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Review article

Healing activity of *Stryphnodendron adstringens* (Mart.), a Brazilian tannin-rich species: A review of the literature and a case series

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ABSTRACT

Introduction: *Stryphnodendron adstringens,*commonly known as "barbatimão", is a Brazilian savannah plant that has been long used in folk medicine due to its wound healing properties. However, there is a lack of integrated analyses of its healing activity based on scientific evidence.
Methods: The present study provides a literature review based on articles published in journals indexed in PUBMED and SCIELO databases. Moreover, a case series of four patients treated with a commercial barbatimão bark extract ointment is described.
Results and discussion: Forty-two publications on barbatimão were included in this review, most of which were published in English. From these studies, several biological and clinical actions of barbatimão were identified including anti-inflammatory, antioxidant, anti-ulcer, antimicrobial, and anti-parasitic effects, in addition to healing properties. The healing ability of barbatimão is scientifically described using evidence mainly obtained from animal experimental studies, and only one clinical trial exists that describes its healing effect on decubitus ulcers. Therefore, it was considered relevant to report a case series of patients subjected to barbatimão treatment for wounds caused by intense involuntary physical trauma (external accidents) or surgery. Considering all cases, the complete wound healing duration was 3.6 ± 0.8 months. Barbatimão is a tannin-rich plant, and chemical matrix analysis suggests that its wound healing effect is mainly due to high levels of epigallocatechin-gallate (EGCG) and gallic acid molecules.
Conclusion: Considering the difficulty in treating chronic or extensive wounds, barbatimão could be an effective, low-cost phytotherapy formulation with low levels of toxicity.

1. Introduction

Wound healing is a biological process that involves four distinct and subsequent phases (haemostasis, inflammation, proliferation, and tissue remodelling) in order to restore injured tissues [1]. Due to the complexity of this process, searching for natural products with effective and safe healing activities could be considered beneficial [2]. Brazil is a megadiverse country in terms of plant species, with some species long being used as wound healing treatments by several indigenous and mixed-race traditional communities (caboclo, caiçara, and descendants of enslaved Africans, named quilombolas) [3]. This is the case for *Stryphnodendron adstringens* (Mart.) Coville, a tannin-rich species commonly known as barbatimão (Fig. 1). Barbatimão is native to the Brazilian Cerrado biome, and is considered an endemic species as is distributed in all Brazilian geographic regions [4].

The name "barbatimão' originated from the indigenous Tupi-Guarani language and means "the tree that tightens" [5]. The traditional curative properties of barbatimão were recognized long ago by Auguste de Saint-Hilaire and other European naturalists that travelled inner Brazil in the 19th century [6]. Prior studies have been performed using barbatimão bark in order to verify its efficacy in the treatment of wounds and existing some evidences related with its clinical action [7,8]. Due its important wound healing effects, the purpose of this report is to review the literature relating to the wound healing properties

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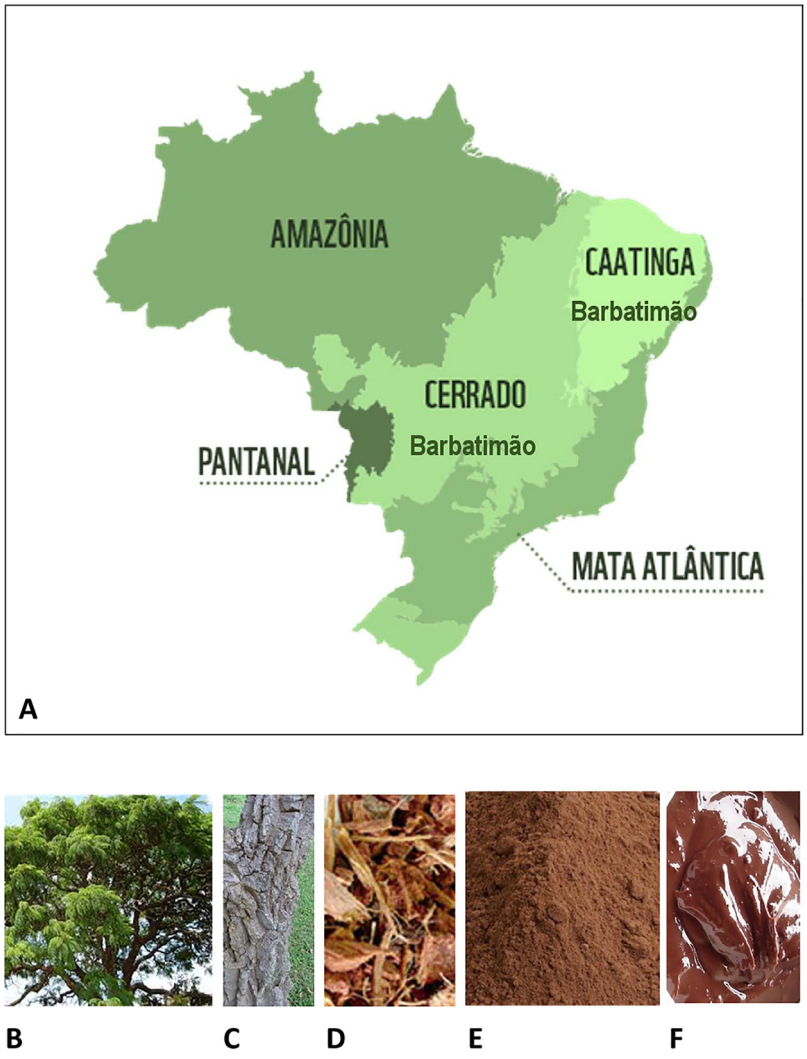

Fig. 1. Figure 1 *Stryphnodendron adstringens* (Mar.) (barbatimão) is a leguminosae belongs to Fabaceae family. (A) barbatimão is native from Brazilian Savannah Biomes (Cerrado and Caatinga); (B) the species is a small tree, hermaphrodite, deciduous, tortuous trunk and each thick and light-colored rough; (C,D) traditionally, pieces of barbatimão bark are collected and (E) can be macerated to turn into a powder that is boiled and the infusion is used for washing of the affected area in the form of baths. A cloth gauze or cotton soaked with barbatimão can also be applied directly over the wound. (F) dry extract of barbatimão can commercially prepare as an ointment to 50% of extract (60 mg/ g) with polyethylene glycol, propylene glycol, methylparaben and propyl paraben excipients. 60 mg of barbatimão's dry extract corresponds to 40 mg of total phenols and 27 mg of total tannins.

of this plant, and to present a case series of wound healing using barbatimão extract for voluntary (surgery) and involuntary (physical injures) trauma.

2. Methods

2.1. Selection of papers

The papers analyzed in the present review were selected from two electronic databases, PUBMED and SCIELO, accessed on May 01, 2017 using the following search filters: "*Stryphnodendron adstringens*"; "*Stryphnodendron adstringens* wound healing"; "barbatimão"; and "barbatimão wound healing". Studies describing information potentially associated with the wound healing activity of barbatimão were also considered, such as those focusing on the chemical characterization of bioactive molecules present in barbatimão bark extracts, and studies addressing the proliferative, inflammatory, and antimicrobial activities of barbatimão. Most referenced studies were published in English, however, in exceptional cases, some studies published in Portuguese were also included.

2.2. Case series

The study was part of a project previously approved by the Ethics Committee of the Universidade Federal de Santa Maria and was conducted according to Resolution # 1/88 of the National Health Council. However, patients did not sign their consent because a retrospective case series was performed based on clinical information and photographs found in the medical records of the Public and Free Service of Nursing School of Universidade Federal de Santa Maria, Palmeira das Missões, Brazil. The series analysis included four patients (two males and two females) that had suffered some physical trauma and were treated by the same nurse professional using the only commercial phytotherapeutic preparation of barbatimão approved for clinical use by ANVISA (National Agency of Sanitary Vigilance of Brazilian Health Ministry), which has a similar role to the Food and Drug Administration agency (FDA, US).

The commercial formulation contained 50% dried barbatimão aqueous extract (60 mg) solved in an excipient containing macrogol, propylene glycol, methylparaben, and propylparaben (1 g). Sixty milligrams of dried barbatimão extract contains approximately 30 mg total phenol and 27 mg total tannins. It is important to point out that this medicinal preparation containing barbatimão cannot be used for injuries that cause impairment of bones or supporting structures (such as tendons, for example). It should also not be used in cases involving osteomyelitis, arthritis, or an infected wound. The procedures prior to the application of the ointment were those standardized for the treatment of open lesions and included wound cleaning and local asepsis. The ointment was applied to the wound twice day in a sufficient quantity to cover the entire injured area. All wound healing cases presented here were treated by the same highly trained nurse and Fitoscar® was prescribed by a physician.

Since photography material present in the medical records of each patient was used for the case series, the evolution of wound healing was evaluated using Digimizer, a free image analysis software that estimates and compares the area of wounds using pixels as a general unit. The area and perimeter of the wound at time 0 was considered as 100% open wound, and two other subsequent measurements were carried out and compared in order to examine the % of the wound that remained open at the times analyzed.

2.3. Statistical analysis

The statistical tests were performed using Graph Pad Prism Software. The case series was reported using descriptive statistics expressed as mean ± standard deviation (SD) or relative frequency (%).

3. Results and discussion

In the present review a total of 39 articles were identified using "*Stryphnodendron adstringens*" as a filter, and 21 using "barbatimão" as a filter in the PUBMED database. In this database, just nine articles were identified using "*Stryphnodendron adstringens*and wound healing" as a filter. From the SCIELO database, a total of 29 articles were identified using "*Stryphnodendron adstringens*", and 67 were identified using "barbatimão" as filter words. The "Barbatimão and healing" filter identified seven articles in this database. From PUBMED, three articles about barbatimão were excluded because they were botanical studies unrelated to the biological function or chemical characterization of barbatimão. Studies published in English and Portuguese involving barbatimão and the main results of these studies relating to its chemical characterization and biological effects are listed in Table 1. However, in this review, analysis of the chemical and functional activities of barbatimão was mostly based on English Language articles directly and indirectly addressing its wound healing effects.

Table 1
Studies on the chemical characterization or main biological effects of *Stryphnodendron adstringens* (barbatimão) identified from PUBMED and SCIELO databases.

Main Results	Publications		
	Language	N*	References
Chemical characterization	English	09	[9–17]
	Portuguese	02	[18,19],
Antioxidant activity	English	03	[16,17,20],
Cytotoxicity against cancer cells	English	03	[16,17,21]
Wound healing	English	03	[7,22,23]
	Portuguese	02	[24,25]
Anti-inflammatory	English	01	[26]
Antibacterial\Antiseptic	English	02	[20,27]
	Portuguese	02	[28,29]
Antifungal	English	07	[27,30–35]
Antiviral	English	01	[36]
Antiparasitic	English	01	[37]
	Portuguese	01	[38]
Gastroprotective	English	02	[39,40]
Antinociceptive	English	01	[41]
Protective effect against amyloid-beta peptide-induced toxicity	English	01	[42]
Inhibitory activity of α-amylase and α-glucosidase	English	01	[43]
Suppressive terminal hair growth effect	English	01	[44]
Energy metabolism modulation in the rat liver	English	01	[45]
No-cytotoxic and no-genotoxic/ genoprotective effect	English	04	[46–49]
Cytotoxic and genotoxic effect	English	02	[5,50]
	Portuguese	01	[51]
Angiogenic activity	Portuguese	01	[52]
Abortive	English	01	[53]

* Some articles described more than one biological activity and for this reason there are some repeated references in the table.

3.1. Plant characteristics and its traditional external use

Barbatimão is a plant belonging to the Fabaceae family. It is a small, hermaphroditic, deciduous tree with a rough, light-colored, thick, tortuous trunk. The leaves alternate between composed and binary. Its fruits are thick, fleshy pods, which are light brown in color and produce many brown seeds. Flowering occurs in September. The species also has the following botanical synonyms: *Acacia adstringens* Mart., *Mimosa barbadetimam* Vell., *Mimosa virginalis* Arruda, and *Stryphnodendron barbatimam* Mart. Because of its astringent properties, the plant is popularly known as the "bark of virginity" [54]. According to Brazilian Pharmacopeia [55], barbatimão vegetal drug is mainly composed of dried stem bark. However, there are Brazilian studies describing the pharmacological uses of other barbatimão organs such as leaves, flowers, beans, roots, fruits, and seeds. Popular uses of this species include barbatimão preparations in the form of decocts, infusions, and tinctures [56].

Traditional external uses (topical administrations) of preparations obtained from peels, stalks, and skeletons of barbatimão can include the treatment of uterine and vaginal disorders, urinary infections, inflammation, circulatory conditions, and cutaneous and ulcerative wounds [56].

A dust of the bark decoction is traditionally used in wound healing. This dust is reddish brown in color, and has a characteristic smell and an astringent taste. In general, average diameter of the bark powder, stems bark, and peel of barbatimão varies from 150 to 440 mm.

3.2. Evidence of barbatimão biological and clinical properties

Previous investigations have indicated that extracts of barbatimão stem bark have several potentially medically useful properties, such as anti-inflammatory [26], antioxidant [16,17,20], antimicrobial [27–30], and antiulcerogenic action effects [39,40]. A recent investigation also reported potential anticarcinogenic properties of barbatimão against breast cancer cell lines [17]. Studies analyzing the wound healing effects of barbatimão will be outlined in more detail below. Some of these studies could help to understand the causal mechanism behind the wound healing properties of barbatimão extract.

3.3. Barbatimão wound healing properties: evidence from in vitro and in vivo studies

Looking at the healing effects of barbatimão extracts and peels and considering the beneficial properties of ointments containing bark extracts and bark from the stems, it appears that this plant aids both the healing process of cutaneous wounds and the epithelization of lesions treated with ointments. Topical application of ointments containing *S. adstringens* also stimulates cell proliferation, without affecting keratinocyte migration or wound contraction [7].

It is well-known that diabetes mellitus causes problems related to scarring. Based on this knowledge, Pinto et al. [22] evaluated the healing action of barbatimão on streptozotocin-induced diabetic rats. Two skin lesions were made on the rats, which were treated daily for 4, 7, 10, and 14 days with gel containing 1% crude or gel-based extract. The results showed that the raw extract repaired the lesions through the stimulation of collagen fiber formation at the site of cauterization, better organization of the extracellular matrix, and super-regulation of cyclooxygenase-2 and vascular endothelial growth factor, which are two key molecules in the regenerative process.

Another study that should be considered was developed by Silva et al. [23]. Five percent barbatimão bark extract was applied to treat bovine digital dermatitis in 180 affected cattle. Treatment with barbatimão was effective during the postoperative period (surgical curettage of the lesions).

Table 2
Characteristics baseline and wound healing data outcome analysis.

Subject N°/sex	Age (years)	Trauma type	Healing time* (months)	Wound outcomes								
				Measure (Month)/Area (px)		%	Measure (Month)/Area (px)		%	Measure (Month)/Area (px)		%
1-Male	59	Nail drilling	04	0	9988.6	100	01	2370.8	23.7	03	22.2	0.22
2-Male	19	Injury to a tractor wheel	06	0	5594.3	100	02	3809.4	68.1	06	76.6	0.13
3-Female	41	Compartment syndrome	03	0	9734.3	100	03	112.2	1.15	03	0	0
4-Female	60	Rejection of breast graft	03	0	31803.5	100	02	112.2	0,75	03	35.8	0.24

3.4. Toxicological studies of barbatimão

Toxicological studies (acute, sub-chronic, and chronic) of barbatimão have also been produced. Most investigations did not indicate acute toxicity, chronic toxicity, or genotoxicity of barbatimão extracts or their major bioactive compounds [46–49]. However, until now no studies have been published describing the potential for barbatimão to cause dermal sensitization, skin, or eye irritation.

A recent *in vitro* study by Pellenz et al. [48] clarified that barbatimão stem bark hydroalcoholic extract used in Brazilian commercial formulations has genotoxic effects on two commercial cell lines of keratinocytes (HaCaT) and fibroblasts (HFF-1). Initially, authors evaluated the potential genomodulatory action of barbatimão using a noncellular DNA protocol (GEMO assay) on H_2O_2-exposed calf thymus DNA. The results showed no-genotoxicity a potential genoprotective action on DNA fragmentation triggered by H_2O_2. Moreover, barbatimão was able to decrease cytotoxic events on keratinocytes and fibroblast cells by downregulation of proapoptotic BAX, caspase 3, and caspase 8, and by upregulation of Bcl-2, an anti-apoptotic gene.

Another issue is the potential allergic effect of barbatimão, since it can be applied topically for long periods of time. Generally, the public perceives that botanical phythotherapies used in personal care and in wound healing are safe. However, some molecules present in the chemical matrix of these products, particularly proteins have the potential to cause immediate-type (IgE-mediated) respiratory allergic reactions. Although reports of such reactions are uncommon, when they do occur, they can be severe. Therefore, contact allergies induced by certain chemicals is a common health concern [57].

In fact, the present review did not find specific studies focusing on the sensitization potency of barbatimão. This lack of scientific studies may be because it is a product that has been used by traditional Brazilian communities, possibly since pre-Columbian times. Because of this, it is unlikely that this adverse effect is very common. However, additional studies on the potential allergic effect of barbatimão under controlled and standardized conditions could help to determine the safety of this herbal product.

It is also important to note that several studies in experimental animals suggest that barbatimão has abortive effects [53]. However, in a review conducted by Yasbek et al. [58] on medicinal plants used by women from traditional communities during maternity and to regulate the menstrual cycle, the authors reported that barbatimão is an herb used by healers and as a Brazilian Popular Medicine to treat inflammation of the ovaries and uterus. In any case, the potential abortifacient effects of barbatimão must be considered when using it to treat pregnant women's wounds.

3.5. Barbatimão wound healing properties: clinical trials

Unfortunately, until now, clinical trials involving barbatimão are incipient and only two such studies exist: an investigation conducted to evaluate the effect of topical administration of pharmaceutical products containing extracts of barbatimão on the reduction of body hair in female subjects [44], and an investigation into the effectiveness of barbatimão in healing decubitus ulcers [59].

The latter study, which was published in Portuguese, included 22 patients with ischemic compression ulcers caused by lesions of the Central Nervous System, geriatric pathologies, and long periods of bed immobilization. Fifty-one decubitus ulcers located in different regions of the body (ischium, gluteal region, trochanter, sacrum, Achilles tendon, calcaneus, malleolus, occipital region, and spinal process) were considered and classified according the depth of the lesion. The herbal medicine, in the form of ointment, contained 3% active barbatimão and was developed by the Faculty of Pharmacy of the UNAERP. The formula was entered into the National Institute of Industrial Property (PI0305535-3). This formula is currently used in Fitoscar® commercial ointment. In the study, ointment was applied to the bedsores once a day after saline hygiene. Patients who received the treatment were observed weekly for a period of 6 months. Results showed that, on average, grade I and II lesions were healed within 3–6 weeks and grade III lesions were healed between 10 and 18 weeks. During the study, 100% of the lesions treated with the drug healed completely.

Due to the scarcity of clinical studies involving barbatimão extract, descriptions of case series that used barbatimão in the healing of traumatic or chronic wounds could be beneficial.

3.6. Case series description

Baseline characteristics of the five subjects (two males and three females), their ages (48.8 ± 16.9 years), and wound healing data outcomes are presented in Table 2. Pictures of wounds at different points during healing are shown in Fig. 2, causes of wounds were either intense involuntary actions (accident) or voluntary (surgery) physical trauma. However, considering all cases, wound healing duration was 3.6 ± 0.8 months.

The first case was a diabetic patient that suffered a physical trauma (nail drilling), which did not heal well and led to the loss of the fourth toe. Considering the severity of the trauma and the fact that diabetes has a highly negative impact on wounds, the healing time was rapid. In the second case, although the patient was young, the trauma involved bone fractures and required surgery. Again, considering the severity of the trauma, healing was relatively rapid. The three female's patients all suffered surgical traumas, including a rejection of a breast graft. Again, healing was relatively fast considering the extent of the injuries.

3.7. Barbatimão chemical matrix: main molecules and their potential wound healing effects

The case series shows the efficacy of barbatimão treatment on different types of wound healing, and its action is likely due to a chemical matrix rich in bioactive molecules. Tannins, mucilage, flavonoids, and saponins have been reported in bark, stem bark, and intercrop extracts from barbatimão. Tannins have also been reported in hydro alcoholic extract of barbatimão leaves, as well as steroids, simple phenols, flavonoids, flavanones, flavanols, and saponins. In fact, barbatimão vegetal drugs contain at least 8% total tannins, determined in relation to the dry vegetable drug [54].

According to the Monograph of Species on barbatimão published in 2014 by the Brazilian Health Ministry [54], the only drug so far

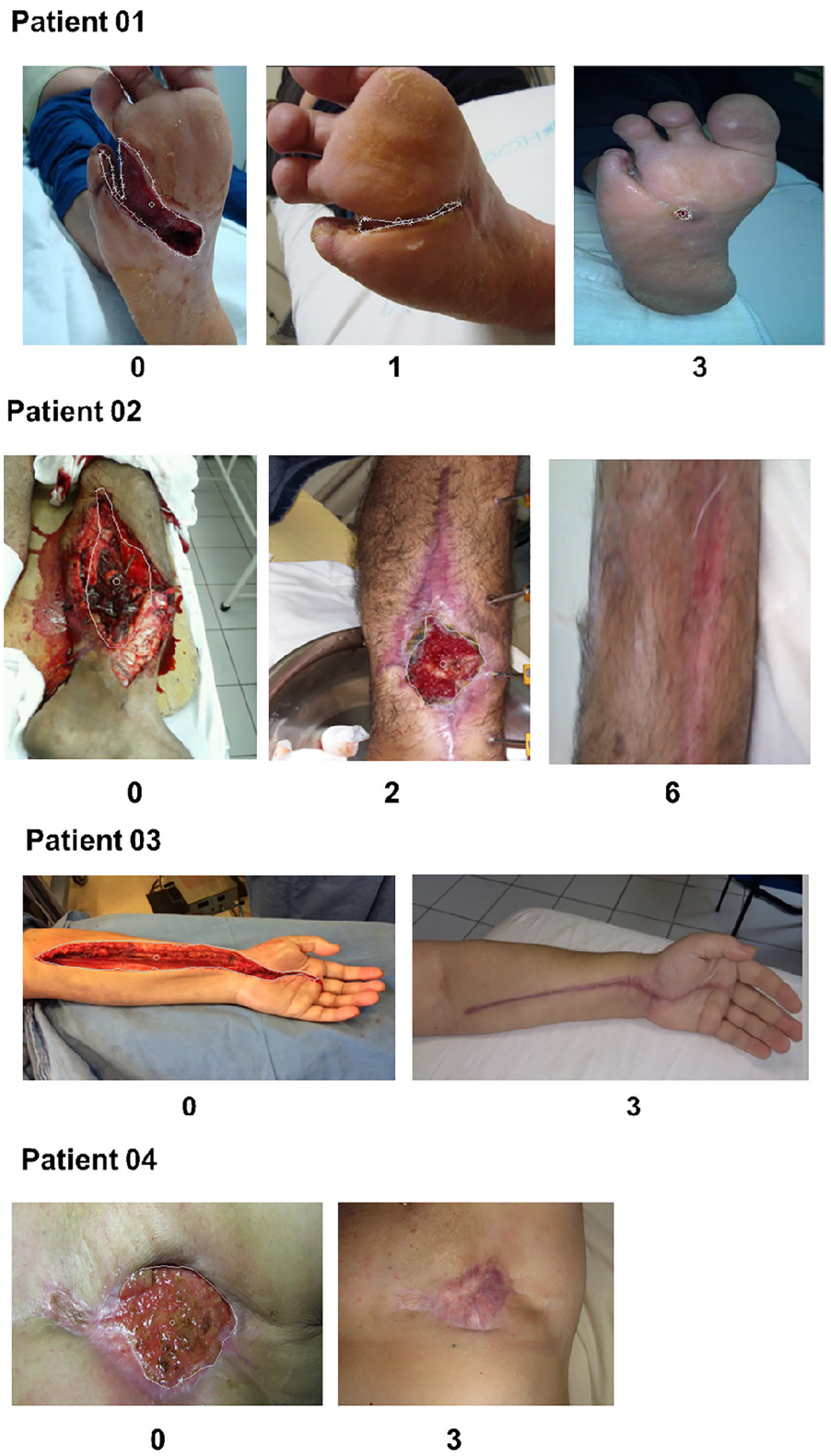

Fig. 2. Series cases of *Stryphnodendron adstringens* (Mar.) (barbatimão) wound healing activity in five patients with physical lesions: (01) nail drilling; (2) injury to a tractor wheel; (3) compartment syndrome surgery; (4) rejection of breast graft; (5) safenectomy. Cases were selected from medical records of Public and Free Service offered by Nursing School of Universidade Federal de Santa Maria, Palmeiras Campi, Brazil. All patients were treated by same nurse professional.

registered in ANVISA was Fitoscar (registration number 101180605, valid of 12/2017). The Fitoscar product is presented as a topical ointment containing 60 mg of dry barbatimão extract at 50% per gram of ointment. Each 60 mg of 50% dry extract contains 30 mg total phenols and 27 mg total tannins. Because of this, Fitoscar, dry extract of barbatimão, is advertised as a cicatrizing agent for several types of lesions.

The total phenol content in extracts and fractions obtained from barbatimão varies from 1.5 to 80%. The total tannins content in extracts and fractions of bark and fruits of barbatimão ranges between 20 and

40%. An analysis of the tannins in barbatimão revealed pyrogallol (C6H6O3; 126,11), of which at least 0.2 mg g^{-1} was gallic acid (C7H6O5; 170.1) and 0.3 mg g^{-1} corresponded to gallocatechin (C15H14O7; 306.27) [54]. Flavan-3-ols, prodelphinidins, and prorobinetinidins such as 4′-O-methyl-gallocatechin, 4′-O-methylgallocatechin-(4α→8)-4′-O-methylgallocatechin, catechin, and epigallocatechin-3-O-gallate (EGCG) have been isolated and identified from bark barbatimão extracts [9–11,15].

It is relevant that EGCG is the main bioactive molecule found in green tea, which is an important and recognized antioxidant with antimutagenic and anticarcinogenic properties [60,61]. Regarding the skin, evidence has suggested that EGCG regulates the secretion of cytokines and the activation of cells during healing. Kim et al. [62] evaluated the effects of several concentrations of EGCG added to lactic-co-gyclic poly-acid (PLGA) membranes on the healing of cuts made in nude mice (genetically modified to have no fur). Results suggested that 1% concentration of EGCG in the membrane was able to improve healing, accelerate cell infiltration, and to promote re-epithelialization and angiogenesis. It has also been shown that EGCG is capable of accelerating the healing of indomethacin-induced stomach ulcers in mice [63]. This compound has also been shown to promote healing of cutaneous lesions in diabetic mice [64].

Additional studies have confirmed that EGCG has important wound healing properties, such as Shin et al. [65], which developed biodegradable nanofiber membranes that control the release of EGCG in order to prevent postoperative adhesions associated with surgeries involving the peritoneum. The study initially characterized the biomechanical properties of the nanofibers containing EGCG and also evaluated the potential antioxidant action of EGCG *in vitro*. To test the anti-adherence effect, surgical incisions were made on the peritoneum of rats. The results showed anti-adherence efficacy of nanofibers containing EGCG after one week of surgery. Furthermore, it has already been demonstrated that EGCG can suppress the appearance of keloids by suppressing both collagen production and proliferation of fibroblasts that form keloids [66]. A potential causal mechanism involved in the wound healing capacity of EGCG is its action on mesenchymal stem cells present in the skin [67].

Moreover, Chen et al. [68] showed that treatment with antioxidant compounds containing EGCG, alpha-lipolic acid, and gold nanoparticles promoted the healing of diabetic wounds through the regulation of angiogenesis and anti-inflammatory effects. In this case, catechins such as EGCG also participate in the process by increasing levels of vascular endothelial growth factor (VEGF-A), which in turn increases cell viability and aids proliferation of fibroblasts and keratinocytes. Moreover, catechins act directly in the inflammatory pattern by triggering decreases in the levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) [69].

Unlike barbatimão, there have been several clinical trials involving the effects of catechins from green tea on wound healing. For example, a recent randomized, double-blind, placebo-controlled clinical trial reported that green tea ointment was effective in relieving episiotomy pain and that it improved wound healing in primiparous women [70].

Another important component present in barbatimão, green tea, and other plant species with wound healing properties is gallic acid. This bioactive molecule is found in some plants, such as *Caesalpinia mimosoides* Lam., an important traditional folk medicinal plant used by healers in Uttara Kannada district (India) for the treatment of skin diseases and wounds [71], *Lythrum salicaria* L. and *Hypericum scabrum* L., both used to treat burn wounds [72], and *Calotropis procera* bark, used to treat surgical wounds [73].

The specific wound healing effects of gallic acid were studied by Yang et al. [74]. Authors investigated these wound healing properties in human keratinocytes and fibroblasts under both normal and hyperglucidic conditions, to mimic diabetes. The results showed that gallic acid accelerated cell migration of keratinocytes and fibroblasts under both tested conditions. Moreover, gallic acid was able to activate production of some factors known to be hallmarks of wound healing, such as focal adhesion kinases (FAK), c-Jun N-terminal kinases (JNK), and extracellular signal-regulated kinases (Erk).

4. Conclusions

Considering the difficulty of treating chronic or extensive wounds, barbatimão could be an effective, low-cost, and low-toxicity phytotherapy formulation. Barbatimão seems to possess wound healing activity due to its chemical matrix being rich in tannins, especially EGCG and gallic acid. It is probable that the antioxidant, anti-inflammatory, and proliferative effects of barbatimão extract could contribute to the healing activity of this plant. However, complementary studies on the causal mechanisms behind the healing activities of barbatimão need to be performed.

Ethical Statement

The study was part of a project previously approved by the Ethics Committee of the Universidade Federal de Santa Maria and was conducted according to Resolution # 1/88 of the National Health Council. However, patients did not sign their consent because a retrospective case series was performed based on clinical information and photographs found in the medical records of the Public and Free Service of Nursing School of Universidade Federal de Santa Maria, Palmeira das Missões, Brazil.

Financial disclosure

No financial statement, since the project did not have funding, besides the researchers themselves, to contribute with the necessary materials.

Declaration of Competing Interest

All authors declare no conflict of interest.

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