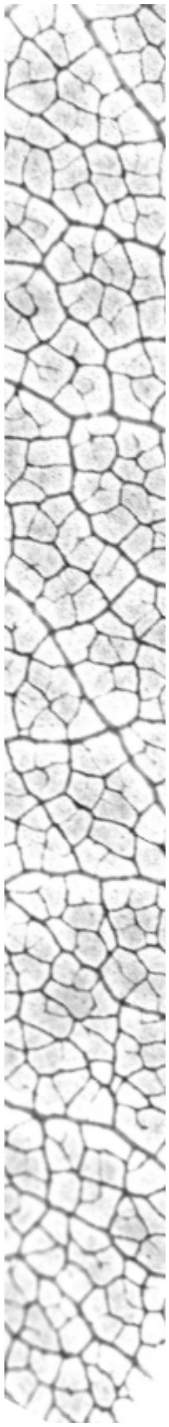

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Histological and immunohistochemical study of the healing role of the extract of *Ipomoea batatas* sweet potato extract in the gastric ulcer developed by aspirin in male albino rats

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Abstract

The study was conducted in the animal house of the faculty of veterinary medicine / university of al-Qadisiyah in order to identify the role of the alcoholic extract of sweet potato roots *Ipomoea batatas portrico* in the treatment of aspirin induced gastric ulcer by using 70 male rats of *Rattus norvegicus*. The animals was divided into two main groups as follows: the negative control group (C) was given the standard diet and distilled water only and the treatment groups (T), which developed peptic ulcer through oral dosage of (100 mg / kg body weight aspirin) for one week and then sacrificed 5 animals to confirm the presence of gastric ulcer and conducting the gross examination of the test. The treatment groups were divided into three groups, the first treatment group was considered as a positive control group (T1) or aspirin group only. The second group (T2) treated with (800 mg / kg body weight) extract of the sweet potato root by oral dose once daily for three consecutive weeks. The third treatment group (T3) was treated omeprazole orally (20 mg/kg bw) once daily for three consecutive weeks. The stomach was removed from each animal for the purpose of examining histological changes using three different stains: haematoxylin and eosin, Masson´s trichrome and periodic acid-schiff stain (PAS). The immunohistochemical teqnique was used to identify the epidermal growth factor receptors. The results of the histological examination using hematoxylin and eosin showed histopathological changes in the treatment group with aspirin in the gastric tissue represents by ulceration, congestion and infiltration of the inflammatory cells, bleeding, and thickening of the muscularis mucosae was observed in gastric tissue, While the disappearance of ulcers, bleeding and signs of congestion and gradual healing by the progressing of the experiment in animals treated with the extract of sweet potatoes(T2). The results showed by using (Masson and PAS) stains that there was a small or no amount of mucus and collagen fibers in the treatment group with aspirin (T1). However, there was a gradual increase in the amount of mucus and collagen fibers in the stomach tissue in the second and third treatment groups (T2, T3). The results of immunohistochemistry in the stomach showed no immune reaction to epidermal growth factor receptors in the (T1) treated animals group. The immunhistochemical staining was either very poor or absent, while a gradual increase in immune reaction and pigment strength was observed in the two groups of sweet potato extract (T2) and omeprazole (T1) groups with the duration of treatment.it was more pronounced in the animals of the second group (T2). The study concluded that the use of sweet potato root extract in the treatment of gastric ulcer had clear positive effects and was closed to omeprazole treatment.

Keywords: histological study, Immunohistochemical study, healing role

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INTRODUCTION

Gastric Ulcer describes the ulcers that occur in the mucosa of the stomach due to a number of factors, most notably the imbalance in the secretion of gastric acid and Pepsin, which affect the proportions of bicarbonate and Prostaglandin, which are important defensive factors (Matsui et al. 2015). And in general, gastric ulcer is produced by digesting the mucosa with acid and pepsin

Another important cause of the gastric ulcer is the infection of Helicobacter pylori and the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, which are used as an anti-inflammatory or to

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prevent the occurrence of blood clots, and the excessive use of these drugs led to increased secretion of acid (Lanas et al. 2015). Although there are several types of medicines in the treatment of ulcers such as antacids, Proton pump inhibitors such as Omeprazole and H2-Receptors antagonists such as Ranitidine and the success of these drugs in the healing of many cases of ulcers, but these drugs have side effects such as heart arrhythmias, dry mouth, difficulty breathing and headaches (Kasimovskaya et al. 208, Ozsay et al. 2018, Zhou et al. 2014) and therefore was directed to nature to find alternatives to plant or animal safe Free from side effects or that their effects are limited. Two-thirds of the world's population uses alternative therapies, including plant medicines, as a primary source of health care and natural products. These are pure compounds extracted or derived from primary and secondary metabolites of cells and tissues or as secretions of microorganisms, plants and animals as they are present in terrestrial and marine environments (Debas et al. 2006) Are chemically designed and chemically different from the basic molecules manufactured, and are able to regulate biological systems because of their ability to interact with different molecules Sweet potato is one of the most valuable nutritional and economic crops and a source of energy and plant chemicals. It is one of the world's sixth most abundant food crops. Its full parts of leaves, stems and roots are an important source of human nutrition and animal feed (Milind 2015). Its thick roots and sweet taste are a high source of carbohydrate, dietary fiber, vitamins A, B, C, starch and minerals (iron, potassium, manganese and calcium) and have anti-diabetic, viral and bacterial uses (Shekhar et al. 2015).

Aim of the Study

To strengthen and confirm the role of sweet potatoes as a means of promoting health and alternative treatment of gastric ulcer.

MATERIALS AND METHODS

Collection and Preparation of Plant Samples

The sweet potato plant was obtained Ipomoea. Department of Horticulture - Faculty of Agriculture - University of Baghdad. And then brought to the laboratory isolated the roots of the plant and washed with distilled water to remove the dust and dirt, then cut the knife into small pieces and dried in the shade to get rid of water and then use the electric oven at a temperature of 40 m for the disposal of the rest of the water. The dry roots were grinded using an electric mill and the crushed material was kept in glass containers until extraction. Has been classified at the College of Agriculture \ University of Baghdad as the local type Ipomoea potato. 20gm of Sweet Potato powdered leaves were taken and extracted with soxhlet apparatus ethanol 70% Within 24 hours, and then taking the extract and place it in a ptry dish and put in the oven at a temperature of 40°C within 48 hours, The result of extract was stored at 4°C until use (Harborne 1984, Goli et al. 2013).

Experimental Animals

Rattus norvegicsus was obtained from the Animal House at the Faculty of Veterinary Medicine, University of Qadisiyah. It was placed in plastic cages 50 x 35 x 15 centimeters in size and weighing between 200-250 grams. The floor of the cages was sprayed with sawdust and the cages were cleaned and sterilized with disinfectants. The animals were subjected to the same laboratory conditions in terms of ventilation, temperature (23-25 °C) and humidity (45-50%). Lighting was organized at 14 hours lighting and 10 hours darkness length of study. Animals were given a standard laboratory food feed (19% protein and 3000 calories energy).

Experimental Design

In this study, 70 male rats with a weight of 200-250 mg were used. After one week of acclimatization, they were divided into four equal groups.

1- Negative control group (non-treatment) (C): This group was given distilled water only for the duration of the experiment.

2- Positive control group (T1): which developed ulcer by giving the drug aspirin (100 mg / kg body weight) for a period of (7) consecutive days.

3- Treatment group II (T2): The ulcer was developed by giving aspirin (100 mg / kg body weight) for 7 consecutive days. The sweet extract of sweet potato roots was given 800 ml / kg body weight daily for 21 consecutive days.

4- Treatment group III (T3): also was developed ulcer by giving the drug aspirin (100 mg / kg body weight) for a period of (7) consecutive days. The drug was then given Omeprazole (20 mg / kg) of body weight for 21 consecutive years.

Preparation of aspirin and omeprazole: In order to obtain the required dose aspirin and omeprazole a solution was prepared depending on (Wang et al. 2011, Wilde et al. 2014).

Development of gastric ulcer: gastric ulcer was introduced in all experimental groups except the negative control group by giving aspirin (100 mg / kg) of body weight by a single dose daily after starving the animals for 14 hours before giving aspirin for 7 consecutive days. Five animals were killed each A group to confirm the infection of the ulcer by anesthetizing the animals then sacrificed five animals from each group at the end of the first week and the second and third after 7 and 14 and 21 days to detect the healing of the ulcer.

Histological Sections: The method (Bancroft and Gamble 2008) was followed for the purpose of preparing textile sections. The special stains The method (Carson and Christa 2009, Malatesta 2016) were followed for the purpose of preparing textile sections.

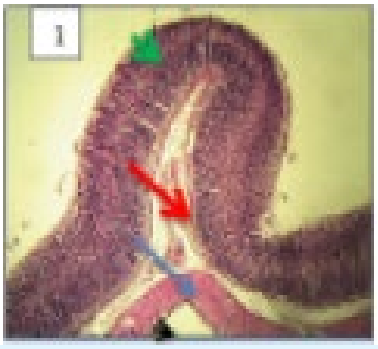

Fig. 1. A section in the rat's stomach of the control group (C) showing a natural structure of the four main layers: - mucus layer (green arrow), subcutaneous layer (red arrow), external muscle layer (blue arrow) (Black arrow) (H & E, 20X)

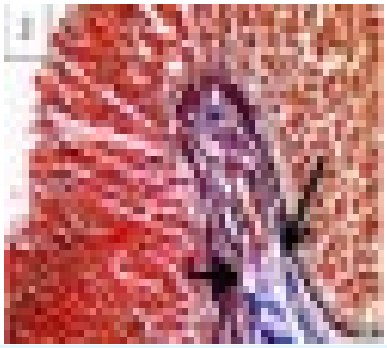

Fig. 2. A section in the rat's stomach of the control group (C) shows a normal gastric tissue and a dense presence of blue collagen fibers (Masson, 200X)

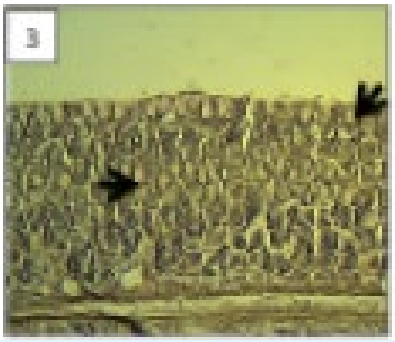

Fig. 3. A section in the rat's stomach of the control group (C) shows a positive interaction of mucous cells in the gastric glands (PAS, 50X)

Study of immunohistochemical: Textile sections were prepared according to manufacturer's instructions (DAKO EnVision FLEX, Denmark).

RESULTS

The results of the microscopic examination of transverse sections of the male rats of the negative control group (C) indicated that they were composed of four main layers, respectively, from the inside out: mucus layer Mucosa layer mutates the epithelial tissue in a gastric pits that opens a number of glands Gastric glands are observed below these glands. Muscularis

Fig. 4. A section in the rat's stomach of the first treatment group (T1) showing Complete mucus extraction (blue arrow) and infiltration of inflammatory cells in the mucous and subcutaneous layer (green arrow) with bleeding (black arrow) and expansion of blood vessels (red arrow) (H & E, 50X)

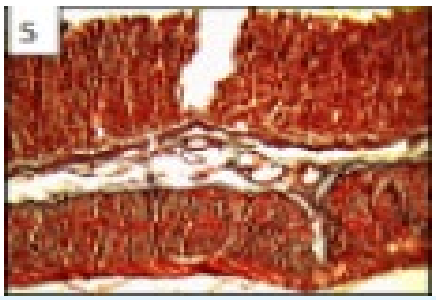

Fig. 5. A section in the rat's stomach from the first treatment group (T1) shows an ulcer in the mucous layer (green arrow) with a slight presence of collagen fibers (black arrow) (Masson, 50X)

mucosae, which is based on dissociated connective tissue, is a submolecular layer that is bordered on the outside by the external muscle layer Muscularis externa, which appears as two secondary muscle layers, one of which is a circular inner circle For longitudinal arrangement Longitudinal Outer longitudinal The outer wall of the stomach is enveloped by serosa layer (**Fig. 1**).

On the other hand, the tissue was exposed using the special stain, the Masson's trichrome stain, to detect collagen fibers and periodic acid-Schiff Stain (PAS) to detect carbohydrate (mucus) a dense presence of collagen fibers (**Fig. 2**) and positive interaction of mucous cells (**Fig. 3**).

The histological examination of haematoxylin and eosin-stained gastric sections of the first treatment group only aspirin (T1) showed to have clear ulcers characterized by complete detachment of the mucous layer and infiltration of inflammatory cells in the mucous and subcutaneous layers as well as bleeding and clear dilation (**Fig. 4**). In the tissue sections stained with Masson (T1), there was a slight or slight presence of collagen fibers in the subcutaneous layer (**Fig. 5**). The results also showed very poor interaction of mucous cells with periodic acid stain (**Fig. 6**) compared to negative control group animals.

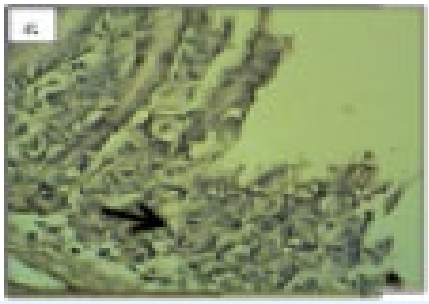

Fig. 6. A section in the rat´s stomach of the first treatment group (T1) showing a weak reaction (-) with the pigment (black arrow) (PAS,200X)

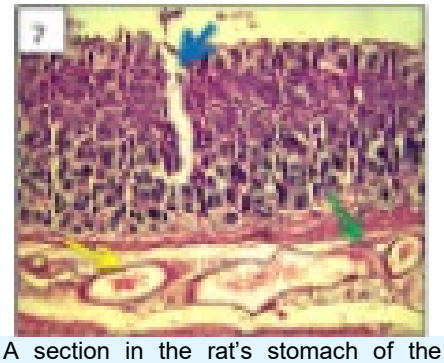

Fig. 7. A section in the rat's stomach of the second treatment group (T2) in the first week, showing the re-formation of the epithelial cells (the blue arrow), the proliferation of the glands of the glands (red arrow), the infiltration of the inflammatory cells (the green arrow) with congestion in the blood vessels (yellow arrow) (H & E , 50X)

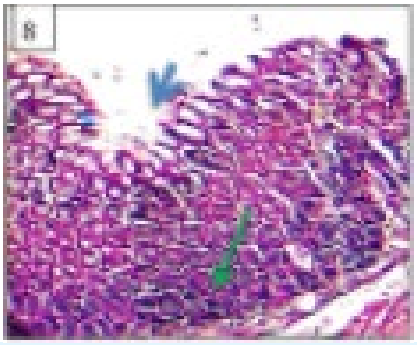

Fig. 8. A section in the rat's stomach of the second treatment group (T2) in the second week of shows the proliferation of epithelial cells leaving a small ulcer and the proliferation of intestinal glands in the mucous layer (green arrow) (H & E, 50X)

On the other hand, the histological examination of heamatoxlin and eosin-stained tissue sections of the animal preparation treated with 800 mg / kg of sweet potato extract (T2) at the end of the first week of the treatment showed a re-formation of epithelial cells and proliferation of the gastric glands in the mucous layer, (**Fig. 7**). At the end of the second week there was a marked increase in the proliferation and proliferation of epithelial cells and intestinal glands, leaving small ulcers on the surface of the mucosa (**Fig. 8**) and at the end of Third week, a high splitting activity and full healing of ulcers were observed as shown in **Fig. 9**. When using

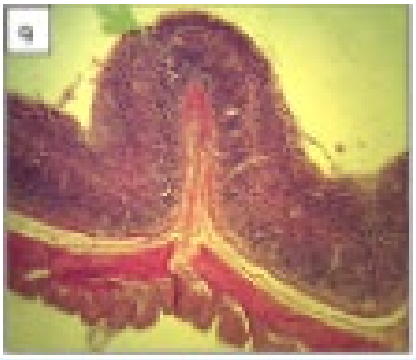

Fig. 9. A section in the rat's stomach of the second treatment group (T2) In the third week, complete healing of the ulcer site (green arrow) (H & E, 20X)

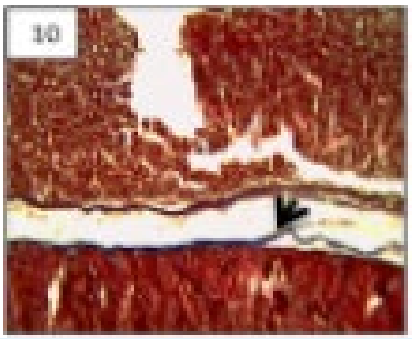

Fig. 10. A section in the rat's stomach of the second treatment group (T2) in the first week, showed a small presence of collagen fibers (black arrow) (Masson, 50X)

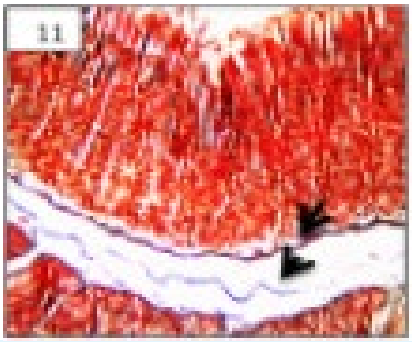

Fig. 11. A section in the rat's stomach of the second treatment group (T2) in the second week of shows Medium collagen fibers appear (black arrow) (Masson, 50X)

Masson´s trichrome stain, there was a gradual increase in the amount of collagen fiber in the subcutaneous layer that was directly proportional to the duration of the treatment. The collagen fibers showed a blue color in low numbers at the end of the first week (**Fig. 10**) and increased at the end of the week (**Fig. 11**). At the end of the third week, collagen fiber density increased as shown in **Fig. 12**. On the other hand, the detection of mucus using PAS showed positive interaction at the end of the first week and gradually increased in the second week. The interaction reached its peak at the end of the third week (**Figs. 13**, **14**, **15**).

The tissue examination of the T3-treated patients with a concentration of 20 mg / kg body weight and dyed

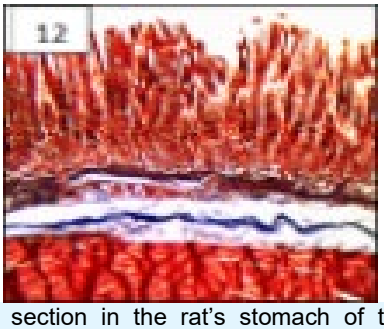

Fig. 12. A section in the rat's stomach of the second treatment group (T2) In the third week shows the collagen fibers appear thickly (black arrow) (Masson, 50X)

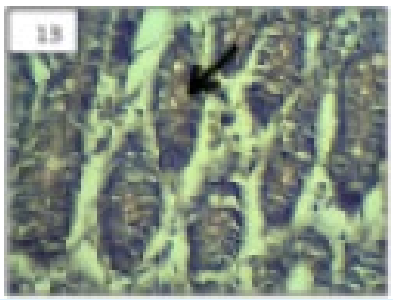

Fig. 13. A section in the rat's stomach of the second treatment group (T2) in the first week,shows Positive reaction (+) with pigment (black arrow) (PAS, 200X)

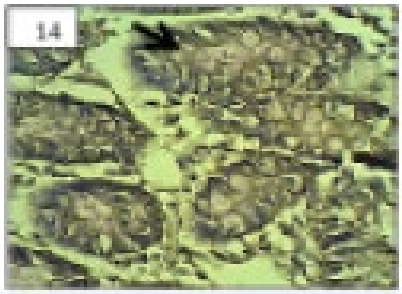

Fig. 14. A section in the rat's stomach of the second treatment group (T2) in the second week of shows Positive reaction (++) (black arrow) (PAS, 200X)

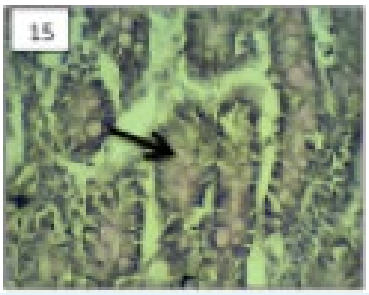

Fig. 15. A section in the rat's stomach of the second treatment group (T2) In the third week shows Positive reaction (+++) (black arrow) (PAS, 200X)

with haematoxylin and Eosin at the end of the first week showed a narrow ulcers in the mucosa wall of the stomach with a clear thicken of mucosal muscle layer and multiplication Clear of glandular cells and expansion of blood vessels in the subcutaneous layer as well as the

Fig. 16. A section in the rat's stomach of the third treatment group (T3) in the first week,shows an emphysema with an ulcer (blue arrow), thickening of the mucous layer (green arrow), congestion of blood vessels in the subcutaneous layer (black arrow) and inflammation of inflammatory cells (red arrow) (H & E, 50X)

Fig. 17. A section in the rat's stomach of the third treatment group (T3) in the second week,shows Partial healing of the ulcer(blue arrow), proliferation of infectious glands (green arrow) and inflammation of the inflammatory cells (yellow arrow) with slight congestion (black arrow) in the subcutaneous layer (H & E, 50X)

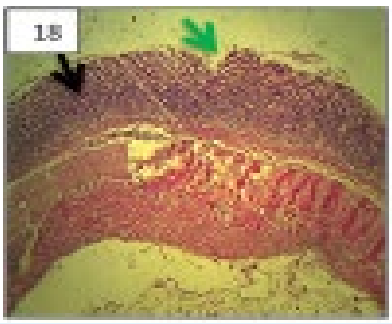

Fig. 18. A section in the rat's stomach of the third treatment group (T3) in the third week shows The healing of the ulcer (green arrow) and the proliferation of cells in the muscle layer (black arrow) (H & E, 20X)

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presence of infiltration of inflammatory cells in both mucous and subcutaneous layers (**Fig. 16**).

The second week saw the beginning of partial healing of the gastric ulcer accompanied by splitting activity and high proliferation of endocrine glands with infiltration of inflammatory cells and simple congestion of blood vessels in the subcutaneous layer (**Fig. 17**). At the end of the experiment in the third week, complete healing of infectious ulcers and clear proliferation of mucosal cells of the gastric mucosa in the infectious pressure area was observed (**Fig. 18**). The

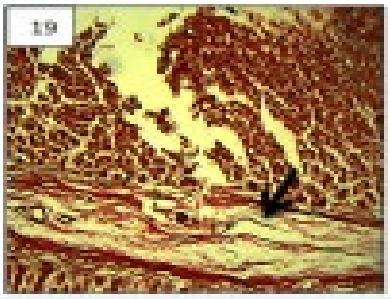

Fig. 19. A section in the rat's stomach from the third treatment group (T3) in the first week showed a weak presence of collagen fiber (black arrow) (Masson, 50X)

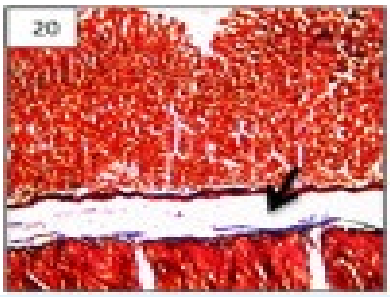

Fig. 20. A section in the rat´s stomach from the third treatment group (T3) in the second week showed medium presence of collagen fibers (black arrow) (Masson, 50X)

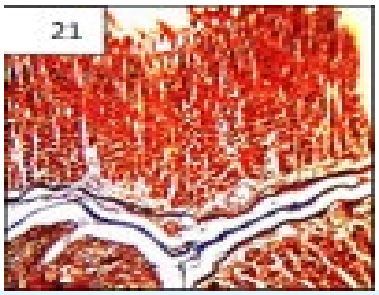

Fig. 21. A section in the rat's stomach from the third treatment group (T3) in the third week showed thick collagen fibers (black arrow) (Masson, 50X)

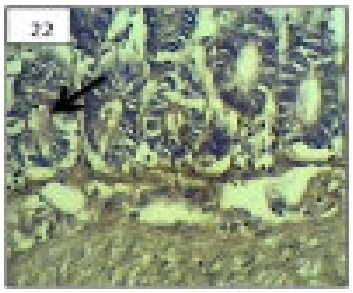

Fig. 22. A section in the rat's stomach from the third treatment group (T3) in the first week showed a weak reaction (+) (black arrow) (PAS, 200X)

histopathological examination of stained Masson gastric sections showed a gradient in collagen fiber deposition intensity, and this amount was proportional to the increased duration of treatment during the glacial period (**Figs. 19**, **20**, **21**) When pigmented tissue was dyed (PAS) it was observed that there was a gradual increase in the interaction of dye with mucous cells gradually

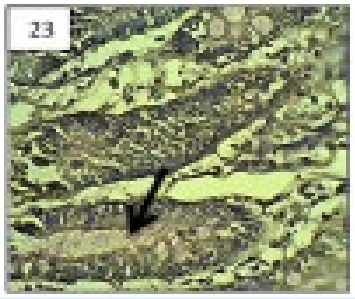

Fig. 23. A section in the rat's stomach from the third treatment group (T3) in the second week showed Positive reaction (++) (black arrow) (PAS, 200X)

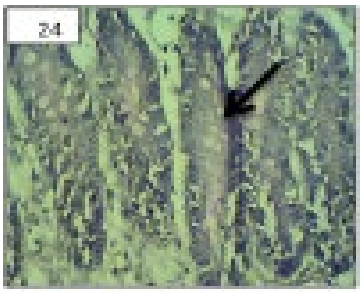

Fig. 24. A section in the rat's stomach from the third treatment group (T3) in the third week showed Positive reaction (+++) (black arrow) (PAS, 200X)

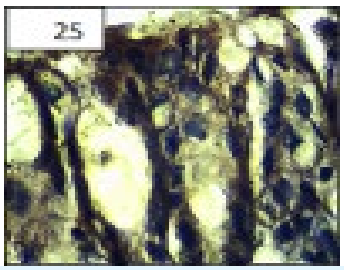

Fig. 25. A section in the rat's stomach of the control group (C) shows the intensity of the EGFR (positive reaction) as well as the pigment strength (brown) (red arrow) (IHC, 500X)

escalated in the three weeks and the intensity of the reaction was evident at the end of the third week (**Figs. 22**, **23**, **24**).

The results of the study of immunohistochemical to detect the epidermal growth factor receptors in the mucosa of the gastric wall in the animals of the negative control group (C) showed a positive interaction by the presence of large numbers of positive stain cells (**Fig. 25**). However, this interaction is almost non-existent or weak and the pigment strength is weak in the animals of the positive control group representing the first treatment group (T1). This is illustrated by the **Fig. 26**. On the other hand, the results of immunoglobulin of the gastric sections of the treated group of the sweet potato extract (T2) showed that there was a gradual increase in the number of positive cells that reacted clearly with the stain as the intensity of the immune reaction increased with the duration of treatment. The third week of treatment with the extract, as indicated by the

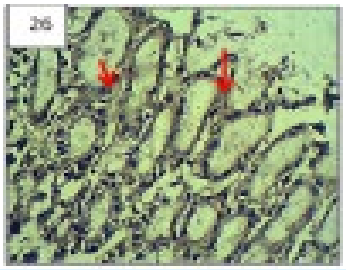

Fig. 26. A section in the rat's stomach of the first treatment group (T1) showing a weak immune reaction (negative reaction) and very low pigmentation strength (red arrow) (IHC, 200X)

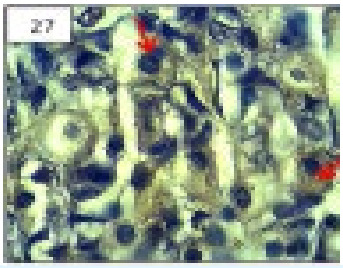

Fig. 27. A section in the rat's stomach of the second treatment group (T2) in the first week showed Low EGFR (-) with weak immunoglobulin (Red Arrow) (IHC, 500)

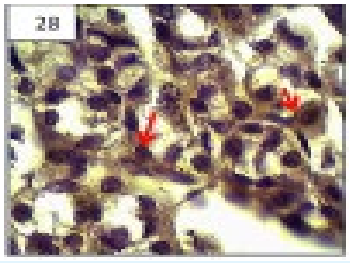

Fig. 28. A section in the rat's stomach of the second treatment group (T2) in the second week showed Medium-density immunoglobulin reaction + with immunoglobulin strength (red arrow) (IHC, 500X)

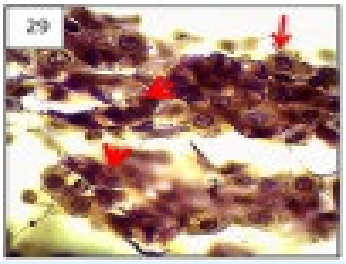

Fig. 29. A section in the rat's stomach of the second treatment group (T2) in the third week showed the intensity of the immune response +++ and the immunoglobulin strength of the brown color (red arrow) (IHC, 500X)

immunological tissue sections of the stomach (**Figs. 27**, **28**, **29**). At the treatment of standard treatment (omeprazole) in the animals of the third treatment group (T3) in stomach there was also a gradual increase in the intensity of the immune reaction gradually escalated as the treatment progressed but was less clear than in the treatment group The second (T2) images are also indicated taken from the stomach (**Figs. 30**, **31**, **32**).

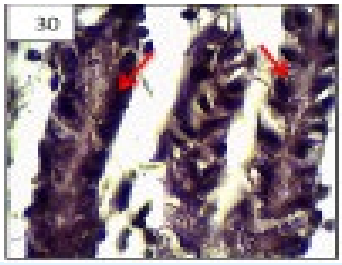

Fig. 30. A section in the rat's stomach of the third treatment group (T3) in the first week showed Interaction and immunoglobulin are weak (red arrow) (IHC, 500X)

Fig. 31. A section in the rat's stomach of the third treatment group (T3) in the second week showed Intermediate immunoglobulin reaction ++ and immunoglobulin strength Brown (red arrow) (IHC, 500X)

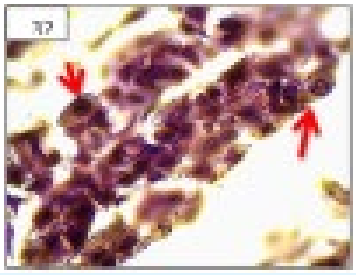

Fig. 32. A section in the rat's stomach of the third treatment group (T3) in the third week showed The intensity of the immune response +++ and the immunoglobulin strength of the brown color (red arrow) (IHC, 500X)

DISCUSSION

The results of tissue shredding were indicated in the stomach and stained with heamatoxylin and Eosin were indicated by the presence of clear signs of malformation, degeneration of the mucous layer and dissolution of the vesicles with signs of blood vessel congestion and hemorrhage in the first treatment group (T1). Khalil et al. (2010) said there were signs of congestion and hemorrhage in the mucous and sub-mucous layer of rats was treated with aspirin for 6 weeks The results showed the safety of the mucous membrane of the stomach with no changes in the disease and the disappearance of signs of congestion and bleeding, which shows the reconstitution of the damaged tissue and the disappearance of signs of dislocation and congestion and bleeding and recovery and is observed is the absence of differences between the group (T3). These changes are due to the therapeutic role of sweet potato extract in the reduction of pathological changes

significantly due to having clear therapeutic properties such as containing structural proteins such as amino acids Which has protective and immunological functions and contains many vitamins such as vitamin C, E and A and important minerals such as Mg and Fe, Cu and Zn, which are anti-oxidants and works to curb the effects of free radicals and reduce tissue damage (Adewoye and Salami 2013, Huligol et al. 2012), which found hemorrhagic ulcers in the stomach of indomethacin-treated rats and the disappearance of these ulcers when treated with vitamin E. The results of the present study showed a gradual increase in the density of collagen fibers in the subcutaneous layer of the stomach. This indicates the effectiveness of the treatment used in the healing of the ulcer, whether sweet potato (T2) or omeprazole (T3) during the treatment weeks. Collagen fibers were more likely to be treated with sweet potato extract, possibly because they are rich in vitamin A, which is an effective ingredient in collagen synthesis (Kavalukas and Barbul 2011).

On the other hand, previous studies have indicated the importance of collagen fibers in healing other conditions such as arthritis in multiple stages of treatment (Graham et al. 1988) and oral ulcers (Longo and São Dimas 2011) where an increase in the number of cells producing fiber Fibroblasts and collagen fibers as well as many studies of infectious ulcers and duodenal ulcers such as the study by Devaraj et al. (2007), which demonstrated the effect of leaves and fruits of *Moringa oleifera* in the healing of gastric and duodenal ulcers and indicated a clear increase in numbers Fiber-producing cells and collagen fibers and their active contribution to the occurrence For healing. In the present study, there was positive interaction with the PAS stain in the stomach by observing the pink color in the region of the glands through the interaction of the cells of this region with the stain and characterized this region by containing the glycogen and mucus, The rate of cell interaction with stain gradually according to the weeks of treatment, which helps to predict the effectiveness of the treatment used. Shaoul et al. (2000) has already referred to the role of epithelial cells through their proliferation and increased mucus secretion in the healing of the duodenal ulcers. Schumacher et al. (2004) studied a comparative study of the amount of mucus isolated from the glandular glands and Bronner's glands in the treatment of ulcers and the role of mucus in promoting healing.

The current study was conducted Epidermal Growth Factor Receptors (EGFR), which is an indication of the proliferation of epithelial cells and their migration to the base of the ulcer and evidence of EGF, is the largest contributor to healing. The growth factor receptor is a membrane receptor (170 kD) When linked to growth factor the factors, a series of oxidative phosphorylation and chemical changes eventually result in healing (Balbaa 2013).

The results showed positive EGFR during the treatment weeks of the second treatment group (T2) and the third (T3) in the gastric tissues and the results showed that the group (T2) was pigmentation and the immune interaction in it stronger than the interaction in the group (T3) The therapeutic efficacy of the sweet potato plant and its ability to cure because it contains high levels of antioxidants, vitamins and minerals, which have the potential to stimulate and grow epithelial cells and their reproduction, as well as contain sweet potatoes on the elements of iron and copper are very important in the formation of blood vessels Angiogenesis (Bovell-Benjamin 2007). On the other hand, several previous studies have indicated that the current results, such as the study of Jawi et al. (2014), in which the water extract of sweet potato plant have been used in the treatment of high cholesterol in the rabbit. The immune expression of Nrf2 showed an increase in epithelial epithelial cells (Al Rashdi 2013) comparing the *Jasminum Sambac* and omeprazole extract in the healing of the peptic ulcer using IHC technique, where the plant cause increased immune expression of the Hsp70 protein which has a role in healing.

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