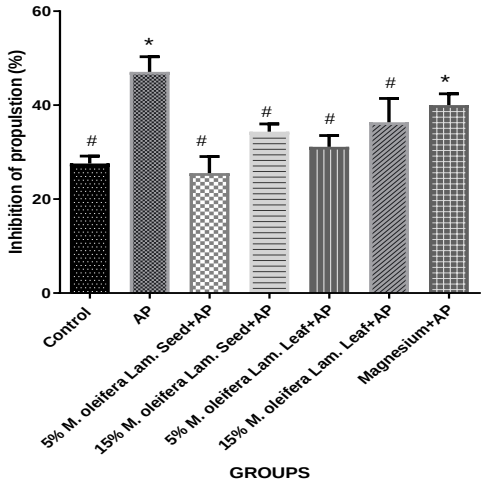

Figure 3b: Inhibition of small intestinal propulsion

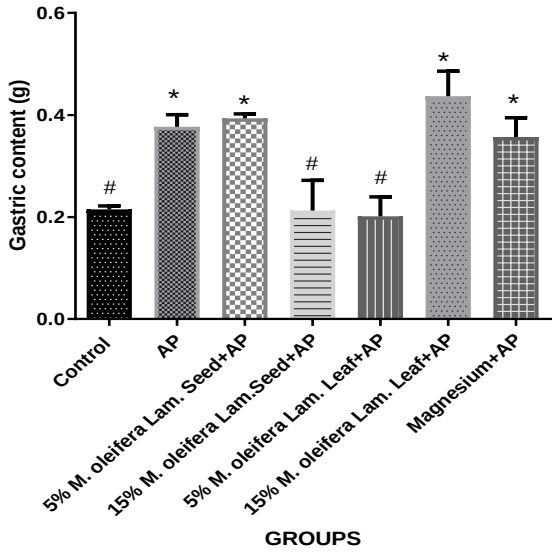

Figure 3c: Gastric emptying

Figure 3: Effect of *Moringa oleifera* Lam on gastrointestinal motility 72 hours following induction of acute pancreatitis. All results are expressed as mean ± SEM. * and # significant when compared to control and AP respectively

Conclusion

In conclusion, *Moringa oleifera* Lam seed and leaf may be able to improve gastric emptying and intestinal propulsion index as well as serum oxidative stress associated with acute pancreatitis. The ameliorative action of oxidative stress could be a possible mechanism in improving gastrointestinal dysmotility. It was however noticed that magnesium could not improve gastrointestinal dysmotility in AP despite decreasing oxidative stress, suggesting some other mechanisms of action of *Moringa oleifera* Lam other than just inhibiting systemic inflammation. Further research is therefore needed in this area to determine other possible mechanism(s) of action of *Moringa oleifera* Lam in improving gastrointestinal dysmotility in acute pancreatitis.

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