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Allicin and propolisbenzofuran B: Interaction pattern with ATP-binding cassete B1 (ABCB1) transporter

Estela Fernandes e Silva [a]; Paula Fernandes e Silva [b]; Timóteo Matthies Rico [c]; Juliana Silva Lemões [d]*

a Doctor in Physiological Sciences by Universidade Federal do Rio Grande - FURG, Rio Grande (Rio Grande do Sul), Brasil
b Dentist by Universidade Federal de Pelotas, Pelotas (Rio Grande do Sul), Brasil
c Doctor in Health Sciences by Universidade Federal do Rio Grande - FURG, Professor at Instituto-Federal-Sul-Riograndense, Jaguarão (Rio Grande do Sul), Brasil
d Doctor in Chemistry by Universidade Federal do Rio Grande do Sul – UFRGS, Professor at Universidade Federal do Pampa, Bagé (Rio Grande do Sul), Brasil
**e-mail address: star.fs@hotmail.com*

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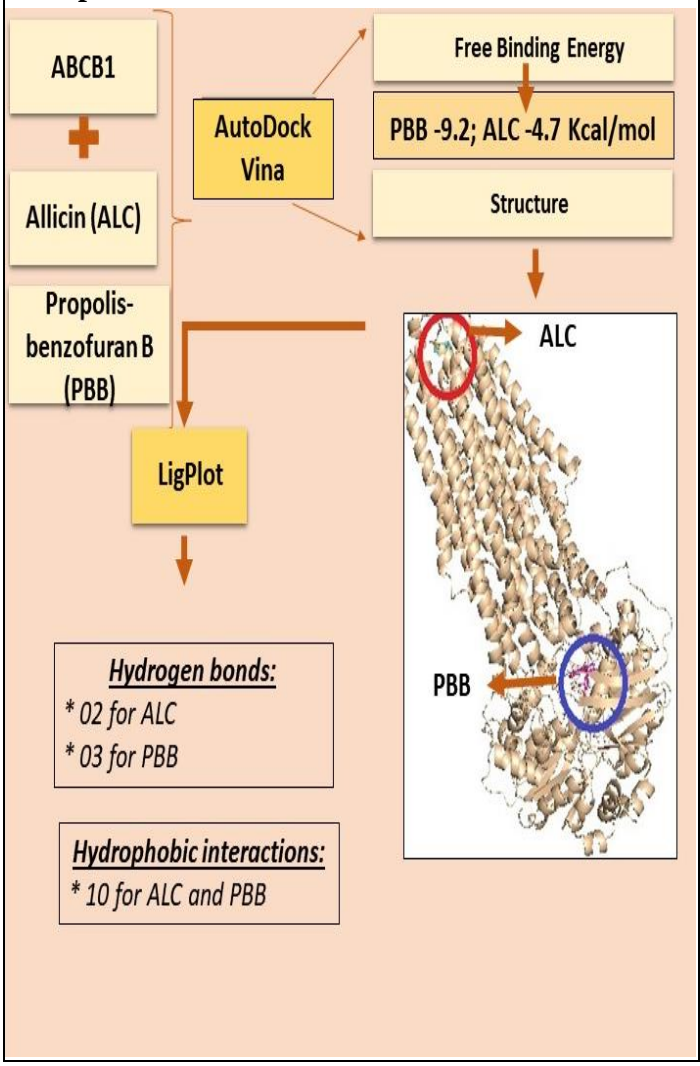
Graphical Abstract



Abstract. *Natural products have been the mainstay of chemotherapy for years. Drug resistance in tumor cells is a major cause of failure in chemotherapy treatment. Several factors support this resistance and one of the main factors is the presence of drug efflux pumps such as ABCB1 transporters. The search for molecules capable of blocking the efflux by ABCB1 is important to increase the success of chemotherapy treatment. The Allicin (ALC) is one of the most biologically active compounds in freshly crushed garlic and the propolis-benzofuran B (PBB), a bioactive natural product isolated from honeybee propolis resin. ALC and PBB have already demonstrated anti-tumor effects, so they could block ABCB1. Comparing the binding pattern of ALC and PBB with ABCB1 through molecular docking was the main objective of this study. The docking simulation by AutoDock Vina demonstrated a binding energy with the ABCB1 more negative for PBB (-9.2 Kcal/mol) and less negative for ALC (-4.7 Kcal/mol). ALC linked to an extracellular region of ABCB1, whereas PBB bounded close to the nucleotide binding domain (intracellular portion) of ABCB1. The ALC established 02 and PBB 03 Hydrogen bonds with ABCB1. The number of hydrophobic interactions with ABCB1 was the same (10 interactions) for both molecules. Considering the more negative binding energy*

	and the higher number of hydrogen bonds (evidence of greater affinity and stability) PBB appears to be a better ABCB1 inhibitor. However, it is necessary to continue in vitro and in vivo studies.

Introduction

. *Drug resistance in tumor cells is a major cause of failure in cancer chemotherapy treatment. Several factors support this resistance and one of the main factors is the presence of drug efflux pumps such as ABCB1 transporters* (1). *Natural products have been the basis of cancer chemotherapy for the last 30 years* (2). *The Allicin (ALC) is one of the most biologically active compounds in freshly crushed garlic* (3) *and the (PBB), a bioactive natural product isolated from honeybee propolis resin* (4). *ALC and PBB have already demonstrated anti-tumor effects* (3,5), *so they could block ABCB1. The search for molecules capable of blocking the efflux by ABCB1 is important to increase the success of chemotherapy treatment. Comparing the binding pattern of ALC and PBB with ABCB1 through molecular docking was the main objective of this study.*

Materials and Methods

The ABCB1 structure (receptor) was obtained from Protein Data Bank PDB (PDB ID: 6C0V) (6) *and ligands ALC and PBB were obtained from Pubchem (PubChem ID: 65036 for ALC and 10455788 for PBB)* (7). *Firstly, using the UCSF chimera (available to download at http://www.cgl.ucsf.edu/chimera/download.html*) *we remove heteroatoms from the ABCB1. Then, we prepare receptor and ligand input files using AutoDockTools software for AutoDockVina* (8). *To perform docking simulations, we configure grid box as: size x = 62 Å; size y = 90 Å; and size z = 126 Å; and center box coordinates are x = 162.664 Å center; y = 167.261 Å center; z = 149.020 Å; considering exhaustiveness as 500. Molecular docking simulations were performed with AutoDock Vina* (8). *The more negative FEB indicates the greater stability of ligand-receptor complex. Visual analysis of docking results was performed with PyMol (available for download https://pymol.org/2/) and for check the types of connections between molecules we used the LigPlot* (9).

Results and Discussion

The docking simulation by AutoDock Vina demonstrated a binding energy with the ABCB1 more negative for PBB (-9.2 Kcal/mol) and less negative for ALC (-4.7 Kcal/mol). ALC linked to an extracellular region of ABCB1, whereas PBB bounded close to the nucleotide binding domain (intracellular portion) of ABCB1 (Fig. 1A). The ALC established 02 (Fig 1B) and PBB 03 Hydrogen bonds with ABCB1 (Fig 1C). The number of hydrophobic interactions with ABCB1 was the same (10 interactions) for both molecules (Fig 1B and C).

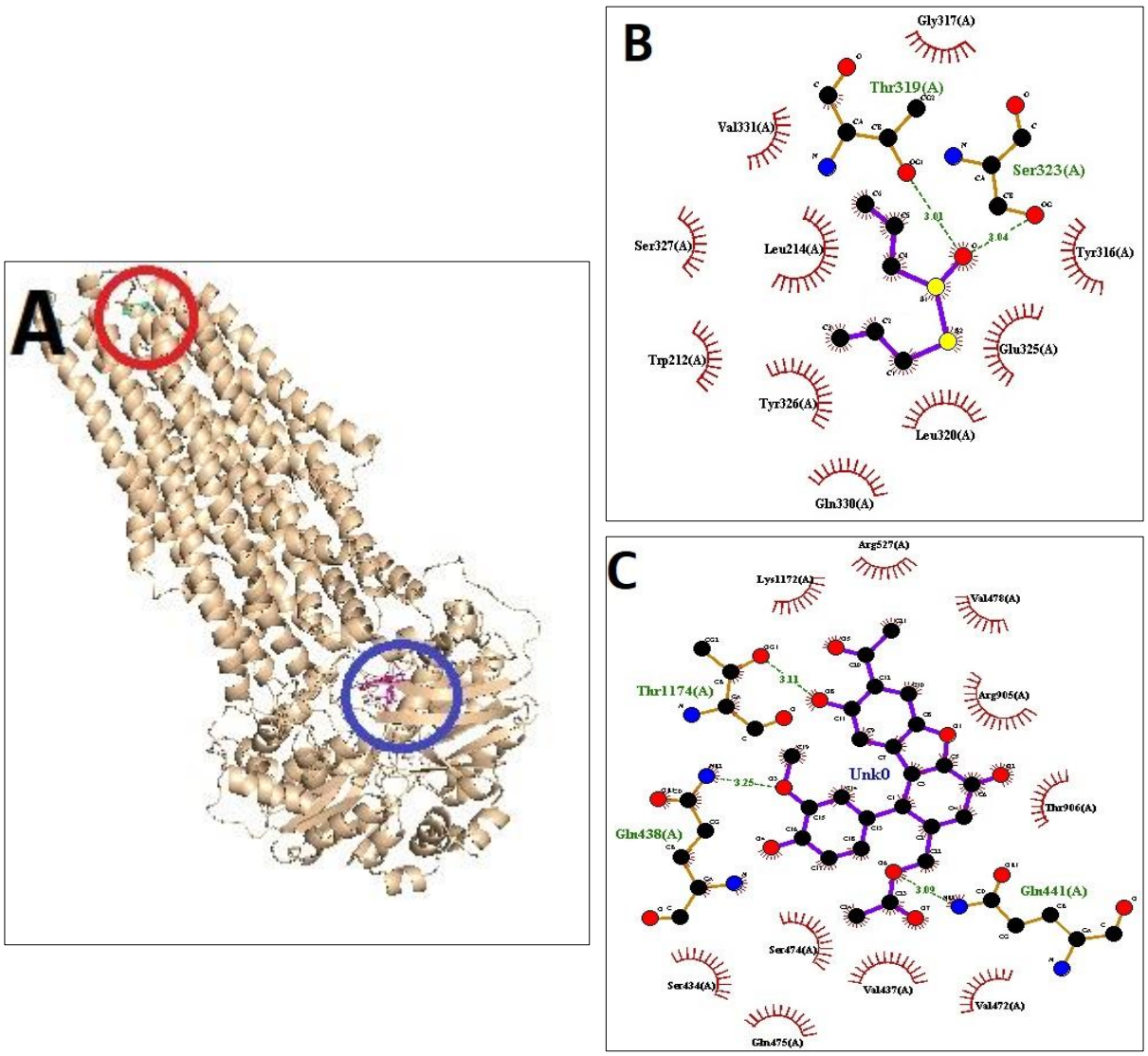


Figure 1: ABCB1 (wheat color), Allicin (cyan strokes with red circle around) and Propolis-benzofuran B (violet strokes with blue circle around) (A). ABCB1 and Allicin interaction (B). ABCB1 and PBB interaction (C). For B and C: Black, blue, red or yellow circles – ABCB1 or Allicin or Propolis-benzofuran B atoms; Purple strokes – bonds between the atoms of Allicin or Propolis-benzofuran B; Orange strokes – bonds between the atoms of Abcb1; Dotted green lines – Hydrogen bonds with distances (numbers) between ABCB1 and Allicin (B) or Propolis-benzofuran B (C); Red semi-circles with lines - hydrophobic interactions.

Conclusions

Considering the more negative binding energy and the higher number of hydrogen bonds (evidence of greater affinity and stability) PBB appears to be a better ABCB1 inhibitor. However, it is necessary to continue in vitro and in vivo studies.

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