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Biological potential of plant species *Xylopia frutescens*: An integrative review

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ABSTRACT

The aim of this study was to analyze the scientific production that has been produced about biological activities of Xylopia frutescens. This is an integrative review conducted in databases: Latin American and Caribbean Center on Health Sciences Information; Medical Literature Analysis and Retrieval System Online; Scopus and virtual libraries Scientific Electronic Library Online, SciFinder Scholar and PubMed. The papers were analyzed with variables as title of articles, authors, country, journal, database, year of publication, language, approach, and study type, parts of studied plant species, results and conclusion of articles. It were found 75 articles and after analysis were selected 11 articles, 8 (72.7%) articles in Scopus database, 3 (27.3%) in Scifinder, other periodic presented repeated articles and others were not found. The articles were published from 1982 to 2016. The studies were conducted in Brazil (72.7%), Germany (9.1%), French Guiana (9.1%) and France (9.1%). The parts of the plant species used were leaves, fruits, stem bark, stem and seeds. The activities evidenced in the articles were antimicrobial, antifungal, anti-inflammatory, antitumor, trypanocidal, spasmolytic and antiplasmódico. Hence, it is concluded that plant species in question presented in the articles analyzed a wide biological activity, providing significant information for designing new studies with Xylopia frutescens.

Keywords: Biological activity; Medicinal plant, *Xylopia frutescens*.

INTRODUCTION

In the middle of many practise diffused culturally by population, have always been a fundamental importance for several reasons, and reinforced its therapeutic potential applied over the generations [1].

The existence of man in the world made him to adapt to environment searching for ways and resources from nature to provide the improvement of its lifestyle [2], therefore, the use of medicinal plants as a complementary practice is as old as the emergence of humanity, being part of family and community care [1].

In order to improve therapy with medicinal plants in nineteenth century with the Industrial Revolution and the development of organic chemistry, there was a considerable advance for science and technology allowing intense social and commercial changes [3], enabling isolation of chemical compounds for manufacture of synthetic drugs that have potentially more active and safe actions, against the use of products from nature, since they are associated to the magical-religious significance, without scientific and pharmacological value [4].

The appearance of side effects caused by this type of drug, impossibility of access to drug treatment, high cost of the same and appearance of resistance of microorganisms has become factors, which promoted return by alternative therapy with natural products, especially those from medicinal plants [5].

Phytotherapy is understood as a wide area, making it necessary to understand and know some important meanings that covers, emphasizing the need to differentiate medicinal plant and herbal medicine [6]. The definition of medicinal plant is "cultivated plant species or not for therapeutic purposes," however, the herbal medicine is a "product obtained from a medicinal plant, or derivatives, except isolated substances with a prophylactic, curative or palliative purpose" [7].

Being skin lesions the most frequently assisted at healthcare units, practice of using natural products has become important in the treatment of wounds by communities [8]. Medicinal plant practice in the treatment of wounds is an area that remains resisting the technological innovations that can be found in biomedical sciences, however, by becoming one method of choice in the treatment of wounds due to its relevance in the healing process, it is suggested research documents demonstrating healing potential, clinical finding and the cost benefit of plant species [9].

In Brazil, the government's interest to invest in use of natural products is associating with existing biodiversity. Among many species of the Atlantic Forest, some are widely used by the population as in the case of pequi (*Caryocar brasiliense*), espinheira-santa (*Maytenus ilicifolia*) barbatimão (*Stryphnodendron adstringens*) jenipapo (*G. americana*) and pindaíba (*Xylopia frutescens*) [10].

Among many species with medicinal properties may be mentioned genus of Annonaceae family, which *Xylopia* is composed of 150 species, some are known for their ethnomedicinal uses and provide a variety of medicinal properties [11].

X. frutescens in the Amazon region as breu branco or simply breu. In the north of the country is also known as Pimenta-do-sertão, Ibira, Pau-de-imbira, Pindaíba, Pindaúba. *X. frutescens* is used as aromatic agents, stimulants of the bladder and are useful as a digestive and leukorrhea versus stoma cramps, however, 60% of native plant species require pharmacological and phytochemicals studies [12].

Considering the explanation, this research aims to analyse the scientific production that has been produced about biological activities of *Xylopia frutescens*.

EXPERIMENTAL SECTION

This is an integrative review with the following question: what has been produced in national and international literature about *Xylopia frutescens*? The research was conducted from December 2015 to March 2016 in the following databases: Latin American and Caribbean Center on Health Sciences Information; Medical Literature Analysis and Retrieval System Online; Scopus and virtual libraries Scientific Electronic Library Online, SciFinder Scholar and PubMed.

In the selection of articles were utilized the keywords Medicinal Plants and *Xylopia frutescens* that are contemplated in the Descriptors in Health Sciences (DeCS). It was used the Boolean operator AND, and as research strategies, it was performed the cross of descriptors in Portuguese, English and Spanish. Such as *Xylopia frutescens*, Plants, Medicinal AND *Xylopia frutescens*, in Portuguese, English and Spanish.

Inclusion criteria for articles selection were articles published in Portuguese, English, Spanish and French that have portrayed in its entirety the study theme. Articles that were not related to the biological activities of *X. frutescens* and duplicates articles were excluded. The studies found in more than one journal were considered only once.

For analyse the articles, it were selected variables as title of articles, authors, country, journal, database, year of publication, language, approach, study type, parts of the studied plant species, and form of extraction, results and conclusion. Articles that attended inclusion criteria were analysed by means of a form that included item identification information in order to consolidate all the results presented in scientific production.

RESULTS AND DISCUSSION

It were found 75 articles that approached the theme and after analysis were selected 11 articles, 8 (72,7%) articles in the Scopus database, 3 (27,3%) in Scifinder in Pubmed and Scielo and articles found were excluded as were repeated on other bases and no articles were found in Medline and Lilacs periodic (Table 1).

It was observed that 72,7% of the studies were conducted in Brazil, and most of the articles were published in English composing 90,9% of the studies. All selected articles showed research with a quantitative approach (100%),

and 90.9% of these were studies of experimental type and one integrative review (9,9%), it was evidenced that experiments were performed *in vitro* (75%) and *in vivo* (16,7%) as shown in table 1.

Table 1. Articles bibliometric analysis, Brazil, in 2016

VARIABLES	n (%)
DATABASES	
Pubmed	0 (0)
Scielo	0 (0)
Medline	0 (0)
Lilacs	0 (0)
Scopus	8 (72,7)
Scifinder	3 (27,3)
COUNTRY	
Brazil	8 (72,7)
Germany	1(9,1)
French Guiana	1(9,1)
France	1(9,1)
LANGUAGE	
English	10 (90,9)
French	1(9,1)
APPROACH	
Quantitative	11 (100)
STUDY DESIGN	
Integrative review	1 (9,1)
Experimental	10 (90,9)
TYPE OF EXPERIMENT	
Integrative review	1 (8,3)
In vitro	9 (75)
In vivo	2 (16,7)

Note: Researchers Authorship, 2016.

In Table 2 are arranged articles tittles, as well as authors and journals of these. The articles were published in the period 1982-2016, with this; it was possible to cover the highest number of studies that addressed the theme in question. It was observed, regarding the year of publication, two were published in 1999, the largest quantity of articles published in 2013 with three of the 11 selected articles.

Table 2. Selected articles from databases, Brazil, 2016

S.No.	Title	Authors	Journal	Year
1	Alcalodes des annonacées. XLIII: alcaloides du *Xylopia frutescens* aubl.	Leboeu, M. et al.	Plantes Medicinales et Pliytothérapie	1982
2	In vitro antifungal activity of essential oils against clinical isolates of dermatophytes	Lima, E. O. et al.	Journal of Microbiology	1992
3	Volatile Constituents of *Xylopia frutescens*, *X. pynaertii* and *X. sericea*: Chemical and Biological Study	Fournier, G. at al.	Phytotherapy Research	1994
4	Screening Brazilian plant species for *in vitro* inhibition of 5-lipoxygenase	Braga, F. C. et al.	Phytomedicine	1999
5	In vitro antiplasmodial activity of Central American medicinal plants	Jenett-Siems, K. et al.	Tropical Medicine and International Health	1999
6	Antibacterial activity of eight Brazilian Annonaceae plants	Takahashi, J. A. et al.	Natural Product Research,	2006
7	Antitumour properties of the leaf essential oil of *Xylopia frutescens* Aubl. (Annonaceae)	Ferraz, R. P.C. et al.	Food Chemistry	2013
8	Genus *Xylopia* (Annonaceae): Chemical and Biological Aspects	Moreira, I. C. et al.	Chemistry & Biodiversity	2013
9	Chemical Composition and Anti-*Trypanosoma cruzi* Activity of Essential Oils Obtained from Leaves of *Xylopia frutescens* and *X. laevigata* (Annonaceae)	Silva, T. B. et al.	Natural Product Communications	2013
10	Essential oil from *Xylopia frutescens* Aubl. reduces cytosolic calcium levels on guinea pig ileum: mechanism underlying its spasmolytic potential	Souza, I. L. L. et al.	BMC Complementary and Alternative Medicine	2015
11	Synthesis, in vitro Antimalarial Activity and in silico Studies of Hybrid Kauranoid 1,2,3-Triazoles Derived from Naturally Occurring Diterpenes	Santos, J. O. et al.	Journal of the Brazilian Chemical Society	2016

Note: Researchers Authorship, 2016.

It was observed in the studies that that were utilized all parts of *X. frutescens* and the leaves and fruits were the most evident, in five and three publications, respectively. Regarding the extraction method of the parts of plant species, it was observed that the essential oil appeared in five publications, followed by hexane and ethanolic extracts, as evidenced in Table 3.

Table 3. Analysis of biological activities found in the articles, Brazil, in 2016

Number	Part of plant	Extraction form	Biological activity	Conclusion
1	Stem bark, Stem, Leaves	Ethanolic extract	Antimicrobial, antifungal, and spasmolytic	The extracts showed antibacterial activity against strains *Staphylococcus*, *Streptococcus* and *Bacillus subtilis*, modest antifungal activity against the *Microsporum canis* and *Cryptococcus neoformans*. Thus as shown with anti-inflammatory and spasmolytic properties.
2	Leaves	essential oil	Antifungal	*Xylopia frutescens* showed excellent activity causing inhibition of 81% of the studied strains.
3	Stem bark	essential oil	Antimicrobial and Antifungal	Essential oil of *Xylopia frutescens* was effective against *Staphylococcus aureus* and *Mycobacterium smegmatis* and did not present fungal activity against *Candida albicans*.
4	Seeds	Hexane extract	Anti-inflammatory	The *Xylopia frutescens* has a high anti-inflammatory activity.
5	Seeds	hydrophilic extract	Antispasmodic	Extracts of *Xylopia frutescens*, proved to be active against resistant strain of *Plasmodium falciparum*.
6	Fruits	Hexane and methanol extract	Antimicrobial	*Xylopia frutescens* has antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*.
7	Leaves	essential oil	Antitumor	The plant species exhibited *in vitro* and *in vivo* anticancer effects without significant toxicity.
8	Fruits	Ethanolic extract	Antimicrobial	Presented inhibition front the bacterial strain *Bacillus subtilis*.
9	Leaves	essential oil	Trypanocidal	The essential oil showed a significant concentration for trypanocidal activity.
10	Leaves	essential oil	Spasmolytic	The spasmolytic action in the ileum of guinea pigs involved the antagonism of histamine receptors and can block Ca.
11	Fruits	Hexane extract	Antispasmodic	Compounds isolated from *Xylopia frutescens* showed antiplasmodial activity against *P. falciparum*.

Note: *Researchers Authorship, 2016.*

The biological activities identified in the analysis of the articles showed antimicrobial action (4 studies), antifungal (3 studies), being these two activities the most relevant studies. It was also observed anti-inflammatory activity, antitumor, trypanocidal, spasmolytic and antispasmodic, these data show biological potential of *X. frutescens*.

Regarding the antimicrobial activity, Leboeuf et al. [13] evaluated this activity with leaves and stem bark of the plant species in question, and observed that the bacterial strains *Staphylococcus* spp, *Streptococcus* spp and *Bacillus subtilis* were sensitive to stem bark extract and this antimicrobial activity could be related to alkaloid class found in extract of the sample used. It was also evident that aqueous extract of the leaves did not present antimicrobial activity against any of strains used.

In research conducted by Takahashi et al. [14] was also observed activity against *B. subtilis* and *Staphylococcus aureus* at a concentration of 100 μg/mL, in this study was isolated a secondary constituent, xylopic acid (a diterpene), and activity against the bacterial strains would be related to action exerted by this compound. However, the extract showed no activity against *Escherichia coli, Pseudomonas aeruginosa* and *Micrococcus luteus*, these data are similar with study conducted by Leboeuf et al. [13] mentioned above, on these Gram-positive bacterial strains.

In a study conducted in France with stem bark essential oil presented effective antimicrobial activity against *S. aureus* and *Mycobacterium smegmatis*, with minimum inhibitory concentration of 10 and 2 mg/mL, respectively. This study presented also that for bacteria *E. coli* and *P. aeruginosa* was not demonstrated satisfactory activity because it showed inhibition with higher values at 20 mg/ mL [14].

Moreira et al. [16] in his research with genus *Xylopia* evidenced that fruits of *X. frutescens* showed inhibitory activity against *B. subtilis*, as well as *X. sericea* in which the seeds had action against *B. subtilis* and *S. aureus*. In the same study, it was demonstrated that antimicrobial activity was possibly related to the presence of secondary constituents as terpenoids and alkaloids of benzylisoquinoline type, which has such biological properties.

In a recent study conducted in Malaysia with three species of genus *Xylopia*, through Broth Microdilution Method to obtain the minimum inhibitory concentration (MIC), the species showed activity against *S. aureus* and *S. epidermidis*. With regard to gram negative stems *P. aeruginosa* and *E. coli*, inhibition occurred at high concentrations and with MIC of 5000 μg/mL, with this, it may be suggested to exposed resistance of these bacteria with the species of the genus *Xylopia* [17].

Antifungal activities found in the studies showed that in the study by Lima et al. [18] with six plant species used in Brazil northeastern, among these *X frutescens*, which evaluated the fungicidal action of *Trichophyton rubrum, T. mentagrophytes, Microsporum canis* and *Epidermophyton floccosun*, isolated from patients with dermatophytosis, showed that the essential oil of the species in question has potential inhibition of 81% compared to positive control ketoconazole.

In other research conducted with the ethanolic extract of the leaves of *X. frutescens* showed moderate antifungal activity against *Cryptococcus neoformans* and *Microsporum canis*. However, in this same study the extract of the

stem bark did not present satisfactory activity against strains used in the test [13]. In another research with the stem bark essential oil, revealed that against the *Candida albicans* organism was not detected antifungal activity [15].

Antifungal activity was evaluated in another study of *X. laevigata*, against six species of the genus *Candida*, and it was observed that the essential oil of leaves showed activity against *C. albicans* and *C. tropicalis* with MIC 5000-100μg/mL, respectively, these data would be possibly related to synergistic action of the present compounds in the essential oil, it was reported that the presence of sesquiterpenes constituents [19].

It was also found in articles of this review anti-spasmodic activity, which was tested by Leboeuf et al. [13], and showed that stem extract exerted a slight activity on isolated organs and cardiovascular cells, an activity was still observed moderate in gastric antisecretory cells in anti-histamines type receptors.

In another study of the essential oil from the leaves of *X. frutescens* was observable spasmolytic action in mice ileum cells, this mechanism is related to calcium efflux (Ca^{2+}) cells, causing relaxation of smooth muscle. Another possibility was demonstrated in the research antagonism of histaminergic and possibly blocking the dependent Ca^{2+} channels. Suggesting to further studies with the essential oil from the perspective of a possible antidiarrheal agent [20].

This activity is reported in research with other species of genus *Xylopia*, and it was found that two isolated compounds belonging to class of diterpenes found in plant species *X. langsdorfiana* caused the blocking of Ca^{2+} channels and presented spasmolytic effect. It may be suggested that this secondary constituent could be present in *X. frutescens* species, which would justify the spasmolytic activity evidenced in the studies cited above. [21].

In a study conducted in Minas Gerais - Brazil, with native species, in which was evaluated anti-inflammatory activity, it showed that extract from seeds of *X. frutescens* presented antiphlogistic potential, causing inhibition of 5-lipoxygenase, this is one of pathways of inflammatory process, which would justify the use by the population for the treatment of diseases that are associated with inflammation [22].

Woguem et al. [23] evaluated anti-inflammatory activity of fruits essential oil of *X. parviflora* and showed that this species had a satisfactory activity in the reduction of nitrogen oxides, with a percentage of 37%, compared to untreated cells with essential oil, this activity is related to the secondary compound terpene in this species. Another action was evaluated in this study was antitumor activity, in which was evaluated sample against human cancer cells, and showed strong activity against these cells, with IC^{50} values of 7,47 to 6,56 μg/mL, depending on the type cell.

Essential oil from the leaves of *X. frutescens* was also evaluated for its antitumor activity, the research showed that ovarian adenocarcinoma cells, carcinoma bronch alveolar lung and metastatic prostate cancer, showed IC^{50} ranging from 40 to 14,9 μg/mL, this activity was observed in vivo and in vitro assays, and analysing the body of animals used in tests, no significant changes furthermore, it was found that the essential oil stimulated the amount of peripheral blood leukocytes compared to controls [24].

About *X. laevigata* were performed in vitro and in vivo tests with tumor and mononuclear cells and both evidenced antitumor potential of essential oil of leaves. In which it has been observed IC^{50} ranging from 14,4 to 31,6 μg/mL, these data are similar to the studies cited above, which was observed ranging inhibition from 6,5 to 40 μg/mL. The antitumor action would be related to δ-cadinene, germacrene β, α-copaene, sesquiterpene, bicyclogermacrene and (E) caryophyllene, which were the main constituents found in *X. laevigata* and has significant potential anti-cancer [25].

Essential oil of *X. frutescens* was also tested for in vitro trypanocidal activity and demonstrated significant activity with values less than 30 μg/mL-1 and 15 μg/mL front epimastigote and trypomastigote forms of *Trypanosoma cruzi*, it was observed that essential oil significantly reduced infected macrophages as well as the amount of intracellular parasites, and did not present toxicity at tested concentrations in macrophages [26].

Costa et al. [19] evaluated trypanocidal activity of *X. laevigata* essential oil against epimastigotes, and found inhibition with IC^{50} values of 93,9 ± 2,6 μg/mL, these data are considered promising for a possible therapeutic option in anticipation of the development of a future drug.

The analysis of the articles allowed the identification of antiplasmodial activity exercised by *X. frutescens*, in research conducted by Jenett-Siems et al. [27], performed with extracts of seeds was demonstrated antimalarial activity against *P. falciparum* strain, *in vitro* tests with IC^{50} values ranging from 3,0 μg /mL to 21,9 μg /mL.

Another recent study in Brazil, with the fruits of the plant species in question, which was isolated and tested xylopic acid compound belonging to this class of diterpenes was observable antimalarial activity against *P. falciparum* that is resistant to chloroquine and sensitive to mefloquine, with IC^{50} values of 41-67 μg /mL at concentrations of 25 and 50 μg /mL, respectively, these data are similar with those produced in the above study thus can demonstrate the biological potential of the species *X. frutescens* as antispasmodic [28].

Biological activities presented in this study may justify the use of *X. frutescens* by population, since it is used in folk medicine as an analgesic and anti-inflammatory, and bark decoction is used in inhalation form, acting in colds and headaches, among others [12].

CONCLUSION

Xylopia frutescens is promising in the search for new therapeutic methods and can be used as complementary practices facing the activities presented in this study, in addition to being a Brazilian native species that is easily accessible to the population.

The species has been evidenced in studies as promising in antimicrobial, antifungal, spasmolytic, antiplasmodial, anti-inflammatory, antitumor and trypanocidal activities. Hence, we emphasize the importance of further studies with this plant species, in order to enhance activities reported in the studies in this review and discover new biological properties

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