RESEARCH ARTICLE

Synthesis and structural characterization of folic acid-conjugated mesoporous silica nanoparticles loaded with thymol and investigating their cytotoxic effects on HT-29 colorectal cancer cells

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ABSTRACT

The gradual malignant transformation of normal cells can result from DNA lesions caused by endogenous errors during replication, inherent chemical instability of some DNA bases, or oxidative damage due to free radicals produced during metabolism. Colorectal cancer (CRC) poses a major health threat and a model to study the molecular mechanisms involved in the malignancy. In terms of origin, CRC can be either familial, hereditary, or without a traceable link to these factors. Researchers have been seeking targeted treatments for CRC. In the early 1990s, upon the discovery of M41S molecular sieves, mesoporous silica materials and subsequently nanoparticles (MSNs) attracted special attention as they could offer promising features in terms of tunable physiochemical and structural characteristics (e.g., drug release, stability, size, and porosity), suggesting them as drug carriers, biosensors, etc. MSNs are safe toward various cells and can be easily internalized by them, as another distinctive feature of MSNs. In this research, folate-coated MSNs were loaded with thymol and subjected to anticancer activity analysis, including cytotoxicity (MTT test) and apoptosis (AOPI staining by flow cytometry). The average size of MSNs was 296.40 nm with semi-spherical morphology. Significant anti-growth activity was observed against HT29 cancer cells, which was associated with apoptosis induction, confirmed by AOPI staining. These results highlighted the anticancer properties of MSNs against CRC cells.

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INTRODUCTION

Colorectal cancer (CRC), as the third most common malignancy in developed and developing countries, poses a dreadful health concern across the globe (1-3). In men, CRC commonly affects the lung and prostate, with a peak incidence at ages between 50 and 65 years. In 2008, the World Health Organization (WHO) confirmed the demise of around 600,000 people worldwide due to CRC, partly because of late diagnosis, rapid dissemination, and distant metastases facilitated via the bloodstream. These hurdles are primary causes making achieving effective treatments problematic. The wide geographical variations in the incidence of CRC may root in dietary habits, environmental exposures, and the unique genetic signature of populations.

Two Nobel Prize winners are the first minds behind today's nano-based technological advances. Richard Zygmunt first introduced the word "nanometer" in 1925 to refer to the size of particles such as gold colloids visualized under a microscope, and Richard Feynman who is known as the father of modern nanotechnology, the winner of the 1965 Nobel Prize in physics. These days, modern nanotechnology is exploited to address one of the greatest cancer therapy challenges, namely targeted drug delivery to cancerous cells without harming adjacent healthy tissues, which has been proven

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to be achievable using nano-based drug delivery systems (DDSs) (4-10). Due to non-specific uptake of cytotoxic drugs by healthy cells, traditional cancer therapies often suffer from serious side effects, limiting their therapeutic applicability. Therefore, a variety of nano-based carrier systems have been studied to improve targeted drug delivery and overcome the aforementioned limitations (11-15).

In the past decade, nanomedicine has made great strides thanks to rapid advances in nanomaterials (16-18). Mesoporous silica nanoparticles (MSNs), whose unique properties include uniform mesopores, easy functionalization, porous structure, and high specific surface area, have recently attracted much attention for biomedical applications (19-21). On top of these, MSNs have shown excellent in vivo biocompatibility, facile surface modifiability, and great cellular uptake. Porous materials have shown great promise during recent years for addressing health problems, including cancer (22-24). Silica nanoparticles contain a silica adduct and offer high pore volume enabling the loading of various drug and non-drug molecules (25-27). The silica also provides an interface between surface-bound anionic molecules and pores, conferring the structure hydrophilic properties that empower structural repulsion, which is necessary for constructional stability. In addition, MSNs' diagnostic and therapeutic applications can be expanded by tunning their physical and chemical features by surface modification strategies. These modifications optimize MSNs in terms of biocompatibility, as well as specific adsorption and cargo-loading capacity via providing additional functional groups. The surface of MSNs can be modified using a range of physical and chemical approaches, including chemical surface functionalization and layer-by-layer self-assembly (LSA), respectively. Surface specifications such as the presence of active groups, their biosafety, and electrical charge, are important features along with size and morphology, which collectively determine the biocompatibility and efficacy of DDSs, including MSNs. Another important feature that makes MSNs promising for drug delivery applications is their ability to encapsulate various types of cargo molecules into their porous channels (28-30). The encapsulation of drugs protects them from enzymatic degradation. Generally, particles are loaded into the carrier by being soaked into a drug solution, while other molecules may be incorporated by surface adsorption. The cargo molecules and the carrier are usually attached together via hydrogen bonding and electrostatic interactions. The adsorption capacity of MSNs is partly dictated by their specific surface area and porous network.

The high porous capacity of MSNs is a unique facet that improves the delivery of various hydrophobic anticancer drugs into the bloodstream. Thymol is a naturally occurring monoterpene phenolic compound known as 2-isopropyl-5-methylphenol (IPMP). Many plants contain thymol, which is particularly known for its antimicrobial, antifungal, and antibacterial effects (31-33). Studies have also pronounced the antipyretic and antispasmodic properties of thymol. The aim of this study was to synthesize folate-conjugated thymol-loaded MSNs and investigate their anticancer effects.

MATERIALS & METHODS

Materials

For cell culture, the HT-29 human colon cancer cell line was obtained from Pasteur Institute of Iran (Tehran, Iran). Other materials for cell culture, including DMEM medium, antibiotics, fetal bovine serum (FBS), and trypsin were procured from Sigma-Aldrich (Poole, United Kingdom). For cytotoxicity testing, the 3,4,5-Dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide (MTT) reagent, and for apoptosis analysis, acridine orange dye, were also from Sigma-Aldrich**.** Other materials were from Merck (Germany).

Synthesis of Thymol-loaded Folic Acid-Conjugated MSNs

First, MSNs were prepared by the sol-gel method. Then tetraethyl orthosilicate (TEOS) was hydrolyzed and condensed in a reaction environment containing a structure-directing agent to create a mesoporous structure. Also, folic acid was covalently attached to the MSNs' surface through a suitable linker to ensure stable folic acid incorporation (FA-MSNs). In the next step, the active ingredient (thymol) was loaded into folic acid-modified MSNs using a suitable encapsulation method (FA-T-MSNs), and the loading capacity was calculated as the ratio of the active ingredient to MSNs.

Nanoparticle Characterization

Dynamic light scattering (DLS) was used to

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evaluate MSNs' average size and dispersion index using a Zetasizer instrument (Nano-ZS, Malvern, UK). In addition, zeta potential was determined as an index of the surface charge of nanoparticles (Nano-ZS, Malvern, UK). Further, MSNs' size and morphology were evaluated using FE-SEM (JEOL, Japan) and their functional groups via FTIR (Perkin Elmer, Walthman, MA, USA).

MTT Test

The cytotoxicity of MSNs was assessed against HT29 cells cultured in DMEM supplemented with 10% FBS and streptomycin and penicillin. The cells (5×10^3 cells/well in a 96-well plate) were incubated in a humidified atmosphere containing 5% CO_2 for 24 hours to allow them attach to the bottom of the plate. Then the culture medium was removed and replaced with different concentrations of FA-T-MSNs (0, 7.8, 15.6, 31.2, 62.5 and 125 µg/mL) for 48 hours, after which the medium was drained, and the MTT reagent was added to each well. In order to complete the reaction, the plate was kept in the incubator for 4 hours. Finally, the MTT solution was drained, and 100 µL of DMSO was added to the wells, followed by reading OD at the wavelength of 570 nm. Cell viability % was calculated using the following formula.

$$\text{Cell viability\%} = (OD_{sample}/OD_{control}) \times 100$$

Apoptosis Assay

Acridine Orange/Propidium Iodide Staining

Acridine-orange (AO) assay was used to assess apoptosis induction in HT-29 cells treated with FA-T-MSNs. Living cells are permeable to AO, emitting green fluorescence while propidium iodide (PI) enters non-alive cells due to their lack of membrane integrity, emitting red fluorescence. After 24 hours of seeding the cells in culture flasks, the culture medium was discarded and replaced with 15 mg/mL of FA-T-MSNs for 48 hours. Trypsin was added to detach cells from the bottom of the flask. The cells were then settled by centrifugation (3000 rpm, 5 minutes), diluted with PBS, and exposed to AO and PI (10 µL of each of the cell suspension, AO, and PI). After 5-minute incubation, the mixture was spread on a slide, and the slides were inspected under a fluorescence microscope (XDS-3FL/3FL4, OPTICA, Italy).

Apoptosis Assessment by Flow Cytometry

In order to perform flow cytometry, cells seeded in 6-well plates were exposed to 15 mg/mL of FA-T-MSNs for 48 hours. After that, 1 mg/ml PBS was used for washing before adding PI to the cell suspension. A final 30-minute incubation phase was considered before analyzing the cells by flow cytometry (BD FACS Calibur).

Data Analysis

Cell viability values and apoptosis rates were analyzed by SPSS software and one-way ANOVA. For drawing graphs, Microsoft Excel software was used. Three-star markers were used to indicate p values <0.001. All data were collected from three independent replications and presented as mean ± standard deviation (SD).

RESULTS

Study of Nanoparticle Size

The accuracy of DLS has made this technique ideal for characterizing the size distribution of nanoparticles. However, the presence of scatterers and wide size distribution may cause errors in DLS particle size analysis. According to **Figure 1**, the average size of FA-T-MSNs was obtained as 296.40 nm.

FE-SEM Analysis

As an advanced imaging technology, FE-SEM is a common method for visualizing nano-materials. This microscopy technique employes a high vacuum environment where an electron beam is disrupted by gas molecules, and secondary and backscattered electrons are emitted. FE-SEM is able to detect minute contaminations at electron accelerating voltages (0.5 to 30 kV), so low-voltage high-quality pictures with partial electrical charging can be obtained from samples. Another distinctive feature of FE-SEM is that the insulating material does not need to be covered with conductive material. Our results obtained from electron microscopy revealed semi-spherical morphology for FA-T-MSNs (**Figure 2**).

Zeta Potential

Based on zeta potential values, nanoparticles can be considered as either neutral (±10 mV) or strongly cationic/anionic (±30 mV). Phospholipids as the main building blocks of biological cell membranes are negatively charged, so zeta potential influences nanoparticles' ability to pass through these membranes. Accordingly, cationic particles usually exhibit greater toxicity by disrupting the cell membrane. In our research, the zeta potential of FA-

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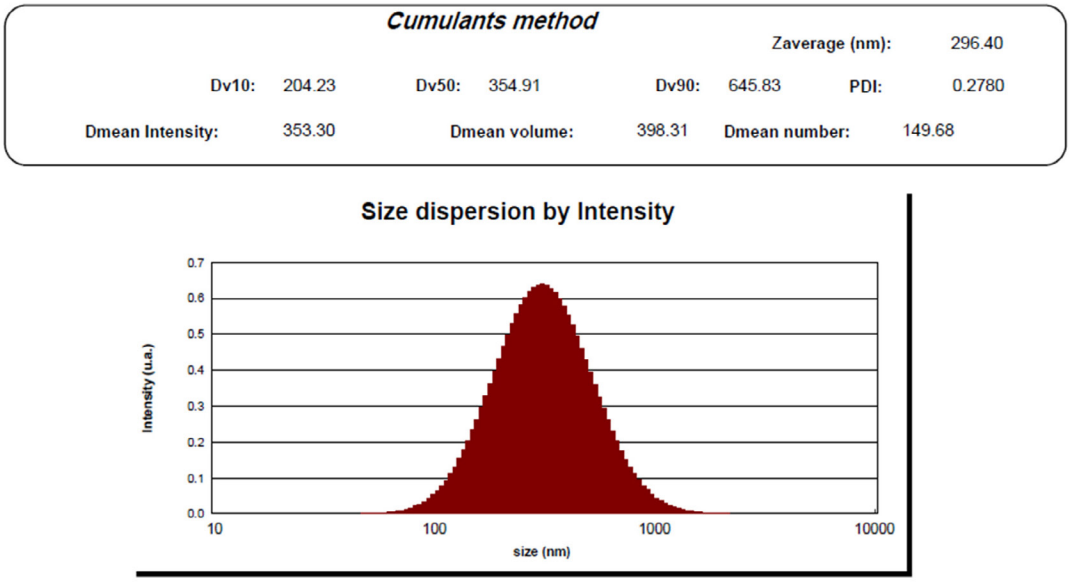

Fig. 1. Dynamic light scattering for size analysis of thymol-loaded folate-decorated mesoporous silica nanoparticles.

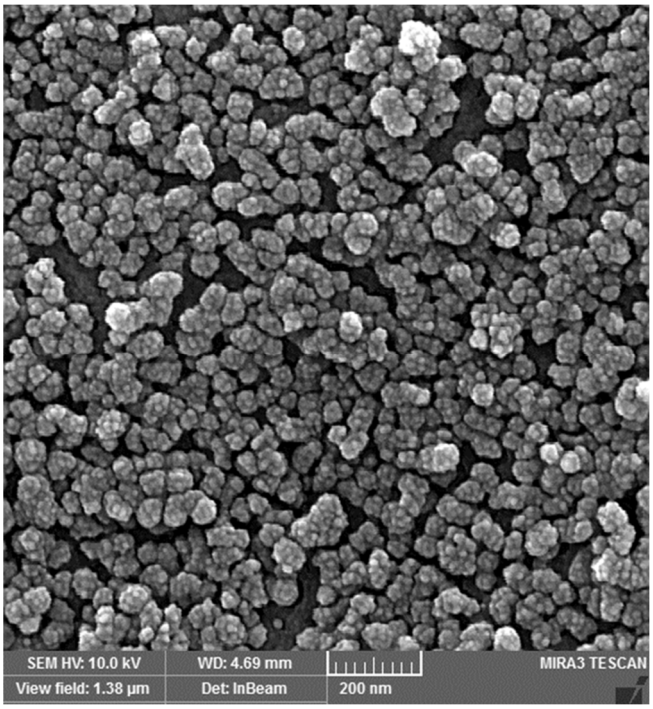

Fig. 2. FE-SEM image of thymol-loaded mesoporous silica nanoparticles conjugated with folic acid. These nanoparticles had a semi-spherical appearance.

T-MSNs was obtained as -23.70 mV (Figure 3).

FTIR spectrum

Figure 4A shows the FTIR spectrum MSNs. The band at 1096.75 cm-1 was related to the asymmetric stretching vibration of Si–O–Si bonds. Also, the small bands at 107.958 cm-1 and 802.66 cm-1 indicated the bending vibrations of Si-O-H and Si-O, respectively.

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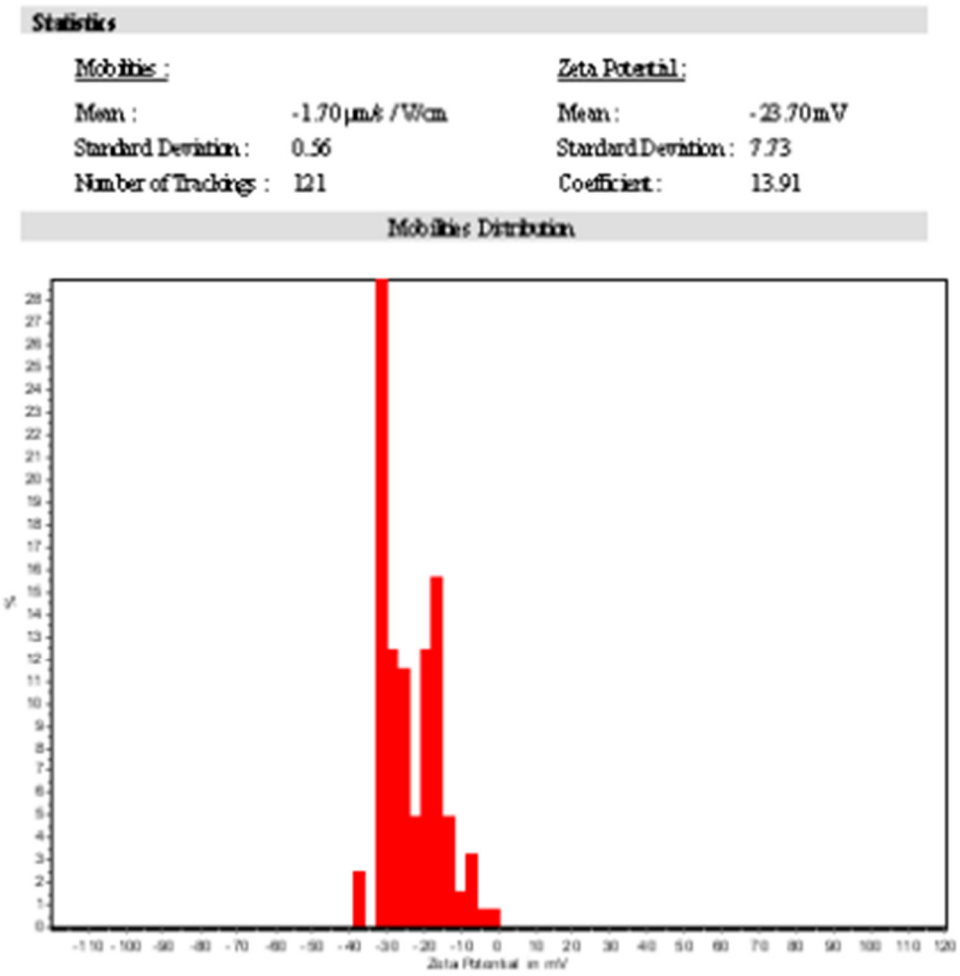

Fig. 3. Zeta potential of thymol-loaded folic acid-decorated mesoporous silica nanoparticles

Figure 4B shows the FTIR spectrum thymol. Also, 550 cm-1 to 850 cm-1 peaks were attributed to stretching bonds, and the peak at 1000 to 1320 cm-1 represented C-O bonds, which could be related to compounds such as ethers, esters, carboxylic acids, and alcohols. The peaks at 1622.01 cm-1, 2958.23 cm-1, and 3232.08 cm-1 corresponded to C-C, C-H, and O-H bonds, respectively. **Figure 4C** shows the FTIR spectrum FA-T-MSNs. The band at 3385.38 cm-1 was related to the N-H stretching vibration of the pteridine ring, and the peak at 2930.13 cm-1 was attributed to the C-H vibration of the CH2 groups of folate's pteridine ring and glutamic acid.

Investigation of the Cytotoxicity of Nanoparticles

With increasing the concentration of FA-T-MSNs, the viability of HT-29 cancer cells decreased so that at the concentration of 125 µg/ml, the viability of the cancerous cells reached almost zero percent (**Figure 5**), with 15.6 µg/ml as the IC50 value. In general, FA-T-MSNs were found to have significant toxicity effects on HT-29 cancer cells.

Evaluation of FA-T-MSNs' Apoptotic Activity
Cell Cycle Assessment

In this study, cells treated with FA-T-MSNs showed a rise in the sub-G1 peak compared to untreated cells, indicating the blocking of cell proliferation and enrichment of non-viable cells in the sub-G1 segment. As shown in **Figure 6**, the rate of apoptosis in HT-29 cells reached 54.6% at the dose of 15 µg/ml.

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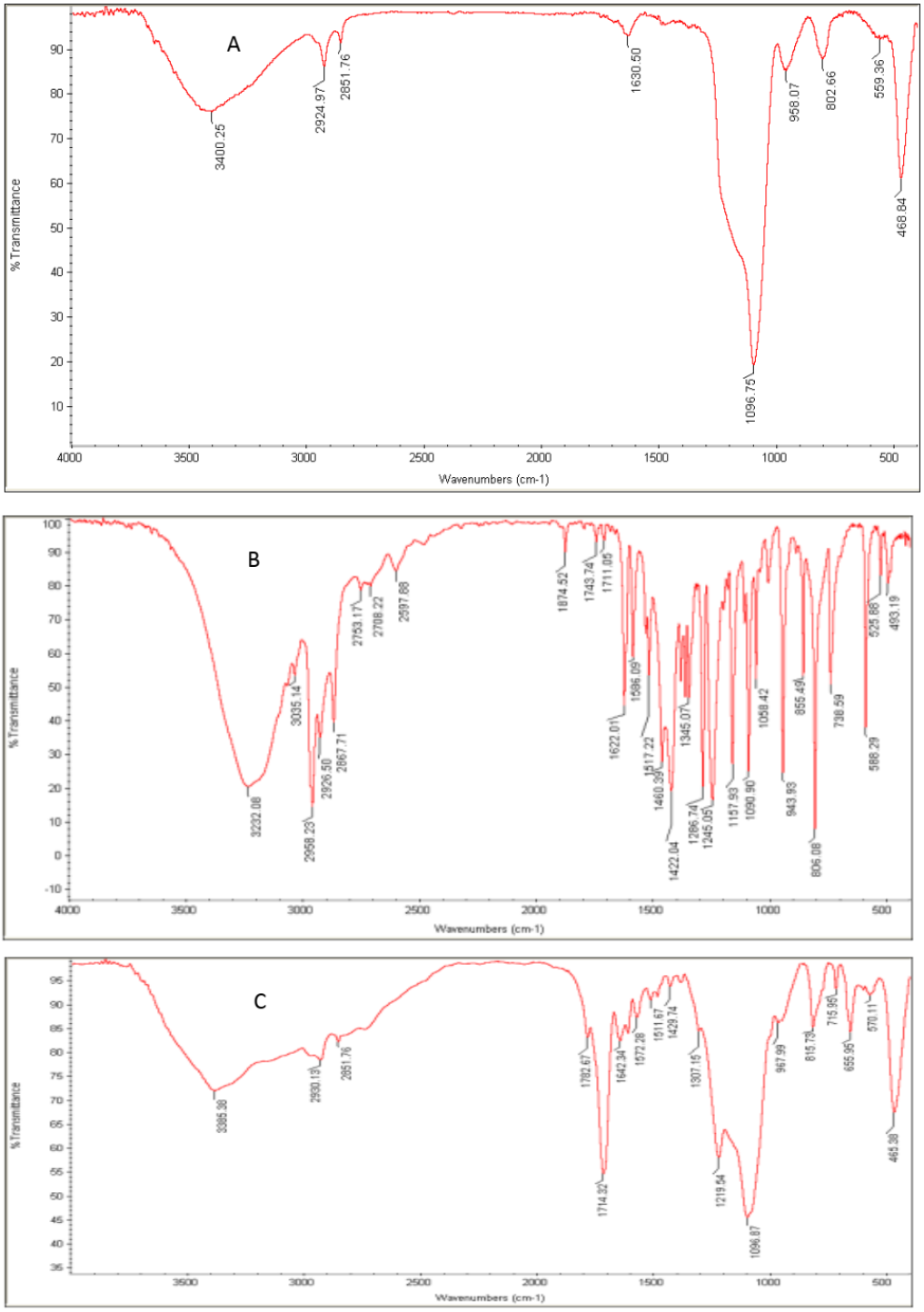

Fig. 4. FTIR spectra of (a) mesoporous silica nanoparticles, (b) Thymol, and (c) folic acid-coated mesoporous silica nanoparticles loaded with thymol.

Acridine Orange/ Propidium Iodide Staining

As indicated in **Figure 7**, HT-29 cancer cells treated with FA-T-MSNs absorbed propidium iodide, and a change in the luminescence of the sol to red-orange suggested the occurrence of apoptosis. Control cells displayed normal and

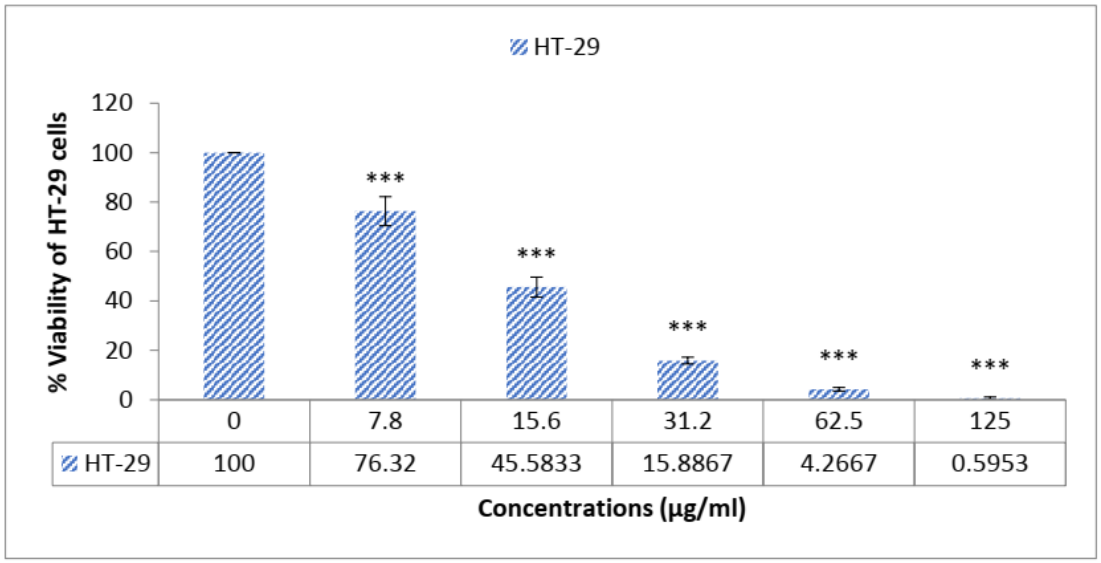

Fig. 5: The cytotoxicity of folic acid-conjugated thymol-loaded mesoporous silica nanoparticles against HT29 cells.

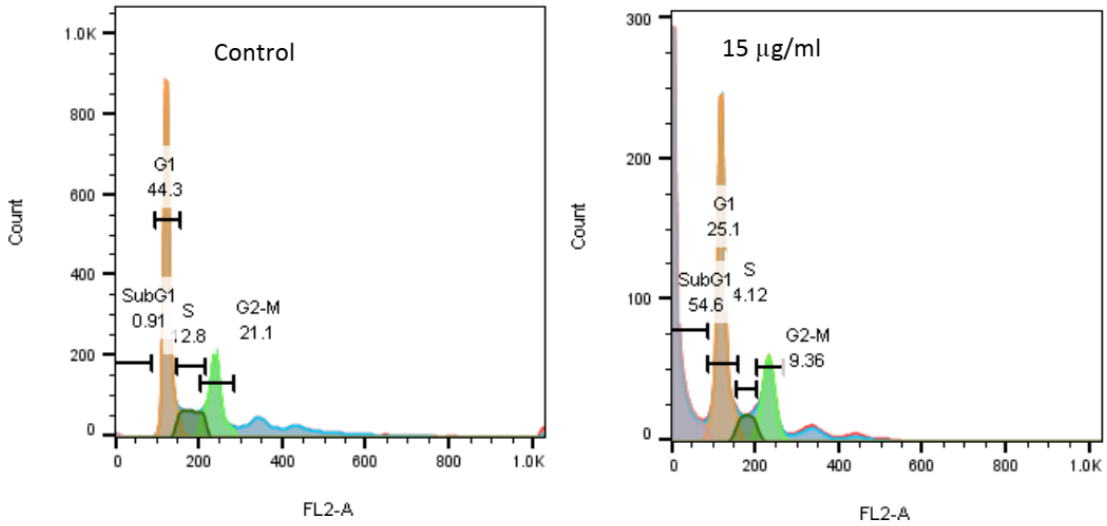

Fig. 6. Flow cytometry-based cell cycle monitoring in HT-29 cancer cells treated with mesoporous silica nanoparticles containing folic acid and thymol compared to the control group. A: Control, B: treatment with 15 mg/ml of the nanoparticles, at which the Sub-G1 peak reached 54.6%.

uniform nuclei, emitting green fluorescent as a result of the internalization of acridine orange.

DISCUSSION

The advent of nano-based medication delivery systems has substantially improved targeted drug delivery, partly by taking advantage of their intrinsic tendency for inactive accumulation at the tumor site (34-36). Moreover, active targeted drug delivery can be achieved today using nanotechnology to carry drugs toward specific organs or tissues. Targeted drug delivery can reduce off-target toxicity associated with traditional chemotherapy. For this purpose, nanocarriers are usually decorated with membrane-targeting ligands, improving their uptake and internalization by cells. In 2020, Song and colleagues prepared myristicin (Myr)-loaded MSNs with multidrug resistance protein (MRP-1) siRNA, attached folic acid on their surface to enhance their therapeutic

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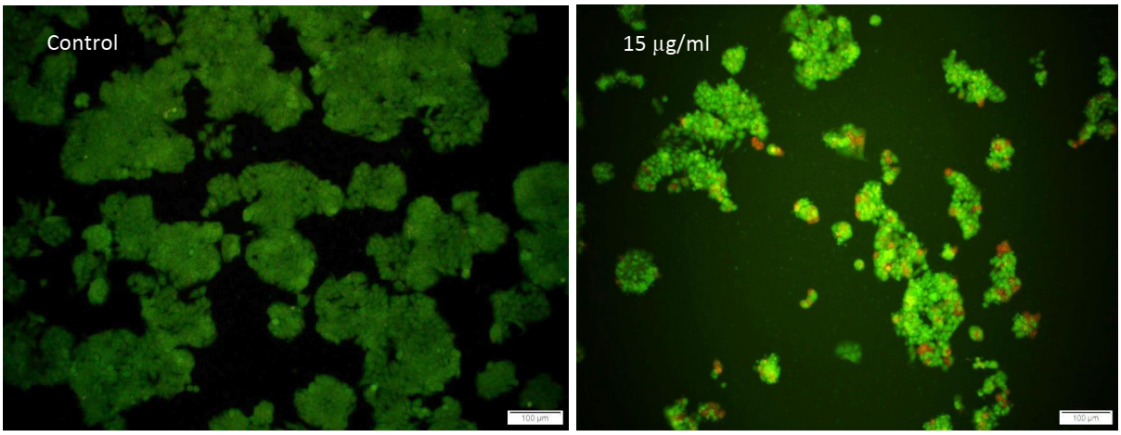

Fig. 7. AO/PI fluorescent labeling of HT-29 cells confirmed apoptosis in cells treated with folic acid-conjugated thymol-loaded mesoporous silica nanoparticles compared to untreated cells.

efficacy against lung tumor cells, which could efficiently internalize MSNs compared to non-conjugated nanoparticles. In another study, nano-sized folic acid conjugated topotecan-loaded MSNs (i.e., FTMN) enhanced the medication's therapeutic efficacy against retinoblastoma cells, evidenced by sustained drug release under physiological conditions and effective uptake of the modified MSNs vs. non-targeted nanoparticles by cancer cells, possibly via receptor-mediated endocytosis. The higher cellular uptake of FTMNs resulted in considerably greater cytotoxic effects on Y79 cancer cells, evidenced by nuclear fragmentation and an increased ratio of apoptotic cancer cells to ~58%. These results clearly demonstrated that in comparison to free drug and non-targeted carriers, encapsulated topotecan (TPT) showed higher anticancer efficacy against Y79 cancer cells. Doxorubicin is one of the most widely used drugs for treating breast cancer; however, adverse complications such as cardiac abnormalities limit its utilization. Tunbol et al. (2021) tried to develop an effective doxorubicin formulation by encapsulating the drug into small-sized (~50 nm) MSNs, which were actively targeted by folic acid conjugation (37). The folic acid conjugated nanoparticles supported a pH-dependent drug release profile and were more efficiently penetrated into ZR-75-1 and T47-D breast cancer cells, delivering a higher dose of doxorubicin to these cells as confirmed by fluorescence microscopy and flow cytometry. The higher uptake of small MSNs by these cancer cells was attributed to the presence of folic acid.

In the present study, folic acid decorated MSNs loaded with thymol (i.e., FA-T-MSNs) had significant growth inhibitory effects on HT29 colorectal cancer cells. The large loading capacity of MSNs and their extended surface offer great opportunities for the effective delivery of adequate doses of therapeutics to target cells. Thymol (5-methyl-2-isopropylphenol), a monoterpene and the main ingredient of thyme essential oil, is an aromatic oxygenated compound with antioxidant and antiproliferative properties. Elbe et al. (2020), investigating the anti-cancer effects of thymol on lung cancer (KLN205), breast cancer (MDA-MB-231), and prostate cancer (PC-3, DU145) cell lines, reported the dose- and time-dependent cytotoxic and pro-apoptotic effects of thymol on these cells, suggesting this compound as a possible source of anti-tumor therapeutics (38).

Kong et al. also discovered that thymol had anti-cancer effects on human gastric AGS cells through a combination of anti-growth, pro-apoptosis, and pro-oxidative activities, as well as mitochondrial membrane depolarization and inducing Bax, a mitochondrial pro-apoptotic protein. Consistently, thymol was reported to promote apoptotic death in gastric adenocarcinoma (AGS) cells through the intrinsic mitochondrial pathway (39), and inducing genotoxic effects as evidenced by Günes-Bayir et al.'s report. In vitro and in vivo assays on healthy cells confirmed that thymol could protect these cells against carcinogenic processes, supported by measuring ROS and glutathione (GSH) levels. As well, this compound was offered as a novel and effective therapeutic agent against gastric cancer regarding its anti-cancer effects on malignant cells (40).

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Thymol is a major component of many plants from the Lamiaceae family and is often used for medicinal and culinary purposes in Mediterranean countries. Thymol is also known for its beneficial effects as an antitumor agent; however, the exact anti-cancer mechanisms of thymol have not been fully divulged. We here assessed the anticancer activity of thymol loaded into FA-functionalized MSNs against human colorectal cancer cells. The viability and apoptosis of HT29 cells exposed to different concentrations of thymol were assessed, obtaining an IC50 dose of 15 µg/mL upon 24 hours of treatment. We further showed that the cytotoxic activity of thymol against HT-29 cells might be partly related to cell cycle arrest at the G0/G1 interface. The anti-cancer effects of thymol were enhanced when loaded into MSNs conjugated with folic acid.

CONCLUSIONS

Thymol-loaded folic-acid conjugated MSNs were successfully synthesized with an acceptable nanometric size range and high stability. The anticancer effects of these nanoparticles were confirmed by investigating their cytotoxicity and pro-apoptotic activity in HT29 cells, where they significantly reduced survival and boosted apoptosis in cancerous cells. According to these results, thymol-loaded folic-acid conjugated MSNs can be suggested as an effective therapeutic agent for colorectal cancer.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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