Angiogenic potential of "Quina do Cerrado" (*Strychnos pseudoquina* A.St.-Hil.)

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ABSTRACT

Leaf and bark infusions of the *Strychnos pseudoquina* A.St.-Hil., Loganiaceae, plant have long been used in Brazilian traditional medicine for the treatment of various diseases and medical conditions, showing apparent antipyretic, gastric cicatrizant, and especially antimalarial effects. The literature contains abundant reports of plants that possess bioactive components with therapeutic properties. The search for natural substances that promote or inhibit angiogenesis is the focus of current research, since numerous drugs derived from plants have these effects. Thus, in this study, we investigated the angiogenic potential of *S. pseudoquina*, using the embryonated chicken egg chorioallantoic membrane assay for the angiogenesis tests. Three concentrations of an aqueous extract of *S. pseudoquina* bark were tested: 15, 30, and 60 mg/ml. The mean percentages of vascularization of CAMs treated with these three extract concentrations were 15.4%, 17.1%, and 17.2%, respectively, which were significantly higher (p<0.05) than that in the negative (8.9%) and inhibitor controls (2.2%). Therefore, it was concluded that the aqueous extract of *S. pseudoquina* can promote angiogenesis at the concentrations tested.

Keywords: *Strychnos pseudoquina,* Angiogenesis, Chorioallantoic membrane

INTRODUCTION

In Brazil, the use of medicinal plants and herbal medicines is a culturally rooted and common practice throughout the country. This tradition is sustained by the oral transmission of information about the properties of medicinal plants over generations (Firmo et al. 2011). Medicinal plants often represent the main resource for treating diseases (Patrício et al. 2021; Souza et al. 2020). However, the transmission of popular knowledge highlights the need for scientific research that validates and complements this information, aiming to guarantee the effectiveness and safety of herbal treatments included in the SUS (Silva et al. 2021). This is in accordance with the National Policies on Integrative and Complementary Practices and Medicinal Plants and Phytotherapeutics, established in 2006, ensuring the right of SUS users to treatment with phytotherapy, with an emphasis on basic care (Brazil 2021).

As one of the countries with the greatest biodiversity in the world, Brazil is a highly promising source of plants that can be potentially used for the development of new drugs (Ferreira 1998). According to Harvey (2000), natural products are the most successful sources for therapeutic use and new drug production (Koehn and Carter 2005; Bernardini et al. 2018).

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Strychnos pseudoquina A.St.-Hil., *a tree* belonging to the Loganiaceae family and widely known by the common names “quina-quina”, “quina-branca”, “aromatic bark”, and “quina do cerrado”, is native to the Brazilian Cerrado (Gontijo et al. 2017). Infusions of the leaves and bark of this tree are widely used in Brazilian folk medicine. However, the bark has garnered the most attention owing to its popular use in the form of a very bitter preparation (called “English water”) to treat comorbidities in the gastrointestinal system and to exert antipyretic, gastric cicatrizant, aphrodisiac, and antimalarial effects (Bonamin et al. 2011; Gontijo et al. 2017; Brandão and Rapini 2018).

Angiogenesis, the process in which new blood vessels are formed from a pre-existing vascular network (Carmeliet 2000), has been shown to have a range of therapeutic applications, such as for improving blood perfusion, ischemic tissue recovery (ischemic heart disease), wound healing (diabetic lower limb ulcers, venous leg ulcerations, pressure ulcers, arterial ulcers), and the replacement of large caliber arteries (Yoshida 2005; Yoo and Kwon 2013). Moreover, aside from being important for a variety of ocular pathologies (Bhadada 2011; Pinho 2017), the development of antiangiogenic drugs (i.e., those capable of inhibiting blood vessel formation) (Papetti et al. 2002) as a strategy to inhibit tumor growth and metastasis is one of the most promising research areas in the field of oncology.

The literature contains an abundance of reports on plants that possess active components with bioactivities of great interest. Therefore, much research is currently being conducted to search for plants with angiogenic or antiangiogenic capacities for the development of new drugs for the treatment of various diseases (Mendonça and Coutinho-Netto 2009). The use of *S. pseudoquina* as a medicinal plant is based on anecdotal evidence and traditions, since scientific studies on its applicability, safety, and efficacy remain scarce (Pignal 2014). In this context, investigating whether this plant exerts angiogenic or antiangiogenic activity would be important (Chaves 2015). Therefore, this study was carried out to determine whether the aqueous extract of *S. pseudoquina* possesses angiogenic or antiangiogenic properties, using the chorioallantoic membrane (CAM) of embryonated chicken eggs for the evaluation.

MATERIAL AND METHODS

Strychnos pseudoquina drug and extract preparation

S. pseudoquina barks were purchased from Chá e Cia - Ervas Medicinais (Jacareí, Brazil). The product is produced and distributed by J T F Produtos Naturais (São José dos Campos, Brazil; batch: 022021).

An aqueous extract of *S. pseudoquina* bark was prepared according to the manufacturer’s guidelines for popular use. Sixty grams of macerated bark were mixed with 1 l of water, corresponding to the manufacturer’s recommended dose of two tablespoons per liter of water. After heating the mixture to boiling, the container was covered for 10 min. Subsequently, the aqueous extract was ready for use. Three concentrations were prepared by the Laboratory of Experimental Biotechnology Studies at PUC-GO for the testing: 15, 30, and 60 mg/ml.

Embryonated chicken eggs

Eighty eggs from fertile Ross chickens (*Gallus domesticus*) were purchased at the Antônio Ferreira de Oliveira popular fair, known as Feirão do Nova Aurora (located at Avenida Contorno - Vila Nova Aurora, 76380-000, in the city of Goianésia, Goiás).

Experimental procedure

The angiogenic and antiangiogenic activities of the aqueous extract of *S. pseudoquina* bark were evaluated using the embryonated chicken egg CAM assay according to a methodology adapted from Melo-Reis et al. (2010) and Ribatti (2008). The assay was performed in the Laboratory of Experimental and Biotechnological Research of the Masters in Environmental Sciences and Health (MCAS) of PUC-GO.

The embryonated chicken eggs were incubated in an automatic incubator set to 37–38 °C (humidity: between 60% and 70%) and automatically moved laterally every 15 min during the first five days of incubation. On day five, a Dremel® micro grinder was used to create a circular opening (1.0 cm diameter) at the largest base of the shell of each of the incubated eggs. The process of opening the eggs at the circular cutting was performed inside a laminar flow cabinet that had been previously sterilized with ultraviolet light to reduce the risk of contamination.

After opening the eggshell, a syringe was used to deposit a drop of sterile 0.9% (w/v) sodium chloride solution into the interior to aid removal of the membrane, exposing the already vascularized CAM. The opening was then sealed with adhesive tape and the egg was incubated again without periodic shaking.

At the end of the 13th day of incubation, filter paper discs were deposited directly on the chorioallantoic membrane, containing the *S. pseudoquina* solution to be tested, the angiogenesis inducer Regederm (*Hevea brasiliensis* (Willd. ex A.Juss.) Müll.Arg. serum, produced by the company Pele Nova Biotecnologia S.A.), the vascularization inhibitor dexamethasone (injectable dexamethasone disodium phosphate 4 mg/ml, produced by

Farmacêutica Cearense LTDA), and water (Water for Injections – 10 ml Equiplex Indústria Farmacêutica Ltda), which corresponded to the positive, inhibitory, and negative controls, respectively. Subsequently, all eggs were reincubated until day 16.

On day 16, 3.7% (v/v) formalin solution was added to all eggs until the shells opened for 10 minutes, following which the CAMs were carefully cut and removed. Thereafter, the CAMs were photographed using an iPhone 8 Plus smartphone equipped with a wide-angle camera (28 mm of 12 megapixels, ISO 40, full high-definition screen resolution of 1920 × 1080 pixels). Images of 4608 × 2592 pixel resolution were acquired against a white background. A focal length of 14 cm was used to standardize the images for the analysis and quantification of the neoformed vascular network.

Using PhotoScape software, the captured images were standardized with regard to color, cut size (205 × 205), saturation, brightness, and contrast, to obtain the best resolution of the blood vessels. Subsequently, the percentage area of the neoformed vascular network was quantified using ImageJ software (version 1.28)

Evaluation parameters

Because ImageJ can separate intervals of intensity levels, the pixels corresponding to blood vessels on the images can be isolated and quantified. According to Azzarello et al. (2007), Melo-Reis et al. (2010), and Luay et al. (2018), the number of selected pixels is proportional to the level of vascularization on the captured image field. The percentage of vascularization corresponds to the areas marked in red in the images.

Histological analysis

For histological analysis, the embryonated egg CAMs were fixed in 10% formaldehyde solution. Thereafter, the samples were subjected to dehydrated, diaphanization, paraffin impregnation and, finally, embedded in paraffin for microtomy.

Each paraffin block was sectioned at 5 µm thickness using a microtome (model RM 2125, Leica Microsystems Nussloch GmbH, Nussloch, Germany). The CAM-containing paraffin sections were placed in a water bath at 45 °C where they were adhered to glass slides. Then, using classical staining techniques, the sections on the slides were stained with hematoxylin–eosin, and the vascularization was observed under an optical microscope. Images of the histological sections were obtained using a high-definition digital microscope camera (Leica ICC50, serial number 50142125).

Statistical analysis

Statistical analysis of the vascularization data was performed using BioEstat software (version 5.3) (Ayres et al. 2007). The Shapiro–Wilk normality test was used to determine the most appropriate statistical test to be employed. Since normality was observed in the sample data, analysis of variance (ANOVA) was applied, followed by Tukey's *post-hoc* test to compare differences between the groups.

RESULTS

The mean percentage of vascularized area was obtained by analyzing 10 CAMs from each treatment group (*S. pseudoquina* extract at three concentrations and negative, positive, and inhibitor controls). The results are presented in Table 1.

Table 1. Percentage of vascularization of the chorioallantoic membrane of embryonated chicken eggs after treatment with an aqueous extract of *Strychnos pseudoquina* and various control solutions.

CAM No.	Positive control	Negative control	Inhibitor control	*Strychnos* pseudoquina 15 mg/ml[b,c]	*Strychnos* pseudoquina 30 mg/ml[a,b,c]	*Strychnos* pseudoquina 60 mg/ml[a,b,c]
1	17.3	8.6	2.3	15.8	17.4	17.1
2	17.7	9.8	2.6	15.7	17.0	16.3
3	18.3	8.9	2.8	16.4	17.2	17.4
4	18.2	9.2	1.5	16.7	18.6	18.2
5	18.5	9.0	2.9	15.8	17.2	17.9
6	18.4	9.2	2.8	15.7	17.1	17.1
7	17.8	9.0	1.5	15.0	16.7	18.8
8	18.3	7.7	1.4	14.9	17.5	16.9
9	17.0	9.0	1.6	14.6	16.2	16.4
10	19.0	8.8	2.2	13.8	16.2	15.7
Mean	18.1%	8.9%	2.2%	15.4%	17.1%	17.2%
SD*	0.60	0.53	0.61	0.87	0.69	0.94

ANOVA, Tukey test; [a] $p>0.05$ compared with the positive control; [b] $p<0.05$ compared with the negative control; [c] $p<0.05$ compared with the inhibitor control; * SD = standard deviation; CAM = chorioallantoic membrane; positive control = Regederm; inhibitor control = dexamethasone; negative control = water

According to Tukey's *post-hoc* test, there were obvious statistical differences (p<0.05) between the three control groups: Regederm (positive control), dexamethasone (inhibitor control), and water (negative control). The three concentrations of *S. pseudoquina* extract showed significant differences (p<0.05) to the negative and inhibitor controls, demonstrating the angiogenic potential of the plant.

CAMs treated with 30 and 60 mg/ml *S. pseudoquina* extract had a mean percentage of vascularization of 17.1 and 17.2%, respectively, which were not significantly different from the positive control, which had a mean value of 18.1% (p>0.05). This finding demonstrates the significant angiogenic activity of the *S. pseudoquina* bark aqueous extract.

In the statistical analysis of the various groups, only the lowest concentration (15 mg/ml) of *S. pseudoquina* bark (15.4%) showed a significant difference (p<0.05) when compared with the positive control (18.1%); that is, it had angiogenic potential but lower than that of Regederm. Figure 1 clearly illustrates the differences between the extract- and control-treated CAMs according to the percentage of their vascularized areas. The analyses performed with ImageJ software provided a visualization of the neoformed capillary networks with red coloration (Figure 2).

Histological analysis

As shown in Figure 3, the inhibitor control (dexamethasone) had few connective tissue cells and blood vessels. The negative control (water) had fewer blood vessels than the positive control (Regederm), the latter of which had a large amount of neoformed blood vessels. As shown in Figure 4, the CAM treated with 30 mg/ml of *S. pseudoquina* extract had connective tissue, inflammatory elements, and neoformed blood vessels, with erythrocytes in the vascular lumen.

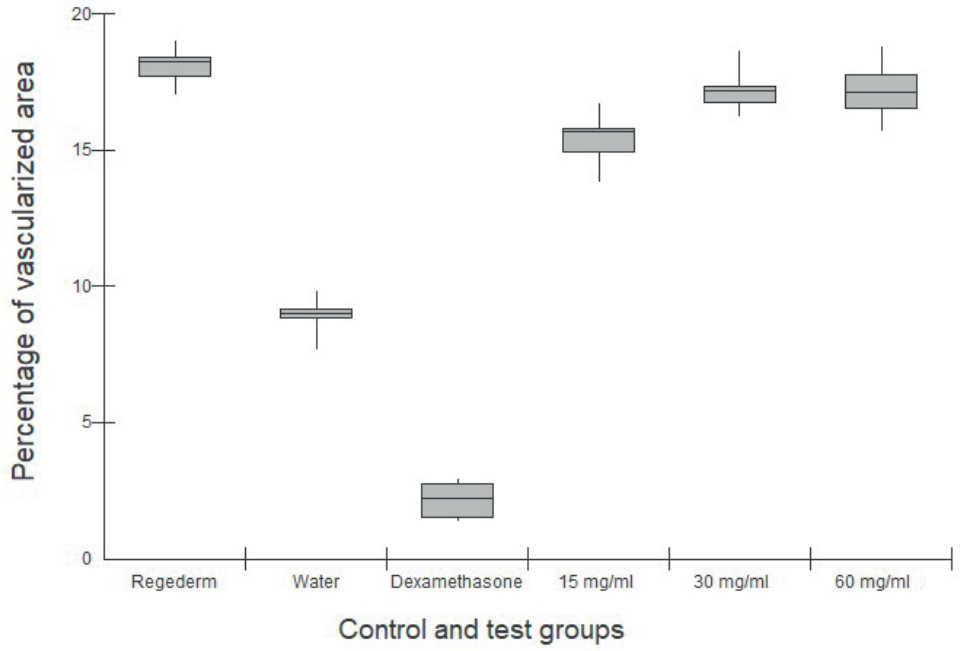

Figure 1. Box-Plot graph of the percentage of vascularized area of the chorioallantoic membrane of embryonated chicken eggs after treatment with aqueous solution of *Strychnos pseudoquina* and controls.

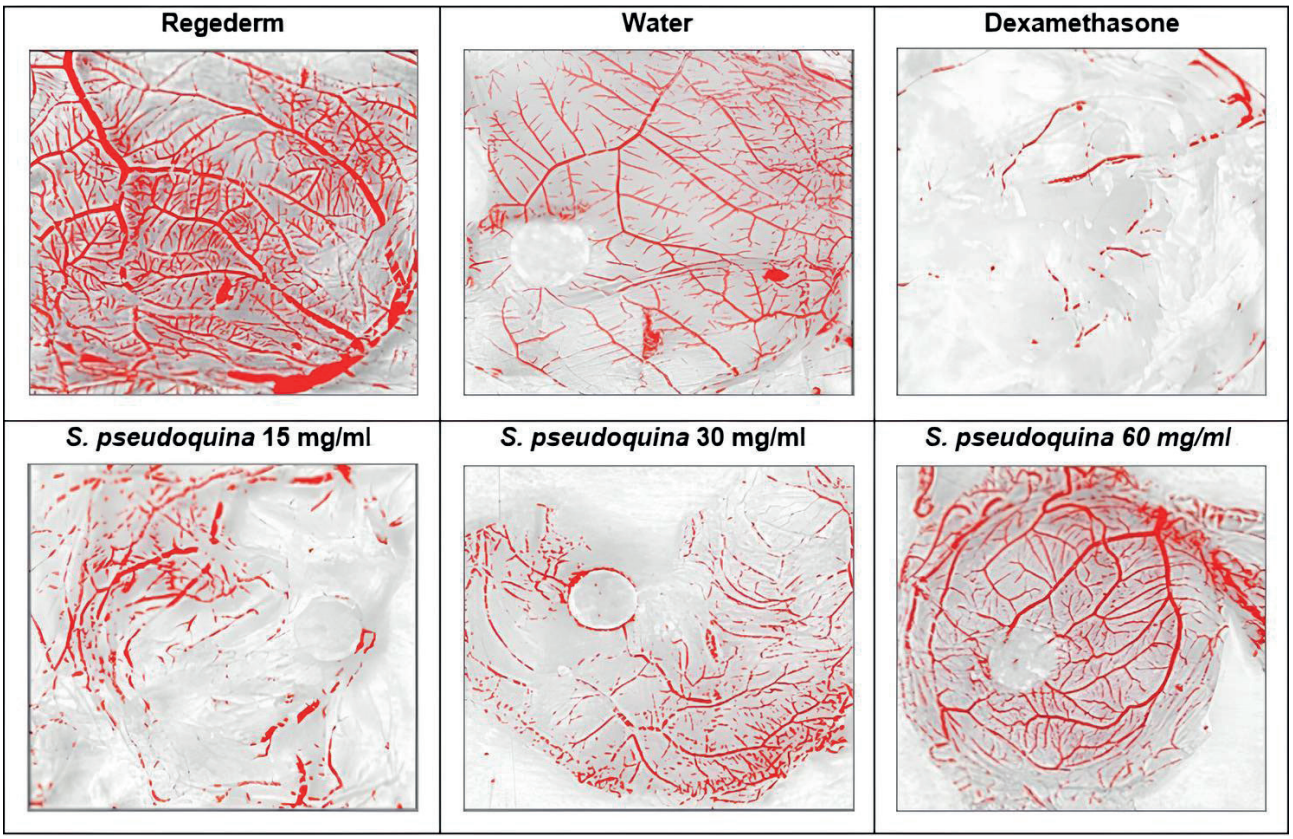

Figure 2. Image analysis of the neoformed vascular network in chorioallantoic membranes of eggs after treatment with respective controls and tests, using the imageJ software.

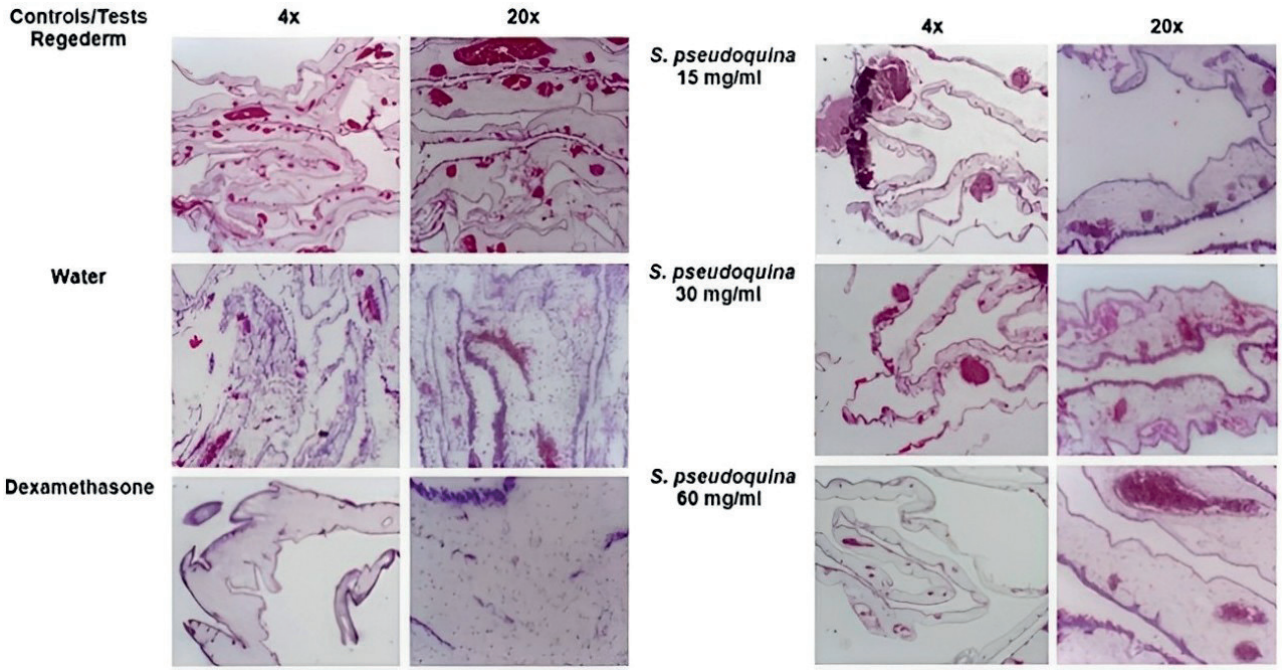

Figure 3. Photomicrograph of histological slides of the newly formed vascular network in chorioallantoic membranes of eggs after treatment with respective controls and tests.

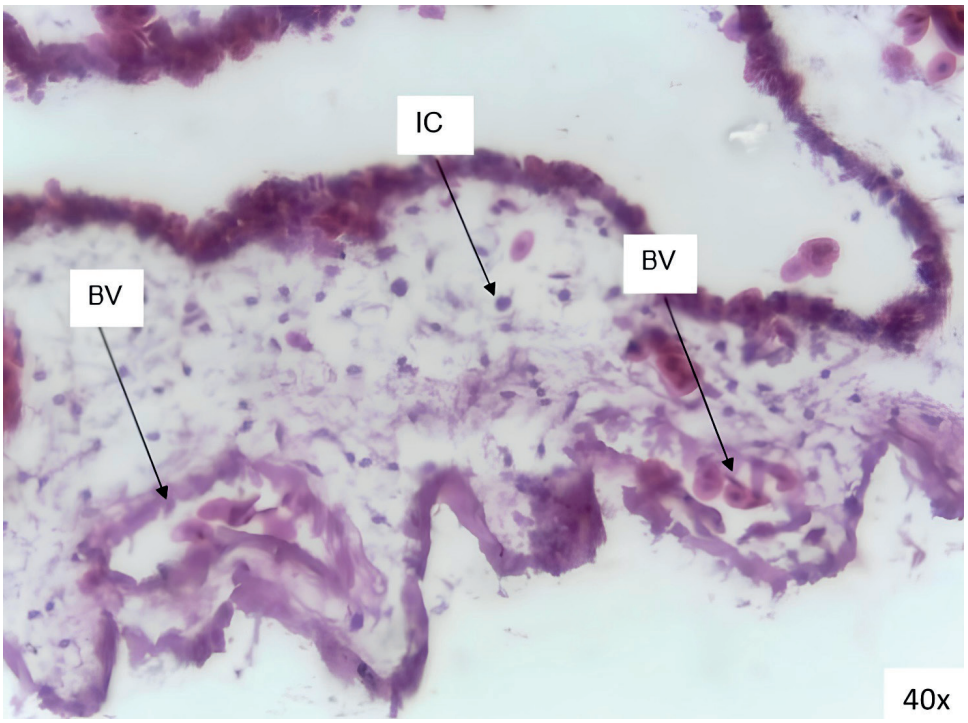

Figure 4. Photomicrograph of the histological section of the chorioallantoic membrane treated with a 30mg/ml solution of *Strychnos pseudoquina*. BV-blood vessel; IC-inflammatory cell.

DISCUSSION

As expected, the negative control (water: percentage of vascularization, 8.9%) and inhibitor control (dexamethasone: percentage of vascularization, 2.2%) had a lower number of blood vessels than the positive control, since no angiogenic stimulators (growth factors) were present in the water control and dexamethasone is known to inhibit the vascularization process (Hori et al. 1996; Nakao et al. 2007). Our *in vivo* study using embryonated eggs demonstrated the ability of the aqueous extract of *S. pseudoquina* bark (at 15, 30, and 60 mg/ml concentrations) to induce the formation of new blood vessels in CAMs.

The angiogenic activities of the 30 and 60 mg/ml extract indicate the relevance of the angiogenic potential of the plant extract at these concentrations when compared with Regederm, a drug with scientifically proven healing efficacy and angiogenic activity (Mendonça 2004; Zimmermann et al. 2018).

Several chemical components of the *S. pseudoquina plant* have been identified, such as polyphenols, proanthocyanidins that are present in larger amounts in stem bark extracts (Gontijo 2017; 2020), and the flavonoids isorhamnetin and strychnobiflavone that are common in the leaves (Nicoletti et al. 1984; Lage et al. 2013). These compounds are directly associated with the healing process (Santos et al. 2021), which is divided into three phases: inflammatory; proliferative, during which angiogenesis occurs; and remodeling (Mendonça and Coutinho-Netto 2009). Such findings explain the process of angiogenesis that was demonstrated and proven in this study.

In a study conducted by Sarandy et al. (2018), the treatment of Wistar rat skin excisions with an *S. pseudoquina*-based ointment was demonstrated to accelerate secondary intention wound healing on the lateral dorsum region. The healing power of the ointment was due to its high concentrations of phenolic compounds, flavonoids, and alkaloids, which proved to be more efficient than silver sulfadiazine in the treatment of the rats in this study.

Another interesting fact in the study by Sarandy et al. (2018) that corroborated our findings is that the wounds treated with the *S. pseudoquina* ointment had a higher number of mast cells, which were one of the main factors related to the healing process owing to the ability of these immune cells to release molecules that stimulate angiogenesis, such as heparin, histamine, tryptase, and cytokines such as transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8), fibroblast growth factor-2 (FGF-2), and vascular endothelial growth factor (VEGF) (Mendonça and Coutinho-Netto 2009; Ng 2010). These factors are directly related to angiogenesis (Ribatti et al. 2001; Ribatti et al. 2003; Souza 2020).

In an earlier study, Sarandy et al. (2017) had evaluated the topical effect of ointments containing a hydroethanolic extract of *S. pseudoquina* stem bark (at concentrations of 5 and 10%) on skin wound healing in diabetic rats. In addition to its antioxidative potential, the plant-based ointment showed a high wound-healing rate, with the wound site exhibiting an increased number of mast cells, fibroblasts, and macrophages as well as blood vessels, as observed in our study.

Bonamin et al. (2011) evaluated the healing effect of a methanolic extract and enriched alkaloid fraction (EAF) of *S. pseudoquina* leaves in a rat model of acetic acid-induced chronic ulcer. Similar to our findings, those authors observed that the number of blood vessels in the gastric mucosa of the EAF-treated rats had increased *significantly* (4 times more than the control treatment). In other words, the treatment with EAF induced wound-healing activity in the gastric mucosa by promoting both cell proliferation in the healing region and the activity of superoxide dismutase, a potent antioxidant that has the ability to eliminate free radicals, accelerate the healing of gastric lesions, and increase angiogenesis.

CONCLUSION

Based on the data obtained in this present study, it is evident that the aqueous extract of *S. pseudoquina* barks possesses angiogenic activity. Thus, the healing potential of this plant could have promising therapeutic application in the clinical setting.

AUTHORS' CONTRIBUTIONS

Conceptualization: ICPS; methodology: ICPS, PRMR, and NSPS; validation: ICPS and PRMR; formal analysis and investigation: ICPS, PRMR, and NSPS; resources: ICPS and PRMR; data analysis and curation: ICPS, PRMR, SLRP, and CGC; writing (original draft): ICPS; writing (revision): ICPS, PRMR, LCC, FM, and VBLQ; visualization: ICPS and PRMR; supervision: ICPS and PRMR; project administration: ICPS. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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