RESEARCH ARTICLE

PRECLINICAL STUDY OF HEALING EFFECT OF METHANOLIC EXTRACT OF *CORIANDRUM SATIVUM* IN WOUNDS OF AN ANIMAL MODEL OF DIABETES

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Abstract: People with Diabetes Mellitus often use medicinal plants to treat this metabolic disease that frequently reports complications, such as impaired wound healing. *Coriandrum sativum* has a wide range of healing properties: antibiotics, antifungals, hypoglycemics and antioxidants to name a few. However, no studies have been conducted on its potential as a wound healing agent. So, the objective of this work was to determine the wound healing effect of the methanolic extract of *C. sativum* seeds in reducing the closing time of surgical lesions in *Long Evans black* rats induced to a diabetes model with alloxane. Material and methods: Toxicity tests were performed using the *Artemia salina* model and phytochemical test were conducted to determine the composition of the extract. The Diabetes model was induced with alloxane and wound was done with a biopsy punch. During the experiment, 6 groups of 5 rats each were included and the diameter of the wound was measured at days 0, 7, 14 and 21. At the end of the observation period, the animals were sacrificed and histological analysis of the wound skin was performed. Results: The alloxane treated group (diabetes model) had delayed wound healing. The group treated with the extract at a concentration of 2000 µg/mL presented wound closure on day 16 and histological characteristics similar to normal tissue of the control group. Conclusions: *C. sativum* methanolic extract accelerated wound healing, which was confirmed by histological analysis.

Keywords: Diabetes Mellitus, Coriandrum sativum, Scarring effect, Hyperglycemia, Healing effect, Wound healing

INTRODUCTION

The skin is the outer tissue covering and the largest organ of the body with important protective and immunological functions (Abbas *et al.*, 2018). It acts as a protective barrier that isolates the organism from the external environment, protecting against pathogens and water loss, and helping to keep its structures intact, it also works as a communication system with the environment and is one of the main sensory organs, it contains nerve endings that act as touch, pressure, pain and temperature receptors (Rojas-Espinosa, 2017). The skin is made up of three layers: 1) epidermis, 2) dermis, and 3) hypodermis. The epidermis varies in thickness according to its location from 30 µm in the eyelids to 1.5mm in the palms of the hands with an average of 0.4mm. The epidermis is divided into 5 strata: corneum, lucidum, granulosum, spinosum, and basale (Gantwerker & Hom, 2011). The most abundant cells in the epidermis are the keratinocytes that reach a proportion of 95% located mainly in the stratum basale (Regueiro-González *et al.*, 2011). The dermis is the layer underlying the epidermis, it comprised mainly lymphatic and blood vessels, follicles, apocrine and eccrine glands. The deeper layer, the hipodermis contains conjunctive tissue, lymphatic and blood vessels, adipocytes, and cutaneous nerves (Zomer & Trentin, 2017). Any damage to the skin regardless of deepness requires wound healing to repair the damage (Pazyar, *et al.*, 2014). Wound healing is a progressive dynamic process that is divided into four overlapping but distinct phases: 1) hemostasis, 2) inflammation, 3) proliferation, and 4) remodeling. This process involves the participation of different molecules and cells types (Nguyen & Soulika, 2019).

The hemostasis phase occurs in the first moments after damage to the skin. During this phase clot forms to prevent further blood loss through an active

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participation of platelets, vasoactive substances, and an infiltration of leukocytes, red blood cells, keratinocytes, fibroblasts, and plasma proteins (Ridiandries *et al.,* 2018). The inflammation phase occurs in the first minutes and until the wound is resolved. During this phase there is an infiltration of neutrophils, macrophages and lymphocytes to the site of the damage and they are mainly responsible for eliminating cellular debris and microorganisms that may be present (Boniakowski *et al.,* 2017).

The proliferation phase consists mainly of damage repairing through reepithelization and extracellular matrix production. Both stages are characterized by the proliferation and infiltration of keratinocytes and stem cells to repopulate the stratum basale (Eming *et al.,* 2014). Angiogenesis, the formation of new blood vessels from pre-existing blood vessels, is important during the phases of inflammation and proliferation (Okonkwo & DiPietro, 2017). Finally, the remodeling phase is characterized by a reorganization of the collagen matrix. The failure of these phases promotes pathologic wound healing such as the development of chronic non-healing wounds. Multiple intrinsic and extrinsic factors affect this process, especially those affecting the immune system such as medication use or disease (Cohen *et al.,* 2016).

Poor wound healing is associated with the most common metabolic disease: Diabetes mellitus (Schmidt, 2018). It is not clear to what extent impaired healing is due to direct effects of hyperglycemia, insulin deficiency, angiogenesis alteration or an excess of inflammation (Guthrie, 2004). For instance, inflammation affects the wound from progressing to the proliferation phase leading to chronic non-healing wounds (Kautzky-Willer *et al.*, 2016). On the other hand, the most common clinical indication of impaired wound healing associated with diabetes is the diabetic skin ulcer where inadequate local angiogenesis is considered a very likely contributor (Eming *et al.,* 2014). Diabetic skin ulcer are painful sores with disintegration of dermal tissue mainly epidermis and dermis.

Wound closure is greatly delayed in diabetes and it is associated to impaired angiogenesis and the chronic presence of inflammation as previously stated. Due to the fact that diabetes affects a high proportion of the world population; besides the fact that, poor wound healing is associated with diabetes; and considering the fact that, coriander seeds are attributed medicinal properties against diabetes and wound healing (Laribi *et al.,* 2015; Muniandy *et al.,* 2019; Silva & Domingues, 2017; Wei *et al.,* 2019). The aim of this study was to evaluate the healing effect of methanolic extract of *Coriandrum sativum* seeds in wounds of an animal model of diabetes.

MATERIALS AND METHODS

Biological material

All protocols used in this study were approved by the Bioethics committee of the Faculty of Medicine, Universidad Autonoma de Coahuila Unidad Torreon (reference number CB071017).

Thirty *Long Evans black* male rats with an age of 12 weeks old, weighing 200-250 grams were used. The animals were divided into six groups of five rats each. The animals were housed in acrylic rat cages using sawdust as bedding with stainless steel grill covers. Water and food were offered *ad libitum*. The environmental parameters were monitored by means of a temperature and relative humidity meter. The photoperiod was 12 hours of light and 12 hours of dark.

The samples of Coriander (*Coriandrum sativum* L.) seeds were obtained from a local market in the city of Torreon, Mexico. An amount of 100 g was washed with water and grindered in a manual mill. The extract was prepared with the macerated infusion of methanol at room temperature (25$\pm$ 2 °C) in a 1:4 ratio for 24 h with constant stirring at a speed of 60 rpm. Subsequently the supernatant was filtered on Whatman No. 40 filter paper and the solvent was evaporated under reduced pressure on a rotary evaporator (Buchi R-210) at a temperature below 60°C and the extract was subjected to complete desiccation in a hot air oven at 40°C. Subsequently, it was collected with a stainless-steel spatula and stored in an amber glass bottle at -20 °C; and dilutions at 10, 100 and 1000 µg/mL were prepared.

Biotoxicity assay with the *Artemia salina* model

To evaluate the biotoxicity of the extract, the *in vivo* biotoxicity assay with the *Artemia salina* model was used. The *Artemia salina* was cultivated by placing 0.01 g of *Artemia salina* eggs in artificial seawater (40 g of sea salt in one liter of distilled water) with 0.06 g of yeast extract. This mixture was placed in an artemia chamber at a temperature of 28°C for 48 hours for the eggs to hatch. Once the eggs of *Artemia salina* hatched, a standard curve of the extract to be evaluated at a concentration of 0, 1, 10, 100, 250, 500, 1000, 5000 µg/mL was prepared in enough seawater for 10 mL. A sample of *Artemia salina* (N=10) was added in triplicate in test tubes for each of the concentrations under study. Potassium dichromate was used at 1000 µg/mL in seawater as a positive control. During this assay, the samples were incubated at 28°C for 24 hours; subsequently, live and dead *Artemia salina* larvae were quantified, and the lethal dose 50% (LD50) was estimated by Probit regression.

Phytochemical tests

These tests were qualitative to identify the main chemical groups of organic compounds present in plant extracts. The principle of these tests based on chemical reactions between the functional chemical groups of organic compounds present in plant extracts and chemical reagents that led to the formation of precipitates or colored substances. For

the following tests, a standard solution of 10 000 µg/mL concentration was used.

Alkaloids (Dragendorff and Mayer' Reagents)

This test based on the presence of nitrogen in the alkaloids which reacted with reagents containing bismuth or mercury and formed insoluble iodides of color bright yellow. For this test, 1 mL of the solution to be evaluated was placed in three test tubes, 1 drop of concentrated hydrochloric acid was added to each tube, the sample was then heated gently and the test tubes were left to cool. Then one drop of the Dragendorff reagent [$Bi(NO_3)_3$:$5H_2O$ 8%; HNO_3 20%; KI 1.6M], Wagner and Mayer [KI 5%; HgCl 0.05M] was added. The development of a bright yellow color indicated the presence of alkaloids. An atropine solution was used as a positive control (Sigma Aldrich St. Louis, MO) and distilled water as a negative control.

Aldehydes (Tollens' Reagent)

This test involved the oxidation of the aldehydes to the corresponding carboxylic acid, using a 5% ammoniacal silver nitrate solution. The positive test consisted of the formation of a silver mirror or a black silver precipitate. For this test, 5 drops of 5% silver nitrate, 1 drop of 2N sodium hydroxide and 3 drops of 10% ammonium hydroxide were placed in a test tube. Until this moment the solution was transparent, then 1 mL of the standard solution to be evaluated was added. A glucose solution was used as a positive control (Sigma Aldrich St. Louis, MO) and distilled water as a negative control.

Carbohydrates (Brady' Reagent)

This reaction based on Brady's Reagent (with the reactant 2,4-dinitrophenylhydrazine) that quickly formed 2,4 dinitrophenylhydrazones with aldehydes and ketones, yellow or red pigments. For this test 1 mL of the standard solution was placed in a test tube and 8 drops of 2,4-dinitrophenylhydrazine 20% were added in concentrated sulfuric acid, plus 3 drops of 70% ethanol. The formation of a red or yellow color indicated the presence of aldehydes or ketones. Glucose and fructose solutions were used as positive controls and distilled water as a negative control.

Flavonoids

This test based on the formation of pigments by the reaction that occurred between the gammabenzopirone ring with hydrochloric acid and Magnesium. For this test, 1 mL of the standard solution to be evaluated was placed in a test tube, a piece of Magnesium metal (10 mg) and 2 drops of concentrated hydrochloric acid were added. The formation of a red or blue color indicated the presence of flavonoids. A catechin solution was used as a positive control (Sigma Aldrich St. Louis, MO) and distilled water as a negative control.

Sterols (Liebermann-Burchard's Reagent)

This test based on the reaction that occurred between the steroid rings with acetic anhydride with the formation of green or blue pigments. For this test, 1 mL of the standard solution to be evaluated was placed in a water bath of 50 °C until the solvent evaporated completely, the sample was solubilized in 2 mL of acetic anhydride and cooled in ice, then 3 drops of concentrated sulfuric acid were added. The formation of a green or blue color indicated the presence of the steroid ring. Vitamin D was used as a positive control and distilled water as a negative control.

Tannins

This test based on the tannins property to form precipitates of urea-soluble proteins which form pigments with ferric chloride. For this test, 1 mL of the standard solution to be evaluated was placed in a test tube, 1 mL of a solution of gelatin 1% in physiological saline solution was added, and afterwards the sample was centrifuged at 3500 rpm for 5 minutes. The precipitate was resuspended in 1 mL of 10M urea, and then 3 drops of 5% ferric trichloride were added. The formation of a blue color indicated the presence of tannins. A tannic acid solution was used as a positive control (Sigma Aldrich St. Louis, MO) and distilled water as a negative control.

Terpenoids

For this test, 1 mL of the standard solution to be evaluated was placed in a water bath at 50°C until the solvent evaporated in its entirety, 1 mL of a solution of glacial acetic acid and sulfuric acid [1:1] was added, then 1 mL of chloroform was added. The formation of a red or blue color indicated the presence of terpenoids. An ursolic acid solution in DMSO was used as a positive control (Sigma Aldrich St. Louis, MO) and distilled water as negative control.

Quantification of total phenolic compounds (Folin Ciocalteu method)

A sample of 150 µL of standard solution or sample was mixed with 150 µL of Folin Ciocalteu 0.2 N reagent (Sigma Aldrich St. Louis, MO). The mixture incubated at room temperature and left in the dark for 5 minutes, and the reaction was stopped with 300 µL of 0.35 M sodium hydroxide solution. The absorbance was measured on a UV spectrophotometer (Spectronic 20 Genesys) at a wavelength of 760 nm. This result was extrapolated in a standard curve with concentrations of 0, 2, 4, 8, 10, 15, 20, 30 and 50 µg/mL of gallic acid (Sigma Aldrich St. Louis, MO).

Experimental procedures

The animal model of diabetes was induced by means of intraperitoneal administration of alloxane (3 doses) 125 mg per kg-weight until reaching a glucose concentration over 300 mg/dL; blood glucose was measured, with an Accu-check glucometer, during the induction period and one week after reaching the 300 mg/dL threshold. The experimental animals underwent a circular wound on the back with a 1.5 cm^2 biopsy punch 2 mm deep. The wound was measured on days 0, 7, 14 and 21, in which glycemic record was also kept. The Coriander treatment was

administrated via topical route on days 0, 7 and 14. It consisted of 500 µL of methanolic coriander seeds extract at concentrations of 1000, 2000 or 4000 µg/mL prepared in a 1.6% carboxymethyl cellulose (CMC) solution with phosphate-buffered saline (PBS) as diluent. The healing percentage was determined using the following formula:

$$\text{Healing percentage} = \frac{(\text{Wound area}^{\text{Day 0}} - \text{Wound area}^{\text{Day N}})\ (100)}{\text{Wound area}^{\text{Day 0}}}$$

The animal groups were as follows: 1) Control group (without any treatment); 2) Alloxane treatment; 3) Alloxane and CMC/PBS treatment; 4) Alloxane and extract (1000 µg/mL) treatment; 5) Alloxane and extract (2000 µg/mL) treatment; and 6) Alloxane and extract (4000 µg/mL) treatment.

Histological analysis

Animals were sacrificed by cervical dislocation; subsequently, an elliptical incision was made which covered the area of the healing process. The samples were dehydrated and embedded in paraffin to make microtome cuts 5 µm thick subjected to hematoxylin and eosin (HE) and Masson's trichrome (MT) stains for analysis.

Statistical analysis

The variables of the phytochemical tests were nominal. The rest of the variables were continuous and they were described with means and standard deviation. ANOVA and posthoc Dunnet test were used to evaluate the difference of means among study groups; linear regression and Probit regression were calculated with IBM SPSS 21 and GraphPadPrism 6 software.

RESULT AND DISCUSSION

Biotoxicity assay with the *Artemia salina* model

Based on the results of the biotoxicity assay with the *Artemia salina* model, a LD50 of 5424.82 µg/mL (95%CI 4365.73-6483.90) was calculated. Therefore, we proceeded to evaluate the coriander seeds extract at concentrations lower than the LD50 that were 1000, 2000 and 4000µg/mL.

Phytochemical tests

The phytochemical tests of the coriander seeds extract showed the presence of flavonoids, tannins and terpenoids as seen in Table 1.

Table 1. Phytochemical tests of the methanolic extract of Coriander seeds.

Phytochemical test	Result
Alkaloids	-
Aldehydes	-
Carbohydrates	-
Flavonoids	+
Sterols	-
Tannins	+
Terpenoids	+

+ Positive. – Negative.

Scarring analysis

After the establishment of the diabetes model through the application of intraperitoneal alloxane, the surgical wound was performed under general anesthesia supervised by the veterinarian in charge of the Faculty's bioterium. The wound healing progress was measured on days 0, 7, 14 and 21 as shown in Figure 1. Scarring analysis among animals showed complete wound closure by day 21 in all study groups but group 2 with only alloxane treatment which is the control group for the diabetes model. Wound closure was carried out more quickly in the groups with coriander treatment, especially quick in group 5 at a 2000 µg/mL concentration. Statistically significant differences ($p<0.05$) were found by ANOVA test as shown in Table 2 among healing percentages of study groups. Posthoc Dunnet test showed statistically significant differences ($p<0.01$) among all the measures on days 0, 7, 14 and 21 of the coriander treatment at a 2000 µg/mL concentration. Even though, the three groups receiving any coriander treatment showed statistically significant differences ($p<0.01$) on day 21, the mean of days for full epithelization was 17.4, 16.2 and 18.4; respectively, from lower to highest coriander seed extract concentration. The results for both healing percentages and days for full epithelization indicated the best concentration of extract for treatment at 2000 µg/mL.

In contrast, on day 21 of observation the wound in the group 2, with only alloxane treatment which is the control group for the diabetes model, had not completely healed. The group 3 treated with alloxane and CMC/PBS showed statistically significant differences ($p<0.05$) on days 7 and 14. However, full epithelization was not reached by day 21.

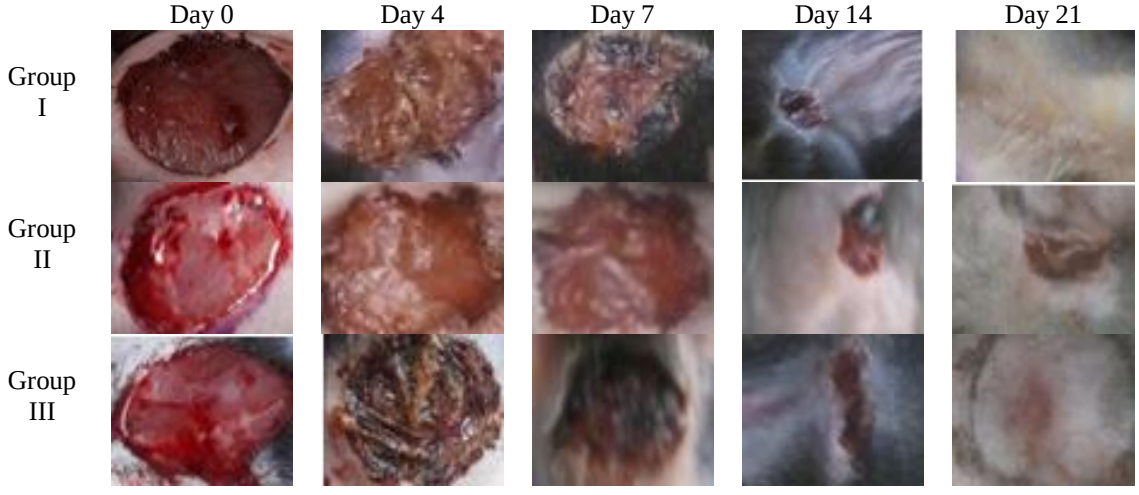
Table 2. Healing percentage and mean of days for full epithelization among study groups.

	Day 4 (%)	Day 7 (%)	Day 14 (%)	Day 21 (%)	Full epithelization (Days)
GROUP I	16.13 ± 2.46	28.13 ± 5.14	80.39 ± 1.80	100 ± 0	19 ± 0.7
GROUP II	10.26 ± 7.90	17.99 ± 5.33	71.19 ± 5.7	97.86 ± 1.09	20.8 ± 0.44
GROUP III	26.65 ± 3.61*	33.99 ± 4.34	77.06 ± 5.7**	99.86 ± 0.29	19.8 ± 1.09
GROUP IV	26.65 ± 3.87	42. 06 ± 2.83**	79.71 ± 6.98	100 ± 0**	17.4 ± 0.54
GROUP V	31.59 ± 6.35**	43.06 ± 5.13**	94.93 ± 1.97**	100 ± 0**	16.2 ± 0.38
GROUPVI	14.06 ± 2.85**	26.19 ± 2.76*	79.19 ± 5.62*	100 ± 0**	18.4 ± 1.23

Results are expressed as means and ± standard deviation. p values <0.05 and <0.01 were considered statistically significant. Dunnet Test *.

Histological analysis

At the end of the 21-day observation period, the animals were sacrificed and samples were obtained from the area of injury for analysis. Two different stains were performed: Hematoxylin-Eosin and Masson's Trichrome, which are presented in Figure 2. In general, all groups presented a keratinized stratified flat epithelium (white arrow). In the case of Group I (A), the characteristics of the epithelium were normal, with abundant hair follicles in transverse and longitudinal sections in the dermis (purple arrow), little inflammatory infiltrate, and irregular dense connective tissue (yellow arrow and lower box 40x). With Masson's Trichrome stain, the irregularly arranged collagen fibers were shown in blue. Group II (B) presented a thinned epithelium in the peripheral area of the lesion with the absence of keratin in the central area. Absence of hair follicles was observed in the dermis of the injured area with irregular dense connective tissue and a moderate inflammatory infiltrate. Irregular dense connective tissue was observed using Masson's Trichrome stain. Group III (C) showed an epithelium of normal characteristics at the ends of the lesion area with thinning in the center and absence of keratin and hair follicles, as well as abundant vascular congestion (red arrow) and irregular connective tissue with the presence of an infiltrate (lower box 40x). Moderate inflammatory infiltrate was observed. Masson's Trichrome staining revealed irregular connective tissue. Group IV (D) presented a decrease in the area of scarring and moderate fibrosis compared to the groups described above. Mild inflammatory infiltrate was observed. Using Masson's Trichrome stain, it was possible to visualize moderate fibrosis. Group V (E) presented an epithelium with characteristics similar to non-injured tissue with areas of chronic infiltrate and mild vascular congestion, along with some hair follicles and irregular connective tissue. Masson's Trichrome stain shows connective tissue of irregular disposition which agrees with the normal histological description of the dermis. Group VI (F) shows an epithelium with some areas with no keratin and few hair follicles, irregular connective tissue, and the inflammatory infiltrate is moderate. Masson's Trichrome stain shows irregular connective tissue.



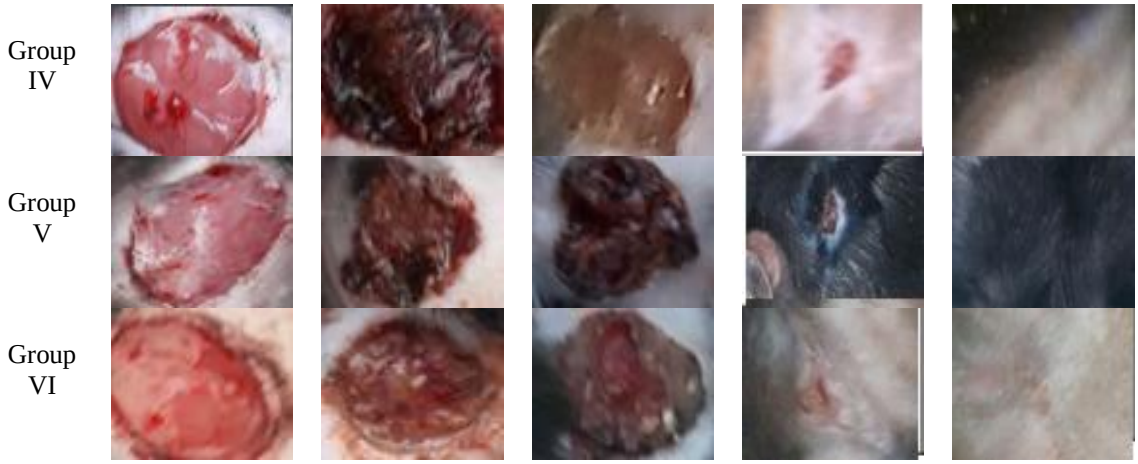


Fig. 1. Photographs of macroscopic wound healing progress among study groups.

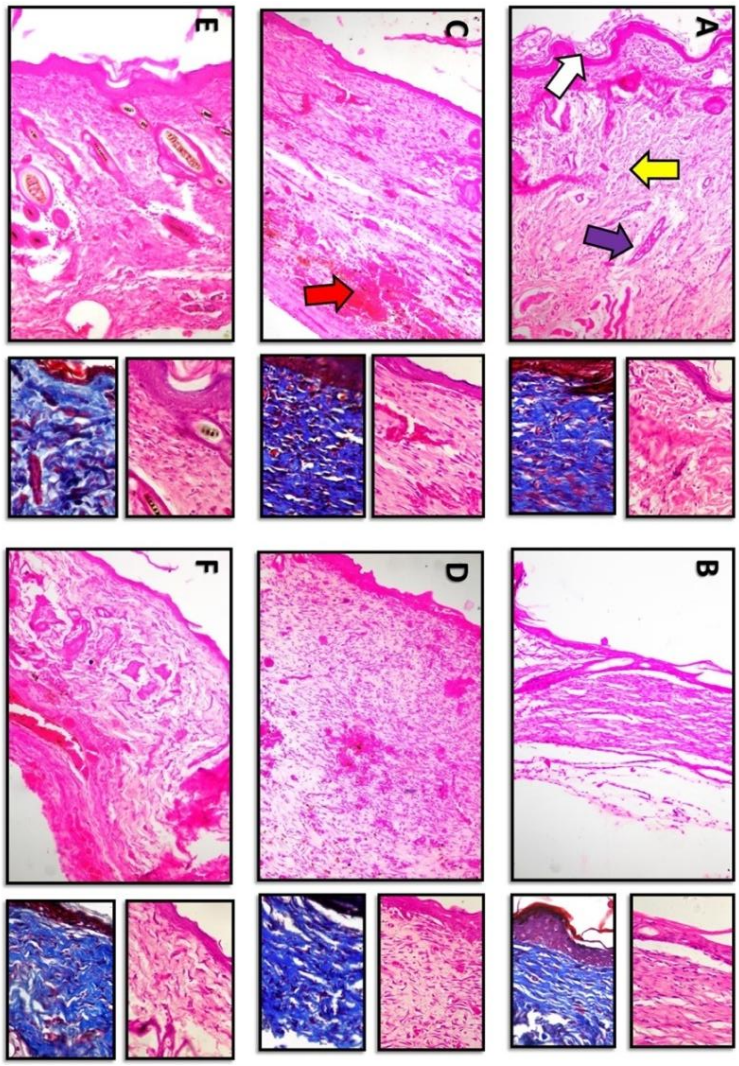


Figure 2. Skin photomicrographs of the study groups: Groups I-VI from A to F. Main figure stained with 10x HE, the upper and lower boxes were observed at 40x and were stained with HE and MT, respectively.

CONCLUSION

The methanolic extract from coriander seeds was shown to be non-toxic based on the biotoxicity assay with the *Artemia salina* model. Among the experimental groups, those that were treated with the extract presented faster and better healing based on histological analysis. This could be largely due to the

phytochemical compounds in the extract, since their properties would help decrease the duration of inflammation, and stimulate the production and viability of collagen fibers. The phytochemical compounds flavonoids, tannins and terpenoids seems to favor the elimination of free radicals and decrease oxidative stress damage leading to an improvement in wound healing.

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