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Antioxidant and healing potential of fresh *Morus alba* extracts

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Abstract

Mulberry is considered a valuable forage plant, mostly because of its bioactive phytochemical components that exert positive effects on human and animal health. Based on this, a study was conducted with the following objectives: to determine quantitatively the concentration of flavonoids, to compare the specific activities of the antioxidant enzymes catalase and peroxidase and to evaluate the *in vivo* healing effect of the fresh leaf, bark and root extracts, in the variety tigreada of *Morus alba*. The simple classification ANOVA and Duncan's multiple range test were carried out for mean comparison ($p < 0,05$). The leaf extract showed the highest concentration of flavonoids, catalase and peroxidase, and significantly differed from the bark and the root which did not differ from each other. In order to evaluate the healing capacity, Wistar rats were used as animal model. Eighteen days after the incision was made, the leaf and root extracts did not differ from the control, because the percentages of closed wounds were 99,92 and 99,94 %, respectively; while the bark extract was significantly lower, but higher than the negative control, and showed 90,50 % of closing. The antioxidant and healing potential of fresh mulberry leaf and root extracts was proven, increasing its value as multipurpose plant.

Keywords: catalase, plant extracts, flavonoids

Introduction

Plant extracts are widely used in traditional medicine to fight certain ailments, which include wound and burn healing. For this type of treatment different plant parts are used, such as flowers, leaves, fruits, roots, stems and bark. The increase of resistance to antibiotics and the infection of wounds by pathogen organisms have propitiated an increase in the interest in plant extracts as new alternative of antiseptics and antimicrobial agents (Agyare *et al*., 2013b). The medicinal value of the plant kingdom lies on its bioactive phytochemical components, which cause a physiological action on human and animal organisms. These constituents include several chemical families, such as alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins and phenolic compounds (Pereira and Bártolo, 2016).

The variety tigreada of *Morus alba* is well established and has been widely studied in Cuba from the morphoagronomic and bromatological point of view; however, many of its medicinal benefits are still to be researched (Noda and Martín, 2014; Pentón *et al*., 2014; Prieto-Abreu *et al*., 2016). Mulberry is a plant that has very good antioxidant properties, which could be mainly given by the content of flavonoids. They comprise a group of phenolic compounds product of the secondary metabolism of plants. Recent studies indicate that this species is a rich source of polyphenolic substances, such as kaempferol, quercetin, kuwanons, morusin, rutin, sanggenons, among others (Chan *et al*., 2016).

The antioxidant activity of flavonoids is given by their iron-chelating and free radical sequestering properties, inhibition of oxidases and stimulation of other enzymes with acknowledged antioxidant properties, such as catalase and superoxide dismutase (Pérez-Trueba and Martínez-Sánchez, 2001).

The healing process is divided into three phases which overlap in a continuous and temporary way: inflammatory, proliferative and remodeling (Mendoça and Countinho-Netto, 2009). These phases are coordinated in such a way that one of their main functions is to recover the integrity of the damaged area through complex and dynamic restoration mechanisms of the cell structures and tissue layers. In this process many cell types are involved, like: cytokines, chemokines, growth factors and proteolytic enzymes (Sgonc and Gruber, 2013).

Wound healing can be adversely affected by many factors, such as the presence of oxidant agents, inflammation and microbial infections. Wounds can be treated in different ways, depending on how they occur and the lesion degree (Agyare *et al*., 2013b).

The objectives of this research were: to determine quantitatively the concentration of flavonoids, to compare the specific activities of the antioxidant enzymes catalase and peroxidase, and to evaluate the *in vivo* healing effect of the different fresh mulberry extracts (leaf, bark and root).

Materials and Methods

Plant material. For the essays the leaf, bark and root of the variety tigreada of *M. alba*, collected and referenced in the herbarium of the Pastures and Forages Research Station Indio Hatuey –Matanzas province, Cuba–, were used. The collection was carried out at the same time, and the organs with similar vegetative growth and health conditions were selected. All the chosen plant material was washed with distilled water, dried, frozen in liquid nitrogen and stored until its maceration.

Extract preparation. Leaf, bark and root samples were randomly collected from different plants of the studied variety. The fresh plant material was homogenized and 5 g were extracted of each organ in triplicate. Those samples were weighed, macerated in liquid nitrogen and then cold-homogenized in sodium phosphate buffer solution, 100 mM, pH 7,0 and with a 1:2 mass/volume ratio. They were agitated in vortex during 2 minutes and in horizontal agitation for 24 h at 100 rpm. The samples were centrifuged afterwards at 10 000 rpm, at 15 ºC during 15 minutes, and the supernatant was collected for later trials. The final concentration was 500 mg mL^{-1}.

Determination of total flavonoids. The content of total flavonoids was estimated by the aluminum chloride method (Yang *et al*., 2007). A sample concentration of 100 mg mL^{-1} was used, obtained from a 1/5 dilution of 500 mg mL^{-1}. A mixture was made with 100 µL of the plant extracts with 400 µL of distilled water and 60 µL of a sodium nitrite solution ($NaNO_2$) at 5 %. The content was mixed in vortex during 10 seconds and it was left to settle at room temperature for five minutes. Then 60 µL of aluminum chloride ($AlCl_3$) (10 %), 400 µL of NaOH (1 mM) and 980 µL of distilled water, were added. The solutions were well mixed and left to settle during 15 minutes. The absorbance of each sample was read at 415 nm. Standard quercetin solutions were prepared to obtain the calibration curve, in a concentration interval of 2,5 to 100 µg mL^{-1}. The total flavonoid content was calculated using the calibration curve of quercetin standards. The results were expressed in quercetin equivalent milligrams (QE) per gram of extract.

Specific catalase and peroxidase activities. The processing of the plant material, determination of the catalase and guaiacol peroxidase activities, protein concentration and calculation of specific activity were performed according to Díaz *et al.* (2010).

Animals and experimental groups. Male albino Wistar rats, supplied by the National Center for the Production of Laboratory Animals (CENPALAB, for its initials in Spanish) –Havana, Cuba–, were used. The approximate weight of the animals was 250 g, and they were randomly distributed into five groups of eight animals each (table 1).

Table 1. Groups and treatments used in the experiments.

Group	Treatment
Group I	Positive control (Herbermin cream)
Group II	Negative control (distilled water)
Group III	Leaf extract
Group IV	Bark extract
Group V	Root extract

The animals were anesthetized with diethyl ether. An incision in the skin and in the cutaneous cell tissue of 2 cm diameter was practiced on all of them in the dorsal region, and the different treatments and their components were applied to them every 24 h. The regulations and ethical principles of animal experimentation were respected.

Evaluation of the *in vivo* healing activity. The wounds were observed daily during 21 days, sufficient time for the closing of the incisions. The observation was blindly made and the animals were kept in optimum aseptic feeding and environmental conditions, to prevent a stress that could distort the results. The presence of secondary infections was avoided. During the period the presence of scab, signs of infection, thickness of the wound edge, color and aspect of the regenerated skin were controlled.

The healing percentage was determined from the following equation:

Where:

H1: initial size of the wound (mm).

H2: Final size of the wound (mm).

Statistical analysis. A simple classification variance analysis (ANOVA) was made to determine differences among the variables: flavonoid content, catalase and peroxidase activities and percentage of healed wounds. The inequalities among means were determined through Duncan's (1955) multiple range comparison test, for which all values of

$p < 0,05$ were considered significant. The statistical package INFOSTAT free version was used.

Results and Discussion

For determining flavonoids in the plant extracts quercetin was used as standard. The pattern line showed R^2 of 0,9937 (fig. 1). Under these conditions it can be stated that this equation can be used for the quantitative determination of flavonoids, expressed as quercetin milligrams.

It has been recently proven that quercetin is a strong therapeutic agent for healing the wounds caused by burns. It has been suggested that the reactive oxygen species (ROS), produced due to the burning lesion by macrophages and neutrophils, could lead to oxidative damage that affects not only the burned skin, but also the surrounding area. Quercetin inhibits the process carried out by free radical in the cells; thus, it protects the cell populations of cutaneous tissue, fibroblasts, keratinocytes and endothelial cells from oxidative stress (Gouma *et al*., 2016).

Quercetin also shows important anti-inflammatory actions. It is stronger than other flavonoids in the inhibition of edema after contact with inflammagens. In addition, it has inhibitory activities on NF-$_K$B (nuclear factor kappa-light-chain-enhancer of activated B cells which participates in the transcription of pro-inflammatory genes) and in the release of several cytokines involved in inflammation. This dual role of antioxidant/anti-inflammatory turns this metabolite into a promising molecule for the treatment of chronic wounds (Hatahet *et al*., 2016).

The flavonoid concentration in the different mulberry extracts, expressed in quercetin milligrams per grams of fresh extract, is shown in figure 2. The leaf extract showed the highest values and differed significantly from the bark and root ones, which did not show significant differences between them.

Mulberry leaves have high concentrations of quercetin, which is responsible for reducing the *in vivo* as well as *in vitro* oxidative processes (Priyanka, 2015). Flavonoids participate in healing because they prevent the release of prostaglandins and histamines, and the migration of formed elements (neutrophils and others). In addition, they stabilize the cell membrane because they capture the free radicals present and prevent cell damage through the activation of the complex biochemical system for tissue regeneration (Havsteen, 2002).

Table 2 shows the specific activity of antioxidant enzymes catalase and peroxidase. As can be observed, in both enzymes the leaf extracts showed higher and significantly different values from the bark and root ones, which were similar and did not differ statistically. Similar results were reported for 10 *M. alba* varieties and hybrids, in which the leaf

Table 2. Specific catalase and peroxidase activity of the different *M. alba* extracts.

Plant extract	Specific activity (U/mg)	
	catalase	peroxidase
Leaf	1 077,84[a]	10,03[a]
Bark	186,85[b]	1,62[b]
Root	92,45[b]	0,87[b]

Values with different superscripts in the same row differ at $p<0,05$

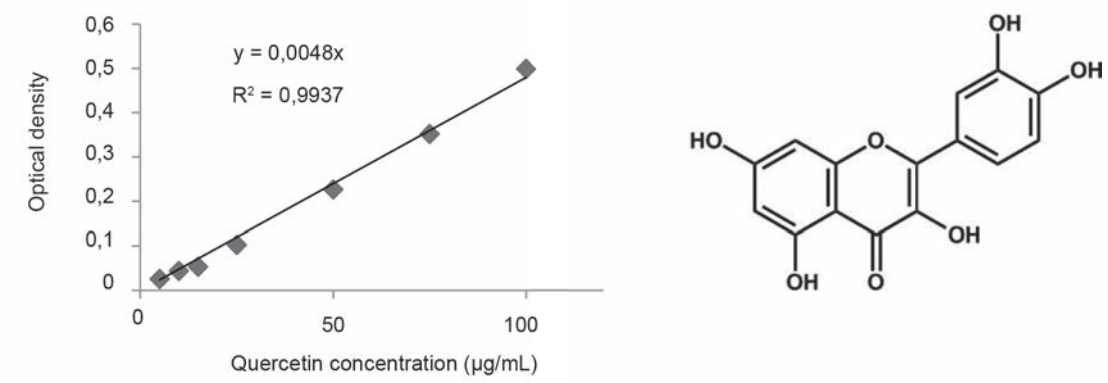

Figure 1. Pattern curve and chemical structure of quercetin.

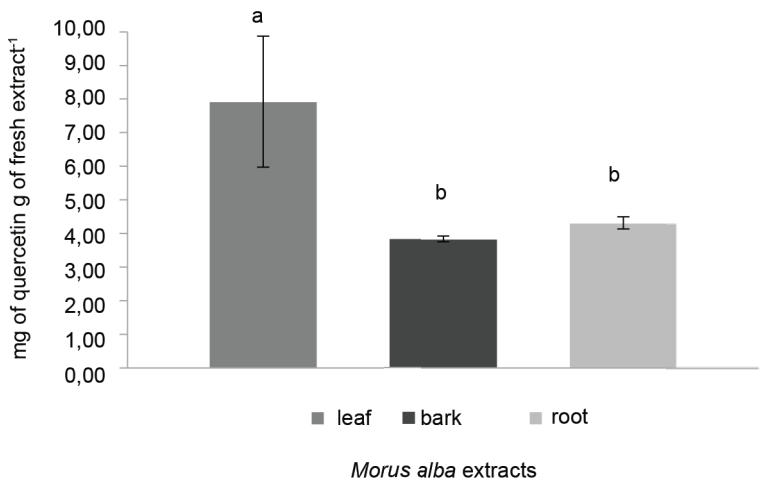

Figure 2. Flavonoid concentration in the different *M. alba* extract.

showed the highest activity, followed by the bark and root (Díaz *et al*., 2010).

A group of researchers tested the synthetic superoxide dismutase (SOD)/catalase mimetic product, EUK-207, to examine the causative role of oxidative stress in dermic lesions. For such purpose, they used a combined model of skin irradiation and wound injuries in rats, used as experiment animals. It was proven that, administered by systemic way, EUK-207 mitigated the radiation dermatitis, suppressed indicators of tissue oxidative stress, and favored wound healing. In addition, they observed the significant positive regulation of several key genes involved in detoxication of reactive oxygen and nitrogen species (Doctrow *et al*., 2013).

Flavonoids are capable of increasing the availability of endogenous antioxidants, as well as the activity of antioxidant enzymes (Pérez Trueba and Martínez Sánchez, 2001). Hence the similar performance of the antioxidant enzymes catalase and peroxidase could be justified by the quercetin concentration present in each one of the extracts, and among the three the leaf showed the highest value, followed by the bark and root which did not differ from each other.

The research data were collected in the proliferative phase of healing. Such phase is derived from the inflammation process and is precursor of the maturation phase; it starts towards the third day and lasts approximately 15-20 days. The objective of this phase is to generate a protective barrier, in order to increase the regenerative processes and prevent the entrance of noxious agents; it is characterized by the activation of two large processes: angiogenesis and fibroblast migration, which facilitate the formation of a provisional extracellular matrix (ECM) that provides support for cell migration and synthesis of a mature ECM (Guarín-Corredor and Quiroga-Santamaría, 2013). Figure 3 shows the appearance of the skin of the Wistar rats of each treatment, 18 days after the injury.

The healing process stimulated through the use of plant bioactive compounds can be monitored by following up the reduction of the incision size. The results of the macroscopic observations of the wound closing are described below. Within the evaluated indicators, coloring was taken into consideration, which showed clinical evolution within the foreseen parameters for each healing phase. In all the groups the predominance of pink coloring could be observed, which is characteristic of epithelization and represents the final phase of tissue repair. Almost all the animals started showing the formation of scab between three and four days after the incision and its fall started since day six, without differences among the treatments. From the eighth day the wound closing was observed in the different groups and after 18 days the wounds in groups I, III and V were completely closed; this proved the effectiveness of the fresh leaf and root extracts with regards to the control (fig. 4).

Table 3 shows the percentages of the wounds closed as the healing days passed. The leaf (group III) and root extract (group V) did not show

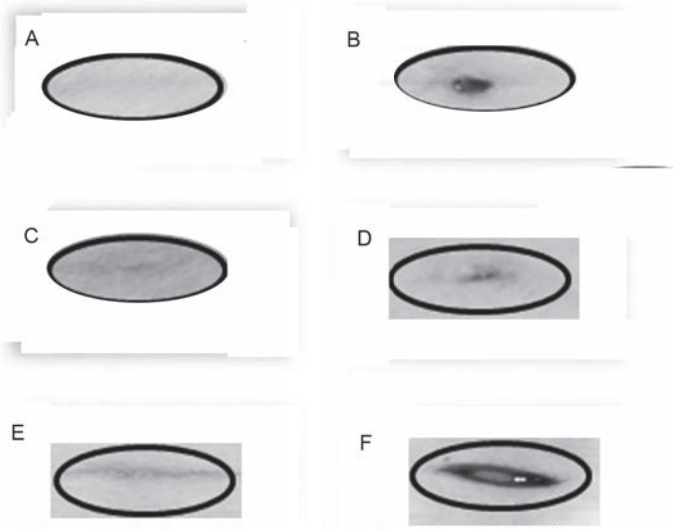

Figure 3. Closing of the wounds 18 days after the incision. A: group I (positive control, Hebermin), B: group II (negative control), C: group III (leaf extract), D: group IV (bark extract), E: group V (root extract), F: recently made wound.

significant differences with the control (group I) 18 days after the incision was made. The bark extract (group IV) was significantly lower than the above-described ones, but higher than the negative control (group II), and showed 90,5 % of closing. This could suggest that the concentrations of secondary metabolites of such tissue could be acting positively on the regeneration process of the damaged area, although without the efficiency of the ones present in the leaf and root.

The results suggest that the healing activity is closely related to the antioxidant properties, be-

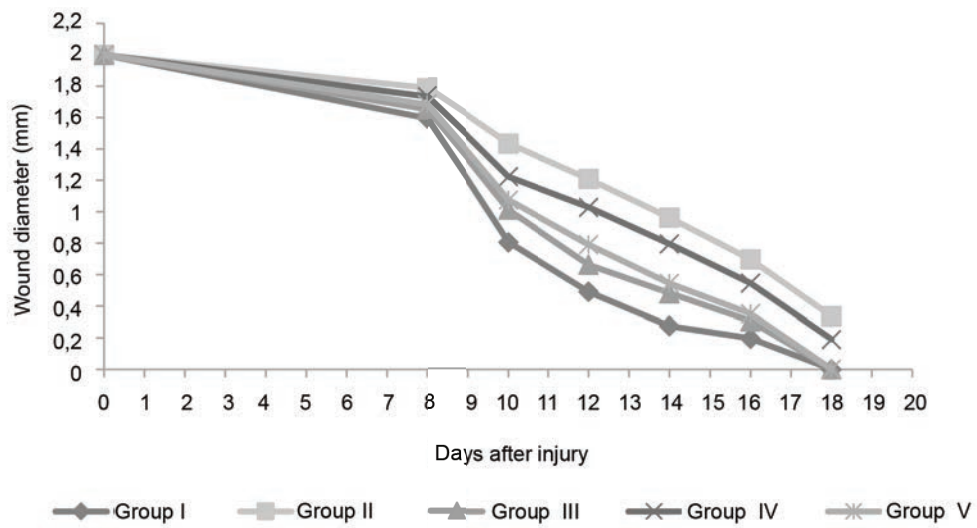

Figure 4. Influence of the fresh *M. alba* extracts on the closing of wounds during 18 days in Wistar rats. The diameter values are expressed as the mean ± SD (n = 8).

Table 3. Accumulated value (%) of closed wounds in the different observation days.

Treatment day	8	10	12	14	16	18
Group I	20,21[a]	59,66[a]	75,45[a]	86,23[a]	90,17[a]	100,00[a]
Group II	10,55[e]	28,22[e]	39,51[e]	51,88[e]	65,12[e]	83,21[c]
Group III	17,34[b]	49,32[b]	66,87[b]	75,87[b]	84,69[b]	99,92[a]
Group IV	13,28[d]	38,79[d]	48,52[d]	60,24[d]	72,67[d]	90,50[b]
Group V	15,81[c]	46,20[c]	60,44[c]	72,80[c]	82,38[c]	99,94[a]

Means followed by different letters in each group indicate significant differences for $p \leq 0,05$ per observation day.

cause by adding fresh mulberry extracts the activity of antioxidant enzymes could be increased in the animals of the different treatments, and they are the ones responsible for the conversion of reactive oxygen species in less damaging molecules, so that they protect lipids from the oxidative damage in the emerging tissue. In addition, the presence of flavonoids could contribute favorably to the complex system of biochemical processes involved in inflammation and healing.

The chlorophylls and carotenes present in the plants are considered to be pigments that contribute favorably to the healing process. Besides, as they contain vitamins and minerals that regenerate the tissues damaged by wounds, prevent the formation of new scars and the risk of infection (Mancebo Dorvigny *et al*., 2016).

Although the concentrations of flavonoids, catalase and peroxidase of the root extract were significantly different from those of the leaf, this extract showed 100 % of wound closing. This could be given by the presence of bioactive compounds in the root extract, also related to the inflammatory and healing processes. Some secondary metabolites, such as flavonoids, alkaloids and tannins, among others have been studied for their healing activity in different models, *in vitro* as well as *in vivo* (Agyare *et al*., 2013a).

In the root extract of *Albizia lebbeck* a high healing potential was found and the presence of flavonoids, saponins, phenols and tannins was reported (Joshi *et al*., 2013); in *Mirabilis jalapa* the action of terpenoids and flavonoids was studied (Gogoi *et al*., 2014); in *Strophanthus hispidus* alkaloids, saponins, steroids, carbohydrates and tannins were detected (Agyare *et al*., 2013b); in *Ficus racemosa* saponins, tannins, alkaloids and flavonoids were reported (Murti and Kumar, 2012). In the *M. alba* roots phytochemicals such as: terpenoids, alkaloids, flavonoids and coumarins have been recently described (Chan *et al*., 2016). In addition, in molecular studies it was proven that the *M. alba* root extract showed high wound repair capacity due to the positive regulation of keratin filaments and by inducing signalization of the metabolic pathway CXCL12 / CXCR4 in cultures of skin explants (Kim *et al*., 2015).

The bioactive compounds present in the extracts could also be the ones responsible for preventing the infection by pathogens. The synergic effect between the antimicrobial and antioxidant activity accelerates the wound healing process (Dwivedi *et al*., 2016). Flavonoids have been characterized by having multiple biological effects, which include antioxidant, healing and antimicrobial ones (Aditya *et al*., 2012).

Diverse studies indicate that there are evidences of correlation between the antimicrobial activity and wound healing, because the infection can cause serious problems for recovery due to the poor granulation in the formation of new tissue, which affects epithelization and causes undesirable odors (Mulisa *et al*., 2015). Positive results have been reported in this sense in *Mallotus oppositifolius*, *Momordica charantia* (Agyare *et al*., 2014), *Justicia flava*, *Lannea welwitschii* (Agyare *et al*., 2013a), *Kigelia africana*, *Strophanthus hispidus* (Agyare *et al*., 2013b), *Pinus caribaea* (Mancebo Dorvigny *et al*., 2016), *Pongamia pinnata* (Dwivedi *et al*., 2016) and *Anthocephalus cadamba* (Sanjay *et al*., 2007), among others. In *M. alba* the presence, in the root, of kuwanon G (Park *et al*., 2003), mulberrofuran G and albanol B, with strong antimicrobial activity, has been described (Sohn *et al*., 2004). Likewise, activity against pathogens has been reported in extracts elaborated from dry material of mulberry leaves (Tirupathi *et al*., 2011; Omidiran *et al*., 2012; Rao *et al*., 2012) and from fresh tissue of different varieties (Díaz-Solares *et al*., 2017). The results of this research reaffirm the healing and antioxidant activity of the fresh extracts of mulberry leaf and root.

Conclusions

The presence of flavonoids and antioxidant enzymes in the extracts of the mulberry variety tigreada could be considered among the main factors that influence the healing process. The topical application of the fresh leaf and root extracts produced almost 100 % of closed wounds, for which they could be recommended to be used in the repair of cutaneous wounds in humans and animals as phytotherapeutic medicine.

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