



Therapeutic and technological potential of 7-chloro-4-phenylselanyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice



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ABSTRACT

This study investigated the main effects of the oral treatment with 7-chloro-4-phenylselanyl quinoline (4-PSQ) on symptoms, inflammatory and oxidative parameters in an atopic dermatitis (AD) model in BALB/c mice. In addition, the possibility of antioxidant property of 4-PSQ improves the potential of a biofilm (based on chitosan/poly(vinyl alcohol) (PVA)/ bovine bone powder (BBP)) for the treatment of AD-like skin lesions was evaluated. 2,4-Dinitrochlorobenzene (DNCB) was applied to the dorsal skin on days 1–3 for sensitization. Mice were challenged with DNCB on the ear (on days 14–29) and dorsal skin (on days 14, 17, 20, 23, 26, and 29) and treated with 4-PSQ, dexamethasone, biofilm (biofilm sample without 4-PSQ) or 4-PSQ-loaded biofilms. On the day 30, skin severity scores and scratching behavior were determined. After that, animals were sacrificed, and ears and dorsal skin were removed for determination of inflammatory and oxidative parameters. DNCB induced the skin lesions, scratching behavior and ear swelling, increased myeloperoxidase (MPO) activity (ear and back) and reactive species (RS) levels (back). 4-PSQ, 4-PSQ-loaded biofilms and biofilm treatments ameliorated skin severity scores, scratching behavior and inflammatory response induced by DNCB. 4-PSQ and 4-PSQ-loaded biofilm treatments partially protected against the increase in the RS levels induced by DNCB. Our results revealed that the incorporation of 4-PSQ improved the therapeutic effect of the biofilm. The efficacy of 4-PSQ in treating AD-like lesions was similar or better than dexamethasone. In summary, 4-PSQ has a potential therapeutic advantage in the treatment and management of AD.

1. Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that is characterized by intense itching and recurrent eczematous lesions. Patients with AD suffer from severe psychological stress, which markedly increases the prevalence rate of depression and anxiety disorders in later life [1]. The manifestation of AD is rising dramatically, especially in developed countries, and it now affects up to 30% of children and 10% of adults [2–4]. AD attacks are characterized by wound with intensely pruritic erythematous papules associated with excoriation and serous exudates. The skin affected by AD has redness and itching in the responsive skin, as well as excessive scratching can cause skin wounds and fluid leakage [5].

Treatment of AD consists mainly of steroids, such as

dexamethasone, applied to the skin [6]. However, steroids are immunosuppressants and increase the risk of bacterial infection [7]. Furthermore, long-term use of topical steroids also leads to thinning of the skin and to cracking and bleeding [8]. Therefore, these numerous side effects have disadvantaged long-term use of therapies used to AD [9]. In this way, there is a great need to develop new and effective treatment and strategies for AD.

Quinolines are synthetic or natural heterocyclic compounds with interesting biological activities [10–16]. Compounds with quinoline in their structure are receiving great attention in studies for the treatment of inflammatory diseases [17–19]. In turn, the essential element selenium (Se) is of fundamental importance to human health. As a constituent of the small group of selenocysteine containing selenoproteins, Se elicits important structural and enzymatic functions [20]. Dietary Se,

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plays an important role in inflammation and immunity. Adequate levels of Se are important for initiating immunity, but they are also involved in regulating excessive immune responses and chronic inflammation [21].

Based on major pharmacological properties of quinolines derivatives and Se, our research group targets the design of the 7-chloro-4-phenylselenanyl quinoline (4-PSQ), with the objective of structural improvement. A literature survey indicates that only a few publications have mentioned the incorporation of a selenium atom in the quinoline nucleus [22–24]. Consequently, synthesis and biological screening of selenoquinoline derivatives may be considered a relevant research area. Indeed, 4-PSQ revealed potential antioxidant, antinociceptive and anti-inflammatory actions [22,25]. Recently, our research group demonstrated that a single dose of 4-PSQ exerts anxiolytic activity in mice [23]. 4-PSQ exerts pharmacological actions without causing locomotor disorders and kidney, liver and brain toxicities [22,23].

In view of our continued interest in the pharmacology of this compound, the first objective of this study was to evaluate the effects of oral treatment with 4-PSQ on AD-like lesions induced by DNCB in mice. In line with our results of the first set of experiments, we were motivated to evaluate if the antioxidant property of 4-PSQ could improve the potential of a biofilm previously studied by our research group for the treatment of AD-like skin lesions.

2. Materials and methods

2.1. Animals and ethical approval

The experiments were conducted using female BALB/c mice (6–8 weeks old). Animals were kept in a separate animal room, on a 12 h light/dark cycles, with lights on at 7:00 a.m., at room temperature (22 ± 1 °C), with free access to food and water. The biological assays were conducted according to the institutional and national guidelines for the care and use of animals. The Local Committee for Care and Use of Laboratory Animals of the Federal University of Pelotas (Pelotas, Brazil) approved the research (Code number: 4294-2015). The number of animals was the minimum necessary to demonstrate the consistent effects of the drugs treatments and all efforts were taken to minimize their suffering.

2.2. Chemicals and drugs

DNCB was obtained commercially and it was used as an inductor of AD. 4-PSQ (Fig. 1) was prepared and characterized in our laboratory by the method previously described by Duarte et al. [24]. Analysis of the ^1H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with 4-PSQ assigned structure. The chemical purity of 4-PSQ (99.9%) was determined by GC/MS. Dexamethasone was

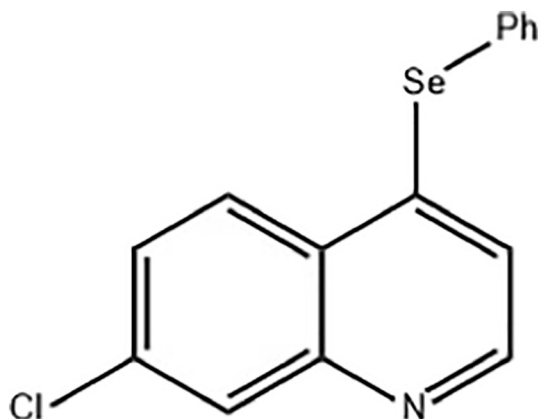


Fig. 1. Chemical structure of 4-PSQ.

obtained commercially and it was used as a reference drug. For oral treatment, 4-PSQ was dissolved in canola oil, while dexamethasone was dissolved in 0.9% saline solution. The oral administration (p.o.) of 4-PSQ or dexamethasone was by intragastric gavage, at a constant volume of 10 ml/kg body weight. For topical treatment, 4-PSQ was loaded into a biofilm (as described below) and applied as a bandage.

Chitosan 85% deacetylated was purchased from Golden-Shell Biochemical (China). Poly(vinyl alcohol) (PVA) with M_w of 124,000 g/mol and 99% hydrolyzed was purchased from Sigma-Aldrich (USA). Sodium tripolyphosphate (TPP, $\text{Na}_5\text{P}_3\text{O}_{10}$) and acetic acid were purchased Synth (Brazil). Bovine bone powder (BBP, particle size < 80-mesh) was obtained according to the protocol described by Alves et al. [26]. All other chemicals of analytical grade were used as received without further purification.

2.3. Synthesis of 4-PSQ-loaded biofilms

The 4-PSQ-loaded biofilms were synthesized using conventional solvent casting method. PVA (200 mg) was solubilized in distilled water (30 ml) at 75 °C for 4 h under stirring. Separately, chitosan (600 mg) was solubilized in acetic acid solution (30 ml, 2 v/v-%) at room temperature for 1 h. These two solutions were blended at room temperature and, then, BBP (40 mg) was added to the system. This resulting system was stirred for 30 min. Next, 4-PSQ (80 mg) was added under vigorous stirring for 15 min at room temperature. The biofilmogenic solution was poured into Petri dishes (polystyrene, round-plate shape 85×10 mm) and the solvent was evaporated in an oven (40 °C for 48 h). The as-dried biofilm was peeled off from the Petri dishes and physically crosslinked by immersion in TPP solution (10 wt/v-%) for 1 h. During this step, the pH of the crosslinking medium was adjusted to 4 using HCl (1 M). Then, the crosslinked biofilms were soaked in NaOH solution (0.5 M) for a short while and subsequently, washed several times with distilled water up to neutral pH. Finally, the biofilms were oven-dried (40 °C for 24 h) to a constant weight. A biofilm sample without 4-PSQ was synthesized using a similar procedure.

2.4. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of pure 4-PSQ, 4-PSQ-loaded biofilm, and pristine biofilm were recorded using a Shimadzu spectrometer (model Affinity, Japan) operating in the spectral region of $4000\text{--}600\text{ cm}^{-1}$ with a resolution of 4 cm^{-1} . The samples were ground with spectroscopic grade KBr and pressed into disks.

2.5. Experimental protocol

AD-like skin lesions in mice were induced by DNCB as previously described [27]. Mice were shaved of dorsal hair and 200 μl of 0.5 v/v-% DNCB in acetone/olive oil (3:1 ratio) was applied to the shaved area on experimental days 1–3 for sensitization. Mice were challenged with 20 μl of 1 v/v-% DNCB on the ear on days 14–29 and 200 μl on the dorsal skin on days 14, 17, 20, 23, 26, and 29 (Fig. 2). Mice were randomly divided into six groups ($n = 8\text{--}10$ animals/group): normal control mice (control group) were sensitized and challenged with acetone/olive oil (3:1); sensitized control mice (DNCB group) were sensitized and challenged with DNCB; and experimental mice were sensitized and challenged with DNCB and received the treatment with 4-PSQ at the dose of 5 mg/kg, biofilm (biofilm sample without 4-PSQ), 4-PSQ-loaded biofilms or dexamethasone at dose of 5 mg/kg (groups designated as DNCB + 4-PSQ; DNCB + biofilm; DNCB + biofilm-4-PSQ and DNCB + DEXA). Oral treatment with 4-PSQ or dexamethasone was by intragastric gavage, daily, from days 14 to 29. In order to compare with the 4-PSQ effect, the dose of dexamethasone used was 5 mg/kg. Biofilms treatments were applied in the dorsal region of animal and secured with a bandage starting on 14th day. On DNCB application days (14, 17, 20, 23, 26, and 29) in the dorsal region, the

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