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RESEARCH ARTICLE

Multi-Drug Loaded Rgd-Pegylated Chitosan Nanocomposite as a Targeted Therapeutic Strategy for Mda-Mb-231 Cell Line

R. Mohan[1], S. Suja[2]*, Abirami. S[3], Sindhu. B4, Sneha. S[5], Kanimozhi. A[6], M. Subasri[7]
[1]Department of Biochemistry, Bharathiar University, Coimbatore, India – 631046
[2]Department of Biochemistry, Bharathiar University, Coimbatore, India – 631046
[3]Pasteur Institute of India, Coonoor, India - 643103
[4]Pasteur Institute of India, Coonoor, India - 643103
[5]Pasteur Institute of India, Coonoor, India - 643103
[6]Department of Biochemistry, Bharathiar University, Coimbatore, India – 631046
[7]Department of Biochemistry, Bharathiar University, Coimbatore, India – 631046

*Corresponding Author
Dr. S. Suja

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Abstract: ***Background***: Triple-negative breast cancer (TNBC) remains one of the most challenging Breast Cancer (BC) subtypes due to its aggressive progression, high metastatic potential, and lack of effective targeted therapies. This study introduces a multifunctional nanoplatform based on Arginine-Glycine-Aspartate (RGD) functionalized, PEGylated chitosan nanocomposites (RGD-PEG-CSNC) co-loaded with three potent anticancer agents: Curcumin (diferuloylmethane) (CUR), Carboplatin (CAR), and Docetaxel (DOC). The system exploits integrin-mediated active targeting facilitated by the RGD peptide, which selectively binds integrin receptors overexpressed on MDA-MB-231 cell line, enhancing cellular uptake and drug delivery specificity. Cytotoxicity assays demonstrated significant, dose-dependent inhibition of cancer cell proliferation, with the triple-drug loaded formulation achieving a notably low half maximal inhibitory concentration (IC_{50}) of 7.8 ± 1.28 µg/ml, outperforming single and dual-drug counterparts. Additionally, wound healing studies revealed effective suppression of TNBC metastatic potential. The observed therapeutic synergy results from combined modulation of oncogenic pathways and improved bioavailability via sustained, targeted drug release. This promising approach potentially overcomes drug resistance and reduces systemic toxicity, warranting further preclinical exploration for TNBC therapy.

Keywords: Triple-negative breast cancer, Chitosan, RGD, Curcumin, Docetaxel, Carboplatin.

INTRODUCTION

BC is the most commonly diagnosed malignancy in women and a leading cause of cancer related mortality. In 2020, it accounted for 2.3 million new cases and 685,000 deaths worldwide [1], and by 2050, annual cases may rise to 3.2 million, with 1.1 million deaths, disproportionately affecting low- Human Development Index (HDI) countries [2]. In India, nearly 310,720 women were diagnosed in 2024, 16% of whom were under 50 years, with a new diagnosis occurring every four minutes and a death every eight minutes [3]. Among BC subtypes, TNBC, which lacks expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal growth factor Receptor 2 (HER2), is particularly aggressive and represents 15–20% of, cases [4]. The high incidence and aggressive nature of TNBC underscores the urgent need for more effective therapeutic strategies.

Despite advances in conventional therapies, including surgery, chemotherapy, radiotherapy, and immunotherapy, clinical outcomes are often limited by nonspecific targeting, systemic toxicity, poor bioavailability, and the development of multidrug resistance [5]. These limitations highlight the necessity of novel approaches that can improve therapeutic specificity and efficacy while minimizing side effects. In this context, nanotechnology-based drug delivery systems have emerged as promising solutions, offering enhanced tumor-specific accumulation and improved pharmacokinetics [6].

Among nanocarriers, chitosan nanoparticles (CSNP) are particularly attractive due to their biocompatibility, biodegradability, and ease of surface modification. CSNP can protect encapsulated drugs from degradation, enable sustained release, and improve bioavailability, while PEGylation further enhances solubility, stability, and circulation time [7,8,9]. Moreover, the therapeutic potential of CSNP can be significantly enhanced through active targeting strategies. RGD peptides, which bind integrins αvβ3, αvβ5, and α5β1 overexpressed in tumors, facilitate selective uptake, inhibit invasion and angiogenesis, and modulate Wnt/β-catenin signaling pathways that regulate proliferation, stemness, and drug resistance [10,11,12,13].

In addition to targeted delivery, combination therapy provides a strategic advantage by enhancing therapeutic efficacy while reducing the likelihood of resistance. CUR, a natural polyphenol derived from Curcuma longa, exhibits antiproliferative, proapoptotic, and chemosensitizing effects with minimal toxicity. When combined with CAR and DOC, CUR synergistically inhibits proliferation, migration, and colony formation in

MDA-MB-231 cell lines, demonstrating potential as part of a multi-drug therapeutic approach [14,15,16].

Building on these insights, we developed RGD-PEG-CSNC co-encapsulating CUR, CAR, and DOC (RGD-PEG-CSNC-CUR-CAR-DOC) specifically for TNBC therapy. Using MDA-MB-231 cell line, we evaluated cytotoxic effects via 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and assessed cell migration using the wound healing assay to investigate the anticancer potential of this targeted multi-drug nanotherapeutic. This study aims to elucidate how the co-delivery system influences TNBC cell viability and migratory behavior, highlighting its promise as a more effective, targeted, and synergistic therapeutic strategy.

MATERIALS AND METHODS

CUR, CAR and DOC, CS, PEG (MW6000), and RGD peptide were obtained from Sigma-Aldrich (St. Louis, MO, USA). Dulbecco's Modified Eagle's Medium (DMEM), Fetal Bovine Serum (FBS), L-glutamine, penicillin–streptomycin antibiotic solution, and phosphate-buffered saline (PBS) were procured from HiMedia Laboratories (Mumbai, India). The MDA-MB-231 cell line was obtained from the National Centre for Cell Science (NCCS), Pune, India. All chemicals and reagents used in this study were of analytical grade. Distilled water and HPLC-grade solvents were used throughout the experiments. All glassware and plasticware were sterilized prior to use under aseptic conditions in a laminar airflow hood.

METHODS

Cell culture

The MDA-MB-231 cell line, a well-established, characterized, and extensively studied model representing the TNBC phenotype, was procured from the NCCS, Pune, India.

Cytotoxicity Assay

MDA-MB-231 cells were seeded in 96-well plates at a density of 5,000 cells per well and allowed to adhere overnight. Solutions of RGD-PEG-CSNC-CUR, RGD-PEG-CSNC-DOC, RGD-PEG-CSNC-CAR, RGD-PEG-CSNC-CUR-DOC, RGD-PEG-CSNC-CUR-CAR and RGD-PEG-CSNC-CUR-DOC-CAR were prepared in DMEM medium without FBS and added to the cells at various concentrations of µg/ml (5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, and 25µg/ml). After 24 h of incubation, the media were removed, and 20 µL of MTT reagent was added to each well and incubated for 5 h. Subsequently, 100 µL of Dimethyl Sulfoxide (DMSO) was added to dissolve the formazan crystals. The absorbance of the resulting colored solution was measured using a microplate reader (Multiskan Go, Thermo Fisher, USA) at 570 nm [17].

The half-maximal inhibitory concentration (IC_{50}) values were calculated using GraphPad Prism version 8.0.1. Cell viability inhibition was determined using the following equation:

$$\%Inhibition = \frac{Opticaldensityofcontrolgroup - Opticaldensityoftestgroup}{Opticaldensityofcontrolgroup} \times 100$$

In vitro wound healing assay

MDA-MB-231 cells were seeded in 24-well plates at a density of 3×10^5 cells per well and allowed to form a monolayer over 24 h. A sterile 20–200 µL pipette tip was then used to create a cross-shaped scratch in each well. Detached cells were removed by washing the wells with 500 µL of PBS. Fresh medium containing each RGD-PEG-CSNC-based formulations, RGD-PEG-CSNC-CUR, RGD-PEG-CSNC-DOC, RGD-PEG-CSNC-CAR, RGD-PEG-CSNC-CUR-DOC, RGD-PEG-CSNC-CUR-CAR, and RGD-PEG-CSNC-CUR-DOC-CAR at their respective IC_{50} concentrations was then added to the appropriate wells, while control wells received medium without test compounds. All wells were incubated for 24 h. Prior to imaging, wells were gently washed with 500 µL of PBS and shaken for 30 seconds. The closure of the scratch was then monitored and imaged using an inverted microscope (Nikon, ECLIPSE Ti2, Tokyo, Japan) at 4X magnification [18,19]

Statistical Analysis

The statistical data presented in this study are shown as mean ± standard deviation. A student's t-test was carried out to assess the significance between the formulations. Statistical significance was observed at non-significant ns ($p > 0.05$), **$p \leq 0.01$, ***$p \leq 0.001$, and ****$p \leq 0.0001$.

RESULTS AND OBSERVATIONS:

Cytotoxicity Assay

The bar graph presented as Fig.1 provides a comparative overview of the percentage of inhibition for MDA-MB-231 cell lines treated with a panel of RGD-PEG-CSNC based drug formulations. The MTT cytotoxicity assay revealed a clear concentration dependent inhibition of MDA-MB-231 cells proliferation across all formulations. Single drug Nano formulations showed moderate antiproliferative activity, with IC_{50} values of 11.3 ± 1.0 µg/ml (RGD-PEG-CSNC-CUR), 19.5 ± 0.8 µg/ml (RGD-PEG-CSNC-DOC), and 23.3 ± 1.35 µg/ml (RGD-PEG-CSNC-CAR) after 24 h. Dual-drug systems exhibited a pronounced cytotoxic enhancement, with IC_{50} values of 12.3 ± 0.64 µg/ml (RGD-PEG-CSNC-CUR-DOC) and

10.2 ± 0.87 µg/ml (RGD-PEG-CSNC-CUR-CAR), suggesting additive and synergistic interactions between the encapsulated agents. Notably, the triple-drug formulation (RGD-PEG-CSNC-CUR-DOC-CAR) displayed the most potent cytotoxic response with a significantly reduced IC_{50} value of 7.8 ± 1.28 µg/ml, outperforming all other groups.

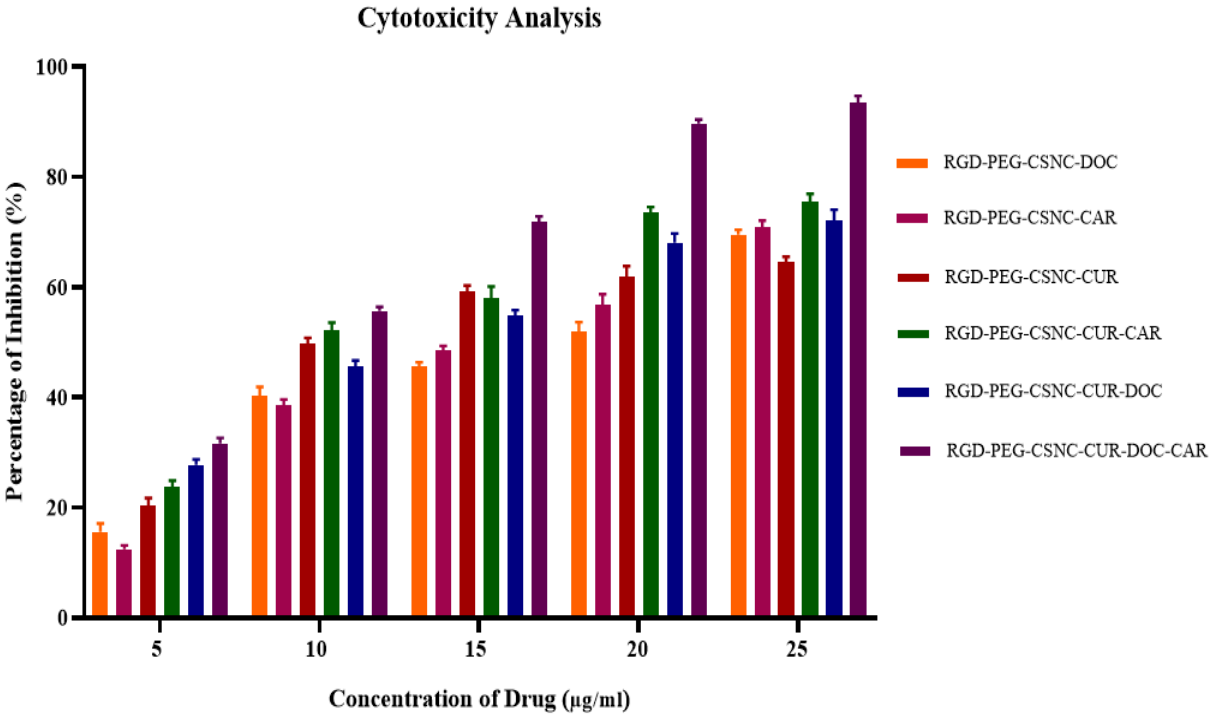

Fig.1 Cytotoxic effect of RGD-PEG-CSNC formulations on MDA-MB-231 cell line.

Table 1 IC_{50} values of RGD-PEG-CSNC formulations on MDA-MB-231 BC Cell Line

S.No	Treatment Category	IC_{50} (µg/ml ± SD)
1	RGD-PEG-CSNC-CUR	11.3 ± 1.0
2	RGD-PEG-CSNC-DOC	19.5 ± 0.8
3	RGD-PEG-CSNC-CAR	23.3 ± 1.35
4	RGD-PEG-CSNC-CUR-DOC	12.3 ± 0.64
5	RGD-PEG-CSNC-CUR-CAR	10.2 ± 0.87
6	RGD-PEG-CSNC-CUR-DOC-CAR	7.8 ± 1.28

Previous studies have reported the cytotoxic effects of CUR and DOC in MDA-MB-231 cell line, and CAR in MCF-7 cell line. After 24 hours of treatment, the IC_{50} values of CUR and DOC in MDA-MB-231 cells were 79.58 µg/mL and 56.07 µg/mL, respectively [20,21]. The IC_{50} value of CAR was reported as 256.6 µg/mL in MCF-7 cells [22]. These findings suggest that CUR and DOC possess notable cytotoxic activity in MDA-MB-231 cell line within 24 hours of exposure, whereas CAR shows limited efficacy in MCF-7 cell line..

Wound healing Assay

To evaluate metastatic inhibition, a wound healing assay was performed at 0 h and 24 h. The initial wound width (106–160 µm) (Fig.2) was uniform among all treatment groups. After 24 h, the control cells nearly closed the wound completely, indicating high migratory capacity. In contrast, drug treated cells exhibited restricted migration. Single drug treatments retained partial wound widths of 46 µm (RGD-PEG-CSNC-CUR), 47 µm (RGD-PEG-CSNC-CAR), and 30 µm (RGD-PEG-CSNC-DOC). The dual combinations RGD-PEG-CSNC-CUR-DOC and RGD-PEG-CSNC-CUR-CAR further suppressed migration, maintaining wound widths of 35 µm and 70 µm, respectively (Fig.3). The RGD-PEG-CSNC-CUR-DOC-CAR formulation exhibited exceptional wound healing effect, maintaining a wound width of approximately 95 µm, indicative of significant inhibition of cellular motility. Visual and quantitative analyses confirmed that migration suppression correlated positively with drug loading complexity and concentration. The graph (Fig.4**)** shows wound closure (in µm) at 0 h and 24 h for MDA-MB-231 cell line treated with different RGD-PEG-CSNC formulations.

Previous studies have reported that CUR significantly inhibits migration and wound closure in MDA-MB-231 cell lines in a dose- and time-dependent manner [23]. DOC reduces migration via mitotic catastrophe and apoptosis, and

combination treatments (e.g., with Ku-0063794 or thymoquinone) further suppress epithelial mesenchymal transition (EMT) and autophagy, enhancing anti-migratory effects. In esophageal cancer cells, CUR and DOC individually reduce migration, while their combination exerts synergistic inhibition [24,25]. Sequential treatment of talazoparib followed by CAR in MDA-MB-231 cell line decreases migration by over 70%, reduces invasion and metastases, lowers MCP-1 levels, and shows less toxicity than concurrent treatment, representing a promising strategy for metastatic TNBC [26].

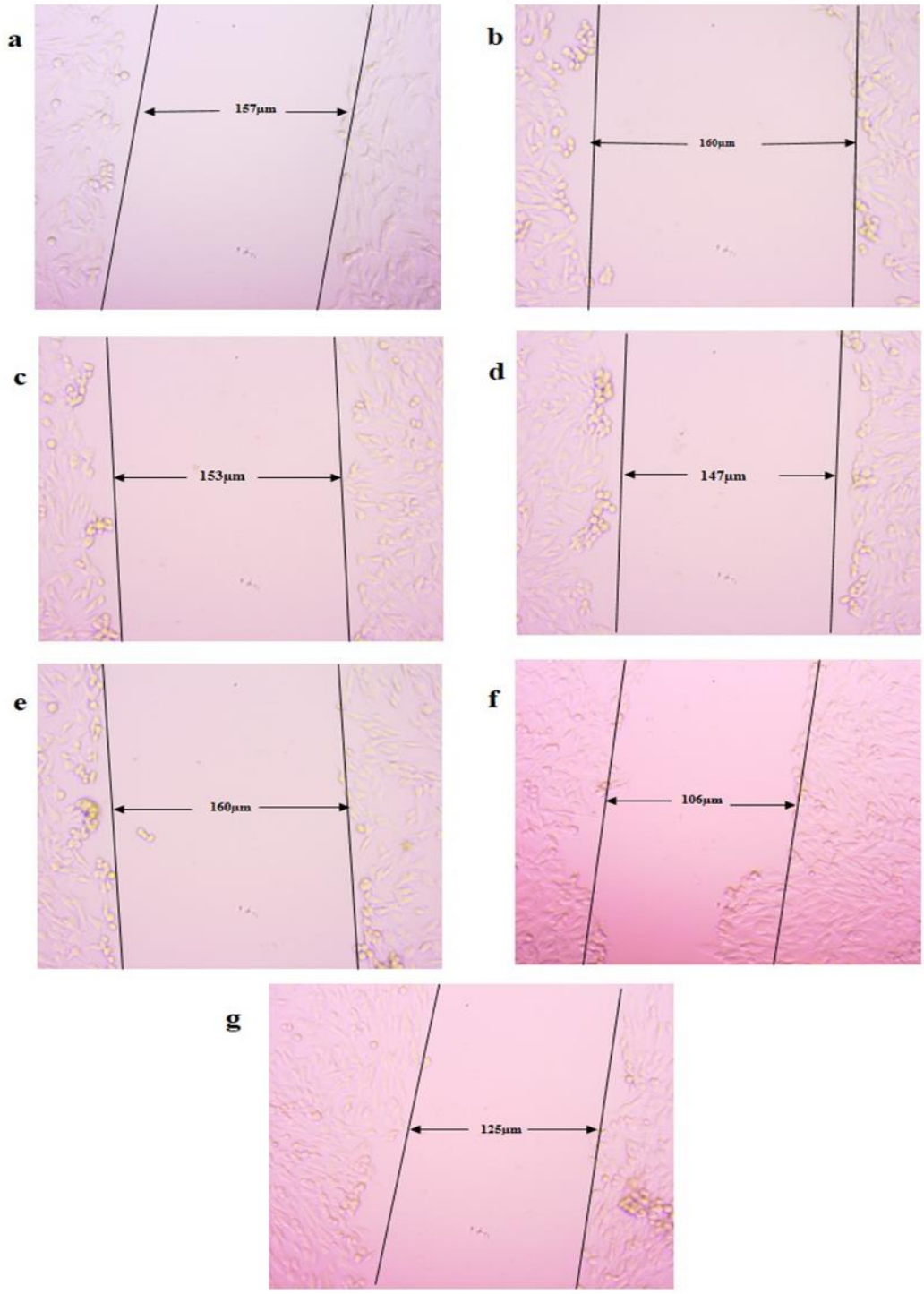

Fig.2 Wound healing assay of RGD-PEG-CSNC formulations on MDA-MB-231 Cell line at 0th hour (a)Control, (b) RGD-PEG-CSNC-CUR, (c) RGD-PEG-CSNC–CAR, (d) RGD-PEG-CSNC-DOC, (e) RGD-PEG-CSNC-CUR-CAR, (f) RGD-PEG-CSNC-CUR-DOC and (g) RGD-PEG-CSNC-CUR-DOC-CAR

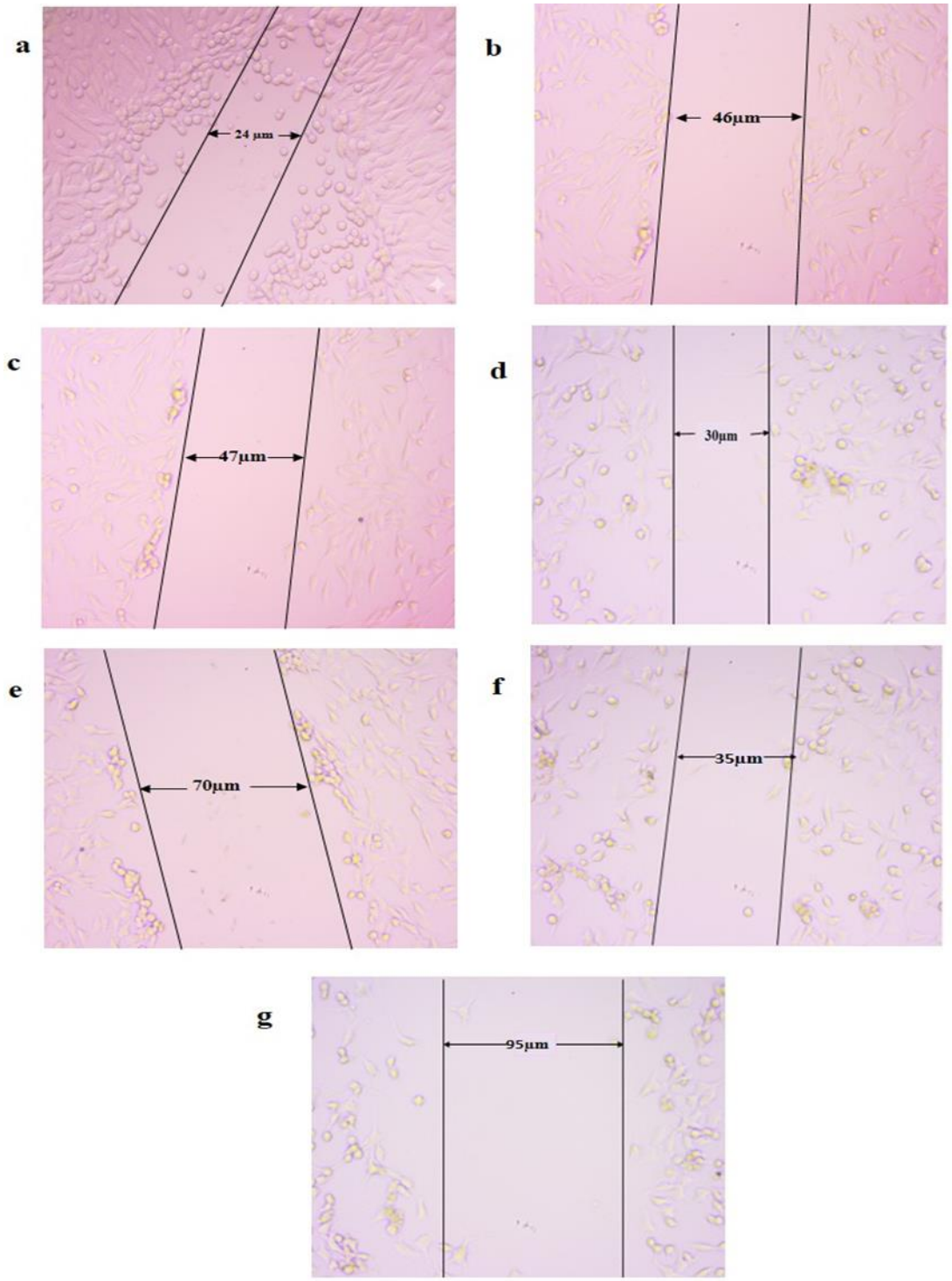

Fig.3 Wound Healing Assay of RGD-PEG-CSNC formulations on MDA-MB-231 Cell line at 24th hour (a)Control, (b) RGD-PEG-CSNC-CUR, (c) RGD-PEG-CSNC–CAR, (d) RGD-PEG-CSNC-DOC,(e) RGD-PEG-CSNC-CUR-CAR, (f) RGD-PEG-CSNC-CUR-DOC and (g) RGD-PEG-CSNC-CUR-DOC-CAR

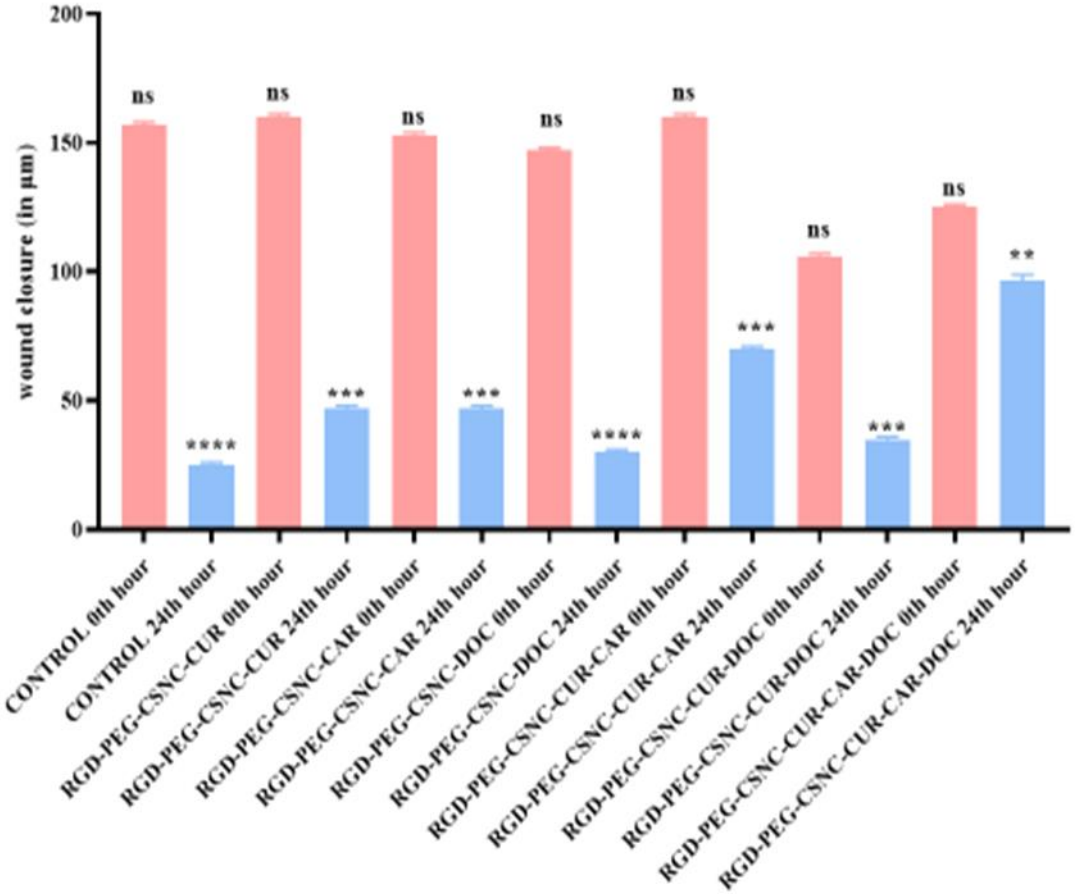

Fig.4 Graph Showing Wound Closure of MDA-MB-231 cell line

DISCUSSION

The enhanced cytotoxic and wound healing potential observed in the RGD-PEG-CSNC-CUR-DOC-CAR formulation can be attributed to the synergistic interplay of the co-encapsulated drugs and the integrin-targeted delivery mechanism facilitated by the RGD ligand. The RGD motif provides selective binding to αvβ3 and αvβ5 integrins overexpressed on MDA-MB-231 cell line, enabling receptor-mediated endocytosis and improving intracellular drug uptake [27]. Upon internalization, simultaneous release of CUC, DOC, and CAR activates multiple anti-cancer pathways that collectively enhance cytotoxic efficacy CUC suppresses NF-κB, PI3K/Akt, and Wnt/β-catenin signaling cascades, thereby reducing proliferation and EMT [28,29], whereas DOC stabilizes microtubules preventing mitotic progression [30] and CAR induces DNA crosslinking-mediated apoptosis [31]. These complementary actions lead to a marked reduction in IC_{50} values, confirming strong synergism within the triple-drug nanoformulation. PEGylated CS further provides biocompatibility and sustained drug release, averting premature clearance and off target effects. The pronounced inhibition of wound closure in treated groups corresponds with downregulation of Wnt-associated EMT signaling, highlighting suppression of motility and metastatic potential. Collectively, these results corroborate previous studies reporting that multi drug loaded, ligand functionalized nanocomposites significantly improve therapeutic efficacy, overcome drug resistance, and reduce systemic toxicity in aggressive cancer models [32,33,34].

CONCLUSION

The present study demonstrates that RGD-PEG-CSNC-CUR-DOC-CAR, a triple-drug-loaded, RGD-functionalized, PEGylated CSNC system, exhibits remarkable cytotoxic and wound healing efficacy against the MDA-MB-231 cell line. Compared to single- and dual-drug nanoformulations, this multifunctional system achieved the lowest IC_{50} value and the highest inhibition of wound closure, confirming its superior potency at significantly reduced concentrations. The enhanced performance results from the synergistic therapeutic actions of CUC, DOC, and CAR each targeting distinct molecular pathways coupled with integrin mediated active targeting via the RGD peptide that ensures selective uptake. The PEG-modified CS matrix contributes additional stability, biocompatibility, and sustained drug release, enabling efficient delivery of multiple chemotherapeutics simultaneously. Overall, the RGD-PEG-CSNC-CUR-DOC-CAR system represents a

comprehensive nanotherapeutic platform capable of overcoming drug resistance, minimizing systemic toxicity, and effectively restricting migration and proliferation in aggressive BC models. These findings strongly support its potential for further in vivo validation and clinical translation as a next generation targeted drug delivery system for TNBC.

AUTHORS' CONTRIBUTIONS

R. Mohan and S. Suja conceptualized and designed the study. R. Mohan established the theoretical framework, conducted the experiments, and performed the data analysis. Sindhu .B, Sneha. S , and Abirami .S assisted with experimental procedures and data collection. Kanimozhi. A and M. Subasri contributed to material preparation and supported data interpretation. S. Suja supervised the project, provided critical insights, and guided the interpretation of findings. R. Mohan drafted the manuscript with contributions from all authors. All authors reviewed, discussed, and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:
Not applicable.

HUMAN AND ANIMAL RIGHTS
No animals/humans were used in this research.

CONSENT FOR PUBLICATION
Not applicable.

AVAILABILITY OF DATA AND MATERIALS:
The data used in this study are available.

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