CHEMOPREVENTIVE POTENTIAL OF NATURAL PRODUCTS ISOLATED FROM *ALCHORNEA GLANDULOSA*, *PTEROGYNE NITENS* AND ITS SEMI-SYNTHETIC ANALOGS

MAURO C. CAFUNDÓ DE MORAIS[1,2]; LAURA MARLER[2]; SUAIB LUQMAN[2,3]; TAMARA P. KONDRATYUK[2]; MAICON S. PETRÔNIO[4]; LUIS O. REGASINI[4]; DULCE H. S. SILVA[4]; VANDERLAN S. BOLZANI[4]; CHRISTIANE P. SOARES[1]; JOHN M. PEZZUTO[2]

[1]School of Pharmaceutical Sciences, Sao Paulo State University (UNESP), Araraquara-SP, Brazil; [2]College of Pharmacy, University of Hawaii, Hilo, USA; [3]IUSSTF Fellow, Central Institute of Medicinal and Aromatic Plants (CSIR), Lucknow, India; [4]Institute of Chemistry, Sao Paulo State University (UNESP), Araraquara-SP, Brazil.

INTRODUCTION

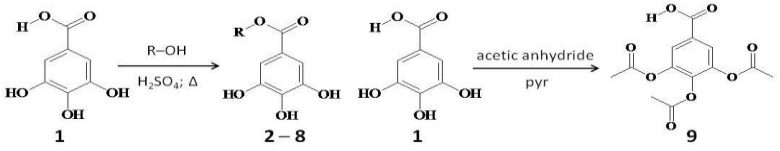
Chemoprevention involves the use of natural or synthetic substances to reduce the risk of developing cancer. Gallic acid (**1**) was found to possess several pharmacological activities, such as anti-oxidant and anti-inflammatory. Guanidine alkaloids nitensidine A (**10**) and B (**11**) display a broad spectrum of biological activities and its cytotoxic effect were well investigated.

OBJECTIVES

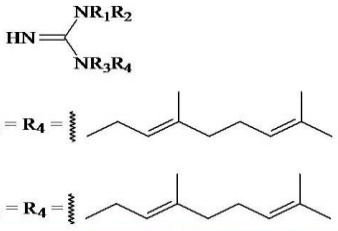
The present study evaluated the chemopreventive potential of **1**, semi-synthetic alkyl gallates (**2** – **9**) and guanidine alkaloids **10** and **11** using quinone reductase (QR) induction (Prochaska et al., 1992), aromatase inhibition (Stresser et al., 2000) and the suppression of NFκB activity (Homhual et al., 2006), which are well established strategies for screening compounds to cancer chemoprevention.

METHODS

Gallic acid (**1**) was isolated from *Alchornea glandulosa*, and alkyl gallates (**2** – **9**) were prepared from the reaction of the corresponding alcohols with gallic acid or from the reaction with acetic anhydride. The guanidine alkaloids nitensidines A (**10**) and B (**11**) were isolated from *Pterogyne nitens*. All compounds were evaluated for QR induction using murine hepatoma cell line Hepa 1c1c7 and two mutant cell lines; for *in vitro* aromatase inhibition; and against TNFα-induced NFκB activation with stable transfected 293/NFκB-Luc human embryonic kidney cells. Compounds were tested at 20 µg/mL following 1:3 serial dilutions.

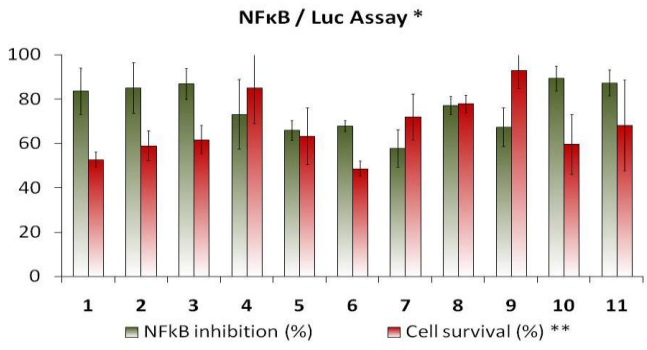


R= methyl (**2**), ethyl (**3**), *n*-propyl (**4**), isopropyl (**5**), *n*-butyl (**6**), isobutyl (**7**), *n*-pentyl (**8**)

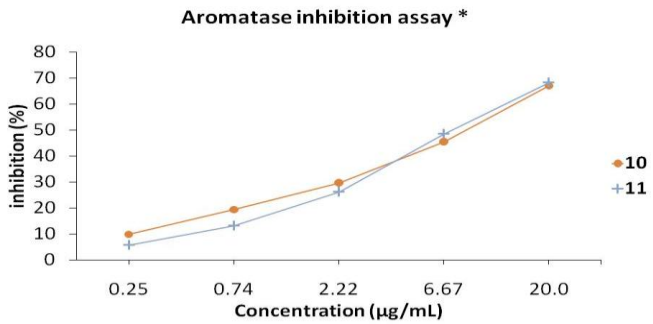


RESULTS

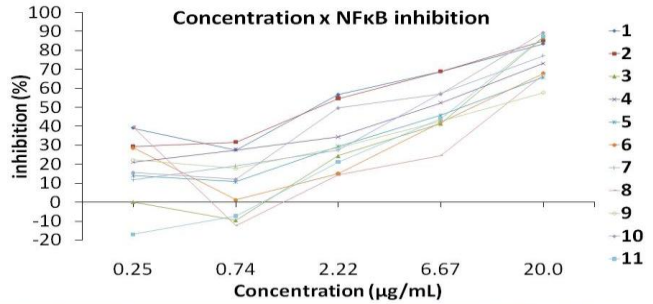
No QR induction was observed at tested concentrations. Nitensidine A and B showed aromatase inhibition (IC_{50} 19.7 ± 6.3 and 17.9 ± 6.3 µM, respectively), but moderately cytotoxic to Hepa 1c1c7 cells (IC_{50} 6.0 ± 0.5 and 6.4 ± 0.8 µM, respectively). With IC_{50} values in a range of 10 to 50 µM, all the gallic acid esters mediated NFκB inhibitory activity. In addition, gallic acid mediated a modest cytotoxic effect, but none of the gallate esters affected cell viability at the tested concentrations.



* TPCK was adopted as positive control showing NFκB inhibition 99.8 ± 0.1 %
** 293/NFκB-Luc human embryonic kidney cell survival in SRB assay (Skehan et al., 1990)



* naringenin was adopted as positive control showing IC_{50} 2.0 ± 0.5 µg/mL



CONCLUSIONS

Gallic acid, alkyl gallates and guanidine alkaloids doesn't induce quinone-reductase at tested concentrations. **10** and **11** are *in vitro* aromatase inhibitors, but also cytotoxic at inhibitory concentrations. Based on these intracellular responses, we suggest that gallate esters are related to suppression of NFκB activation, which it could play a chemopreventive role in carcinogenesis.

ACKNOWLEDGMENT

The authors would like to thank FAPESP and CNPq, for fellowship support. This work was supported in part by program project P01 CA48112 awarded by the National Cancer Institute (John M. Pezzuto, Project Director). SL acknowledge IUSSTF for research fellowship