Biomedicine & Pharmacotherapy 103 (2018) 1253–1261

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Tea tree oil presents *in vitro* antitumor activity on breast cancer cells without cytotoxic effects on fibroblasts and on peripheral blood mononuclear cells

Charles Elias Assmann[a], Francine Carla Cadoná[b], Beatriz da Silva Rosa Bonadiman[c], Eduardo Bortoluzzi Dornelles[a], Gabriela Trevisan[d], Ivana Beatrice Mânica da Cruz[a,d,*]

[a] Graduate Program in Biological Sciences: Toxicological Biochemistry, Federal University of Santa Maria, Santa Maria, RS, Brazil
[b] Graduate Program in Biosciences and Health, University of the West of Santa Catarina, Joaçaba, SC, Brazil
[c] Graduate Program in Biochemistry, Federal University of Santa Catarina, Florianópolis, SC, Brazil
[d] Graduate Program in Pharmacology, Federal University of Santa Maria, Santa Maria, RS, Brazil

ARTICLE INFO

Keywords:
Melaleuca alternifolia
Cytotoxicity
Apoptosis
Cell cycle
Gene expression
Locally advanced breast cancer

ABSTRACT

The purpose of this study was to investigate some possible mechanisms underlying the *in vitro* antitumor activity of tea tree oil (TTO) on human and mouse breast cancer cells (MCF-7 and 4T1, respectively) and its cytotoxicity on fibroblasts (HFF-1) and on peripheral blood mononuclear cells (PBMCs). TTO High-Resolution Gas Chromatography (HRGC) showed seventeen main constituents, such as Terpinen-4-ol, γ-Terpinene, and α-Terpinene. High TTO concentrations (≥ 600 μg/mL) showed a remarkable antitumor activity, decreasing cell viability and cell proliferation of MCF-7 and 4T1 cells. TTO at 300 μg/mL increased the number of MCF-7 cells in the early stages of apoptosis and increased the *BAX/BCL-2* genes ratio. TTO, mainly at 300 μg/mL, decreased cell growth and arrested MCF-7 cells in the S phase of the cell cycle. Lower antitumor concentrations (≤300 μg/mL) evaluated in MCF-7 and 4T1 cells were not cytotoxic to PBMCs and HFF-1. Also, TTO (300 μg/mL) was able to induce cell proliferation in fibroblasts after 72 h, indicating non-cytotoxic effect in these cells. TTO exhibited *in vitro* antitumor effect on MCF-7 and 4T1 cells by decreasing cell viability and modulating apoptotic pathways and cell cycle arrestment of MCF-7 cells. In this sense, our study provides new perspectives on the potential use of TTO for the development of new alternative therapies to treat topically locally advanced breast cancer (LABC).

1. Introduction

Melaleuca alternifolia (Maiden & Betche) Cheel (Myrtaceae), popularly known as tea tree, is an Australian native plant. Its essential oil, known as tea tree oil (TTO), is topically used in folk medicine for several treatments, such as acne vulgaris and wounds related to the herpes virus. Scientific evidence has demonstrated that TTO presents many biological properties, such as antimicrobial, antifungal, anti-inflammatory, and antitumor activity [1–5]. Moreover, TTO was suggested to reduce skin inflammation and improve healing processes [3,5].

Due to TTO bioactive chemical matrix, some studies also postulated its use to treat superficial cancer types. Some investigations reported that TTO, when applied topically, could inhibit tumor growth through its cytotoxic action by mechanisms possibly related to its skin-penetrating antioxidant components [6–8]. Terpenes are present in abundance in TTO and well-known for their positive biological activities. Terpinen-4-ol, for example, one of the main constituents of TTO, has been related to the *in vitro* inhibition of human melanoma cells growth [9].

Although there are many investigations assessing the effects of TTO or several TTO isolated components, especially on melanoma tumors, most of these studies were restricted to skin cancer cells due to the toxicity of its bioactive molecules [8]. However, a former research performed by Nielsen [10] suggested that TTO could present some important antiproliferative effect against breast cancer cells, however, the antitumor causal mechanisms remain unknown.

In fact, breast cancer is the most prevalent diagnosed cancer worldwide and the second leading cause of cancer mortality in women in the world [11]. Although there are extensive and effective treatments for some breast cancer types, including surgery, chemotherapy, radiotherapy and immunotherapy, approximately 30–40% of patients develop advanced breast cancer to either distant tumor spreading (metastasis) or locally advanced breast cancer (LABC). LABC includes primary cancers with extensive nodal or skin involvement that are not amenable to initial surgery or radiotherapy with curative intent.

* Corresponding author at 1000 Roraima Av., Building 19, Room 3101, Santa Maria, RS, 97105900, Brazil.
E-mail address: ibmcruz@hotmail.com (I.B.M.d. Cruz).

https://doi.org/10.1016/j.biopha.2018.04.096
Received 12 November 2017; Received in revised form 9 April 2018; Accepted 13 April 2018
0753-3322/ © 2018 Elsevier Masson SAS. All rights reserved.