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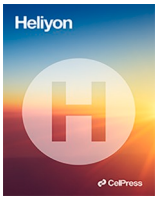

Research article

Investigating the effect of femtosecond laser pulses on noscapine and curcumin cellular uptake and improving drug delivery in gastric cancer cells

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ABSTRACT

The MKN45 cell line, a type of gastric cancer cell, exhibits resistance to chemotherapy agents through various mechanisms. Curcumin and noscapine, two plant-derived anticancer compounds, exhibit selective cytotoxicity towards cancer cells. However, their bioavailability is poor both in vitro and in vivo. In this study, we used femtosecond laser pulses in the near-infrared region (central wavelength of 1040 nm) with a pulse duration of 200 fs, a beam diameter of 4 mm, and different pulse energies and average powers to perforate the plasma membrane. We standardized the necessary conditions while minimizing cellular necrosis. MKN45 cells were treated with 25–200 μM curcumin and noscapine for 24 h after irradiation with an optimized femtosecond laser exposure (40 mW, 40sec) or without irradiation. The MTT cell viability assay revealed that pre-treatment with femtosecond (fs) laser pulses significantly increased cellular sensitivity to the treatment. Overall, the findings suggest that fs laser pulses irradiation enhance the bioavailability of both curcumin and noscapine. The combined treatment of femtosecond laser pulses and drugs can improve the drug's efficacy and the overall treatment outcome.

1. Introduction

Gastric cancer, like other types of cancer, can develop resistance to existing drugs through various mechanisms. These include alternative drug export pumps, changes in metabolic pathways, deregulation of the mismatch repair mechanism, mutations, drug efflux due to P-glycoproteins, and poor drug permeability [1]. In the MKN45 cell line, drug efflux caused by P-glycoprotein and low drug permeability are particularly common and critical mechanisms of drug resistance [2]. Noscapine, an alkaloid derived from Papaver somniferum, and curcumin, an active component derived from the rhizome of Curcuma longa L., are utilized to treat different types of inflammatory diseases and cancers, including stomach cancer [3,4]. However, the therapeutic applications of curcumin and noscapine are limited due to their low bioavailability [4–6]. Several factors contribute to this bioavailability, such as poor solubility in aqueous solutions [7], retention in the gastrointestinal mucosal layer [8], limited permeability [9,10], and efflux through ABC transporters [8,11,12], etc. Therefore, it is crucial to develop innovative strategies to improve the bioavailability of curcumin and noscapine, especially in treating gastric cancer. Studies have shown that adequate doses or extended incubation times with curcumin

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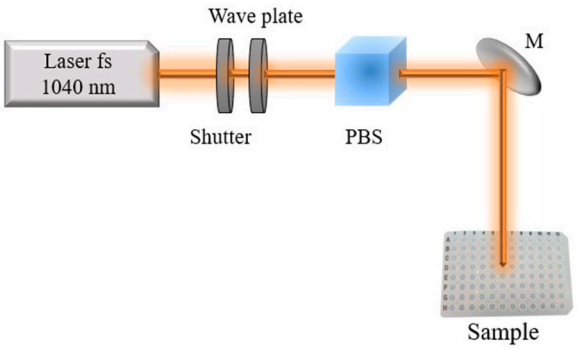

Fig. 1. A Schematic of the experimental setup.

can induce cell death in colorectal cancer cells [13]. The MKN45 cell line, derived from a gastric adenocarcinoma, is frequently used as an in vitro-cultured biopsy specimen to study tumor development mechanisms and assess the effectiveness of potential therapeutic agents for gastric cancer [14].

Curcumin and noscapine have been shown to inhibit the growth of MKN45 cells effectively. Additionally, they have been found to improve the effectiveness of existing drugs by targeting specific molecular pathways. These findings highlight the potential of curcumin and noscapine in cancer therapy and emphasize the need to enhance their ability to enter cells for the treatment of various types of cancers.

One of the main challenges in cancer treatment is the ability to access and manipulate cells without causing damage to surrounding tissues [15]. Recent advancements in femtosecond laser technology have proved to be highly useful in various biological fields, including cellular and molecular studies. Unlike other types of lasers, femtosecond lasers can alter cell structure without causing thermal damage. Moreover, their impact is confined to the treated area, minimizing structural changes to adjacent cells. This advanced laser technology acts like microscopic scissors, allowing precise and three-dimensional manipulation of biological samples [16–18].

Furthermore, femtosecond laser-assisted photoporation has emerged as an effective technique for increasing the permeability of drugs that are typically unable to penetrate cells [19]. Previous research has shown that fs-laser pulses can modulate various biological functions such as muscle contraction [20,21], blood-brain barrier permeabilization [22], cellular activation [23,24], and gene transfection [25]. Additionally, fs-laser pulses can induce the generation of Reactive Oxygen Species (ROS) in cancer cells [26]. While laser-induced ROS can have reversible effects on biological functions [27], it has also been linked to laser-induced cytotoxicity [28]. Recent studies suggest that the fusion of cancer cells may result in apoptosis [29]. It has also been investigated that a tunable femtosecond laser suppresses the proliferation of breast cancer in vitro [30]. Furthermore, it has been demonstrated that using femtosecond lasers can enhance the effectiveness of curcumin on 562 k cells [31].

This study presents results on exploiting femtosecond laser pulses in the near-infrared (NIR) region (1040 nm) in order to create pores in cell plasma membranes. Cells that were exposed to this type of irradiation showed increased sensitivity to curcumin and noscapine compared to cells that were not exposed. In addition, the study determined the threshold power for laser exposure, the time required for membrane regeneration, and the half-maximal inhibitory concentration (IC50) for both noscapine and curcumin under both irradiated and non-irradiated conditions. These findings suggest that combining femtosecond laser radiation with these medications can enhance the effectiveness of the drugs and improve treatment outcomes.

2. Materials and methods

2.1. Chemicals and reagents

Curcumin, noscapine, and trypan blue, all of biological grade, were purchased from Sigma Company in Germany. The cell culture medium and reagents for cell culture were sourced from Gibco Company in England.

2.2. Fs-laser setup details

A homemade femtosecond fiber laser, operating at a wavelength of 1040 nm and emitting pulses of 200 fs duration with TEM00 spatial mode and horizontal polarization was used as the light source to create transient pores in the plasma membrane of cells. The laser has a maximum energy of 5 nJ per pulse and a repetition rate of 23 MHz. The wavelength of 1040 nm is in the near-infrared region (NIR), which is in the transparency range of biological cells and can drastically inhibit genetic mutations. Femtosecond laser pulses are preferred in biological research because they can deliver high peak powers while maintaining low pulse energy. The experimental setup is depicted schematically in Fig. 1. The cell exposure was conducted using a beam with a diameter of 4 mm. To control the intensity of the laser beam, a half-wave plate, and a polarizing beam splitter were placed in the beam path. A mechanical shutter was also used to control the exposure time of the laser. The unfocused laser pulses were then directed onto the sample using the M mirror.

To select the optimal exposure parameters, we performed nine experiments with different laser powers, namely 20, 40, 60 mW,

Table 1
fs-laser pulse irradiation parameters.

	Repetition rate (MHz)	Power (mW)	Per Pulse (nJ)	Fluence (nJ/cm^2)	Exposure Time (s)
A	23	20	0.86	0.043	20-40-60
B	23	40	1.7	0.085	20-40-60
C	23	60	2.6	0.13	20-40-60

with exposure times of 20, 40, 60 s for each laser power and labeled them as A, B, and C groups, respectively (Table 1). The repetition rate in all experiments adjusted to 23 MHz. For group A each pulse carrying 0.86 nJ of energy, i.e. a power of 20 mW. For groups B and C the laser power increased to 40 mW and 60 mW, which correspond to the pulse energies of 1.7 nJ and 2.6 nJ respectively.

2.3. Cell line and culture

The MKN45 cell line, derived from a poorly differentiated gastric adenocarcinoma, displays epithelial morphology and is commonly employed for assessing therapeutic agents. This cell line was acquired from the National Cell Bank of Iran (Pasteur Institute, Iran). To cultivate the cells, RPMI-1640 medium (Gibco), supplemented with 10 % fetal bovine serum (Gibco) and antibiotics (100 μg/ml streptomycin and 100 U/ml penicillin), was utilized. The cells were incubated at 37 °C in a humidified atmosphere containing 5 % CO2. When the cells reached 80 % confluency, they were passaged using 1X trypsin/EDTA (Gibco) and phosphate-buffered saline (PBS).

2.4. Cell treatment and MTT cell viability assay

The Cells were initially separated from the cell culture flask using a trypsin/EDTA solution. Since MKN45 cells are not strongly adherent to the flask and are suspended in a culture medium, the trypsin/EDTA treatment was brief. The cells were then collected, resuspended in the culture medium, and seeded into a 96-well plate. Each well had a final volume of 200 μl of culture medium and 1.5 $\times$ 10^4 cells.

The plated cells were divided into two groups to treat the cells with noscapine and curcumin. In the first group, cells were treated with five dilutions of noscapine and curcumin (12.5–200 μM), with each dilution done in triplicate for 24 h. In the second group, the plated cells were first subjected to laser pulses (40 mW power) for 40 s to create pores in the cell membrane. After that, the cells were treated with noscapine and curcumin under the previously mentioned conditions.

To assess the impact of laser pulses on cell viability, cells plated in wells were subjected to different powers and exposure times of laser pulses (see Table 1). Then, the cells were incubated for 24 h before the MTT assay. The MTT assay was used to determine the viability of cells after treatment with the drug in combination with laser pulses at various exposure times and power levels. After the incubation period, the medium was removed while the MKN45 cells remained undisturbed in the wells. Then, 200 μl of MTT solution (0.5 mg/ml in phosphate-buffered saline) from Sigma, which contains 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, was added to each well. The plate was incubated at 37 °C for 4 h. Subsequently, the MTT solution was discarded and 100 μl of dimethyl sulfoxide was added to each well. The plate was placed on a shaker at 37 °C until the crystals were completely dissolved. Cell viability was determined by measuring the absorbance of the solution at 570 nm using an ELISA reader (Wave XS2, BioTek, USA). The concentration of the extract that caused 50 % inhibition of cell growth (IC50) was calculated from the dose-response curves.

The cell experiments were conducted in triplicate, and each assay was independently performed twice. Error bars represent the standard deviation from the two independent experiments for each assay.

2.5. Morphological changes of MKN45 cells

To study the changes in the cell membrane of MKN45 cells, we conducted an experiment where we exposed approximately 15$\times$ 10^3 cells to laser irradiation under three different conditions: A, B, and C, as outlined in Table 1. We used an optical microscope to observe and compare the alterations in cell shape and size with non-irradiated cells (control). Given that the diameter of the laser beam, measured at 1/e^2 intensity, is 4 mm (corresponding to an area of 12.5 mm^2), and considering that the area of the bottom of each well is 0.33 mm^2, it can be inferred that the intensity distribution at the bottom of the well can be assumed nearly as uniform.

2.6. Trypan blue staining

We conducted Trypan blue staining to determine the duration of pore openings in the cell plasma membrane after irradiation. Trypan blue, which is a water-soluble dye, cannot enter healthy cell membranes. However, when the integrity of the cell membrane is compromised due to cell death or artificial stimuli, Trypan blue can penetrate the cell and cause cell lysis. Therefore, the presence of blue cells under a light microscope indicates successful microporation induced by the laser pulse.

We cultured MKN45 cells in a 96-well plate and exposed them to irradiation under three different conditions: A, B, and C (outlined in Table 1). The control group consisted of MKN45 cells that were not subjected to any radiation. Immediately after irradiation, we added a 0.4 % w/w concentration of Trypan blue dye to the first well. After 5 min, the second well received the same concentration of dye. We repeated this process for the third well at 10 min and the fourth well at 15 min after irradiation. We then observed the cells

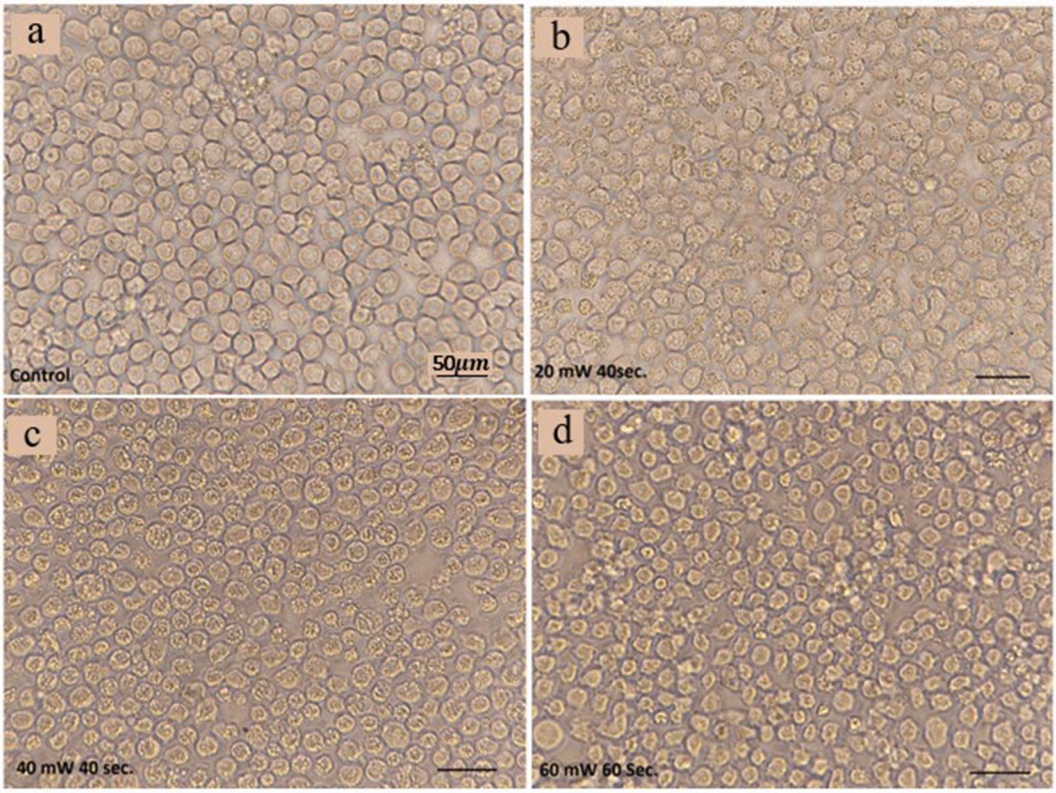

Fig. 2. Morphological changes in MKN45 cells after irradiation with femtosecond laser pulse with different irradiation conditions; a) control, b) at 20 mW for 40 s, c) at 40 mW for 40 s, d) at 60 mW for 60 s.

under a light microscope to assess morphological changes and recorded the count of blue-stained cells.

In condition A, the number of blue cells was minimal. However, in condition C, a high number of blue cells were observed. Furthermore, even after a 15-min interval, a significant number of blue cells were still present. The results obtained in condition B showed that when the cells were irradiated for 40 s and the dye was immediately added, 10 out of 30 cells turned blue. Adding the dye after 5 min resulted in 8 blue cells, and after 10 and 15 min, only 5 blue cells were observed. These findings suggest that the uptake of dye decreases over time after irradiation.

The Trypan blue assay indicated that while cell viability remained at 85 % in the MTT assay across power and duration settings of 40 mW for 40 s, 60 mW for 20 s, and 20 mW for 40 s, the optimal setting was identified as 40 mW for 40 s. At 20 mW for 40 s, 8 out of every 30 cells stained blue, indicating lower cellular uptake compared to the 40-s irradiation. Moreover, cells stained blue at 60 mW for 20 s exhibited increased cell fusion. At the latter power level, a higher number of necrotic cells were observed, suggesting that 60 mW negatively impacts the cell membrane, leading to necrotic cell death, which is not desired. Therefore, based on the observations and cell staining at 40 mW for 40 s, this setting is deemed optimal as it resulted in the most effective perforation.

Additionally, based on the evidence presented in Fig. 3(c), it can be inferred that irradiating cells with a power of 40 mW for 40 s leads to the death of a significant number of cells, as indicated by the presence of blue cells. Based on our observations, it seems that adding dye to the irradiated cells did not result in dye uptake after 10 min. Therefore, we can conclude that the optimal time to add medicine or dye to the cells is within the first 5 min after irradiation.

3. Results and discussion

Our observations have revealed that radiation elicits a dynamic cellular response, resulting in morphological changes in MKN45 cells under all irradiation conditions (Fig. 2(a–d)). Notably, the photoporation effect was prominent in irradiation condition B compared to the control cells (refer to Fig. 3(a–d). Condition B exhibited a reduced occurrence of cell membrane blebbing formation compared to condition A. Conversely, condition C showed a higher incidence of irreversible cell wall damage, leading to a decreased cell survival rate. Additionally, some cells in condition C displayed necrotic morphology and fusion events between adjacent cells. Based on the results and observations of stained cells at a power of 40 mW (Fig. 3), this power setting was selected for subsequent experiments. Our combined data demonstrate that femtosecond (fs) laser pulses can induce controlled photoporation in MKN45 cells. These laser pulses create pores in the cell membrane, facilitating drug absorption and reducing the IC50 value. This process enhances drug delivery efficiency, as schematically depicted in Fig. 4(a and b). Furthermore, the extent of photoporation depends on factors such

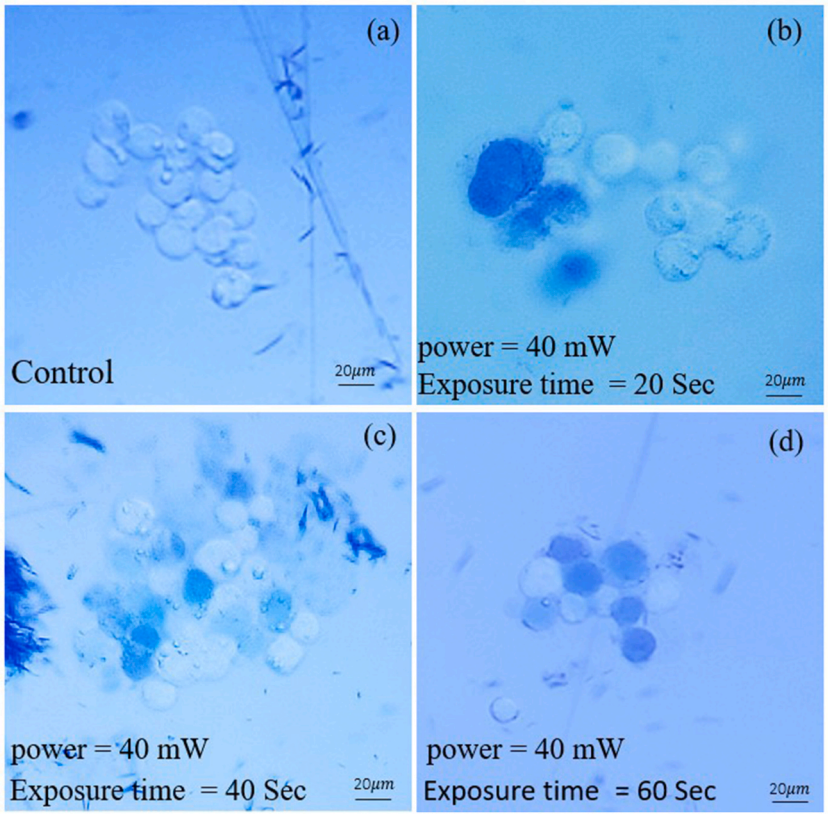

Fig. 3. Morphological observations of MKN45 cells treated with femtosecond laser pulse and dye addition, a) control, (b) 20 s under irradiation, c) 40 s under irradiation, d) 60 s under irradiation.

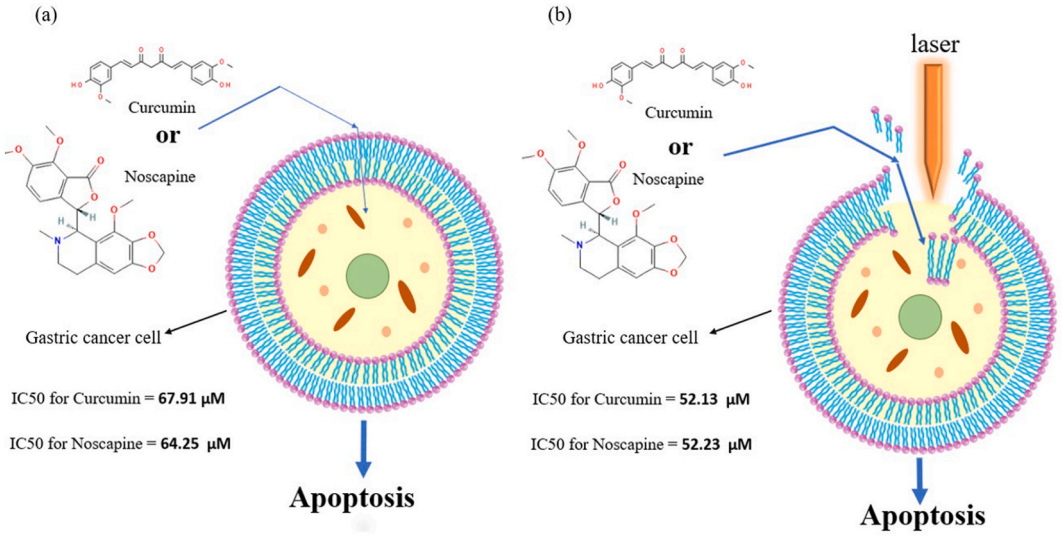

Fig. 4. Graphic representation of apoptosis induction treated with curcumin and noscapine in MKN 45 cells, a) without radiation and b) under radiation.

as pulse energy, power, time exposure, and repetition rate of the laser pulse. The MTT cell viability assay results revealed that both noscapine and curcumin effectively inhibit the proliferation of MKN45 cells, with 24-h IC50 values of 64.2 ± 3 μM and 67.9 ± 4 μM, respectively. When MKN45 cells were exposed to femtosecond laser pulses at 40 mW for 40 s, and then incubated at 37 °C for 24 h, the IC50 values of both compounds decreased (52.2 μM and 52.1 μM for noscapine and curcumin, respectively). This indicates that laser-

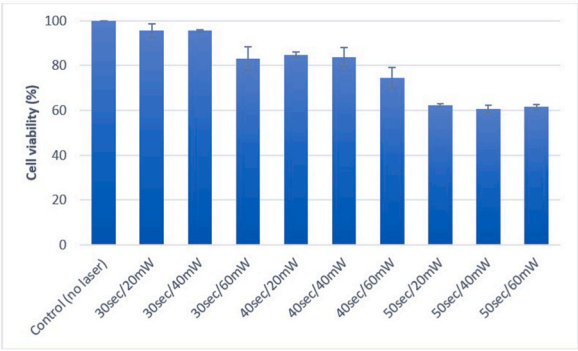

Fig. 5. Cell survival under the irradiation of fs laser pulses with different powers and exposure times in the absence of drugs.

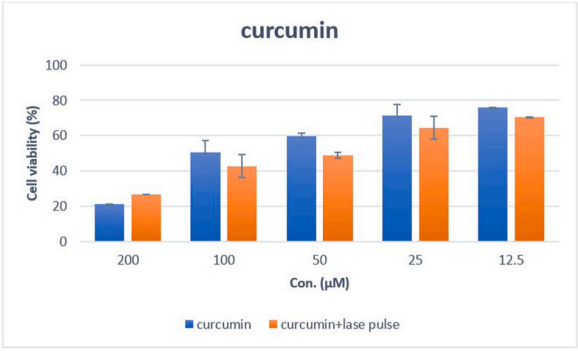

Fig. 6. Comparison of cell viability in MKN45 cells exposed to pulsed laser and those unexposed, across various curcumin concentrations over a 24-h treatment period.

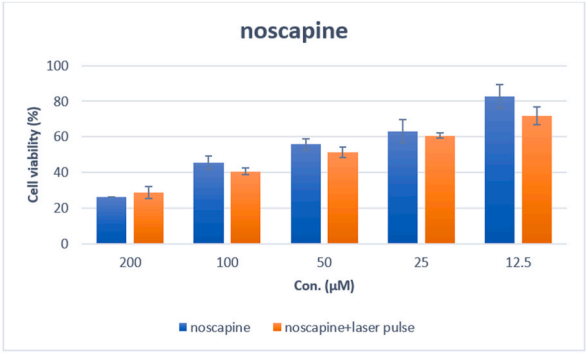

Fig. 7. Comparison of cell viability in MKN45 cells exposed to pulsed laser and those unexposed, across various noscapine concentrations over a 24-h treatment period.

assisted microporation benefits the cytoplasmic membrane of MKN45 cells, enhancing drug absorption and reducing the required effective dosage. The reduction in IC50 was more pronounced for curcumin. Additionally, the impact of femtosecond (fs) laser pulses at different powers and exposure durations on cells without the drug was evaluated to assess the laser's influence on cell viability. As shown in Fig. 5, subjecting MKN45 cells to varying powers of fs laser pulses from 20 to 40 s had a negligible effect on cell viability. However, extending the exposure time to 60 s resulted in a significant decrease in cell viability. Based on this data, the optimal parameters of femtosecond laser pulses were identified. Fig. 5 demonstrates that MKN cells maintain 85 % viability when exposed to fs laser pulses for 40 s at 40 mW power. Therefore, to expose cells to laser pulses before drug treatment, 40 s/40 mW laser pulses were utilized.

Subsequently, we individually treated MKN 45 cells with noscapine and curcumin under optimal conditions, both with and without laser light irradiation.

MTT assay studies showed that cells treated solely with curcumin had an IC50 value of 67.91 μM (Fig. 6). However, when the cells were exposed to curcumin along with pulsed laser irradiation, the IC50 value dropped to 52.13 μM.

This reduction in the required curcumin concentration suggests that laser pulses enhance the entry of the drug into the cells, improving cellular uptake and potentially increasing its effectiveness.

The IC50 value for cells treated solely with noscapine was 64.52 μM, which decreased to 52.23 μM when the cells were subjected to laser pulses (Fig. 7). Similar to curcumin, the reduced noscapine concentration indicates that femtosecond laser pulses enhance its effectiveness on cells. These laser pulses can selectively remove the plasma membrane, causing perforation and exposing the cells to high levels of acceleration and shearing forces. Precise control of systematically controlled lasers is necessary to accurately pierce the cell membrane and enable direct drug delivery. Therefore, the perforation rate is regulated by different fs laser pulse parameters and the cell viability is carefully assessed.

Our morphological observations demonstrate successful phototransduction in MKN 45 cells under optimal laser irradiation conditions (state B in Table 1). The optimal threshold power for this experiment was determined to be 40 mW. Lower power settings did not produce significant changes, while higher power levels caused increased shear forces that damaged the cell membrane and led to cell fusion. Cell viability assay results indicate that cells irradiated with 40 mW power maintain higher viability compared to those exposed to higher power levels (see Fig. 5). This suggests that cells irradiated under these conditions experience reversible cell wall damage, while irreversible damage leads to cell death or cell fusion.

In the next phase of the study, a group of cells exposed to the conditions described in Table 1 were incubated with 200–12.5 μM of noscapine and curcumin for 24 h. The results were then compared to those of cells treated solely with curcumin and noscapine, as well as control cells that received no treatment. Interestingly, the irradiated cells demonstrated greater sensitivity than the other populations, indicating that the irradiation facilitated the direct transport of curcumin and noscapine into the cellular environment.

4. Conclusion

In summary, this research shows that using fs laser pulses is an effective and innovative method for delivering drugs to gastric cancer cells (MKN 45). Morphological analysis confirms that photoporation is successful, as cells treated with a 40 mW power of the femtosecond laser exhibit reversible perforations in their cell walls. Additionally, these irradiated cells demonstrate increased cell death and a decrease in IC50 compared to other cell populations. The MTT cell viability assay results revealed that both noscapine and curcumin without laser radiation effectively inhibit the proliferation of MKN45 cells. However, when MKN45 cells were exposed to femtosecond laser pulses at 40 mW for 40 s, the IC50 values of both compounds decreased. Therefore, the findings of this study suggest that laser-assisted microporation benefits the cytoplasmic membrane of MKN45 cells, enhancing drug absorption and reducing the required effective dosage. Femtosecond laser pulse irradiation improves the sensitivity of MKN 45 cells to curcumin and noscapine by facilitating the direct transfer of these drugs into cells through reversible holes in the cell membrane.

CRediT authorship contribution statement

Nastaran Kahrarian: Writing – original draft, Methodology, Investigation, Formal analysis. **Hossein Behboudi:** Writing – original draft, Validation, Formal analysis, Data curation. **Atoosa Sadat Arabanian:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation. **Abolfazl Abedi:** Validation, Methodology. **Reza Massudi:** Writing – review & editing, Validation, Supervision.

Data and code availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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