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Evaluation of mutagenic and antimutagenic activities of α-bisabolol in the *Salmonella*/microsome assay

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Abstract

α-Bisabolol (BISA) is a sesquiterpene alcohol found in the oils of chamomile (*Matricaria chamomilla*) and other plants. BISA has been widely used in dermatological and cosmetic formulations. This study was undertaken to investigate the mutagenicity and antimutagenicity of BISA in the *Salmonella*/microsome assay. Mutagenicity of BISA was evaluated with TA100, TA98, TA97a and TA1535 *Salmonella typhimurium* strains, without and with addition of S9 mixture. No increase in the number of *his*$^+$ revertant colonies over the negative (solvent) control values was observed with any of the four tester strains. In the antimutagenicity assays, BISA was tested up to the highest nontoxic dose (i.e. 50 and 150 μg/plate, with and without S9 mix, respectively) against direct-acting (sodium azide, SA; 4-nitroquinoline-*N*-oxide, 4-NQNO; 2-nitrofluorene, 2-NF; and nitro-*o*-phenylenediamine, NPD) as well as indirect-acting (cyclophosphamide, CP; benzo[*a*]pyrene, B[*a*]P; aflatoxin B1, AFB1; 2-aminoanthracene, 2-AA; and 2-aminofluorene, 2-AF) mutagens. BISA did not alter mutagenic activity of SA and of NPD, and showed only a weak inhibitory effect on the mutagenicity induced by 4-NQNO and 2-NF. The mutagenic effects of AFB1, CP, B[*a*]P, 2-AA and 2-AF, on the other hand, were all markedly and dose-dependently reduced by BISA. It was also found that BISA inhibited pentoxyresorufin-*o*-depentylase (PROD, IC_{50} 2.76 μM) and ethoxyresorufin-*o*-deethylase (EROD, 33.67 μM), which are markers for cytochromes CYP2B1 and 1A1 in rat liver microsomes. Since CYP2B1 converts AFB1 and CP into mutagenic metabolites, and CYP1A1 activates B[*a*]P, 2-AA and 2-AF, results suggest that BISA-induced antimutagenicity could be mediated by an inhibitory effect on the metabolic activation of these promutagens.

Keywords: Sesquiterpenes; α-Bisabolol; Mutagenicity; Antimutagenicity; *Salmonella typhimurium*; Ames test

1. Introduction

(−) α-Bisabolol (1-methyl-4(1,5-dimethyl-1-hydr oxhex-4(5)-enyl)-cyclohexen-1; CAS Nr. 23089-26-1) (BISA) is a monocyclic sesquiterpene alcohol (Fig. 1)

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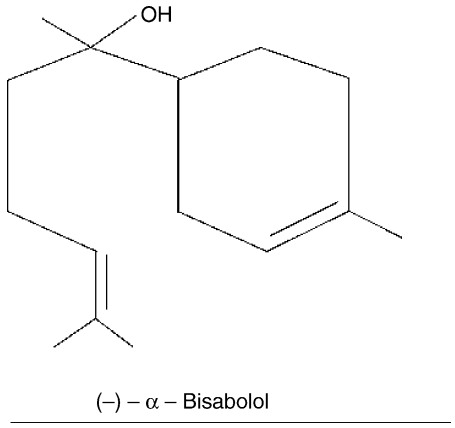

Fig. 1. Molecular structure of α-bisabolol, a sesquiterpene alcohol ($C_{15}H_{26}O$).

found in the essential oils of a variety of plants such as chamomile (*Matricaria chamomilla*, Compositae, syn. *M. recutita*), arnica (*Arnica amplexicaulis* and *A. chamissonis*), salvia (*Salvia stenophylla*) and others [1–3].

Owing to their pleasant floral-sweet odor and apparent harmlessness, chamomile oil and BISA have been widely used as ingredients of dermatological and cosmetic preparations such as after-shaving formulations, hand- and body-lotions, underarm deodorants, lipsticks, sun-care and after-sun products, baby and elderly people-care products and sport-creams. In some European countries, teas of chamomile have long been employed in folk medicine to treat inflammatory disorders, fever and diarrhea and for menstrual pain relief. Chamomile oil has a high content of BISA and thus findings from animal studies showing that BISA possesses anti-inflammatory, analgesic, antibiotic and gastric-protective properties seem to provide scientific support to some of the traditional uses of this plant [4–7]. Moreover, BISA has been shown to enhance transdermal penetration of several drugs [8] and to prevent skin penetration of *Schistosoma mansoni* cercaria in rodents [9].

BISA has generally been regarded as a relatively nontoxic substance for topical use on the skin, but its toxicological profile is still far from being comprehensively studied. No evaluation of BISA genotoxic potential, for instance, was found in the literature (MEDLINE data base). It has recently been reported that α-bisabolol inhibited rat and human malignant glioma cells growth and survival, at concentrations which otherwise show no toxic effect on normal glial cells, a finding that suggests its possible therapeutic usefulness as an antineoplastic agent [10]. As far as we are aware, however, no study has investigated the antimutagenic activity of this sesquiterpene alcohol.

The present study was undertaken to evaluate the mutagenic and antimutagenic activities of α-bisabolol in the *Salmonella*/microsome assay.

2. Materials and methods

2.1. Chemicals

(−)-α-Bisabolol was obtained from Farmanguinhos® (Oswaldo Cruz Foundation, Rio de Janeiro, Brazil). 4-Nitroquinoline-*N*-oxide (4-NQNO), 2-aminofluorene (2-AF), nitro-*o*-phenilene-diamine (NPD), 2-aminoanthracene (2AA), benzo-[*a*]-pyrene (B[*a*]P), cyclophosphamide (CP), aflatoxin B1 (AFB1), dimethylsulfoxide USP grade (DMSO), glucose-6-phosphate, glucose-6-phosphate-dehydrogenase, β-NADP and 7-ethoxyresorufin were all purchased from Sigma Chemical Co (St. Louis, MO, USA) and sodium azide (SA), 2-nitrofluorene (2-NF) and resorufin were from Aldrich Chemical Co. Inc. (Milwaukee, WI, USA). 7-Pentoxyresorufin was bought from Boehringer-Mannhein GmbH (Mannhein, Germany) and ethanol analytical grade from Vetec® (Rio de Janeiro, Brazil). Purity of all tested substances was 95% or higher.

2.2. Metabolic activation system (S9 mixture)

Lyophilized rat liver S9 fraction induced by Aroclor 1254 was obtained from Moltox® (Molecular Toxicology Inc., Boone, NC, USA). The S9 mixture was prepared as described in details by Gomes-Carneiro et al. [11]

2.3. Bacterial strains

TA100, TA98, TA97a and TA1535 strains of *Salmonella typhimurium* were kindly supplied by Dr. Bruce N. Ames from University of California, Berkeley, USA. For all assays, an inoculum (200 μl) of a thawed permanent culture was added to 20 ml of