academicJournals

Vol. 11(48), pp. 1688-1692, 28 December, 2017
DOI: 10.5897/AJMR2016.8380
Article Number: E3118DF55613
ISSN 1996-0808

http://www.academicjournals.org/AJMR

African Journal of Microbiology Research

Review

Solanum paniculatum Linn: A potential antimicrobial agent against oral microorganisms

Maria Regina Macêdo-Costa[1*] , Pedro Henrique Sette-de-Souza[2] , Shenia Eliane do Rego Carneiro[3] , Julia Morais Fernandes[3] , Silvana Maria Zucolotto Langassner[3] , Maria do Socorro Vieira Pereira[4] and Kenio Costa Lima[1]

[1]Department of Dentistry, Federal University of Rio Grande do Norte, Natal, Brazil.
[2]Department of Dentistry, University of Pernambuco, Arcoverde, Brazil.
[3]Department of Pharmacy, Federal University of Rio Grande do Norte, Natal, Brazil.
[4]Department of Medicine, Faculty of Medical Sciences of Paraíba FACENE/FAMENE, UNIPÊ University Center of João Pessoa, João Pessoa, Brazil.

Received 13 November, 2016; Accepted 29 December, 2017

In Brazil, several species of potentially medicinal native plants exist, including *Solanum paniculatum.* This species is commonly known as "*jurubeba*" and belongs to the *Solanaceae* family, which is found in several regions in Brazil. It is widely used as a remedy for bronchitis, coughs, arthritis, jaundice, hepatitis, fever and stomach problems. The plant is believed to possess anti-viral, anti-cancer, anti-inflammatory, antioxidant, diuretic, hepatoprotective and antimicrobial properties. The chemical constitution of the species contains flavonoids, amides, steroids, lignans, steroidal saponins and steroidal alkaloids. This species is listed in the Brazilian Pharmacopoeia and the "National Report on Medicinal Plants of Interest to the Single Health System (Renisus), due to its potential for use in products of interest to the Brazilian Ministry of Health. Therefore, the value of the present review manuscript lies in its aim to discuss the antimicrobial, antiadherent, bactericidal, fungicidal and anti-inflammatory action of *S. paniculatum* Linn (*jurubeba*). Furthermore, it is extremely important to characterize their chemical profile and cytotoxicity, thereby favoring the safe application of natural bioactive substances. A phytotherapeutic agent causes less damage to the body, is inexpensive and is more accessible to the general public. The present review is important to provide the concrete possibility of using phytotherapeutic and medicinal plants as a therapeutic resource in Basic Healthcare Units operated by the *Sistema Único de Saúde* (SUS), particularly those represented by the Family Health Strategy.

Key words: *Solanum paniculatum,* microbiology, phytotherapy, toxicity, chromatography.

INTRODUCTION

Over the centuries, humanity has benefited from the natural medicine to treat or prevent a wide range of diseases. Secondary metabolites of plants and microbial and marine products have been considered a valuable

*Corresponding author. E-mail: wachukwuck@yahoo.com, wachukwu.confidence@ust.edu.ng.

source of novel molecules with potential for drug development (Newman, 1860). Several conditions affecting oral health can be prevented, controlled and/or treated with the use of natural resources - drugs or formulations. There is a long list-based and derived from natural products drugs, mouthwashes, toothpastes, among others, that are available for consumption or are administered as prescription (Cragg, 2014). However, the reasons for seeking new treatment modalities did not cease: microbial resistance, short and long-term toxicity, adverse and side effects and high costs. Thus, it seems accepted that there is a continuing need to obtain more potent, effective formulations for oral hygiene and low cost, with microbiota being safe and well tolerated (Rosalen, 2016). Accordingly, the use of plants in the prevention and treatment of oral infectious diseases, and as antibiofilm agent continues to be valued in many parts of the world, it is recommended by World Health Organization (WHO) (1987) and in our country. Many studies have been developed to assess the popular use of plants in dentistry, making it possible to identify plant species with potential biological activity (Ocheng et al, 2014; Mogosanu et al, 2015).

In Brazil, there are several potentially medicinal plants such as *Solanum paniculatum* Linn. This species is listed in the Brazilian Pharmacopoeia (Brasil, 1959) and belongs to the "National List of Medicinal Plants of Interest to the Unified Health System (Renisus)" (Brasil, 2009) to present potential to generate products of interest to the Ministry of Health. *S. paniculatum* Linn it is a species, commonly known as Jurubeba whose main pharmacogens are leaves, roots and fruits that are widely used in traditional medicine as a tonic, antipyretic in the treatment of gastric disorders, bronchitis, anemia, arthritis, jaundice and hepatitis. Jurubeba root is considered the most active part of the plant (Mesia-Vela et al., 2002; Botion et al., 2005). As regards, the scientific aspects are ascertained antibacterial, antifungal, antiviral, molluscicide, anticancer, anti-inflammatory, anti-oxidant, diuretic, antidiarrheal, hepatoprotective, gastroprotective and antiulcer.

However, *S. paniculatum* L. can determine signs of toxicity, diarrhea, nausea, vomiting, gastritis and erosive duodenitis, elevated liver enzymes and possibly neurological symptoms (Mesia-Vela et al., 2002; Oliveira et al, 2006; Carvalho et al., 2007; Valadares et al, 2009; Lôbo et al., 2010; Vieira et al., 2013; Silva et al., 2013; Macêdo-Costa et al., 2014; Vieira-Júnior et al., 2015; Gregoris et al., 2013; Stehmann et al., 2015; Martins et al., 2015; Macêdo-Costa, 2016; Clementino-Neto et al., 2016). Due to the biological potential of *S. paniculatum* L., the aim of this study was to review the literature on the antimicrobial activity of this plant.

GENERAL OVERVIEW OF *S. paniculatum* Linn

The genus *Solanum* is considered one of the largest and complex among angiosperms, having 1500 species (Hameed; Hussain, 2015). Native to Brazil, belongs to the *Solanaceae* family, common in several states, extends from the limits of the Guianas to São Paulo and Minas Gerais. It is also commonly found in Paraguay, Bolivia and Argentina. This plant is already component of several pharmaceutical formulations including syrups, infusions and decoctions, extracts, tinctures and elixirs. Infused flowers are indicated for bronchitis and cough, while the macerated roots are recommended for arthritis and fruit for anemia. The decoction of leaves is used to treat intestinal parasites, but is also suitable for stomach disorders (Mesia-Vela et al., 2002; Botion et al., 2005).

There is a plant protection in Brazil, which has in its formulation fluid extract of leaves of *S. paniculatum*, the Lerobina® (Belfar Laboratory, Belo Horizonte, Brazil). The product, marketed for decades, also has extracts *Remijia ferruginea*, Jacaranda carob, and exotic *Erythraea centarium*. With the exception of the latter, these plants occur in Brazil and are popularly employed for treating different diseases, among which is dyspepsia (280 mg/kg/day). However, more studies are needed to identify the compounds responsible for antidispépica action Lerobina® (Botion et al., 2005; Tagliati et al., 2008).

There are other products on the market that have *S. paniculatum* in its composition, such as Jurubeba Composed Elixir® (Infabra Ind. Farm. Bras. Ltda, Rio de Janeiro, Brazil) and the Watchtower Jurubeba® (Farmabraz, Rio de Janeiro, Brazil). Both have jurubeba and boldo extracts in their composition, and are indicated as choleretic / bile duct, in dyspepsia, flatulence and gastrointestinal discomfort. Classic drinks like spirits Jurubeba Lion Norte® (North Ltda Lion, Bahia, Brazil), Jurubeba Nordestina® (Pernambuco, Brazil) and Coleguinha Jurubeba® (Colonial, Ceará, Brazil) represent a combination of macerated fruit jurubeba, extracts alcoholics herbs, decoctions of bitter plants, cane sugar syrup and ethanol. Users highlight the medicinal properties of the plant and its qualities liver, digestive, tonic and aphrodisiac.

Justifying the numerous medicinal properties, some of the chemical constituents of jurubeba used are the alkaloids (jurubebina, jubebina, isojuripidina); the solaninas (solamina, solanidina, solasodine); resins (jupebina and jupebenina); saponins (isojurubidina, isopaniculidina, and isojurupidina jurubidina); steroidal nitrogenous compounds (paniculina, jurubina); aglycone; fatty acids; organic acids; glycosides (paniculoninas A and B), and mucilages, and bitter principles (Ripperger 1966; Ripperger et al., 1967; Blankemeyer et al., 1998; Mesia-Vela et al., 2002). Phytochemical analysis performed with the ethanol extract of root jurubeba also indicate the existence of flobabênicos tannins (condensed or catechin tannins), flavonols, flavanones, free pentacyclic triterpenoid and saponins (Cordeiro, 2008). In various phytochemical studies of the genus

Solanum species, many alkaloids have been isolated as described earlier, as well as a large variety of steroids, saponins, glycoalkaloids and flavonoids which are important in the natural defense of plants and have various biological activities (Silva et al., 2005; Cheng et al., 2008; Li et al., 2014; Mannanase et al., 2012; Miranda et al., 2013; Pinto et al., 2013; Zhang et al., 2013). A study by Lôbo (2009) detected an average tanífero 4.6% (46g TC/kg of DM) of *S. paniculatum* root, using the Stiasny method (Guangcheng et al., 1991), adapted by Paes et al. (2006).

By fractionation of the ethanol extracts (70%) of aerial parts (leaves and branches) of *S. paniculatum*, Vieira Junior et al. (2014) isolated new saponins, (22R, 23S, 25R) 3b, 6a, 23-trihydroxy-5a -spirostane 6-OBD-xylopyranosyl-O- [bD-quinovopyranosyl - O- [al-rhamnopyranosy - OBD-quinovopyranoside (1) and diosgenin 3-OBD-glucopyranosyl-ObD-glucopyranoside (2) as well as four known components: caffeic acid (3), diosgenin bD-glucopyranoside (4), rutin (5) and quercetin 3-OaL -ramnopiranosil-ObD-glucopyranoside (6).

Macedo-Costa et al. (2014) and Macedo-Costa (2016) analyzed the extract from the root of *S. paniculatum* by preliminary phytochemical screening and fingerprints Thin-Layer chromatography (TLC) with different developers in order to identify the classes of secondary metabolites. The pharmacological results confirm previous studies, and revealed the presence of phenols (among which strokes pyrogallol tannins and flavonoids), gums, lactones and alkaloids (in the presence of reactive Dragendorff and Bertrand), and saponins. Qualitative analysis of phenols in relation to flavonoids and tannins, met suggestive spot isovitexin and tannic acid, respectively.

ANTIMICROBIAL POTENTIAL

In view of the potential antimicrobial activity of these compounds was evaluated *in vitro* action on planktonic *S. paniculatum* oral microorganisms and organized in biofilms. Macedo-Costa et al. (2014) evaluated the antibacterial action of *S. paniculatum* root extract on endogenous oral bacteria in planktonic form: *Streptococcus mitis*, *Streptococcus mutans, Streptococcus sanguinis, Streptococcus oralis, Streptococcus salivarius* and *Lactobacillus casei*. The extract showed minimum inhibitory concentration (MIC) of 7.81 mg / mL, minimum inhibitory concentration of adherence (MICA) of 62.5 mg / mL and bactericidal in the concentration of 500 mg / ml in 2 h of contact with *S. mutans* and MIC for 4 h. This study also evaluated the action of crude extract and diluted MIC of *S.paniculatum* on microorganisms in mixed culture in planktonic form and organized in biofilms, from human saliva. It was observed that the crude extract of jurubeba presented antimicrobial activity on the microorganisms in mixed culture in planktonic form and organized in biofilms, however, considering its MIC did not present such action.

Macedo-Costa (2016) also evaluated the antimicrobial activity of *S. paniculatum* on superinfecting microorganisms of the oral environment: *Enterococcus faecalis* and *Candida* albicans ATCC (American Type Culture Collection) and clinical isolates. *S. paniculatum* presented bacteriostatic and fungistatic action, and there was a statistically significant difference between the extract and the positive control (chlorhexidine digluconate 0.12% and Nystatin 100,000 IU) to dilutions/concentrations: 1: 64/7.81 mg/mL (*E. faecalis* ATCC), 1:32/15.65 mg/mL (*E. faecalis* isolated from the oral environment - AB) 1:128/3.90 mg/mL (*C. albicans* AB) and 1:64/3.90 mg/mL (*C. albicans* ATCC). Non-stick action (1:512/0.97 mg/mL) was seen to be higher than controls and bactericidal.

Lôbo et al. (2010) and Pereira et al. (2010) found the antibacterial action of roots of *S. paniculatum* of *S. aureus* (ATCC, and bovine), *Escherichia coli* and *Pseudomonas aeruginosa*. Valadares et al. (2009) evaluated *in vitro* antiviral activity of leaf extract of *S. paniculatum* Herpes virus type I (HSV-1), murine encephalomyocarditis virus (EMCV), and vaccinia virus. *S. paniculatum* inhibited the replication of HSV-1 (50% effective concentration antiviral = (298.0 ± 11.2) g/mL) and showed no effect on the EMCV and VACV.

Different doses (31.25 to 500 mg/kg) of ethanolic extract of leaves of *S. paniculatum* were evaluated against induced gastric ulcer in rats. The lowest dose of the extract was able to promote anti-ulcer effect which was 125 mg/kg. Treatment with *S. paniculatum* orally was able to decrease the area of gastric lesion, and also reduce levels of myeloperoxidase (MPO) in the gastric mucosa (Vieira-Júnior et al., 2014). Endringer et al. (2010) found Brazilian plants with anti-inflammatory activity, among which *S. paniculatum* are promising sources of chemopreventive agents of cancer. However, studies are needed to identify the active principles that are related to this pharmacological action.

With respect to toxicity, Vieira et al. (2010) evaluated the cytotoxic and mutagenic activities of ethanolic extracts of leaves and fruits of *S. paniculatum*, using the micronucleus test in bone marrow of mice. The results indicated that the ethanol extracts, both the leaves as the fruits of *S. paniculatum* showed no mutagenic action in bone marrow of mice, but at higher doses, both extracts showed cytotoxic activity. However, this study did not show an increase in cytotoxicity dose-response of 200 and 300 mg/kg.

The acute toxicity of root *S. paniculatum* in mice by determining the lethal dose (LD50) and the cytotoxic potential of human erythrocytes were assessed according to the study of Macedo-Costa et al. (2014). The extract did not cause mortality in any of the tested concentrations (500 mg / ml-0.97 mg / ml) after 24, 72 h and 15 days. As the major behavioral changes observed in mice treated

with the extract at times 30, 60, 90 and 240 min, and piloerection were observed only intense movements vibrissae until the first 60 min until the concentration of 31.25 mg / ml (dilution 1:16).

There were no serious side effects, and the animals showed only minor behavioral changes suggestive of CNS stimulation. In cytotoxicity assessment, it was observed in this study that *S. paniculatum* induced a low hemolytic activity (less than 50%) compared to 158 of human erythrocytes types A, B, O and AB at a concentration of 7.81 mg/mL (MIC), however showed cytotoxicity at a concentration of 250 mg/mL (dilution 1:2).

CONCLUSION

Several studies have shown that *S. paniculatum* Linn presents bacteriostatic activity, fungistatic, nonstick, bactericidal, fungicidal and antiviral *in vitro* on microbial suspension monoculture, mixed culture planktonic and biofilm on multispecies justified by pharmacological findings. Virtually no deleterious effects in preclinical toxicological, enabling the completion of a randomized controlled trial and stimulating research of bioactive natural substances for the treatment of oral infections associated with endogenous and superinfecting microorganisms was shown. Clearly, there is great potential for the use of therapeutically relevant compounds from nature. These should be the result of interdisciplinary collaboration based on empirical knowledge from the "healers", "bushmen", "mourners", herbalists, healers, shamans and others; combined with ethnopharmacology, botany, chemistry of natural compounds, microbiology and pharmacology to minimize the gap between *in vitro* and *in vivo*, providing clinical efficacy and safety in humans. Until then some progress has been achieved, but there is still a long way to overcome.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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