EFFECTS OF *E Mal*$^{(R)}$ (α, β-ARTEETHER) ON GASTROINTESTINAL FUNCTION IN ALBINO WISTAR RATS

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ABSTRACT
It has been demonstrated that some anti-malarial drugs influence gastric mucosal integrity, but there is paucity of information on *E MAL*$^{(R)}$(α,β-arteether), a drug of choice, across all age-groups, for the management of multi-drug resistant *P. falciparum* complicated and uncomplicated malaria. This study, therefore, investigated the effect of *EMAL*$^{(R)}$, an artemisinin derivative, on gastrointestinal function in albino Wistar rats. The animals, of both sexes, weighing 200±20g, were randomly assigned to five batches. Each batch was subdivided into five groups (n=5) for control, 1.5, 3.0, 5.0 and 10.0 mg *E MAL*$^{(R)}$/kg body weight, respectively. The test drug was administered intramuscularly, once daily for three consecutive days. At the end of the three-day administration, the relevant parameters for gastrointestinal function were assessed. The results showed *E MAL*$^{(R)}$ given, respectively, at 1.5, 3.0, 5.0 and 10.0 (mg/kg body weight) significantly decreased gastric acid secretion, ulcer scores, pepsin concentration and intestinal motility. However, gastric mucus output, intestinal transit and food intake were not significantly different from control. At the dose of 5.0 mg/kg body weight of *E MAL*$^{(R)}$, gastric mucus output was significantly increased. There was no significant difference in food intake, mucus output, intestinal transit and pepsin concentration compared to control. It may be concluded that *E MAL*$^{(R)}$ enhances mucogenic, anti-gastrosecretory, anti-ulcerogenic, effects with decreased motility in rats.

Keywords: E Mal(R) (α, β-Arteether), Gastrointestinal Function, Malaria, Wistar rats.

INTRODUCTION

Malaria causes major health and economic burdens in most tropical countries[1]. More than forty percent of the world's population live in malaria-endemic areas. An estimated 300-500 million cases and 1.5 -2.7 million deaths occur each year due to malaria[2]. *Plasmodium falciparum* most commonly causes severe (life threatening) malaria if not treated timely. It affects all age groups, although the reported mortality varies considerably depending upon the age, immunity, clinical complications and access to appropriate treatment[3]. The situation has been further complicated by the spread of chloroquine-resistant malaria.

The wide-spread resistance of *P. falciparum* to chloroquine precludes the use of this drug in the treatment of severe malaria. Therefore, the essential choice is between quinine and artemisinin derivatives. Quinine has undesirable side effects including hypoglycaemia and cinchonism. Moreso, quinine has to be given three times a day as an intravenous infusion that requires close medical supervision. Considerable impetus to the management of malaria has been given by the artemisinin (qinghaosu) derivatives, which were first isolated in 1971 by Chinese chemists. Artemisinin and its derivatives are known for their potent anti-malarial activity, characterized by an almost immediate onset and rapid reduction of parasitemia,

with complete clearance in most cases within forty-eight hours[4]. They are also preferred because of fewer side effects and ease of administration.

Arteether is the ethyl ether derivative of dihydroartemisinin. The drug has been proven to be 100% effective in treating patients for acute chloroquine resistant, complicated as well as uncomplicated *falciparium* malaria[5]. In an open randomized study in cerebral malaria patients, α, β-arteetther was shown to expedite coma recovery ($p<0.02$) and had fewer deaths (6.67% versus 27.27%, $p<0.02$) compared with chloroquine[6]. The efficacy and safety of arteether have been established[7]. However, there is paucity of investigations on the effect of this drug on the function of the gastrointestinal tract (GIT). The major aim of this research was to study the effect of *E Mal*$^{(R)}$ (α, β-Arteether) on gastrointestinal function in albino rats and the specific objectives were to determine the effect of *E Mal*$^{(R)}$ on gastric acid secretion, on pepsin secretion, on mucus secretion in the stomach and to determine the effect of *E Mal*$^{(R)}$ on gastric ulceration.

METHODOLOGY OF STUDY

Chemicals, Reagents and equipment

Chemicals and reagents: Acetic acid, potassium iodide, sodium thiosulphate (0.1M) (May and Baker Dagenham, U.K.), starch solution (1%), chloroform, bromine, 95% alcohol, 0.1m NaOH, phenolphthalein (1&%), Sodium thiopentone 6mg/100g, body weight (Rotex Medica GMBH Germany), distilled water, NaOH (20g)(May and Baker, Dagenham England) , HNO_3 (2N) 20ML, Mercuric Nitrate (3g), Diphenyl carbazene (100g).

Standard chloride solution 100 meg/L), Dry NaOH (5.83g), Diazotized sulphanilic acid, Benzoate Urea, Urethane (Sigma Chemical Company Poole UK). Cholesterol end point (Colorimeter kit Randox Laboratories, Isotonic saline (0.9%), Haematoxylin, Eosin, Bovine pepsin, Hcl (0.1N), 10% Trichloroacetic Acid (10ml), Casein, 0.1% Alcian Blue (10ml), Sucrose Solution, Sodium Acetate, $Mgcl_2$ (0.5m), Methanol (70%), Tyrode solution (Nacl 0.8gm%, $NaHCO_3$ 0.01gm%, $Cacl_2$ 0.02gm% Kcl 0.02gm%, NaH_2PO_4 0.005 gm%.

Equipment: The Glassware and equipment were 2.5ml flask, Measuring cylinder, Pipettes/burettes, conical flasks, Fume cupboard, Microscope and slides, heating mantle. Beakers, Stainless steel pot, Weighing balance, Calibrated Water bottles, Portex, Cannula (0.5mm), Flame photometer (410c), Spectrophotometer, Refrigerator, Centrifuge Oessophageal Cannula, Vernia Calipers, Organ bath, Kymograph/drum, Meter rule, Electric lamp, Intubating syringe, Gallenkamp shaker, Thermometers, pH meter, Whatman filter paper (No1) and Volumetric flask.

Drug procurement

The test drug, *E Mal*$^{(R)}$, was purchased from ROTECS Pharmacy RC. 1027569, Ebis Mechanic Road, Amarata, Yenagoa, Bayelsa State. Each 2ml vial of *E Mal*$^{(R)}$ contained 150mg α, β-Arteether with NAFDAC REG. NO. 04-8383.

Drug formulation for the experiments

The test drug was prepared as a 150 mg/10ml stock. The original *E Mal*$^{(R)}$ (150mg/2ml) was introduced into a sterile plain bottle; then, 8 ml of sterile water (water for injection) were added, in order to obtain the stock from which the appropriate dose (weight/volume) was taken for administration in the corresponding animal.

$$Dose\ per\ rat = (mg\ E\ Mal(R) required\ x\ 10\ ml\ stock\ E\ Mal(R))/(2\ mg\ E\ Mal(R)\ ) = ml\ of\ E\ Mal(R) stock$$

Where,

mg *E Mal*$^{(R)}$ required = group designation (mg *E Mal*$^{(R)}$/ kg body weight) x body weight (kg)

Mode of administration of *E Mal*$^{(R)}$

E Mal$^{(R)}$ is approved for intramuscular administration only. The appropriate dose (w/v) from the stock drug was given at the anterior aspect of the mid-thigh muscle, using alternate limb, 24-hour interval, for 72 hours. One-millilitre hypodermic (insulin giving type) syringe-and-needle was used per injection. Wistar rats were administered graded doses of the drug intramuscularly once a day for three consecutive days.

Animal groupings per drug strength

The animals (both sexes), 220 ± 40 grams body weight, were randomly assigned to five batches. Each batch was subdivided into five groups of five rats each based on the strength of *E Mal*$^{(R)}$ administered.

Group I: Control (rat, chow, water *ad libitum,* No drug)

Group II: 1.5 mg *E Mal*$^{(R)}$/ kg body weight (rat chow, water *ad libitum,* drug)
Group III: 3.0 mg *E Mal*$^{(R)}$/ /kg body weight (rat chow, water *ad libitum,* drug)
Group IV: 5.0 mg *E Mal*$^{(R)}$/ /kg body weight (rat chow, water *ad libitum,* drug)
Group V: 10.0 mg *E Mal*$^{(R)}$/ /kg body weight (rat chow, water *ad libitum,* drug)

Experimental animals and maintenance

Albino rats of the Wistar strain were used for this research. The rats weighed between 200 and 220g at start of experiments and were randomly chosen from both sexes. They were all kept in plastic cages with wire net covers. The ethics for the use of experimental animals were strictly adhered to. They were maintained in the animal facility of the Physiology Department, University of Calabar, at a temperature of 28 ± 2°C, 12 hours light and dark cycles. Each rat was kept in a separate cage. The cages were always kept neat. Food and water intake per rat was determined on daily basis and their individual body weight measured using an animal weighing balance.

Determination of food and water intake

Water intake was measured using calibrated feeding bottle with stainless steel nozzles. The daily water intake was obtained by subtracting the volume of water remaining at the end of 24 hours of feeding from the initial amount in the feeding bottle at start of the day. The difference was the amount consumed for the day. The food intake was measured by weighing the amount of food left in the container after 24 hours and subtracting it from the initial amount of food at start of the day's feeding. The food containers were medium sized stainless steel plates to avoid spillage of food.

Measurement of gastric acid

Measurement of gastric acid was done by the continuous perfusion method of Gosh and Schlid[8] as modified by Osim *et al.,*[9]. Rats from the control, drug tested groups were fasted 18 hours before the start of experiments. 6 mls/kg of 25%(v/v) solution of urethane (Sigma UK) was given intraperitoneally to anaesthesize the rats. The trachea was exposed and cannulated; another cannula was passed through the mouth and oesophagus until it reached the stomach. It was then tied firmly in place with a ligature around the oesophagus in the neck. The abdomen was then opened along the *linea alba* to minimize bleeding. The stomach was exposed and the pyloric end cannulated at its junction with the duodenum. Isotonic (0.9%) saline was introduced gently via the oesophageal cannula to wash out any stomach content. The perfusate was allowed to flow freely after clearing the food particles. The abdominal incision was then covered with a moist cotton wool dipped in normal saline. The stomach was continuously perfused with normal saline at the rate of 1ml/min.

The pH of the saline was maintained at 7.0 and the body temperature of the rat was maintained at 37°C by a heating lamp and a rectal thermometer was inserted in the rat to monitor its body temperature. The flow was adjusted to give an effluent volume of about 1ml per minute. The effluent was collected at 10-minute intervals and care was taken not to ligate the blood vessels as this may lead to stained perfusate. Each 10-minute perfusate after adding two drops of phenolphthalein as indicator was titrated against 0.01N NaOH (May and Baker UK) to determine total acidity. The experiments were repeated using histamine as acid secretagogue. The dose of the histamine was 100mg/kg body weight administered subcutaneously.

Analysis of gastric acid

Gastric acid output in the effluent sample was measured by titrimetric analysis. The calculation of acid in millimole per litre per hour (mMol/L/Hr), was by principle that states that a gram equivalent of acid balances a gram equivalent of base at neutralization point. This means that N acid × V base. From the above equation, since normality (N) of base is known (0.01N) and the volume of base needed for neutralization is known, the gram equivalent of base ($N_B \times V_B$) can be calculated. This, at the end point is also the gram equivalent of acid. If the volume is in mls, the total acid output becomes mili-equivalent. For a small animal like the rat, milli equivalent of the acid will be too small and so always converted μeq or μmol per unit time of collection e.g. 10minutes.

Collection of pepsin

Gastric juice used for analysis of pepsin was collected according to the method of Shay *et al.,*[10]. The animals were fasted for 36 hours to ensure that their stomachs were completely empty. Water was however allowed *ad libitum.* Under light diethyl ester anaesthesia, the abdomen of the rats was shaved and midline incision was made extending 2cm downward from the xyphoid,

the junction between the pylorus and duodenum was picked gently with curved probe. The stomach itself was not disturbed. A pyloric ligature was made using silk thread and care was taken to avoid damage to blood vessels or traction on the stomach. The abdomen was then closed by interrupted sutures. The abdominal wounds were cleaned thoroughly with physiological saline, dried and covered with a solution of flexible collodion. The anaesthesia was discontinued and the animals usually recovered consciousness within 10minutes. Four hours later, the animals were again anaesthetized with diethyl ether, the abdomen was opened, the pylorus, duodenum and appropriate peritoneal ligature were clamped. The stomach was removed and washed in physiological saline and dried. The stomach dried. An opening was made along the greater curvature and the gastric juice was drained into a small centrifuge tube and then centrifuged 3000g for 10 minutes and the supernatant collected for pepsin analysis.

Measurement of pepsin

The determination of proteolytic activity of gastric secretion (which is the basis for measurement of pepsin) was performed according to the method of Hirschowitz (1999). Pepsin was incubated with denatured haemoglobin (substrate) for 19 minutes. At the end of the incubation time all undigested protein was precipitated by 10% Trichloroacetic acid (TCA). This was filtered and the filtrate contains soluble peptides that have phenolic amino acids, tyrosine, tryptophan and phenylalanine. The phenolic amino acids were developed to form a blue color with Folin Ciocaltreau reagent under alkaline conditions. The depth of color produced was measured on a photometer using a red filter. Blank tube was prepared with each activity tube and the optical density used was that figure found to be the difference between blank and activity. This was converted to mM Tyrosine, using the standard solution conversion.

Extraction of adherent mucus

Adherent gastric mucus was determined by the procedures described by Ofem *et al.,*[11]. The stomach was removed and washed in normal saline and then opened along the greater curvature. It was again rinsed in saline and pined to a cork board with dissecting pins. Mucus was extracted using a spatula from the spread stomach into a known weight of beaker containing 4ml of water. The weight of mucus was derived from the difference between the initial and the final weights of beaker + 4 ml of water as follows:

Weight of beaker + 4 ml of water = x

Weight of beaker + 4 ml of water + mucus = y

Weight of mucus = (y – x) in grams

Gastric ulceration

The animals were starved for 24 hours. Under anaesthesia (6ml/kg of 25% v/v solution of urethane), a pyloric incision was made and a cannula inserted and kept in place by tying with a thread. The stomach of the animals was instilled with 1.5ml of acid alcohol, prepared from equivolume of 0.1N HCl and 70% ethanol. The instillation was via the pyloric incision.

Grade	Interpretation
0.0	No lesions (normal stomach)
0.5	Pin size ulcer
1.0	2 or more haemorrhagic or small linear ulcer
2.0	Ulcer spots greater than 3mm

The animal was left to stay for an hour. Then, the stomach was isolated, washed and cut open along the greater curvature and rinsed with normal saline. Pins were used to fasten the tissue in place for proper visualization. A magnifying lens and a vernier calliper were used to measure the extent of ulceration.

Scoring of ulcer spots was by the method of Alphin and Wards[12]

Ulcer score was done according to the grading system below.

$$Ulcer\ index\ for\ each\ group = (Number\ of\ rats\ x\ number\ of\ grades)/(Total\ number\ of\ rats\ in\ a\ group)$$

$$Ulcer\ incidence\ (\%) = (Number\ of\ rats\ with\ ulcer\ \times\ 100)/(Total\ number\ of\ rats)$$

Intestinal motility

Rats were starved 24 hours prior to experiment. This was to ensure that there was no food in the stomach and small intestine. The animals were sacrificed by stunning and incision quickly made through the linea alba to expose the intestine. The proximal ileum was located and isolated, then placed in a container of Tyrode solution and aerated. The ileum was then cut

into segments of about 3 cm long, and mounted at one end to a fixed support in an organ bath. The other end of the ileum was fixed to a horizontal balance writing lever tangential to the kymograph drum. The tissue was allowed to equilibrate for 60 minutes during this period the bathing solution was replaced with Tyrode solution at 15 minutes interval to avoid accumulation of metabolites. The tissue was later challenged with graded doses of acetylcholine (ACh) and later on atropine was administered.

Intestinal Transit (Uwagboe and Orimilikwe[13])

The rats in the different groups studied were deprived of food but were allowed water for 24 hours before the experiment. 50 g chow (Supplied by Pfizer company Nigerian limited) was ground to powder, sieved and mixed with 200 ml of water. The mixture was allowed to stand for 30 minutes and it settled into three layers namely topmost, middle and bottom layers. Both the topmost and bottom layers were discarded. The middle layer is more homogenized and richer in nutrients. Leishman's stain (0.15 g) mixed with charcoal (for effect) was prepared in 100ml of phosphate buffer. 20 ml of Leishman – charcoal mixture was then mixed with the middle layer of the homogenized chow.

All the rats were fed orally with 3 ml of Leishman's stained food mixture using an 8 cm long metallic intubating syringe. The experiment was timed for 90 minutes to allow room for food to move from the small intestine completely. At the end of 90 minutes, the rats were sacrificed by decapitation and the abdomen cut open immediately. The location of the Leishman's stained food mixture in the intestine was measured using meter rule. The intestinal transit was calculated as:

$$\frac{Length\ travelled\ by\ the\ black\ marker}{Total\ length\ of\ the\ small\ intestine} \times 100$$

Precautions

Tracheal cannulation was done immediately after the animal was made to sleep to avoid suffocation.

The animal was dissected along the *lineaalba* to avoid excessive bleeding.

A lamp was placed near the animal to avoid hypothermia. The right doses of the chemicals were always used. The intubating syringe was carefully inserted into the oesophagus to avoid entrance of dye into the lungs.

Statistical analysis

All results are presented as mean ± standard error of mean. Three sets of data were analyzed using one way ANOVA, followed by the least significant difference (LSD) procedure for significant F values. $P<0.05$ was considered significant. Computer Software (SPSS and Excel Analyzer) was used for the analysis.

RESULTS AND DISCUSSION

Effect of *E Mal*$^{(R)}$ on water intake

The mean daily water intake in the control group was 16.03+1.88ml, while that for 1.5mg/kg, 3.0mg/kg, 5.0mg/kg and 10.0mg/kg body weight were 21.50+0.90, 21.25+2.08, 16.65+1.76, and 21.95+0.47ml respectively (Figure 1). There was no significant difference between control group and *E Mal*$^{(R)}$ treated 1.5, 3.0 or 5.0mg/kg groups. However, the change in water intake was significantly higher ($p<0.05$) in 10.0mg/kg body weight when compared with control.

Effect of *E Mal*$^{(R)}$ on gastric acid secretion

Figure 2 shows histamine stimulated gastric acid secretion in control and drug-tested groups. There was significant decrease ($p<0.05$) in basal acid secretion in test groups that in the control groups. However, following administration of histamine, the peak acid output was higher significantly ($p<0.05$) in 5.0mg/kg group than in control and 3.0mg/kg groups respectively. Cimetidine significantly reduced histamine-stimulated acid although it did not completely abort the effect (Figure 3).

Effect of *E Mal*$^{(R)}$ on pepsin secretion

The concentration of gastric pepsin (mg/100ml) for control, 1.5mg/kg body weight, 3.0, 5.0 and 10.0mg/kg was 0.75+0.04, 0.53+0.04, 0.39+0.04, 0.54+0.04 and 0.61+0.10 respectively. The pepsin concentration in 3.0 mg/kg group was significantly lower ($p<0.05$) than in the test group as shown in Figure 4.

Effect of *E Mal*$^{(R)}$ on gastric mucus secretion

The concentration of the adherent gastric mucus in control, 1.5 mg/kg, 3.0 mg/kg, 5.0 mg/kg and 10.0 mg/kg body weight was respectively 0.06±0.01 grams, 0.06±0.01 grams, 0.07±0.07 grams, 0.13±0.04 grams and 0.10±0.01 grams respectively (Figure 5). The 5.0

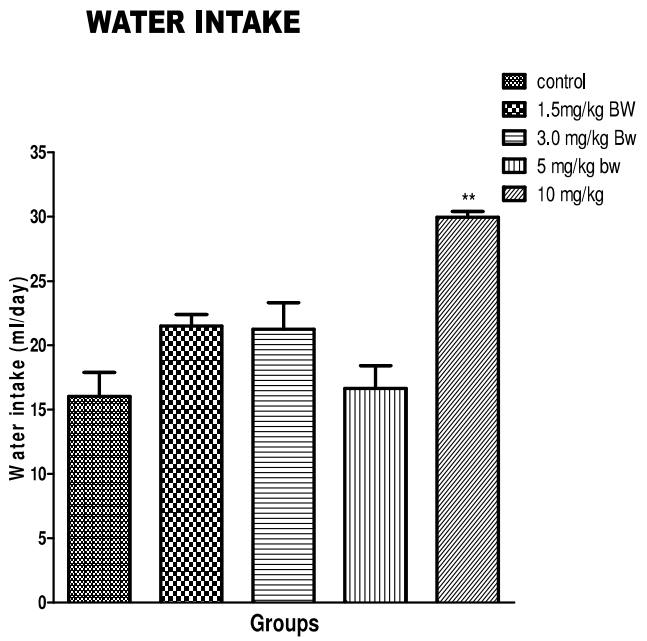

FIGURE 1: Mean Water intake in the different experimental groups. Values are expressed as Mean ± SEM, n=5
**p <0.05 versus Control

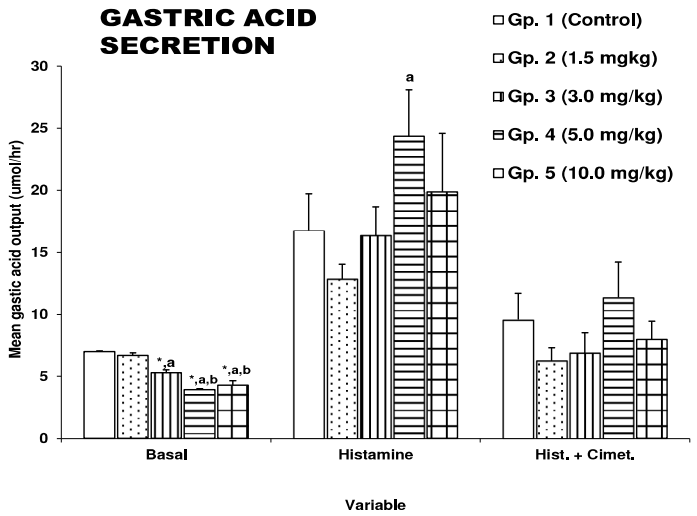

Figure 2: Mean basal gastric acid output and effect of administration of histamine and cimetidine on gastric acid output in control and test groups. Values are expressed as mean ± SEM, n = 5

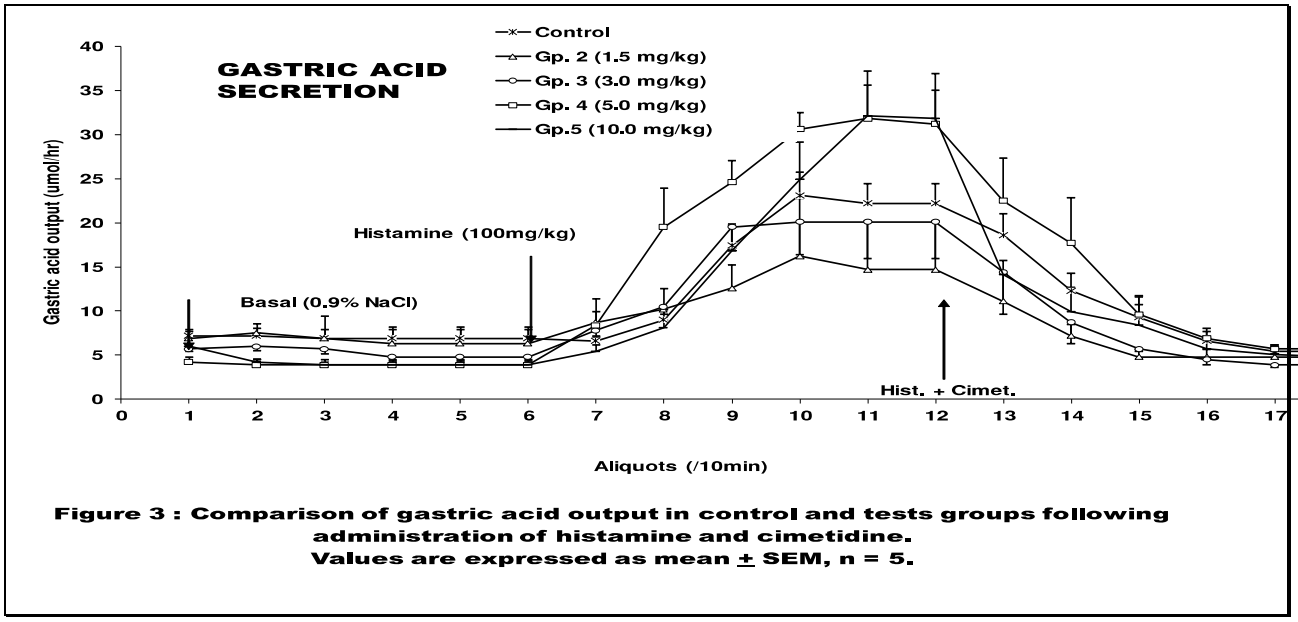

Figure 3 : Comparison of gastric acid output in control and tests groups following administration of histamine and cimetidine. Values are expressed as mean ± SEM, n = 5.

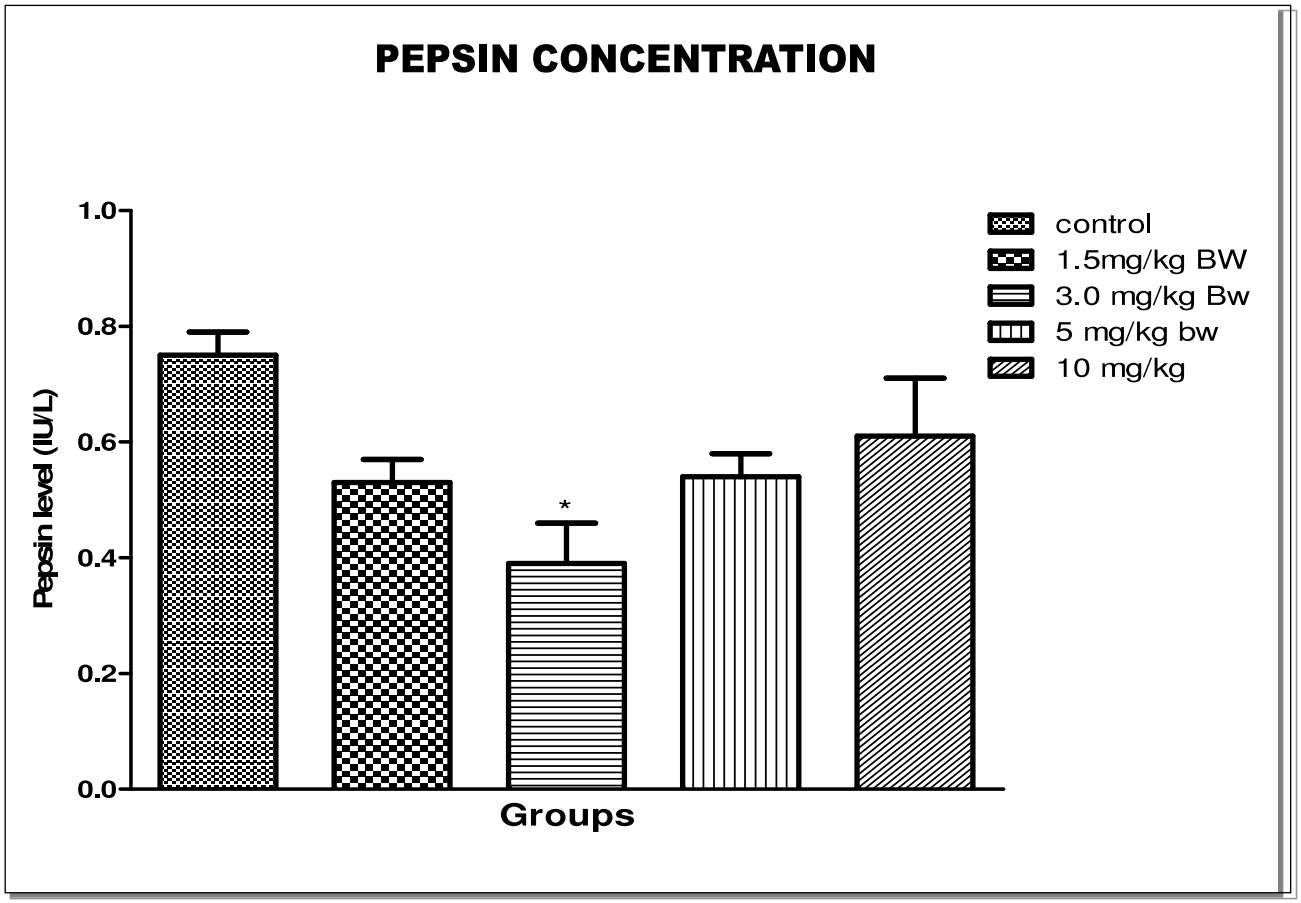

Figure 4: Mean Pepsin Concentration in the Various Experimental Group. Values are expressed as Mean ± SEM, n= 5, p< 0.005

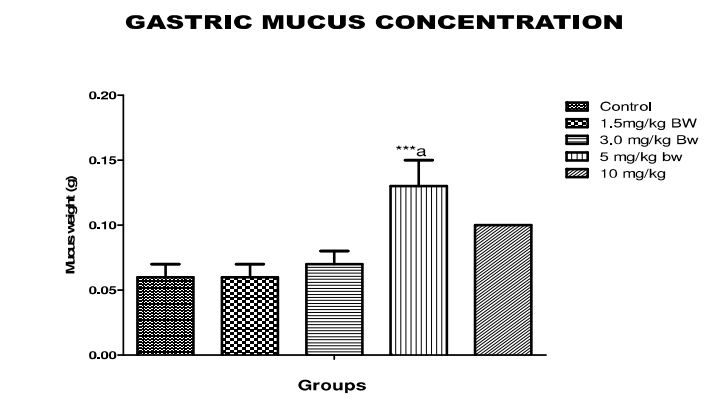

FIGURE 5: Mean Gastric Mucus concentration in the different experimental rats. Values are expressed as Mean ± SEM, n=5 ; ***p<0.05 versus Control; a= p<0.05 versus 10.0mg/kg group.

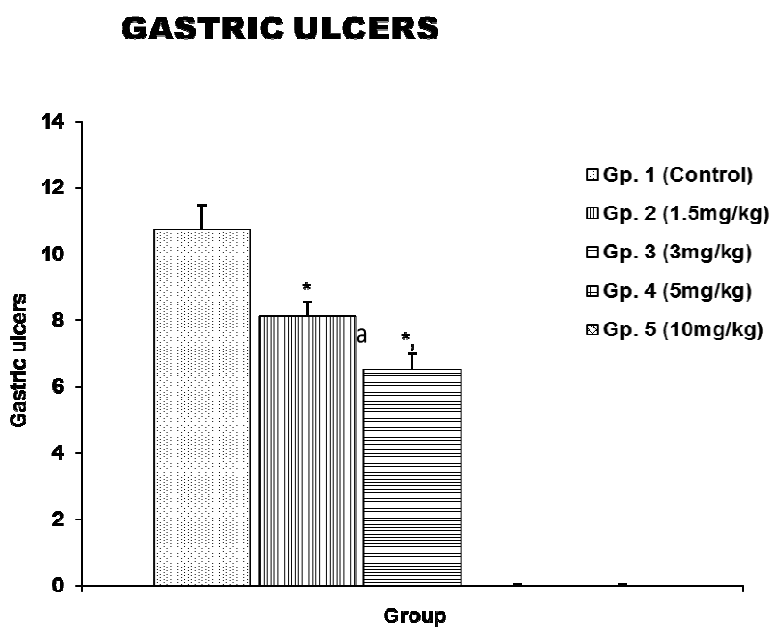

Figure 6: Mean Gastric Ulcer Scores in the Various Experimental Group. Values are expressed as Mean ± SEM, n= 5, p< 0.005

mg/kg body weight *E Mal*$^{(R)}$ dose elicited significantly (p<0.05) highest mucus secretion.

Effect of *E Mal*$^{(R)}$ on gastric ulceration

The mean ulcer scores for control, 1.5mg/kg body weight, 3.0, 5.0, 10.0mg/kg body weight were respectively 10.75±0.72, 8.13±0.43, 6.50±0.50, 0.00±0.00 and 0.00±0.00 with significant differences between control and *E Mal*$^{(R)}$ treated groups and also among drug-tested groups (Figure 6). The effect was lowest with 5.0 mg/kg and 10.0 mg/kg doses, although there was no significant difference between these two groups at 95% confidence level.

The effect of *E MAL*$^{(R)}$ (α, β-arteether) on gastrointestinal function in the albino Wistar rat was studied. The gastric mucosa is normally resistant to the harsh conditions of low pH and pepsin activity in gastric juice[9]. Gastric ulceration may occur due to

imbalance between gastroprotective and aggressive factors. In this study, *E MAL(R)* demonstrated anti-ulcerogenic effect dose dependently, correlated with low ulcer index, reduced gastric acid secretion, low pepsin concentration and increased mucus secretion.

Gastric acid secretion is an aggressive factor. Histaminergic augmentation of gastric acid secretion by chloroquine and amodiaquine in the rat has been reported Ajeigbe *et al,*[14]. Artesunate has been shown to produce a dual effect of inhibiting histamine receptors and stimulating acetylcholine receptors in the gastric mucosa in rats[15]. *E MAL(R)* at 3.0, 5.0 and 10.0 mg/kg body weight reduced basal gastric acid output in our study. The histamine-induced increase in gastric acid output was highest in 5.0mg/kg group (558.44%), followed by 10.0 mg/kg (350.00%), 3.0mg/kg (208.11), and 1.5mg/kg (110.66%) compared to control (179.29%). Administration of cimetidine caused a reduction in histamine-induced gastric acid secretion in all groups. There seems to be a synergism between the *E MAL(R)* and the H2-histamine antagonist drug. Previous studies have reported that antimalarial drugs like artesunate (an artemisinin-derivative) and sulfadoxine-pyrimethamine attenuate the effect of indomethacin and acidified ethanol on gastric juice volume, pH and acid output[16, 17].

Pepsin activity is another aggressive factor. E MAL(R has been shown, in this study, to elicit low levels of pepsin compared with control. Pepsin solublizes gastric mucus thereby exposing the gastric lumen to acid attack18. The reduced concentration of pepsin and gastric acid coupled with high amount of adherent mucus may be responsible for the low gastric ulceration in the E MAL(R- treated rats compared to control.

Mucus concentration is a gastro-protective factor. According to Kauffinan19, prostaglandins play a role in mucus synthesis in goblet and mucous neck cells. Gastric mucus output was highest in the 5.0 mg/kg body weight group followed by the 10.0mg/kg body weight group.

In our study, the ulcer index was lowest in the 5.0 and 10.0mg/kg body weight doses of E MAL(R) whose pepsin levels were higher compared with the 3.0 and 1.5mg/kg group. The balance between the aggressive and gastro-protective factors may favour the latter. The mechanism of action of arteether is not well defined. However, the activity of an endoperoxide moiety, lipid peroxidation and inhibition of protein synthesis has been postulated[20]. Foglio *et al.,* [21] had demonstrated that artemisinin extraction by-product exhibited intense anti-ulcerogenic activity in ulcer models induced by indomethacin and ethanol comparable to the standard drug, carbenoxolone. Clinically, therefore, known peptic ulcer patients, and subjects predisposed to the disease condition might benefit from *E MAL(R)* for its anti-ulcerogenic effect.

CONCLUSION

Results from our study showed that *E MAL(R)* (α, β-arteether) enhances anti-gastro-secretory, anti-ulcerogenic and mucogenic effects with decreased small intestinal motility in the albino Wistar rat. The drug might promote absorption of water, nutrients and electrolytes in the gastrointestinal tract. The current anti-malarial regimen of 150 mg (for adults) and 3 mg/kg body weight (for children), per day for three consecutive days may be well tolerated. The findings in this investigation may be extrapolated to man. The mucogenic, anti-gastrosecretory, anti-ulcerogenic and anti-motilitic effects of *EMAL* would be useful in peptic ulcer conditions.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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