ROLE OF INTERMEDIARY BIOMARKERS IN DETERMINING THE ANTICANCER EFFICACY OF MARINE COMPOUNDS

Jamal M. Arif*, Mohammed Kunhi1, Yunus M. Siddiqui1, Khalid A. El Sayed2, Khaled Y. Orabi3, Amal Al-Hazzani1, Mohammed N. Al-Ahdal1 and Fahad M. Al-Khodairy1

1Biological and Medical Research, King Faisal Specialist Hospital and Research Institute, P.O. Box 3354, Riyadh 11211, Saudi Arabia; 2Department of Basic Pharmaceutical Sciences, School of Pharmacy, University of Louisiana at Monroe, 700 University Avenue, Monroe, Louisiana 71209, USA; and 3Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, Safat 13110, Kuwait.

Abstract. In the present study, two of the probable dominant marine compounds, manzamine A and sarcopine, were screened using benzo[a]pyrene (BP)-derived DNA adduct formation in MCF-7 cells as intermediary biomarker. Briefly, MCF-7 cells were treated with the compounds for 24 h followed by treatment with BP (0.5 μM). After 24h incubation, cellular DNA was isolated and analyzed for BP-derived DNA adducts by 32P-postlabeling technique. Manzamine A and sarcopine increased the BP-DNA adducts by 2 to 4-folds. Further, manzamine A (50 μM) substantially down regulated the expression of p53 while sarcopine (50 μM) slightly induced the level of p21. The residual DNA repair ability was almost completely abolished by manzamine A while sarcopine was ineffective. Based on our preliminary results, these compounds may be classified as potential genotoxic.

Introduction

Marine organisms provided numerous novel compounds with sensational multiple pharmacological properties. In the past two decades, thousands of novel marine compounds and their derivatives have been reported with diverse biological activities ranging from antiviral to antitumor(1). However, until recently, very few anticancer drugs

Corresponding author: E-mail: arifjm@yahoo.com
from marine origin have been commercially developed. Based on the preliminary anticancer activities in pre-clinical *in vitro* models, many promising marine anticancer compounds made it to the clinical trials but due to their extreme toxicity some of them were later withdrawn (2). Most of these compounds were tested *in vitro* by high-throughput cost-effective screening assays using exclusively human or rodent cancer cell lines or in xenograft models for their anticancer potentials (3,4). Long-term animal carcinogenesis studies with marine compounds currently in the clinical trials are scarce (Figure 1) (2). Only cytarabine and KRN7000 have been tested in animal carcinogenesis models (2). DNA adducts have been widely used as biomarker of choice to determine the anticancer and/or genotoxic potentials of natural compounds, but none of the studies with marine compounds, except chitosan, have used this biological marker. Chlorophyllin-chitosan complex inhibited the DNA adduct formation by >90% and the mutagenic action of 3-amino-1-methyl-5h-pyrido[4,3-b]indole in *rps1* transgenic mice (5,6).

![Diagram](image_url)

**Figure 1:** Marine bioactive compounds. This figure summarizes the data from several publications (1-4).

Manzamine A, a beta-carboline alkaloid, from several marine sponge species, inhibits the growth of the rodent malarial parasite *Plasmodium berghei in vivo* (7). It exhibits moderate antitumor and anti-HSV-II activity (8), and was found to be cytotoxic in mouse lymphoma cells (9). Sarcophine, a furanocembrane diterpene, isolated in a good yield from the Red Sea soft coral *Sarcophyton glaucum*, was found to serve as an effective inhibitor of JB6 cell transformation