Study of wound healing in rat skin treated with extract of *Hedera helix, L*

Estudo da cura de feridas na pele de rato tratada com extrato de *Hedera helix, L*

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ABSTRACT
The Hera (*Hedera helix* L.) is part of the ARALIACEAE family, is included in the group of plants that produce saponins, has antifungal action, is hypocholesterolemic, has anti-inflammatory activity, is expectorant, antispasmodic and purifying. It was evaluated, by histological studies, the wound healing action of the extract of Hera leaves on skin wounds, as well as changes in the epithelial tissue and wound healing period. 75 Wistar rats were used and divided into five groups, according to the treatment: negative control (PBS), Hera 10 mg/ml, Hera 30 mg/ml, Hera 50 mg/ml and the positive control (Nebacetin). The animals were anesthetized and undergone through a cut of 4 cm in the dorsal region, exposing their muscle fascias. Right after, daily, the suitable substance to each group was applied in the lesion. After periods of 3, 7, 14, 21 days after the surgery, the animals were killed to collect fragments of the lesion. The material was prepared in stained slides with H&E and toluidine blue for histologic analysis. The results showed that at day 14 of treatment, the animals under effect of 30 mg/ml and 50 mg/ml of Hera extract did not present edema. It was also observed a reduction in vascular congestion in the Hera of 30 mg/ml, Hera 50 mg/ml and Nebacetin groups compared to the other groups analyzed. All groups treated with Hera extract showed a reduction of inflammatory cells in day 14 post-lesion, besides the increase of fibroblast this period, showing acceleration in the chronicity of the lesion. Regarding the number of mast cells, a significant increase in the early lesion, in the 3 and 7 days periods was observed, in Hera 50 mg/ml and 30 mg/ml groups, respectively. According to the results, the Hera extract, especially at concentrations of 30 mg/ml and 50 mg/ml accelerated the healing process; based on the decreased permanence period of the edema and congestion of the vessels, as well as changes in the number of cells related to inflammation of lesions.

Keywords: *Hedera helix*, Hera, Wound Healing, Inflammation, Tissue Repair.

RESUMO
A hera (*Hedera helix* L.) faz parte da família araliaceae, está incluída no grupo das plantas produtoras de saponinas, tem ação antifúngica, é hipocolesterolêmica, tem atividade antiinflamatória, é expectorante, antiespasmódico e purificante. Foi avaliada, por meio de estudos histológicos, a ação cicatrizante do extrato das folhas de hera sobre feridas cutâneas, bem como alterações no tecido epitelial e período de cicatrização das feridas. Foram utilizados 75 ratos wistar, divididos em cinco grupos, de acordo com o tratamento: controle negativo (pbs), hera 10 mg / ml, hera 30 mg / ml, hera 50 mg / ml e o controle...
positivo (nebacetina). Os animais foram anestesiados e submetidos a um corte de 4 cm na região dorsal, expondo suas fásicas musculares. Em seguida, diariamente, era aplicada na lesão a substância adequada a cada grupo. Após períodos de 3, 7, 14, 21 dias após a cirurgia, os animais foram sacrificados para coleta de fragmentos da lesão. O material foi preparado em lâminas coradas com h&e e azul de toluidina para análise histológica. Os resultados mostraram que no 14º dia de tratamento, os animais sob efeito de 30 mg / ml e 50 mg / ml de extrato de hera não apresentaram edema. Também foi observada redução da congestão vascular nos grupos hera 30 mg / ml, hera 50 mg / ml e nebacetina em relação aos demais grupos analisados. Todos os grupos tratados com extrato de hera apresentaram redução das células inflamatórias no 14º dia pós-lesão, além do aumento do fibroblasto neste período, evidenciando aceleração na cronicidade da lesão. Em relação ao número de mastócitos, observou-se aumento significativo no início da lesão, nos períodos de 3 e 7 dias, nos grupos hera 50 mg / ml e 30 mg / ml, respectivamente. De acordo com os resultados, o extrato de hera, principalmente nas concentrações de 30 mg / ml e 50 mg / ml, acelerou o processo de cicatrização; baseado na diminuição do tempo de permanência do edema e congestão dos vasos, bem como alterações no número de células relacionadas à inflamação das lesões.

Palavras-chave: hedera helix, hera, cicatrização de feridas, inflamação, reparo de tecidos.

1 INTRODUCTION

Maintaining body homeostasis has been studied since the dawn of mankind, and one of the main concerns of our ancestors was wound healing. Every time you locate a lesion, the body defends itself by physiological processes, such as wound healing, which targets the reestablishment of tissue integrity. This wound healing capacity is crucial for survival, because without it, all wounds would be the gateway for microorganisms and systemic diseases installations (Kim, Mustoe, Clark, 2015; Leoni et al., 2005). Thus, a large number of researches and attempts aimed at discovering substances which could promote acceleration in the healing process.

Currently, the wound healing process is well characterized and involves consecutive stages (Leoni et al., 2005; Gurtner et al., 2008). The first is the inflammatory stage, characterized by increased expression of inflammatory mediators, and consequent migration of leukocytes across the vascular wall and the formation of a plasma flow from the inside out of the vessel. As a result, it was observed in the wound location, an exudate, which is characterized by pain and edema (Schoenmakers, Reitsma, Spek, 2005). After a few days, it is settled the stage of proliferation, in which it is observed a strong mitosis of epithelial cells that lead to the restoration of the continuity of the epithelium. It also presents a greater presence of fibroblasts responsible for the production and turnover of
collagen fibers. This cell proliferation will lead to granulation tissue that fills the space resulting from the removal of necrotic tissues. The last step is the tissue maturation, in which the cell population is replaced by normalizing the amount of collagen fibers and where we observe the complete reestablishment of the epithelial tissue (Kim, Mustoe, Clark, 2015; Leoni et al., 2005; Gurtner et al., 2008). Although well studied and characterized, the epithelial wound healing process requires a difficult to be changed physiological equilibrium, without suffering damage. Thus, the wound healing drug must act controlling the immune/inflammatory response without being completely inhibited; a fact that is not quite easy, since we are still looking for the ideal wound healing agent.

Historically, it is quoted in the literature the ability of different plants in the tissue repair process (Maver et al., 2015). Among them, is the Hera (*Hedera helix* L.), belonging to the ARALIACEAE family. It is originally from Europe and was distributed in temperate regions, especially Asia, North Africa and southern Brazil. Its use as ornamental or medicinal plant dates from the beginning of the Greek and Egyptian civilizations, being widely grown since then (Gepdiremen et al., 2004; Mantle, Gok, Lennard, 2001). Its medicinal properties were recognized in the beginning of the twentieth century, when the Hera berry was used as a violent purgative, due to its high content of hederin saponin, and kidney stones dissolvent (Gepdiremen et al., 2004; Mantle, Gok, Lennard, 2001).

Studies are references to the external use of the plant, in which the decoction of the leaves has been used to heal wounds. Furthermore, its leaves are also widely used to relieve neuralgic pain, heal ulcers and burns (Chiummariello et al., 2009). It is reported that both the crude extract and the purified extract of saponins of Hera leaves have anti-inflammatory effects (Gepdiremen et al., 2005; Suleyman et al., 2003). The compounds having biological activity, responsible for the medicinal use of hera, as saponins (2.5 - 6%), glycosides (0.1 - 4.8%), the hederin (0.1 - 0.3%), and phenolic compounds (phenolic acids, flavonoids, anthocyanins, coumarins), amino acids, steroids and lectins (Gepdiremen et al., 2005) are described. And, these compounds possess anti-inflammatory functions with great wound healing potential.

This work evaluated, by histological studies, the wound healing action of the extract of Hera leaves on skin wounds in rats, as well as observed changes in epithelial tissue and the wound healing period.
2 MATERIAL AND METHODS

2.1 HERA EXTRACT

The entire experimental protocol was approved by the institutional ethics committee - CEUA (N°: 003-04/2004). The experiments started with obtaining powder of Hera leaves, donated by the Herbarium Laboratório Botânico Ltda® (Colombo, PR. Brazil). The crude extract was obtained according to the protocol described by (Driessen et al., 2003) with a few changes (Pereira et al., 2009). 100 g of the powder of the leaves was solubilized in 1000 ml of 70% alcohol. For ninety-six hours, the mixture remained in the percolator, and the material obtained went to rota-evaporation in vacuum, maintaining the approximate temperature of 50°C; it was obtained, approximately, 200 ml of the hidroalcoholic solution, which was subjected to a lyophilization process, resulting in 26.82 g of derived material from Hera leaves. After, it was macerated, weighed and diluted in PBS buffer to the following concentrations: 10 mg/ml, 30 mg/ml and 50 mg/ml. We used Nebacetin® as positive control, the same was acquired in a specialized establishment (compounding pharmacy). Its composition was 1083.3 IU of neomycin sulfate and 83.3 IU of bacitracin per ml in physiological saline solution (manufacturer data), considering the gold standard in epithelial wound healing.

2.1.1 Experimental Design

In the vivarium of the Pontifical Catholic University of Paraná (PUCPR), seventy-five male Wistar rats were kept separately and fed with rat food and ad libitum water, divided into five groups of fifteen animals each, according to the type of treatment; negative control (PBS), Hera extract 10 m/ml, Hera extract 30 mg/ml, Hera extract 50 mg/ml and positive control (Nebacetin). Each group was divided into five subgroups of three animals, corresponding to the stages of the experiment to be analyzed, in other words, 3, 7, 14, 21 and 28 days of the postoperative. The animals were submitted to anesthesia induction by sodium thiopental (100 mg/kg). The trichotomy and antisepsis of the dorsal thorax region was performed and a linear cut of 4 cm in the skin was made, exposing their muscle fascia. After the surgery, all animals received flunixin meglumina analgesic in a single dose of 2.5 mg.kg⁻¹ intramuscularly.

All rats were treated once a day, in the morning, and the wounds were not occluded, becoming exposed to the environment. After the pre-set periods of 3, 7, 14, 21 and 28 days after surgery, the animals were killed by over-dosage of anesthetic (sodium thiopental 200 mg/kg), for collecting fragments of the lesion; that, following, were fixed
in 10% formalin for later inclusion in paraffin and preparation of slides for histological analysis. The blades of the histological sections were stained with hematoxylin-eosin (H&E) and toluidine blue. The prospection of the laminas was performed (blind test) by a single evaluator and according to pre-established scores: None - the absence of a significant target; Scarce: small amount, but existing and very spaced; Moderate: moderate amount in spaced regions; Intense: exacerbated and prominently presence. In the histological examination, it was evaluated the tissue repair of the wounds of different groups, considering edema, congestion of vessels, fibroblasts and polymorphonuclear cells.

Cells were counted separately in sections of ulcerated area using a light microscope OLYMPUS BX50 equipped with an objective PLAN 10X / 00:25 and oculars WH10X-H / 22 (OLYMPUS, Tokyo, Japan). This microscope was connected to the Color video camera CCD-IRIS (SONY, Tokyo, Japan) that allowed the capture of images in the fields of histology slides. Image Pro Plus software version 4.0.1 (MEDIA CYBERNETICS, Atlanta, GA, USA) was used to counting cells. Cells were counted in counting four fields per section at 100x magnification. In order to evaluate distribution, the histological fields were analyzed together in two areas: Superficial (Epithelium/connective tissue interface) and Deeper (Submucosa region). The number of cells was the expresso cells/mm² (average ± SD).

2.1.2 Statistical Analysis

The statistical analysis was based in average and standard deviation, concomitant with the T-student test, in which, the statistical significance* was considered p < 0.05 for the groups analyzed.

3 RESULTS

3.1 HERA EXTRACT, 30 MG/ML AND 50 MG/ML, REDUCES EDEMA AND VASCULAR CONGESTION IN THE EPITHELIAL WOUND HEALING PROCESS IN RATS.

The vascular congestion and edema are shown as two classic events during acute and chronic inflammation and influence the initial severity and, subsequently, the total epithelial wound healing period. Thus, our first step evaluated the level of edema intensity and vascular congestion in the process of epithelial wound healing in rat dorsum. There was intense edema and vascular congestion in the 3rd and 7th postoperative (PO) days in
all groups (Figure 1a, 1b). In contrast, in the 14th observation, it was found that the animals treated with Hera 30 mg/ml and 50 mg/ml did not present edema conditions. The animals treated with PBS and Hera 10 mg/ml did not present edema and vascular congestion from day 21 PO. On the positive control (Nebacetin), there was a small amount of edema in the 14th postoperative day, disappearing in the subsequent days (Figure 1a). Regarding the vascular congestion, it was observed that on the 14th postoperative day, there was a slight congestion in groups Hera 30 mg/ml and 50 mg/ml, disappearing in subsequent days. The PBS and Hera 10 mg/ml groups showed an intense congestion at day 14, and the Nebacetin group presented a moderate amount (Figure 1).

Figure 1: Evaluation of edema and vascular congestion in the epithelial wound healing process in rats being treated with Hera extract. We evaluated the healing process of 75 rats, three of each period (n = 3), regarding: a) presence and intensity of edema; b) presence and intensity of vascular congestion. The indices used were: None: significant absence; Scarce: small amount, but existing; Moderate: moderate amount in spaced regions; Intense: exacerbated and prominently. Statistical and other procedures are written in the M&M. Source: Author himself.

3.2 THE HERA EXTRACT ACCELERATES THE REDUCTION OF INFLAMMATORY CELLS AND PREDICTS THE PRESENCE OF FIBROBLASTS IN THE EPITHELIAL WOUND HEALING PROCESS.

As to polymorphonuclear cells, it was observed that in their succession, the epithelial wound healing condition, during the process, presented a reduction of these inflammatory cells and an increase of repairing tissue cells, the fibroblasts. It was observed that the Hera 10 mg/ml, 30 mg/ml and 50 mg/ml groups had a small amount of polymorphonuclear inflammatory cells on the 14th postoperative day, disappearing in the subsequent days (Figure 2a). In contrast, it was observed, in the 14th postoperative day, an intense inflammatory infiltrate in PBS and Nebacetin groups, and on the 21st postoperative day, it also presented a small presence of inflammatory cells in Nebacetin.
group (Figure 2a). Regarding the presence of fibroblasts, both Hera extracts as Nebacetin groups promoted acceleration of the genesis when compared with the control group, which showed a significant number of fibroblasts only after 21 days (Figure 2b).

Figure 2: Evaluation of the presence and intensity of inflammatory cells and fibroblasts in the epithelial wound healing process in rats. We evaluated the wound healing process of 75 rats, three in each period (n = 3), regarding: a) the presence and intensity of polymorphonuclear cells; b) the presence and intensity of fibroblasts. The indices used were; None: significant absence; Scarce: small amount, but existing; Moderate: moderate amount in spaced regions; Intense: exacerbated and prominently. The statistics and other procedures are written in the M&M. Source: Author himself.

3.3 EVALUATION OF THE PRESENCE OF MAST CELLS IN THE EPITHELIAL WOUND HEALING PROCESS TREATED WITH HERA EXTRACTS.

Once the study examines the treatment with Hera extract in different concentrations, it should be verified if the extract promotes allergic reactions that possibly prevent or hinder the normal process of epithelial wound healing. Thus, it was verified the presence of mast cells, the main cell responsible for the allergic response. The results demonstrated that in initial periods of 3 and 7 postoperative days, the Hera 50 mg/ml and 30 mg/ml groups, respectively, presented a significant increase in the number of mast cells when compared to the PBS group. Any results were not observed in other periods from the 14th postoperative day (Figure 3).
Figure 3: Presence of mast cells of epithelial wound healing process in rats treated with Hera extract. We evaluated the healing process of 75 rats, three of each period (n = 3), regarding the presence of mast cells. The cells were counted separately in an optical microscope at 100x magnification, with the aid of a reticle, in which: a) comparison between all analyzed groups; b) Comparison of the number of mast cells between the PBS and Hera 10 mg/ml groups; c) Comparison between PBS and Hera 30 mg/ml groups; d) Comparison between PBS and Hera 50 mg/ml groups; d) Comparison between PBS and Nebacetin groups. T-student test, that* denotes statistical differences among the groups (p < 0.05). Source: Author himself.

In fact, when we analyze the histological images of the 14th postoperative day, period in which the biggest differences were observed, it was found that Hera extract 30 mg/ml, 50 mg/ml and Nebacetin showed the epithelium in the damaged area completely restored, this phenomenon did not occur in the blades of PBS and Hera 10 mg/ml groups (Figure 4).

Figure 4: Histological images of epithelial wound healing process in rats within 14 postoperative days. Pictures referring to the wound healing process of 75 rats, three were analyzed in each period (n = 3), the samples of lesions were properly processed and stained with H&E for evidencing the presence of epithelial tissue, and inflammatory and scarring process. Source: Author himself.
4 DISCUSSION

In classical wound healing works, it is described, in detail, the steps of this important regenerative phenomenon, in our experiments we tried to keep this consecrated methodological basis (Ross, Odland, 1968; Madden, Peacock, 1971). Within such phenomenon, components present in Hera extract show great potential to interfere positively in epithelial wound healing. In fact, for some time, the Hera is used topically or systemically, in treating various chronic inflammatory diseases, some of which share mechanisms similar to the tissue repair process. However, the exact mechanism of action of topical solution of Hera in epithelial repair process remains unknown. Thus, for being an easily accessible plant and the formulation its solution presents low-cost, we evaluated its effect on the wound healing process in the epithelium of rats.

The first noticeable effect of the inflammatory wound healing process is the increase of the tissue area, due to edema and vascular congestion. When the edema and congestion data were evaluated, it was observed that the Hera extracts decreased the period of time of these phenomena in the wounds. Some biologically active components extracted from the *H. helix*, such as α-hederin, hederasaponin-C (HsC) and hederacolchiside-F (HcF) possess inhibiting characteristics of inflammatory mediators and bradykinin. In fact, by injecting carrageenan (a potent inducer of the acute inflammation phase) in the paw of rats, it is observed that the group treated with Hera extract shows a significantly reduced edema to the untreated group, with results similar to drugs like indomethacin (Gepdiremen et al., 2005). This fact has also been described by several studies that observed the regression of inflammatory processes, when treating ulcers with Hera (Driessen et al., 2003; Mahesh, Ramkanth, Saleem, 2011). These phenomena, comparatively, were also observed and described in other plants that have similar composition to *H. helix*, as Copaíba, which has anti-inflammatory and wound healing activities (Veiga et al., 2007; Veiga et al., 2006).

It is known that in the regenerative processes, the controlled presence of defense cells is essential for wound healing (Gepdiremen et al., 2004; Driessen et al., 2003). On the one hand, if inflammatory cells are required in the wound healing process, their presence, in an exacerbated way, may contribute to a delay in the full restoration of the tissue. Macrophage and other defensive cells are producing sources of various mediators, such as classical pro-inflammatory cytokines and oxidising agents. Thus, most of the commercialized wound healing drugs have anti-inflammatory characteristics, aiming the partial reduction of the polymorphonuclear cells (Vieira et al., 2006).
In evaluating the data from polymorphonuclear cells, important changes were verified, the Hera extract, initially, decreased the presence of polymorphonuclear cells, and in the chronic stage, it stimulated the exchange for monomorphonuclear cells, basic condition for the completion of the inflammatory and regenerative process. In fact, in vitro tests, components of the Hera, as the α-hederin, completely deplete the intracellular glutathionine, which consequently do not produce reactive to oxygen species (ROS) (Gülçin et al., 2004). Thus, the decrease of the release of nitric oxide determines a smaller expression of NF-kappa B, transcription factor of inflammatory cytokines (i.e. TNF-α, IL1-β) and chemokines responsible for the migration of inflammatory cells (i.e. CCL3, CCL5), demonstrating that the Hera extract can not only operate in polymorphonuclear migration control, as well as decrease the activation of macrophages.

Another important factor in wound healing is the emergence of fibroblasts; Driessen and collaborators (2003) described the presence of these cells from the 14th day (Driessen et al., 2003). A similar result to that observed in our experiments, in which there was a greater presence of fibroblasts in the groups treated with Hera extract. Interestingly, in vitro experiments demonstrate that the Hera has anti-proliferative characteristics in fibroblasts, and its use is discussed in the use of the treatment of melanomas (Danloy et al., 1994). In fact, in our results there was an anticipation of the presence of fibroblasts, which may be due to favorable homeostasis, such as smaller number of inflammatory cells, assigned to Hera extract. Moreover, mainly by flavonoids, the Hera has anti-apoptotic capacity and decreases the formation of new vessels. However, when we analyze the angiogenesis of the wounds, no significant differences between groups were found (results not shown).

One possibility that should be considered when testing a new wound healing extract is whether this will develop some kind of allergic immune response in the animal's dermis or not. Generally, Hera leaf is considered a very safe herb for use with adults and children. Hera allergy is very rare (less than 1 in 10,000 people) and may cause shortness of breath, swelling, reddening of the skin or itching. However, fresh leaves of H. helix and the fluid contained in the leaf (leaf juice), through falcariol, can cause small allergic dermatitis; and it is not uncommon to find allergy symptoms in the skin, eyes and respiratory tract of gardeners (Jors, 2003).

By analyzing the presence of mast cells in the connective tissue adjacent to the experimental incision, it has been observed that Hera extract in low concentration presented itself similar to the physiological wound healing process, and that, in the Hera
30 and 50 mg/ml groups, it was observed an increase in the presence of mast cells in specific days, not featuring an allergic process or interfering in the normal epithelial wound healing. Indeed, it already is well characterized the ability of Hera extract in response pathology treatment of allergic origin, such as asthmatic bronchitis. In fact, the Hera extract was effective in treating allergic bronchoconstriction induced by albumin OVA in guinea pigs and is used, effectively, in the treatment of children with asthma (Hocaoglu et al., 2012).

According to the above and with the results found, the Hera extract (30 mg/ml and 50 mg/ml) reduced the edema and vascular congestion in the epithelial wound healing process in rats in 14 days, this fact is corroborated by reports in literature. It was also observed that the Hera extract (10 mg/ml, 30 mg/ml and 50 mg/ml) accelerates the reduction of inflammatory cells and predicts the presence of fibroblasts in the epithelial wound healing process. Furthermore, it was found that, in the presence of Hera extract (50 mg/ml and 30 mg/ml respectively), there was a significant increase in the number of mast cells when compared to the PBS group, in days 3 and 7, not being significant on the 14th, 21st and the 28th days; confirming the probable anti-inflammatory and wound healing effects of Hera extract.

5 CONCLUSION

Therefore, according to the results, mainly the Hera extract in concentrations of 30 and 50 mg/ml, promoted acceleration in the wound healing-related phenomena. This is supported by the decrease in the permanence period of edema and vessel congestion, as well as change in the number of cells related to the inflammation process of the wounds compared to the control.
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