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LIPOSOMAL ENCAPSULATION OF RESVERATROL ENHANCES HEPATOPROTECTIVE EFFICACY AGAINST THIOACETAMIDE-INDUCED HEPATOCELLULAR CARCINOMA IN ALBINO RATS

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ABSTRACT: Resveratrol is a natural polyphenol with potent antioxidant and anticancer properties, but is limited in therapeutic application due to poor solubility, stability, and bioavailability. Liposomal encapsulation offers a promising approach to overcome these limitations and improve its pharmacological efficacy. Objective: The present study aimed to develop and evaluate resveratrol-loaded liposomes for improved drug release and hepatoprotective efficacy against TAA-induced hepatocellular carcinoma (HCC) in rats. Methods: Resveratrol liposomes were prepared and characterized for entrapment efficiency and in vitro drug release using the USP dissolution apparatus I (basket method) in phosphate buffer pH 6.5 and 7.5. The *in vivo* hepatoprotective effect was assessed in TAA-induced HCC rats, comparing control, negative control, standard (silymarin), free resveratrol, and liposomal resveratrol (low and high dose) groups. Body weight changes, serum biochemical markers, and histopathological observations were recorded. Results: Liposomal formulations demonstrated high entrapment efficiency and sustained drug release compared with free resveratrol. *In vivo* studies showed significant improvement in body weight, normalization of liver function parameters, and reduced necrotic and inflammatory changes in liposomal resveratrol-treated groups. Notably, the high-dose liposomal group exhibited near-normal hepatic architecture and superior hepatoprotection, comparable to the standard drug. Conclusion: Liposomal encapsulation of resveratrol enhanced its release profile, stability, and therapeutic potential against TAA-induced hepatocellular carcinoma. These findings suggest that liposomal resveratrol could serve as a promising nanoformulation strategy for improving bioavailability and therapeutic efficacy in liver cancer management.

Keywords: Resveratrol, Liposomes, Drug release, Thioacetamide, Hepatocellular carcinoma.

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1. INTRODUCTION

One of the most common and deadly types of liver cancer in the world, hepatocellular carcinoma (HCC) is a leading contributor to cancer-related death. Current treatment options, including surgical resection, chemotherapy, and targeted therapies, are often limited by toxicity, drug resistance, and poor patient prognosis. Hence, there is a growing need to develop novel therapeutic strategies that are both effective and safe for long-term management of HCC [1]. Natural compounds, particularly polyphenols, have attracted increasing attention as promising chemopreventive and therapeutic agents due to their pleiotropic biological activities and favorable safety profiles [2]. The pharmacological effects of resveratrol, a naturally occurring stilbene and polyphenolic compound widely found in berries, peanuts, and grapes, have been extensively studied. It has potent anti-inflammatory, anti-proliferative, anti-angiogenic, and antioxidant qualities [3]. Preclinical studies have demonstrated its ability to induce apoptosis, restore redox balance, suppress tumor growth, and modulate key signaling pathways implicated in hepatocarcinogenesis [4]. In addition, resveratrol has shown hepatoprotective effects in various models of liver injury, making it a promising candidate for the prevention and treatment of HCC. Despite its therapeutic potential, the clinical application of resveratrol remains severely hampered by its poor aqueous solubility, rapid metabolism, and low bioavailability, which significantly reduce its effectiveness *in vivo* [5]. To overcome these limitations, nanocarrier systems such as liposomes have been widely explored [6]. Liposomes, owing to their biocompatibility, ability to encapsulate hydrophobic compounds, and potential for targeted delivery, offer a promising strategy to enhance the stability, solubility, and pharmacokinetic profile of resveratrol. Moreover, liposomal encapsulation can provide sustained drug release, protect the active compound from premature degradation, and improve tissue distribution, thereby maximizing therapeutic efficacy [7]. In this context, the present study was designed to develop and characterize resveratrol-loaded liposomes using the solvent ether-injection method, followed by evaluation of their physicochemical properties, entrapment efficiency, and morphology. Furthermore, in vitro drug release studies and *in vivo* assessments in a TAA-induced hepatocellular carcinoma rat model were performed to investigate the therapeutic efficacy of liposomal resveratrol in comparison with free resveratrol and standard treatment[8,9]. Although

several preclinical studies have reported the hepatoprotective and anticancer potential of resveratrol, the majority have been limited to its free form, which suffers from poor solubility, rapid metabolism, and low bioavailability. Furthermore, few studies have compared resveratrol's efficacy against clinically relevant drugs in validated *in vivo* cancer models. To address this gap, the present study introduces a liposomal nanocarrier system for resveratrol, designed to enhance its entrapment efficiency, stability, and sustained release. Unlike prior reports, our work provides a systematic evaluation of liposomal resveratrol in a thioacetamide-induced hepatocellular carcinoma rat model and compares its therapeutic efficacy not only with free resveratrol but also with the standard drug Lenvatinib, thereby establishing its translational potential in HCC therapy.

2. MATERIALS AND METHODS

Resveratrol (purity > 98%) was purchased from a reputable supplier. Phosphatidylcholine (soy lecithin) and cholesterol were used as the lipid components. Diethyl ether and ethanol (analytical grade) acted as organic solvents. Phosphate-buffered saline (pH 7.4) was used as the aqueous solution. Sucrose was used as a cryoprotectant. All other chemicals were of analytical grade. Standard enzymatic kits were used for serum biochemical tests like SGOT/AST, SGPT/ALT, and total bilirubin [10].

2.1. Preparation of Resveratrol-Loaded Liposomes

Resveratrol-loaded liposomes were made using the solvent ether-injection method. First, phosphatidylcholine and cholesterol were measured precisely at the selected molar ratio and dissolved in diethyl ether. A small amount of ethanol was added to help dissolve resveratrol. The organic solution was then injected into warm PBS (pH 7.4, kept at 60 °C) under continuous stirring (600–900 rpm) at a controlled rate of 0.1–0.5 mL/min using a syringe pump. As diethyl ether evaporated quickly, phospholipids formed vesicles that trapped resveratrol. The resulting mixture was cooled to room temperature and sonicated to reduce the size and variation of the vesicles. The solution was then centrifuged (15,000 rpm, 30 minutes, 4 °C) to remove any drug not trapped inside the liposomes. For freeze-drying, sucrose (5–10% w/v) was added as a cryoprotectant. The samples were frozen at –80 °C and then freeze-dried under standard conditions. After freeze-drying, the formulations were mixed with sterile PBS before further testing [11].

2.2. Entrapment Efficiency (EE%)

Entrapment efficiency was measured by checking the total and free drug quantities. A resveratrol solution was made, and dilutions were used to make a calibration curve at 306 nm using a UV–Visible spectrophotometer [12]. The liposomal formulations (F1: 10 mg resveratrol; F2: 20 mg resveratrol) were centrifuged at 15,000 rpm for 30 minutes. The liquid containing untrapped resveratrol was collected and measured. Entrapment efficiency (EE%) was calculated as:

$$EE\% = (Total\ drug - Free\ drug) / Total\ drug \times 100$$

Formulation F1 showed an EE% of 87.85 ± 0.20%, and F2 showed 81.75 ± 0.15%.

2.3. Scanning Electron Microscopy (SEM) Analysis

The SEM analysis was used to characterize the shape and surface of the resveratrol-loaded liposomes. The samples were attached to aluminum stubs, coated with gold, and viewed under appropriate magnification. The liposomes appeared spherical or nearly spherical, had smooth surfaces, and ranged in size from 100–250 nm, confirming they were successfully made at the nanoscale with good stability [13].

2.4. *In Vitro* Drug Release Study

The USP dissolving apparatus I (basket technique) was used to investigate the release of resveratrol from liposomes. The basket was filled with liposomal formulations that contained 50 mg of resveratrol. The basket was then rotated at 100 rpm while immersed in 900 mL of dissolution media that was maintained at 37 ± 0.5 °C. Phosphate buffer at pH 6.5 and pH 7.5 were the two media types that were employed. To maintain conditions, 5 mL samples were obtained at predetermined intervals (0.5, 1, 2, 4, 6, 8, 12, and 24 hours) and replaced with equivalent quantities of warm medium. After filtering the samples (0.45 μm), the cumulative proportion of medication released was computed, adjusted for dilution, and quantified at 306 nm using UV spectrophotometry [14].

2.5. In Vivo study

2.5.1. Experimental Animals

Healthy adult Albino rats (150–200 g) were procured and acclimatized for one week under standard laboratory conditions (temperature 25 ± 2 °C, 12-hour light/dark cycle) with free access to standard pellet diet and water ad libitum [15]. All experimental procedures were carried out in accordance with the guidelines of the Committee for Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and were approved by the Institutional Animal Ethics Committee (IAEC) of SBCP (Approval No.: SBCP/2024-25/CCSEA/IAEC/I(2)F16/363).

2.5.2. Study Design

Animals were randomized into six groups (n=6 each), such as Group I (saline control), Group II (TAA-induced untreated), Group III (Lenvatinib 4 mg/kg, p.o.), Group IV (resveratrol 30 mg/kg, p.o.), Group V (liposomal resveratrol 15 mg/kg, p.o.), and Group VI (liposomal resveratrol 30 mg/kg, p.o.)

2.5.3. Induction of Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma was induced by oral administration of thioacetamide (TAA). Rats received TAA at a dose of 200 mg/kg body weight, dissolved in olive oil, administered twice weekly for six consecutive weeks. Olive oil (3 mL/kg, twice weekly) was given alongside to facilitate solubilization and enhance hepatic insult. During the induction period, body weight, food intake, and general health were monitored to assess systemic toxicity and ensure animal welfare [16].

2.5.4. Body Weight Monitoring

The body weights of the animals were measured at the start and end of the study to see how cancer

and the treatments affected their weight[17].

2.5.5. Liver Function Tests

At the end of the study, blood samples were taken and spun to get serum. Enzymatic kits were used to measure serum levels of SGOT/AST, SGPT/ALT, and total bilirubin[18].

2.5.6. Histopathological Examination

Liver tissues were removed, fixed in 10% neutral buffered formalin, processed, and stained with hematoxylin and eosin (H&E). Tissue sections were examined under a microscope for changes in liver cells, such as necrosis, inflammation, and structural alterations across the different treatment groups [19].

3. RESULTS AND DISCUSSION

3.1. Liposome Preparation and Entrapment Efficiency

Resveratrol-loaded liposomes were successfully prepared using the solvent-injection method with phosphatidylcholine and cholesterol as the primary lipid components. The method produced stable dispersions with good drug entrapment. Entrapment efficiency (EE%) analysis revealed high values for both formulations: 87.85 ± 0.20% for F1 (10 mg resveratrol) and 81.75 ± 0.15% for F2 (20 mg resveratrol). These results indicate excellent compatibility of resveratrol with the lipid bilayer and efficient incorporation within the vesicles. High EE% is attributed to the lipophilic nature of resveratrol, which favors partitioning into the lipid bilayers. Similar high EE% values have been reported for liposomal formulations of other polyphenolic compounds, suggesting the reliability of the ether-injection method for encapsulating hydrophobic bioactives.

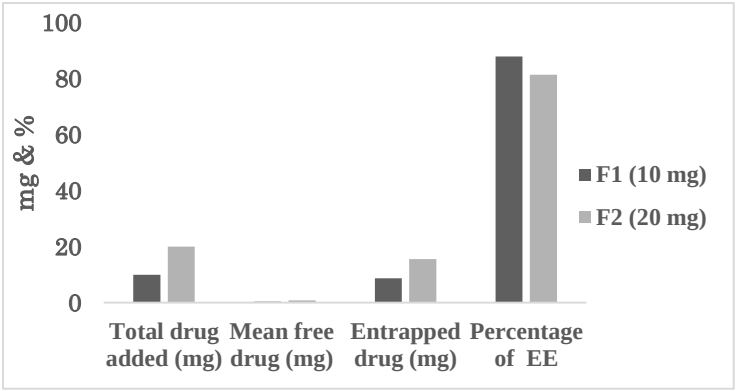

Figure 1. Comparative evaluation of resveratrol entrapment in liposomal formulations F1 (10 mg) and F2 (20 mg).

3.2. Morphological Characterization by SEM

Scanning electron microscopy (SEM) revealed that resveratrol-loaded liposomes were predominantly spherical to near-spherical, with smooth surfaces and uniform distribution. The particle size ranged between 100 and 250 nm, confirming nanoscale vesicle formation. The smooth morphology reflects intact bilayer structures with good colloidal stability, a desirable feature for

improving systemic bioavailability. Nanometer-sized vesicles are advantageous as they enhance gastrointestinal absorption and facilitate passive targeting to hepatic tissues. The observed morphology, coupled with high EE%, highlights the successful development of stable liposomal carriers for resveratrol delivery [20,21].

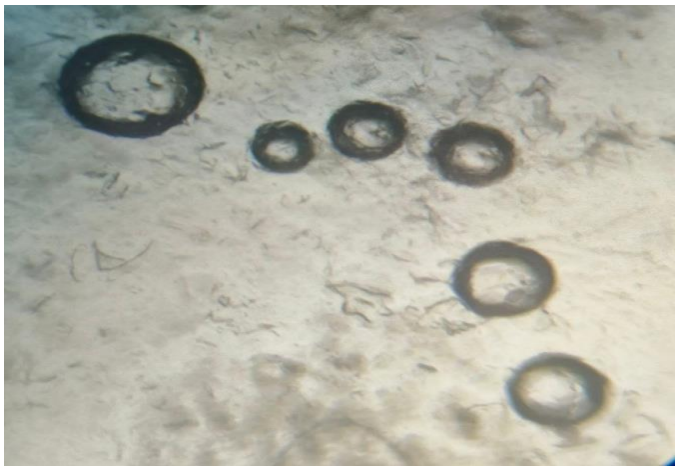

Figure 2. The preparation of liposomes was observed under the microscope

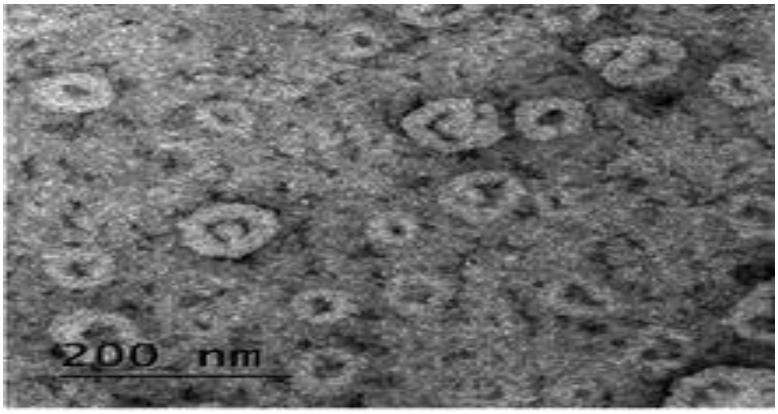

Figure 3. Scanning Electron Microscopy (SEM) image of liposomes showing spherical vesicular morphology with uniform distribution. Scale bar: 200 nm

3.3. *In Vitro* Drug Release Study

The *in vitro* release of resveratrol from liposomes was investigated using the USP dissolution basket method in different buffer systems (pH 6.5 and pH 7.5). Both formulations exhibited a sustained and controlled drug release profile up to 24 h. At early time points (0.5–2 h), a burst release was observed, likely due to surface-associated resveratrol. This was followed by a slower, diffusion-controlled release phase attributed to the drug being entrapped within the lipid bilayers. Notably, the release rate was higher in the pH 7.5 buffer than in the pH 6.5 buffer, reflecting pH-dependent solubility and stability of resveratrol. The sustained release pattern ensures prolonged drug availability, which may improve therapeutic efficacy by reducing the frequency of dosing and

maintaining consistent plasma levels. These findings are consistent with earlier studies reporting prolonged release of polyphenols from liposomal systems, thereby enhancing bioavailability.

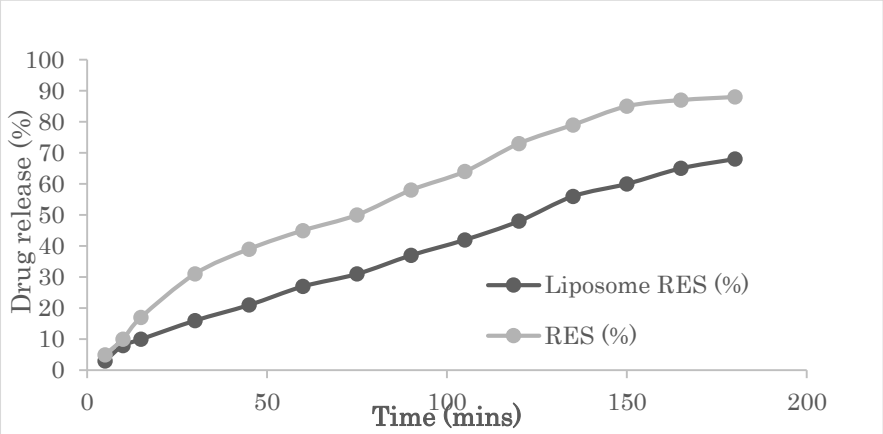

Figure 4. *In vitro* drug release profile of resveratrol and liposome-loaded resveratrol

3.4. *In Vivo* Body Weight Changes

Body weight monitoring served as a general indicator of health status in TAA-induced hepatocellular carcinoma (HCC) rats. The normal control group exhibited stable weight gain, whereas the negative control group (TAA) showed significant body weight reduction, reflecting systemic toxicity and disease progression. Treatment with the standard drug (Lenvatinib) partially prevented weight loss, while free resveratrol produced only moderate protection. Importantly, liposomal resveratrol, particularly at the high dose (30 mg/kg), demonstrated a significant improvement in body weight compared to the negative control group. These results suggest that liposomal delivery enhanced the therapeutic effect of resveratrol in maintaining physiological stability during hepatocarcinogenesis.

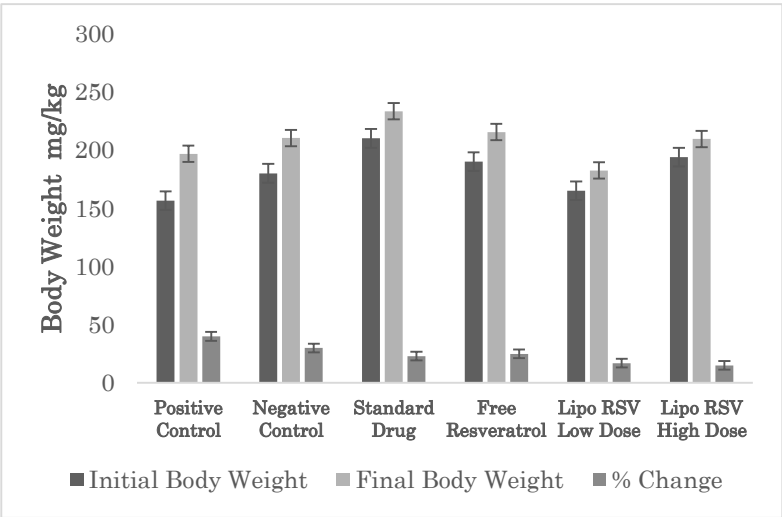

Figure 5. Effect of different treatments on body weight in experimental groups. The bar graph represents the initial and final body weights (g) of animals across treatment groups. The percentage change in body weight is indicated above the final body weight bars. Values are expressed as mean ± SEM (n = 6).

3.5. Liver Function Tests (SGOT, SGPT, and Total Bilirubin)

Biochemical parameters confirmed the hepatoprotective efficacy of liposomal resveratrol. TAA administration (negative control) significantly elevated serum SGOT, SGPT, and total bilirubin levels, indicative of hepatocellular injury and impaired hepatic clearance. Treatment with Lenvatinib reduced these biomarkers, validating the experimental model. Free resveratrol also lowered enzyme levels, but the effect was modest compared to liposomal formulations. Both low- and high-dose liposomal resveratrol groups demonstrated a pronounced reduction in SGOT, SGPT, and bilirubin, with the high-dose group nearly normalizing values to those of the healthy control. The superior performance of liposomal resveratrol may be attributed to its improved solubility, enhanced stability in circulation, and better hepatic uptake compared to free resveratrol.

3.6. Histopathological Observations

Histopathological evaluation provided further evidence of the therapeutic potential of liposomal resveratrol. The normal control group showed intact hepatic architecture with no pathological alterations. In contrast, the negative control group displayed severe hepatic damage characterized by mononuclear cell infiltration, multifocal necrosis, and disrupted architecture. The standard drug group exhibited reduced necrosis and mild infiltration, confirming its hepatoprotective effect. Free resveratrol treatment showed partial improvement, with mild reductions in necrotic and inflammatory changes. Strikingly, both low- and high-dose liposomal resveratrol treatments revealed significant hepatic protection, as evidenced by minimal infiltrates and necrosis, along with near-normal hepatocyte morphology. The high-dose liposomal group demonstrated the most profound protective effect, comparable to that of the standard treatment group.

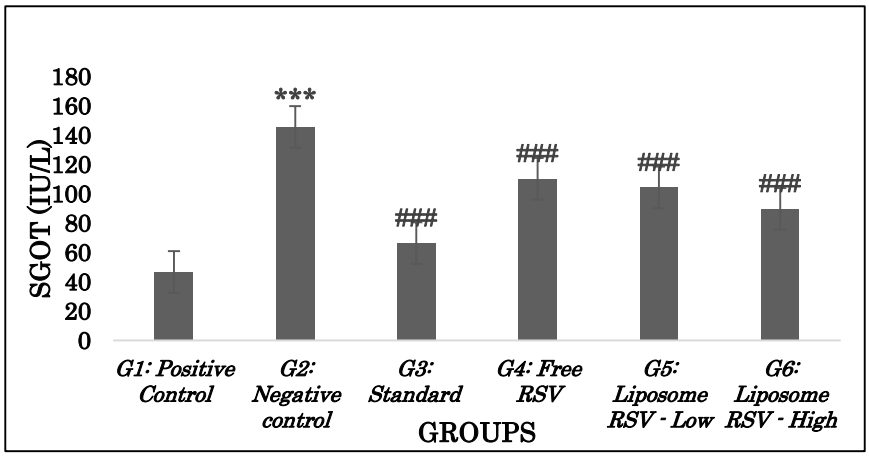

Figure 6. Effect of free resveratrol and liposomal resveratrol formulations on serum SGOT levels in rats. Values are expressed as mean ± SEM (n = 6 per group). ***p < 0.001 vs. Group 1 (Normal control); ###p < 0.001 vs. Group 2 (TAA control).

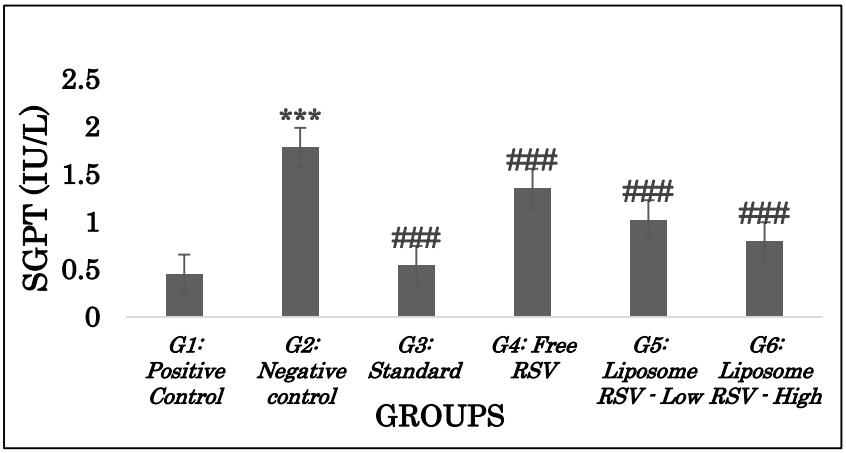

Figure 7. SGPT (IU/L) levels are expressed as mean ± SEM (n = 6 per group). *** p < 0.001 vs. Positive Control (Group 1); ### p < 0.001 vs. Negative Control (Group 2).

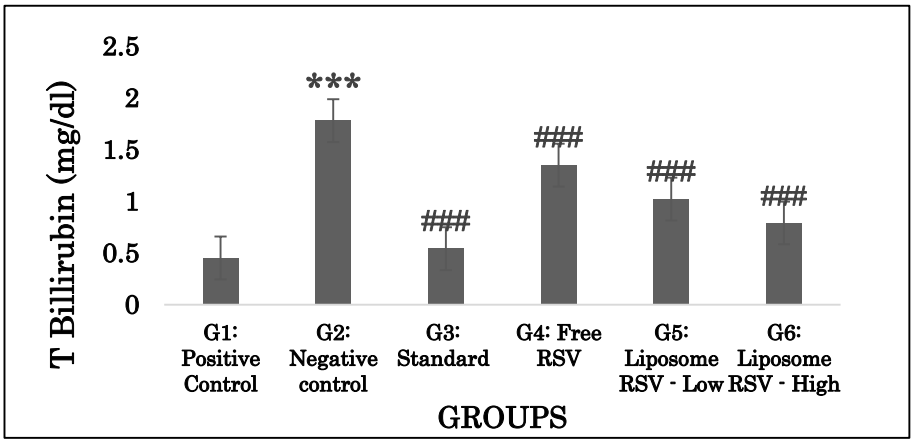

Figure 8. Effect of resveratrol (RSV) and RSV-loaded liposomes on total bilirubin levels in experimental rats. Values are expressed as mean ± SEM (n = 6). The negative control group (TAA-induced) showed a significant elevation in total bilirubin compared to the positive control group (* p < 0.001).**

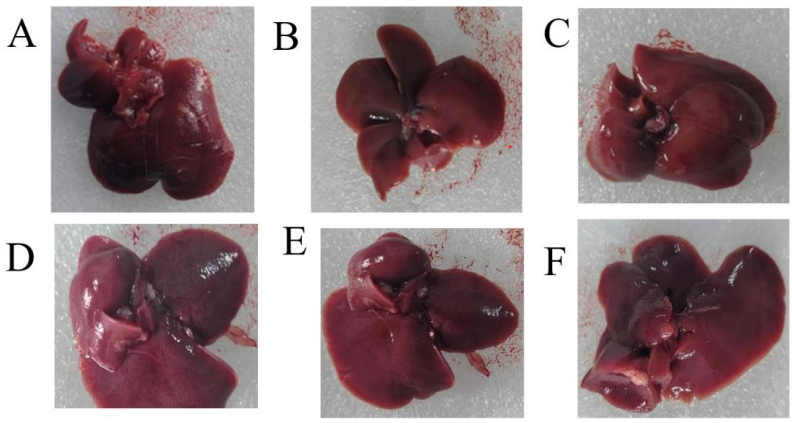

Figure 9. Section examination of liver tissues from experimental groups. (A) Positive control – normal saline (p.o.), (B) Negative control – TAA + olive oil (3 ml/kg; 1:1, p.o.). (C) Standard drug – Lenvatinib (4 mg/kg, p.o.), (D) Free resveratrol (25 mg/kg, p.o.), showing

moderate hepatoprotective effects with partial restoration of hepatocyte structure. (E) Liposome RSV – low dose (15 mg/kg, p.o.), (F) Liposome RSV – high dose (30 mg/kg, p.o.)

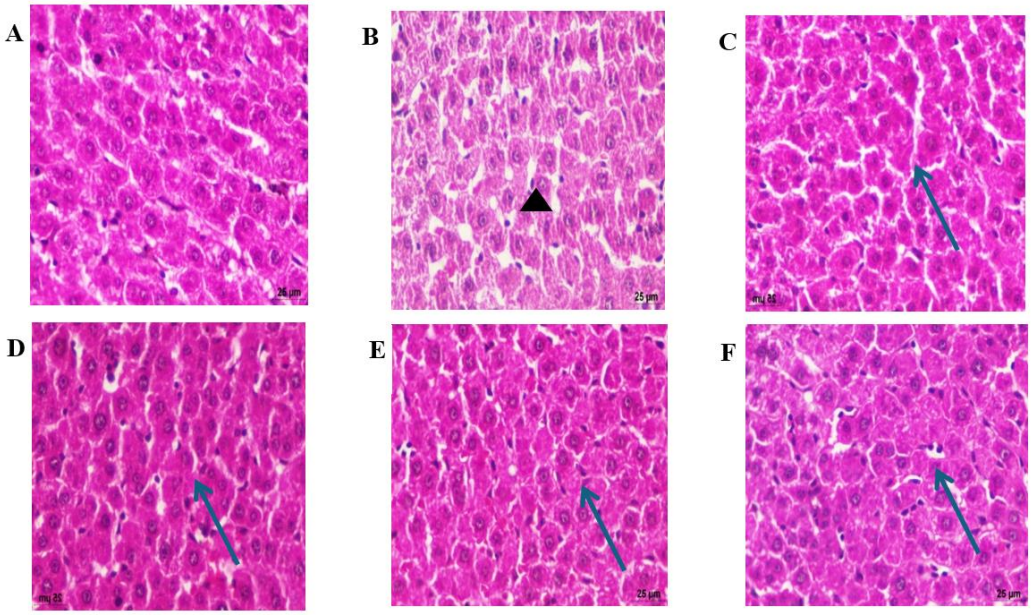

Figure 10. Histopathological examination of liver sections stained with hematoxylin and eosin (H&E). (A) The control, (B) Negative control group (c) Standard group (D) Free resveratrol group (E) Treatment I – low-dose RES liposome (15 mg/kg, p.o.) group (F) Treatment II – high-dose RES liposome (30 mg/kg, p.o.) group.

Table 1. Entrapment Efficiency of Resveratrol-loaded Liposomes

Formulation	Total drug added (mg)	Mean free drug (mg)	Entrapped drug (mg)	Percentage of EE
F1 (10 mg)	10.00	0.215 ± 0.02	8.785	87.85 ± 0.20
F2 (20 mg)	20.00	0.430 ± 0.03	16.57	81.75 ± 0.15

Table 2: Effect of treatments on initial and final body weights and percentage changes in TAA-induced hepatocellular carcinoma rats.

Groups	Treatment	Initial body Weight (first week)	Final body weight (last week)	% changes in body weight
I	Positive Control (normal saline) p.o	156.6 ± 5.2	196.7 ± 1.5	40%
II	Negative Control TAA + olive oil (3 ml/kg; 1:1, p.o)	180 ± 1.2*	210.3 ± 2.5*	30%
III	Standard Drug Lenvatinib (4 mg/kg) p.o	210 ± 2.3*	233.3 ± 3*	23 %
IV	Free Resveratrol 25mg/kg (p.o)	190 ± 4.1*	215.4 ± 4.4*	25%
V	Liposome RSV - Low Dose 15mg/kg (p.o)	165 ± 3.3*	182.5 ± 1.2 *	17%
VI	Liposome RSV- High Dose 30mg/kg (p.o)	194 ± 5.7*	209.5 ± 5.3	15%

Effect of various treatments on initial body weight, final body weight, and percentage change in TAA-induced hepatocellular carcinoma rats. Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 compared with the negative control group.

Table 3: Effect of resveratrol and its liposomal formulations on liver function biomarkers (SGOT, SGPT, and total bilirubin) in TAA-induced hepatotoxic rats.

Groups	Treatment	SGOT (IU/L)	SGPT (IU/L)	T Billirubin
I	Positive Control (normal saline) p.o	46.8 ±0.7	35.8±0.8	0.45±0.1
II	Negative Control TAA + olive oil (3 ml/kg; 1:1, p.o)	145.47 ±1.2***	139.97±1.5***	1.78 ±0.22***
III	Standard Drug Lenvatinib (4 mg/kg) p.o	55.3 ±0.4###	46.98±0.45###	0.54 ±0.11###
IV	Free Resveratrol 25mg/kg (p.o)	110. 34 ±0.6###	78.64±0.46###	1.35 ±0.21###
V	Liposome RSV - Low Dose 15mg/kg (p.o)	104.41 ± 1.2###	66.05 ± 0.5###	1.02 ±0.04###
VI	Liposome RSV- High Dose 30mg/kg (p.o)	98.4 ± 0.1###	59.5± 0.9###	0.79 ±0.1###

Values are expressed as Mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. ***p < 0.001 vs. normal control; ###p < 0.001 vs. TAA control.

DISCUSSION

The novelty of this study lies in its demonstration that liposomal encapsulation markedly enhances the hepatoprotective efficacy of resveratrol in an *in vivo* model of hepatocellular carcinoma. Previous investigations have largely emphasized the antioxidant, anti-inflammatory, and anti-proliferative roles of free resveratrol, but these benefits have been consistently hampered by its poor solubility, rapid metabolism, and limited systemic availability. In contrast, our findings reveal that liposomal resveratrol overcomes these pharmacokinetic limitations, achieving superior biochemical recovery, stabilization of body weight, and restoration of hepatic architecture when compared to free resveratrol. Importantly, the high-dose liposomal formulation demonstrated therapeutic efficacy comparable to Lenvatinib, a clinically approved frontline drug for HCC. To our knowledge, this represents one of the first *in vivo* validations where a resveratrol nanoformulation achieved efficacy on par with a standard chemotherapeutic agent, thereby underscoring its translational potential as a supportive or alternative therapy in HCC management [22]. The liposomal formulations were prepared using the solvent ether-injection method with phosphatidylcholine and cholesterol, resulting in nanosized vesicles with high entrapment efficiency. Entrapment efficiency values exceeded 80%, confirming successful incorporation of resveratrol into the lipid bilayer and ensuring effective drug loading [23]. SEM analysis revealed spherical to near-spherical vesicles of uniform distribution (100–250 nm) with smooth surfaces, indicating good colloidal stability and suitability for oral delivery. These structural and physicochemical characteristics are critical for enhancing gastrointestinal absorption, improving circulation stability, and ensuring sustained drug availability at the target site. *In vitro* drug release experiments further validated the sustained-release capacity of liposomal resveratrol, with an initial burst phase followed by a controlled release over 24 hours. This biphasic profile ensures both early therapeutic onset and prolonged bioavailability, a key pharmacological advantage over free resveratrol. Such controlled release is likely to reduce dosing frequency [24] and maintain steady plasma concentrations, thereby enhancing therapeutic effectiveness and the *in vivo* studies in thioacetamide (TAA)-induced hepatocellular carcinoma rats provided compelling confirmation of the superiority of liposomal delivery. Body weight monitoring demonstrated that animals treated with liposomal resveratrol, particularly the high-dose group, exhibited the lowest percentage loss, indicating improved systemic protection against cancer-induced cachexia. Biochemical markers of hepatic injury (SGOT, SGPT, and total bilirubin) were significantly elevated in the TAA control group, while treatment with liposomal resveratrol produced a marked reduction, surpassing the effects of free resveratrol. Notably, the high-dose liposomal formulation nearly normalized these markers, reflecting profound hepatoprotective efficacy [25]. Histopathological examination supported these biochemical observations. While the TAA control group displayed severe necrosis and inflammatory infiltrates, the liposomal resveratrol groups showed remarkable improvement, with minimal necrotic lesions and near-normal hepatic

architecture [26,27]. The high-dose liposomal group exhibited histological features comparable to the standard drug Lenvatinib, providing strong evidence for its therapeutic equivalence. Taken together, these findings demonstrate that liposomal encapsulation not only improves the pharmacokinetic profile of resveratrol but also translates into superior therapeutic efficacy against hepatocellular carcinoma. By combining high entrapment efficiency, nanoscale morphology, sustained drug release, and robust *in vivo* protection, this study establishes liposomal resveratrol as a promising nanocarrier-based strategy with significant clinical relevance for liver cancer therapy [28,29,30,31].

4. CONCLUSION

The study demonstrates the enhanced therapeutic efficacy of resveratrol through liposomal encapsulation in a hepatocellular carcinoma model. The developed resveratrol-loaded liposomes show high entrapment efficiency, uniform size distribution, and a sustained drug release profile. *In vivo* studies confirm the superior hepatoprotective effects of liposomal resveratrol, with high-dose formulations attenuating TAA-induced hepatocellular injury and improving liver function biomarkers. These findings highlight the potential of resveratrol-loaded liposomes as a promising nanocarrier system for effective treatment of hepatocellular carcinoma, offering enhanced stability, bioavailability, and targeted delivery. Further clinical investigations are warranted to translate these promising preclinical results into patient care.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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