RESEARCH ARTICLE

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Thiosemicarbazide Derivative of Captopril (8) imposes Cellular-Dependent Death Modalities on Breast Cancer Cell Lines

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Abstract

Objective: Breast cancer prevalence is continuing to rise worldwide. Despite the diversity of the current approaches and protocols to treat this heterogeneous disease, most of these face the challenges of side effects and resistance. Hence, novel and innovative approaches to the treatment of breast cancer are almost constantly needed. This study aimed to investigate the antiproliferative and death modalities induced by three thiosemicarbazide derivatives of captopril in two subtypes of breast cancer cell lines, the Estrogen- receptor positive MCF-7, and the Estrogen/progesterone-receptor-negative AMJ13. **Methods:** MTT assay was used to determine the cytotoxicity of the derivatives and their parent compound Captopril, Hematoxylin and Eosin (H&E) staining, Acridine Orange/ Ethidium Bromide (AO/ EtBr) staining, Caspase immunocytochemistry analysis and ROS generation by Human ROMO1 ELISA assays were conducted to explore the type of cellular death induced by these derivatives. **Results:** One of the derivatives denoted as (8) demonstrated the best antiproliferative profile recording the highest cytotoxic effect with IC_{50} of (88.06 µM) and (66.82 µM) compared to that of captopril (849.8 µM),(1075µM) in MCF-7 and AMJ13 breast cancer cells respectively. In MCF-7 cells, derivative (8) imposed an apoptotic cellular death with the involvement of *caspase-3*, and *caspase-9* and displayed a time-dependent ROS generation. In AMJ13 breast cancer cells, results revealed an extensive vacuole forming, non-apoptotic cellular death, without ROS generation, but with a significant implication of *caspase-9*. **Conclusion:** This study demonstrated the thiosemicarbazide derivative of captopril (8) as a promising antiproliferative agent against breast cancer cells displaying different cellular death modalities, signifying the versatility of the derivative and suggesting multitarget pathways. This study strongly recommends derivative (8) as a future leading molecule.

Keywords: Thiosemicarbazide Derivative of Captopril- Breast Cancer Cell Lines Antiproliferative- Death modalities

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Introduction

In 2020, female breast cancer took the lead over lung cancer in the number of newly diagnosed cases worldwide [1]. The disease is characterized as highly heterogeneous with diverse subtypes classified on different bases. Molecularly and depending on gene expression of estrogen ER, progesterone PR and epidermal growth factor 2 into: luminal A (ER and /or PR)+, HER2 -), luminal B ((ER and /or PR)+, HER2 ±), HER2 overexpression (ER/PR)- HER2 +), and basal-like (triple negative) TNBC (ER/ PR)- HER2-) [2, 3].

Over the years, many therapies have been developed for the treatment of all types of breast cancer, but almost all of them share the same challenges of side effects and resistance. In addition to that, the most aggressive with the worst prognosis TNBC still lacks standardized effective treatment [4].

As such, the pursuit of novel approaches seems in constant demand, and one of these new approaches is the Renin-Angiotensin System (RAS), which is implicated in almost all cancer hallmarks [5], including breast [6, 7]. Moreover, recent attention has been driven towards Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin II type 1 Receptor Blockers (ARBs) role in oncology as potential chemopreventative, adjuvant or even anticancer agents [5, 8, 9].

Captopril, the first member of the ACEi family with a characteristic sulfhydryl group [10] was among those that were investigated for its potential role in the treatment of breast cancer with positive results [11-13].

Recently, Al-Saad and colleagues (2019) synthesized novel derivatives of captopril that demonstrated higher antiplatelet [14] and ACE inhibition activity than their

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