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Research Article

Anti-ulcer activity of arachidonic acid (PUFA) oils in different induced ulcer animal models

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ABSTRACT

Background: Ulcers of the lower part of the oesophagus, the stomach and the first part of the duodenum are also known as peptic ulcers. Peptic ulcers can affect people of any age, but they are more common as you get older. There is a focus on research for better tolerated and efficacious anti-ulcer agents.
Methods: Effect of anti-ulcer activity of fish oil and Arasco oil was evaluated in different animal models of ulcers i.e. ethanol induced, water immersion and pyloric ligation techniques. The Superoxide dismutase activity in gastric tissue was also ascertained in two groups of animals. The animals received either fish oil (40 µl, PO), Arasco oil (40 µl, PO), omeprazole (20 mg/kg PO) or ranitidine (30 mg/kg PO). The gastro-protection was calculated based on ulcer index, pH and gastric juice volume.
Results: The results of this study suggest that poly unsaturated fatty acid (PUFA) contained in fish oil and Arasco oil have moderate anti-ulcer activity although probably lesser in potency than the available anti-ulcer drugs like omeprazole and ranitidine.
Conclusion: These results have shown that PUFA containing oils provided moderate gastrointestinal protection in all the induced ulcer models employed. Thus it can be concluded that PUFA containing oils like the Fish oil and Arasco oil have anti-ulcer properties and the mechanisms involved in these actions need to be investigated.

Keywords: PUFA, Ethanol, Ulcer, Omeprazole, Rats, Gastric juice, Pyloric

INTRODUCTION

Peptic ulcer diseases comprise of heterogeneous disorders, which manifest as a lesion in the lining of the gastrointestinal mucosa bathed by acid and pepsin. It is the most predominant of the gastrointestinal diseases[1,2] with a worldwide prevalence of about 33% in the developed countries and 50% affliction in humans in the developing countries due to H. pylori infection. It is generally recognized that peptic ulcer is caused by a lack of equilibrium between the gastric aggressive factors and the mucosal defensive factors.[3] However, the peptic ulcer, characterized by mucosal damage, is predominantly caused by Helicobacter pylori or anti-platelet agents such as acetylsalicylic acid,[4] Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and oral bisphosphonates, potassium chloride, immunosuppressive medications,[5] serotonin reuptake inhibitors,[6] alcohol consumption, as well as cigarette smoking.[7] Symptoms of peptic ulcer disease include abdominal pain, vomiting, and reflux symptoms. Other general symptoms of peptic ulcer disease include loss of appetite and weight.[8] The disease may lead to upper gastrointestinal haemorrhage and perforation,[9] which may have high morbidity and mortality rates. In the majority of cases, H. pylori increases the production of reactive oxygen species

(ROS) and Reactive Nitrogen Species (RNS) in the human stomach[10] which results in oxidative stress on the gastric mucosa.[11] NSAIDs can cause submucosal erosion and inhibit cyclooxygenase, which reduces the formation of prostaglandins and weakens the protection by the gastric mucosal layer.[12] In spite of the multifaceted pathogenesis of peptic ulcers, increased secretion of gastric acid is still recognized as a critical aetiological factor of this disease. Therefore, the main therapeutic target is to control acid secretion using antacids, H_2 receptor blockers (ranitidine and famotidine), or proton pump inhibitors (omeprazole and lansoprazole).[13] The combination of antacids, antisecretory drugs, and antimicrobial agents has been suggested for peptic ulcer treatment. A combination treatment of H_2 receptor antagonists such as the H_2 receptor antagonists famotidine and ranitidine,[14] proton pump inhibitors,[15] and clarithromycin, amoxicillin, or metronidazole serves as the routine standard therapeutic regimen. Although various endoscopic and pharmacological therapies are available for peptic ulcer disease, these treatments mostly show limited efficacy against gastric diseases and are often associated with moderate side effects. In contrast, natural products have shown effective therapeutic properties with reduced side effects,[16] and several studies have been performed in this area.[17] In addition, the pharmaceutical industry has become more inclined to investigate the advantages of herbal therapeutics. Looking at the importance of PUFAs in various clinical disorders, it has been suggested that deficiency of PUFAs especially gamma-linolenic acid, di-homo-gamma-linolenic acid, arachidonic acid & eicosapentaenoic acid may be responsible for peptic ulcer.[18,19] PUFAs have the ability to inhibit the growth of helicobacter pylori, suppress acid production both in experimental animals and in humans and also improve liver conditions like the acute hepatitis C.[20,21] PUFAs could heal the ulcer and offer cytoprotective action by increasing PGE_1. The primary objective of the study was to analyze the anti-ulcer and ulcer-healing activity of PUFA. The present study was undertaken to investigate anti-ulcer effect of polyunsaturated fatty acids in experimentally induced ulcer models in rats.

METHODS

Animals used

Wistar albino rats of either sex weighing between 250-300 g were utilized for this study. The animals were placed randomly and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at temperature of 24 ± 2°C and relative humidity of 30-70%. A 12:12 dark: light cycle was followed during the experiments. All the animals were allowed to free access to water *ad libitum* and fed with standard commercial pelleted rat chaw (M/s. Hindustan Lever Ltd., Mumbai). All the experimental procedures and protocols used in this study were reviewed by the institutional animal ethical committee and were in accordance with the guidelines of the CPCSEA.

Drugs and chemicals

Fish oil - an n3 rich oil Maxepa (EPA & DHA) was procured from Merck, India and Arachidonic acid - rich in n6 from the Cayman chemical, USA were used as source of PUFAs. Omeprazole (OMEZ) Sigma, USA were suspended in 1% Sodium Carboxy Methyl Cellulose (SCMC) and administered to the animals for anti-ulcer studies. All drugs are administered orally. Fish oil – an n3 rich oil and Arasco - rich in n6 AA were used as source of PUFAs. Anti-ulcer drugs, ranitidine and omeprazole (OMEZ) were suspended in 1% Sodium Carboxy Methyl Cellulose (SCMC) and administered to the animals for anti-ulcer studies. All drugs were administered orally. The reagents and chemicals used for superoxide dismutase activity were procured from Sigma and Fisher chemicals.

Ethanol induced ulcer (Mucosal damage)

Ethanol (absolute) induced gastric lesions are a reproducible method in experimental animals.[22] Wistar rats, weighing 250 to 300 grams are used for the experiment. The animals were fed with Standard animal feed. They are fasted for 12 hours but given water *ad libitum.* After this, 0.1 % tween 80, given to the animals orally. One hour later, 1 ml/200 gm b.w. of absolute 99.9% ethanol was given orally to each rat. After one hour the animal were euthanized with excess of anesthetic ether and stomach was dissected and opened along the greater curvature, residual matter was cleared with saline and the inner surface was examined for ulcer lesions in the glandular region using magnifying lens and degree of severity of ulcer was graded.

Water immersion (Swim) stress Induced gastric ulcer

The technique used was based on earlier published work.[23] Wistar albino rats were divided into six groups of 6 each (n=6). The ulcer was induced from group I to group V by fasting the animals for 24 hours and forced to swim in the glass cylinder (height 45 cm, diameter 25 cm) containing water to the height of 35 cm maintained at 25°C for 3 hours. The group I served as normal control. The drug solutions were prepared and given as 0.2 ml/200g of body weight, 20 minutes prior to forced swimming. The different groups were assigned as described below.

Pyloric ligation method

Fish oil or AA - rich oil or vehicle control or positive control drug was administered 20 minutes prior to pyloric ligation. Under light ether anaesthesia, the abdomen was opened and pylorus was ligated. The abdomen was then sutured. At the end of 4 hours after ligation, the animals were sacrificed with excess of anaesthetic ether, and the

stomach was dissected out. Gastric juice was collected and its volume was measured. The glandular portion was then exposed and examined for ulceration and ulcer index was determined.[24]

Estimation of superoxide dismutase

Superoxide dismutase activity was evaluated based on earlier method.[25] To 0.25 ml of tissue homogenate, 0.75 ml of ethanol and 0.2 ml of ice cold chloroform were added and centrifuged. The supernatant was taken and 0.6 ml of 0.6 nM EDTA solution and 1.2 ml of buffer (0.1 M pH 10.1) were added and mixed well. The reaction was initiated by the addition of 0.5 ml of fresh epinephrine (1.8 nM) and the increase in absorbance was measured at 480 nm. The reaction mixture without tissue homogenate was used as blank. The enzyme activity was expressed as U/ml.

Statistical analysis

All the data's were expressed as mean ± SEM. The statistical analyses were carried out by one way analysis of variance (ANOVA) followed by Dunnett's test using Graphpad Prism Instat version 3. Statistically significant difference was ascertained by '*P*' value which is considered significant at the level of $P<0.05$ and highly significant at $P<0.001$.

Determination of various parameters

The determination of the ulcer index was done based on previous methods.[26]

Determination of ulcer index (UI)

The ulcerative index was calculated by severity of gastric mucosal lesions and graded as below;

Score	Erosions
1	1 mm or less
2	1-2 mm
3	More than 2 mm

Then UI was calculated by using the formula:

UI = 1 (No. of lesions of score 1) + 2 (No. of lesions of score 2) + 3 (No. of lesions of score 3)/10

Then the overall score was divided by a factor 10, which was designed as ulcer index.

$$\% \text{ gastro protection} = \frac{(\text{UIC} - \text{UIT})}{\text{UIC} \times 100}$$

Where,
UIC - Ulcer index of Control,
UIT - Ulcer index of Test

Determination of free acidity

The free acidity was calculated as per previously shown formula.[27]

1. Gastric juice (1 ml) was taken in to a 100 ml conical flask, to this 2-3 drops of Topfer's reagent was added and titrated with 0.01 NaOH until all traces of red colour disappears and the colour of the solution turns yellowish orange (end point).

2. The volume of alkali added was noted. This volume corresponds to free acidity.

3. 2-3 drops of phenolphthalein solution was added and titration was continued until a defined red tinge reappears.

4. The volume of alkali added was noted which corresponds to total acidity. Acidity was calculated by using the formula:

Acidity (mEq/Litre) = Volume of NaOH x Normality of NaOH x 100/0.1 gm

RESULTS

The results of this study are depicted in Table 1 & 2.

Based on our results the PUFA containing oils i.e. fish oil and Arasco oil were able to attenuate the ulcer index although to a lesser extent than the pharmaceutical drugs. For e.g. the reduction seen in ulcer index with fish oil and Arasco oil was 35.16% and 32.14% in ethanol induced ulcers as compared with ranitidine and omeprazole causing a reduction in 71.04 % and 75.13% which was highly significant.

A similar trend was seen with ranitidine and omeprazole in the swim stress induced ulcers i.e. reduction of 30.58 % and 42.95 % in ulcer index as compared the PUFA containing oils i.e. fish oil and Arasco oil showed a decrease of 20.82 % and 24.72% only respectively.

A similar trend was seen with the pyloric ligation induced gastric juice volume i.e. the volume was only 2.9 ml ranitidine treated animals but was 5.61 and 6.03 ml in fish oil and Arasco oil treated animals.

A similar pattern was seen in free acidity levels as shown in Figure 2.

The activity of the superoxide dismutase was ascertained in two groups of few animals. The superoxide dismutase levels were slightly decreased in ulcerative control animals but were moderately increased with omeprazole.

Data still preliminary and not depicted in this article.

Table 1: Effect of fish oil and Arasco oil in comparison with standard drugs on ulcer index and % gastro protection in ethanol induced gastric ulcer in rats.

Group No.	Treatment (mg/kg)	Ulcer index (Mean ± SEM)	% gastro protection
Gp-I	Ulcerated control (Ethanol 1 ml/200 gm, p.o.)	5.63 ± 0.18	-
Gp-II	Ranitidine (30 mg/kg, p.o.), 20 minutes prior to swim stress	1.63 ± 0.10**	71.04
Gp-III	Omeprazole (20 mg/kg, p.o.) followed by ethanol treatment.	1.40 ± 0.18**	75.13
Gp-IV	Fish oil (40 µl/day, p.o.) followed by ethanol treatment.	3.65 ± 0.21*	35.16
Gp-V	AA-Rich oil (40 µl/day, p.o.) followed by ethanol treatment.	3.82 ± 0.75*	32.14

Values are expressed as mean ± SEM (n=6), *P <0.05 and **P <0.01 compared to ulcerated control group. The data were analysed by one-way ANOVA followed by Dunnett's test.

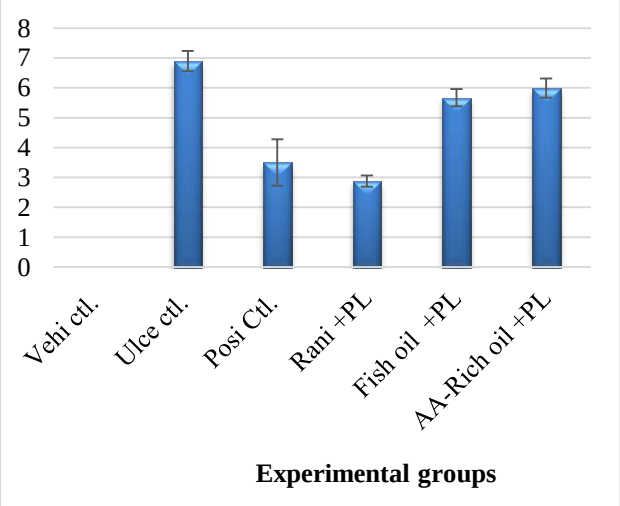

Figure 1: Pyloric ligation.

Values are expressed as Mean ± SEM. V. Control - Vehicle control, U. Control - Ulcerative control, Pos. Control - Positive control, Rani + EtOH - Ranitidine and pyloric ligation FO + EtOH - Fish oil in ethanol treatment, AA + EtOH - Arachidonic acid in ethanol treatment.

Table 2: Effect of fish oil and Arasco oil in comparison with standard drugs on ulcer index and % gastro protection on water immersion (swim) stress induced gastric ulcer in rats.

Group No.	Treatment (mg/kg)	Ulcer index (Mean ± SEM)	% gastro protection
Gp-I	Ulcerated control (Swim stress control)	4.61 ± 0.18	-
Gp-II	Ranitidine (30 mg/kg, p.o.) 20 minutes prior to swim stress	3.2 ± 0.10**	30.58
Gp-III	Omeprazole (20 mg/kg, p.o.) 20 mins prior to swim stress.	2.63 ± 0.18**	42.95
Gp-IV	Fish oil (40 µl/day, p.o.) 20 mins prior to swim stress.	3.65 ± 0.21	20.82
Gp-V	AA-Rich oil (40 µl/day, p.o.) 20 mins prior to swim stress.	3.47 ± 0.75*	24.72

Values are expressed as Mean ± SEM (n=6), *P <0.05 and **P <0.01 compared to ulcerated control group. The data were analysed by one-way ANOVA followed by Dunnett's test.

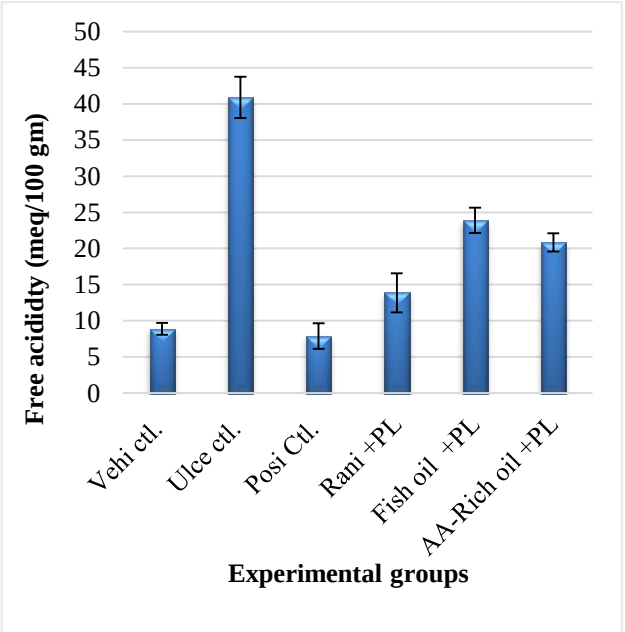

Figure 2: Free acidity.

Values are expressed as Mean ± SEM. V. Control - Vehicle control, U. Control - Ulcerative control, Pos. Control - Positive control, Rani + PL, FO + EtOH - Fish oil in ethanol treatment, AA + EtOH - Arachidonic acid in ethanol treatment.

DISCUSSION

The gastric acid is an important contributor for the genesis of ulceration in experimentally induced animal models. Current gastric ulcer therapies show moderate efficacy against gastric mucosal lesions/ulceration but are often associated with several side effects.[8] There is always look out for more nutraceuticals based therapy for gastric ulcer disorders like the gastric/peptic ulcers. Hence the studies are done on natural products which can either settle peptic ulceration or reduce hyperacidity to a normal level so that stomach can functions its physiological role. PUFA are such agents that can come to some expectations in this regard. They may or may not be as good as modern medicines used in hyperacidity or peptic ulceration, however they can allow stomach to function normally which can serve the purpose and balance can be established in this regard.

The secretion of gastric acid can increase the incidence of peptic ulcer disease. Maintaining secretion at a normal level is the main therapeutic target. Stress can arise from prolonged anxiety, tension, and emotion, severe physical discomfort, haemorrhage and surgical shock, burns and trauma, thereby resulting in severe gastric ulceration.

Currently the experimental *in vivo* models still are the best and cost effective way to evaluate the efficacy and potency of novel anti-ulcer drugs and their mechanisms. In this study, we used three models of ulcer formation i.e. ethanol induced ulcers, swim stress induced ulcers and the pyloric ligation induced ulcers. The data obtained from our study suggests that the PUFA containing oils used in this study i.e. the fish oil and the n-6 PUFA containing Arasco oil were able to attenuate the ulcer formation as calculated based on the ulcer index. The results are shown in Table 1 and Table 2. There was also an associated reduction in the acid formation as evaluated by free acid levels.

Several studies suggest that the EtOH-induced gastric lesions are thought to arise as a result of direct damage of gastric mucosal cells, resulting in the development of free radicals and hyperoxidation of lipid.[21] EtOH treated rats showed a significant increase in plasma concentrations of the gastric hormone, gastrin and an increase in the gastric mucosal H^+K^+ATPase activity. The H^+K^+ATPase is the dimeric enzyme responsible for H^+ secretion by the gastric parietal cells. H^+K^+ATPase is selectively blocked by the action of Lansoprazole, an acid blocker used to treat gastric ulcers.[28] Activation of cAMP pathway stimulates the H^+K^+ATPase on parietal cells, a high capacity proton pump,with its insertion into the apical membrane leads to the formation of a secretory canaliculi.[29] In the recent years, the drugs that reduce the acid secretion and H^+K^+ATPase inhibition have become preferred therapeutic choice due to their clinical efficacy.[30] The inhibition of H^+K^+ATPase results in the reduction of gastric acid secretion,[31] which is concordant with the present study. While the Pylorus ligation-induced gastric ulcerations are caused by enhanced acid–pepsin secretion leading to auto digestion of the gastric mucosa and breakdown of mucosal barrier. A copious amount of gastric mucus is secreted during superficial mucosal damage and provides a favorable microenvironment in repair by restitution. Hence, estimation of mucin secretion is valuable for the study of mucosal defensive mechanisms against ulcerogens. While on the other hand the water immersion stress-induced ulcers are caused by an increase in gastric acid secretion[32] and decreases in mucosal microcirculation and mucus content.[33] It decreases mucin, surface active phospholipids bicarbonate secretion, mucosal proliferation and also produces damage by formation of free radicals.[34]

Fish oil showed significant ulcer protective effect in different experimental models, whose aetiopathogenesis of ulceration are different. Dietary supplementation with n-6 fatty acid rich in LA has been found to influence the physiological function of various blood components, producing an inhibitory effect on leucocyte adhesion, platelet count, platelet aggregation and collagen formation.[35] From these studies it can be suggested that the cytoprotective effects of the n-6 fatty acids in the present study could also be attributable to modulation of leucocyte adhesion.[35] In conclusion, this study has shown that PUFA has a significant anti-ulcer and cytoprotective effect on various experimentally induced gastric lesions. Thus in the present study the PUFA containing oils protected albeit to a lesser extent than commercially available drugs. We also investigated some preliminary effects of omeprazole on the superoxide dismutase activity and our initial results suggest that there is moderate increase in the activity of this enzyme and this is a good pointer to its mechanism in ulcer healing using the free radical scavenger systems.

Dietary supplementation with n-3 PUFAs improved colonic anastomoses healing. n-3 PUFAs enhance the colonic wound healing in a rat model. Finally, n-3 PUFAs may prompt faster resolution of inflammation within the wound microenvironment, which leads to facilitated regeneration and re-epithelialization. A small randomized controlled trial evaluated a formula supplemented with fish oil in patients with pressure ulcers and noted decreased progression of pressure ulcers in those receiving fish oil supplementation.

There is growing evidence that the diverse biological roles of n-3 PUFAs contribute to their regenerative actions against chronic inflammatory disease. This could effectively help resolve the inflammation and promote a transition from the inflammatory to the proliferative and remodeling phases of wound healing. n-3 PUFAs can be incorporated into membrane phospholipids, which causes reduced membrane fluidity. It could be associated with lipid raft assembly and function. Lipid rafts are cholesterol-rich microdomains at the host cell surface and

are required for NF-κB-dependent responses to H. pylori. Recently, several studies have suggested that n-3 PUFAs can be converted into bioactive mediators, including resolvins, which exert inflammation-resolving properties via counterregulation of lipid mediators including proinflammatory leukotriene (LTs) and prostaglandin (PGs). Thus, some research groups have investigated long-term treatment of n-3 PUFAs in an H. pylori-infected animal model and found that n-3 PUFAs administration ameliorated H. pylori-induced gastric inflammation and atrophic gastritis.[36] It also reduced the incidence of H. pylori-associated gastric carcinogenesis. This could be the first group to document the rejuvenating action of n-3 PUFAs on H. pylori-associated atrophic changes in stomach.[37] As the use of n-3 PUFAs for treatment of H. pylori-induced GI disorders is rapidly moving into clinical settings with more studies explaining the mechanism of action, detailed randomized controlled trials are required to obtain strong evidence for the incorporation n-3 PUFAs into the therapeutic armamentarium in near future.

EPO also known as the evening promise oil and a herbal product is effective orally against gastric secretion and gastric damage in various experimental models. The results of some studies show that EPO prevents an increase in acid secretion in pylorus-ligated rats, and inhibits the formation of gastric ulcers induced by different ulcerogenic drugs, by cyto-destructive agents and by stress caused by hypothermic restraint. Several studies have shown that EPO or PUFAs of n-6 series reduce gastric damage in humans and experimental animals.[38,39] Biochemical events, are the factors possibly contributing to the processes underlying ulcerogenesis, in the present experimental models. It is therefore speculated that the anti-secretory activity of PUFA may account for antiulcer activity in various experimental models used in the present study, where gastric secretion is involved in the pathogenesis of gastric ulcers. These results have shown that PUFA containing oils provided moderate gastrointestinal protection in all the induced ulcer models. Thus it can be concluded that PUFA containing oils like the Fish oil and Arasco oil have anti-ulcer properties and the mechanisms involved in these actions are being investigated.

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