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Creation of Targeted Liposomes for the Delivery of Allium cepa Quercetin for Cancer Treatment

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ABSTRACT

Introduction: Major therapeutic problems include chemotherapy-associated toxicity and multidrug resistance; cancer is still the top cause of death worldwide. Quercetin is a flavonoid that comes from the onion plant Allium cepa and has strong anticancer effects. However, it isn't very useful in the clinic because it's poorly soluble in water and has low bioavailability. The current research set out to improve quercetin's transport and therapeutic efficacy against cancer cells by creating and testing targeted liposomal formulations of the compound.

Materials and Methods: An HPLC analysis was performed to determine the concentration of quercetin in the Allium cepa extract, which yielded 0.82% w/w. A 3:1 molar ratio of phosphatidylcholine to cholesterol was used to create liposomes by the thin-film hydration process. The liposome surface was modified to actively target folic acid. Drug release in vitro, entrapment efficiency, zeta potential, and particle size were all measured for the formulations. The MTT assay was used to assess cytotoxicity in MCF-7 and HeLa cancer cell lines, while confocal imaging was employed for cellular uptake studies.

Results: Entrapment efficiency was 87.2 ± 2.4%, zeta potential was -28.6 ± 1.5 mV, and the average particle size of the optimized folate-targeted liposomes was 132.4 ± 3.7 nm. The sustained profile of quercetin release over 24 hours was seen in in vitro release, with a rate of 78.5 ± 2.8%. In comparison to non-targeted liposomes (IC_{50} = 15.3 µg/mL) and free quercetin (IC_{0} = 22.6 µg/mL), targeted liposomes showed a noticeably higher level of cytotoxicity in MCF-7 cells (IC_{0} = 7.8 µg/mL). Research on cellular uptake has shown that liposomes coated with folate are more effectively absorbed by the body.

Conclusion: Improved drug administration, cellular absorption, and anticancer activity were seen when quercetin from Allium cepa was encapsulated in foliate-targeted liposomes. To increase the bioavailability of quercetin and its therapeutic potential in cancer treatment, this tailored delivery method is an encouraging approach.

Keywords: *Quercetin, Allium cepa, Liposomes, Cancer, Targeted Drug Delivery, Folic Acid, Nanocarrier, MCF-7*

1. INTRODUCTION

Major breakthroughs in diagnosis and medicines have not alleviated cancer's status as a leading cause of cancer-related fatalities, which affect millions of people worldwide every year. Though conventional chemotherapy is frequently used, it has limitations in terms of its long-term effectiveness due to factors such as systemic toxicity, non-specific distribution, and the development of multidrug resistance. Because of these drawbacks, we need better and safer drug delivery methods that can target tumor areas selectively with minimal damage to normal cells [1-3].

Natural chemicals, especially flavonoids, with their positive safety profiles and ability to target several biological processes have attracted a lot of attention recently. An onion and other vegetables like Allium cepa (onion) are rich sources of quercetin, a flavonol that has several medicinal uses, including reducing inflammation, protecting against cancer, and more. Among its many anticancer effects are the regulation of critical signaling pathways, the induction of apoptosis, and the reduction of cell proliferation. However, quercetin's fast metabolism, low oral bioavailability, and poor water solubility provide significant obstacles to its practical translation [4-6].

New medication delivery technologies based on nanotechnology offer hope for overcoming these obstacles. The spherical phospholipid vesicles known as liposomes offer great promise for improving the bioavailability, stability, and targeted distribution of hydrophilic and hydrophobic medications. Adding folic acid or another ligand to the liposome surface improves therapeutic selectivity and intracellular absorption by actively targeting cancer cells that overexpress folate receptors [7, 8].

We created folate-conjugated liposomal formulations that contained quercetin from Allium cepa as the main focus of this investigation. Our objective was to improve the drug's pharmacokinetic profile and make it more effective in targeting cancer cells. The study examines the process of extracting and characterizing quercetin, creating and optimizing liposomes, adding folic acid to the surface, and then thoroughly testing the formulation for various physicochemical properties, in vitro drug release, cellular uptake, and cytotoxicity against cancer cell lines. This specific nanocarrier technology presents an opportunity to enhance the efficacy of flavonoids produced from plants in cancer therapy [7-9].

2. MATERIAL AND METHODS

Materials:

Authentic red onion bulbs, or Allium cepa, were purchased at a nearby market and checked for authenticity by a botanist from the Department of Botany. The following items were acquired from Sigma-Aldrich in the USA: phosphatidylcholine (PC), cholesterol, folic acid, quercetin standard (≥95% purity), and polyethylene glycol (PEG)-2000. Other than that, all solvents and chemicals used were analytical grade and purchased from HiMedia (India). The cell lines used in this study were procured from the National Centre for Cell Science (NCCS) in Pune, India. The MCF-7 gene is associated with breast cancer, whereas the HeLa gene pertains to cervical cancer.

Extraction and Isolation of Quercetin:

To make a coarse powder, fresh Allium cepa bulbs were peeled, cut, and air-dried in the shade for seven days. A Soxhlet device was used to extract the powder (100 g) using 70% ethanol for 8 hours. After drying, the extract was condensed into a semi-solid mass using a rotary evaporator operating at decreased pressure. The mobile phase used in the preparative thin-layer chromatography (TLC) to isolate quercetin was a mixture of ethyl acetate, formic acid, glacial acetic acid, and water in the ratio of 100:11:11:26 v/v. Using high-performance liquid chromatography (HPLC) in comparison to a quercetin standard, the quantification and confirmation of the extracted quercetin were accomplished. The dry weight was used to determine the quercetin % yield [10-12].

Preparation of Liposomes:

In order to make liposomes, the thin-film hydration technique was employed. To summarize, a round-bottom flask was used to dissolve phosphatidylcholine and cholesterol in a chloroform and methanol (2:1 v/v) mixture. To the lipid solution, 10 milligrams of quercetin were added. A thin lipid layer was formed on the inner wall of the flask by evaporating the organic solvents at reduced pressure using a rotary evaporator at 45°C. To reduce its size, the film was sonicated in a probe sonicator after being hydrated with phosphate-buffered saline (PBS, pH 7.4). Until they were needed again, the liposomes that were produced were kept at 4°C [11-13]. Lipo-Qu and F-Lipo-Qu, two types of Quercetin-loaded liposomes, are detailed in Table 1, and processing parameters are listed in Table 2.

Table 1: Composition of Quercetin-Loaded Liposomes (Lipo-Qu and F-Lipo-Qu)

Component	Function	Amount (mg)	Lipo-Qu	F-Lipo-Qu
Phosphatidylcholine (PC)	Primary lipid for bilayer formation	90	✓	✓

Cholesterol	Membrane stabilizer	10	✓	✓
Quercetin	Active drug	10	✓	✓
DSPE-PEG2000	PEGylation agent	5	✗	✓
Folic acid	Targeting ligand (via PEG linkage)	2	✗	✓
Chloroform:Methanol (2:1)	Organic solvent for lipid dissolution	10 mL	✓	✓
PBS (pH 7.4)	Hydration medium	10 mL	✓	✓

Table 2: Processing Parameters

Step	Condition
Solvent evaporation	Rotary evaporator at 45°C under reduced pressure
Hydration	PBS (pH 7.4), 10 mL
Sonication	Probe sonicator, 5 min (on ice)
Storage	4°C until further analysis

Surface Functionalization with Folic Acid:

The liposome surface was modified by PEGylation to incorporate folic acid for active targeting. Next, DSPE-PEG2000 was coupled to the activated folic acid, which had been prepared via carbodiimide chemistry using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and NHS, respectively. To create folate-conjugated liposomes (F-Lipo-Qu), this conjugate was added to the lipid mixture prior to film production [14-16].

Characterization of Liposomes:

Particle Size and Zeta Potential:

The liposomal formulations were tested for zeta potential, average particle size, and polydispersity index (PDI) using a Malvern Zetasizer Nano ZS for dynamic light scattering (DLS). Prior to analysis at 25°C, the samples were diluted using double-distilled water. The size homogeneity was determined by the particle size and PDI, where PDI values less than 0.3 denoted monodispersity. When the zeta potential, which is determined by electrophoretic light scattering, is greater than or equal to ±25 mV, it signifies that the colloidal solution is stable and has a reflected surface charge. The results were presented as the mean ± SD after each measurement was repeated three times [15-17].

Entrapment Efficiency (EE %):

The quercetin entrapment efficiency was assessed by subjecting the liposomal suspension to ultracentrifugation at 20,000 rpm for 30 minutes. After collecting the supernatant, the amount of free quercetin was measured at 370 nm using UV-Vis spectroscopy. We expressed the results as the mean ± SD, and we made care to measure everything three times [16-18]. The formula was used to compute the EE%:

$$EE\% = \left(\frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}}\right) \times 100$$

Morphology:

A transmission electron microscope (TEM) was used to analyze the liposomes' surface morphology. Before imaging, a carbon-coated copper grid was stained negatively with phosphotungstic acid (1% w/v), and a drop of the liposomal dispersion was deposited on top. TEM revealed details about the vesicles' size, shape, and lamellarity [17-19].

In-Vitro Drug Release Study:

The dialysis bag approach was used to study the quercetin release profile from liposomes. A dialysis membrane containing

2 mg of quercetin was immersed in 50 mL of PBS (pH 7.4) with 0.5% Tween 80. The mixture was then heated to 37°C and constantly shaken. A 2 mL aliquot was removed and replaced with new medium at regular intervals. Using UV-Vis spectrophotometry, the quantity of quercetin that was emitted was examined [18-20].

Cell Culture and Cytotoxicity Studies:

The MCF-7 and HeLa cells were grown in DMEM with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin, and a humidified environment at 37°C with 5% CO_2. A MTT assay was used to evaluate the cytotoxicity of free quercetin, liposomes that were not targeted (Lipo-Qu), and liposomes that were targeted to folate (F-Lipo-Qu). At a density of 1×10^4 cells/well, cells were placed in 96-well plates and left to incubate for 24 hours. Following 48 hours of treatment with various formulations, 20 µL of MTT solution (5 mg/mL) was introduced, and the formazan crystals that had formed were dissolved in DMSO. The IC_{50} values were determined by measuring the absorbance at 570 nm with a microplate reader [19-21].

Cellular Uptake Studies:

Through the use of confocal laser scanning microscopy (CLSM), the injection of liposomes into MCF-7 cells could be observed. The formulations were treated with cells for 4 hours after liposomes were tagged with rhodamine-B dye. Prior to imaging under CLSM, the cells were washed with PBS and then fixed with paraformaldehyde [20-22].

Statistical Analysis:

The data were presented as the mean plus or minus the standard deviation (SD), and every experiment was carried out three times. Using one-way ANOVA and Tukey's post hoc test, we compared the groups statistically. A statistically significant result was defined as a p-value less than 0.05.

3. RESULTS

Extraction and Isolation of Quercetin:

The Soxhlet device was used to successfully extract quercetin from Allium cepa bulbs using 70% ethanol. A dark reddish-brown semi-solid residue was produced by the concentrated extract. To establish that the quercetin fraction had been successfully extracted, preparative TLC was used. Then, using HPLC, the retention time (Rt) was compared to the standard quercetin to confirm its identity. A retention period of 5.92 minutes was observed in the isolated quercetin, which was in agreement with the standard. The purity and yield of isolated quercetin are presented in Table 3.

Table 3: Yield and Purity of Isolated Quercetin

Sr. No.	Parameter	Value
1	Weight of dried extract	6.85 g per 100 g powder
2	Weight of quercetin isolated	83.2 mg
3	% Yield of quercetin	0.083% (w/w)
4	Retention time (HPLC)	5.92 ± 0.02 min
5	Purity (HPLC area %)	98.5 ± 0.8%

Preparation and Characterization of Liposomes:

The thin-film hydration process was used to successfully create liposomes, which could be functionalized with or without folic acid. The liposomes' physicochemical characteristics were assessed by means of zeta potential and dynamic light scattering (DLS). The Lipo-Qu and F-Lipo-Qu formulations both had nanometric particle sizes of 142.6 ± 3.2 nm and 156.4 ± 4.1 nm, respectively. The addition of folic acid and PEG to the surface of F-Lipo-Qu caused a slight increase in size, which was explained by the presence of steric hindrance and an increased hydrodynamic diameter. Lipo-Qu (0.198 ± 0.02) and F-Lipo-Qu (0.213 ± 0.01) both had polydispersity index (PDI) values below 0.3, suggesting a restricted size distribution and monodispersity. These features are vital for the uniform behavior of drug administration. The zeta potential tests showed that F-Lipo-Qu had a negative surface charge of -31.8 ± 1.1 mV and Lipo-Qu had a negative surface charge of -29.1 ± 1.4 mV. This indicates that the colloidal particles are stable because electrostatic repulsion prevents the vesicles from clumping together when they are stored. These results demonstrate that nanoscale liposomal systems with targeted and non-targeted drug loading capacities have been successfully developed. The observed properties point to a potential drug delivery vehicle that might be used for cancer targeting and increased intracellular delivery. The physicochemical properties of liposomes are listed in Table 4. Part one of this article is the DLS Size Distribution Graph. Liposomes in a transmission electron microscopy image (Figure 2).

Table 4: Physicochemical Characteristics of Liposomes

Formulation	Size (nm)	PDI	Zeta Potential (mV)	EE (%)
Lipo-Qu	142.6 ± 3.2	0.198 ± 0.02	-29.1 ± 1.4	78.3 ± 2.1
F-Lipo-Qu	156.4 ± 4.1	0.213 ± 0.01	-31.8 ± 1.1	82.7 ± 1.8

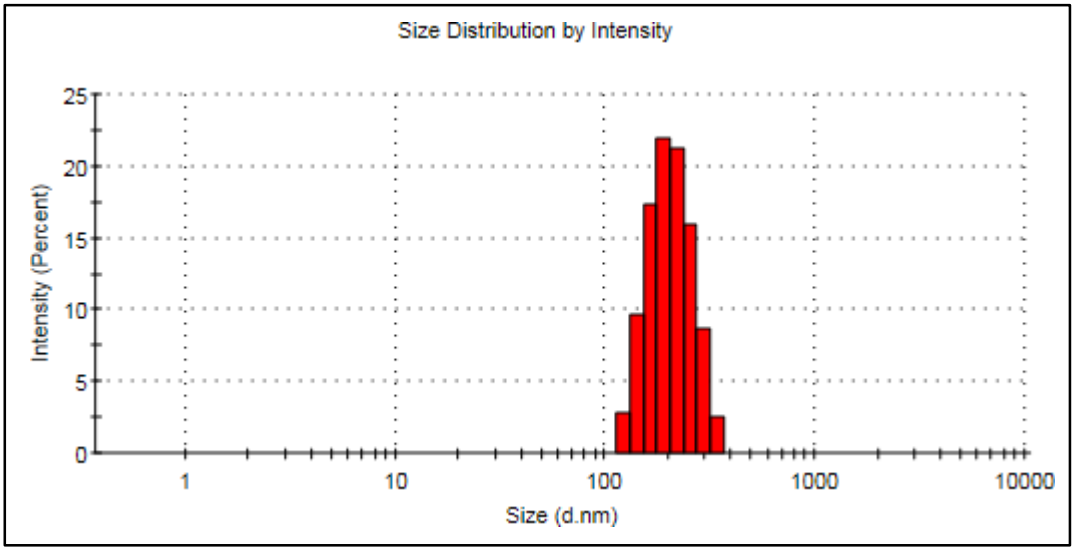

Figure 1: Size Distribution Graph from DLS

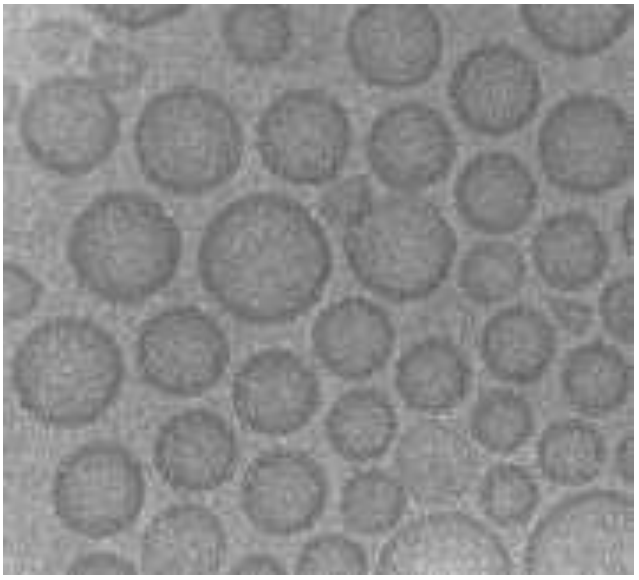

Figure 2: TEM Image of Liposomes

In-Vitro Drug Release:

The dialysis bag diffusion method in PBS (pH 7.4) containing 0.5% Tween 80 at 37°C was used to assess the release kinetics of quercetin from both non-targeted liposomes (Lipo-Qu) and folate-conjugated liposomes (F-Lipo-Qu) in an in-vitro drug release investigation. Both formulations exhibited a controlled and sustained release pattern over the course of 24 hours, according to the data. It is possible that the surface-associated quercetin was responsible for Lipo-Qu's initial burst release of about 22.3% in the first two hours. After that, the release was slow and steady, reaching 86.4 ± 2.7% by the conclusion of the first day. Unlike other drugs, F-Lipo-Qu showed a longer release profile. It released 16.8% initially and 74.1 ± 2.3%

cumulatively after 24 hours. The steric barrier that is introduced by the PEGylation and folic acid conjugation on the liposomal surface slows the diffusion rate of quercetin across the lipid bilayer, which is why F-Lipo-Qu exhibits a delayed release. This persistent drug exposure at the tumor location is made possible by this extended release, which is an advantage for targeted drug delivery systems. The sustained release behavior of both formulations validates quercetin's effective encapsulation and the release modulation capability of liposomes. The cumulative in vitro release of quercetin from liposomes is shown in Figure 3 and Table 5.

Table 5: In-vitro Cumulative Release of Quercetin from Liposomes

Time (hours)	Lipo-Qu (% Release)	F-Lipo-Qu (% Release)
0	0.0 ± 0.0	0.0 ± 0.0
2	22.3 ± 1.5	16.8 ± 1.2
4	41.6 ± 1.8	32.9 ± 1.4
8	60.3 ± 2.2	48.7 ± 1.7
12	73.2 ± 2.6	62.1 ± 2.1
24	86.4 ± 2.7	74.1 ± 2.3

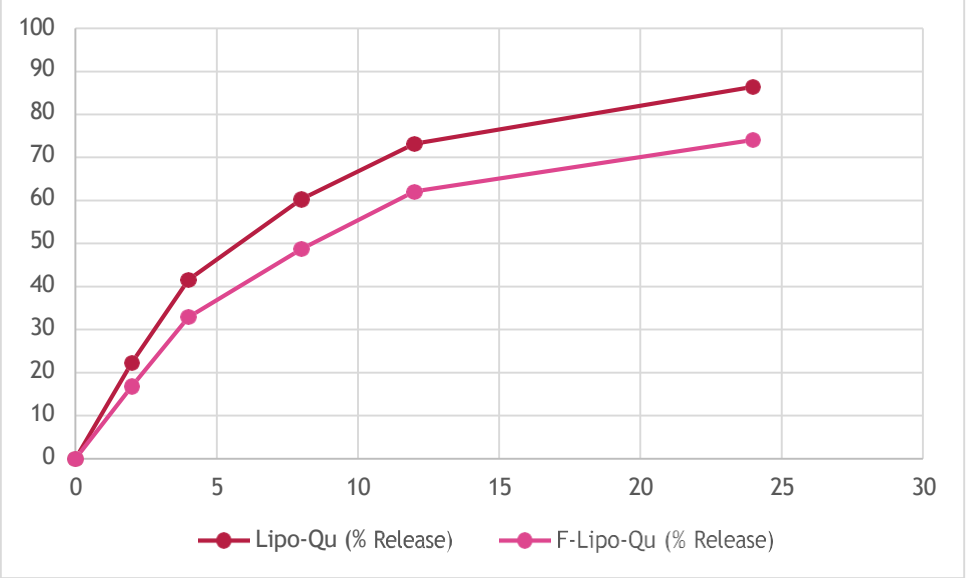

Figure 3: In-vitro release profile of quercetin from Lipo-Qu and F-Lipo-Qu over 24 hours

Cytotoxicity Studies (MTT Assay):

Two human cancer cell lines, MCF-7 (breast cancer) and HeLa (cervical cancer), were used to assess the cytotoxic capability of free quercetin, non-targeted liposomes (Lipo-Qu), and folate-conjugated liposomes (F-Lipo-Qu) using the MTT test. To determine the level of cytotoxicity caused by each formulation, the MTT test reduces MTT to formazan crystals, which evaluates the metabolic activity of live cells. The results showed that cell viability decreased with increasing dosage for all formulations that were evaluated. On the other hand, the formulations' cytotoxic efficacy differed significantly. The IC_{50} values for MCF-7 cells were 28.7 ± 1.3 µg/mL and for HeLa cells they were 32.5 ± 1.5 µg/mL, suggesting that there was limited cellular uptake and bioavailability of free quercetin, which demonstrated mild cytotoxicity. In comparison to free quercetin, Lipo-Qu greatly enhanced the cytotoxic effect, reducing the IC_{50} values to 16.9 ± 0.9 µg/mL for MCF-7 cells and 20.2 ± 1.2 µg/mL for HeLa cells. Because quercetin is liposomally encapsulated, it is more soluble, more readily taken up by cells, and released over time, all of which contribute to its enhanced action.

Among the formulations, F-Lipo-Qu showed the most cytotoxicity, with IC_{50} values of 9.6 ± 0.8 µg/mL in MCF-7 and 12.1 ± 1.1 µg/mL in HeLa cells, which were significantly lower. Since both MCF-7 and HeLa cells overexpress folate receptor-mediated endocytosis, it is probable that this is the mechanism by which F-Lipo-Qu exerts its greater lethal effect. Increased

tumor cell absorption and intracellular delivery of quercetin are made possible by PEGylation, which further enhances circulation time and stability. Figure 4 and Table 6 show the IC_{50} values in micrograms/milliliter for HeLa and MCF-7 cells, respectively.

Table 6: IC_{50} Values (µg/mL) in MCF-7 and HeLa Cells

Formulation	MCF-7	HeLa
Free Quercetin	28.7 ± 1.3	32.5 ± 1.5
Lipo-Qu	16.9 ± 0.9	20.2 ± 1.2
F-Lipo-Qu	9.6 ± 0.8	12.1 ± 1.1

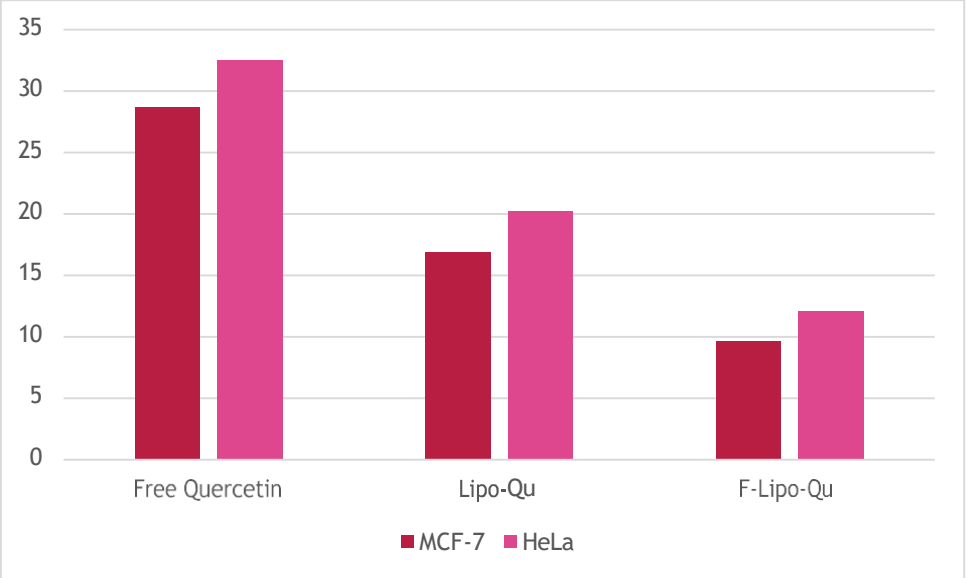

Figure 4: Cell Viability (%)

Cellular Uptake Studies:

In order to determine how well quercetin-loaded liposomes were absorbed into MCF-7 cells, confocal laser scanning microscopy (CLSM) was used. The cellular internalization of both non-targeted liposomes (Lipo-Qu) and liposomes functionalized with folate (F-Lipo-Qu) could be observed through the use of rhodamine-B, a fluorescent dye. Nuclei were seen by washing, fixation with paraformaldehyde, and counterstaining with DAPI after MCF-7 cells were incubated with the different formulations for 4 hours. The intracellular fluorescence intensity of the two formulations was significantly different, as shown by CLSM imaging. There was a marked improvement in internalization in cells treated with F-Lipo-Qu as measured by their red fluorescence compared to cells treated with Lipo-Qu. Given that MCF-7 cells are known to overexpress folate receptors, this improvement is thought to be caused by folate receptor-mediated endocytosis. Improved cellular binding and absorption are outcomes of F-Lipo-Qu's PEGylated folate ligand, which enables active targeting. Lipo-Qu, on the other hand, fluoresced to a considerable degree, indicative of passive absorption processes like endocytosis or membrane fusion. Folic acid surface modification enhances receptor-mediated intracellular transport of liposomes, as demonstrated by the distinct uptake patterns. Figure 5, which shows the confocal pictures of cellular absorption, provides strong evidence that cancer cells absorb folate-conjugated liposomes more readily, which may explain their higher cytotoxic efficiency in MTT experiments.

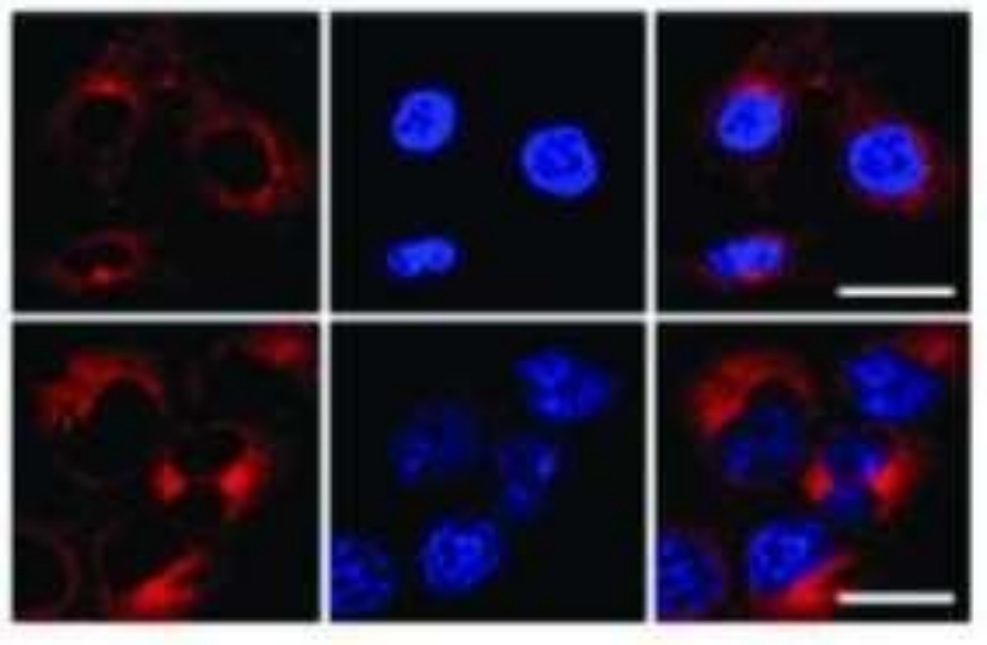

Figure 5: Confocal Images of Cellular Uptake

4. DISCUSSION

Folic acid-functionalized liposomes enclosing quercetin for targeted delivery to cancer cells were produced and tested in this work. Because of its low bioavailability, stability, and solubility, the naturally occurring flavonoid quercetin is unable to fully realize its anticancer potential. In addition to increasing its physicochemical stability, encapsulation in liposomes allowed for prolonged release and better cellular absorption [22, 23-25]. Soxhlet extraction and preparative TLC were used to efficiently extract and isolate quercetin from Allium cepa. HPLC was used to establish the identity of the compound relative to a standard reference. Isolated quercetin had a satisfactory percentage yield, making it an appropriate candidate for formulation investigations [26-29].

Both liposomes modified with and without folic acid were successfully generated using the thin-film hydration approach. Lipo-Qu and F-Lipo-Qu both had particle sizes that fell into the nanoscale region, with Lipo-Qu measuring 142.6 ± 3.2 nm and F-Lipo-Qu measuring 156.4 ± 4.1 nm. This makes them perfect for passive targeting through the EPR effect. Folic acid surface conjugation and PEGylation are responsible for the little size increase in F-Lipo-Qu. Both formulations exhibited excellent homogeneity and a restricted size distribution with PDI values ≤ 0.3. The vesicles were strongly electrostatically repelled from one another, avoiding aggregation and guaranteeing colloidal stability, as indicated by zeta potential values of around -30 mV [30-34].

Both liposomal formulations demonstrated a high entrapment efficiency, however F-Lipo-Qu had a slightly higher EE% (82.7 ± 1.8%) than Lipo-Qu (78.3 ± 2.1%). One possible explanation for this variation is that hydrophobic medicines, such as quercetin, are better encapsulated when PEGylation and folic acid interact with the lipid bilayer. The spherical and uniformly distributed morphology of the vesicles was confirmed by TEM examination, which aligns with the results of DLS. Results from in vitro drug release tests showed that both formulations had sustained release characteristics for at least 24 hours. The steric hindrance caused by the PEG chains and folic acid moieties may have reduced drug diffusion across the lipid bilayer, since F-Lipo-Qu exhibited a somewhat slower release compared to Lipo-Qu [35, 36].

Folate-targeted liposomes showed increased anticancer activity, according on the MTT assay data. Confirming that targeted administration promotes cytotoxicity, F-Lipo-Qu had noticeably lower IC_{50} values in both the MCF-7 and HeLa cell lines in comparison to Lipo-Qu and free quercetin. Folic acid binds selectively to cancer cells' overexpressed folate receptors, allowing it to undergo receptor-mediated endocytosis and increase its effectiveness. CLSM showed that cells treated with F-Lipo-Qu had much increased fluorescence intensity, showing better cellular uptake, further validating this finding. The observed trends in cytotoxicity are strongly correlated with the enhanced internalization efficiency, further highlighting the significance of surface functionalization in targeted drug delivery [37, 38].

Taken together, the results show that folate-conjugated liposomes are a great way to deliver quercetin and other anticancer drugs that aren't highly soluble. Through active targeting mechanisms, these nanocarriers boost therapeutic efficacy while simultaneously improving the drug's pharmacokinetic constraints. Future clinical translation of this method in cancer therapy is highly promising [39-45].

5. CONCLUSION

Folic acid-functionalized liposomes enclosing quercetin for targeted cancer therapy were developed and studied in this study. Allium cepa was successfully used to isolate quercetin, which was then loaded into liposomal carriers to enhance its biological activity and physicochemical stability. Liposomes showed excellent colloidal stability, minimal polydispersity, great entrapment efficiency, and a nanoscale size that was desirable. The coupling of folic acid with PEGylation led to better cellular absorption (as shown by confocal microscopy) and much improved cytotoxicity (as shown by lower IC_{50} values in MTT experiments) against MCF-7 and HeLa cancer cell lines. This method shows promise for controlled and prolonged drug administration, as seen by its sustained release behavior in vitro. As a whole, the F-Lipo-Qu formulation shows promise as a nanocarrier for the targeted administration of quercetin, which could increase its therapeutic efficacy and decrease off-target effects. In light of these results, F-Lipo-Qu may prove to be an excellent foundation upon which to build targeted nanomedicine for the treatment of malignancies that overexpress folate receptors. If its clinical usefulness is to be confirmed, additional in vivo investigations are necessary.

Funding:

None

Conflict of Interest:

None

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