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Evaluation Of The Antiulcer Activity Of Aqueous-Ethanolic Extract OfThe Brown Algae "*Cystoseira Sensu Lato*" In Rats

Djahida HADJ MERABET [1*] (ORCID iD: 0009-0007-7561-6159) , Nour el Houda BRAHIMI [2] , Fayza BAGHLI [3], Kaddour Hicham BENARIBA[4] , Djihene BALI[4], Asma RAHMOUN[4]

[*1] Laboratory of Physiology, Physiopathology and Biochemistry of Nutrition, Department of Biology, Faculty ofNatural and Life Sciences, Earth and Universe, University of Tlemcen, Algeria.

[2]University Abou Bekr BELKAID , Faculty of Natural sciences and life, earth and universe , Department of Biology , Tlemcen, Algeria

[3]Laboratory of Organic Chemistry, Natural Substances, and Analysis, Faculty of Natural and Life Sciences, Earthand Universe Sciences. Department of Biology. University of Tlemcen, Algeria.

[4]Laboratory of Natural Products, Department of Agronomy, Faculty of Natural Sciences Earth and Universe,University of Tlemcen , Algeria

Corresponding author: Djahda HADJ MERABET

Laboratory of Physiology, Physiopathology and Biochemistry of Nutrition, Department of Biology, Faculty ofNatural and Life Sciences, Earth and Universe, University of Tlemcen, Algeria.

e-mail: djahida.hadjmerabet@univ-tlemcen.dz & hadjmerabetd@gmail.com

Tel : 213 553 933 653

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Abstract

Background.The present study was carried out to evaluate the anti-ulcer activity of the brown seaweed "Cystoseira sensu lato".Methods. An acute toxicity study of the aqueous ethanol extract and the powder of "Cystoseira sensu lato" on wistar rats were carried out, and the LD50 were determined. Various concentrations of the brown seaweed (50, 100, and 150 mg/kg) were used to determine the anti-gastric ulcer activities of the algae in rats in an ethanol-induced model and the ED50 was determined .Omeprazole (50 mg/kg) was used as a reference drug. Results. The data obtained showed a zero degree of toxicity with an LD50 equal to 10,000 mg/kg. A strong anti-ulcer effect was noted for C. sensu lato algal powder.The different doses of seaweed (50, 100 and 150 mg/kg) significantly reduced the percentage of ulceration with a high percentage of inhibition. It was found that "Cystoseira sensu lato" at 150 mg/kg gave a maximum effect in reducing gastric ulceration .By following the dose-effect curve, we can estimate ED50 at 75 mg/kg. Conclusion.The study showed that the brown algae "Cystoseira sensu lato" possess remarkable antiulcer activity .It would therefore be interesting to carry out further studies to confirm other therapeutic activities of this miraculous algae.

Keywords: "Cystoseira sensu lato", Anti-ulcer activity , Wistar rats , Aqueous-Ethanolic extract

1. Introduction

Digestive diseases now affect almost one person in five. They represent a major public health problem, especially as they are increasing at an unexplained rate. Gastric ulcer is one of the major digestive disorders in the world, affecting 10% of the world's population **[1-2]** .This clinical condition represents a worldwide health problem because of its high morbidity, mortality and economic loss **[3-4]** Gastric ulcer is an erosion in the lining of the stomach, basically it corresponds to an inflamed rupture in the skin of the mucosa lining the digestive tract **[5]** Ulceration is the ultimate consequence of a disequilibrium between aggressive injurious factors and defensive mucosa-protective factors**[6]** The most common cause of gastrointestinal ulcer disease are infection with Helicobacter pylori (H. pylori) **[7]** and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen **[8].** Many drugs have been used to treat this condition, including antacids, H2 antihistamines, topicals or gastrointestinal dressings, proton pump inhibitors, antagonists. However, many of them not only produce side effects, including osteoporosis **[9]**, arrhythmia, diarrhea, hypersensitivity, impotence, hypergastrinemia **[10],** they are also expensive. Hence the need to look for another source suitable for medicinal plants considered as an alternative therapy, for the treatment and management of gastric ulcers **[11]**. Among these resources, marine organisms are a rich source of structurally novel and biologically active metabolites. Recently, researchers have described a wide range of biological activities for algal compounds including anti-HIV, anti-neoplastic, cytotoxic and antipyretic activities. Secondary or primary metabolites produced by these organisms may be potential bioactive compounds of interest to the pharmaceutical industry. These active principls include seaweed polysaccharides, which are highly active natural substances with interesting applications. The best-known polysaccharides found in brown algae are alginates and fucoidans. Algeria is characterized by an algal diversity due to its geographical location and rich topography. However, knowledge of algae is limited to inventories and ecological studies carried out in the centre and west of the country **[12;13;14;15;16;17;19]**.
Our study aimed to evaluate the anti-ulcer activity of the brown seaweed *'cystoseira sensu lato'*, a seaweed that has never been used as an anti ulcer. Our project is an innovative idea that falls within the Decree 1275. The brown alga *'cystoseira sensu lato'* is very rich in secondary metabolites and contains more than 50% of its weight of active ingredients including alginate, fucoidan and laminarin.

2. Materials and Methods

2.1 Algal material

The brown algae "cystoseira sensu lato" (Fig 01) was collected in the coastal region of Mostaganem (Northwest Algeria), in February 2023, at a depth between 1 and 4 m which is located between the beach "La Crique" and the other end of the salamander port "Front de mer, W384+WV9, Mostaganem" – city of Mostaganem (35° 56′ 00″ north, 0° 05′ 00″ east). The

species of algae was identified and authenticated by 'Myriam Benali' algae specialist at the University of Algiers through detailed observation of different vegetative parts and reproductive systems of the algae. The freshly collected seaweed fronds were first washed in sea water, then rinsed in distilled water to eliminate all possible impurities: salts, sand, shells and epiphytes to avoid all risks of contamination.

2.2 Preparation of the extracts

Part of the algal material was air-dried, protected from light and humidity, for three weeks, and another part was dried using an oven at a temperature of 40°C for 72 hours. Once dried, the algal material was ground into powder using a brand-name electric grinder (RM 200), and stored in a dark place in the refrigerator until use.

Under optimal temperature and darkness conditions that ensure the preservation of the seaweed's bioactive compounds, the crude extracts of the seaweed species are obtained by maceration. This method involves leaving a quantity of each powder previously obtained in contact with a volume of extraction solvent.

The technique involves placing 10 g of seaweed powder in 100 ml of solvent (ethanol-water(1:1)). The mixture obtained is then subjected to continuous maceration in the dark with mechanical stirring in a shaker-incubator at room temperature (25°C) for 24 hours. After 24 hours, filtration was carried out under vacuum using N°1 wattman paper. The extracts obtained were centrifuged at 3500 rpm for 10 min at 4°C and filtered. The filtrate obtained was evaporated under reduced pressure using a Hahnvapor HS-2005-N rotary evaporator. Thus obtained residual extracts were kept in desiccator for further investigation. The yield of the aqueous-ethanol extract was 9.26% w/w.

2.3 Experimental Animals

Healthy adult Wistar albino rats of either sex, weighing between 150 and 300 g were used in the experiments. The animals were acclimatized to laboratory conditions of temperature, humidity (60±5%), 12 h light-dark cycles and fed with standard pellet diet and water *ad libitum* and the principles of laboratory animal care were followed. The animals were fasted for 16 h, and were provided with water alone before the commencement of experiments. The experiments were carried out in the Department of Biology LAPRONA research laboratory at the University of Tlemcen. Experimental procedures were conducted in accordance with the guidelines provided by the Institutional Animal Ethics Committee.

2.4 Acute oral toxicity

Wistar rats weighing about 150-300g were used for acute toxicity study. The study was carried out as per the Organization for Economic Co-operation and Development guideline for the evaluation of acute oral toxicity (OECD, 2001) **[20]**.

Five (5) batches (n=4) of either sex selected through random sampling technique were formed, including one control group. The day before the treatment, all the rats were weighed and starved

for, but had water at their disposal until 3 hours before the administration of the extract. They were weighed again the next day before the force-feeding.
For the first stage, the batch 1(control) received 1 ml of distilled water per 100 g body weight and the rats of the four other batches received each the suspension of aqueous-ethanol extract (w/v) in graded doses (150,300, 500, 800 mg/kg) body weight by oral administration .

The animals were observed individually for the first 30 minutes. Particular attention was paid to the animals for the first 4 hours in order to detect any signs of toxicity. Observation was extended to 24 hours and then daily for a total of 14 days. Animals were observed individually for signs of toxicity or pre-terminal death and recorded if they occurred. Once a week, the individual body weights of all animals were monitored to determine any drastic changes. The color and consistency of the feces as well as changes in the animal's coat and skin, mucous membranes (nasal) and eyes were observed weekly.
Physical observations such as changes in the circulatory (heart rate), respiratory (rate), autonomic (piloerection, lacrimation, salivation, urinary incontinence and defecation) and central nervous (drowsiness, ptosis, gait, eye prominence, eyelids) systems were observed weekly.
As there were no deaths after the first day, the same protocol was repeated 24 hours later with C.sensu lato powder with the doses (2500, 5000 et 10 000 mg/k).
Finally, the number of survivors was noted and LD50 was described by Behrens and Karber method [**21]**

2.5 Gastric ulcer activity

2.5.1 Gastric ulcer Modele

In order to test the gastro-protective effect of the active components of the brown algae "*cystoseira sensu lato*" on wistar rats, gastric lesions were induced by an ulcerogenic agent, ethanol (80%).
Thirty six wistar rats made up of equally distributed males and females, were randomly divided into nine groups, with four animals/group. They were deprived of food and water for 24 hours and 1 hour respectively, preceding the experiment. The rats from the different groups were weighed and marked before the intragastric administration of the different treatments. The groups used were divided as follows:

Group I: Normal control group: In this group, the animals received normal saline.
Group II: Disease control group: Ulceration group: ulceration was induced by administration of 80% (v/v) ethanol (5 mL/kg body weight).
Group III: Standard drug treatment group: These animals received omeprazole (50 mg/kg body weight in distilled water) given as a single oral dose at 2 h prior to ethanol administration.

Group IV , V & VI The animals received the powder of the brown algae "*cystoseira sensu lato*" at graded doses (50, 100 and 150 mg/kg body weight) respectively in distilled orally at 2 h prior to administration of 80 % (v/v) ethanol.

Group VII , VIII & IX The animals received the powder of the brown algae "*cystoseira sensu lato*" at graded doses (50, 100 and 150 mg/kg body weight) respectively in distilled orally at 2 h after administration of 80 % (v/v) ethanol.

Rats were sacrificed by cervical dislocation under chloroform anaesthesia. The stomachs were removed following ventromedial dissection, then opened along the greater curvature, washed with saline and finally spread out on a watch glass to better observe the lesions formed. gastric juice was collected and centrifuged at 3000 rpm for 30 minutes. The total volume of gastric juice, its pH, and total acidity were estimated. Observations were made with the naked eye and a binocular magnifier at 0.8X and 2.5X magnification.

2.5.2 Evaluation of anti-ulcer activity

The score method was used to evaluate the inhibitory action and treating effect of the brown algae "*cystoseira sensu lato*" on induced ulcer in rats by comparing it with the standard treatment Using the observations, the degree of gastric lesions is organised into scores, these were presented as follows **[22]**:

A score for the ulcer was made as follows:

- 0: normal colouration;
- 0.5: red colouration;
- 1: spot ulcers;
- 1.5: haemorrhagic streaks;
- 2: ulcers >3 mm but < 5 mm;
- 3: perforation.

The average of the ulceration scores for each rat gives the ulceration index.

In addition, the ulcer index and the percentage of ulcer inhibition were determined by measuring the overall mucosal surface area as well as the total ulcerated surface area. The ulcer index (U.I.) was determined according to the method used in previously published work **[23]**, applying the following equation:

$$U:I = \frac{\text{Ulcerated area}}{\text{Totalstomacharea}} \times 100$$

The % inhibition of ulceration was calculated as follows:

$$\%\text{Inhibition} = \frac{\text{Ulcer index of control} - \text{Ulcer index of test}}{\text{Ulcer index of control}}$$

2.6 Statistical analysis

Statistical analyses were performed with SPSS ver.16, professional edition using ANOVA analysis. Differences were considered significant at $p < 0.05$.

3. Results

3.1 Acute oral toxicity

Single oral administration of 150, 300, 500 and 800 mg/kg of the aqueous-ethanol extract of the brown seaweed "*cystoseira sensu lato*" did not result in any mortality. In addition, no clinical signs of toxicity were recorded. Thus, this brown alga extract was reported to have an LD50 greater than 800 mg/kg body weight. The LD50 was determined using the arithmetic method of Karber and Behrens **[21]**.

DL100= 800mg/kg therefore DL50= DL100 - Σ (ab)/n = 800 - 0 = 800 mg/kg

Single oral administration of 2500, 5000 and 10,000 mg/kg of the brown seaweed powder "*cystoseira sensu lato*" resulted in no mortality. Furthermore, no clinical signs of toxicity were recorded. Thus, this brown algae powder would have an LD50 greater than 10,000 mg/kg body weight. The LD50 was determined by the arithmetic method of Karber and Behrens **[21]**

LD100= 10,000mg/kg therefore LD50= LD100 - Σ (ab)/n = 10,000 - 0 = 10,000 mg/kg

3.2 Anti ulcer activity

This study enabled us to evaluate the degree of protection of the brown seaweed "*cystoseira sensu lato*" on the gastric mucosa against ulcerations caused by the ulcerogenic agent Ethanol (80%) .

3.2.1 Macroscopic observations

The normal control group (GI), which did not receive ethanol, had intact stomachs with a normal appearance (Fig 02).

Rats given ethanol (disease control group) (GII) developed characteristic gastric lesions in the glandular portion of the stomach, represented by ulcerations, reddish or even blackish appearance of the mucosa, oedema, haemorrhages and erosions. (Fig 02)

Unlike the stomachs of rats treated with omeprazole 50mg/kg (GIII), which had an almost normal appearance, omeprazole, which is a recognised gastro protective drug, largely reduced the ulcerations observed in the (GII) (Fig 02).

Test groups GIV, GV and GVI, pre-treated with the brown seaweed "*cystoseira sensu lato*" at concentrations of 50, 100 and 150 mg/kg, showed protection and a visible reduction in gastric lesions and ulcerations compared with the lesions and ulcerations observed in group (GII) (Fig 02).

Similarly, the GVII, GVIII and GIX test groups treated with "*cystoseira sensu lato*" brown seaweed at concentrations of 50, 100 and 150 mg/kg showed protection and a reduction in visible

gastric lesions and ulcerations compared with the lesions and ulcerations observed in group (GII) (Figure 02).

3.2.2 Ulcer Index (Score)

The protective effect of the brown alga powder "*cystoseira sensu lato*" significantly reduced gastric lesions in pre-treated and treated rats, as indicated by the ulcer index calculated from the scores of macroscopic observations (Table 01&02)

Our results show that "*cystoseira sensu lato*" brown alga powder at 50, 100 and 150 mg/kg significantly reduced the percentage of ulceration with a high percentage of inhibition.
It can also be seen that the brown alga powder "*cystoseira sensu lato*" at 150 mg/kg gave a maximum effect in reducing gastric ulceration.
By following the dose-effect curve, we can estimate the ED50 of the brown alga "*cystoseira sensu lato*" at 75mg/kg.

4. Discussion

The purpose of the present study is to study the anti ulcer activity of brown seaweed. More precisely, the object of the present invention is a process for manufacturing an anti-ulcer food supplement based on brown algae of the "*cystoseira sensu lato*" type.
Acute toxicity study of the aqueous-ethanol extract and the powder of "cystoseira sensu lato" showed no mortality up to 10000 mg/kg body weight.
According to the Hodge and Sterner (2005) toxicity scale guideline **[24]** (Table 03), this plant would be almost non-toxic or relatively harmless depending on whether the LD50 is between 5,000 and 15,000 mg/kg or greater than 15,000 mg/kg body weight. This potentiality supports its safety as a pharmaceutical substance.

Table 03. Hodge and sterner toxicity scale [24]

S. No.	Term	LD50 (Rat, Oral)
1	Extremely Toxic	Less than 1 mg/kg
2	Highly Toxic	1- 50 mg/kg
3	Moderately Toxic	50 - 500 mg/kg
4	Slightly Toxic	500 - 5000 mg/kg
5	Practically Non-Toxic	5000 - 15,000 mg/kg

When compared to the Group I normal control, all the groups pre treated and treated of brown seaweed "cystoseira sensu lato" showed antiulcer activity

The protective effect of the brown seaweed powder "*cystoseira sensu lato*" significantly reduced gastric lesions in pre-treated and treated rats, as indicated by the ulcer index calculated from the scores of macroscopic observations. There was a significant difference between the GII and the various III, IV, V, VI, VII, VIII and IX groups.

Our results show that the powder of brown alga "*cystoseira sensu lato*" at 50, 100 and 150 mg/kg, significantly reduced the percentage of ulceration with a significant percentage of inhibition. The volume of gastric secretion and total acidity was significantly reduced in all drug pre treated and treated groups as compared to disease control.

It can also be seen that the brown alga powder "*cystoseira sensu lato*" at 150 mg/kg gave a maximum effect in reducing gastric ulceration.

By following the dose-effect curve, we can estimate the ED50 of the brown alga "cystoseira sensu lato" at 75mg/kg.

Peptic ulcer disease is one of the most common gastroenterological diseases. Peptic ulcer disease affects almost 10% of the world's population, with an overall incidence of 3 new cases per 100,000 populations **[25]** Brown macro-algae are important raw materials for commercial food supplements. Depending on the species, various extracts such as polysaccharides, phenolic compounds, pigments and minerals are extracted and used in food supplements. the composition of brown seaweed is rich in bioactive compounds (Fucoidan , Laminarins , Fucoxanthin , alginate) which have been the subject of research in terms of protection against inflammation, diabetes, cancer and many other diseases **[26&27&28]**

Several studies have examined the gastroprotective effects of fucoidan on gastric ulcers induced by ulcerogenic agents. The researchers found that administration of fucoidan reduced ulcer formation, decreased oxidative stress and improved antioxidant enzyme activity, suggesting its potential as a protective agent against gastric ulcers. Fucoidan is a sulphated polysaccharide found mainly in various species of brown seaweeds. **[29&30]**

5. Conclusion

The aim of this work was to evaluate the anti-ulcer potential of the brown alga "cystoseira *sensu lato"*. Its choice was dictated by its richness in bioactive components and its significant antioxidant power. However, the literature review carried out showed that this plant had never been tested for its gastro-protective effects.

Our experimental procedure was carried out by applying the ethanol-induced ulceration model which can be used to test the anti-ulcer potency of the algal powder. Our results show that the brown alga powder "cystoseira sensu lato" at 50, 100 and 150 mg/kg, significantly reduced the percentage of ulceration with a significant percentage of inhibition. We also noted that the brown alga powder 'Cystoseira sensu lato' at 150 mg/kg gave a maximum effect of reduction of gastric ulcer. It would therefore be interesting to conduct further studies to confirm and analyse the other therapeutic activities of this miraculous algae.

Declaration

-Ethics approval and consent to participate

By submitting my article I agree to pay the APC in full if my article is accepted for publication (unless it is covered by an institutional agreement or journal partner, or a full waiver has been granted).

The study was conducted in accordance with the the guidelines provided by the Institutional Animal Ethics Committee and approved by the Institutional Review Board (or Ethics Committee) of the Director of Health and Population of the city of Tlemcen (Algeria) in December 2022 , following the approval N. 299 of 15 April 2014.

-Consent for publication

The results/data/figures in this manuscript have not been published elsewhere, nor are they under consideration (from you or one of your Contributing Authors) by another publisher.

-Availability of data and materials

The authors confirm that all data generated or analysed during this study are included in this published article

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-Competing interests

I declare that the authors have no competing interests as defined by Springer, or other interests that might be perceived to influence the results and/or discussion reported in this paper

-Funding

None

-Authors' contributions

DHM wrote the main manuscript text , DHM and NHB prepared figures and Tables , NHB , FB , KHB , DB and AR participate on data collection . All authors reviewed the manuscript."

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TABLE I - Antiulcer activity of Seaweed "*cystoseira sensu lato*" against ethanol induced gastric ulcer (Ulcer score , % ulceration , % of Ulcer Inhibition)

Treatment	Group	Dose (mg/kg)	Ulcer Score	% Ulcération	% of Ulcer inhibition
Normal Control	**I**	**-**	**-**	**-**	**-**
Disease Control	**II**	**-**	**6,4 ± 1,87**	**94,94**	**-**
Omeprazole	**III**	**50**	**0,5 ± 0,86*** **	**2,11*** **	**96,22%**
Pre-treated	**IV**	**50**	**1,60 ± 1,51*** **	**8,73*** **	**83,77%**
Pre-treated	**V**	**100**	**1,1 ± 1,02*** **	**6,88*** **	**87,45%**
Pre-treated	**VI**	**150**	**0,60 ± 0,65*** **	**3,31%*** **	**91,29%**
Treated	**VII**	**50**	**1,12 ± 0,35*** **	**5,92%*** **	**89,12%**
Treated	**VIII**	**100**	**0,30 ± 0,32*** **	**3,92%*** **	**94,11%**
Treated	**IX**	**150**	**0,1 ± 0,22*** **	**1,12%*** **	**97,82%**

Data are expressed as the mean ± standard deviation (SD) . Significant difference from Disease control group: *p<0.05, **p < 0.01, ***p < 0.001.

TABLE II - Antiulcer activity of Seaweed "*cystoseira sensu lato*" against ethanol induced gastric ulcer (gastric volume, Ph and Total acidity)

Treatment	Group	Dose (mg/kg)	Gastric Volume	Ph	Total Acifity
Normal Control	**I**	**-**	**-**	**-**	**-**
Disease Control	**II**	**-**	**3,25±0,4**	**3,29±0,2**	**89,03±2,8**
Omeprazole	**III**	**50**	**1,32±0,3**	**2,95±0,2***	**48,37±1,7*** **
Pre-treated	**IV**	**50**	**2,48±0,5**	**3,10±0,2**	**53,66±2,2*** **
Pre-treated	**V**	**100**	**2,31±0,3**	**3,22±0,3**	**46,31±0,9*** **
Pre-treated	**VI**	**150**	**3,8±0,3**	**3,31±0,2**	**39,45±0,6*** **
Treated	**VII**	**50**	**2,20±0,2**	**2,88±0,1***	**57,17±0,6*** **
Treated	**VIII**	**100**	**1,56±0,3**	**2,91±0,2***	**42,04±0,7*** **
Treated	**IX**	**150**	**2,73±0,4**	**2,11±0,1****	**38,27±0,3*** **

Data are expressed as the mean ± standard deviation (SD) . Significant difference from Disease control group: *p<0.05, **p < 0.01, ***p < 0.001.

Table III - Hodge and sterner toxicity scale [24]

S. No.	Term	LD50 (Rat, Oral)
1	Extremely Toxic	Less than 1 mg/kg
2	Highly Toxic	1- 50 mg/kg
3	Moderately Toxic	50 - 500 mg/kg
4	Slightly Toxic	500 - 5000 mg/kg
5	Practically Non-Toxic	5000 - 15,000 mg/kg

Fig 01: "cystoseira sensu lato" 16/02/2023 FRONT DE MER- Mostaganem

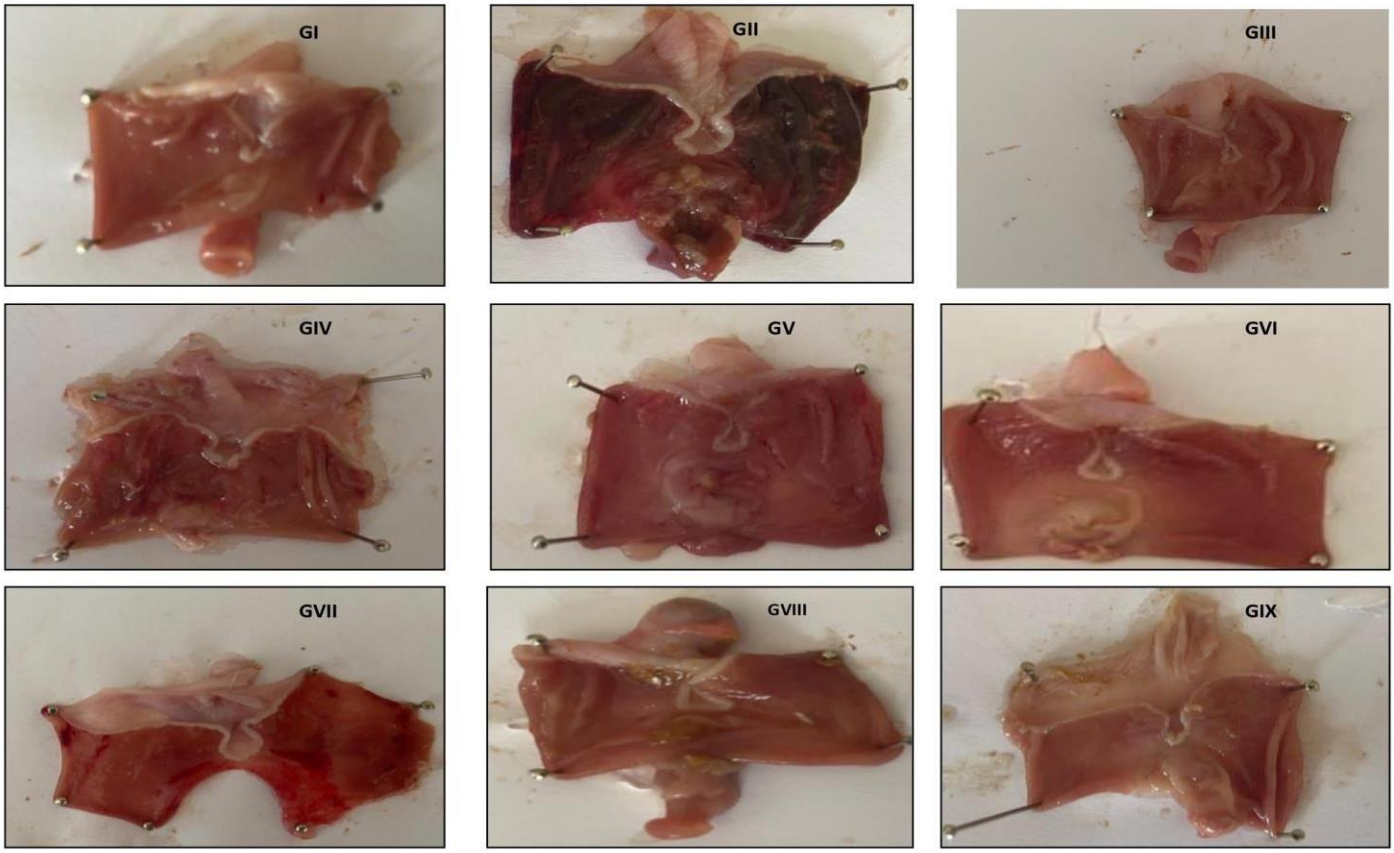

Fig 02 : Original photograph of groups G stomachs (GI – GIX)