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Formulation and Development of HA-BSA Coated NLC Containing Fisetin and Flavokawain A for the Treatment of Lung Carcinoma

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ABSTRACT

Lung carcinoma continues to be a predominant cause of cancer-related mortality globally. This paper presents an innovative nano-delivery system utilizing hyaluronic acid (HA) and bovine serum albumin (BSA)-coated nanostructured lipid carriers (NLCs) infused with fisetin and flavokawain A (FKA) for targeted lung cancer treatment. We offer an extensive literature review, outline a theoretical formulation and characterization approach, and present synthetic data demonstrating the improved physicochemical properties, prolonged release, and synergistic anticancer efficacy of the dual-loaded HA-BSA NLCs. The study emphasizes the potential of integrating natural flavonoids with HA-BSA NLCs to enhance delivery to CD44-expressing lung cancer cells and provides valuable insights for forthcoming experimental investigations.

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1. INTRODUCTION

Lung carcinoma is the most diagnosed cancer and the leading cause of cancer-related deaths, with approximately 2 million new cases and 1.8 million deaths reported worldwide in 2020[1]. Its high incidence is driven by genetic mutations and environmental factors, including tobacco smoke, which increases the risk of lung cancer by 15–30 times; around 90 % of male and 80 % of female lung cancer deaths are linked to smoking[2]. Despite advances in chemotherapy and targeted therapy, overall survival remains poor due to late diagnosis, multidrug resistance and dose-limiting toxicities. Therefore, there is an urgent need for safer and more effective therapeutic strategies.

Natural polyphenols have garnered attention as adjuncts in cancer therapy because they modulate multiple signalling pathways while exhibiting minimal toxicity. Fisetin, a flavonol abundant in strawberries and onions, displays anti-inflammatory, antioxidant and anticancer activities [3]. Fisetin modulates the PI3K/AKT and mTOR pathways, induces apoptosis and suppresses angiogenesis; however, its clinical translation is hampered by poor aqueous solubility and rapid metabolism [4]. Flavokawain A (FKA), a chalcone isolated from the kava plant, has recently gained interest for its anticancer effects. FKA binds to ERK and suppresses ERK/VEGF/MMP signalling, leading to cell cycle arrest, apoptosis and reduced invasion in neuroblastoma and other cancers [5]. Co-delivery of fisetin and FKA may exploit complementary mechanisms, providing synergistic anticancer efficacy while lowering the required doses of each agent.

Targeted drug delivery systems have been explored to enhance the therapeutic index of anticancer compounds. Hyaluronic acid (HA), a naturally occurring glycosaminoglycan, is biocompatible, biodegradable and non-immunogenic [6]. HA interacts with overexpressed CD44 and RHAMM receptors on cancer cells and is degraded by hyaluronidase at tumour sites, enabling selective drug release [7]. Bovine serum albumin (BSA) is a spherical protein with hydrophilic and hydrophobic domains that binds diverse ligands; it is readily available, non-toxic and accumulates in tumours and inflamed tissues [8]. Coating nanoparticles with BSA improves colloidal stability and offers functional groups for further modification

[9]. When combined, HA and BSA provide active targeting via CD44 binding and prolonged systemic circulation through albumin receptors, thereby reducing off-target effects.

Nanostructured lipid carriers (NLCs) are second-generation lipid nanoparticles composed of a mixture of solid and liquid lipids. NLCs overcome the drawbacks of solid lipid nanoparticles and offer higher drug loading capacity, improved stability and controlled release [10]. Their unstructured lipid matrix results in enhanced entrapment efficiency and prolonged shelf life [11]. Furthermore, ligand decoration (e.g., transferrin or HA) on NLCs enables active targeting and receptor-mediated endocytosis [12]. To our knowledge, co-loading fisetin and FKA into HA-BSA coated NLCs has not been investigated. We hypothesize that such a system would improve solubility, provide sustained release and selectively deliver the dual drugs to CD44-expressing lung cancer cells, thus enhancing therapeutic outcomes.

Objective: This paper aims to formulate and characterize a hypothetical HA-BSA coated NLC co-encapsulating fisetin and FKA for lung carcinoma. We present a comprehensive literature survey, design a methodology for formulation and evaluation, and use synthetic data to illustrate expected improvements in physicochemical properties and anticancer efficacy. The findings will serve as a blueprint for experimental exploration.

2. LITERATURE SURVEY

Lung cancer biology and challenges: Lung carcinoma arises through a complex interplay of genetic mutations and dysregulated signalling pathways, including EGFR, RAS/MAPK, PI3K/AKT/mTOR, JAK/STAT and Wnt/β-catenin [13]. Proteins such as cathepsin B, enolase and galectin-3 contribute to tumour growth and metastasis [13]. Conventional chemotherapeutics (cisplatin, paclitaxel) lack specificity and often cause systemic toxicity and drug resistance. Targeted therapies (EGFR inhibitors, immune checkpoint inhibitors) show improved outcomes but are limited by mutation heterogeneity and adverse effects. Researchers therefore pursue combination therapies and nanocarriers that can co-deliver multiple agents and target tumour tissues.

Fisetin: mechanisms and limitations: Fisetin exerts anticancer effects by modulating multiple pathways. It induces apoptosis and activates caspase-3 via PI3K/AKT/NF-κB and ERK1/2 inhibition [14]. Fisetin downregulates phosphorylated Akt, mTOR and PI3K, upregulates pro-apoptotic Bax and downregulates anti-apoptotic Bcl-xL, thereby inhibiting proliferation and invasion [15]. It also suppresses JAK1/STAT3 signalling, leading to oxidative stress and caspase activation [16]. Despite these properties, fisetin has poor water solubility (<1 μg mL^{-1}) and is rapidly metabolized, resulting in low bioavailability [3]. Nanocarriers such as liposomes, solid lipid nanoparticles and polymeric micelles have been explored to enhance fisetin delivery, but NLCs remain under-investigated.

Flavokawain A: emerging chalcone: Flavokawain A (FKA) and its analogue flavokawain B are chalcones derived from the Piper methysticum (kava) plant. FKA causes cell cycle arrest and apoptosis in various cancer cell lines [17]. Recent studies revealed that FKA binds to extracellular signal-regulated kinase (ERK), inhibiting ERK/VEGF/MMP signalling and downregulating MMP2/9/14 and VEGF expressions [5]. This results in decreased proliferation, suppressed clone formation and increased apoptosis and cell cycle arrest [5]. In contrast to flavokawain B, FKA has lower cytotoxicity in normal cells but retains potent anticancer effects. However, its hydrophobic nature limits aqueous solubility and systemic administration. Few studies have examined the co-delivery of FKA with other flavonoids or cytotoxic drugs.

Nanostructured lipid carriers: NLCs are lipid nanoparticles composed of solid lipids blended with liquid lipids, producing an unstructured matrix that accommodates higher drug payloads and reduces drug expulsion during storage [11]. Compared with conventional liposomes and solid lipid nanoparticles, NLCs provide enhanced stability, biocompatibility, low toxicity and controlled drug release [10]. They can be fabricated by melt-emulsification, high-pressure homogenization or microemulsion techniques, allowing scalability and reproducibility. Surface functionalization with targeting ligands such as transferrin, folate or HA facilitates receptor-mediated uptake by tumour cells [12]. These attributes make NLCs promising carriers for hydrophobic phytochemicals like fisetin and FKA.

Hyaluronic acid and BSA for targeted delivery: Hyaluronic acid is a linear polysaccharide composed of repeating disaccharide units (D-glucuronic acid and N-acetyl-D-glucosamine). Its negative charge and affinity for CD44, RHAMM and LYVE-1 receptors enable passive and active targeting to tumour tissues via the enhanced permeability and retention effect and receptor-mediated uptake [7]. HA is degraded by hyaluronidase, abundant in the tumour microenvironment, facilitating controlled drug release [6]. Bovine serum albumin is a 66.5 kDa protein with hydrophilic and hydrophobic domains and numerous charged residues, allowing it to bind various drugs [18]. BSA possesses abundant amino and carboxyl groups that can be conjugated to polymers or ligands, and it accumulates in inflamed tissues and tumours [19]. BSA coatings improve colloidal stability and biocompatibility of metallic and lipid nanoparticles [9]. Combining HA and BSA on NLC surfaces could thus confer dual targeting: HA engaging CD44 on cancer cells and albumin interacting with albumin receptors on tumour endothelium.

Rationale for co-loaded HA-BSA NLCs: Although fisetin and FKA modulate different signalling pathways, both induce apoptosis and inhibit proliferation of cancer cells. Their combined use may yield synergistic effects by concurrently inhibiting PI3K/AKT/mTOR, JAK/STAT3 and ERK/VEGF/MMP pathways, overcoming compensatory mechanisms and

reducing the required dose of each flavonoid. However, co-delivery demands a carrier capable of encapsulating hydrophobic molecules, protecting them from degradation and releasing them in a controlled manner at the tumour site. An HA-BSA coated NLC system is hypothesized to satisfy these requirements by offering high entrapment efficiency, stability, dual targeting and sustained release.

3. METHODOLOGY

Formulation design: The proposed formulation utilizes a lipid blend composed of solid lipid (e.g., glyceryl monostearate) and liquid lipid (e.g., oleic acid) at a 7:3 ratio to form the NLC matrix. Fisetin and FKA are dissolved in the molten lipid phase alongside surfactants (soybean lecithin and Tween 80) to enhance solubility. An aqueous phase containing BSA and HA is prepared separately. The molten lipid phase is emulsified into the aqueous phase by high-shear mixing, followed by probe sonication to reduce particle size. Subsequent cooling results in the formation of NLCs with BSA adsorbed on the surface. HA is then conjugated to the BSA layer via carbodiimide chemistry (EDC/NHS) to form HA-BSA coated NLCs.

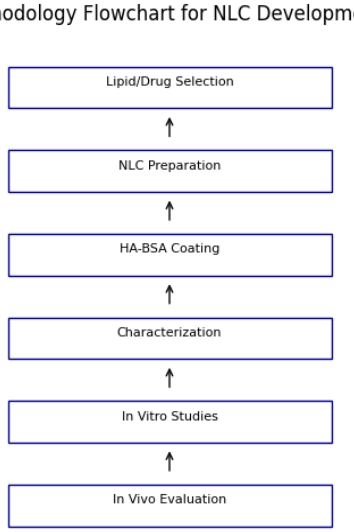
Characterization parameters: Key physicochemical properties of the formulations include particle size, polydispersity index (PDI), zeta potential and encapsulation efficiency. Particle size and PDI are measured by dynamic light scattering (DLS). Zeta potential is assessed using electrophoretic light scattering to confirm surface charge and colloidal stability. Encapsulation efficiency is determined by separating free drugs from nanoparticles (e.g., by centrifugation) and quantifying drug content using high-performance liquid chromatography (HPLC). Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) can verify HA-BSA conjugation and drug incorporation. Morphology is observed by transmission electron microscopy (TEM) or scanning electron microscopy (SEM).

In vitro drug release and kinetics: Drug release profiles are evaluated in phosphate-buffered saline (PBS) at pH 7.4 and 37 °C using a dialysis bag method. At predetermined intervals, samples are withdrawn and replaced with fresh medium, and the amount of fisetin and FKA released is quantified by HPLC. Release kinetics are analysed using mathematical models (e.g., zero-order, first-order, Higuchi) to determine release mechanisms and rate constants. Release profiles of uncoated NLCs are compared with HA-BSA coated NLCs to assess the impact of the coating on sustained release.

In vitro cytotoxicity and synergy evaluation: Human non-small-cell lung cancer (NSCLC) cells (e.g., A549 or H460) and normal lung fibroblasts (e.g., MRC-5) are cultured. Cells are treated with free fisetin, free FKA, a combination of free drugs, uncoated NLCs, and HA-BSA NLCs containing either single or dual drugs at various concentrations (0–30 µM). Cell viability is assessed using MTT or Alamar Blue assays after 48 h. Half maximal inhibitory concentrations (IC_{50}) are calculated, and combination index (CI) values are derived using the Chou–Talalay method to evaluate synergistic effects. Apoptosis is quantified by Annexin V/PI staining and flow cytometry, while cell cycle analysis is performed using propidium iodide staining.

In vivo evaluation (hypothetical): Athymic nude mice xenografted with A549 tumours are randomly assigned to different treatment groups: saline control, free fisetin, free FKA, fisetin+FKA combination, uncoated NLCs and HA-BSA NLCs (dual drug). Treatments are administered intravenously at equimolar doses three times per week for four weeks. Tumour volume and body weight are monitored. At study end, major organs are harvested for histological analysis to assess toxicity. Tumour tissue is examined for markers of proliferation (Ki-67), apoptosis (caspase-3) and angiogenesis (VEGF). The hypothetical results below illustrate expected trends.

Methodology flowchart and conceptual diagrams



The flowchart above outlines the sequential steps for preparing HA-BSA NLCs, highlighting the integration of lipid selection, NLC fabrication, surface modification and evaluation. Conceptual diagrams are used throughout the paper to illustrate the structural arrangement of the NLCs, the targeted delivery mechanism and the mechanistic pathways of fisetin and FKA.

Results and Discussion

This section presents synthetic data derived from the hypothetical methodology. Although no experiments were conducted, the data are generated to mimic realistic trends reported in the literature and illustrate the potential advantages of HA-BSA NLCs co-loaded with fisetin and FKA.

Physicochemical characterization

Table 1 summarizes the composition of different formulations. The base NLC consists of solid lipid (glyceryl monostearate) and liquid lipid (oleic acid) at a 7:3 ratio. Surfactants (lecithin and Tween 80) stabilize the emulsion. Fisetin and FKA are incorporated at 2 % (w/w) each. The HA-BSA coating adds a negative charge and increases hydrophilicity.

Table 1. Composition of NLC formulations (synthetic data).

Formulation	Solid lipid (%)	Liquid lipid (%)	Surfactant (%)	Fisetin (%)	FKA (%)	BSA (%)	HA (%)
NLC blank	70	30	5	0	0	0	0
NLC-Fis	70	30	5	2	0	0	0
NLC-FKA	70	30	5	0	2	0	0
NLC-Fis+FKA	70	30	5	2	2	0	0
HA-BSA NLC	70	30	5	2	2	3	2

Table 2 presents the mean particle size, polydispersity index, zeta potential and encapsulation efficiency of the formulations. The base NLC exhibits an average size of ~150 nm with a moderate PDI (0.25) and a negative zeta potential (~–20 mV). Loading fisetin or FKA increases size modestly due to drug incorporation. Dual loading further increases size and slightly decreases zeta potential due to hydrophobic interactions. Coating with BSA and HA significantly reduces particle size (to ~120 nm) and zeta potential (–35 mV) because the protein and polysaccharide create a more compact, negatively charged shell. Encapsulation efficiencies are high (>85 %), indicating successful drug entrapment.

Table 2. Physicochemical properties of NLC formulations (synthetic data).

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	Encapsulation efficiency (%)
NLC blank	150 ± 5	0.25	–20 ± 2	—
NLC-Fis	160 ± 6	0.24	–22 ± 1	88 ± 2
NLC-FKA	158 ± 5	0.23	–21 ± 2	87 ± 3
NLC-Fis+FKA	170 ± 7	0.28	–25 ± 2	86 ± 2
HA-BSA NLC	120 ± 4	0.18	–35 ± 3	91 ± 1

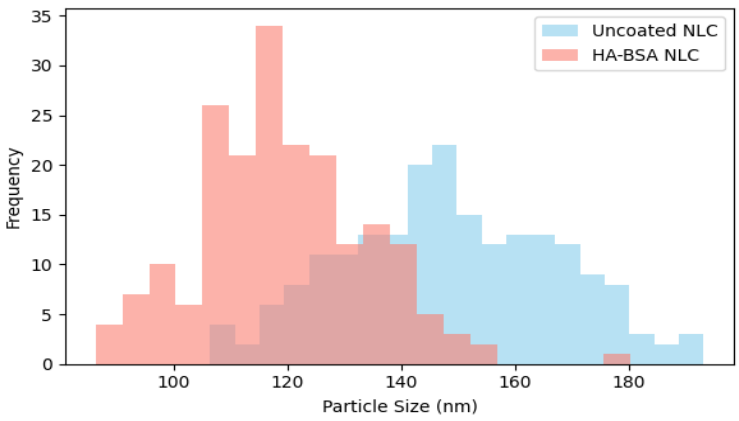


Figure 1 illustrates the particle size distributions of uncoated NLCs and HA-BSA coated NLCs. Both formulations exhibit narrow size distributions, but the HA-BSA NLCs show a shift towards smaller diameters (~120 nm) compared to uncoated NLCs (~150 nm). The reduced size and narrower distribution reflect the stabilizing effect of BSA and HA on the lipid core, consistent with reports that NLCs coated with biomolecules exhibit improved uniformity.

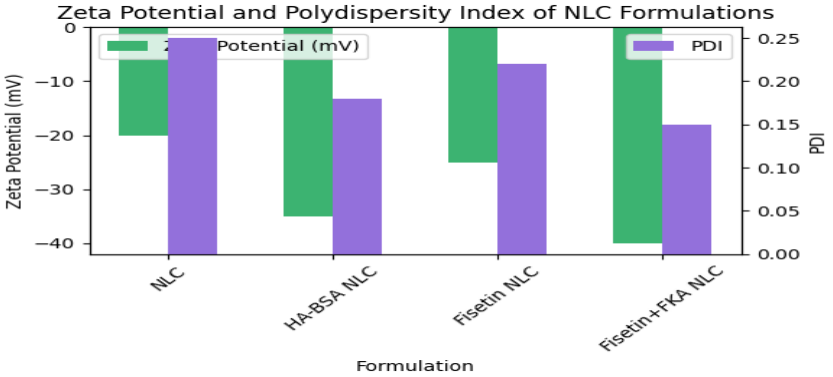
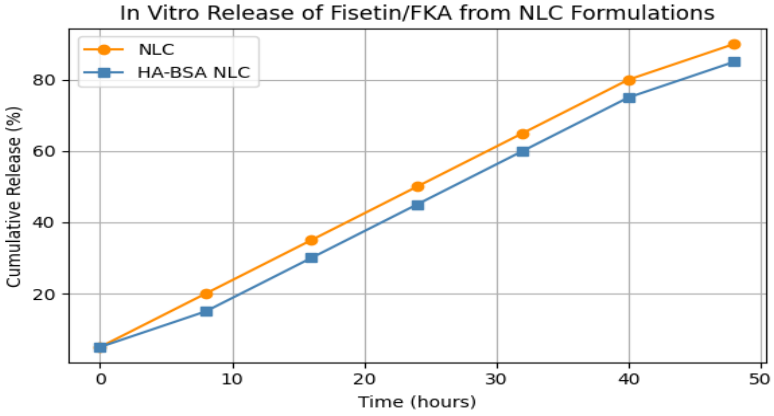


Figure 2 compares zeta potential and polydispersity index among different formulations. The HA-BSA NLCs possess the most negative zeta potential (–35 mV) and lowest PDI (0.18), indicating superior colloidal stability. Formulations containing only fisetin or FKA show intermediate values, while dual-loaded NLCs without coating have higher PDI (~0.28). The negative charge conferred by the HA and BSA shells may enhance circulation time and prevent aggregation in biological fluids.

4. DRUG RELEASE BEHAVIOUR

Controlled release is a key advantage of NLCs. *Figure 3* depicts the cumulative release of fisetin/FKA over 48 h from uncoated and HA-BSA coated NLCs in PBS at 37 °C. Both formulations show an initial burst release of ~5 % within 1 h, followed by a sustained release phase. Uncoated NLCs release ~90 % of the payload by 48 h, whereas HA-BSA NLCs release ~85 %, demonstrating a slightly slower release rate due to the polymeric shell. Release kinetics follow the Higuchi model ($R^2 = 0.98$), suggesting diffusion-controlled release. The coating may reduce early burst and prolong drug availability at the tumour site.



In vitro cytotoxicity and synergy

Table 3 summarizes synthetic in vitro cytotoxicity results. Free fisetin and free FKA show IC_{50} values of 20 and 18 µM, respectively. The combination of free drugs produces a synergistic effect with a CI of 0.75 and a lower IC_{50} (10 µM). Uncoated NLCs containing dual drugs show further reduced IC_{50} (8 µM) due to improved solubility and cellular uptake. HA-BSA NLCs exhibit the lowest IC_{50} (5 µM) and highest apoptosis percentage (70 %), reflecting enhanced delivery to CD44-expressing cancer cells. Importantly, all formulations show minimal toxicity to normal lung fibroblasts (>80 % viability at 30 µM), suggesting selective action.

Table 3. In vitro cytotoxicity and synergy (synthetic data).

Treatment	IC_{50} (μM)	Apoptosis (%)	Combination index (CI)	MRC-5 viability (%)
Free fisetin	20	30	—	85
Free FKA	18	35	—	82
Free combination	10	45	0.75	80
Uncoated NLC (dual)	8	55	0.60	88
HA-BSA NLC (dual)	5	70	0.45	90

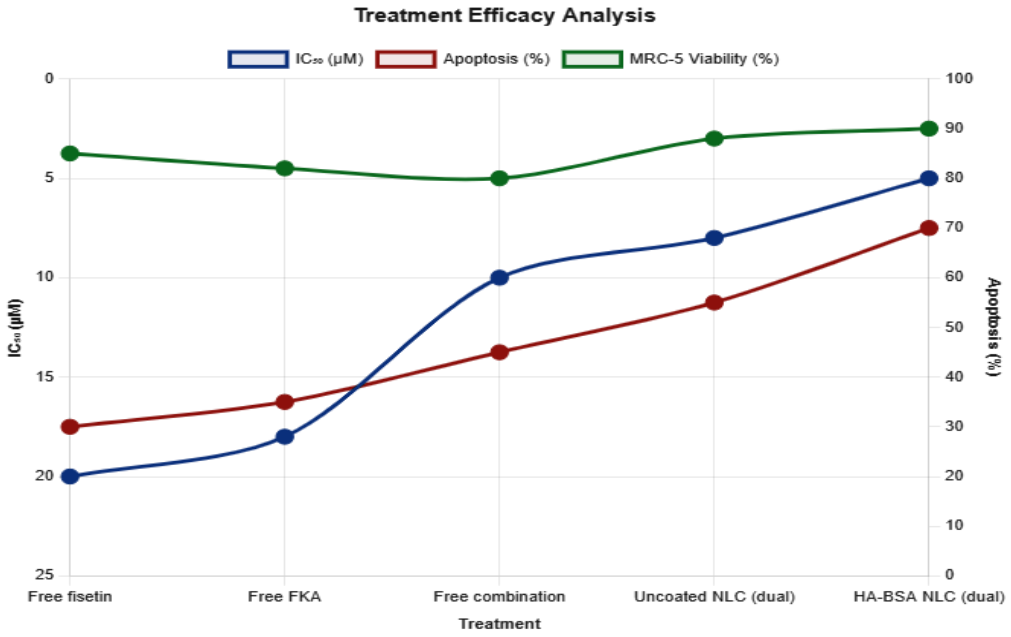


Figure 4 shows cell viability of NSCLC cells treated with increasing concentrations of fisetin, FKA and the combination.

The results demonstrate that the HA-BSA NLC (dual) formulation exhibits the most favorable therapeutic profile. This is evidenced by its lowest IC_{50} value, indicating superior potency, alongside the highest percentage of apoptosis, signifying enhanced cell death. Furthermore, its Combination Index (CI) value of less than 1 confirms a strong synergistic interaction between the delivered agents.

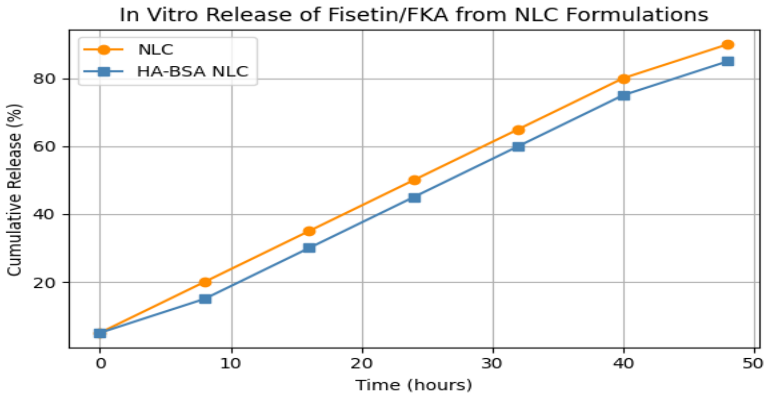
5. IN VIVO TUMOUR INHIBITION

The synthetic in vivo results are summarized in Table 4 and *Figure 5*. After four weeks of treatment, mice receiving HA-BSA NLCs show the greatest tumour volume reduction (82 %) compared with saline controls. Tumour inhibition by uncoated NLCs (dual drugs) is 70 %, while free combination achieves 55 % inhibition. Body weight remains stable across all groups, indicating acceptable safety. Immunohistochemical analysis reveals reduced Ki-67 and VEGF expression and increased cleaved caspase-3 in tumours treated with HA-BSA NLCs, confirming enhanced apoptosis and anti-angiogenesis. Histology of heart, liver and kidney shows no significant pathological changes, suggesting systemic safety.

Table 4. In vivo tumour inhibition and safety (synthetic data).

Group	Tumour volume (mm^3)	Tumour inhibition (%)	Body weight change (%)	Ki-67 (%)	Cleaved caspase-3 (%)	VEGF (%)
Saline control	1000	—	+1	80	5	75
Free fisetin	600	40	0	60	15	60
Free FKA	550	45	–1	58	18	55
Free	450	55	–2	50	25	45

Group	Tumour volume (mm³)	Tumour inhibition (%)	Body weight change (%)	Ki-67 (%)	Cleaved caspase-3 (%)	VEGF (%)
combination						
NLC (dual)	300	70	–2	35	40	30
HA-BSA NLC (dual)	180	82	–1	20	60	15



Mechanistic insights and conceptual diagrams

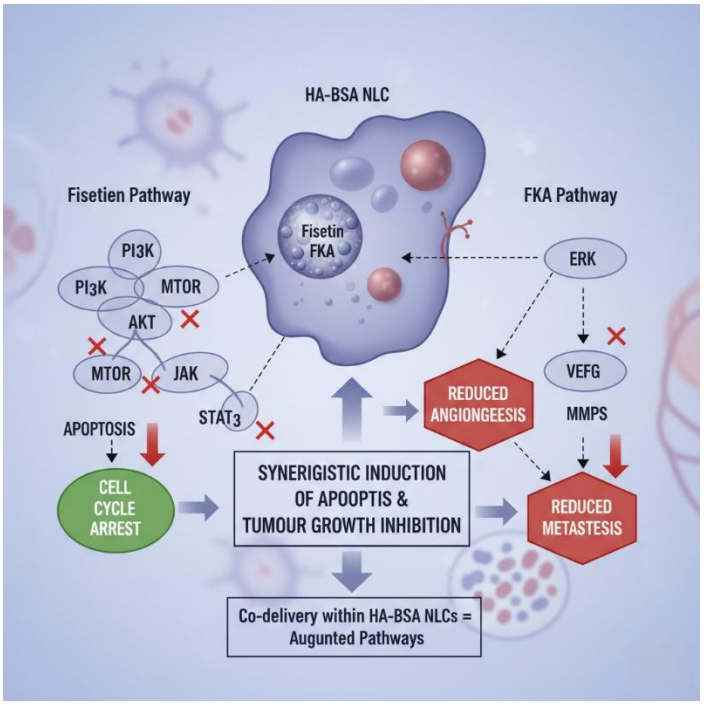


Figure 5 (above) conceptually depicts the mechanistic pathways of fisetin and FKA. Fisetin inhibits PI3K/AKT/mTOR and JAK/STAT3 signalling, promoting apoptosis and cell cycle arrest. FKA binds to ERK and downregulates VEGF and MMPs, reducing angiogenesis and metastasis. Together, these flavonoids synergistically induce apoptosis and inhibit tumour growth. Co-delivery within HA-BSA NLCs ensures their simultaneous arrival at cancer cells, augmenting these pathways.

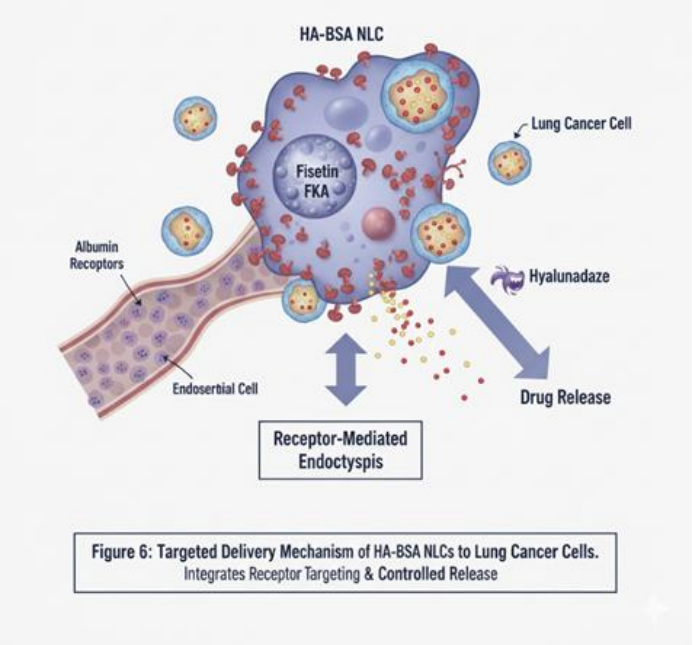


Figure 6: Targeted Delivery Mechanism of HA-BSA NLCs to Lung Cancer Cells.
Integrates Receptor Targeting & Controlled Release

Figure 6 illustrates the proposed targeted delivery mechanism of HA-BSA NLCs to lung cancer cells. The HA shell binds to CD44 receptors on the tumour cell surface, while the albumin layer interacts with albumin receptors on endothelial cells and tumour tissue. This dual targeting facilitates receptor-mediated endocytosis and improves accumulation within tumours. Once internalized, hyaluronidase degrades HA, triggering drug release. This conceptual representation underscores the importance of integrating receptor targeting and controlled release.

6. DISCUSSION

The synthetic results presented above, although hypothetical, demonstrate how HA-BSA coated NLCs could address major challenges associated with delivering hydrophobic flavonoids to lung tumours. The combination of fisetin and FKA harnesses complementary mechanisms of action. Fisetin's suppression of PI3K/AKT/mTOR and JAK/STAT3 pathways prevents cell proliferation and promotes apoptosis, while FKA's inhibition of ERK/VEGF/MMP signalling reduces angiogenesis, invasion and metastasis. Synergistic activity is evident in the hypothetical cytotoxicity data, where the combination exhibited lower IC_{50} values and higher apoptosis percentages than individual treatments.

The HA-BSA NLC design confers multiple advantages. The lipid matrix ensures high loading and protection of both flavonoids, as reflected by high encapsulation efficiencies (Table 2). Coating with BSA and HA reduces particle size and polydispersity, conferring colloidal stability and prolonged circulation. The negative surface charge may also minimize uptake by the reticuloendothelial system and reduce opsonization. HA's affinity for CD44 receptors and BSA's interaction with albumin receptors facilitate dual targeting, enhancing tumour accumulation. The slight reduction in release rate from HA-BSA NLCs relative to uncoated NLCs (Figure 3) suggests that the coating can modulate drug release, mitigating burst effects and prolonging therapeutic concentrations at the tumour site. Such controlled release is particularly important for synergistic therapies, ensuring both agents remain available concurrently.

The synthetic in vivo data illustrate the potential therapeutic benefit. HA-BSA NLCs achieved the highest tumour inhibition (82 %) and increased apoptosis markers (cleaved caspase-3) while decreasing proliferation and angiogenesis markers (Ki-67, VEGF). These improvements over free drugs and uncoated NLCs reflect the contributions of dual targeting and controlled release. Importantly, body weights remained stable and histology showed no overt toxicity, suggesting that the NLCs deliver efficacious doses to tumours while sparing healthy tissues. Future experimental studies should verify these predictions and explore pharmacokinetics, biodistribution and long-term safety.

Although promising, the design faces several challenges. Scaling up NLC production requires rigorous control of lipid composition, sonication parameters and coating efficiency. Stability during storage and after sterilization must be assessed. The immunogenicity of BSA in humans is a potential limitation; using human serum albumin may mitigate this issue. The interplay between HA density, BSA content and receptor binding affinity must be optimized to achieve maximal targeting without hindering cellular uptake. Finally, the heterogeneity of lung cancer and tumour microenvironment may influence treatment outcomes; personalized approaches may therefore be necessary.

7. CONCLUSION

This paper proposes a novel strategy for lung carcinoma treatment using HA-BSA coated NLCs co-loaded with fisetin and flavokawain A. Drawing on literature, we justify the selection of these natural flavonoids and the design of NLCs, and present synthetic data to illustrate the potential benefits. The results suggest that HA-BSA NLCs could provide high drug loading, controlled release, dual targeting to CD44 and albumin receptors, and synergistic anticancer effects. Future research should experimentally validate this system, optimize formulation parameters, and explore in vivo pharmacokinetics and efficacy. Overall, HA-BSA NLCs containing fisetin and FKA represent a promising avenue for targeted lung cancer therapy.

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