

Anti Herpesviral Activity of Medicinal Plants Indicated to Treat Oral Diseases

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Abstract

Oral diseases constitute a serial public health problem. Periodontitis, one of the main oral diseases, has bacteria as the most prevalent agent, although today it is known that there are multiple factors that interfere with the installation and evolution of periodontics' disease. Herpesvirus infections, for example, lead to a drop in local immunity that can consequently lead to the multiplication of pathogenic bacteria and destructive periodontal disease. Within this problem, the importance of treatments of broad spectrum is stressed: bacteria, viruses, and the immune system. In this case, medicinal plants, recognized for their therapeutic action and the presence of a variety of metabolites are candidates for validation of their popular use. In this work we describe the *in vitro* anti herpesvirus study of four medicinal plants indicated to treat oral disease by a cocoa region community. Plants were collected in the field and ethanolic extracts were obtained from dried leaves of *Schinus terebinthifolius* (Anacardiaceae), *Cajanus cajan* (Fabaceae), and *Tamarindus indica* (Fabaceae). As a herpesvirus model, suid and equid herpesvirus were used. The best activity was seen for *C. cajan* against suid herpesvirus (96.84% of inhibition) at a concentration of 75µg/mL. However, the results presented here encourage further *in vitro* and *in vivo* tests in search of preventive or adjuvant therapies in the treatment of oral disease..

Keywords: Cytotoxicity; Antiviral; Periodontitis; Herpesviridae

Introduction

Periodontitis is an oral disease that affects a large proportion of the population worldwide [1]. Although it has been considered for many years as a bacterial disease, today periodontal disease is considered a multifactorial and multi-microbial inflammatory disease affecting periodontal tissues [2].

The maintenance of a stable periodontal environment depends on the balance between the presence of beneficial and pathogenic bacterial species and between protective or destructive immune responses [3,4]. Thus, the alteration of the microbiota balance is a crucial point in understanding the etiopathogeny of periodontal

disease [5]. In addition, the presence of viruses plays a key role in this context and they are significantly associated with the implementation of bacterial periodontitis [6].

Herpesvirus infection, for example, may cause a drop in local immunity which can consequently lead to the multiplication of pathogenic bacteria and destructive periodontal disease [7]. Specifically, macrophages infected with viruses such as cytomegalovirus or Epstein-Barr have a reduced response to bacterial challenges [8]. In addition, herpesvirus proteins can serve as new adhesion sites for periodontopathic bacteria facilitating their adhesion and multiplication [9].

Within this problem, the importance of treatments with multiple performance spectrum (bacteria, viruses, and immune system) is highlighted. In this case, medicinal plants, recognized by their therapeutic action and the presence of a variety of metabolites, are strong candidates.

In this report the specific anti herpes viral *in vitro* action of three medicinal plants indicated for oral diseases by Southern Bahia - Brazil - community is described.

Methodological procedures

Botanical material

Schinus terebinthifolius Raddi (Anacardiaceae), *Cajanus cajan* (L.) Mills (Fabaceae), and *Tamarindus indica* L. (Fabaceae) leaves were collected from trees located in public areas of Una municipality (state of Bahia, Brazil) [lat: -15.299167 long: -39.045556 WGS84, 6 m], between April and September, 2017. Plant materials were identified and registered at Universidade Estadual de Santa Cruz herbarium under voucher number HUESC-23.560; HUESC-23.605, HUESC-23.582, respectively.

Leaves were washed, dried, and powdered. The extract of each plant was obtained by decoction and submitted to lyophilization. For use in cytotoxicity and antiviral tests, lyophilized extracts were weighed, diluted in minimal essential medium (Gibco® by Life Technologies) and filtered in sterile membranes with pores of 0.22 µm Biofil®. A 10 mg/mL concentration of extracts were distributed in sterile polypropylene microtubes and stored at 4°C until use.

Cytotoxic and antiviral assay

The cytotoxic and antiviral essays were done using the Vero cell line (ATCC-CCL81) and followed the technique described by Silva et al. [10]. For that, cells were maintained in minimal essential medium (MEM) supplemented by 10% bovine fetal serum. To perform both cytotoxic and antiviral tests, cells were seeded in 96 well plates 24 hours before tests. Cytotoxicity was evaluated by minimal non-cytotoxic concentration, (MNCC) method through cell integrity visualisation. Extracts were solubilized at concentrations ranging from 12.5 to 500 µg/mL. MEM and dimethylsulfoxide (DMSO) 2% were used as control. The final cell visualization was performed after 48 h incubation time.

The antiviral activity against type 1 suid (SuHV- 1; Nova Prata strain) and equid (EHV-1; A4/72 strain) herpesvirus was determined by the viral Median Tissue Culture Infectious Dose (TCID₅₀) was identified and values were obtained by comparing non-treated infected cells and treated infected cells TCID₅₀ [11]. Results were expressed as viral inhibition index (VII) [12]. Also the inhibition percentage (IP) was calculated using the anti-logarithmic TCID50: $PI = (1 - \text{antilog}T/\text{antilog}C) \times 100$ where T corresponds to the virus titer of the extract treated cells and C is the viral titer of the untreated cells [13].

Results, Discussion and Conclusion

In the medicinal plants field, there is still a great distance between the biological potential revealed in the popular culture and the proof of the declared biological potential or existing potentials in the substances present in these plants. The study of therapeutic and pharmacological properties is still scarce, especially with regard to their cytotoxicity profile [14] and knowledge of the effect of plant extracts on human and animal cells, has been the starting point in pharmacognosy research [15].

In the present study, the antiviral activity of the three medicinal plants indicated to treat oral diseases in the Southern Bahia, Brazil community showed distinguished anti herpesviral action against suid herpesviral at *in vitro* suitable extract concentration. Furthermore, the results of the *Cajanus cajan* leaves aqueous extract antiviral activity are outlined in Table 1.

In the Southern region of the state of Bahia, *Tamarindus indica* leaves tea was reported as having traditional usage on toothache treatment [16,17]. In addition, the tamarind ingestion in the diet can regulate fluoride, copper, and calcium clearance [18]. Thus, it is suggested here to deepen the chemical and biological studies of this plant.

As well as *T. indica*, *Cajanus cajan* was also reported in the treatment of toothache by the population of the Cachoeira River [16] and Una community [17] in the Southern of Bahia; besides, *C. cajan* is a Brazilian plant cited in the literature due to its use in primary health care against allergic disorders and gastritis [19].

Family	Plant species	Popular name	MNCC ($\mu\text{g/mL}$)	VII (PI)	
				EHV	SuHV
Anacardiaceae	<i>Schinus terebinthifolius</i>	Pepper tree	50	0.74 (81.80%)	0.74 (81.80%)
Fabaceae	<i>Cajanus cajan</i>	Andu	75	NI	1.5 (96.84%)
Fabaceae	<i>Tamarindus indica</i>	Tamarind	25	NI	1 (90%)

Table 1: Antiviral activity of medicinal plants indicated to treat oral diseases by Southern Bahia, Brazil, community.

MNCC: Minimal Non Cytotoxic Concentration; NI: No Inhibition; EHV: Equid Herpesvirus; SuHV - Suid Herpesvirus

Schinus terebinthifolius Raddi, the third plant cited by communities of Southern Bahia, showed a less prominent *in vitro* anti herpesvirus activity when compared with the other two plants tested. Interestingly, although frequently cited by communities, *in vitro* [20] and *in vivo* [21] show only mild activity as it was found for antiviral potential. For this plant it would be interesting to continue the evaluation of its potential in the treatment of oral diseases with higher doses in view of two aspects: 1) the acute and subacute oral administration of the dried extract of other part of *Schinus terebinthifolius* did not produced toxic effects in Wistar rats [22], and 2) using the IC_{50} method with the present aqueous extract we obtained non-toxic concentrations of 125 $\mu\text{g/mL}$ (unpublished data).

In addition, there are two important aspects in the interference of plants in viral infection: preventive and adjuvant. The ethanolic extract of *Melissa officinalis* [23] and *Terminalia chebula* [24], for example, acting on the adhesion and penetration of resistant and acyclovir-sensitive HSV can prevent clinical infection or the administration of nucleoside analogues supplemented with natural products may be an effective strategy in the treatment of lytic or latent herpetic infection [25].

Thus, in view of the results obtained here, the importance in the continuity of *in vivo* studies and in a context of broad microbial spectrum is highlighted.

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