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*Original Research Article*

# *In Vivo* Evaluation of the Wound Healing Potential of the Aerial Parts of *Globularia arabica* Aqueous and Methanol Extracts Grown in Jordan

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ABSTRACT

*Globularia arabica* is a wild, rare, and endangered medicinal plant that is used in folk medicine in Jordan. This study aimed to assess the wound healing potential, total phenol and flavonoid contents, antioxidant activity, and cytotoxic potential of *G. arabica* extracts that were extracted from the aerial parts. *In vivo* wound healing assays were performed using an excision wound model in rats. Animals were treated with a hydrogel formula enriched with plant extracts in two different concentrations (2% and 5%). The results demonstrated that wound healing activity was improved and statistically significant ($p < 0.05$) after topical application of both doses of 2% (w/v) and 5% (w/v) of methanolic (ME) and aqueous extracts (AE) of aerial parts of *G. arabica*. The total phenol and flavonoid contents were appreciably associated with the reductive capacities of both extracts. With respect to the DPPH, the $IC_{50}$ was 26.54 mg/mL for AE, while for ME; it was 18.77 mg/mL, ME and AE were selectively noncytotoxic on PDL fibroblasts.ME was exceptionally more effective than AE, exhibiting pronounced viability reduction propensities for aggressively resistant CACO2 cancer cells. While AE was ascribed more substantial growth inhibition properties in T47D breast adenocarcinoma.
In conclusion, the study revealed that the ME and AE of *G. arabica* displayed remarkable wound healing activity, corroborating its traditional use. Moreover, phytochemical fingerprinting of both crude extracts can associate *G. arabica'*smaximal biological and pharmacological effects with bioactive metabolites.

***Keywords*:** Wound healing, Medicinal plant, Cytotoxicity, Aerial parts, *Globularia arabica*..

## Introduction

Chemical components in natural goods may act as precursors in the manufacture of pharmaceuticals. Plants have been utilized as healers since the dawn of time, and numerous bioactive substances derived from herbal sources are now used as medications or as starting materials for the synthesis of new drugs.[1] Standardized herbal formulations are a well-liked substitute for synthetic medications in Europe, where herbal medicine is frequently used as supportive therapy in the form of teas and decoctions. Almost 80% of the world's population (mainly in underdeveloped nations) continues to use herbal medicine to treat various illnesses and maintain health.[1] Cancer is one of the most serious health issues in the world. Recent research has revealed a strong link between oxidative stress and cancer.[2] In fact, if there is a significant amount of oxygen free radicals present and the cancer process is starting, significant alterations in the cell that suggest the onset of a cancer phenotype can be identified. However, the inflammatory process might lead to the development of cancer.[2] The oxidative damage caused by reactive oxygen species and other free radicals to biomolecules can harm a number of significant types of biological molecules, including DNA, proteins, and lipids.

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This damage may be the cause of numerous human disorders, including inflammatory diseases, cancer, diabetes, heart disease, and arteriosclerosis.[3]
The largest organ in the body is the skin. It serves as the initial line of defense against the internal organs being invaded from the outside. The injury that cracks the skin and leaves a wound can be either acute or chronic, depending on how long it takes for the wound to heal.[4] Inflammation is regarded as a basic physiologic defense against a variety of stressors, including infection, burns, toxic chemicals, allergies, and other stimuli.[3] Burn wound healing is a complex process that includes three stages: inflammation, proliferation, and extracellular matrix remodeling. The healing process's goal is to keep pathogens out, affirm the integrity of damaged tissue, and restore skin physiological function.[5] Chronic inflammation raises the likelihood of resistance and tumor recurrence in cancers including brain and breast cancer, implying that reducing inflammation could be viable cancer prevention and treatment method.[3]Numerous *in vitro*, *in vivo*, and clinical studies have demonstrated the antibacterial and wound-healing abilities of various medicinal plants used in traditional medicine.[6] The variety of plant species in the Jordanian flora is impressive. There are more than 2000 species in Jordan, which are divided into 120 families and 719 genera. 20% of Jordan's total flora is thought to be made up of medicinal plants, which are employed both in conventional medicine and the pharmaceutical sector.[7]
Plants belonging to the genus *Globularia* are found in the Mediterranean, Europe, and North East Africa. They comprise herbs, chamaephytes, and shrubs.[8]*G. arabica*, a member of the Plantaginaceae family, is a rare, wild, and endangered medicinal plant that grows in Jordan. Arabic names for *G. arabica* include Zraiga. The leaves are used to heal ulcers, cancer, cancerous tumors, and rheumatism.[9]Moreover, *Globularia* species are known for their anti-microbial and anti-tumor properties.[10-11] The therapeutic significance

of *G arabica*, as well as the scarcity of knowledge on its chemical structure, and its anti-microbial, anti-proliferative, antioxidant, and wound healing capabilities in living systems, make this study important. Furthermore, this study will highlight the significance of this medicinal herb in Jordanian traditional medicine.

## Materials and Methods

*Plant materials*

The aerial parts of *G. arabica* studied were collected from Jordan in April 2022, specifically the Dana Reserve and Petra areas in the south of Jordan. The plants were identified and authenticated by Prof. Dr. Sawsan Oran, a plant taxonomist. Voucher specimen Ga1 was deposited at the Herbarium, the University of Jordan.

*Plant extraction*

The dried powder of aerial parts of *G. arabica* was extracted with water (AE) and methanol (ME). *G. arabica* aerial parts were carefully cleaned three times in distilled water before being shade dried at room temperature (23–25°C) for 2–3 weeks at the botany research lab at the department of biological sciences at the University of Jordan; dried aerial parts were powdered using an electrical blender. One hundred grams of powder were dissolved in 1000 ml of methanol (10:1 v/w ratio) and stirred for 3 days using a magnetic stirrer. Whitman No. 1 filter paper was used to filter the extraction. The filtrate was then concentrated using a rotary evaporator (Laborota 4000, Heidolph, Germany) at 45 °C under reduced pressure to remove the solvent from the extract. The extract was kept in the refrigerator for further study.[12-13] The AE of *G. arabica* aerial parts was made by soaking 100 grams of dried plant materials in 1000 ml of distilled water for 72 hours. After that, the mixture was filtered to eliminate any particle materials before being lyophilized. The extract (the solid-like substance that precipitated) was kept at -4°C until further examination.[14]

*Determination of total phenolic content (TPC)`*

Using gallic acid as a reference, the total phenolic content of each *G. arabica* extract was determined using the Folin-Ciocalteu reagent technique.[15] The concentration of each *G. arabica* extract was diluted in distilled water to 1 mg/mL, and then 0.5 mL of the dissolved extract was combined with 2.5 mL of the Folin-Ciocalteu reagent (previously diluted 10-fold with distilled water). The mixture was combined and incubated for 3 minutes in the dark, and then 2 mL of $NaHCO_3$ (7.5%) was added. The absorbance at 760 nm was measured against a blank sample using a spectrophotometer after 30 min at room temperature in the dark (ISKRA, MA9523-SPEKOL 211). For each analysis, the samples were produced in triplicate, and the mean absorbance was calculated. Gallic acid concentrations (Sigma-Aldrich, USA) ranging from 0.03 to 0.5 mg/mL are used for the calibration of a standard curve. The unit (mg gallic acid equivalent/g) was used as an equivalent for measuring total phenol content in these assays.

*Determination of total flavonoid content (TFC)*

The aluminum chloride colorimetric method is used to determine total flavonoid concentration.[16] 3 ml methanol, 0.2 ml potassium acetate (1 M), 0.2 ml $AlCl_3$ (10%), and 5.6 ml distilled water are mixed with 1 ml of a diluted solution (with a concentration of 1 mg/ml) of each *G. arabica* extract. Except for extraction, the blank is prepared in the same way. For 30 minutes, the mixture is incubated at 25 °C. At 415 nm, the absorbance is measured. The calibration curve is made with quercetin (100-200 µg/ml). TFC is measured in milligrams of quercetin equivalent (QE) per gram of extract. All of the numbers are repeated three times.

*Antioxidant activity determined by 2,2-diphenyl-1-picrylhydrazyl(DPPH) assay*

According to the procedure outlined by Mariem*et al*. (2014),[17] the antioxidant activity of *G. arabica* extracts was assessed in terms of hydrogen-donating or radical-scavenging capacity using the stable free radical DPPH as a reagent. 0.5 mL of the test sample at varying concentrations (1–10 mg/mL) was mixed with 0.125 mL of the 0.5 mM DPPH solution (0.1 mM in ethanol) and 0.5 mL of 99.5% ethanol. After shaking, the mixture was incubated for 60 minutes at room temperature in the dark before the absorbance at 517 nm was measured using a blank (methanol). Ascorbic acid (5-400 µg/mL) was used as a positive control.

The extract's inhibition of the DPPH radical is estimated using the following equation:

$$\text{Percentage of inhibition} = \frac{\text{Absorbance of control} - \text{absorbance of sample}}{\text{Absorbance of control}} x\ 100$$

All reagents were added for the control, excluding extracts. The reaction mixture's lower absorbance suggested a higher level of DPPH scavenging activity. The $IC_{50}$ value is calculated using a calibration curve of free radical scavenging activity percent versus extract concentrations (the concentration of the extract required to scavenge 50 % of DPPH free radicals).[18] The antioxidant activity increases as the $IC_{50}$ value decreases. The standard utilized was ascorbic acid.

*Wound healing activity*

*Preparation of plant extract-loaded hydrogel formula for in vivo wound healing study*

The hydroxyapatite (0.5 g) was mixed with 98 ml of distilled water until completely dispersed; then the AE or ME was added (in two concentrations each: 2 percent and 5 percent). As a control, an extract-free recipe was employed. The flask was filled with 25 grams of Pluronic F-127, which was cooled in the refrigerator for 3-4 hours until the poloxamer was entirely dissolved. Chitosan (3 g) was added with agitation, and then 2 ml of acetic acid was added to solubilize the chitosan. Finally, drop-wise addition of 100 µL of 2% aqueous glutaraldehyde solution, which functions as a cross-linking agent for chitosan, with stirring results in a hydrogel consistency suited for topical application.[19]

*Excision wound model*

The rats were divided into six major grouping, each with six rats. Before beginning the tests, the rats were acclimatized to laboratory settings for 7 days. A normal pellet meal, as well as water ad libitum, was given to all of the rats. Rats were kept in individual cages for the duration of the trial. A day before starting the wound healing experiment, an electrical clipper was used to shave the animals' dorsal skin (a Gemey professional hair clipper), and the animals were randomly divided into six groups: Group 1, the negative control group was treated with ointment base only; Group 2, the positive control group was treated with Ialuset® Plus cream; Group 3 was treated with a hydrogel formula containing 2 % AE; Group 4 was treated with a hydrogel formula containing 5 % AE; Group 5 was treated with a hydrogel formula containing 2% ME; and Group 6 was treated with a hydrogel formula containing 5 % ME.

The following day (d1), full anesthesia was achieved by inhalation using diethyl ether. After that, a full-thickness excision wound with dimensions of 10×10 mm was formed using a 10-mm-diameter circular biopsy (Disposable Biopsy Punch, ROBBINS Instrument, University of Jordan).[22]

The wound was cleaned with a cotton swab soaked in alcohol and the plant extracts and hyaluronic acid were applied on the wound (as an ointment on the wound area) extending slightly outside the wound region to ensure that the wound borders were included. The initial application took place right after the wound has been inducted. Starting on day 1, the wound area was measured as follows (0, 4, 7, 10 and 14 days) by digital caliper (ACCURATE MEASUREMENT WWW.ACCUD.COM, University of Jordan) and photographed picture using digital camera.

The percentage change from the initial wound size using the following formula:

$$\text{Percentage Wound Contraction} = \frac{\text{Initial wound size} - \text{specific day wound size}}{\text{Initial wound size}} x\ 100$$

*In vitro antiproliferation assay*

*Cell culture*

*G. arabica* extracts were tested on human cancer cell lines to see if they were cytotoxic. The American Type Culture Collection (ATCC)

company sold cell lines for colorectal adenocarcinoma (Caco II) (ATCC® HTB-37), breast cancer (T47D) (ATCC® HTB-133D), and Normal human fibroblast (PDL) (ATCC® PCS-201-041) as a control. All cell lines were cultured in Dulbecco's modified eagle medium (DMEM), supplemented with 50 ml heat-inactivated fetal bovine serum (10% FBS), 5 ml of 1% L-glutamine (2 mM), and 5 ml penicillin (100U/ml)-streptomycin (100 µg/ml), and they were kept at 37 degrees Celsius in a vented flask in a 5% CO2 atmosphere with 95% humidity. All cell culture work was done in a sterile environment in a laminar airflow cabinet.[20]

*Viability assay for antiproliferative capacities of test extracts: In vitro cytotoxicity*

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) test was used to assess the cytotoxic activity of plant extracts. After incubation with varying concentrations of plant extracts, the MTT test was performed to determine cell viability. The succinate dehydrogenase system of mitochondrial live cells reduces MTT (yellow, water-soluble tetrazolium salt), resulting in water-insoluble purple formazan crystals that may be quantified spectrophotometrically following solubilization (Peng *et al.*, 2005).[21] MTT has been used for a long time to measure cell viability in cell proliferation and cytotoxicity because the amount of formazan produced is directly proportional to the number of viable cells in the culture (Peng e*t al.*, 2005).[21] The MTT assay was performed using the procedures previously described by Bustanji*et al.* (2012).[20] MTT was dissolved in PBS at a concentration of 5 mg/ml. Blank wells containing only fresh media and negative control wells without treatment (cells with media). The indicated extract samples were dissolved in 100 µl of media, and they were added to the cells at final concentrations of 3.125, 6.25, 12.5, 25, and 50, 100, 200, 400, and 800 µg/mL, respectively (96 wells in total). As a positive control, nine different concentrations of Doxorubicin (an anticancer drug) were generated at 200, 100, 50, 25, 10, 5, 1, 0.5, and 0.1 µg/ml and as a robust and classical antineoplastic apoptogenic reference agent; cisplatin (1-200 µM) was recruited for comparison purposes. After 72 hours of incubation, added 20 µL of MTT to each well and incubated them for 3 hours. After that, the MTT was carefully removed, and 200 µL of DMSO was added to each well to dissolve the crystal that had formed. On a plate reader (BIO-TEK UQUANT MXQ200), the absorbance at 570 nm and 630 nm was measured, and the difference between the readings was used to analyze the data.

The percentage of cells that survived was computed as follows:

$$\text{Survival cells (\%)} = \frac{100 - \text{Absorbance of control} - \text{Absorbance of treated}}{Absrobance\ of\ control} \ x\ 100$$

The $IC_{50}$ values were defined as doses that inhibited cell growth by 50% in any of the tested cell lines. The average of three replicates was used to detect $IC_{50}$ values. The selectivity index (SI) was computed by dividing the $IC_{50}$ value of the normal cell line (fibroblast) by the $IC_{50}$ value obtained for the cancer cell line.

*Statistical analysis*

Considering the nonparametric test. Wound contractions were compared using the paired t test. $p < 0.05$ were considered statistically significant over control. Data were analyzed using GraphPad Prism version 9.5.0 software.

*Ethical clearance*

All applicable guidelines for the care and use of animals were followed. The experimental protocols involving the rats used in this study were reviewed and approved by the animal ethics committee at the University of Jordan (decision number 88-2022).

## Results and Discussion

Because it exhibits a broad range of biological properties, many of which are exploited in the pharmaceutical industries, the genus *Globulari*a is of great interest in traditional medicine. In Jordan, however, there is little information available regarding the biological activity of AE and ME of *G. arabica*. As a result, in the current study, AE and ME from the aerial parts of *G. arabica* were assessed for their antioxidant, wound-healing, and cytotoxic properties. Furthermore, estimates of the total phenolic and flavonoid contents were determined by colorimetric methods. The obtained results revealed that the amount of phenol was 32.3±1.89 mg GAE/g, and the total flavonoid content was 78.5±2.08 mg QE/g in the AE, while the amount of phenol was 64.0±3.38 mg GAE/g, and the total flavonoid content was 172.9±4.28 mg QE/g in the ME**(Table 1).** These findings highlight the plant's enormous potential as an anti-inflammatory, antibacterial, and antioxidant. The majority of flavonoids have been found to have anti-inflammatory, antioxidant, and free radical scavenging properties. [23-29] With respect to the DPPH radical scavenging activity, the $IC_{50}$ was 26.54 mg/mL for the *G. arabica* AE, while for the *G. arabica* ME, it was 18.77 mg/mL (Table 2).

*Wound healing potentials of methanolic and aqueous extracts of aerial parts of G. arabica in the rat.*

The results of the present study showed that wound healing activity was improved and statistically significant ($p < 0.05$) after topical application of both doses of 2 % (w/v) and 5 % (w/v) of ME and AE of aerial parts of *G. arabica*, these results in agreement with study of most recently *In vitro* and *in vivo* wound healing activities Alsarayreh *et al*[30] and burn wound healing (Alsarayreh *et al*., 2022b)[31] of *G. arabica* leaf methanol extract in diabetic rats who reported that diabetes is a factor that affects the healing process since the wound contraction in the control non-diabetic untreated groups was substantially ($p < 0.05$) higher than in the control untreated diabetic groups.

Using the rat excision model, different doses of plant extracts were used as an ointment on the wound area. There was a highly significant increase in wound contraction compared to the control group, and wound healing was noted in the 2% and 5% *G. arabica*-treated groups. Table 3 records the contraction that the wounds of various groups have decreased over the course of 14 days. At 0 days, 4 days, 7 days, 10 days, and 14 days following surgery, the wound area in wound rats in all groups was measured. There was a very high and significant rate of wound closure between days 7 and 14. When compared to the control groups treated with hyaluronic acid and silver sulfadiazine, the ME and AE of aerial parts of *G. arabica* have significantly greater ($p < 0.05$) wound healing activity. For rats treated with *G. arabica*, the 14th day was shown to be the morphological depiction of wound contraction (Figure 1). In addition, 5% *G. arabica* treatments significantly improved wound healing in wound rats compared to the control group (Table 3).

The outcomes of the plant extracts when applied topically were evaluated in this study. The various stages of wound healing, including collagen synthesis, fibroplasia, and wound contraction, may be positively influenced by the plants, leading to quicker recovery.[32] The results of this study demonstrated that neither the ME nor the AE of *G. arabica*'s aerial parts caused the rats any discomfort or irritability while the wounds were being treated.

**Table 1:** Total phenol and flavonoid contents in aqueous and methanol extracts of *G. arabica*

| Sample | Phenol (mg GAE/g extract) | Flavonoid (mg QE/g extract) |
|---|---|---|
| *G. arabica* AE | 32.3 ± 1.89 | 78.5 ± 2.08 |
| *G. arabica* ME | 64.0 ± 3.38 | 172.9 ± 4.28 |

**AE**: Aqueous Extracts. **ME**: Methanol Extracts. **GAE**: Gallic Acid Equivalent. **QE**: Quercetin Equivalent.

**Table 2**: DPPH-radical scavenging properties vs. ascorbic acid of the tested extracts (µg/mL).

| Sample | DPPH- $IC_{50}$ value | Ascorbic Acid |
|---|---|---|
| *G. arabica* AE | 26.54 ± 1.02 µg/mL | 7.49 ± 1.36 µM |
| *G. arabica* ME | 18.77 ± 1.02 µg/mL | 7.49 ± 1.36 µM |

**AE**: Aqueous Extracts. **ME**: Methanol Extracts.

This outcome is consistent with a study by Kadmi (2012)[33] that found no evidence of biting, restlessness, or scratching at the location of the wound when the extracts were applied.

The results of this study showed that the ME and AE of aerial parts used in this study have a real impact on how quickly excision wounds healed. When compared to the control group, which was left untreated or treated with hyaluronic acid and silver sulfadiazine, the treated excision wounds showed a higher rate of wound contraction and a larger healed area. According to the findings of this investigation, the AE and ME of *G. arabica* considerably ($p < 0.05$) accelerated the healing of wounds in injured rats. These findings concur with those of a study by Es-Safi *et al*., (2007)[32], which suggested that the hydromethanolic extract of *G. alypum* might be employed as a source of antioxidants, boost the activities of wound healing, and have a function in food technology for medical purposes. Additionally, 73 different chemicals were found in the *G. alypum* ethyl acetate extract. The results confirm the significance of this plant as a natural antioxidant source.[34]

**Table 3:** Effect of *G. arabica* methanolic and aqueous extracts on wound contraction in an excision wound model in rats

| Day | Wound diameter (mm) mean ± SD (percentage of wound contraction) | | | | | |
|---|---|---|---|---|---|---|
| | **Group 1 Negative control (Ointment base only)** | **Group 2 Positive control (Hyaluronic acid + silver sulfadiazine)** | **Group 3 2% AE** | **Group 4 5% AE** | **Group 5 2% ME** | **Group 6 5% ME** |
| 0 | 10.55 ± 0.95 | 10.41 ± 0.49 | 10.6 ± 0.9 | 10.56 ± 0.8 | 10.58 ± 0.8 | 10.58 ± 0.86 |
| | (0 %) | (0 %) | (0 %) | (0 %) | (0 %) | (0 %) |
| 4 | 9.96 ± 0.85 | 9.7 ± 0.56 | 9.5 ± 0.8 | 9.23 ± 0.4 | 9.5 ± 0.99 | 9.23 ± 0.7 |
| | (5.4 %) | (6.8 %) | (10.7 %) | (12.8 %) | (11.9 %) | (12.7 %) |
| 7 | 8.48 ± 0.47 | 8.21 ± 0.64 | 7.25 ± 0.4 | 6.81 ± 0.83 | 6.76 ± 0.68 | 6.44 ± 0.56 |
| | (19.6 %) | (21 %) | (31.7 %) | (35.6 %) | (36 %) | (39 %) |
| 10 | 6.42 ± 0.39 | 5.8 ± 0.79 | 4.8 ± 0.7 | 4.4 ± 0.56 | 3.96 ± 0.7 | 3.76 ± 0.88 |
| | (39 %) | (44 %) | (55 %) | (58 %) | (62.6 %) | (64.5 %) |
| 14 | 4.1 ± 0.85 | 3.24 ± 0.7 | 2.1 ± 0.44 | 1.8 ± 0.8 | 1.95 ± 0.8 | 1.79 ± 0.83 |
| | (61.5 %) | (69 %) | (81 %) | (83 %) | (81.5 %) | (83 %) |

**AE**: Aqueous extracts. **ME**: Methanol extracts **SD:** Standard deviation **mm:** millimeter

Additionally, *G. alypum* has been demonstrated to have anti-ulcer properties against stomach mucosal injury by preventing intraepithelial lymphocyte migration, according to a study by Harzallah*et al*. (2010).[35] Additionally, the *G. alypum* leaf aqueous extracts contain significant amounts of antibacterial and antigenotoxic substances, suggesting that they may be useful for chemoprevention. [36] In addition, *G. alypum* leaf hydroethanolic extract (HEGA) contains flavonoids, polyphenols, and anthocyanins, and when tested in HeLa cells, it demonstrated significant antioxidant and wound healing activities.[37] The methanol extract of *G. alypum* also contains high concentrations of flavonoids and phenolic chemicals, which contributed to the plant's potent wound-healing properties and demonstrated excellent antioxidant activity.[38]

Additionally, the wound diameter measures are included in **Figure 2** by comparing different group treatments with the negative group. To make topical application to the wounds easier, the extracts were added to a hydrogel composition made of cross-linked chitosan, hydroxyapatite, and pluronic F127. A topical application of ME and AE of aerial parts of *G. arabica* to the rounded region of the excision wound considerably accelerated the rate of wound healing, as shown by the wound diameter (mm) mean ± SD of all wounds for different groups. For instance, beginning on day 7, two dosages of the AE and ME of aerial parts of *G. arabica* (2 % w/v and 5 % w/v) showed a reduction in the wound diameter (mm), as shown by an decreeing in the wound diameter (mm) mean ± SD (7.25 ± 0.4, 6.81 ± 0.83, 6.76 ± 0.68, and 6.44 ± 0.56, respectively), as compared to wound diameter (mm) mean ± SD in the negative control. Day 14 marked the conclusion of the experiment; the 5% (w/v) concentration of ME and AE of aerial parts of *G. arabica* acquired the minimum of wound diameter (mm) mean ± SD (1.79 ± 0.83, and 1.8 ± 0.8, respectively), followed by the 2% (w/v) concentration of ME and AE of aerial parts of *G. arabica* (1.95 ± 0.8, and 2.1 ± 0.44, respectively). On the other hand, the negative group showed a maximal of wound diameter (4.1 ± 0.85).

*In vitro cytotoxicity of G. arabica extracts*

In Tables 4 doxorubicin had highly pronounced antiproliferation efficacies of 5nM< $IC_{50}$ values <15 µM in cancer monolayers of gastrointestinal (colorectal), and breast. Using MTT bioassay; Cisplatin exerted marked dose-dependent viability reductions of (0.4-61.85 µM) in colorectal cancer cells of CACO2 as well as T47D breast cancer cells. ME of *G. arabica* were exceptionally more effective than AE exhibiting pronounced viability reduction propensities for aggressively resistant CACO2 cancer cells (the same Table).Unlike cisplatin's dose-dependent apoptogenicantitumorigenesis effectiveness of $IC_{50}$ values ≤30 µM in breast cancer monolayers;*G. arabica's* crude AE of aerial parts was ascribed more substantial growth inhibition properties in T47D breast adenocarcinoma 72hr incubations vs. those of crude ME.Unlike cisplatin's lack of selective cytotoxicity, all tested aqueous and methanolic extracts were selectively noncytotoxic on the periodontal ligament (PDL) fibroblasts, showing a remarkable similarity to cytotoxic doxorubicin. As can be shown, a human fibroblast cell line was not affected negatively by the ME and AE of *G. arabica*. In the current study, the cytotoxic potential of both crude extracts was evaluated for the first time. Since there are few publications on *G. arabica*, more phytochemical research and fractionation toward activity seem to be advised.

## Conclusion

The experimental data revealed that the ME and AE of *G. arabica* displayed remarkable wound healing activity, corroborating its traditional use. Moreover, phytochemical fingerprinting of both crude extracts can associate *G. arabica'*smaximal biological and pharmacological effects with bioactive metabolites.

## Conflict of Interest

The authors declare no conflict of interest.

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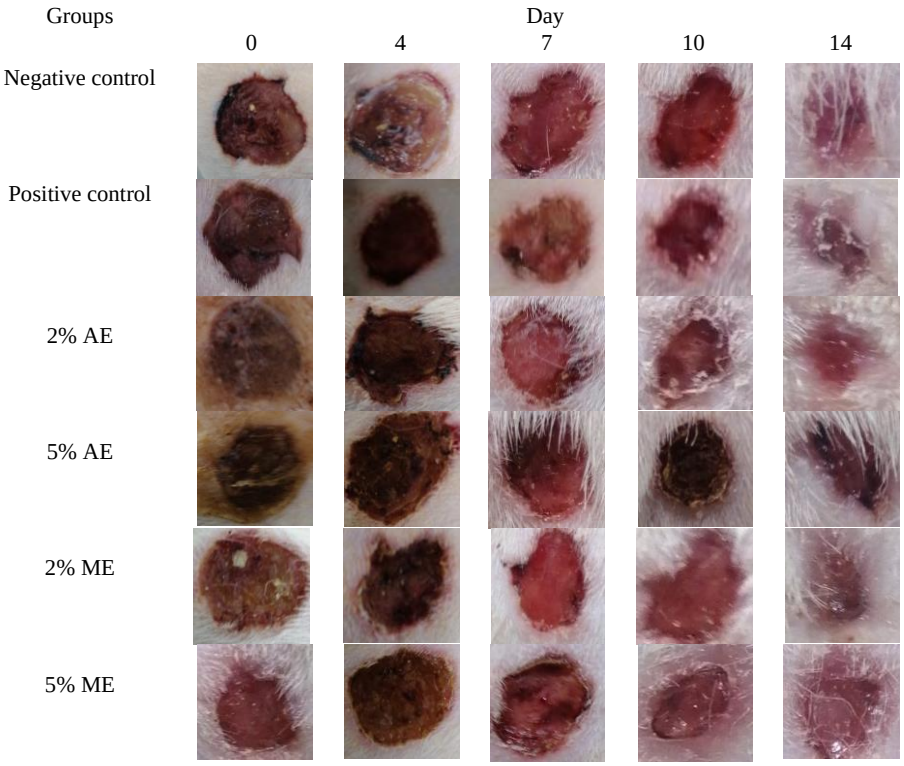


**Figure 1:** Morphological representations of excision wound contraction treated with *G. arabica* aqueous and methanolic extracts in rats

**Table 4:** Cytotoxicity $IC_{50}$ values of test extracts (µg/mL) vs. reference agents (µM) against colorectal, breast cancer cells and PDLfibroblasts.

| Treatment | CACO2 | T47D breast cancer | PDL fibroblasts |
|---|---|---|---|
| *G. arabica* AE | 322.2 ± 34.68 µg/mL | 276.43 ± 26.67 µg/mL | 765.51 ± 124.04 µg/mL |
| *G. arabica* ME | 221.67 ± 43.25 µg/mL | NI µg/mL | 900.3 ± 142.58 µg/mL |
| Cisplatin | 4.88 ± 0.59 µM | 16.85 ± 2.19µM | 5.6 ± 0.53 µM |
| Doxorubicin | 1.90 ± 0.1µM | 0.02 ± 0.00µM | NI |

**NI:** Non-Inhibitory within testing dose range. **AE**: Aqueous Extracts. **ME**: Methanol Extracts.

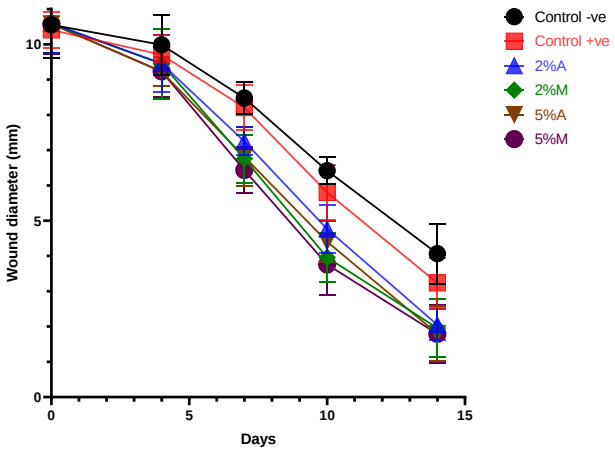


**Figure 2**: The wound diameter (mm) mean ± standard deviation of all wounds vs. negative control. The significance of the time in days on the wound healing was highly significant, $p < 0.05$. In addition, the number of rats is 6 in each group from day 0 to day 14, and n = 6 until the end of the experiment.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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