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Evaluating the Cytotoxic Impact of 5FU and Green-Synthesized Silver Chloride Nanoparticles on Gastric Cancer Cells

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Abstract

Aim: This study aims to comprehensively evaluate the cytotoxic effects of silver chloride nanoparticles and 5-fluorouracil (5FU) on gastric cancer cells, comparing them to non-cancerous HEK293 cells and investigating the potential synergistic effects of their combined treatment.

Background and Objective: Nanoparticles and chemotherapeutic agents have demonstrated potential in inducing cytotoxic effects in cancer cells. However, the synergistic effects of silver chloride nanoparticles and 5FU on gastric cancer cells remain insufficiently understood.

Methods and Analysis: In this experimental study, gastric cancer cells were allocated into four groups: control (untreated), groups treated exclusively with silver chloride nanoparticles, groups treated exclusively with 5FU, and groups receiving a combination of silver chloride nanoparticles and 5FU. Cell viability was assessed using the MTT assay 24 hours post-treatment. Data were analyzed using one-way analysis of variance (ANOVA) to identify statistically significant differences among the treatment groups.

Results: The cytotoxic effects of 5FU on AGS cells were comparable to its effects on non-cancerous HEK293 cells. Silver chloride nanoparticles exhibited cytotoxic effects at concentrations exceeding 12 µg/mL in HEK293 cells and concentrations exceeding 3.1 µg/mL in gastric cancer cells. While individual treatments with 5FU or silver chloride nanoparticles induced dose-dependent cytotoxic effects on gastric cancer cells, the combined treatment exhibited enhanced cytotoxicity compared to either agent alone. Notably, the combination of 5FU and silver chloride nanoparticles at specific concentrations led to a significant reduction in cell viability, suggesting synergistic effects.

Conclusion: The findings of this study indicate that the co-administration of silver chloride nanoparticles and 5FU exerts greater cytotoxic effects on gastric cancer cells compared to 5FU monotherapy.

Keywords: Silver chloride nanoparticles, 5FU, Gastric cancer

1. Introduction

Gastric cancer, characterized by the uncontrolled proliferation of malignant cells in the stomach lining, remains a significant global health challenge, contributing substantially to morbidity and mortality. The disease exhibits a notably higher incidence in men, who are twice as likely to develop gastric cancer as women, making it the fourth most common cancer worldwide (Mamun et al., 2024). The primary etiological factor for gastric cancer is Helicobacter pylori infection, which accounts for over 60% of reported cases (Dunan et al., 2025). Other major risk factors include smoking, dietary habits (e.g., high consumption of pickled vegetables), obesity, and genetic predisposition (Vahid & Davoodi, 2021). Early symptoms often include heartburn, upper abdominal discomfort, nausea, loss of appetite, weight loss, jaundice, vomiting, and hematochezia (Nagaich & Sharma, 2018).

Nanoparticles, particularly silver nanoparticles, have demonstrated significant anticancer properties across various cancer cell lines, making them a promising area of study in cancer research. Their unique physicochemical properties have driven interest in their potential therapeutic applications in oncology (Huy et al., 2020; Faridi et al., 2023). The emergence of nanoparticle-based therapies represents a new frontier in precision medicine, offering innovative strategies for improving cancer treatment outcomes.

Chemotherapy remains the cornerstone of gastric cancer treatment, with 5-fluorouracil (5FU) being one of the most extensively studied and widely used chemotherapeutic agents. 5FU, commonly marketed under the trade name Adrucil, is a cytotoxic drug known for its efficacy against various malignancies, particularly gastrointestinal cancers (Yuan et al., 2021). Its role in gastric cancer therapy is well-established, whether used as a monotherapy or in combination with other agents (Na et al., 2021; Yamashita et al., 2021; Wolpin et al., 2007).

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Recent studies suggest that combining 5FU with other compounds, including nanoparticles, may improve therapeutic efficacy and enhance postoperative survival rates in gastric cancer patients (Hong and Feng, 2021). This growing body of research underscores the potential of combination therapies, particularly those incorporating nanoparticles, as a promising avenue for optimizing treatment strategies (Guo et al., 2025; Meng et al., 2025).

Nanoparticles hold immense potential as novel therapeutic agents for gastrointestinal cancers (Mittal et al., 2018). Studies have investigated their cytotoxic effects on gastrointestinal cancer cell lines, as well as their influence on apoptotic gene expression. The cytotoxicity of nanoparticles against gastric cancer cells has been shown to be dose- and time-dependent (Miethling-Graff et al., 2014). Additionally, research examining the cytotoxic effects of nanoparticles on human gastric cancer cells has highlighted their significant impact on cell viability (Li et al., 2017). A growing number of studies has also explored the green synthesis of silver chloride nanoparticles using plant extracts, revealing their potent anticancer properties (Rani et al., 2022). The eco-friendly, cost-effective green synthesis method has gained traction due to its simplicity and its demonstrated cytotoxic effects against AGS cells (gastric adenocarcinoma) (Aslany et al., 2020).

Given the substantial global burden of gastric cancer and its profound clinical, social, and economic impact, there is a critical need for novel and more effective treatment strategies. While previous research has largely focused on the individual effects of nanoparticles on cancer cells, there remains a notable gap in understanding their combined effects with conventional chemotherapeutic agents. Therefore, this study aims to investigate the synergistic effects of 5FU and silver chloride nanoparticles on gastric cancer cells. The findings from this research could provide valuable insights into optimizing treatment approaches and improving therapeutic outcomes for gastric cancer patients.

2. Material and Methods

In this experimental study, we obtained cancer cell lines HEK293 and AGS from the molecular cell bank of the Pasteur Institute of Iran and maintained them under strictly sterile and standardized conditions within liquid nitrogen tanks. We categorized gastric cancer cells into specific groups for analysis, including control (untreated), groups treated solely with silver chloride nanoparticles, groups treated solely with 5-fluorouracil (5FU), and groups exposed to a combination of silver chloride nanoparticles and 5FU. The determination of all concentrations, both individual and combined, was carefully carried out based on the collective expertise of the researchers and preliminary pilot studies conducted in the laboratory.

For drug preparation, 5FU powder was obtained from Aburaihan Pharmaceutical Company. 5FU was then dissolved in phosphate-buffered saline (PBS), sterilized, and prepared at various concentrations. Silver chloride nanoparticles were synthesized through an environmentally friendly and green method using a plant extract, as described in previous studies. Fresh leaves of the cotton thistle plant (Onopordum acanthium) were harvested, thoroughly washed, and homogenized to obtain a uniform aqueous extract. The extract was then mixed with a silver chloride solution, and the resulting mixture was incubated at room temperature. The reduction of silver ions to AgCl nanoparticles was facilitated by the bioactive compounds in the plant extract. The change in color observed in the reaction mixture served as an indicator of nanoparticle formation.

The identity, size, morphology, and crystalline structure of the green-synthesized AgCl nanoparticles were characterized using scanning electron microscopy (SEM) and X-ray diffraction (XRD). SEM was employed to analyze the surface morphology and particle size distribution, providing high-resolution images to confirm the structural integrity and shape of the nanoparticles. XRD analysis was conducted to determine the crystalline phase and purity of the nanoparticles, identifying characteristic diffraction peaks corresponding to silver chloride. These techniques collectively ensured the precise characterization of the synthesized nanoparticles, confirming their successful formation and structural properties.

HEK293 and AGS cells were treated with varying doses of 5FU and AgCl nanoparticles, both independently and in combination. Control groups without any treatment were included for baseline comparison. Following treatment initiation, the cells were incubated for 24 hours to assess their responses to the administered treatments. Subsequently, the viability of HEK293 and AGS cells was evaluated using the MTT colorimetric assay method, allowing for a comprehensive analysis of cellular viability across different concentration gradients.

After the incubation period, the cell culture medium was carefully aspirated, and an MTT solution with a concentration of 5.0 mg/ml was added to each well. The cells were then incubated for an additional 4 hours at 37°C, enabling viable cells to convert the yellow tetrazolium salt into formazan crystals. At the end of this incubation period, the MTT solution was removed, and the formazan crystals were dissolved using dimethyl sulfoxide (DMSO). The absorbance of the resulting solution at a wavelength of 570 nanometers was then measured using a microplate reader. The data obtained from the MTT assay were used to construct dose-response curves, facilitating the determination of IC50 values, which represent the concentrations of 5FU and AgCl nanoparticles required to inhibit cell viability by 50%.

For statistical analysis, we employed SPSS 20 software, with the normal distribution of data confirmed using the Kolmogorov-Smirnov test. Group comparisons were conducted using one-way analysis of variance (ANOVA) among the subjects, followed by Tukey's post hoc test for further analysis. Significance levels were set at $P < 0.05$ to determine differences between groups.

3. Results

The morphology of the synthesized AgNPs was analyzed using SEM to assess their shape, size, and surface characteristics. Figure 1 presents a high-resolution microscopic image of the AgNPs, providing detailed insight into their structural properties. A point-to-point analysis conducted through SEM confirmed that the nanoparticles exhibit a size distribution ranging between 50 and 70 nm. The observed variations in nanoparticle size

may be attributed to factors such as synthesis conditions, plant extract composition, and reaction kinetics. Additionally, the SEM images indicate that the nanoparticles possess a relatively uniform spherical or quasi-spherical morphology with minimal aggregation, further supporting the successful formation of AgNPs through the green synthesis method.

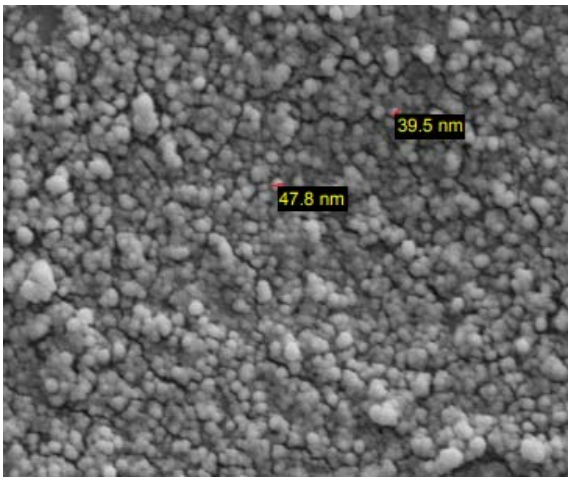

Figure 1. SEM Image of green-synthesized AgNPs showing size distribution and morphology.

Silver chloride nanoparticles (AgNPs) were characterized using X-ray diffraction (XRD) analysis to investigate their composition and purity. Figure 2 presents the XRD patterns of AgNPs synthesized using plant leaf extract. The characteristic diffraction peaks observed in the XRD pattern appeared at 2θ values of 38.4°, 44.5°, and 64.8°, corresponding to the (111), (200), and (220) crystallographic planes of the face-centered cubic (FCC) structure of silver, respectively, as per the Joint Committee on Powder Diffraction Standards (JCPDS) file No. 04-0783. The absence of any additional diffraction peaks indicates that no impurities were present, confirming the high purity and successful synthesis of AgNPs.

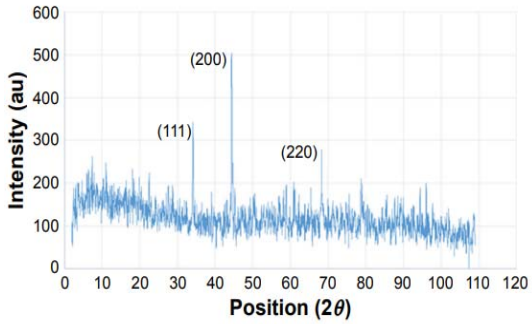

Figure 2: XRD pattern of green-synthesized AgNPs

The MTT assay results showed no significant difference in the cell viability of HEK cells treated with 3.9, 7.8, and 15.6 µg/mL of 5FU compared to the control group. However, significant reductions in cell viability were observed at higher concentrations of 5FU (31.2, 62.5, 125, 250, and 500 µg/mL) relative to the control group ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively) (Figure 3). The IC50 value for 5FU in HEK cells was determined to be 174 µg/mL (Figure 4).

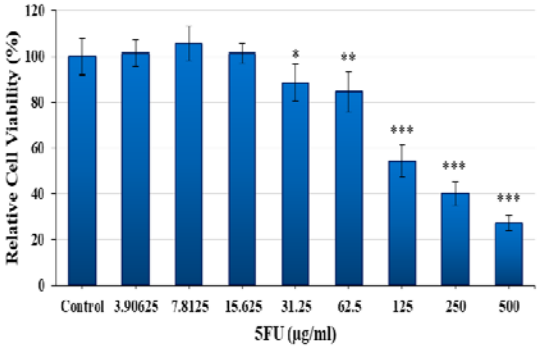

Figure 3. Cell viability of HEK293 cells at various concentrations of 5FU (µg/ml). The * symbol indicates a significant difference compared to the control group (**: $p < 0.01$, ***: $p < 0.001$).

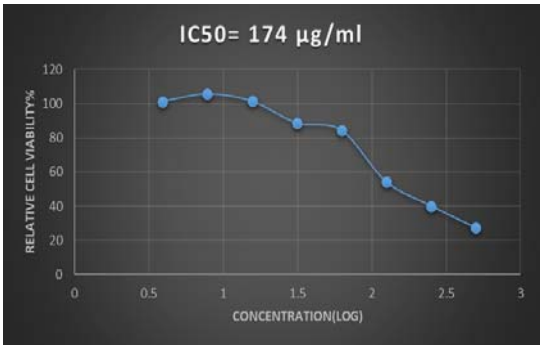

Figure 4. Plot illustrating the calculation of IC50 corresponding to the cytotoxic effects of 5FU on HEK293 cells.

Similarly, in the AGS cell line, no significant difference in viability was observed at 3.9, 7.8, and 15.6 µg/mL of 5FU compared to the control. However, cell viability significantly decreased at concentrations of 31.2, 62.5, 125, 250, and 500 µg/mL ($p < 0.001$) (Figure 5). The IC50 value for 5FU in AGS cells was found to be 92 µg/mL (Figure 6).

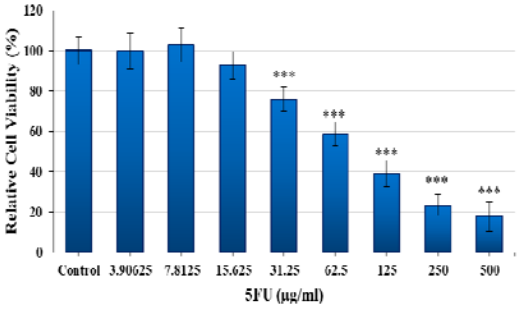

Figure 5. Cell viability of AGS cells exposed to different doses of 5FU (µg/ml). The * symbol indicates a significant difference compared to the control group (***:$p<0.001$).

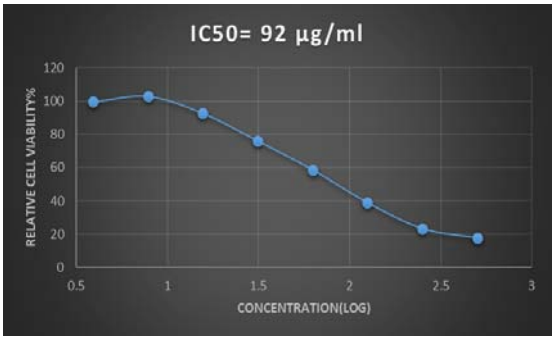

Figure 6. The graph illustrates the calculation of IC50 corresponding to the cytotoxic effects of 5FU on AGS cells.

For AgCl, the viability of HEK293 cells showed no significant difference at concentrations of 1.5, 3.1, and 6.2 µg/mL compared to the control group. However, significant reductions in viability were observed at concentrations of 12.5, 25, and 50 µg/mL ($p < 0.001$) (Figure 7). The IC50 value for AgCl in HEK293 cells was calculated to be 16.2 µg/mL (Figure 8).

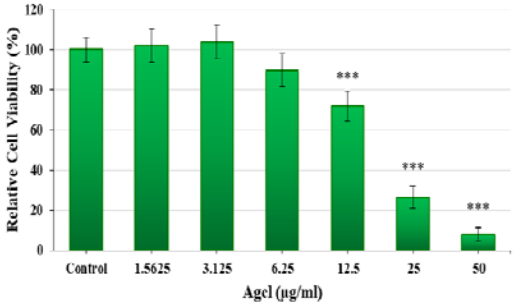

Figure 7. Viability of HEK293 cells exposed to different doses of green-synthesized silver chloride nanoparticles (µg/ml). The * symbol indicates a significant difference compared to the control group (***: $p<0.001$).

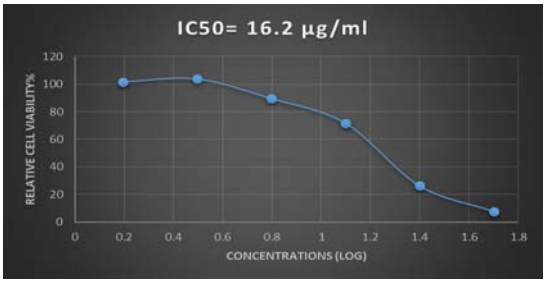

Figure 8. Graph depicting the calculation of IC50 for the cytotoxic effects of silver chloride nanoparticles on HEK293 cells.

For AgCl, the viability of HEK293 cells showed no significant difference at concentrations of 1.5, 3.1, and 6.2 µg/mL compared to the control group. However, significant reductions in viability were observed at concentrations of 12.5, 25, and 50 µg/mL ($p < 0.001$) (Figure 9). The IC50 value for AgCl in HEK293 cells was calculated to be 16.2 µg/mL (Figure 10).

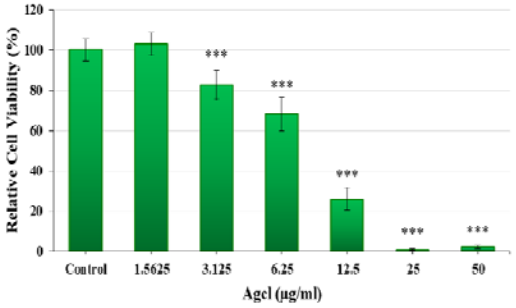

Figure 9. Cell viability of AGS cells exposed to various doses of green-synthesized silver chloride nanoparticles (µg/ml). The * symbol indicates a significant difference compared to the control group (***: $p<0.001$).

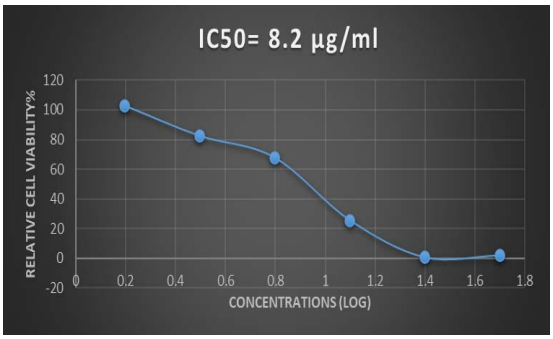

Figure 10. Graph depicting the calculation of IC50 related to the cytotoxic effects of silver chloride nanoparticles on AGS cancer cells.

For the combination of 5FU and AgCl, HEK293 cell viability was not significantly affected at concentrations of 3.9, 7.8, 15.6, and 31.2 µg/mL compared to the control. However, significant reductions in viability were observed at concentrations of 62.5, 125, 250, and 500 µg/mL ($p < 0.01$, $p < 0.001$, respectively) (Figure 11). The IC50 value for the 5FU + AgCl combination in HEK293 cells was 181 µg/mL (Figure 12).

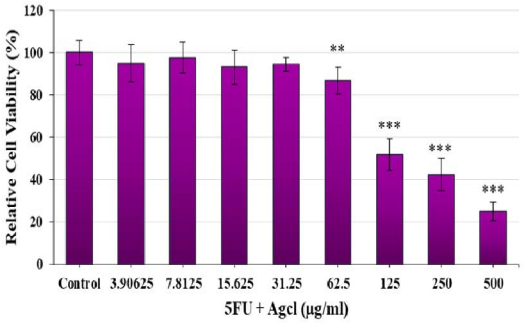

Figure 11. Viability of HEK293 cells exposed to different doses of 5FU+AgCl (µg/ml). The * symbol indicates a significant difference compared to the control group(**: $p<0.01$, ***: $p<0.001$).

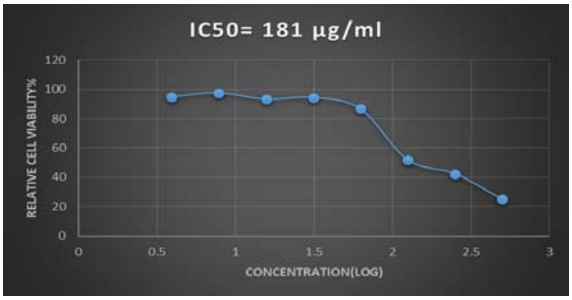

Figure 12. IC50 plot related to the synergistic cytotoxic effects of silver chloride nanoparticles and 5FU on HEK293 cells.

In AGS cells, the 5FU+AgCl combination at 3.9 µg/mL had no significant effect on viability compared to the control. However, concentrations of 7.8, 15.6, 31.2, 62.5, 125, 250, and 500 µg/mL caused significant reductions in viability ($p < 0.001$) (Figure 13). The IC50 for the combination in AGS cells was 43 µg/mL (Figure 14).

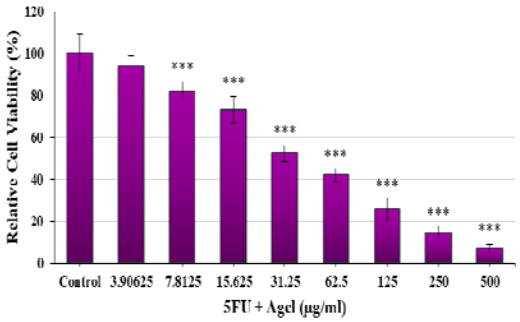

Figure13. Viability of AGS cells exposed to various doses of 5FU+AgCl (µg/ml). The * symbol indicates a significant difference compared to the control group (***: p<0.001).

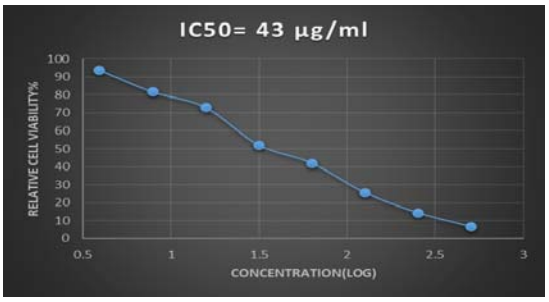

Figure 14. IC50 plot related to the synergistic cytotoxic effects of silver chloride nanoparticles and 5FU on AGS cells.

4. Discussion

The experimental results of this study provide valuable insights into the dose-dependent reduction in the viability of gastric cancer cells (AGS) and human non-cancerous cells (HEK293) following exposure to varying concentrations of 5-fluorouracil (5FU), silver chloride (AgCl) nanoparticles, and their combination. The data reveal a proportional decrease in cell survival as drug and nanoparticle concentrations increase, highlighting the cytotoxic effects of both agents on gastric cancer cells and their potential as therapeutic candidates.

The anti-cancer effects of 5FU are attributed to its inhibition of thymidylate synthase and disruption of DNA synthesis, while silver chloride nanoparticles contribute cytotoxic properties that enhance overall treatment efficacy (Dongsar et al., 2023; Rojas-Cessa et al., 2024). Notably, concentrations of 5FU below 31 µg/mL did not significantly impact cell survival compared to controls. However, above this threshold, a distinct and statistically significant reduction in viability was observed. The combination of 5FU and AgCl nanoparticles exhibited a more pronounced cytotoxic effect on AGS cells than 5FU alone, suggesting a synergistic therapeutic interaction.

The IC50 values further illustrate differential cellular responses to treatment. In HEK293 cells, the IC50 for 5FU was 174 µg/mL, while AGS cells exhibited a lower IC50 of 92 µg/mL, indicating higher sensitivity in cancer cells. Similarly, AGS cells demonstrated greater susceptibility to silver chloride nanoparticles compared to HEK293 cells. The combination therapy resulted in IC50 values of 181 µg/mL for HEK293 cells and 43 µg/mL for AGS cells, reinforcing the enhanced cytotoxicity in gastric cancer cells.

Extensive research has explored the anti-proliferative and apoptosis-inducing effects of nanoparticles, particularly their potential in cancer treatment (Do et al., 2025; Sepand et al., 2020). Nanoparticles such as zinc oxide, nickel, and magnesium oxide have demonstrated efficacy against gastric cancer cells (Hosseinkhah et al., 2022; Mittag et al., 2019; Tang et al., 2020), while silver nanoparticles exhibit notable anticancer activity due to their antimicrobial and pro-apoptotic properties (Hashemi et al., 2020; Rojas-Cessa et al., 2024). Recent clinical studies also report the synergistic effects of chemotherapeutic agents with flavonoids (Abd El Latif et al., 2024) and nanoparticles, suggesting that nanoparticles enhance drug permeability while simultaneously inducing apoptosis through multiple pathways (Karimbaevna et al., 2024; Shrestha et al., 2019).

In alignment with these findings, this study demonstrates a significant anticancer effect when green-synthesized silver chloride nanoparticles are combined with 5FU in gastric cancer cells. The proposed mechanism involves enhanced cellular uptake of 5FU facilitated by AgCl nanoparticles, alongside concurrent apoptosis induction through multiple pathways (Cai et al., 2024).

However, the cytotoxic effects of 5FU and AgCl nanoparticles were not limited to gastric cancer cells, as HEK293 cells also exhibited dose-dependent toxicity. While this highlights the broad-spectrum activity of these agents, it underscores the necessity for optimized treatment protocols to minimize potential off-target effects on healthy cells. The combination of 5FU and AgCl nanoparticles presents a promising therapeutic approach for gastric cancer, leveraging synergistic effects to enhance treatment efficacy while potentially reducing individual drug dosages and associated side effects.

Nevertheless, this study is limited by its reliance on in vitro cell culture models. Further in vivo investigations and clinical trials are essential to validate these findings and assess the safety and efficacy of this combination therapy in a physiologically relevant setting. Additionally, elucidating the molecular mechanisms underlying the observed synergy would provide critical insights for the development of targeted therapeutic strategies tailored to individual patient needs.

5. Conclusion

This study demonstrates the dose-dependent cytotoxic effects of 5-fluorouracil (5FU) and silver chloride (AgCl) nanoparticles on gastric cancer (AGS) and human non-cancerous (HEK293) cells. The findings highlight a significant reduction in cancer cell viability, particularly with the combined treatment, suggesting a potential synergistic therapeutic effect. The lower IC50 values observed in AGS cells compared to HEK293 cells further indicate the selective efficacy of this approach against gastric cancer. Given the enhanced cytotoxicity observed with the combination therapy, AgCl nanoparticles may serve as effective drug carriers, improving 5FU's cellular uptake and amplifying its anticancer effects. However, the observed toxicity in non-cancerous cells underscores the need for careful dose optimization to minimize off-target effects. While these in vitro findings are promising, further in vivo and clinical studies are required to validate the safety and therapeutic efficacy of this combination. Understanding the molecular mechanisms underlying their interaction will be crucial in optimizing treatment strategies. Overall, the combination of 5FU and AgCl nanoparticles presents a compelling avenue for enhancing gastric cancer treatment and warrants further investigation.

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Conflict of Interests

There is no conflict of interests.

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