ZITA MEDICAL MANAGEMENT

www.hsmc.gr/en/pharmakeftiki-journal/

PHARMAKEFTIKI, 37, 2S, 2025 | 149-153 RESEARCH

https://doi.org/10.60988/p.v37i2S.163

Cytotoxic and molecular effects of captopril on a colon cancer cell-line: an *in vitro* study

Teeb Ali Al-Saady[1,*], Ooroba M. S. Ibrahim[2], Hany Akeel Al-Hussaniy[3]

[1]Department of Pharmacology, College of Pharmacy, University of Hilla, Hillah, Iraq
[2]Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq
[3]Department of Pharmacology, College of Pharmacy, Al-Nisour University, Baghdad, Iraq

KEY WORDS:
cisplatin; captopril; colon cancer cell-line; PIK3CA gene; cytotoxicity

ARTICLE INFO:
Received: December 07, 2024
Revised: February 21, 2025
Accepted: February 21, 2025
Available online: October 10, 2025

*** CORRESPONDING AUTHOR:**
Teeb Ali Al-Saady, Department of Pharmacology, College of Pharmacy, University of Hilla, Hillah, Iraq; e-mail: teeb_ali@hilla-unc.edu.iq

ABSTRACT

Colorectal carcinoma originates from aberrant cellular proliferation within the colonic or rectal mucosa, culminating in malignant neoplastic growth. As of 2018, cancer accounted for approximately 9.6 million deaths worldwide, ranking as the second leading cause of mortality. This study investigates the antiproliferative effects of captopril, an angiotensin-converting enzyme inhibitor, on the SW480 colorectal adenocarcinoma cell line. SW480 cells were treated with increasing concentrations of cisplatin (15.6–500 μg/mL) and captopril (31.25–1,000 μg/mL), administered both individually and in combination. Cisplatin achieved maximal cytotoxicity at 62.5 μg/mL, whereas captopril required 2,000 μg/mL in order to elicit a comparable effect. The most pronounced anticancer synergy was observed with a captopril / cisplatin combination at 31.25 / 15.6 μg/mL, thereby indicating enhanced chemotherapeutic efficacy through drug interaction. Real-time PCR analysis of PIK3CA gene expression revealed a concentration-dependent transcriptional response. The highest levels of *PIK3CA* upregulation occurred at 250 μg/mL for cisplatin, 62.5 μg/mL for captopril, and 20 / 1000 μg/mL for their combination. *PIK3CA*, a key oncogene implicated in cellular proliferation and survival, exhibited significant modulation across the herein examined treatment conditions. These findings underscore captopril's potential as a novel adjuvant in colorectal cancer therapy, capable of influencing critical oncogenic pathways and amplifying the cytotoxic effects of standard chemotherapeutic agents.

PHARMAKEFTIKI, 37, 2S, 2025 | 149-153

1. Introduction

Colorectal cancer is among the most frequently diagnosed cancers worldwide, ranking as the third most common malignancy across all cancer types. It is a leading cause of cancer-related morbidity and mortality, with over one million new cases reported annually. Despite advances in screening and treatment, colorectal cancer remains the third leading cause of cancer-related deaths in both men and women, particularly in the United States[1,2]. The disease originates in the epithelial cells lining the colon or the rectum, which are characterized by a high rate of proliferation and turnover. Colorectal carcinoma develops when these cells undergo genetic and epigenetic alterations, leading to uncontrolled proliferation and the formation of an abnormal mass. These tumours may be benign or malignant[2,3].

Multiple approaches have been employed for the assessment of colorectal cancer. In Iraq, research has examined associations among gender, age, tumor recurrence, tumor characteristics, and medical treatment outcomes[1,2]. Globally, colorectal cancer remains a major public health concern, affecting over one million individuals each year[4]. In Iraq, colorectal cancer predominantly affects the elderly, with rising incidence and mortality observed across all age groups. These trends necessitate a re-evaluation of public health policy concerning colorectal cancer, including improved public awareness, screening protocols, and management strategies[5]. Males aged 50 to 60 years are more likely to develop colorectal cancer than females, while right-sided colon cancer is more prevalent among Iraqi patients[6].

Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, are primarily prescribed for the management of hypertension and cardiovascular diseases. Captopril inhibits the conversion of angiotensin I to angiotensin II and deactivates bradykinin; a vasodilatory peptide. Emerging research indicates that captopril possesses anti-angiogenic properties that can inhibit the formation of new blood vessels required for tumor growth and metastasis[7]. Angiogenesis plays a critical role in tumour progression by supplying cancer cells with oxygen and essential nutrients. Tumours activate the "angiogenic switch" in order to promote the release of pro-angiogenic factors, such as vascular endothelial growth factor, which correlates with tumour aggressiveness and metastatic potential[8]. Inhibiting angiogenesis – by using agents like captopril – may suppress tumour progression by restricting nutrient delivery to cancer cells. Interestingly, observational data suggest that patients treated with captopril for hypertension exhibit a lower risk of developing cancer, prompting further investigation into its potential anticancer effects[9].

This study evaluates the impact of captopril on the SW480 colorectal cancer cell line, examining its influence on cell proliferation and its potential as an adjunctive therapy for colorectal cancer.

2. Methodology

2.1. Cell lines

The SW480 colorectal adenocarcinoma cell line was obtained from Rwafid Alelom Limited. Treatment concentrations were as follows: cisplatin at 15.6, 31.25, 62.5, 125, 250, and 500 μg/mL and captopril at 31.25, 62.5, 125, 250, 500, and 1,000 μg/mL. Cell viability was assessed following exposure to captopril, cisplatin, and their combination. SW480 cells were cultured in RPMI-1640 medium supplemented with 10% foetal bovine serum, and 100 U/mL penicillin and streptomycin. Cultures were maintained at 37°C in a humidified atmosphere containing 5% CO_2.

2.2. MTT assay

The MTT assay was employed in order to assess the cytotoxic effects of captopril and its combination with cisplatin on tumor cell viability. The MTT assay measures mitochondrial metabolic activity as an indicator of cell viability, proliferation, and cytotoxicity. In this colorimetric, non-radioactive method, the intensity of the resulting formazan dye reflects the number of metabolically active cells. The Cell Proliferation Kit I (MTT) provides a quantitative and scalable platform suitable for rapid analysis of multiple samples.

PHARMAKEFTIKI, 37, 2S, 2025 | 149-153

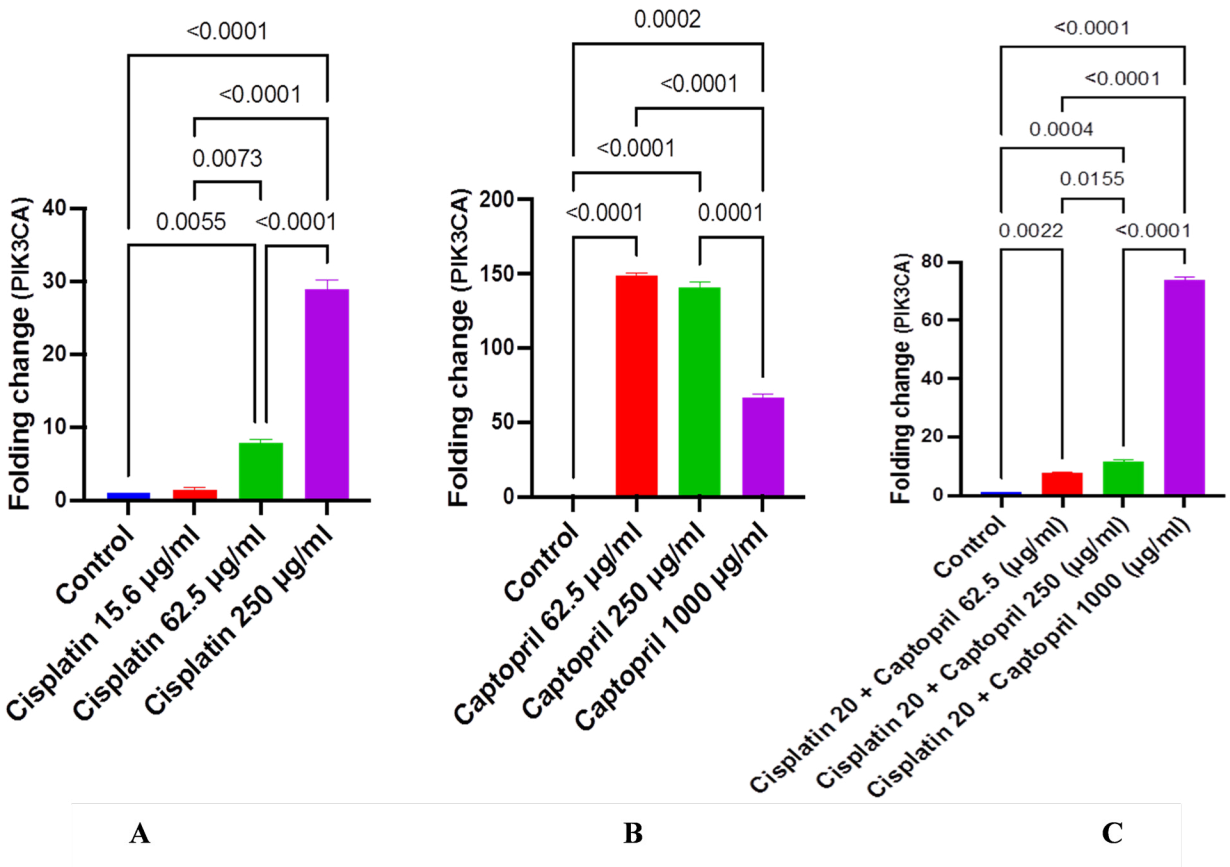

Figure 1. *Effects of cisplatin, captopril, and their combination on PIK3CA gene expression in SW480 cells. (A): Cisplatin treatment resulted in the highest PIK3CA expression at 250 µg/mL. (B): Captopril treatment yielded peak PIK3CA expression at 62.5 µg/mL. (C): Combination therapy (captopril / cisplatin) induced maximal PIK-3CA expression at 20 / 1,000 µg/mL, thereby demonstrating a synergistic dose-dependent effect.*

2.3. Gene expression analysis of *PIK3CA*

Total RNA was extracted using the Easy-spin™ (DNA-free) RNA extraction kit. Lyophilized primers were reconstituted in nuclease-free ddH_2O to a final concentration of 100 pM/µL, according to the supplier's protocol. The working concentration for primer use was adjusted to 10 pM/µL. Primers were stored at -20°C until use.

2.4. Statistical analysis

Statistical analyses were conducted using GraphPad Prism version 5.0 (GraphPad Software Inc., USA). The Wilcoxon signed-rank test was applied in order to assess differences in gene expression for cisplatin, captopril, and their combinations. Mean gene expression levels in SW480 cells were compared using two-way ANOVA. All experiments were repeated at least three times in triplicate. A *p*-value below 0.05 was considered as statistically significant.

3. Results and Discussion

The cytotoxic effects of cisplatin, captopril, and their combination on SW480 colorectal cancer cells were evaluated using cell counting and MTT assays. Cisplatin demonstrated effective cytotoxicity at a con-

PHARMAKEFTIKI, 37, 2S, 2025 | 149-153

centration of 62.5 μg/mL, while the maximal lethal concentration of captopril was 2,000 μg/mL. Combined treatment exhibited the highest cytotoxic effect at 31.25 / 15.6 μg/mL for captopril / cisplatin, thereby indicating a synergistic interaction.

The impact of cisplatin, captopril, and their combination on *PIK3CA* expression was also assessed. Peak expression levels were observed at 250 μg/mL for cisplatin, 62.5 μg/mL for captopril, and 20 / 1,000 μg/mL for the combination therapy, revealing dose-dependent modulation of gene regulation (Figure 1).

Captopril, a widely prescribed ACE inhibitor, has exhibited immunomodulatory and anti-angiogenic properties that may contribute to cancer management by attenuating tumor progression and influencing immune pathways. These findings are consistent with those of previous reports confirming captopril's cytotoxic activity against colorectal cancer cells and its role in tumor reduction. The PI3K signalling pathway and, specifically, the PIK3CA oncogene, plays a central role in colorectal carcinogenesis by promoting cellular proliferation and inhibiting apoptosis. Mutations in *PIK3CA*, frequently identified in colorectal cancer, can activate downstream targets such as AKT, thereby driving tumor growth and resistance to programmed cell death. The herein reported results suggest that captopril may modulate *PIK3CA* expression, thereby offering a promising target for therapeutic intervention.

4. Conclusion

This study demonstrates the potential of captopril as an adjuvant therapeutic agent in the treatment of colorectal cancer, with observable effects in reducing SW480 cell proliferation and modulating *PIK3CA* expression. These findings support the hypothesis that captopril may enhance the efficacy of conventional chemotherapy by targeting critical molecular pathways involved in tumor growth and survival.

Acknowledgements

The authors express their sincere appreciation to the College of Pharmacy of the University of Hilla, for its continuous support and encouragement of ongoing research efforts.

Conflicts of interest

None exist.

ORCIDs

0009-0001-7397-8769 (T.A. Al-Saady); 0000-0002-0682-8621 (O.M.S. Ibrahim); 0000-0003-2647-8574 (H.A. Al-Hussaniy)

References

1. Kuipers E.J., Rösch T., Bretthauer M. Colorectal cancer screening -- optimizing current strategies and new directions. *Nat. Rev. Clin. Oncol.* 10(3), 130–142, 2013. DOI: 10.1038/nrclinonc.2013.12
2. Nabi U., Nagi A.H., Riaz S., Sami W. Morphological evaluation of colorectal carcinoma with grading staging and histological types. *J. Pak. Med. Assoc.* 60(12), 998–1001, 2010.
3. AlSaady T.A., Madlum K.N., Obied H.N. Effect of antioxidants on cisplatin-induced cytotoxicity and oxidative stress in colon cancer cells. *Eurasia J. Biosci.* 14, 5375–5382, 2020.
4. Morgan E., Arnold M., Gini A., Lorenzoni V., Cabasag C.J., Laversanne M., *et al.* Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut* 72(2), 338–344, 2023. DOI: 10.1136/gutjnl-2022-327736
5. Ibrahem S., Ahmed H., Zangana S. Trends in colorectal cancer in Iraq over two decades: incidence, mortality, topography and morphology. *Ann. Saudi Med.* 42(4), 252–261, 2022. DOI: 10.5144/0256-4947.2022.252
6. Meryud Abood A., Mohammud Habash M., Mohammed M. Epidemiology of colonic cancer in Baghdad City, Iraq. *Iran. J. War Public Health* 14(3), 12, 2022.

PHARMAKEFTIKI, 37, 2S, 2025 | 149-153

7. Odaka C., Mizuochi T. Angiotensin-converting enzyme inhibitor captopril prevents activation-induced apoptosis by interfering with T cell activation signals. *Clin. Exp. Immunol.* 121(3), 515–522, 2000. DOI: 10.1046/j.1365-2249.2000.01323.x
8. Sahib H.B. The anti-angiogenic and anti-proliferative activity of methyl hydroxychalcone. *Asian Pac. J. Cancer Prev.* 23(6), 2071–2077, 2022. DOI: 10.31557/APJCP.2022.23.6.2071
9. Shebl R.I. Anti-cancer potential of captopril and botulinum toxin type-A and associated p53 gene apototic stimulating activity. *Iran. J. Pharm. Res.* 18(4), 1967–1977, 2019. DOI: 10.22037/ijpr.2019.1100800

HOW TO CITE:
Al-Saady T.A., Ibrahim O.M.S., Al-Hussaniy H.A. Cytotoxic and molecular effects of captopril on a colon cancer cell-line: an *in vitro* study. *Pharmakeftiki* 37(2s), 149-153, 2025. https://doi.org/ 10.60988/p.v37i2S.163