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In vitro cytotoxic and molecular effects of metoprolol, alone or combined with cisplatin, on colon cancer cells

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

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ABSTRACT

Colorectal cancer ranks among the most prevalent malignancies worldwide, with surgical interventions frequently associated with substantial postoperative mortality and complications. Contemporary therapies often target molecular pathways such as the epidermal growth factor receptor and vascular endothelial growth factor. Recently, antihypertensive agents have been investigated for their potential anticancer properties, though results remain inconclusive. This study has assessed the cytotoxic effects of metoprolol, both as a monotherapy and in combination with cisplatin, on the SW480 colon cancer cell line using the MTT assay. Cisplatin achieved the highest cytotoxic activity at a concentration of 62.5 µg/mL, while metoprolol alone exhibited maximal cell-killing effects at 1,000 µg/mL. Notably, the combination of metoprolol (1,000 µg/mL) with cisplatin (15.6 µg/mL) demonstrated the most pronounced cytotoxic effect, thereby indicating potential synergistic activity. The findings suggest the potential of repurposing metoprolol as an adjunctive agent in combination chemotherapy, in order to enhance therapeutic outcomes in colorectal cancer treatment.

*** 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

1. Introduction

Colorectal cancer remains a significant global health concern, with surgical intervention serving as the primary curative modality. However, colorectal cancer surgery has historically been associated with considerable postoperative morbidity and mortality[1]. Despite

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advances in perioperative care and postoperative surveillance, the rate of postoperative mortality has remained relatively stable over the past decade, highlighting the ongoing complexity of surgical outcomes in colorectal cancer patients[2]. Recent therapeutic developments have concentrated on targeted approaches – particularly those inhibiting the vascular endothelial growth factor and the epidermal growth factor receptor pathways – which are critical for tumour angiogenesis and cellular proliferation[3]. Colorectal cancer patients often present with multiple comorbid conditions requiring continuous pharmacological management. This overlap stems from shared risk factors between colorectal cancer and chronic diseases such as metabolic syndrome and cardiovascular disorders[4].

Hypertension, a widespread chronic condition, affects approximately 25% of the adult population in Canada[5]. Owing to its high prevalence, antihypertensive medications represent the most commonly prescribed drug class in the country, with over four million prescriptions dispensed monthly[6]. Emerging research suggests that antihypertensive agents may exert dual influences on carcinogenesis, either by promoting or by inhibiting tumour progression through distinct cellular pathways. This duality has prompted focused investigation into the oncological implications of the five major classes of antihypertensive drugs, especially in the context of colorectal cancer. Although many studies have examined the relationship between antihypertensive drug use and colorectal cancer risk, results remain inconclusive, warranting further inquiry into the underlying mechanisms and clinical outcomes[7].

2. Methodology

2.1. Cell lines

The SW480 colon adenocarcinoma cell line was obtained from Rwafid Alelom Limited. Treatment concentrations for cisplatin were 15.6, 31.25, 62.5, 125, 250, and 500 μg/mL, while for metoprolol were 31.25, 62.5, 125, 250, 500, and 1,000 μg/mL. Cell viability was subsequently assessed following exposure to cisplatin, metoprolol, and their combination. Cells were cultured in RPMI-1640 medium supplemented with 10% foetal bovine serum, along with 100 U/mL penicillin and streptomycin. All cultures were maintained at 37°C in a humidified 5% CO_2 atmosphere.

2.2. MTT assay

SW480 cells were seeded into 96-well plates and were incubated overnight until reaching approximately 80% confluence. Subsequently, 200 μL of complete growth medium was replaced with medium containing varying concentrations of cisplatin, metoprolol, and their combination, followed by 24-h incubation at 37°C, 5% CO_2. Each concentration was tested in five replicates. Cell viability was evaluated using the MTT cytotoxicity assay. The assay measures mitochondrial metabolic activity as a surrogate for cell proliferation, survival, and cytotoxicity. In this non-radioactive colorimetric method, darker solutions indicate a higher number of metabolically active cells. The Cell Proliferation Kit I (MTT) enables optimized quantitative analysis, facilitating rapid processing of large sample sets[8].

2.3. Statistical analysis

Data analysis was performed using the SPSS software (version 23/2021; IBM, Armonk, NY, USA). One-way ANOVA was utilized in order to assess differences across treatment conditions. Statistical significance was set at $p<0.05$.

3. Results and Discussion

The effects of cisplatin on SW480 colorectal cancer cells were evaluated at varying concentrations (15.6, 31.25, 62.5, 125, 250, and 500 μg/mL), with untreated cells serving as the control. After 24 h of treatment, a statistically significant reduction in cell viability was observed ($p<0.001$), demonstrating a clear dose-dependent cytotoxic effect. The concentration of 62.5 μg/mL produced the most pronounced cytotoxicity, thereby indicating its potency in inducing cell death in SW480 cells (Figure 1A).

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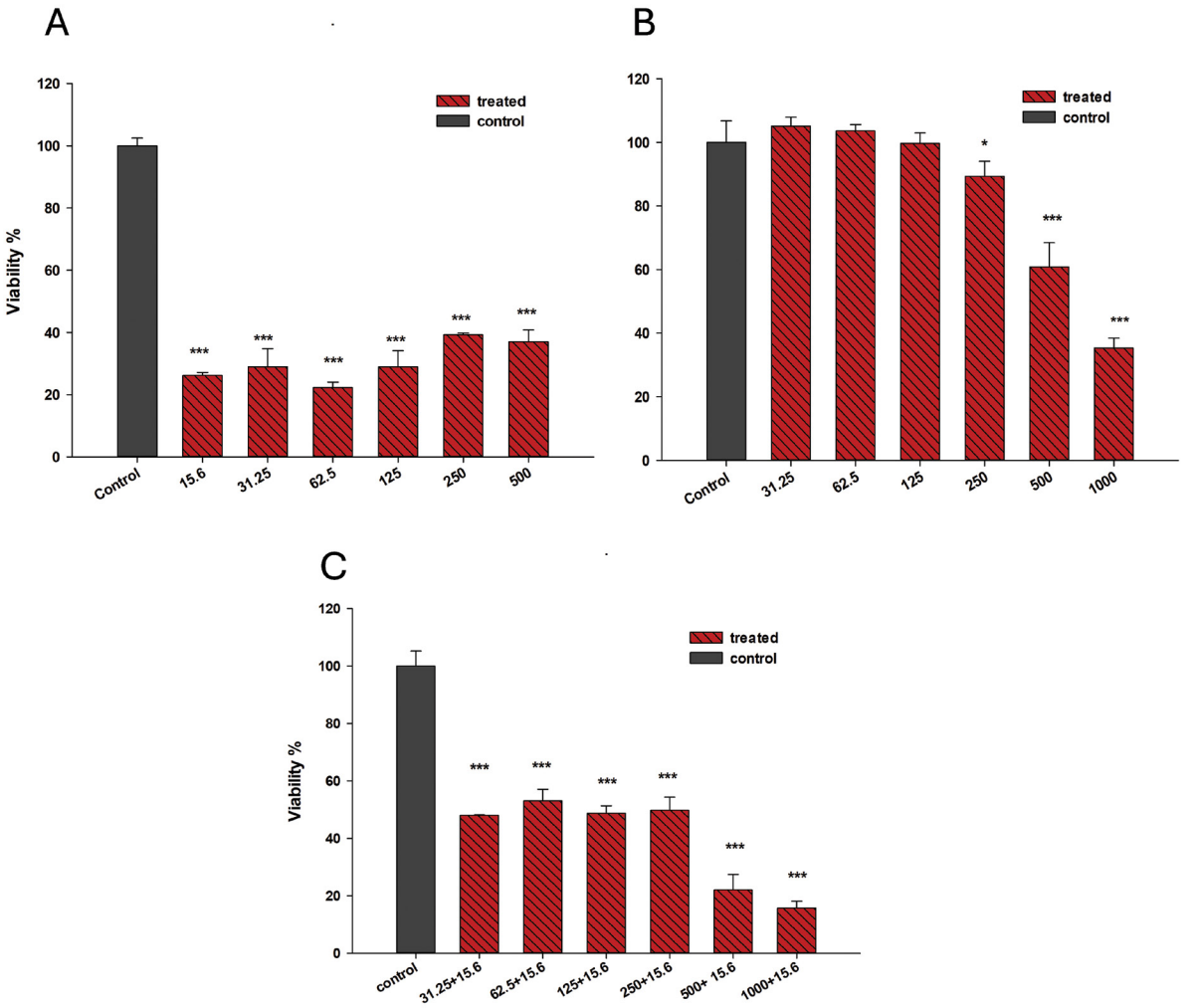

Figure 1. *Cytotoxic effects of cisplatin, metoprolol, and their combination on SW480 colon cancer cells. (A): Treatment with cisplatin demonstrated maximal cytotoxicity at 62.5 μg/mL, representing the most potent concentration for inducing cell death. (B): Exposure to metoprolol revealed that 1,000 μg/mL produced the highest reduction in cell viability. (C): Combined administration of metoprolol (1,000 μg/mL) and cisplatin (15.6 μg/mL) yielded the greatest cytotoxic effect, thereby indicating a synergistic enhancement of cell-killing activity. Notes: *, p<0.05; ***, p<0.001.*

The impact of metoprolol on SW480 cell viability was examined across concentrations of 31.25, 62.5, 125, 250, 500, and 1,000 μg/mL. A significant concentration-dependent decrease in viability was detected (p<0.001), with 1000 μg/mL yielding the highest cytotoxic effect (Figure 1B).

In order to assess the potential synergistic interaction between metoprolol and cisplatin, multiple concentration combinations were tested (Figure 1C). The combination of 1,000 μg/mL metoprolol with 15.6 μg/mL cisplatin resulted in the greatest reduction in cell viability (p<0.001), suggesting a potentiation of cell-killing efficacy when both agents are co-administered. These findings offer valuable

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insights into the individual and combined cytotoxic effects of cisplatin and metoprolol on SW480 colon cancer cells, underscoring their potential therapeutic relevance.

Our results corroborate earlier work by Hajatbeigi and Hajighasemi[9], which has demonstrated the cytotoxic effects of both cisplatin and metoprolol on SW480 cells. Cisplatin, a well-characterized alkylating agent, induces apoptosis by forming intrastrand cross-links between adjacent guanine bases, and subsequently interacting with neighbouring guanine and adenine residues. These DNA modifications disrupt replication and transcription, culminating in programmed cell death. The cytotoxic activity of metoprolol has also been reported by Caldwell *et al.*[10], who have utilized the MTT assay in order to evaluate the drug's impact on cell viability. Their observations align with those of the present study, reinforcing the notion that metoprolol contributes to cancer cell death.

As a β-adrenergic receptor antagonist, metoprolol has attracted attention for its putative anticancer properties, primarily through modulation of pathways involved in carcinogenesis, angiogenesis, and tumor progression. The oncology community has shown increasing interest in the therapeutic potential of β-blockers, particularly given their affordability, widespread availability, and favourable safety profile. Considering the financial burdens and limited survival rates associated with current oncologic treatments, the repurposing of β-blockers offers a compelling avenue for future research in both preclinical and clinical contexts. These findings contribute meaningfully to the growing body of literature supporting the anticancer potential of β-blockers, and they advocate for deeper investigation into the mechanistic foundations and translational relevance of these agents.

4. Conclusion

This study demonstrates the potential of metoprolol as an adjuvant therapeutic agent in the treatment of colorectal cancer, with observable *in vitro* effects in reducing SW480 cell proliferation.

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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)

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