

Synergistic Cytotoxic Effects of Tamoxifen and 5-Fluorouracil in Gastric Cancer MKN-45 Cells

Zeinab Mahdian^{a,b}, Hassan Akrami^{c*}, Mahdi Bagheri^c, Yousef Nikmanesh^c

^a Department of Clinical Biochemistry, School of Medicine, Babol University of Medical Sciences, Babol, Iran.

^b Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

^c Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

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Abstract

Gastric cancer is a major global health concern, and identifying agents that inhibit cancer cell growth can improve treatment outcomes. Tamoxifen and 5-Fluorouracil (5-FU) have demonstrated antitumor effects, and their combination may enhance therapeutic efficacy. In this study, the MKN-45 gastric cancer cell line was cultured in DMEM/F12 medium with 10% FBS and antibiotics. Cytotoxicity of Tamoxifen, 5-FU, and their combination was assessed using the MTT assay, and synergism was analyzed with Compusyn software ($P \leq 0.05$). Tamoxifen and 5-FU reduced cell viability in a dose-dependent manner, with IC_{50} values of 7 $\mu\text{g/ml}$ and 0.9 $\mu\text{g/ml}$, respectively. Their combination further decreased the IC_{50} to 0.7 $\mu\text{g/ml}$. Combination index (CI) analysis showed synergism, with CI values <0.7 at $F_a = 0.25$ and ≈ 0.7 at $F_a = 0.5$ and 0.75 . Dose-reduction index (DRI) values for both drugs were >1 , indicating reduced doses required in combination. These results suggest that combining 5-FU with Tamoxifen may be a promising strategy to enhance gastric cancer treatment.

Keywords: 5-Fluorouracil (5-FU); Cytotoxicity; Gastric cancer; MTT assay; Synergistic effect; Tamoxifen.

1. Introduction

Gastric cancer remains a major global health burden and is the fifth leading cause of cancer-related mortality worldwide [1]. Early-stage disease is usually asymptomatic, which significantly hinders timely diagnosis and contributes to poor clinical outcomes. The highest incidence rates occur in East Asian countries—including Korea, Mongolia, Japan, and China—where annual incidence ranges from 40 to 60 per 1000 individuals [2]. In Iran, in contrast to trends observed in many Western nations and Japan, the incidence of gastric

cancer has been rising over the past two decades [3]. Environmental factors such as *Helicobacter pylori* infection, high salt intake, and smoking have been consistently identified as major contributors to disease onset [4]. Despite improvements in diagnostic tools and therapeutic strategies, the prognosis for patients with advanced gastric cancer remains poor due to the aggressive nature of the tumor, resistance to chemotherapy, and delays in clinical detection. These challenges highlight the need for novel therapeutic approaches capable of improving treatment efficacy and patient survival [5].

* Corresponding Author:

Hassan Akrami, Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: h_akrami@sums.ac.ir.

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One promising strategy is combination therapy, which employs two or more therapeutic agents to target cancer through multiple mechanisms. Such an approach can simultaneously modulate key signaling pathways, limit tumor growth and metastasis, trigger apoptosis, arrest the cell cycle, and reduce cancer stem cell populations [6-8]. Combination regimens offer several advantages over monotherapy, including enhanced therapeutic efficacy, minimized toxicity from high single-agent doses, and reduced likelihood of developing drug resistance by targeting different aspects of cancer cell biology [9, 10]. Recent evidence emphasizes the importance of combination and targeted treatments in addressing the complexity of resistance mechanisms in gastric cancer. By disrupting several tumor survival pathways at once, these strategies aim to exploit specific vulnerabilities in cancer cells and improve overall therapeutic outcomes [11, 12].

Among the essential chemotherapeutic agents used in treating gastric cancer is 5-Fluorouracil (5-FU), a pyrimidine analogue that inhibits DNA and RNA synthesis, thereby preventing cancer cell proliferation and inducing cell death [13, 14]. Its effectiveness has been demonstrated across various malignancies, including gastric cancer. Moreover, combining 5-FU with agents such as oxaliplatin and leucovorin has yielded promising results in metastatic gastric cancer by enhancing cytotoxic activity and counteracting resistance mechanisms [15] [16]. These successes underscore the potential value of exploring additional 5-FU-based drug combinations to uncover further therapeutic benefits.

Tamoxifen, a selective estrogen receptor modulator (SERM), is widely recognized as a first-line therapy for hormone-dependent breast cancer [17]. However, its therapeutic relevance is not limited to breast malignancies. The presence of estrogen receptors (ER) in gastric carcinoma tissue was first reported several decades ago [18], and subsequent studies have confirmed ER expression in subsets of gastric tumors, suggesting that anti-estrogenic compounds may hold therapeutic value in this context [19]. Tamoxifen exerts both estrogen receptor agonist and antagonist effects depending on tissue type, reducing estrogen activity and altering gene expression profiles related to tumor growth and angiogenesis [20]. Beyond its hormone-modulating

actions, tamoxifen also affects several non-hormonal pathways. It has been shown to interfere with cell-cycle regulation, apoptosis induction, and angiogenesis inhibition—mechanisms that are central to cancer progression and metastasis [21]. These multifaceted effects indicate that tamoxifen may have broader anticancer potential than traditionally recognized.

In gastric cancer specifically, emerging evidence supports tamoxifen's therapeutic relevance. For instance, studies have demonstrated that tamoxifen can modulate the expression of Notch1 and DLL1 genes in MKN-45 gastric cancer cells, suggesting potential regulatory roles in pathways associated with tumor initiation and progression [22]. The combination of these off-target actions with its established receptor-mediated effects provides a compelling justification for evaluating tamoxifen in conjunction with conventional cytotoxic agents such as 5-FU.

Given the central role of 5-FU in gastric cancer treatment and the expanding evidence for tamoxifen's antitumor activity in this malignancy, combining these two agents may offer synergistic benefits. The dual modulation of hormone-related and non-hormonal pathways, coupled with the cytotoxic effects of 5-FU, could enhance treatment response, overcome drug resistance, and inhibit tumor growth more effectively than either agent alone. Therefore, this study aims to investigate the combined effects of tamoxifen and 5-FU on the viability of gastric cancer cells. By systematically assessing their interaction profile, the study seeks to determine whether this combination represents a promising therapeutic approach worthy of further investigation.

2. Materials and Methods

2.1. Cell culture

The gastric cancer cell line, MKN-45, was purchased from the National Cell Bank of Iran (NCBI) affiliated with the Iran Pasteur Institute. DMEM/F12 culture medium containing 10% heat-inactivated fetal bovine serum (FBS) (Bioidea, Iran), 100 µg/mL streptomycin sulfate (Sigma, USA), 100 U/mL penicillin (Sigma, USA) and 2 mM L-glutamine (Sigma, USA) was used for cultivation of MKN-45 cells at 37 °C, 95% air, and 5% CO₂.

2.2. MTT Assay

The MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was used to investigate the cytotoxicity of Tamoxifen and 5-FU and their combination. For this, the MKN-45 cells were cultured in 96-well plates at a density of 1×10^4 cells per well in the incubator at 37 °C, 95% air, and 5% CO₂ for 24 h. After that, MKN-45 cells were treated with Tamoxifen (0, 2, 4, 6, 8, 10, and 12 µg/ml), 5-FU (0.1, 0.2, 0.4, 0.6, 0.8, 1, and 2 µg/ml), and selection of concentration for combination assays (0.9 µg/ml 5-FU + 7 µg/ml Tamoxifen) was verified by the IC₅₀ values calculated in the prior assays with different concentrations. The Cell viability was determined after 48 h by reading the absorbance at 530 nm using a microplate reader (BioTEK, USA). In summary, the culture media were discarded and MTT solution was added in each of the wells and then incubation was performed for 4 h at 37 °C. At the final step, the MTT solution was removed and 100 µl of DMSO (Merck, Germany) was added to each of the wells after 15 min shaking, reading the absorbance at 530 nm using a microplate reader was performed (BioTEK, USA). All experiments were done in triplicate. All experiments were performed with three independent biological replicates (n=3), with each data point assayed in triplicate (technical replicates).

2.3. Synergic effects analysis

Compusyn software was used to evaluate synergism via using cell viability inhibitory experiments data. The following formula was used to calculate the combination index (CI). The CI>1, CI=1, and CI<1 respectively show antagonism, additive, and synergism. $CI = [(D_1)/(Dx)_1] + [(D_2)/(Dx)_2] + [(D_1)(D_2)/(Dx_1)(Dx_2)]$. The parameters (D)₁ and (D)₂ indicate the combination concentrations of drugs 1 and 2 in a fixed ratio used together to achieve x% of the total medication effect; and (Dx)₁ and (Dx)₂ are the concentrations of the separate agents to achieve the same efficacy.

The Fa-CI plot, dose-effect curve, and isobologram were produced from CompuSyn. Fa-CI plot shows the actual CI values at various suppressive levels. The DRI (the dose-reduction index) was measured to calculate the folds in dose reduction for each drug in a synergistic combination. DRI=1 indicates dose doesn't reduce, whereas DRI>1 and DRI<1 show favorable and unfavorable dose reduction, respectively.

2.4. Statistical analysis

Graph-pad prism 7.0 statistical software was used for data analysis. Data are presented as mean ± standard deviation (SD) of at least three independent experiments. Statistical significance between multiple groups was determined using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. For comparisons between two specific groups, an unpaired two-tailed Student's t-test was used. A p-value of less than 0.05 was considered statistically significant.

3. Results and Discussion

3.1. The effects of Tamoxifen, 5-FU and Tamoxifen + 5-FU on MKN-45 cells viability

As shown in **Figure 1**, treatment with Tamoxifen or 5-FU decreased MKN-45 cell viability in a dose-dependent manner. The IC₅₀ values were calculated as 0.9 µg/ml for 5-FU and 7 µg/ml for Tamoxifen. The combination of 5-FU and Tamoxifen resulted in an IC₅₀ of 0.7 µg/ml (**Fig. 1**).

3.2. Synergic effects of 5-FU + Tamoxifen on MKN-45 cells

The effectiveness of various Tamoxifen and 5-FU concentrations was assessed in our study using a variable ratio. To ascertain the potential of combination of both drugs, MKN-45 cells were exposed to 5-FU and Tamoxifen at a non-constant ratio for 48 h. The combined effect of both medications was evaluated using a variety of analytical techniques, such as combination index (CI), isobologram analysis, and curve-shift analysis. By showing that combining 5-FU and Tamoxifen is more effective than using either drug alone, the dose-response curves validated the combination therapy's advantages (**Fig. 2A**). Comparing the “m” values of 5-FU and Tamoxifen together shows a sharper sigmoidal curve than either medication alone (“m” = the median-effect plot's slope) (Table 1). R² is the square of “r”, and the “r” value is determined utilizing the linear correlation coefficient associated with the median-effect plot (**Fig. 2B**). Both agents show a strong linear correlation (R² ≥ 0.94), with the dose-dependent effects in vitro consistent with the median effect principle (r ≥ 0.95) (**Table 1**).

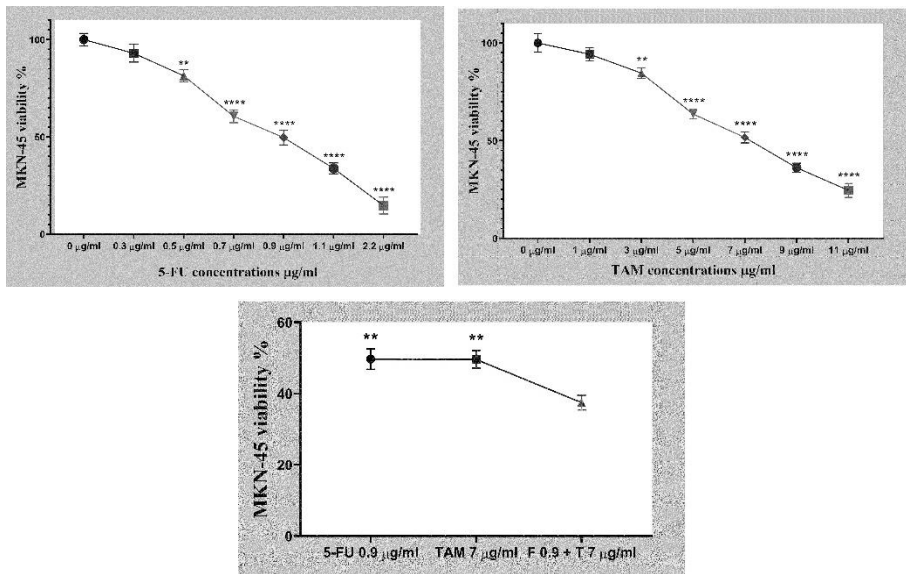


Figure 1: The effects of 5-FU, Tamoxifen and their combination on growth inhibition in dose-dependent and modulation IC50 of 5-FU by Tamoxifen in MKN-45 gastric cancer cells. MKN-45 gastric cancer cell line was treated with different concentrations of Tamoxifen (0, 2, 4, 6, 8, 10, 12 µg/ml) and 5-FU (0, 0.2, 0.4, 0.6, 0.8, 1, 2 µg/ml) drugs for 48 hours. The viability of MKN-45 cells treated with Tamoxifen (A) and 5-FU (B) drugs alone and in combination (C) for 48 hours of incubation was analyzed using the MTT method. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to untreated control.

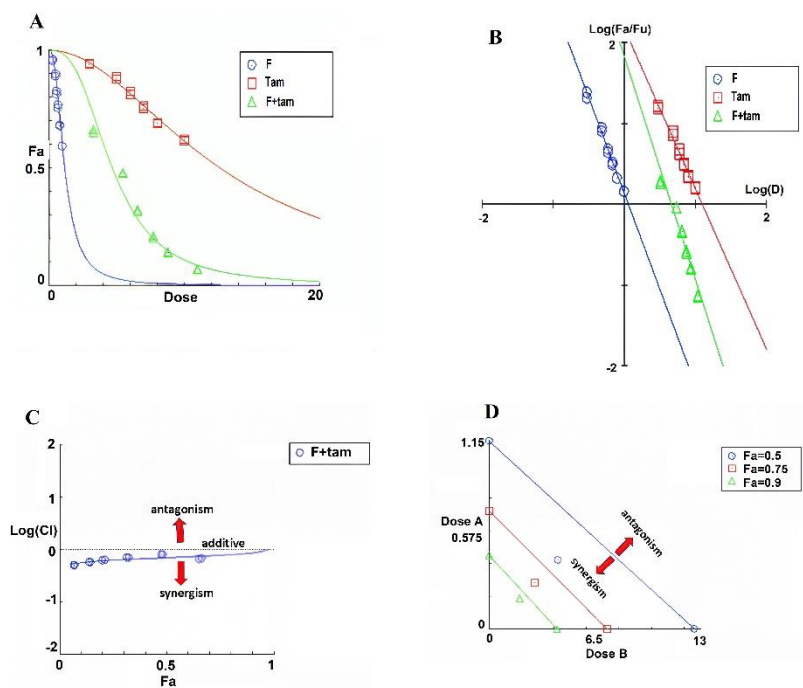


Figure 2: 5-FU, Tamoxifen and combination cytotoxicity on MKN-45 cell line (A) Concentration-dependent cytotoxicity of 5-FU, Tamoxifen via MTT cytotoxicity test at 48 hours treatment. (B) The CI plot of combinations treatment for 5-FU and Tamoxifen. (D) Isobolograms plot, CI values < 1 = synergistic effects; CI values > 1 = antagonistic effects; and CI values $= 1$ are = additive effects. These were automatically generated using the CompuSyn software (Paramus, NJ, USA).

Table 1: The m and R^2 values for each drug and their combinations were determined using CompuSyn software.

	m	r	R^2
5-FU	-2.3	-0.99	0.98
Tam	-1.9	-0.99	0.98
Combination	-2.7	-0.97	0.94

The present study found synergistic effects for all non-constant combinations of Tamoxifen and 5-FU, particularly in inhibiting MKN-45 cell proliferation, as analyzed using CompuSyn software (**Fig. 2C-D**).

The combination index (CI) values, summarized in **Table 2**, indicate synergy when less than 1. Strong synergy is defined as CI values of 0.1–0.3, synergy as 0.3–0.7, moderate synergy as 0.7–0.85, and weak synergy as 0.85–0.9 [23]. Table 2 shows a synergistic effect at $Fa=0.25$ ($CI < 0.7$) and moderate synergy at $Fa=0.5$ and $Fa=0.75$ ($CI \approx 0.7$). Based on the obtained results, the combination of Tamoxifen and 5-FU synergistically reduces cell proliferation in MKN-45 cells. The DRI was used to see how much the dose of each medicine could be lowered when 5-FU and Tamoxifen were combined. The DRI values were above 1, showing favorable dose reduction for both drugs and the beneficial effects of their combination (**Fig. 3**).

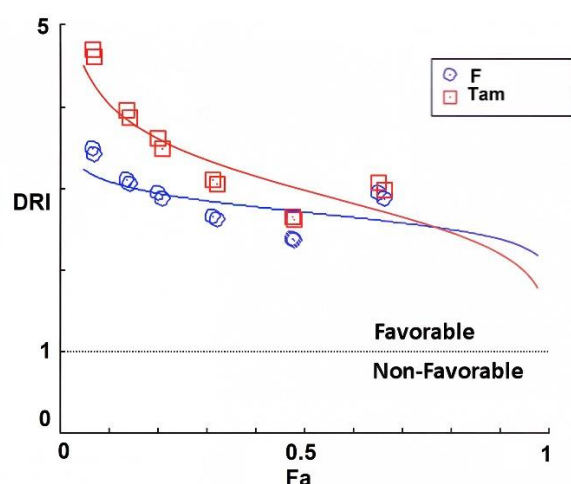


Figure 3: The Dose Reduction Index (DRI) values for combinations of 5-FU and Tamoxifen. DRI less than value 1 indicated unfavorable drug combinations, whereas DRI values more than 1 demonstrated favorable drug combinations.

Table 2: Combination Index (CI), Dose reduction index (DRI) affected fractions (Fa), and matching CI and DRI values to assess the degree of drug combination using the CompuSyn Software.

Effect (Fa)	5-FU Dose	Tamoxifen Dose	CI Value	DRI (5-FU)	DRI (Tamoxifen)
.25	1.82789	21.9248	0.63424	2.89121	3.46788
.50	1.14825	12.6271	0.70465	2.70965	2.97976
.75	0.72132	7.27237	0.78435	2.53949	2.56033

3.3. Discussion

GC remains a major GHC, and despite advances in S, Dx, and PM, S alone is insufficient to prevent PR in a substantial proportion of Pts [24, 25]. This persistent R highlights the importance of effective AdjTx and SysTx capable of targeting RD. CTx-combos have gained attention for their potential to enhance ACE while addressing the limitations of SA-Rgns [26]. Within this context, our ST provides evidence that the combined use of 5-FU and TMX exerts a SYN-CTE on MKN-45 GCCs, pointing toward a possible TA that warrants further ME and TE.

A central consideration in evaluating DCs is CD, as TB must be balanced against TxX [27]. Our RSTs demonstrate that the 5-FU–TMX combo not only suppresses MKN-45 CP more effectively than either D alone but also reduces the individual IC₅₀-Vs of both AGs. This indicates that the combo achieves comparable or greater ACA at significantly lower Ds. C–T ANL further substantiated this observation: CI-Vs remained <1 across MDD-Lvls, confirming a SYN rather than merely ADD interaction. The corresponding DRI-Vs reinforce this conclusion. At $Fa=0.5$, both AGs exhibited DRI-Vs >2, a threshold regarded as CA because it enables meaningful D-MN without compromising TI. Such RDs could be particularly beneficial for GC-Pts, who often experience substantial Tx from Cytos-Rgns. The relevance of our FDs becomes clearer when viewed within the broader CTX context in GC. PSs have shown that combining 5-FU with AGs targeting complementary PWs can improve its ACA, although the specific Ms and degree of benefit vary depending on TB. For ex., 5-FU paired with GLB enhances APS via influencing Bcl-2, Bax, and VEGF regulation [28], while combos such as ALC/5-FU or MET/5-FU augment CH-SNS by attenuating WNT-PW activity and MDR1 expression [29]. These OBVs underscore a recurring THM: GCCs exhibit PW-dependent VNs that can be exploited when multiple SNs are targeted simultaneously. Our RST contributes to this discourse by demonstrating that 5-FU and TMX—two DRs not conventionally paired in GC—also interact cooperatively.

Importantly, our FD mirrors the DRs previously observed between PD and WD GCC-Lns. H-et-al. reported that TMX+5-FU suppressed PF in PD

KATOIII-Ls yet failed to do so in WD MKN28-Ls [30]. The SYN evident in our MKN-45 MDL, which is also PD, suggests that this combo may be particularly effective in GC-STs characterized by HP-PT, GI, or specific PW-DPs. This pattern reinforces the need to consider TH when evaluating CTX-combos.

GC is now recognized as an MD MLN consisting of distinct STs, including EBV+, MSI-H, GS, and CIN. These STs differ markedly in II, MB, and DSPWs, and such MDs may shape TRs. Although our ST did not directly evaluate MST-specific effects, the observed SYN raises important questions about how this DP interacts with established GC-BMs. For ex., 5-FU activity is modulated by p53-ST, which is frequently altered in GC and may influence susceptibility to CH-IAP [31]. TMX, while best known for ER-ANT in BC, also affects non-ER PWs such as PI3K/AKT, which is commonly activated in GC. The interplay between these PWs could underlie the enhanced CTE we observed. Future WK should examine whether HER2-EXP, MSI-STs, PD-L1-Lvls, or other BM-defined FTNs predict RR to this combo.

Although our EXPs did not interrogate UB directly, several MPBs align with known GC-PG features. One plausible explanation is the simultaneous disruption of SP and PF PWs: TMX can inhibit PI3K/AKT-SG, while 5-FU targets TS, impairing DNS [32]. Coordinated inhibition may sensitize CCs to APS by shifting the balance between P-A (Bax) and A-A (Bcl-2) regulators [33]. Additionally, TMX-MD activation of Casp-3 may amplify APS-Rs initiated by 5-FU [34]. These intersecting effects could produce an M-LD disruption of key OPG-PRs, resembling other successful combos such as CUR+5-FU, which achieve SYN partly through COX-2 suppression [35, 36]. Given that COX-2, PI3K/AKT, and APS-REGs are frequently dysregulated in GC, the convergence of these PWs may provide the MB for the SYN we observed.

In sum, our ST supports the concept that 5-FU and TMX together exert a SYN-IHG effect on GC-CGR, allowing for meaningful DRs that may translate into improved TOL and CAP. The FDs highlight a potentially underexplored TI that merits further INV. To advance this WK, future STs should incorporate MA—such as measuring p-AKT, COX-2, Bcl-2, and c-Casp-3—and conduct GEPs to identify SNs most affected by the

combo. Moreover, leveraging BA to analyze datasets such as TCGA and GEO could help contextualize these MCs within the landscape of GC-HTG and guide the selection of PGs most likely to benefit from this strategy [37, 38]. Such efforts will be essential for determining whether the SYN observed *in vitro* can be translated into meaningful CTOs.

This study provides strong *in vitro* evidence for the synergistic cytotoxicity of Tamoxifen and 5-FU in the MKN-45 gastric cancer cell line, but several limitations should be noted. First, the use of a single cell line does not reflect the molecular and phenotypic heterogeneity of gastric cancer. Early validation in additional models—such as MKN-28, AGS, and other molecular subtypes—will be necessary to determine whether the synergy is generalizable. Second, all experiments were conducted in 2D monolayer cultures, which lack the three-dimensional architecture, cellular diversity, and microenvironmental cues of *in vivo* tumors. Incorporating 3D spheroids or patient-derived organoids would enhance the translational relevance of the findings. A further limitation is the absence of *in vivo* studies. Animal models are essential for assessing systemic toxicity, pharmacokinetics, and therapeutic efficacy, which cannot be inferred from *in vitro* assays alone. Additionally, although the study demonstrates clear synergy between Tamoxifen and 5-FU, it remains largely phenomenological. The molecular mechanisms underlying the interaction—potentially involving apoptotic regulation (e.g., Bax/Bcl-2), inflammatory pathways (e.g., COX-2), or tumor suppressor activity (e.g., P53)—remain undefined. Future work should include mechanistic analyses such as western blotting, qPCR, or pathway-specific inhibition assays.

4. Conclusion

This study provides compelling *in vitro* evidence that the combination of Tamoxifen and 5-FU exerts a strong synergistic cytotoxic effect against MKN-45 gastric cancer cells. The significantly reduced IC₅₀ values, consistent synergism (CI < 1), and favorable dose-reduction indices (DRI > 2) form a robust pharmacological foundation for this combination. These findings suggest a promising strategy to enhance therapeutic efficacy while potentially mitigating the dose-limiting toxicities commonly associated with 5-FU monotherapy, thereby improving the therapeutic

index. To realize this potential, future work must focus on validating these findings in vivo to assess the combination's pharmacokinetics, systemic toxicity, and antitumor efficacy in a physiologically relevant model. Furthermore, elucidating the precise molecular mechanisms of synergy and exploring its activity across the diverse molecular subtypes of gastric cancer will be crucial for identifying patient populations most likely to benefit from this therapeutic strategy, ultimately paving the way for its clinical translation.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors Contributions

Zeinab Mahdian conducted experimental works and wrote the manuscript. Hassan Akrami designed, directed the investigation, analyzed the results and revised the manuscript. Mahdi Bagheri contributed to cell culture and writing manuscript. Yousef Nikmanesh contributed to revising the manuscript.

Authors Orcid numbers:

Zeinab mahdian: [0000-0002-6050-6076](https://orcid.org/0000-0002-6050-6076)

Hassan Akrami: [0000-0002-7758-6770](https://orcid.org/0000-0002-7758-6770)

Mahdi Bagheri: [0000-0002-0396-1451](https://orcid.org/0000-0002-0396-1451)

Yousef Nikmanesh: [0000-0002-5865-4694](https://orcid.org/0000-0002-5865-4694)

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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