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Original Article

Warifteine, an alkaloid of *Cissampelos sympodialis*, modulates allergic profile in a chronic allergic rhinitis model

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ABSTRACT

Cissampelos sympodialis Eichler, Menispermaceae, a Brazilian medicinal plant and its alkaloid warifteine present immunomodulatory activity on asthma experimental model by reducing antigen-specific IgE levels, eosinophil infiltration and lung hyperactivity. Allergic rhinitis is a chronic inflammatory disorder of the nasal tissue that affect the quality of life and it is a risk factor for asthma exacerbation. This study evaluated the effect of inhaled warifteine in an allergic ovalbumin rhinitis model. Inhaled warifteine (2 mg/ml) treatment of ovalbumin-sensitized BALB/c mice significant decreased total and differential number of cells on the nasal cavity and decreased ovalbumin-specific IgE serum levels. Hematoxylin & eosin staining of histological preparations of ovalbumin nasal tissues showed changes such as congestion and a massive cell infiltration in the perivascular and subepithelial regions characterizing the nasal inflammatory process. However, inhaled warifteine or dexamethasone treatment decreased cell infiltration into the perivascular regions and it was observed an intact nasal tissue. Periodic acidic staining of nasal epithelium of ovalbumin animals demonstrated high amount of mucus production by goblet cells and inhaled warifteine or dexamethasone treatment modulated the mucus production. In addition, toluidine blue staining of the nasal epithelium of ovalbumin animals demonstrated an increase of mast cells on the tissue and inhaled warifteine or dexamethasone treatment decreased in average of 1.4 times the number of these cells on the nasal epithelium. Taken these data together we postulate that warifteine, an immunomodulatory alkaloid, can be a medicinal molecule prototype to ameliorate the allergic rhinitis conditions.

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Introduction

Medicinal plants and their bioactive components are alternative options to therapies for many diseases. In Brazil, with its enormous biodiversity, the search for new natural products and bioactive molecules is an important goal. *Cissampelos sympodialis* Eichler Menispermaceae, popularly known as “jarrinha” or “milona” is found in Northeastern and Southeast of Brazil and a hot water infusion of its root bark is largely used by indigenous and northeastern population to treat several inflammatory disorders, including

asthma, bronchitis, colds and rheumatism (Barbosa-Filho et al., 1997).

Menispermaceae family is well known for producing different types of alkaloids (De Freitas et al., 1996; Barbosa-Filho et al., 2000). In general, alkaloids present a variety of biological activities such as apoptosis and NFκB signaling inhibition in macrophages (The et al., 1990; Thomas et al., 1997), anti-inflammatory and analgesic effects (Costa et al., 2008) and anti-allergic effect (Bezerra-Santos et al., 2012; Vieira et al., 2013; Ribeiro-Filho et al., 2013). Phytochemical analysis of *C. sympodialis* root extracts leads to isolated several alkaloids including warifteine that showed pharmacological effects such as decreasing the allergic process on the experimental model of asthma (Bezerra-Santos et al., 2006).

Warifteine showed to present immunomodulatory effect (Costa et al., 2008) by reducing the plasma levels of total and

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ovalbumin (OVA)-specific IgE, the eosinophilic infiltration into the bronchoalveolar and pleural cavities, the lung hyperreactivity and inducing INF- γ production in OVA sensitized BALB/c mice (Bezerra-Santos et al., 2004). Related to the potential anti-asthmatic effects of *C. sympodialis* and its alkaloid, recent published data showed that inhaled *C. sympodialis* extract or warifteine on OVA-sensitized BALB/c mice down-regulated airway allergic reaction by reducing lung CD3⁺ T cells and pulmonary hyperactivity (Vieira et al., 2013) on the lung tissue. Therefore, *C. sympodialis* or warifteine effects on allergic rhinitis, a related asthma disease, have not been addressed.

Allergic rhinitis (AR) is defined as an inflammation of the membranes lining the nasal cavity and it is characterized by the following allergic symptoms: sneezing, itching, rhinorrhea, nasal congestion as well as invasion of nasal mucosa by inflammatory cells (Mandhane et al., 2011). A type 2 immune response characterizes AR where the Th2 cell profile predominates as well as eosinophils, mast cells, basophils and macrophages (Palm et al., 2012). The Th2 response is mediated by IL-4, IL-5 and IL-13 and allergic specific immunoglobulin E (IgE) attached to granulocyte cell receptors such as mast cells or circulating basophils. In addition, the AR symptoms occur when the allergen binds to IgE attached to these cells and occurs the release of inflammatory mediator such as histamine, prostaglandins and leukotrienes (Broide et al., 2011).

The incidence of AR has increased in recent years all over the world. Epidemiological surveys indicate that 10–40% of the population, in industrialized and developing countries presents symptoms of rhinitis and its prevalence is about 1.46 billion people worldwide (Véron, 2015). Although AR is not a lethal condition, it can affect quality of life and it is a risk factor for both the development and the exacerbation of asthma (Compalati et al., 2010).

It is well known that antihistamine, anticholinergic agents, intranasal corticosteroids, oral anti leukotrienes and mast cell stabilizers are effective for AR treatment (Stokes et al., 2012) although these treatments can induce adverse side effects including sedation, impaired learning/memory, cardiac arrhythmias and drug tolerance making AR to be less easily control (Mandhane et al., 2011). Therefore, treatments with molecules with potential therapeutic target that causes better effect and less drug tolerance or side effects for AR needs to be explored and developed.

An alternative to ameliorate such condition is medicinal plants and in this scenario the aim of this study was to evaluate the effect of intranasal administration of warifteine, an alkaloid from *C. sympodialis*, as a therapeutic protocol, in an experimental model of allergic rhinitis.

Materials and methods

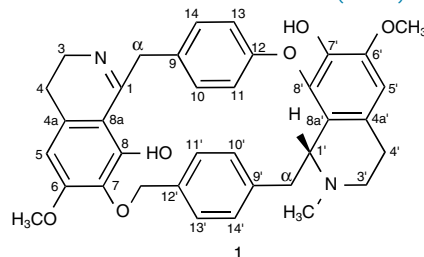
Animals

Isogenic female BALB/c mice (6–8-week-old), weighing between 25 and 30 g, and female Wistar rats, weighing on an average 200 g, were used in the experiments. The animals were kept in cages at a temperature of $22 \pm 2^\circ\text{C}$, 12/12-h light–dark cycle with free access to water and a controlled diet, based on pellets, throughout the trial period. The Animal Facility of the Federal University of Paraíba, Brazil supplied the animal strains. Animal manipulation was performed according to animal care guide and the Committee for Experimentation on Animal Research of UFPB (CEUA N°. 3505/14) approved the experimental protocols. The animals were euthanized with ketamine hydrochloride solution.

Plant material

Cissampelos sympodialis Eichler, Menispermaceae, were obtained from the Botanical Garden of Federal University of

Paraíba (voucher specimen Agra 1456). Warifteine (**1**) identification was performed by ^1H and ^{13}C NMR spectral analyses comparing with those published data (Cerqueira-Lima et al., 2010). The alkaloid was quantified in the leaf extract (CsE) by means of High Performance Liquid Chromatography (HPLC) with ultraviolet detection and it was 96.4% pure. The warifteine solution was prepared using 1 mg of the crystal in 50 μl of HCl 1 N and 800 μl of distilled water. The pH was adjusted to 7.0 with NaOH 1 N and the volume was completed to 1000 μl (Costa et al., 2008). The WAR dose (2 mg/ml) and route (inhaled) for the treatment used in this work was based on studies from Vieira et al. (2013).



Treatment

Four groups ($n=6$) of female BALB/c mice were used in all experimental protocols, and they were divided into saline group (non-sensitized animals), OVA group (OVA-sensitized animals), WAR (**1**) group (OVA-sensitized animals and treated with 2 mg/ml of warifteine), Dexamethasone (DEXA) group (OVA sensitized animals and treated with 2 mg/ml of dexamethasone).

Allergic rhinitis protocol

Mice were ovalbumin sensitized (50 μg OVA emulsified in 5 mg Al (OH) $_3$) on days 0 and 7th by intraperitoneal (i.p.) injection. After a week, mice were challenged by nasal instillation of 50 μg OVA on three successive days in a week for three consecutive weeks (between day 14th to day 35th). Two weeks later, mice were re-challenged seven times (from day 49th to day 55th). The OVA, DEXA or WAR groups were treated with inhaled saline, dexamethasone or warifteine 1 h before OVA re-challenge from day 49th to day 55th. Twenty-four hours after the last challenge on day 56th (Fig. 1), the animals were euthanized (Tranquilli et al., 2007) and the nasal cavity lavage fluid (NALF) was collected. The total cell counts were performed in a Neubauer chamber, using an aliquot of diluted samples (1:20) in Turk solution in an optic microscope (40 $\times$ objective). For differential counts, samples from each NALF of each group were centrifuged on cytospin slides at 1500 rpm for 10 min. The slides were stained with panoptic solution (Panoptic methods/Auto-Hemacolor[®]) and the cells were quantified in a light microscopy. Each slide was analyzed until the count of 100 cells was reached using oil-immersion objective (Wang et al., 2013).

OVA-specific IgE titer

The serum of each animal from each group was collected from vessels of the brachial plexus. Blood was collected with Pasteur pipette, impregnated with heparin to prevent blood clotting, stored in Eppendorf type tubes inclined at 45 degrees to facilitate clots and then collected the serum that was stored at -20°C until used. The OVA-specific IgE titer was determined using the passive cutaneous anaphylaxis (PCA) test. The PCA reaction was performed as follows: 50 μl of serum from each animal was injected by dermal route on the shaved back of Wistar rats. After 24 h, the rats were anesthetized with hydrochloride (270 mg/kg i.p.), and their tails

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