

## **Evidence about properties of the extract of *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) for clinical practice**

**Evidências sobre as propriedades do extrato de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) para a prática clínica**

**Evidencia sobre las propiedades del extracto de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) para la práctica clínica**

Received: 12/19/2020 | Reviewed: 12/26/2020 | Accept: 12/28/2020 | Published: 01/02/2021

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### **Abstract**

The aim of this study was to highlight the evidence about the properties of the extract of *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) and your application to human health. For this purpose, the CAPES Periodic Portal, Scielo, ScienceDirect, PubMed and Scopus databases were searched regarding the period from 2002 to 2019. This is a review of all studies published since 2002 on about properties of the extract of *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão). Although in vitro and in vivo studies have shown that anticancer, antimicrobial, antiviral, fungal, anti-inflammatory and healing properties. In addition, particular clinical conditions also had improvement of the clinical condition in view of the use of Barbatimão including decreases in serum glucose, arthritis and Alzheimer's disease.

**Keywords:** *Stryphnodendron adstringens*; Barbatimão; Systematic review; Clinical practice; Phytotherapics.

### Resumo

O objetivo deste estudo foi destacar as evidências sobre as propriedades do extrato de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) e sua aplicação à saúde humana. Para tanto, foram pesquisadas as bases de dados do Portal de Periódicos da CAPES, Scielo, ScienceDirect, PubMed e Scopus referentes ao período de 2002 a 2019. Esta é uma revisão de todos os estudos publicados desde 2002 sobre as propriedades do extrato de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão). Embora estudos in vitro e in vivo tenham demonstrado propriedades anticâncer, antimicrobianas, antivirais, fúngicas, antiinflamatórias e cicatrizantes. Além disso, determinadas condições clínicas também apresentaram melhora do quadro clínico com o uso do Barbatimão incluindo diminuição da glicose sérica, artrite e doença de Alzheimer.

**Palavras-chave:** *Stryphnodendron adstringens*; Barbatimão; Revisão sistemática; Prática clínica; Fitoterápicos.

### Resumen

El objetivo de este estudio fue resaltar la evidencia sobre las propiedades del extracto de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) y su aplicación a la salud humana. Para este propósito, se realizaron búsquedas en las bases de datos CAPES Periodic Portal, Scielo, ScienceDirect, PubMed y Scopus para el período de 2002 a 2019. Esta es una revisión de todos los estudios publicados desde 2002 sobre propiedades del extracto de *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão). Aunque los estudios in vitro e in vivo han demostrado que tiene propiedades anticancerígenas, antimicrobianas, antivirales, fúngicas, antiinflamatorias y cicatrizantes. Además, condiciones clínicas particulares también mejoraron la condición clínica en vista del uso de Barbatimão, incluyendo disminuciones de glucosa sérica, artritis y enfermedad de Alzheimer.

**Palabras clave:** *Stryphnodendron adstringens*; Barbatimão; Revisión sistemática; Práctica clínica; Fitoterápicos.

## 1. Introduction

Since 2002, the use of phytotherapeutics medical has been considered a part of healthcare due to its potential for the development of new drugs according with World Health Organization (WHO) (Goes et al., 2020; Moraes et al., 2020; Pellenz et al., 2018; Santos et al., 2020). In January 2009, the National Policy for Medicinal Plants and Herbal Medicines (NPMPHM) and the Brazilian National Program for Medicinal Plants and Phytotherapics (BNPMPP) divulged the RENISUS (Brazilian National List of Medicinal Plants of Interest to the SUS). This list has medicinal plants showing potential for generating products of interest to Brazilian Unified Health System, including *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) (Ministério da Saúde, 2006).

*Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) is a native Brazilian species used in traditional medicine and some commercial preparations as natural product (De Santana, Voeks, & Funch, 2016). The barks of this plant have been used for centuries in the traditional Brazilian medicine as astringent (Ricardo & Brandão, 2018). This plant is popularly used to population and scientific research has shown that it has antiulcerogenic potential, antiprotozoal activity, anti-inflammatory effects, antimicrobial activity, and wound healing effects (Hernandes, da Silva Pereira, Palazzo, & de Mello, 2010; T. G. Ribeiro et al., 2015; Sabino et al., 2017; Vilar, D'Oliveira, Santos, & Chen, 2010). Hence, the identification of property from medicinal plants is crucial for developing effective therapies and managing several clinical conditions, as well as promoting knowledge about news perspectives to health. Thus, this paper aimed to described evidence as the properties of the extract of *Stryphnodendron adstringens* (Barbatimão) described in the literature.

## 2. Methodology

Considering the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard, we searched for articles focusing the role of the properties of the extract of *Stryphnodendron adstringens* in clinical and that were published through to 2019. In order to assess eligibility of the studies, we used the method PICOS for delineation of descriptors to identify specific inclusion/exclusion criteria with the overall aim of maximizing inclusion of all relevant, being that (P - population): were human/animals; (I - intervention): was treatment with *Stryphnodendron adstringens*; (C - compared to control groups): others treatments; (O - outcome): result to condition clinical; and (S - study design):

experimental and observational. The search strategy for this review was conducted using the following keywords: *Stryphnodendron adstringens* and Barbatimão with boolean connectors to generate combinations. Articles were identified through searches of Portal of the Periodic of CAPES, Scielo, ScienceDirect, PubMed and Scopus databases and also was searched reference lists of relevant reviews and original articles.

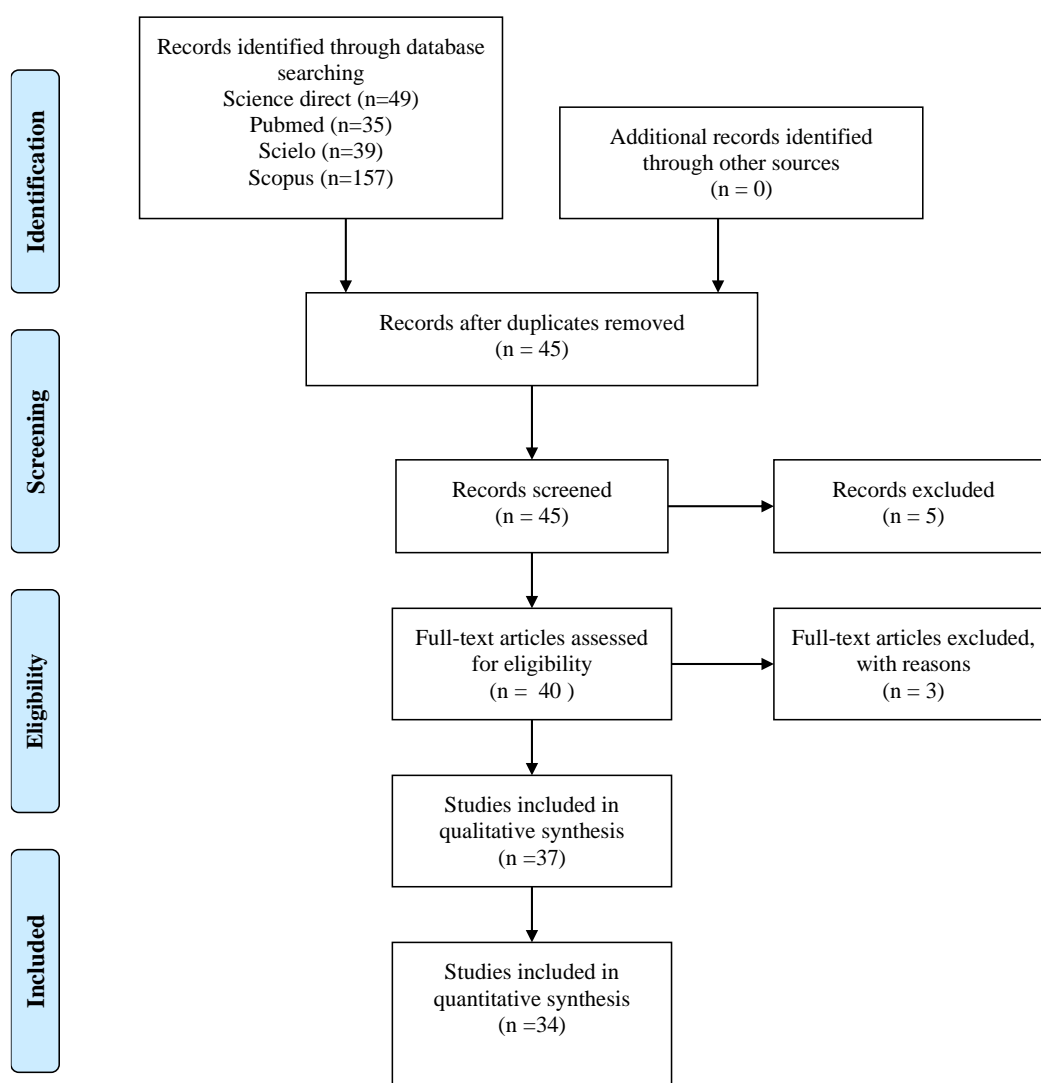
Articles were considered for potential inclusion if they met all the following criteria: (1) articles that investigated the use of the extract to *Stryphnodendron adstringens* (*Barbatimão*), (2) original data and (3) studies in English or Portuguese language, (4) investigations about in vivo and in vitro. Studies were excluded if they met any of the following criteria: (1) duplicate articles; (2) case, book chapter, brief comment, review or articles only with available abstract; (3) articles that did not address the use of the extract to *Stryphnodendron adstringens* (*Barbatimão*).

The titles and abstracts of the papers were evaluated by three authors (C.A.N; A.C.M.S; K.F.F) to define inclusion independently and selected articles of interest. Potential full-text eligible articles were assessed separately by reviewers. Posteriorly, each reviewer concluded data extraction for eligible papers included in this review, and a second reviewer verified all data extracted for evaluation. A third reviewer conferred the data to resolve conflicts. Points of disagreement were discussed until consensus was reached at each step of the extraction process. The information extraction was summarized considering information about author, year, country and results.

### 3. Results

Based on this research proposal, a systematic research review was conducted. The systematic review of the literature aims to detail the studies listed, in particular their main results and limitations, for future repetitions by other researchers (Higgins et al., 2019; A. S. Pereira, Shitsuka, Parreira, & Shitsuka, 2018). Figure 1 show the results of the search strategy used to identify relevant articles as recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. A total of 290 articles were identified from electronic database, after remove the duplicates a total of 40 papers were eligible and selected for full-text review based on the title and abstract information relationship with *Stryphnodendron adstringens* (*Barbatimão*) and pharmaceutical potential to clinical practice. Of these, four were excluded because the review of the record titles and abstract indicated that the papers did not meet eligibility criteria.

**Figure 1.** Flowchart of studies selection;



Source: Authors (2020).

The primary reasons for exclusion included: no full-text access, duplicates and reviews. Finally, after applying the exclusion criteria, 36 records were included in this review. The period of publication of the studies was between 2002 and 2019. These studies were conducted in a variety of geographical locations of the Brazil. Regarding anticancer properties (n = 6), antimicrobial (n = 6), antiviral (n = 2), fungal (n = 5), anti-inflammatory (n = 3), cicatrization (n = 6). Special clinical conditions were investigated for the possible role of Barbatimão including decreases in serum glucose (n = 2), arthritis (n = 1) and Alzheimer's disease (n = 1) (Table 1).

**Table 1.** Qualitative synthesis of studies.

<b>Author, year</b>	<b>Country</b>	<b>Results</b>
Almeida et al, 2017	Brazil	Inhibition of microbial growth bactericidal activity
Baldivia et al., 2018	Brazil	Antioxidant activity with direct elimination of free radicals, oxidative hemolysis and inhibition of lipid peroxidation in human erythrocytes
Furtado et al., 2019	Brazil	Antibacterial and antifungal action
Chaves et al., 2016	Brazil	Angiogenic activity but did not show positivity in the percentage in relation to the vascular network
Coelho et al., 2010	Brazil	Promotion of epithelialization, inflammatory process and neovascularization and production of fibroblasts and collagen
Costa et al., 2010	Brazil	Antifungal properties
Cruz et al 2018	Brazil	Corneal reticulation
Freitas et al., 2018	Brazil	Antifungal properties against <i>C. albicans</i>
Felipe et al., 2006	Brazil	Antiviral properties
Filho et al., 2011	Brazil	Carcinogenic property
Henriques et al., 2016	Brazil	Anti-inflammatory property
Hernandes et al., 2010	Brazil	Wound healing
Herzog-Soares et al., 2002	Brazil	Anti-parasitic property
Ishida et al., 2009	Reino Unido	Antifungal properties
Ishida et al., 2006	EUA	Antifungal properties
Kaplum et al., 2018	Brazil	Carcinogenic property
Melo et al., 2007	Brazil	Peripheral antinociceptive property
Lopes et al., 2005	Brazil	Wound healing
Luiz et al., 2015	Brazil	Antibacterial property
Pellenz et al., 2018	Brazil	Exert genoprotective and antiapoptotic effects on human keratinocytes and fibroblasts
Pereira et al., 2011	Brazil	Antibacterial property

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Pinho et al., 2012	Brazil	Antibacterial property
Pinto et al., 2015	Brazil	Diabetic wounds
Sabino et al., 2017	Brazil	Chemopreventive agent
Sereia et al., 2019	Brazil	Carcinogenic property
Souza et al., 2012	Brazil	Inhibition of $\alpha$ -amylase and $\alpha$ -glucosidase activities to reduce postprandial blood glucose levels
Souza et al., 2007	Brazil	Antiseptic activity
Trolezi et al., 2017	Brazil	Wound phytosis
Souza et al., 2007	Brazil	Antimicrobial and antiseptic property
Sereia et al., 2019	Brazil	Completely inhibits mitochondrial depolarization, superoxide production and lipid peroxidation and the modulating role of beta-amyloid (A $\beta$ ) toxicity in Alzheimer's disease
Felipe et al., 2006	Brazil	Antiviral agent inhibited Bovine Herpesvirus (BHV-1) and Poliovirus (P-1) replication
Filho et al., 2011	Brazil	Anticarcinogenic agent with activity DNA lesion formation decreased significantly micronucleus formation
Pinto et al., 2015	Brazil	Cell migration and proliferation of keratinocytes in diabetic rats

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Source: Authors (2020).

## 4. Discussion

The use of medicinal plants and herbal medicines has gained importance in the scope of national health policy, with increased investments and valorization of programs in the Health System, so studies that investigate their potential in clinical practice is necessary since there are systemic benefits for the human being (L. H. L. Ribeiro & Ribeiro, 2019). We demonstrated in this review that the *Stryphnodendron adstringens* (Barbatimão) has several properties with great potential of clinical applicability among the included studies due to the property antimicrobial, antiparasitic, antifungal, antiviral, healing, antioxidant, anticancer and antinoceptive. In addition, in some clinical situations conditioned by in vitro studies Barbatimão was evidenced as an important agent in the decrease of serum glucose levels and as promising adjuvant in the inhibition of mechanisms protective to Alzheimer's disease.

### 4.1 Antimicrobial and antiviral activities of *Stryphnodendron adstringens*

Probably the most well studied property is the antimicrobial effect in which its effectiveness is shown by several studies, as in a research investigated antimicrobial property and toxicity of the extract of *Stryphnodendron adstringens* with assay using *Escherichia coli* and *Staphylococcus aureus* in the several concentrations administrated by gavage in wistar rats highlighted antimicrobial activity against these species (Almeida et al., 2017). In other study using agar diffusion and the

microdilution assay the antimicrobial activity was evidenced for the species *C. albicans*, *S. mutans*, *S. aureus* and *A. actinomycetemcomitans* (E. M. R. Pereira et al., 2011). A study involving extracts of hydroalcoholic extracts obtained from pepper rosemary (*Lippia sidoides*), aroeira (*Myracrodruon urundeuva*), Barbatimão (*Stryphnodendron adstringens*), barley grass (*Cordia verbenacea*) and pequi fruit bark (*Caryocar brasiliense*) showed no inhibition of *Escherichia coli* growth but showed antimicrobial potential for *Staphylococcus aureus* (Pinho, 2012). In an attempt to determine the minimum concentration of the dry extract and the antiseptic activity of the *S. adstringens* barks and the performance against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Escherichia coli*, we identified in paper that only *S. aureus* presented greater sensitivity in comparison with the others (Souza, Moreira, Pietro, & Isaac, 2007). As for the performance directed to some particular aspects of certain fungi, the results of the studies were positive for a decrease in fungal activity, especially *Candida albicans* fluconazole-resistant (Freitas et al., 2018) and *Cryptococcus neoformans* (Ishida, Rozental, de Mello, & Nakamura, 2009). It was also identified that the extract of Barbatimão (*Stryphnodendron adstringens*) inhibited Bovine Herpesvirus (BHV-1) and Poliovirus (P-1) replication, as well as, blocked the synthesis of viral antigens in infected cell cultures (Felipe et al., 2006).

#### **4.2 Anticancer Potential of *Stryphnodendron adstringens***

Filho et al. identified that Barbatimão promoted inhibited the DNA lesion formation and in the form of water fraction and ethanolic extracts of leaves decreased significantly micronucleus formation in rat bone marrow cells. (Filho, Ferreira, & Gouvêa, 2011) In other study, a model experimental to breast cancer and antitumoral potential concluded that the Barbatimão fractions decreased cancer cell viability as well as cell rounding-up, shrinkage, and nuclear condensation reduction of cell diameter and length and induced apoptosis (Sabino et al., 2017). A recent study demonstrated the in vitro and in vivo anticancer activity of a proanthocyanidin polymer-rich fraction of *Stryphnodendron adstringens* in cervical cancer cell lines HPV-positive (16 and 18), concluding that these cells treated with Barbatimão showed particular increase of free radicals and decrease of antioxidant species, mitochondrial membrane depolarization, progression to apoptosis as well as significant reduction of volume and induced weight tumoral (Kaplum et al., 2018).

In a model murine B16F10Nex-2 melanoma cells, authors administered *Stryphnodendron adstringens* aqueous extracts prepared from the stem bark to assess their antioxidant activity and anticancer effects concluded that antioxidant activity through direct free-radical scavenging as well as through oxidative hemolysis, lipid peroxidation inhibition in human erythrocytes, apoptosis-induced cell death, inducing mitochondrial membrane potential dysfunction and activating caspase-3 (Baldivia et al., 2018).

#### **4.3 Healing Potential of *Stryphnodendron adstringens***

Coelho 2010 et al. Compared the action of silver sulfadiazine, ipê-purple extract and Barbatimão extract on the healing of cutaneous wounds after incision for the development of venous hypertension in Wistar rats, concluding that after 14 days the group treated with *Stryphnodendron adstringens* evidenced and the formation of new vessels. However, there was no significant difference between the two groups (Coelho et al., 2010). In a study to investigate the influence of aqueous solution Barbatimão shell in blood vessel formation process in embryonated egg membrane corioalantoide chicken that had an interesting percentage in the vascularization process (Chaves et al., 2016). In a research that characterize rabbit corneas subjected to enhanced crosslinking using different vegetable extracts prepared from *Stryphnodendron adstringens* concluded that temperature and enthalpy of denaturation during induction of corneal collagen cross-linking samples of rabbit treated with *S. adstringens* were higher than the control group (da Cruz, Moraes, Nogueira, Morandim-Giannetti, & Bersanetti, 2018).

Hernandes et al., 2010, investigated the healing effect of back in wounds made in the skin of rats, after of treatment in which the existence of the stimulated proliferation of the keratinocytes (Hernandes et al., 2010). Other study evaluated the modulation of genotoxicity and apoptosis of the Barbatimão extract on DNA damage in human keratinocytes and dermal fibroblast and identified genoprotective effect on cells by decreasing the levels of DNA oxidation and reactive oxygen species (ROS) levels (Pellenz et al., 2018).

#### 4.4 Other Applications of *Stryphnodendron adstringens*

The effects and properties of the of *Stryphnodendron adstringens* and extract of the beach have been tested in other applications in the health area, as its effect in conditions clinics has been highlighted. In a research, investigated the effect anti-inflammatory of Barbatimão and other species on the production of tumor necrosis factor-alpha (TNF- $\alpha$ ) as well as their anti-arthritis activity in mice found relationship with a decrease of leukocyte migration into the inflammatory site (Henriques et al., 2016). The antinociceptive property of the crude extract and fractions of *Stryphnodendron adstringens* (Martius) Coville (Barbatimão) was also investigated with experimental models of pain initiation being demonstrated that exists an antinociceptive outcome (Melo et al., 2007). In diabetic rats, researchers investigated the healing action of the crude extract of *Stryphnodendron adstringens* concluded that cell migration and proliferation of keratinocytes at the beginning of the treatment in addition to stimulating the replacement of type III collagen (Pinto et al., 2015).

### 5. Conclusion

From this perspective, introducing translational research using *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) is optimizing patient care and developing preventive measures, stopping the progression of the most invasive and painful pathologies and procedures and reducing them of public spending. In this research, we showed the potential antimicrobial, antiparasitic, antifungal, antiviral, healing, antioxidant, anticancer and antinoceptive. The findings encourage the use of *Stryphnodendron adstringens* in traditional medication to treat and management to different conditions clinics.

### Suggestion

This study may suggest the application and use of the *Stryphnodendron adstringens* (Mart.) Coville (Barbatimão) in several thematic areas and which is widely used in clinical trials to verify its viability and effectiveness on the treatment of cancer and neurodegenerative diseases, through clinical trials.

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