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Original Article

Wound Healing Activity of an Ointment from *Solanum tuberosum* L. "Tumbay Yellow Potato" on *Mus musculus* Balb/c

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ABSTRACT

Background: *Solanum tuberosum* L. is an Andean tuber that is mainly characterized by its antioxidant properties. **Objective:** To evaluate the healing activity of an *S. tuberosum*-based ointment on wounds induced in mice. **Material and methods:** Ethanolic extracts of peel and pulp of tubers of *S. tuberosum* "Tumbay yellow potato" were prepared, which were incorporated into 1% and 2% ointment formulations. *Mus musculus* Balb/c with induced wound were distributed in the following working groups: Group I (Negative Control), Group II (Positive Control: Neomycin, Polymyxin B and Bacitracin Ointment) and Groups III and IV (Ointment at 1 % and 2% of *S. tuberosum* extract, respectively), daily administration of topical treatments were carried out for 07 days. Wound closure was determined during the experimentation time, then euthanized with sodium pentobarbital 60 mg/kg b.w. (i.p.) to obtain skin samples for histopathological analysis. **Results:** Groups III and IV showed that better evidence of wound closure and scarring in the histopathological analysis, the greatest effect being in Group IV. **Conclusions:** *S. tuberosum* ointments show healing activity in induced wounds in mice, the most effective treatment being the 2% ointment formulation.

Key words: *Solanum tuberosum*, Yellow potato, Wound healing, Histology, Skin.

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INTRODUCTION

Wound healing in the skin involves dynamic and complex processes such as spatial and temporal synchronization of a variety of cell types with different functions in the stages of hemostasis, inflammation, growth, re-epithelialization, and remodeling.[1-3] Various factors delay the wound healing process, by persuading tissue damage such as repeated injury, infection, oxygenation, generation of free radicals, among others.[4] Therefore, in the search for alternative solutions to this problem, the use of a drug or a natural product with antimicrobial, antioxidant, and anti-inflammatory potential could be an important strategy in wound healing.[5,6]

Many phytoconstituents such as flavonoids and polyphenols can heal wounds, in addition to having antioxidant, anti-inflammatory, and antimicrobial actions that contribute to wound healing processes and are generally easily accessible and have limited side effects.[7-9]

The *Solanum* genus has secondary metabolites of therapeutic interest like steroids, free or glycosylated alkaloids, polyphenols, flavonoids, which have multiple pharmacological activities, such as analgesic, cytotoxic, anticancer, anti-inflammatory, and antimicrobial activities.[10-14]

Solanum tuberosum L. (*S. tuberosum)* "potato" is the third most consumed food crop in the world, mainly in Asia, Africa, and Latin America.[15] *S. tuberosum* is an important source of phenolic compounds such as chlorogenic acid and gallic acid, besides, it has flavonoids principally in its peel, these phytoconstituents exert antioxidant, analgesic, anti-inflammatory activities.[16-20]

S. tuberosum "potato" is used in the elaboration of food products, medicines, and packaging. Likewise, it has recently been found that pigmented potatoes that contain high concentrations of anthocyanins and carotenoids could have potential medicinal utility.[21]

Anthocyanins and phenolic compounds have been used to treat oral healing of topical wounds in rats, and *S. tuberosum* has a higher potential as a source of phenolic compounds.[22] Additionally, *S. tuberosum* has been used as a mask for treating mild acne, maybe for its antibacterial activity, some that can increase its wound healing activity.[23]

This study has the purpose to evaluate the effect of an ointment made from the ethanolic extract of *S. tuberosum* L. var. "Tumbay yellow potato" on skin induced wounds of *Mus musculus* Balb/c.

MATERIALS AND METHODS

Biological material

Mus musculus Balb/c (30 - 35 g) males, 12-14 weeks old, obtained from the Instituto Nacional de Salud (INS), were used for this investigation. All mice were kept in individual cages and standard photoperiod environmental conditions (12:12 dark: light cycle)

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with a temperature of 25 ± 2 °C. They were provided with balanced food and water administered *ad libitum*. The study was approved by the Ethics Committee of the Faculty of Pharmacy and Biochemistry of the Universidad Nacional de Trujillo with the document COD. N°: P-008-19/CEIFYB.

Vegetal material

Tubers of *S. tuberosum* L. collected at 3404 m, in the Villamaria farmhouse, Carabamba district, Julcán province, La Libertad, Peru. Taxonomic identification was carried out in the Truxillense Herbarium of the Universidad Nacional de Trujillo, with code N° 59729.

Preparation of the extract

The tubers were washed and cut, then the peel and pulp were separated to obtain extracts from each one. They were macerated in 96% ethanol for 72 hours in amber flasks, with daily shaking, subsequent filtration, concentration in a rotary evaporator at 40 °C and them, it was brought to dryness in an oven at 40°C for 48 hours. Obtained the dry extracts were stored in an amber bottle and stored at -20 °C.[24]

Determination of total phenolics compounds (TP)

The TP was determined according to the Folin-Ciocalteu modified procedure by Amri. For it, four milligrams of each crude extracts of peel and pulp of *S. tuberosum* were dissolved in 4 ml of methanol. 400 µL each extract sample was taken in other tubes and added to 3 ml of 10% Folin-Ciocalteu and incubated for 5 min at 40° C. Finally, 3 ml of 6% Na_2CO_3 was added and incubated those tubes for 2 h at 40° C with covered test tubes with aluminum foil. After 2 h incubation, UV–Vis spectrophotometer at 760 nm was used to measure the absorbance. The TP was calculated from the standard curve prepared by the addition of two milligrams of gallic acid with 10 ml of methanol. The concentrations (200, 100, 50, 25 and 12.5 µg/ml) were prepared from the stock solution. The results were expressed as mg gallic acid equivalents (GAE) /g extract.[25]

Determination of antioxidant activity

DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) scavenging ability assay was used to evaluate the antioxidant activity of each extract of *S. tuberosum*. The test was conducted in a 96-well plate according to Sembiring et al. 20 µL stock solution of extracts in different concentrations (100, 500, 1000, 1500, 2000 ppm) and 180 µL of DPPH solution 0.147 mM were added to each well. After 30 min incubation at room temperature in a dark room, absorbance was read at 517 nm using a microplate reader. Methanol was used as blank. The scavenging ability (%) was calculated as follows:

$$\%Inhibition = \frac{Absorbance\ of\ standard - Absorbance\ of\ crude\ extract}{Absorbance\ of\ standard}\ x\ 100$$

Ascorbic acid was used as a positive standard. All tests were performed in triplicate. The concentration of samples resulting in 50% inhibition on DPPH (IC_{50} value) was calculated.[26]

Preparation of ointments

The preparation of the base ointment was performed with a formulation containing 30% anhydrous lanolin, 0.02% butylhydroxytoluene and solid petrolatum q.s. 100%. *S. tuberosum* peel and pulp extract (1:1) were incorporated until obtaining the established concentrations (1% and 2%) immediately after the production of each formulation was transferred to double-walled plastic containers. The formulations were packaged, labeled, and stored at room temperature until use.[27,28]

Assessment of healing activity

The back of all mice were depilated for wound induction, 24 hours later, 2% lidocaine cream anesthetic was applied topically, and the cut was made parallel to the longitudinal axis in the dorsal part of the mice, approximately 1 cm in length. Measurement was made with the help of a vernier caliper.[29]

The 32 *Mus musculus* Balb/c were randomized into 4 experimental groups with 8 specimens per group: Group I (Negative Control), which no treatment was applied, Group II (Positive Control: Neomycin Ointment, Polymyxin B and Bacitracin), Group III (Ointment 1%), and Group IV (Ointment 2%) whose ointments were applied daily topically for 7 days using sterile swabs. The wound healing process was recorded through the wound closure measurement parameter, evaluated during the 7 days of treatment.

The wound healing results were expressed as graphics were prepared using Microsoft Excel®, and the data were subjected to an analysis of variance (ANOVA) and Tukey's test for post-hoc comparisons. Values are considered statistically significant at $p < 0.05$.

Histopathological study

After 7 days of treatment, the experimental animals were euthanized using sodium pentobarbital 60 mg/kg v.ip, and skin samples were subsequently obtained by making cuts 1.5 cm long and 1 cm wide around the scar. These samples were stored in sterile vials with a 10% formalin solution for 8 days, then parts of 3-5 µm were selected and fixed in paraffin. Subsequently, they were stained with Hematoxylin-Eosin to perform the reading in a microscope.[30-31]

RESULTS

Determination of total phenolics compounds (TP)

The amount TP of *S. tuberosum* L. extract as determined by the Folin-Ciocalteu method reported as gallic acid equivalents (Figure 1 and Table 1).

Wound healing evaluation

The percentage of wound closure is a parameter that is used to determine the evolution of the healing process. The wound closure percentages on day 7 for Groups III (Ointment 1%) and IV (Ointment 2%) showed a significant difference compared to Group I (Negative Control) and Group II (Positive Control) ($p < 0.05$), this effect is greater in Group IV (Figure 2) but is not significantly different from Group III. Figure 2 shows that there is a higher wound closure rate with the use of the ointment, either at concentrations of 1% or 2%.

Histopathological changes

Histopathological changes in mice skin in Group I (Control) showed less differentiation of the basal cell layer and the presence of the scab or eschar. Few fibroblasts arranged in parallel are shown in the connective tissue, as a sign of physiological scarring, also, there is the presence of inflammatory cells in the tissue evaluated (Figure 3A). Group II showed recovery of dermal ridges or papillae, indicative of re-epithelialization. Besides, a less amount of fibroblasts and collagen fibers are observed, an effect attributable to the activity of healing cream (Figure 3B).

Groups III and IV that received the *S. tuberosum* ointment showed greater healing activity. Group III showed reepithelialization continuity

Table 1: Total Phenolic Content and Antioxidant DPPH Scavenging Activity of *S. tuberosum* extracts.

Sample	Folin-Ciocalteau (mg GAE/g extract)	DPPH assay (% inhibition)
peel	34.53 ± 1.19	76. 39 ± 1.45
pulp	8.02 ± 3.12	213.82 ± 2.34
Ascorbic Acid	-	1.85 ± 0.89

Data are mean ± SEM for triplicate measurements.

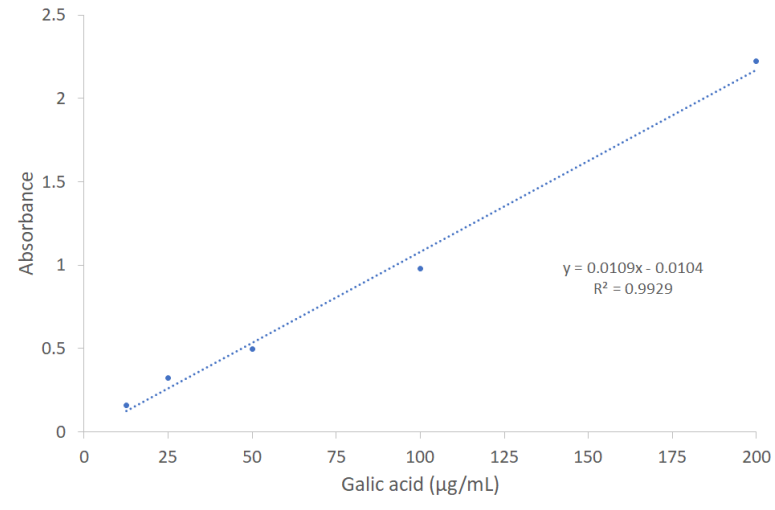

Figure 1: Gallic acid calibration curve.

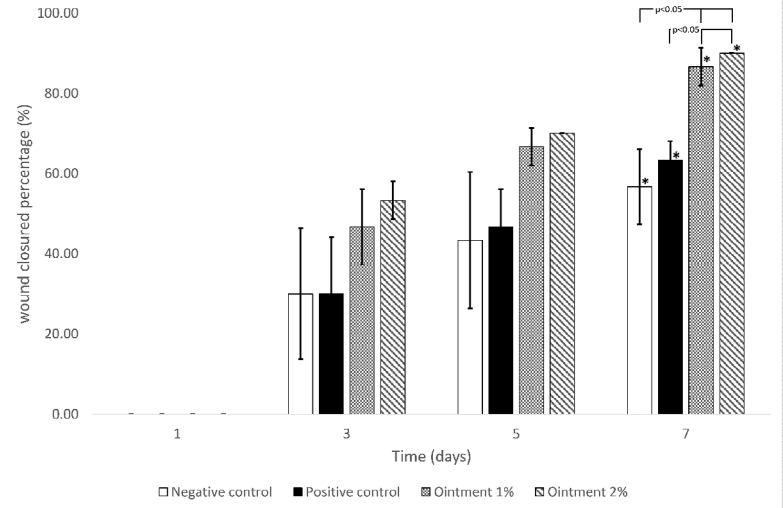

Figure 2: Evaluation of wound closure in the experimental groups. p<0.05, n=8.

at the epidermis level, observing sebaceous glands, appear collagen and fibroblasts that move vertically to the injured area, indicating a favorable prognosis in wound healing (Figure 3C). In group IV, hair follicles were observed and evidence of a large number of fibroblasts arranged in a horizontal arrangement, indicative of a reparative process attributable to the effect of *S. tuberosum* ointment (Figure 3D).

DISCUSSION

Redox signaling and increased oxidative stress play a significant role in normal wound healing by facilitating hemostasis, inflammation, angiogenesis, granulation tissue formation and wound closure. Physiologically, hydrogen peroxide (H_2O_2) and superoxide serve as intracellular messengers stimulating key phases of wound healing including cell recruitment, production of cytokines and angiogenesis. The hydrogen peroxide (H_2O_2) is generated by neutrophils and macrophages *via* NADPH oxidase. Besides, ROS high levels in the skin promote activation of a variety of transcription factors including nuclear factor kappa B (NF-kB), activator protein 1 (AP-1), nuclear factor erythroid-derived 2-like 2 (Nrf2), and mitogen-activated protein kinase (MAPK) pathways.[32-34]

Medicinal plant extracts that have phenolic components have a potent ability to act as an antioxidant, antibacterial and anti-inflammatory agent, which accelerate the rapid healing of damaged skin tissue, as they act at various stages of wound healing, i.e., collagenation, wound closure and epithelialization due to biological properties, in addition to reducing damage caused by oxygen radicals in the area of dermal injury.[35-37]

The phytoconstituents present in both the pulp and peel of potatoes, such as polyphenols, are characterized for possessing antioxidant, anti-inflammatory, and antimicrobial properties.[38-42] The presence of these phytoconstituents would be responsible for promoting the evolution of wound closure until day 7 of treatment, observing that the groups that received the application of *S. tuberosum* ointments showed an acceleration in wound closure compared to the negative control and positive control groups (Figure 2).

Histological analysis of the mice skin sample in group I (Negative Control) shows the presence of scab or eschar with connective tissue containing fibroblasts, initiating the arrangement parallel to the epidermis. This histological result indicates that the physiological

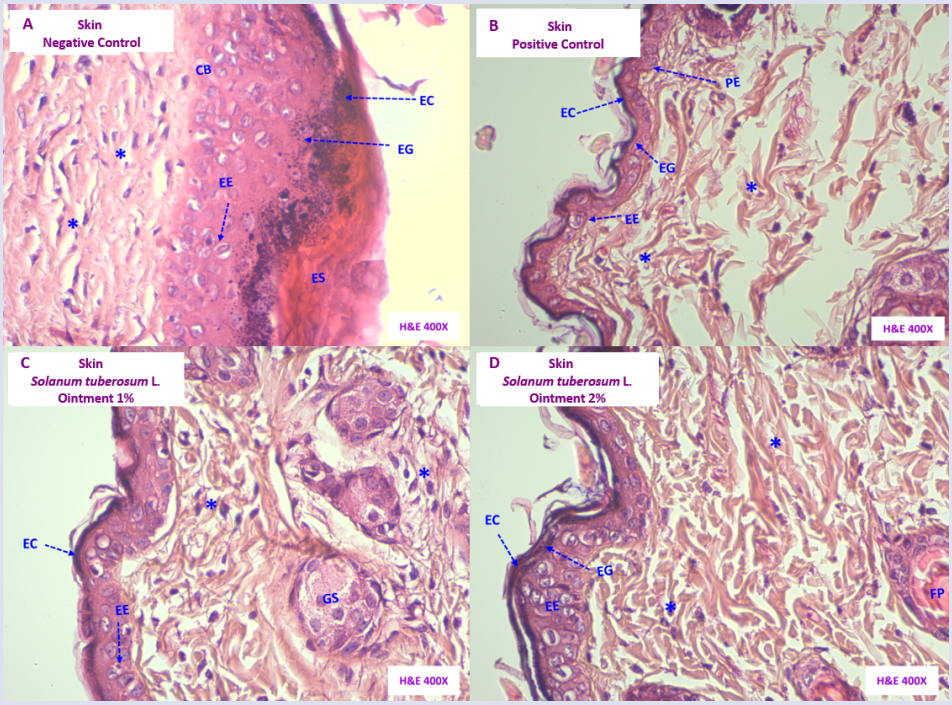

Figure 3: Histopathological cuts of the skin of *Mus musculus* Balb/c. A: Group I (Negative Control). B: Group II. (Positive Control). C: Group III (Ointment 1%). D: Group IV (2% ointment). Keratinous stratum corneum (EC), granular stratum (EG), Langerhans cells in the spinous stratum (EE), basal cells (CB), scab or eschar (ES), dermal papillae (PE), fibroblasts (*), sebaceous glands (GS) (Hematoxylin and Eosin stained, 400X).

healing process has begun, a biological process that is initiated by trauma and often ends by scar formation.[43] However, the groups that received treatment with *S. tuberosum* ointments showed signs of progressive healing with favorable evolution, with the presence of fibroblasts and the absence of crusts or sores. This activity is more evident in the skin analysis of group IV specimens to which 2% ointment was administered, it shows clear evidence of higher fibroblast content (*) in horizontal arrangement indicative of an important advanced reparative process, in addition to the none existing presence of crusts or eschar (Figure 3 D).

S. tuberosum has been previously studied, it was detected that the principal metabolites identified are gallic acid, chlorogenic acid, polyphenols, flavonoids like Rutin, alkaloids like Solanine, among other compounds.[44-47] Within these metabolites, polyphenols and flavonoids have been shown to promote the wound healing process mainly due to their antioxidant, antibacterial capabilities, promoting wound contraction, and increased epithelialization rate. Furthermore, these compounds have been shown to increase collagen synthesis, decreasing the overproduction of free radicals, facilitating oxygen diffusion, and increasing lymphatic drainage, an important event that occurs to improve wound healing.[48-49]

Likewise, the chlorogenic acid reported in *S. tuberosum*, improves the wound healing activity, by acting to produce higher capillary density and promoting the production of collagen. Added to this are its antioxidant and free radical scavenger effects on oxidative parameters, and anti-inflammatory effects on extracellular matrix metalloproteinases (MMP) in wound tissues.[50]

Considering the diversity of the phytoconstituents present in *S. tuberosum*, these can participate individually or give a synergistic effect in wound healing.[51] Likewise, the use of models of wound healing in animals are tools of great importance for the development of new strategies and approaches for the treatment of wound healing.[52] Based on the foregoing, it is postulated that *S. tuberosum* presents a potential source to develop new treatments in wound healing, which allow the achievement of more effective, safe, and affordable medications for patients.[53]

CONCLUSION

S. tuberosum ointment was shown to accelerate the wound healing process induced in the skin of mice, the 2% formulation being the most effective treatment. It is postulated that the healing mechanism of *S. tuberosum* is related to phytoconstituents as phenolic compounds that exert antioxidant, antimicrobial, and anti-inflammatory effects, which contributes to the optimal healing process.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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AUTHOR CONTRIBUTIONS

CRSC and VEVLT wrote the first draft. JCRS collected the plant species and ingressed the specimen to the herbarium. WASG and GPRC carried out the preparation of extracts and topical formulations. AACP and OPS, cared and fed the animals during the investigation, and administered treatments. JLCR and ADGS did the extraction of skin samples for histopathological analysis and JDC and CLAV carried out the statistical analysis and the preparation of images.

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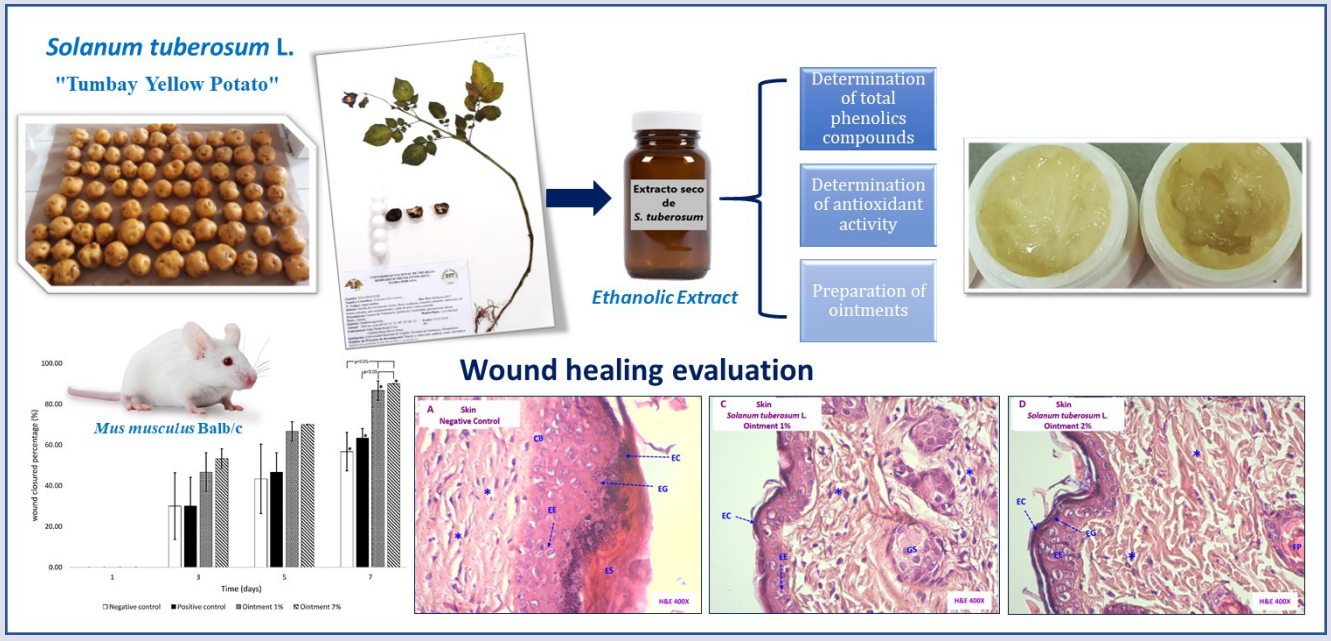
GRAPHICAL ABSTRACT



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