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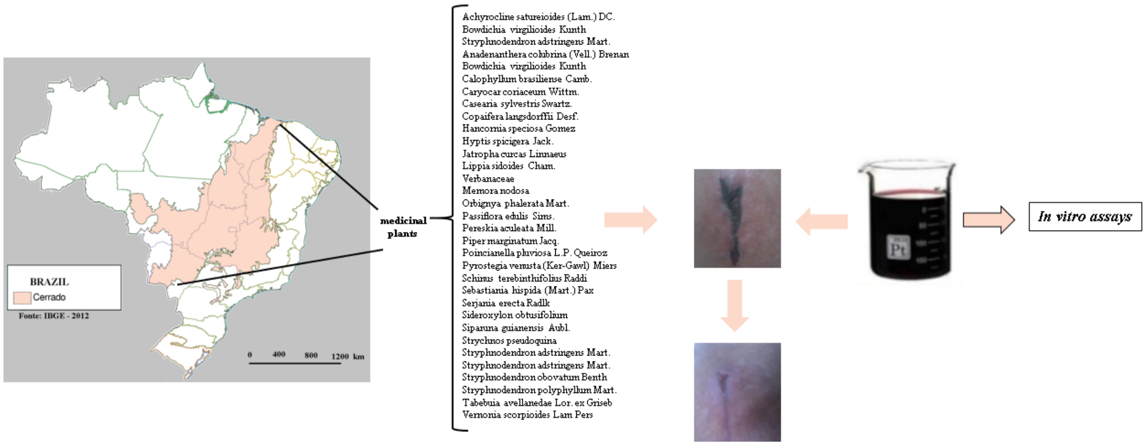
BRAZIL
Cerrado
Fonte: IBGE - 2012
0 400 800 1200 km
medicinal plants
Achyrocline satureioides (Lam.) DC.
Bowdichia virgilioides Kunth
Stryphnodendron adstringens Mart.
Anadenanthera colubrina (Vell.) Brenan
Bowdichia virgilioides Kunth
Calophyllum brasiliense Camb.
Caryocar coriaceum Wittm.
Casearia sylvestris Swartz.
Copaifera langsdorffii Desf.
Hancornia speciosa Gomez
Hyptis spicigera Jack.
Jatropha curcas Linnaeus
Lippia sidoides Cham.
Verbanaceae
Memora nodosa
Orbignya phalerata Mart.
Passiflora edulis Sims.
Pereskia aculeata Mill.
Piper marginatum Jacq.
Poincianella pluviosa L.P. Queiroz
Pyrostegia venusta (Ker-Gawl) Miers
Schinus terebinthifolius Raddi
Sebastiania hispida (Mart.) Pax
Serjania erecta Radlk
Sideroxylon obtusifolium
Siparuna guianensis Aubl.
Strychnos pseudoquina
Stryphnodendron adstringens Mart.
Stryphnodendron adstringens Mart.
Stryphnodendron obovatum Benth
Stryphnodendron polyphyllum Mart.
Tabebuia avellanedae Lor. ex Griseb
Vernonia scorpioides Lam Pers
Pt
In vitro assays

Using the Plants of Brazilian Cerrado for wound healing: from traditional use to scientific approach

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ABSTRACT

Ethnopharmacological relevance

The Brazilian Cerrado is a biome with a remarkable diversity of plant species, many of which are used mainly by local communities as a source of treatment to several pathologic processes, especially for the treatment of wounds. However, no systematic review exists focusing on the plants used in this respect and on the appropriate pharmacological investigations that substantiate the actions that are reported. This study revisits the traditional use of medicinal plants from the Brazilian Cerrado in the treatment of wounds and the pharmacological characteristics of the reported plant species.

Methodology

For the present article, previous studies on plants of the Brazilian Cerrado used for wound healing carried out between 1996 and 2018 were researched on various academic databases (PubMed, Elsevier, Springer, Lilacs, Google Escolar, and Scielo).

Results

A total of 33 studies were carried out on 29 plant species distributed into 18 families, mainly Fabaceae or Leguminosae (9), Bignoniaceae (2), Asteraceae (2), Euphorbiaceae (2). Considering the great diversity of Cerrado plants, only a small number of wound healing studies were carried out between 1996 and 2018. It was observed that there is a large gap between experimentation assay and traditional use. There are only few connections between the form of use by the population and the experiments conducted in the laboratory. We found that only about 12% of these studies considered to use the methodologies, or at least in parts, to obtain extracts such as those used in folk medicine. Approximately 37% of the experiments were performed using the bark as well as the same ratio for leaves, 6% using the fruits, and 9% using the seeds, roots or flowers. In several studies, there are reports of chemical constituents such as flavonoids and tannins, followed by steroid terpenes, saponins, and fatty acids, and alkaloids. However, approximately 35% of the studies did not supply information about compounds present in the preparation or the effect which could be attributed to these agents in respect to wound healing. Regarding treatment, most of the studies employed a topical treatment, though intraperitoneal and oral treatment were also described using either topical, oil-based formulations, but also gel- or saline-based formulations.

Conclusions

Although, there has been an increase in knowledge about the biological actions of plants from Cerrado biome, the scientific basis for the traditional use of these local medicinal plants in wound healing does not provide sufficient information on the efficacy of the treatment, the molecular mechanisms, or, in particular, the effective doses used and the drug interactions. Thus, focused research investigating these hypotheses from traditional knowledge is necessary to prove the evidence of the potential pharmacological action.

KEYWORDS: Brazilian Cerrado; medicinal plants, traditional use, wound healing

List of abbreviations

WHO - World Health Organization; MeSH - Medical Subject of Health; DeCS - Integrated Advanced Information Management Systems; MeSH - Medical Subject of Health; HaCaT - Cultured Human Keratinocyte;

MRC-5 - Medical Research Council cell strain 5; HIV-1 - Human Immunodeficiency Virus 1; COX- Cyclooxygenase; EGF - Epidermal growth factor; TNF-α - tumour necrosis factor;

iNOS - Inducible Nitric Oxide Synthase; COX-2 – Cyclooxygenase-2; VEGF - Vascular endothelial growth factor; 5-LOX - 5-lipoxygenase; IL-1β - Interleukin-1β; IL-6 – Interleukin-6; IL-8 – Interleukin-8; CNPq - National Council for Scientific and Technological Development; FAPEMIG – Fundação de Amparo à Pesquisa do Estado de Minas Gerais.

1. Introduction

Pathologies such as obesity, diabetes and cardiovascular disease, in addition to metabolic syndrome and vascular diseases, often manifest cutaneous wounds as a consequence of the particular disease. Between 0.45% and 3.33% of the world population is estimated to be affected, resulting in a population of 6 million patients whose treatments cost approximately 25 billion dollars annually (Wachholz et al., 2014). The highest incidence of metabolic and vascular disease related wounds is observed in elderly patients.

Wound healing is hallmarked by biological events which aim to repair the wound in the skin. In skin wound healing, several mechanisms have been described involving different molecules and cellular types (Rittié, 2016). This has been divided into three phases: inflammation, proliferation or granulation and remodeling (Campos et al., 2007; Rittié, 2016). The inflammation phase occurs directly after the injury, its major characteristic being a haemostasis and an intense inflammatory process in the wound area. Moreover, during this phase, the release of several biological mediators occurs, such as vasoconstrictor molecules, chemotactic and growth factors by different cellular types near to the wound. Neutrophils and macrophages are involved in the inflammatory process during wound repair with the aim of removing the cellular debris after the injury (Campos et al., 2007). The proliferative phase consists of angiogenesis, granulation, and collagen deposition during wound repair. The remodeling phase is characterized by re-epithelialization and change in the collagen-type deposition. Initially, type III collagen is deposited, which is then replaced with type I collagen, organized in bundles and is well oriented. In this phase, the major cellular type involved is fibroblasts (Campos et al., 2007). Some studies have used medicinal plant extracts or their fractions with the aim to discover new drugs that guarantee that skin wounds to heal quicker and more efficiently (Thomé et al., 2013; Xavier et al., 2017).

The use of different medicinal plants by these patients is rooted in cultural heritage and finds support in the traditionalist example of the nineteenth century, where the therapeutic resources were constituted predominantly by plants and plant extracts of the surrounding flora (Schenkel et al., 2001).

The diverse vegetable or medicinal plant sources, commonly used in infusions, ointments, patches, compresses and lotions, have demonstrated their curative potential, giving rise to information that was transmitted orally between the generations (Martins et al., 2000). Since ancient times, a considerable part of this knowledge has been compiled into potentially interesting historical texts for pharmaceutical research (Rocha et al., 2015).

Since 1978, the World Health Organization (WHO) has recognized the benefits of medicinal plants and defines them as "the best and largest source of drugs for mankind" (Silva Felipe et al., 2012). Brazil began to evaluate herbal medicines according to the same standards of safety and quality of conventional medicines in 2004. Thus, the Brazilian Ministry of Health implemented the National Medicinal and Phytotherapeutic Plants Policy (Brasil, 2006), which, as of 2009, listed 71 medicinal plants with different therapeutic properties, which were then classified as of interest to the Unified Health System (SUS) (Brasil, 2009).

The Cerrado is the second largest Brazilian biome, occupying 21% of the country’s land area (Figure 1). This Biome is considered to be a global hotspot where many native species of plants correspond to approximately 5% of the world's diversity (Brasil, 2010). Cerrado occupies 100% of the Federal District, 97% of Goiás, 91% of Tocantins, 65% of Maranhão, 61% of Mato Grosso do Sul and 57% of Minas Gerais, as well as other, smaller areas.

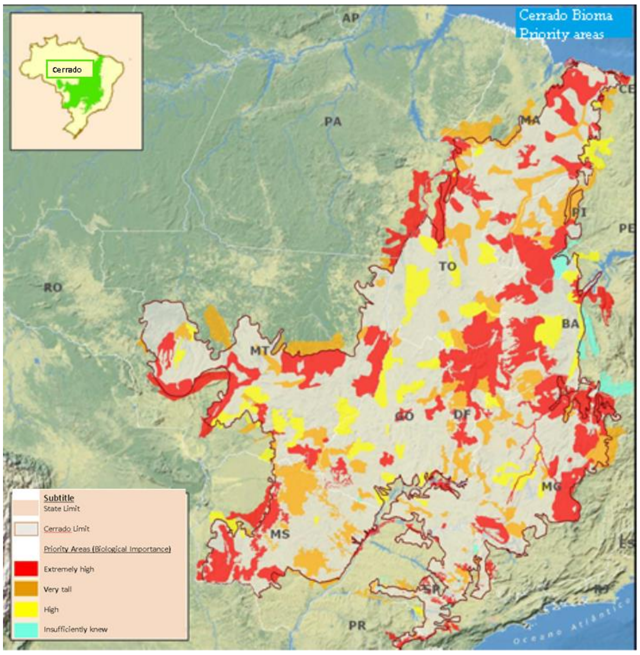

Fig. 1: Location of the Cerrado Biome in Brazilian territory. Adapted from: BRASIL-Ministério do Meio Ambiente. Ministry Environment, 2018.

Few of these species have been studied for their medicinal properties. A plant is considered medicinal when it is used in the reversal of different health conditions, and when this effect is attributed to the action of their constituents whose activity can be scientifically proven (Chen et al., 2004).

Only with progress in the field of pharmacy and chemistry has the study of medicinal plants become a science based on experimental methods (Cechinel, 2012). Formerly and also currently in less developed regions, the medicinal use of plants was usually empirical, and the information was passed between generations in a native population. Thus, this method still persists in rural areas like the Brazilian Cerrado. Faced with the enormous biodiversity of the Brazilian Cerrado, there are few ethnobotanical studies, and few are scientifically proven. Of all Brazilian phytotherapeutic potential, only 8% of the 55,000 plant species catalogued had been yet studied for bioactive compounds and only 1,100 of these species were evaluated for their medicinal properties (Walker, 2013, Simões et al., 2003).

Thus, this review seeks to explore the literature on traditional use of medicinal plants from the Brazilian Cerrado in the treatment of wounds and the pharmacological characteristics of the plant species reported.

2. Methodology

In the present review, articles on the role of Cerrado plants in wound healing were selected from the scientific databases PubMed, Elsevier, Springer, Lilacs, Google Scholar and Scielo. The adopted strategy was to group the descriptors (indexed in the list of DeCS systems – Integrated Advanced Information Management Systems - Trillian Health Sciences Descriptors) and Medical Subject of Health (MeSH) as follows: healing, Brazil, wound healing skin, remedy, treatment and Cerrado. The criteria for inclusion of the complete articles were: 1) publications in English, Portuguese or Spanish between 1996 and August 2018; and 2) studies carried out with Brazilian plants of the Cerrado biome in which results of the investigations show plants that have improved wound healing *in vitro* and/or *in vivo*. Studies without an assay in wound healing and processes related to wound healing were excluded, as well as reviews, and ethnobotanical studies with the citation of the genus only and without specification of its use in folk medicine. The documented information on the natural products analyzed here includes the plant species, the family, common name, the part of the plant used, preparation form, the methods of study conducted (*in vivo / in vitro*), the activity potential and the main active chemical components reported in the articles.

3. Results:

A total of 882 scientific articles, distributed among the six consulted databases, were identified for a preliminary review in which they were subject to both electronic and manual searches. After the removal of duplicates and triage of relevant titles and abstracts, a total of 46 articles underwent a full text review. Thirty-two articles met the inclusion criteria. Twenty-nine plant species are described which are used by different populations as wound healing agents and are also studied using scientific methods (Tables 1 and 2).

The main plant families whose representatives and their extracts improved wound healing activity were Fabaceae (or Leguminosae) (9), Bignoniaceae (2), Asteraceae (2) and Euphorbiaceae (2). According to Pereira et al. (2007), the families Asteraceae and Fabaceae (or Leguminosae) are frequently registered among most surveys about the medicinal flora.

Table 1: Main studies between 1996 and August 2018 relating the species, the part of the plant used in the research, the chemical compounds found, and the effects after the treatments. Main type of study '*in vitro*'. **NR – Not reported**

Table 2: Main studies between 1996 and August 2018 relating the species, the part of the plant used in the research, the chemical compounds found, and the effects after the treatments. Main type of study '*in vivo*'. **NR – Not reported**

Achyrocline satureioides (Lam.) DC family **Asteraceae**

This plant is popularly known as Marcela, Marcela-do-campo or Marcela-da-terra (Almeida, 1993) and occurs from Minas Gerais to Rio Grande do Sul (De Souza et al., 2002). It presents in its extract's different concentrations of flavonoids (Zampieron et al., 2010), quercetin, 3-O-methylquercetin, luteolin (Ferraro et al., 1981), caffeic acid, chlorogenic acid, isochlorogenic acid, glycolipids (Mendes et al., 2006), sesquiterpenes, monoterpenes and immuno-stimulating polysaccharides (Retta et al., 2011). Infusions of the inflorescences from this plant are used in folk medicine as an antispasmodic, hypoglycemic agent (Ritter et al., 2002). It also acts as analgesic, supported constipation, sedative and anti-inflammatory (Barata et al., 2009). This species is among the 10 most widely used tea medicines as alternative medicine from a community of Porto Alegre, RS, Brazil (Vendruscolo et al., 2005). In addition, science has proven immunomodulatory effects (Santos et al., 1999). This species is included in the 'List of traditional phytotherapeutic products of simplified registration' of the Brazilian Ministry of Health and is already included in the Brazilian Public Health System (SUS). In this list, there is the recommendation that consumption of the infusions should not exceed 1.5 g (1/2 tablespoon) in 150 mL (tea cup) two to four times daily. To confirm this property, a test was performed only in cell culture (1μg / mL of dry matter of ethanolic extract) showing efficiency in inducing cellular proliferation of keratinocytes (HaCaT) and fibroblasts (MRC-5) measured by counting viable cells, essential to the wound healing process after treatment (Alerico et al., 2015).

A study by our research group (unpublished data) showed that this species was not effective in decreasing wound closure time in treated mice but was able to reduce the number of myofibroblasts. A high incidence of these cells may induce adverse effects on wound healing, such as hypertrophic scarring (Hinz, 2007). In addition, we found a higher replacement of reticular fibers by collagen, probably because this species contains phenylpropanoid, caffeoyl- and flavonoid derivatives as the major compounds. The inefficiency of treatment can be justified by the findings of the presence of the inflammatory cells in granulation tissue in a study on wounds of mice treated with *A. satureioides* (Pereira et al., 2017).

Anadenanthera colubrina (Vell) Brenan. family **Fabaceae (or Leguminosae)**

This species is popularly called Angico-white or Angico-smooth (Lorenzi, 2002). The preparation of its bark with different solvents provides a solution rich in alkaloids, steroids, flavonoids, phenol terpenoids (Melo et al., 2010) and tannins such as proanthocyanidins. According to Lima et al., (2006), Elixir Sanativo®, an herbal remedy that has several species in its composition, among them Angico (20% in the formula), is traditionally used in the northeast of Brazil because of its anti-inflammatory properties.

Bowdichia virgilioides Kunth **Fabaceae (or Leguminosae)**

Bowdichia virgilioides is a tree typical of the northeast region and west central region of Brazil, where it is popularly known as 'sucupira-do-cerrado' 'sucupira-do-campo', 'paricarana', 'angelim-amargoso' or 'heart-of-negro' (Almeida et al., 1998). The chemical composition of the crude extract presents flavonoids (Juck et al., 2006), benzofuranoids, triterpenoids (Melo et al., 2001) and alkaloids (Barbosa-Filho et al., 2004). It is popularly used as a topical treatment in inflammations (Smiderle and Souza, 2003). It is also used in wound healing processes, and in the treatment of diabetic ulcers (Macedo and Ferreira, 2004). Its seeds are used in the treatment of rheumatism, arthritis and skin diseases (Cruz, 1965). *In vitro*, it presented antimalarial activity (Deharo et al., 2001) and inhibitory activity on the enzyme acetylcholinesterase (Barbosa-Filho et al., 2006). In addition, the use of the bark decoction has anti-ulcer, anti-diabetic, anti-rheumatic, arthritis, used to skin diseases and it has scarring properties. *B. virgilioides* ethanolic extract was also used to evaluate inflammation and nociception in rats. Extract at oral doses of 100 to 1000 mg / kg body weight was found to cause edema inhibition, exudate volume suppression and leukocyte migration. These findings highlight their anti-inflammatory potential and support their traditional use in inflammatory conditions (Barros et al., 2010). Thomazzi et al., 2010 also demonstrated anti-inflammatory activities *in vivo*.

Furthermore, the analysis of the *B. virgilioides* extract at a concentration of 10 mg / kg-1 in an animal model, therefore at a lower concentration than that of popular use, verified an increase in collagen in the treated tissue, without signs of toxicity (Agra et al., 2013). This dose is safe for human treatment in wound repair, if the recommendations of traditional Chinese medicine is considered concerning the use of up to 10g extracts daily when in concentrations higher than 1:5 (Yarnell, 2005).

Calophyllum brasiliense Cambess. **Clusiaceae**

Calophyllum brasiliense Camb. is known popularly as ‘Guanandi’, ‘Guarandi’ or ‘Jacareúba’ (Noldin et al., 2006). It is a plant species rich in compounds such as flavones, flavonols, triterpenoids, steroids and xanthones (Sartori et al., 1999), with emphasis on the xanthones brasixantone A, guanandine, 8-jacareubin and 6-deoxyjacareubin, and coumarins of the calanolides A, B and C, soulatrolide and mammea A and BA (Pretto et al., 2004; Noldin et al., 2006). This species has been used in folk medicine for the treatment of several diseases such as rheumatism, varicose veins, haemorrhoids and chronic ulcers (Corrêa et al., 1978). However, no records were found of how it is prepared.

In vitro, the *C. brasiliense* extract was effective against HIV-1, an action associated with the presence of pyranocoumarins (soulatrolide and calanolids A and B) and calanolide C (Reyes et al., 2004a). The extract of its seeds also presents molluscicide (Ravelonjato et al., 1992), antibacterial (Pretto et al., 2004), antifungal and antiparasitic activity (Abe et al., 2004). Lordani et al. (2015) used a a leave extract standardized on the coumarin mammea A/BB in a rat model achieving better healing, which demonstrates the existence of a pharmacological potential for this extract when used in wound healing.

Caryocar coriaceum Wittm. **Caryocaraceae**

‘Pequi’ occurs in all Brazilian Cerrado (Lorenzi and Mattos, 2008). It is rich in unsaturated, fatty acids and antioxidant components such as vitamins A and E (Sena et al., 2010). The leaves of

C. coriaceum present antioxidant activity associated with tannins, phenols and xanthones (Duavy et al., 2012). In a hydroalcoholic leave extract, which demonstrated anti-inflammatory activity on mice skin inflammation models, the main phytochemicals were found to be chlorogenic acid, rutin, quercetin and lower concentrations of caffeic and gallic acids (Araruna et al., 2014). Moreover, Fruit seed oil is used in the treatment of respiratory diseases and rheumatism (Agra et al., 2007) and it has also shown anti-inflammatory activity on mice edema (Saraiva et al., 2011), antioxidant (Roesler *et al*., 2008) and gastroprotective properties, as well as wound healing (Quirino *et al*., 2009; Batista *et al*., 2010). In folk medicine, its fruit pulp and seed oils have been used for wound healing and as an anti-inflammatory, besides, the crude oil of seeds is also used for the treatment of rheumatic and muscular pains (Matos, 2007). *In vitro*, the topical use of its oil reduced oedema in mice as well as inhibiting the chemotaxis of inflammatory cells, which proves its anti-inflammatory potential against skin diseases (Saraiva et al., 2011). The combination of the oil with the aminoglycosides prevents the development of bacteria and other resistant microorganisms (Saraiva et al., 2008). Pequi oil applied to cutaneous wounds in rats promoted re-epithelialization and increased the number of fibroblasts and collagen fibers (Batista et al., 2010). The beneficial effects of *C. coriaceum* oil are also shown in the treatment of gastric ulcers (Quirino et al., 2009).

C. coriaceum is a species whose therapeutic action according to Roesler et al. (2008) is present in traditional knowledge, although there is no concern about the possible toxicity of its extracts. However, cardiotonic heterosides have been identified in the extracts of this plant, which may indicate that there is some level of toxicity (Rates & Brigi, 2007) which should be further investigated.

Casearia sylvestris Swartz. **Salicaceae**

The C. sylvestris is a small tree which is known as ‘Guaçatonga’, ‘Erva-de-lagarto’, ‘Café-do-diabo’ and ‘Língua-de-teiú’. Its leaves have a high content of essential oils, flavonoids (quercetin, 2-vicenin and hesperitin), diterpenes (A-S casearins, clerodans I-VI, casearvestrins A-C), saponins, tannins, resins, anthocyanosides, caprionic acid and Lachachol (Borges et al., 2000; Oberlies et al., 2002; Tininis et al., 2006). Its extracts have been used extensively in folk medicine as an anti-bacterial, an anti-fungal (Borges et al., 2000, Oberlies et al., 2002). Folk medicine has also made use of this plant by pointing up anti-inflammatory and healing actions in the treatment of burn injuries and cuts (Campos et al., 2015). Further, this species also manifests a protective action against severe gastric lesions without evidence of hepatic, renal or haematological toxicity (Basile et al., 1990). *In vitro*, the hydroalcoholic extract used in the healing process of burns injuries showed the presence of anti-inflammatory, anti-diarrheic, anti-thermal, depurative, anti-rheumatic, anti-ophidian activities in addition to anti-inflammatory and healing activity *in vivo* (Campos et al., 2015).

Copaifera langsdorffii Desf. **Fabaceae or Leguminosae**

This plant species is popularly known as ‘Copaiba’. It is rich in oil where sesquiterpene and diterpenic compounds predominate (Veiga Júnior et al., 2007), it presents antimicrobial action (Deus et al., 2011), it is antitumor (Paiva et al., 1998) and proliferative (Oliveira et al., 2012), anti-inflammatory, gastroprotective and healing (Paiva et al., 2002a & b; Arroyo et al., 2009). The healing activity of *C. langsdorffii* oil, which is obtained from the tree trunk, is due to wound contraction with a reduction in tissue repair time, as well as inducing cell recruitment and stimulating vascular proliferation without, however, interfering in the physiology of collagen (Feitosa Júnior et al., 2018). *In vivo,* the topical application of an ointment containing copaiba oil increases the concentration of the granulation tissue, neo-angiogenesis, in addition to preventing the formation of tissue necrosis (Estevão et al., 2013b). *In vitro* assays showed that in gastric ulcer episodes, the oil was able to decrease the injured area, reducing hyperaemia and haemorrhage (Arroyo et al., 2009), while its systemic administration promotes the improvement of the scar tissue in the bone tissue, raising the rate of epithelial migration (Silva et al., 2013). Dias da Silva et al. (2013) point out that the use of copaiba oil for bone remodeling promotes an increase in local neoformation and leads to an improvement in alveolar bone consolidation. It does, however, cause ulceration and increased counting inflammatory cells. However, the topical treatment in oral wounds with Copaiba extract extracted in Petroleum Ether did not show significant improvement of the wound healing action (Wagner *et al*., 2017).

Pieri, Mussi and Moreira (2009) reported in their work that oil has been extracted from copaíba since ancient times and was used by Latin American Indians to heal the wounds of warriors, as well as to pass through the umbilical stump of newborns. The popular observations on the efficacy of this plant contribute to the dissemination of its therapeutic virtues, and even today this oil is widely used by low-income populations.

Hancornia speciosa Gomez **Apocynaceae**

A *H. speciosa* Gomes is a fruit tree, commonly known as ‘Mangabeira’, whose leaf extracts present L -(+)-bornesitol, quinic acid, chlorogenic acid, kaempferol, quercetin, isoquercetin, rutin, catechin (Endringer *et al*., 2007; Endringer *et al*., 2009; Pereira *et al*., 2012; Pereira *et al*., 2015; Santos *et al*., 2016), phenols, caffeine, epicatechin, quercetin, procyanidins B and C, florizine, floretin, eriodictiol, luteolin, apigenin, coumaroylquinic and protocatectic acid isomers (Bastos *et al*., 2017). *In vitro*, it presents gastroprotective activity (Moraes et al., 2008), as well as antidiabetic (Pereira *et al*., 2015) and anti- inflammatory properties (Marinho *et al*., 2011). Traditionally, the leaves infusion is used in traditional medicine as an antioxidant, an antimicrobial, a cytotoxic agent (Santos *et al*., 2016), and as an anti- inflammatory remedy (Endringer et al., 2009). It is also used to heal wounds (Geller *et al*., 2015), for vasodilation (Ferreira *et al*., 2007), as a antihypertensive (Silva *et al*., 2016[b]), an antidiabetic (Pereira *et al*., 2015) and for acetylcholinesterase inhibitory activity (Penido *et al*., 2017). However, due to the lack of data on how this species is prepared popularly to treat wound healing, and also due to the lack of in vivo experimentation to prove its effectiveness, we can only assume that it can be effective due to its actions in essential stages of the wound healing process.

Hyptis spicigera Lam. **Lamiaceae**

H. spicigera is known as ‘Catirina’, ‘Cheirosa’ or ‘Cheirosa-de-espiga’. Its oil is rich in cineol, beta-pinene and especially alpha-pinene (Maia & Andrade, 2009). According to the composition of the monoterpenes and sesquiterpenes, this species presented several actions (Mercier *et al*., 2009). The essential oil of *H. spicigera* had antiulcerogenic and gastroprotective action by promoting the increase of gastric mucus production, making it an adjuvant in the treatment of chronic inflammatory diseases, as well as having effective wound healing action modulated by increased expression of COX-2 and EGF in the mucosa of gastric tissue. It is used by traditional communities in the treatment of fever, inflammation, gastric disorders (Takayama et al, 2011), cystitis (Bourdy et al., 2000) and in cases of pain and inflammation (Adorjan and Buchbauer, 2010). Studies conducted with test animals have not identified toxicity and are proportionally within the doses considered non-toxic to humans (Takayama *et al*., 2011).

Jatropha curcas Linnaeus **Euphorbiaceae**

This species is popularly known as ‘Knownpurgueira’, ‘pinhão-manso’, ‘jatrofa’, ‘mandubiguaçu’, ‘pinhão-de-purga’ and ‘pinha-de-purga’. Its metabolite content consists of organic acids, cyclic triterpenes, stigmasterol (Lee et al., 1995), glycosides, tannins, phytosterols, flavonoids and steroidal sapogenins (Kim et al., 2002). Traditionally, the roots, stems, leaves, seeds and fruits are broadly used as purgative agents, anthelmintics, abortives and ascites, for the treatment of gout, and for epithelial disorders (Vollesen, 1995). Studies undertaken with its extracts reported activity in fevers, oral infections, jaundice, wounds and joint rheumatism (Oliver-Bever, 1986), as an antiparasitic (Fagbenro-Beyioku et al.; 1998), an antidiarrheal (Mujumdar et al., 2001) a chemotherapeutic (Aiyelaagbe et al., 2007) and as antimicrobial agents (Igbinosa et al., 2009).

Effects as an antimicrobial, an anthelmintic, a coagulative, an anti-rheumatic, an anti-parasitic, an icterus, against fever, as a pesticide and in healing wound are also attributed to it (Júnior et al., 2012), however, its seeds oil did not show cicatricial efficacy in study conducted with test animals (Júnior et al., 2012).

Lippia sidoides Cham **Verbanaceae**

The species *Lippia sidoides*, popularly known as 'alecrim pimenta', is an aromatic shrub found in Cerrado areas. Its essential oil is mainly rich in carvacrol, 1,8-cineol, and thymol as the main compound (Guimarães et al., 2014), as also p-cymene , (E) -cariophylene, Û -terpinene, 1,8-cineole and ù-myrcene (Cavalcanti *et al.*, 2004), Gamma-terpinene, pcymene (Botelho et al., 2007) and (E) -caryophyllene (Fontenelle *et al.*, 2007). In folk medicine, it is used as an antiseptic (Lacoste et al., 1996), anti-bacterial, fungicide, molluscicide, larvicide (Matos, 1996) and to control bacterial plaque growth in dogs' teeth (Girão et al., 2003). Resin obtained from its macerated leaves is used topically in the treatment of acne, wounds, skin and scalp infections. Its infusions are used in the treatment of allergic rhinitis, vaginal, mouth and throat infections (Albuquerque, 2008), as an antiseptic and an anti-inflammatory, and in wound healing (Oliveira et al., 2014). It is recommended (by ANVISA's 'List of traditional herbal products for simplified registration' and the 'List of herbal medicines for simplified registration') that 2 to 3 g of the *L. sidoides* extract be applied topically 2 to 3 times per day. However, it has also been reported that the continuous topical use of *L. sidoides* essential oil at 6% and 12% promotes inflammation and cutaneous irritation but does not delay wound healing process in skin lesions on mice (Oliveira et al., 2014). Still, an increase in skin thickness and inflammatory cells was recorded when compared to the control group. Absence of vascular proliferation (VEGF) was observed mainly in the group treated with the 12% ointment.

Memora nodosa Manso **Bignoneaceae**

Memora nodosa is a common shrub species in Cerrado areas, where it is popularly known as 'Carobinha', 'Carobinha do campo', 'Caroba-amarela' or 'Bambuzinho'. It can reach up to 1.70m in height, exhibiting composite leaves and large yellow flowers (Silva, 1998). Its leaves are rich in natural compounds used in the composition of different drugs, and the floral extract is active as a repellent thanks to the presence of benzaldehyde, the main compound found in this species (Tresvenzol *et al.*, 2010). Flavonoids, carbohydrates and traces of saponin heterosides are found in the leaf extracts. Its stem is rich in flavonoids and traces of saponin heterosides, the root bark is replete with saponin heterosides (Tresvenzol *et al.*, 2005), and in the essential oil benzaldehyde and 1-octen-3-ol are present as major components (Tresvenzol et al., 2009). In traditional medicine, the infusion made from the stem and leaves is used to bathe, and thus treat, external sores and ulcers (Siqueira, 1988). Tea from its roots is used in episodes of intestinal pain (Silva, 1998). The wound healing activity of the root extract promotes the re-epithelization of the wounds and the partial reconstruction of the cellular attachments. This activity appears to be linked to the action of allantoin, isolated from the ethanolic extract of the root. Besides the wound healing activity, the toxicity also was evaluated and only the dose 5000 mg kg^{-1} presented hepatoxicity to mice, demonstrating the safety of the compost for animal consumption (Tresvenzol et al., 2013). Excessive or toxic doses should be avoided, although often, when designing the research project or experiment, the feasibility of use in traditional medicine is not considered.

Orbignya phalerata Mart. **Arecaceae** or **Palmae**

Orbignya phalerata, the 'Babaçu' is a palm tree with multiple uses (Lorenzi, 2004). The ethnopharmacological use of *O. phalerata* demonstrates that many of the extracts from Babaçu and its derived products are used to combat diseases (Souza et al., 2011). Glycerin is obtained from the fruit which has a medicinal potential, and fatty acids are used to obtain fuel, coal and flour (Amorim et al., 2006). about 40% of the oil extracted from chestnut is lauric acid which has recognized anti-inflammatory properties (Wasule et al., 2014). Anti-inflammatory, immunomodulatory, antitumor, and immunocompetent activity was also identified using Babaçu oil (Silva and Parente, 2001). Babaçu mesocarp extract activity was evaluated in the healing process of median laparotomy in rats that were submitted to an incision in the alba linea. This extract (50 mg.kg-1 aqueous solutions) was not effective in wound healing. However, tensiometric findings on the 7th day after treatment showed a significant difference between the experimental and control groups (Filho et al., 2006). Both the healing and the anti-inflammatory activity are attributed to the popular use of the aqueous solution of the mesocarp of the fruit of *O. phalerata* (Pires, 1974). These actions are proven in studies that showed the induction and activation of macrophages and consequent increase in the production of nitric oxide and histamine that stimulated the phagocytic activity (Baxter and Cooke, 1993). Again, there is no information in the literature about the how *O. phalerata* is prepared for ethnobotanic use to compare the scientific findings.

Passiflora edulis Sims. **Passifloraceae**

Among the 530 species listed in the Passifloraceae family (Hansen et al., 2006), about 150 are native to Brazil (Lima et al., 1999), among them the yellow passion fruit 'maracujá' *Passiflora edulis* (Gomes et al., 2006). This plant contains the alkaloids (harmana, harmina, harmalina and harmol), flavonoids and carotenoids associated with analgesic, antipyretic, parasympatholytic and anti-inflammatory activities besides sedative and hypnotic activity (Silva *et al*., 2002). The bark is rich in insoluble fibers (Janebro et al., 2008). In addition, phenolic compounds with antioxidant and anti-inflammatory activity can be found in the use of passionfruit greaves (Zeraik and Yariwak, 2012). Traditional use of yellow passion fruit extract as a sedative, an analgesic, an anti-inflammatory and an anti-erysipelas is very common, as well as its use in wound healing (Bezerra *et al*., 2006). Antitumoral, antioxidant (Goñi and Serrano, 2005), anti-glycemic (Queiroz et al., 2012) and lipemic (Ramos *et al*., 2007) activity have all been described for *P. edulis* extract. Anti-inflammatory activity was recorded by decreasing oedema volume, releasing myeloperoxidase, neutrophil infiltration and expression of TNF-α and iNOS (Silva *et al*., 2011). The topical use of the *P. edulis* extract promoted fibroblastic proliferation and the improvement of the re-epithelialization process with increased leukocyte reaction and intense collagenization (Garros *et al*., 2006). In *in vitro* studies, the presence of analgesic activity by the inhibition of eicosanoid biosynthesis was reported, besides promoting anti-inflammatory activity (Silva et al., 2001).

Pereskia aculeata Mill. **Cactaceae**

'Ora-pro-nóbis' (*Pereskia aculeata*), occurs in regions of Cerrado where they reach up to 10 m in height (Cruz, 1995). It contains monoterpenes, sesquiterpenes and diterpenes in large quantities, as well as polyphenols (Souza *et al*., 2016). Due to the high content of mucilage and essential and non-essential amino acids, especially tryptophan (Takeiti et al., 2009), it is used as an emollient and food source (Filho and Cambraia, 1974). In Brazilian traditional medicine, it is used in therapy to treat anaemia (Damasceno and Barbosa, 2008). Antioxidant, antimicrobial, antifungal and cytotoxic activities are also mentioned in neuroblastoma tumour cells SH-SY5Y (Souza *et al*., 2016). *In vitro* tests confirm emollient action in the relief of inflammation besides helping to heal burns (Sartor et al., 2010). *P. aculeata* extracts promote wound healing activity by increasing the closing velocity, blood flow and deposition of tissue collagen, corroborating its traditional use as an anti-inflammatory and in wound healing (Pinto *et al*., 2016), mainly due to the proliferative action of the tissue fibroblasts (Carvalho et al., 2014), the increase in the collagen deposition and the greater speed of the contraction of the edges of the wounds (Pinto *et al*., 2016).

A study conducted by Pinto et al. (2016) with hexane fraction (HF) and methanol extract (HM) from *P. aculeata* extracts, both at 5%, were applied immediately after the injury and every 48h for a period of 14 days in lesions in mice. In this investigation, the fractions used were effective in wound repair, where increased blood flow and collagen deposition were observed (Pinto et al., 2016).

It is important to mention that the study involving this species was based on the fact that since ancient times, Cactaceae have been widely used in traditional medicine and healers have used these plants as relief from burns and ulcer healing, among other pathologies.

Piper marginatum Jacq. **Piperaceae**

Piper marginatum is known as 'Pimenta de macaco' (Guimarães and Giordano, 2004), and its main secondary metabolites are terpenoids, phenylpropanoids (Andrade et al., 2008), amides and flavonoids (Brú and Guzman, 2016). The characteristic compounds of this species are O-anethole, estragole, isoenergenol methyl ether, 3-farnesyl-4-hydroxybenzoic acid, 3-farnesyl-4-methoxybenzoic acid and vitexin (Parmar *et al*., 1997) and can be used as chemotaxonomic markers (Brú and Guzman, 2016). The extracts obtained from the different parts of the vegetable are used by indigenous communities in the treatment of gastrointestinal, tonic, diuretic and carminative diseases (Stasi and Hiruma-Lima, 2002; Albuquerque *et al*., 2007[a]). In general, leaves and fruits are used in the treatment as antispasmodic, for liver, spleen, intestinal problems and widely used for cough treatment (Pereira et al., 2011). A review of *P. marginatum* has a number of ethnopharmacological applications, and in Brazil local communities use leaves for rheumatism, bleeding from skin wounds, toothache and tumors, and also to reduce swelling (Brú and Guzmam, 2016).

In addition, D'angelo et al. (1997) showed that *P. marginatum* extract caused a positive anti-inflammatory effect on tissue healing in rats and mice, with the vasoconstrictor activity are due mainly to the presence of noradrenaline (D'angelo et al., 1997).

Poincianella pluviosa D.C **Fabaceae** or **Leguminosae**

'Sibipiruna' or 'Pau-Brasil falso' is also known as *Caesalpinia peltophoroides* (Benth.). Phytochemical composition of Sibipiruna reveals an absence of alkaloids and the presence of sterols, tannins, flavonoids and saponins (Rodrigo *et al*., 2010). The essential oil of the flowers is rich in alkane chains (Carvalho et al., 2013), whereas extracts from the stem demonstrate the presence of gallic acid, ethyl ester, rhuschalcona VI, lupeol, betulinic acid and stigmasterol (Flores and Almanza, 2006). Its chemical components have several biological activities (Zanin et al., 2012), such as antimalarial, anti-ulcer, anti-inflammatory and wound healing (Bueno et al., 2014; Bueno et al., 2016). Bueno et al. (2014) showed that the crude extract of *P. pluviosa* bark is rich in hydrolysable tannins, increasing the *in vitro* viability of keratinocytes (HaCaT) and fibroblasts (pNHDF), in addition to stimulating the keratinocytes proliferation. The crude extract of *P. pluviosa* stimulated the formation of new collagen fibers, re-epithelialization and wound healing with increased regulation and tissue protection. This is also due to the antioxidant action of the phenolic compounds that inhibit excess produced oxidizing agents (Bueno et al., 2016).

Pyrostegia venusta (Ker-Gawl) Miers **Bignoniacea**

This is a typical species of the Brazilian Cerrado (Veloso et al., 2010). *Pyrostegia venusta*, known as the ‘Cipó-de São João’ or ‘Dedo de Mica’, is rich in polyphenolic compounds such as flavonoids (Veloso et al., 2010). It presents anti-microbial, antinociceptive, antioxidant and antitumor activity, as well as its traditional use in inflammatory diseases, blemishes and skin infections such as leucoderma and vitiligo (Veloso et al., 2010; Roy et al., 2012). The *P. venusta* flowers extract promoted improved wound contraction, and tensile strength allied and neutrophil reduced when the concentration of 100 mg kg^{-1} was used. In addition, there was an improvement in epithelialization, fibroplasia and neovascularization after treatment. It also caused increased levels of hexosamine and hydroxyproline due to the stabilization of the electrostatic interactions of collagen (Roy et al., 2012). This concentration is within the limit of up to 2,000 mg /kg as being safe for use in animal tests, without any risk of toxic effects developing (Fernandes et al., 2011). Hydroxyproline is most important for the stabilization of the triple helix of collagen molecules, while hexosamines are necessary to guarantee the existence of biomechanical properties in the connective tissue (Koob and Vogel, 1987).

Schinus terebinthifolius Raddi **Anacardiaceae**

The *Schinus terebinthifolius* also called as ‘Aroeira-da-praia’, ‘Aroeira-pimenteira’ or ‘Cambuí’ occurs in Rio Grande do Norte to Rio Grande do Sul (Lorenzi and Matos, 2008). *S. terebinthifolius* extract has tannins, terpenes, saponins and flavonoids that attribute antioxidant activities (Carvalho et al., 2003). Recommendation of its use by the local population include treating respiratory infections, for digestive disorders, for the prevention of diarrhoea (Estevão et al., 2015), as a purgative, an anti-inflammatory and an anticonvulsant (Lipinski et al., 2012). In addition, astringent, antibacterial and antitumoral activities have been attributed to *S. terebinthifolius* extracts, as well as it being an inhibitor of histamine, serotonin and acetylcholine (Lipinski et al., 2012; Fedel-Miyasato et al., 2014). Moreover, *S. terebinthifolius* has been shown to be an antiallergic (Machado et al., 2008), an antibacterial (SILVA et al., 2010), an antioxidant, an antitumour (Bendaoud et al., 2010), and an anti-fungal (Barbieri et al., 2014), with healing and anti-inflammatory properties (Lucena et al., 2006; Lipinski et al., 2012; Estevão et al., 2013[a]). The masticaenoic acid and the 3β-masticadienólico present in *S. terebinthifolius* inhibit the phospholipase A2 and consequently interferes in the degranulation of neutrophils and mast cells in inflammatory murine models

(Medeiros et al., 2007). The hydroalcoholic extract of *S. terebinthifolius* promotes collagen synthesis and vascular neoformation, in addition to reducing inflammation in urinary tract wounds (Lucena et al., 2006). The oil of this species was effective in the treatment of cutaneous wounds as it stimulated the granulation tissue, an increase in more organized collagen fibers and faster epithelization (Estevão et al., 2013[a]). In addition, the topical application of an ointment based on *S. terebinthifolius* promoted an increase in the number of mast cells, fibroblast proliferation and wound contraction (Estevão et al., 2015). Improvement in wound healing and in anti-inflammatory activity observed in the *S. terebinthifolius* leaves extract at 80 mg ml $^{-1.}$ can be due to the presence of flavonoid and phenolic acids (Fedel-Miyasato et al., 2014). *S. terebinthifolius* presents low toxicity in mice and is consumed by humans daily (Pires et al., 2004).

The *S. terebinthifolius Raddi* is recognized as the practice of phytotherapy by the Brazilian Health System and its use is indicated as an antiseptic and an anti-inflammatory (RENAME, 2013).

Sebastiania hispida (Mart) Pax **Euphorbiaceae**

The species *Sebastiania hispida* is popularly known as 'Mercury' It is rich in triterpenes, tannins and saponins (Hnatyszyn et al., 2007), phenolic compounds (gallicin, gallic acid, syringic acid, caffeic acid) and flavonoids (quercetin, kaempferol, campesterol; isorhamnetin; isoquercitrin) (Penna et al., 2001; Hnatyszyn et al., 2007), as well as in steroids (β-sitosterol and stigmasterol) (Lima et al., 2009). It is popularly used as a cicatrizant (Pott and Pott, 1994; Rizzi et al., 2017). This property could be verified by evaluations made with the topical application of *S. hispida* that promoted an increase in the synthesis of type I collagen during tissue regeneration, due to the presence of phenolic compounds and their derivatives (Rizzi et al., 2017).

Serjania erecta Radlk **Sapindaceae**

Serjania erecta is also called 'Timbó' or 'cipó-cinco-folhas' in Brazil. The analysis of extracts has revealed the presence of compounds such as saponins, flavonoids, terpenes, steroids, tannins, alkaloids, fatty acids and amino acids (Rodrigues and Pinto, 2014). These compounds may be responsible for the anti-inflammatory activity found by Gomig et al. (2008), promoting in a dose-dependent manner, the reduction of oedema and the reduction of myeloperoxidase enzyme activity. Moreover, the authors provide empirical support for the popular use of 'cipó-cinco-folhas'for skin inflammatory diseases. Also, it is popularly used in the treatment of stomach pain, ulcers, hypertension (Arruda et al., 2009; Bourdy et al., 2004) and migraines (Artal and Cabrera, 2007). In addition, it has an anti-inflammatory agent (Gomig et al., 2008), an antiproliferative agent (Mesquita et al., 2005) and acts as an antioxidant (Broggini *et al*., 2010).

Sideroxylon obtusifolium (Roem. & Schult.) T.D. Penn. **Sapotaceae**

Sideroxylon obtusifolium, or 'Quixaba', 'Quixabeira' or 'Rompe-gibão' as it is popularly known, has different secondary compounds in the constitution of its extracts, such as pentacyclic triterpenes, saponins, flavonoids, triterpene glycoside, flavonol glycosides, catechin and glycerogalactolipidium (Gingerglycolipid A) (Oliveira et al., 2012). It is a medicinal species with anti-inflammatory, hypoglycaemic, tonic and astringent properties (Agra et al., 2008). The diversity of uses of Quixaba extract adopted in folk medicine has intensified the exploitation of this plant species, leaving it in danger of extinction (Albuquerque et al., 2007[b]). In addition, *Sideroxylon obtusifolium* is popularly associated with use in episodes of ovarian inflammation, diabetes, influenza, gastritis, kidney pain, inflammatory disorders and strokes (Leite et al., 2015). It is also used in the treatment of painful and inflammatory processes (Neto et al., 2010), expectorants (Alburqueque et al., 2007), duodenal ulcers, gastritis, heartburn, chronic inflammation, genital lesions, inflammation of the ovaries, adenitis, colic, kidney problems, heart problems, diabetes and healing (Albuquerque and Oliveira, 2007). Studies by Neto et al. (2010) report that the extract has an antinociceptive action by the inhibition of COX, analgesic and anti-inflammatory, also acting in the blockading of leukocyte migration and in the establishment of antioxidant activity mediated by flavonoids.

Leite et al. (2000) mention that *S. obtusifolium* extract has anti-inflammatory and antioxidant action, thus acting in the inflammatory phase of the cicatricial process and was as efficient as the control used in this study. These results agree with the ethnopharmacological use of this species in inflammatory and painful processes and are an important resource for traditional populations in the treatment of wounds since they present low toxicity (Albuquerque et al., 2007).

Siparuna guianensis Aubl. **Siparunaceae**

Siparuna guianensis is known popularly as 'Negra-mina'. Valentini et al. (2009) report the popular use of compresses and cataplasms for headaches, rheumatism and postpartum, also as an insect repellent and a cicatrizant, the latter of which, however, is an action that is predominantly due to the anti-inflammatory activity (Rodrigues and Carvalho, 2001). Different secondary compounds are present as active compounds in S. *guianensis* extracts in which Epi-α-Cadinol is the main one found, together with monoterpenes, sesquiterpenes, sesquiterpenes alcohols, aliphatic ketones, α-Pinene, Mircene and γ-Cadinene (Viana *et al*., 2002). The study by Renner and Hausner (2005) on the decoction of *S. guianensis* leaves, presents action in the treatment of stomach disorders. Found in a lower concentration in the extracts of *S. guianensis*, liriodenin (2c) has a sedative action in the central nervous system, while alkaloids of the aporphine type have an antioxidant action (Leitão et al., 1999). The extract has cicatricial and re-epithelizing action without mutagenic activity (Thomé et al., 2012).

Strychnos pseudoquina A. St. Hill. **Loganiaceae**

Strychnos pseudoquina St. Hil. is a native plant species of the Brazilian Cerrado of which the phytochemical compounds present in the alcoholic extract are rich in flavonoids and phenols. In folk medicine, their husks (Cortes et al., 2013) and leaves are employed as antipyretic agents, antimalarials and in the treatment of gastrointestinal disorders (Bonamin et al., 2011). These compounds present a protective action of the gastric mucosa of mice against lesions caused by anti-inflammatory drugs and acid solutions of ethanol, as well as reducing the area of lesions and increasing the cellular and vascular proliferation of the injured region (Silva et al., 2005). Unlike the ethnobotanical use described earlier, Sarandy et al., (2018) show that 5% and 10% *S. pseudoquine* extract acts at important stages of skin healing.

Stryphnodendron adstringens Mart. **Fabaceae** or **Leguminosae**

Stryphnodendron adstringens is a deciduous plant commonly known as ‘Barbatimão’ (Lorenzi and Matos, 2008) that was often associated with the treatment of leucorrhea, diarrhoea, haemorrhage, haemorrhoids, conjunctivitis, throat and vaginal inflammation, gastric ulcers and wounds (Silva et al., 2010). Its action is due to the composition of its extracts that are rich in proanthocyanidins, alkaloids, tannic acid, flavonoids and groups of tannins, molecules responsible for the main activities reported (Souza et al., 2007). It presents anti-microbial, antioxidant and antinociceptive (Melo et al., 2007), anti-ulcerative (Minatel et al., 2010), anti-inflammatory (Lima et al., 1998), antiseptic, astringent, haemostatic and cicatrizant activity (Macedo et al., 2008). The healing action of *S. adstringens* on skin wounds is due to the strong promotion of fibroblast multiplication and the increase in collagen levels (Coelho et al., 2010). In diabetic rats, the crude ‘Barbatimão’ bark extract stimulated the production of collagen fibers, favored the remodeling of the extracellular matrix and promoted the regulation of COX-2 and VEGF (Pinto et al., 2015). The epigallocatechin-3-O-gallate, a tannin found in this extract, facilitates re-epithelization, angiogenesis, and activation of myofibroblasts (Minatel et al., 2010). In general, tannins are able to reduce the inflammatory response by interacting with proteins and forming a protective layer of the skin (Haslam, 1996). Hernandes et al. (2010) report that the topical use of ‘Barbatimão’ extract stimulates the proliferation of keratinocytes at the margin of the wound with consequent local re-epithelization due to the action of proanthocyanidins, without interfering with the epithelial migration in the contraction of the wound.

Stryphnodendron obovatum Benth **Leguminosae** or **Leguminosae**

This is another species popularly known as 'Barbatimão'. Its chemicals constituents are alkaloids, flavonoids, terpenes, stilbenes, steroids, protease inhibitors (such as trypsin) and tannins (Vasconcelos et al., 2004). In folk medicine, it is used as a haemostatic, an anti-inflammatory, an anti-oedematogenic, an antiseptic, an anti-diarrheal, an anti-ulcerative, and an anti-haemorrhagic (Soares et al., 2008). Lopes et al., (2005) show that the crude extract and 2.5% ethyl acetate of *S. obovatum* have efficacy as a healing factor thanks to the tannins and other phenols present.

Stryphnodendron polyphyllum Mart. **Leguminosae or Leguminosae**

This species is also known as 'Barbatimão'. It has phenolic compounds in its cortex and is notable for its medicinal properties (Lopes et al., 2005), influenced by environmental and edaphic factors that interfere in the production of tannins and phenols in the bark (Jacobson et al., 2005). In popular medicine, the astringent properties of its extracts are used in the treatment of tonsillitis, pharyngitis, leucorrhoea, diarrhoea, haemorrhoids, rashes, inflammation (Lima et al., 1998), as well as an antiseptic, an anti-inflammatory, a leukorrheal, against diarrhoea, as a coagulant and a cicatrizant (Lopes et al., 2005; Soares et al., 2008). Experimentally, its extracts are active as an antimicrobial (Lopes et al., 2003) and an antioxidant (Souza et al., 2007) – this activity is due to the total phenols content, such as tannins and flavonoids (Choi et al., 2006). Just as is the case with *S. obovatum*, Lopes et al. (2005) attributed to the 2.5% *S. polyphyllum* extract a healing activity due to the presence of tannins and phenolic compounds present.

Tabebuia avellanedae Lor. ex Griseb **Bignoniaceae**

Known as 'Purple Ipê', 'Pau d'arco' or 'Ipê uma' (Bussmann, 2018), this species presents naphthoquinones such as lapachol and lapachone, and some of its derivatives (alpha-lapachol, beta-lapachol, dihydro-lapachol), as well as lapachenol, furanonaftoquinone, anthraquinone, flavonoid (quercetin), hydroxybenzoic acid (Lorenzi and Matos, 2008), tannins; resins; minerals; saponins and coumarins (Panizza, 1997). It is popularly used in the treatment of diabetes and gastric ulcers as well as having analgesic, anti-inflammatory and anti-mutagenic action (Carvalho, 2003) and antimalarial, trypanosomicidal, anti-psoriasis, antiviral, anti-schistosomal, anti-neoplastic, immunomodulatory, anti-inflammatory and antibacterial (Lipinski et al., 2012) properties. Anti-inflammatory and antioxidant actions related to the presence of tannins, quinones and flavonoids are attributed to this plant (Miranda et al., 2001), but the lapachol may also be responsible for these properties (Goulart et al., 2003). *In vitro*, it presents analgesic, diuretic and antifungal action against eczema, and is used to treat Hodgkin's disease, leukaemia, stomatitis, syphilis and ulcers (Miranda et al., 2001). Lapachol and β-lapachona present in the extracts of *T. avellanedae* bark have antimicrobial and cytotoxic activity against strains of multi-resistant *Staphylococcus aureus* (Pereira et al., 2006; Sadananda et al., 2011). The healing action of the extracts of *T. avellanedae* is due to the variety of tannins capable of precipitating proteins present in the superficial cells of the mucosa of the damaged tissues, forming a coating layer that prevents bacterial establishment and promotes antiseptic action (Neto et al., 1996).

Lipinski et al. (2012) do not present the dosage used to attest to the improvement of clinical and histological aspects evaluated in Lipinski's (x) animal model, which prevents reproducibility and the possibility of testifying this efficiency.

Vernonia scorpioides Lam. Pers **Asteraceae**

This is a species known as 'Assa-peixe', 'Piracá', 'Enxuga', 'Erva-de-são-simão', 'Erva-de-preá', 'Capichingui', 'Capichingui-de-bicho' and 'Nogueira'. Its actions are related to the presence of secondary compounds, among them terpenes, flavonoids, polyacetylenes and sesquiterpene lactones (Freire et al., 1996). Root extracts are rich in flavonoids, steroids and polysaccharides (Nergard et al., 2004), while the composition of its essential oil includes germacrene D, transcariophilene, limonene, Δ-cardinene, biciclogermacrene, β-pinene, β-mircene, α-copaene, α-humulene, Allo-Aromadendrene (Toigo et al., 2004), polyacetylene, glaucolide, scorpioidin and sesquiterpene lactones (Warning et al., 1987). Traditionally, it is used topically in the treatment of various skin problems, chronic ulcers, allergies, irritations, pruritus, oedema due to trauma or infection, neuralgia, inflammatory processes and skin lesions in general, while is administered orally to treat gastrointestinal disorders (Monteiro et al., 2001). The prevalent presence of sesquiterpene lactones in extracts of *V. scorpioides* in topical preparation tested in the healing process on excisional wounds in the skin of mice corroborates with traditional use.

Several scientific studies report anti-inflammatory, antipyretic, antitumor and antimalarial actions in extracts of *V. scorpioides* (Iwalewa et al., 2003). It has anti-inflammatory activity (Kumari et al., 2003) promoting the proliferation of lymphocytes, the release of histamine and serotonin and the promotion of exocytosis by neutrophils with inhibition of 5-LOX and leukotriene C4 synthetase leading to a decrease in the production of inflammatory cytokines (IL-1β, IL-6, IL-8 and TNF-α) (Siedle et al., 2003).

4. Conclusion

Although there has been an increase in knowledge about the biological actions of plants, the scientific basis for the use of medicinal plants remains scarce. Herein, we sought to use an approach that would provide information on the traditional use of wound healing plants, or at least that act on some wound healing process. In addition, we sought to undertake a summary that could give other researchers information on what already exists from experimental work with these plants and also their phytochemical composition. Unfortunately, the literature is poor at documenting traditional medicinal use. Little is found about the forms of preparation, and quantities used. Thus, it is difficult to confirm or validate traditional use with laboratory experimentation. Therefore, we try to organize and make this information available and also try to understand how these plants are prepared and tested so that their use is safer.

In summary, this review shows that the great diversity of plant species of the Brazilian's Cerrado still is not well explored by science, at least in terms of wound healing activity.

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Table 1: Main studies between 1996 and August of 2018 relating to the species, the part of the plant used in the research, the chemical compounds found, and the effects after the treatments. Main type of study "*in vitro*". **NR – Not reported**

	Species and Family name / **Vernacular Name**	**Part of the plant used** / **Form of preparation**	**Tested dose**	**Active compound**	**Observed actions**	**Reference**
1	*Achyrocline satureioides* (Lam.) DC. **Asteraceae**	Aerial part	Concentrations of the extract: 1, 5, 10, 25 and 50 µg/mL	Flavonoids, coumarin, phenolic acids, chalcones and fluroglucinol	Ethanolic extract (1µg / mL) increased cell proliferation by 120%. There was no cellular toxicity.	Alerico *et al.*, 2015.
	Macela-do-campo	Decoction or infusion				
2	*Bowdichia virgilioides* Kunth **Fabaceae or Leguminosae**	Bark	Concentrations of the extract: 10 mg/kg^{-1}	NR	Antimicrobial activity against Gram-positive bacteria (*S. aureus*), but without action against Gram negative (*P. aeruginosa*).	Agra *et al.*, 2013.
	Sucupira-amarela	Extraction				
3	*Stryphnodendron adstringens (Mart.)* Coville **Fabaceae or Leguminosae**	Bark	10 to 30 % extract applied topically	Tannins	Fungicidal effect; promoting alteration on the cell wall surface of the pathogen	Trolezi *et al.*, 2017.
	Barbatimão-verdadeiro	Extraction				

Table 2: Main studies between 1996 and August of 2018 relating the species, the part of the plant used in the research, the chemical compounds found, and the effects after the treatments. Main type of study "*in vivo*". **NR – Not reported**

	Species and Family name / Vernacular Name	Part of the plant used / Form of preparation	Tested dose	Active compound	Observed actions	Reference
1	*Anadenanthera colubrina* var. cebil (Griseb.) Altschul **Fabaceae or Leguminosae**	Bark	Topical applications of alcoholic extract of "angico" 5%	Flavonoids (quercetin), Saponins (saponosides), triterpenes, steroids, leucoanthocyanidins and condensed proanthocyanidins.	Increased macrophages, fibroblasts and neovascularization.	Pessoa *et al.*, 2012.
	Angico	Extraction				
2	*Bowdichia virgilioides* Kunth **Fabaceae** or **Leguminosae**	Bark	Topical applications of solution (10 mg/kg^{-1})	NR	Increased collagen deposition and antimicrobial activity against Gram-positive bacteria (*S. aureus*), but without action against Gram negative (*P. aeruginosa*).	Agra *et al.*, 2013.
	Sucupira-amarela	Infusion				
3	*Calophyllum brasiliense* Camb. **Clusiaceae**	Leaves	Topical application of a non-ionic emulsion extracts 10%	Coumarins	*C. brasiliense* accelerated the cutaneous wound healing, with a significant reduction of the epithelialization, decreasing the intensity of acute inflammation, and increased in fibroblasts number.	Lordani *et al.*, 2015.
	Guanandi	Extraction				
4	*Caryocar coriaceum* Wittm. **Caryocaraceae**	Fruit	*C. coriaceum* ointment 6% (v/w) and 12% (v/w)	Oleic acid, palmitic acid, stearic acid and linoleic acid.	Treatment promotes better healing and increased contraction by 96.54% on the seventh day. The inflammatory reduction was dose dependent.	Oliveira *et al.*, 2010.
	Pequizeiro	Fixed oil				

5	*Casearia sylvestris* Swartz. **Salicaceae** Guaçatonga	Leaves Extraction	Animals treated daily with spray containing extract of *C. sylvestris* Sw 20% extract at the 1g concentration	Rutin and other flavonoids	The extract stimulates re-epithelialization and cicatrization by proliferative induction of fibroblasts in addition to promoting the neutralization of the action of irreversible neuromuscular blockade induced by *B. jararacussu*, venom. It has antibacterial action against *A. xylinum*.	Campos *et al.*, 2015.
6	*Copaifera langsdorffii* Desf. **Fabaceae or Leguminosae** Copaíba	Trunk Oil extraction	10% Oil topically applied	NR	The oil had beneficial effects on cutaneous healing in horses.	Lucas *et al.*, 2017.
7	*Hancornia speciosa* Gomes **Apocynaceae** Mangabeira	Leaves Maceration	Alcoholic extract 5-1,000 μg/mL	Chlorophyll a, β-carotene, lycopene, rutin and polyunsaturated fatty acids	The alcoholic extract presents antioxidant, antimutagenic, enzymatic inhibitor, anti-obesity, anti-diabetic and anti-inflammatory action.	Santos *et al.*, 2018.
8	*Hyptis spicigera* Lam. **Lamiaceae** Catirina	Aerial parts (inflorescences, leaves and stems) Extraction	Essential oil (100 mg/Kg) administered once daily for 14 consecutive days	Alpha-pyrene (50.8%), cineol (20.3%) and β-pyrene (18.3%) at a dose of 100 mg / kg.	Accelerated ulcerative reduction by the expression of COX-2 in the gastric mucosa with increased gastric mucus secretion induced by PGE2 with a protective action against gastric lesions.	Takayama *et al.*, 2011.

9	*Jatropha curcas* L. **Euphorbiaceae**	Seed	Not determined	Oleic acid, linoleic acid, palmitic acid and stearic acid.	The oil did not show cicatricial efficacy	Júnior *et al*., 2012.
	Mertiolate	Oil extraction				
10	*Lippia sidoides* Cham. **Verbanaceae**	NR	Ointments at 6% and 12% were applied daily to the wound area until 21 days treatment	Thymol, thymol methyl ether, myrcene, α-Terpene, p-Cymene, γ-Terpene, carvacrol, eugenol, caryophyllene, caryophyllene-oxide.	The oil has no healing action. Topical administration promoted local skin irritation and inflammation in a dose dependent manner without the presence of immunohistochemical labeling for COX-2 and VEGF.	Oliveira *et al*., 2014.
	Estrepa cavalo	Oil extraction				
11	*Memora nodosa* (Silva Manso) Miers *Synonym for: Adenocalymma nodosum* (Silva Manso) L.G. Lohmann **Bignoneaceae**	Root and leaves	Aqueous solutions containing 2% of extracts. 2000 and 5000 mg/kg^{-1} leaves and root, respectively.	Allantoin (root)	Healing activity on skin wounds in rats	Tresvenzol et al., 2013.
	Carobinha	Extraction				
12	*Orbignya phalerata* Mart. **Arecaceae** or **Palmae**	Mesocarp (fruit)	Aqueous solution at 50 mg/kg^{-1} topically applied	NR	The tests showed signs of wound healing favoring the activity of the evaluated extract, even without significant macroscopic and histological differences between the groups.	Filho *et al*., 2006.
	Babaçu	Extraction				

13	*Passiflora edulis* Sims. **Passifloraceae**	Leaves	Intraperitoneal application of the hydro-alcoholic extract at 250 mg/kg^{-1}.	NR	The treatment did not show macroscopic differences but increased the resistance to air insufflation by the increase of the leukocytes and fibroblasts, positively influencing the wound healing.	Bezerra *et al*., 2006.
	Maracujá roxo	Extraction				
14	*Pereskia aculeata* Mill. **Cactaceae**	Leaves	The animals were treated with 30 µL of topical formulations containing gel base (vehicle), 5% hexane fraction or methanol extract 5%.	NR	The compounds hexane fraction (HF) and methanol extract (HM) promoted decrease fibroplasia, blood vessels and inflammatory cells at last day of treatment.	Pinto *et al*., 2016.
	Carne dos pobres	Extraction				
15	*Piper marginatum* Jacq. **Piperaceae**	Leaves	Intraperitoneal injection of the extract (0.1 to 1 g/kg) in mice and rats hydroalcoholic extract at 1%	Noradrenaline, steroids, diterpenes and flavonoids.	The crude extract has an anti-edema and vasoconstrictor effect related to the presence of noradrenaline and positive anti-inflammatory action to healing.	D'angelo *et al*., 1997.
	Capeba	Extraction				
16	*Poincianella pluviosa* DC. Synonym for: *Cenostigma pluviosum* (DC.) E.	Bark	hydroalcoholic extract at 1%	Hydrolyzable tannins	The extract regulates protein levels, stimulates angiogenesis, re-epithelization, keratinocyte proliferation, collagen	Bueno *et al*., 2016.

	Gagnon & G.P. Lewis **Fabaceae** or **Leguminosae**				maturation and increased cell diffusion.	
	Sibibiruna	Extraction				
17	*Pyrostegia venusta* (Ker Gawl.) Miers **Bignoniaceae**	Flowers	treatment with flower (100 mg/kg body weight) extract in vehicle	NR	The extract has antimicrobial and antioxidant action and promotes wound healing by amplifying the expression of hydroxyproline and hexosamine with modulation of cytokines and increased contraction and tissue resistance.	Roy *et al.*, 2012.
	Flor de São João	Extraction				
18	*Schinus terebinthifoliaRaddi* **Anacardiaceae**	Leaves	Ointment containing 5% of *Schinus terebinthifolius* oil	p-Cymen-7-ol, 9-epi-(E) -cariophylene, carvone and verbenone	Increase fibroblasts, collagen deposition in bulky and wound contraction promoting healed.	Estevão *et al.*, 2013.
		Oil extraction				
		Leaves			Increase mast cells and polymorphonuclear cells with healing and local collagen enlargement and tissue remodeling	Estevão *et al.*, 2015.
		Oil extraction				
	Aroeira-vermelha	Leaves	Methanolic extract 80 mg/ml diluted with unbuffered	Flavonoids and phenolic acid	Healing activity and anti-inflammatory action similar to collagenase group with increase induction of apoptosis, splenic	Fedel-Miyasato *et al.*, 2014.
		Extraction				

			physiological saline		phagocytosis and chemoprotection in the absence of cytotoxicity and cellular mutagenicity.	
		Bark Decoction	NR	NR	Efficient in tissue retraction and improvement of clinical and histological aspects of wounds.	Lipinski *et al*., 2012.
19	*Sebastiania hispida* (Mart.) Pax Synonym for *Microstachys hispida* (Mart. & Zucc.) Govaerts **Euphorbiaceae** Mercúrio	Leaves Oil extraction	Ointment made with crude methanol plant extract 2% applied topically	Phenolic compounds and derivatives.	The vegetable extract is more efficient as cicatrizant than the InGaAlP in surgically induced wounds in rats	Rizzi *et al*., 2017.
20	*Serjania erecta* Radlk **Sapindaceae** Timbó	Aerial part Extraction	Topical application of hydroalcoholic extract and fractions	Flavonoids and tannins	Topical anti-inflammatory effect	Gomig et al., 2008.
21	*Sideroxylon obtusifolium* (Roem. & Schult.) T.D. Penn. **Sapotaceae** Quixabeira	Bark Extraction	Ointment made with ethanolic plant extract	Total phenols, tannins, flavonoids, flavones, xanthones, steroids, triterpenoids and saponin heterosides.	Presence of anti-inflammatory, antioxidant action and reduction of cell migration.	Leite *et al*., 2015.
22	*Siparuna guianensis* Aubl. **Siparunaceae**	Leaves	Ointment made with 10% crude extract applied	Steroids, triterpenes and condensed tannins.	The extract has cicatricial and re-epithelizing action without mutagenic activity.	Thomé *et al*., 2012.

	Negramina	Extraction	topically			
23	*Strychnos pseudoquina* A. St.-Hil. **Loganiaceae**	Leaves	topical application of ointment with hydroethanolic extract 5% and 10%	tannins, flavonoids, and alkaloids	The extract promotes an increase in the number of mast cells, collagen and elastic fibers in the wounds besides stimulating the activity of antioxidant enzymes.	Sarandy *et al*., 2018.
	Quina	Extraction				
24	*Stryphnodendron adstringens* (Mart.) Coville **Fabaceae** or **Leguminosae**	Bark	gel containing 1% crude extract	Proanthocyanidins	The crude extract stimulates the migration and proliferation of keratinocytes, inducing the replacement of type III collagen for type I and the increase of COX-2.	Pinto *et al*., 2015.
		Extraction				
	Barbatimão-verdadeiro	Bark/ Stalk	treated by oral and intralesional applications of bark extract 10 to 30 % (v/v)	NR	Increased number of tissue and proliferative mitoses in the epithelium without interference in keratinocyte migration or wound contraction.	Hernandes *et al*., 2010.
		Extraction				
		Bark	10 to 30 % extract applied topically	Compounds present in the crude extract and tannins.	The treated tissues presented contractile improvement, and the compounds interfere in the growth of the hyphae of *P. insidiosum* without causing tissue toxicity.	Trolezi *et al*., 2017.
		Extraction				
25	*Stryphnodendron obovatum* Benth Synonym for *Stryphnodendron*	Bark	Crude lyophilized extract and 2.5% ethyl acetate extract (2.5%)	Tannins, phenolic compounds and phenol.	The extract showed healing and bactericidal efficacy.	Lopes *et al*., 2005.

	rotundifolium Mart. **Fabaceae** or **Leguminosae**		applied topically			
	Barbatimão	Extraction				
26	*Stryphnodendron polyphyllum* Mart. **Fabaceae** or **Leguminosae**	Bark	Ointments containing 2.5% crude lyophilised extract and 2.5% ethyl-acetate lyophilised fraction	Tannins, phenolic compounds and phenol.	The extract showed healing and bactericidal efficacy.	Lopes *et al*., 2005.
	Barbatimão	Extraction				
27	*Tabebuia avellanedae* Lorentz ex Griseb Synonym for *Handroanthus impetiginosus* (Mart. ex DC.) Mattos **Bignoniaceae**	Bark	plant decoction condensed with carboxymethyl cellulose) were directly applied on the wounds daily with a syringe	NR	Efficient in tissue retraction and improvement of clinical and histological aspects of wounds.	Lipinski *et al*., 2012.
	Pau-d'arco	Decoction - boiling 100 g of each material in 1 L of water for 30 min				

28	*Vernonia scorpioides* (Lam.) Pers Synonym for *Cyrtocymura scorpioides* (Lam.) H.Rob. **Asteraceae** or **Compositae**	Leaves	ointment containing 20% of the ethanol extract, topic application	Sesquiterpene lactones	No efficient effects on excisional wounds in the skin of mice	Dalazen *et al*., 2005.
	Piracá	Maceration				