Preliminary Evaluation of Neohesperidin Nanoliposomes for Anti-photodamage Effects

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Abstract The present research aimed to evaluate the protective effects of neohesperidin-loaded nanoliposomes (NH-NL) against UVB-induced photodamage in HaCaT cells. NH-NL were prepared by the thin-film ultrasonication method. UVB-irradiated HaCaT cells were treated with different concentrations of free NH or NH-NL. Cell viability, apoptosis rate, and senescence (SA-β-Gal staining) were assessed. NH exhibited intrinsic UVB absorption (250 - 400 nm). Free NH moderately increased cell viability in a dose-dependent manner, whereas NH-Liposomes markedly improved viability from 19.74% (UVB alone) to 63.90% at 0.2 mg/ml. NH-NL also dose-dependently reduced the UVB-induced apoptosis rate from 31.52% to 15.83% and decreased the number of senescent (SA-β-Gal-positive) cells. The results suggest that NH-NL significantly protect HaCaT cells from UVB radiation-induced cell death, apoptosis, and senescence, demonstrating strong potential as an anti-photoaging nanocarrier system.

Key words Neohesperidin; Nanoliposomes; UVB; Anti-photodamage

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Ultraviolet radiation is the primary environmental factor responsible for skin photoaging[1-2]. Prolonged exposure to UVB (280 - 315 nm) and UVA (315 - 400 nm) induces excessive production of reactive oxygen species (ROS) in the skin, activates signaling pathways such as mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB), and subsequently upregulates the expression of matrix metalloproteinases (MMPs)[3]. This leads to the degradation of collagen and elastin fibers, resulting in typical photoaging features such as roughness, laxity, and deepened wrinkles. Therefore, developing highly effective, low-toxicity natural active ingredients and their delivery systems for the prevention and treatment of photoaging has become a major research focus in the fields of cosmetics and dermatopharmacology[4-5].

Neohesperidin (NH) is a natural flavanone compound primarily found in the peels of citrus plants such as bitter orange (*Citrus aurantium* L. var. *amara* Engl.), sour orange (*Citrus aurantium* L.), and other citrus species including tangerines and pomelos. Its chemical structure consists of a hesperetin core linked via a glycosidic bond to a neohesperidoside moiety—a rhamnose-glucose disaccharide chain. This unique flavonoid skeleton combined with glycosylation confers strong free radical scavenging capacity and metal ion chelating activity. As one of the representative components of citrus flavonoids, neohesperidin has been demonstrated to possess diverse pharmacological activities, including antioxidant, anti-inflammatory, and cardiovascular protective effects[6-11].

Studies have shown that the antioxidant activity of NH is attributed to its chemical structure, which contains multiple phenolic hydroxyl groups. These hydroxyl groups can effectively quench ROS induced by UV and inhibit the excessive expression of MMP-1[12], demonstrating promising potential in preventing photoaging. However, neohesperidin has poor water solubility (<0.1 mg/ml), and its low transdermal bioavailability severely limits its practical application in protecting against skin photodamage due to the barrier effect of the stratum corneum and other skin layers. Traditional formulations such as creams or solutions struggle to achieve efficient drug accumulation in both the epidermis and dermis, and also carry risks of skin irritation and instability.

To overcome these limitations, nano-liposomes are used as a biocompatible carrier. Due to their lipid bilayer structure similar to the stratum corneum, they can effectively enhance the transdermal permeability of active ingredients and achieve sustained-release and targeted delivery[13]. Encapsulating neochlorogenic acid in nano-liposomes not only improves its solubility, but also protects it from environmental degradation. Meanwhile, through passive targeting at the nanoscale, it promotes the retention and absorption of the drug in the skin tissue, thereby synergistically enhancing the anti-photoaging effect.

Materials and Methods

Chemicals and reagents

Neohesperidin was purchased from Pufei De Biotechk Co. Ltd. (Chengdu, China). HaCaT cells, MEM, FBS, L-glutamine, EDTA-trypsin, penicillin-streptomycin, and PBS were purchased from Procell Life Technology (Wuhan, China). β-Galactosidase assay kits were from Solarbio Life Sciences (Beijing, China).

Full UV wavelength scanning

NH was resolved with methanol to 50 μg/ml. Then, 5 μl of

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the solution was loaded on ultra-micro spectrophotometer (Nanodrop 2000, Thermo Scientific, USA) to scan from 250 – 400 nm.

Preparation of NH-loaded nanoliposomes

Neohesperidin-loaded nanoliposomes (NH-NL) were prepared using the thin-film ultrasonication method. Briefly, 337.5 mg of soybean phospholipid was dissolved in 11.25 ml of dichloromethane, and 65 mg of cholesterol was dissolved in 3.25 ml of dichloromethane. Meanwhile, NH (10, 5, or 2.5 mg) was dissolved in dichloromethane. The three solutions containing soybean phospholipid, cholesterol, and NH were transferred into the same pear-shaped flask and mixed thoroughly. The organic solvent was then removed by rotary evaporation under reduced pressure to form a thin film. The flask was placed in a fume hood until the organic solvent had completely evaporated. Subsequently, 50 ml of ultrapure water was added to hydrate the film. The mixture was then subjected to ultrasonication at room temperature for 20 min using an ultrasonic apparatus (200 W). This ultrasonication procedure was repeated three times to obtain NH-NL at final concentrations of 0.2, 0.1, and 0.05 mg/ml. Blank liposomes were prepared using the same procedure without the addition of NH.

For the cell viability assay, MEM basal medium was used instead of ultrapure water for the hydration step.

NH-NL particle size analysis

The particle size and polydispersity index (PDI) of the NH-NL were measured by dynamic light scattering (DLS) using a Zetasizer Nano ZS90 (Malvern Panalytical, UK). Prior to measurement, the nanoliposome suspension was diluted 100-fold with ultrapure water. All measurements were performed in triplicate at 25 ℃ with a scattering angle of 173°. The results were expressed as the Z-average diameter (dnm) and PDI values.

Cytoprotective effects of NH-NL on UVB-irradiated cells

HaCaT cells were cultured in MEM supplemented with 10% Fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37 ℃ in a humidified 5% CO_2 incubator. UVB-induced photoaging cell model was built by HaCaT cells according to our reference[14].

Cells were seeded into 96-well plates at a density of 2×10^5 cells per well and incubated overnight at 37 ℃ to allow attachment. The original culture medium was then discarded. The blank group and the model group received 100 μl of complete culture medium, while the experimental groups were treated with 100 μl of culture medium containing gradient concentrations of neohesperidin-loaded nanoliposomes, followed by incubation at 37 ℃ for 2 h. Subsequently, 70 μl of the culture medium was removed from each well, and the cells were exposed to different doses of UV irradiation. Immediately after irradiation, 70 μl of fresh culture medium was added to each well, and the cells were further incubated for 24 h. Finally, 100 μl of 10% CCK-8 solution was added to each well. The absorbance was measured at 450 nm using a microplate reader, and cell viability was calculated.

Effects of NH-NL on apoptosis of on UVB-irradiated cells

HaCaT cells were seeded in 6-well plates and cultured to 70% – 80% confluence. Cells were divided into control, UVB (90 mJ/cm^2), and TFFAI (0.25, 0.5, 1 mg/ml) + UVB groups. Cell apoptosis rate was evaluated according to reference of Li *et al.*[14].

Effects of NH-NL on cellular senescence of UVB-irradiated cells

HaCaT cells at a density of 0.5×10^5 cells/ml were seeded into 24-well plates at 0.5 ml per well. The experimental groups were as follows: control (Ctr), UVB alone, and NH-treatment groups at concentrations of 0.05, 0.1, and 0.2 mg/ml, with three replicates per group ($n = 3$). After 1 h of drug incubation, the cells were exposed to UVB irradiation at a dose of 30 mJ/cm^2. Subsequently, the culture medium was replaced with fresh medium, and the cells were cultured for 24 h before staining.

Senescence-associated β-galactosidase (SA-β-Gal) staining was performed according to the manufacturer's instructions. At 24, 48, and 72 h after irradiation, the culture medium was removed, and the cells were washed twice with PBS. Then, 0.5 ml of 1 × Fixation buffer was added to each well, and the cells were fixed at room temperature for 15 min. After fixation, the fixative was aspirated, and the cells were washed three times with PBS. Subsequently, 0.5 ml of staining working solution was added to each well. The plates were incubated overnight at 37 ℃ in a CO_2-free incubator until the cells were stained. Finally, images were captured under an optical microscope. In the photoaging cell model, SA-β-Gal-positive (blue-green) cells were identified as senescent cells.

Results and Discussion

Full UV wavelength scanning

The ultraviolet absorption spectrum of neohesperidin (NH) is shown in Fig. 1. A distinct absorption peak was observed within the 250 – 400 nm range, which corresponds precisely to the UVB waveband (280 – 315 nm), confirming that NH possesses intrinsic UVB-absorbing capacity. This property serves as the physicochemical basis for its potential photoprotective activity, as direct UV absorption reduces the amount of radiation reaching the deeper layers of the skin.

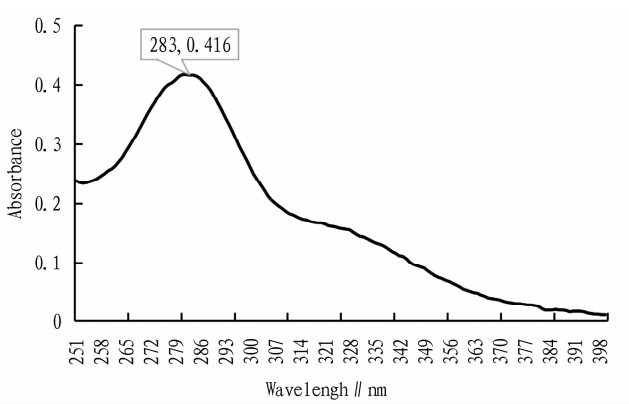


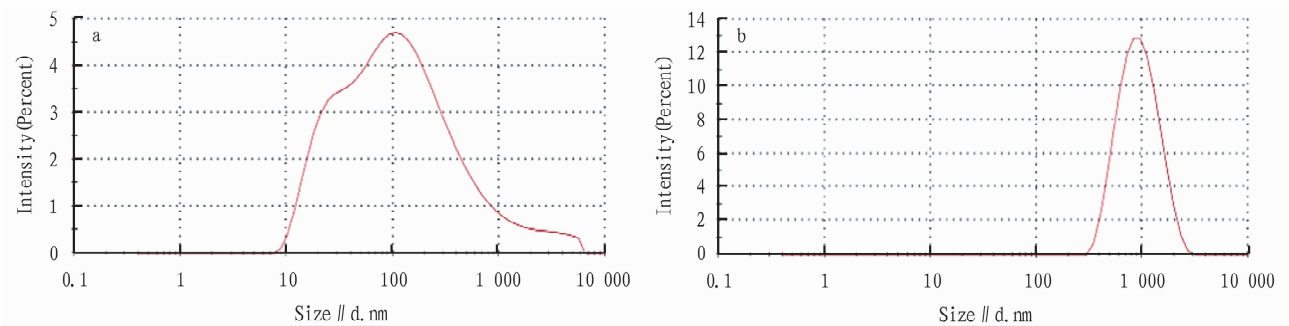
Fig. 1 Full ultraviolet absorption spectrum of NH between 250 to 400 nm

NH-NL particle size analysis

The particle size distribution of blank nanoliposomes and NH-NL were presented in Fig. 2. The blank liposomes (without NH) showed a relatively small Z-average (65.17 d · nm), and the size of peak 1 was 302.7 d · nm with a density percentage of 100% and a polydispersity index (PDI) of 0.536 (Fig. 2a). As loading 0.1 mg/ml of NH, the particle Z-average was 799.2 d · nm, and the size of peak 1 reached 982 d · nm, with a density percentage of 100% and a PDI of 0.184 (Fig. 2b).

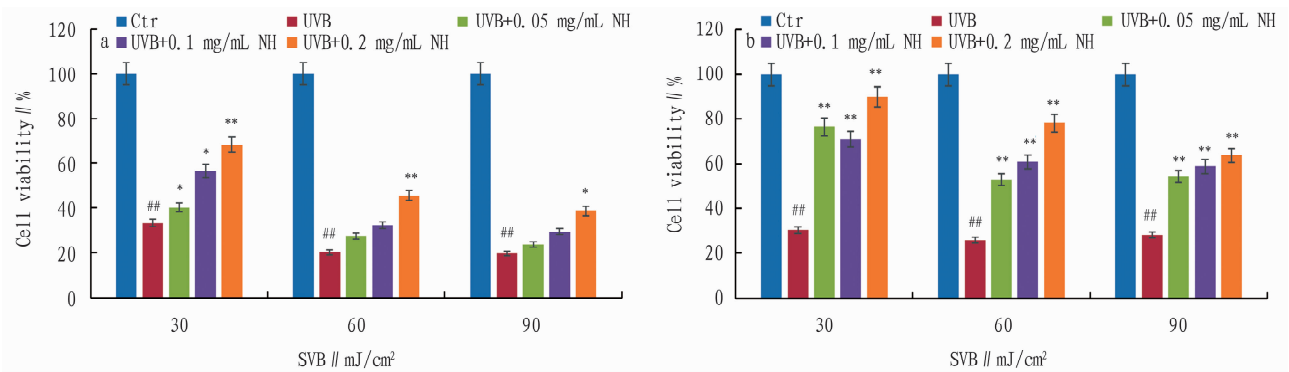
Cytoprotective effects of NH-NL on UVB-irradiated cells

To evaluate the cytoprotective effects of free NH and NH-NL, HaCaT cells were exposed to UVB irradiation, and cell viability was assessed. As shown in Fig. 3a and 3b, UVB irradiation caused a significant, dose-dependent decrease in cell viability. Free NH increased cell viability in a concentration-dependent manner (Fig. 3a). Taking the UVB 90 mJ/cm^2 group as an example, cell viability in the UVB-only group was only 19.74%, whereas treatment with 0.05, 0.1, and 0.2 mg/ml NH increased viability to 23.75%, 29.57%, and 38.81%, respectively. Notably, NH-NL markedly improved cell viability across all UVB dose groups. At 90 mJ/cm^2, cell viability in the groups treated with 0.05, 0.1, and 0.2 mg/ml NH-NL reached 54.44%, 58.85%, and 63.90%, respectively, which were substantially higher than those observed with free NH at the same concentrations (Fig. 3b). These results demonstrate that NH-NL effectively protect epidermal cells from UVB radiation-induced photodamage.



a. Blank nanoliposome group; b. NH (1.0 mg/ml)-nanoliposomes group.

Fig. 2 Size distribution of intensity



UVB group vs Ctr group, $P<0.01$; ** NH groups vs UVB group, $P<0.01$.

Fig. 3 Effects of NH (a) and NH-liposomes (b) on the viability of HaCaT cells exposed to UVB irradiation

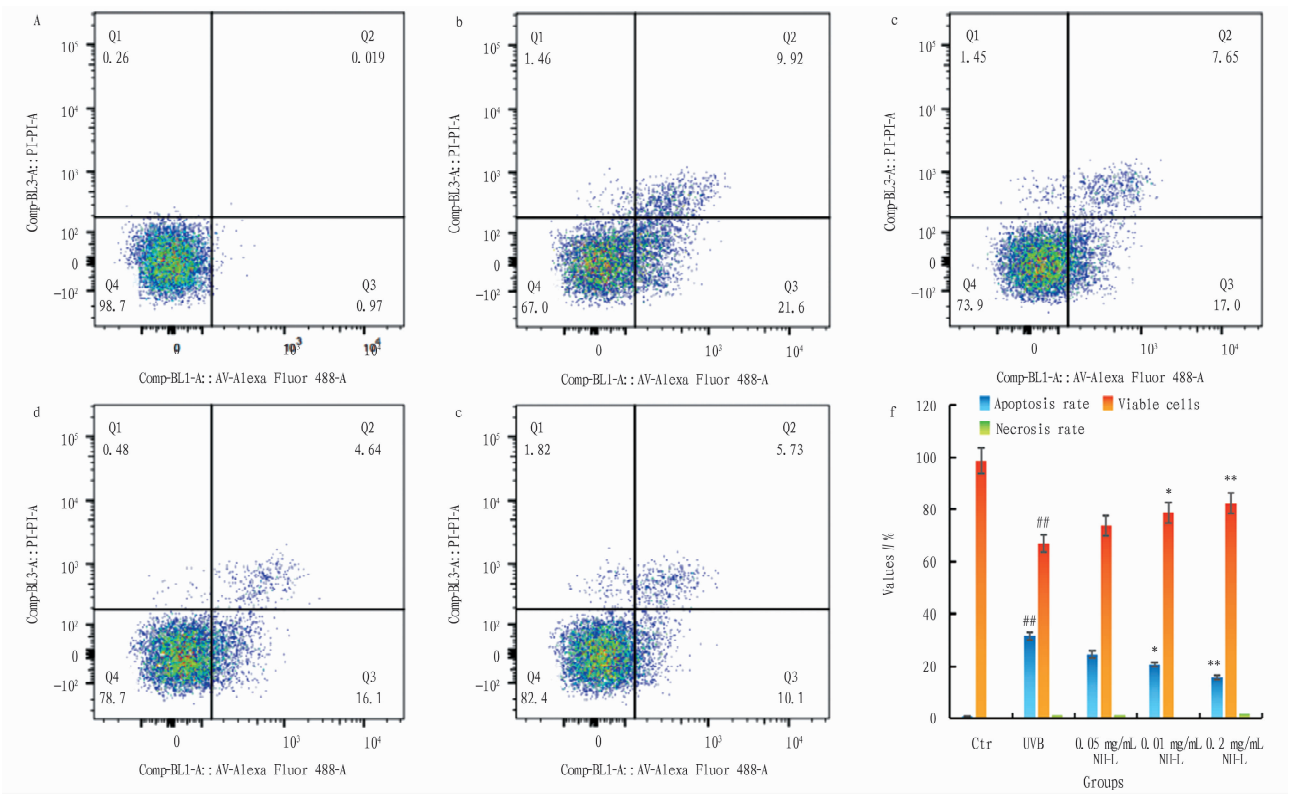
Effects of NH-Liposomes on apoptosis of on UVB-irradiated cells

As shown in Fig. 4, UVB irradiation significantly reduced the number of viable HaCaT cells and markedly increased apoptotic cells, with an apoptosis rate of 31.52%. Treatment with NH nanoliposomes at different concentrations (0.05, 0.1, 0.2 mg/ml) significantly inhibited the apoptosis rate in a dose-dependent manner, resulting in apoptosis rates of 24.65%, 20.74%, and 15.83%, respectively. Accordingly, as the concentration of NH increased, the apoptosis rate decreased significantly and the number of viable cells increased markedly. These results indicate that NH nanoliposomes can effectively ameliorate UVB radiation-induced apoptosis in epidermal cells.

Effects of NH-Liposomes on cellular senescence of UVB-irradiated cells

To investigate the inhibitory effect of NH-liposomes on UVB-induced photoaging of skin cells, we performed senescence-associated β-galactosidase (SA-β-Gal) staining on HaCaT cells. SA-β-Gal activity is an important biomarker of cellular senescence. As shown in Fig. 5, compared with the blank control group (a), the number of SA-β-Gal-positive cells (stained blue-green) in the UVB model group (b) was significantly increased, indicating that UVB irradiation successfully induced cellular senescence. However, after pretreatment with different concentrations (0.05, 0.1, 0.2 mg/ml) of NH-liposome, the number of SA-β-Gal-positive cells decreased in a markedly dose-dependent manner (groups c,

d, e). Specifically, with increasing concentrations of NH-liposomes, the area and intensity of blue-green staining gradually diminished, and the cell morphology became closer to that of normal, young cells. The results suggested that NH-liposome intervention significantly improved the senescent state of cells in a dose-dependent manner. Cellular senescence is one of the core cellular events in skin photoaging. Senescent cells enter an irreversible growth arrest state and secrete a variety of inflammatory factors, chemokines, and matrix-degrading enzymes, forming the so-called senescence-associated secretory phenotype (SASP), which disrupts the tissue microenvironment and exacerbates collagen degradation as well as the decline in skin structure and function. This study visually confirms via SA-β-Gal staining that UVB irradiation is a potent stressor inducing senescence in HaCaT cells.



(a) Ctr; (b) UVB group; (c) containing 0.05 mg/ml NH nanoliposomes; (d) containing 0.1 mg/ml NH nanoliposomes; (e) containing 0.2 mg/ml NH nanoliposomes; (f) bar graph showing the effects of different concentrations of neohesperidin on the apoptosis rate, mortality rate, and survival rate of HaCaT cells. For UVB group vs Ctr group, $^{\#\#}P<0.01$, $^{\#}P<0.05$; For NH-L groups vs UVB group, $^{**}P<0.01$, $^{*}P<0.05$.

Fig. 4 Effects of NH-liposomes (NH-L) on apoptosis of HaCaT cells exposed to UVB irradiation

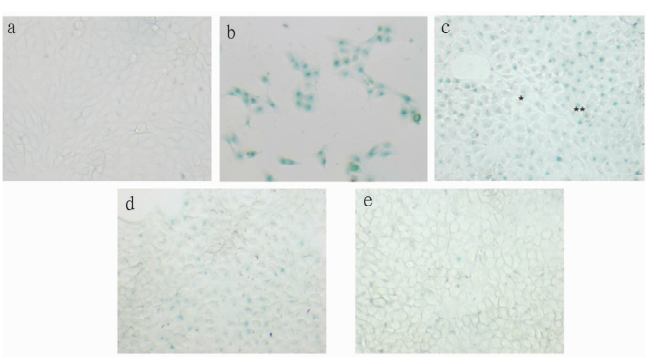


Fig. 5 Effects of NH-liposomes on cellular senescence of HaCaT cells exposed to UVB irradiation (a) Ctr; (b) UVB group; (c) containing 0.05 mg/ml NH nanoliposomes; (d) containing 0.1 mg/ml NH nanoliposomes; (e) containing 0.2 mg/ml NH nanoliposomes. $n=3$.

Chronic exposure to ultraviolet (UV) radiation, particularly UVB, is a major environmental factor driving skin photoaging. In recent years, plant-derived flavonoids have attracted increasing attention as natural anti-photoaging agents due to their potent antioxidant, anti-inflammatory, and MMP-inhibitory properties, coupled with low systemic toxicity. However, the clinical translation of many flavonoids, including neohesperidin (NH), is severely hampered by poor water solubility, low skin permeability, and consequently inadequate bioavailability at target sites. Therefore, investigating the protective effects of flavonoid-loaded nanoliposomes against UVB-induced photodamage not only provides a mechanistic understanding of their action, but also supports the development of more effective, natural-based photoprotective formulations for skin health and cosmetic applications.

In present research, treatment with NH-liposomes dramatically elevated viability, and reduced apoptosis in a concentration-dependent fashion to 24.65%, 20.74%, and 15.83%, respectively. The

anti-photoaging effect of NH-liposomes was further confirmed by SA-β-Gal staining. UVB irradiation markedly increased the number of blue-green SA-β-Gal-positive (senescent) cells, indicating successful induction of cellular senescence. Treatment with NH-liposomes at concentrations of 0.05, 0.1, and 0.2 mg/ml led to a dose-dependent decrease in SA-β-Gal-positive cells. Notably, at the highest concentration, the number and intensity of stained cells were substantially reduced, and cell morphology appeared morphologically similar to that of the untreated control group, suggesting effective amelioration of UVB-induced cellular senescence. The results suggests that NH-loading liposomes showed a significant potential on anti-photoaging field.

Comparing with previous studies on other flavonoids, the cytoprotective efficacy of NH-liposomes stands out prominently. For instance, naringenin, a structurally related flavanone, has been reported to protect keratinocytes against UVB-induced damage, but its efficacy is largely limited to apoptosis inhibition and DNA repair enhancement[15]. Hesperidin, another citrus flavanone, exhibits anti-photoaging activity *in vivo*, yet its effect on cell viability under UVB irradiation has been modest: topical or oral administration of hesperidin (100 mg/kg) primarily attenuates wrinkle formation and epidermal thickening, with less pronounced direct cytoprotection at the cellular level[16]. Moreover, studies on other natural flavonoids delivered via nanoformulations have shown varying degrees of improvement. Apigenin co-loaded with doxycycline in flexible liposomes has demonstrated anti-photoaging effects primarily through MMP inhibition and anti-inflammation, but direct viability enhancement data under UVB stress remain limited[17]. Quercetin encapsulated in deformable liposomes has shown enhanced anti-UVB effects both *in vitro* and *in vivo*. However, the reported viability improvements typically range from 20 – 30% above vehicle-treated UVB-exposed cells[18]. In comparison, NH-liposomes achieved a viability increase of 44.16% at 0.2 mg/ml (from UVB control at 19.74% to 63.90%), representing a markedly higher level of photoprotection. Furthermore, 63.90% viability under high-dose UVB (90 mJ/cm^2) is among the highest reported for natural flavonoid-loaded nanocarriers in HaCaT cells.

The superior performance of NH-liposomes can be attributed to several synergistic factors. First, NH itself possesses strong antioxidant activity due to its multiple phenolic hydroxyl groups, which can effectively quench UV-induced reactive oxygen species (ROS) and inhibit MMP expression[19]. Second, the nanoliposome delivery system addresses the poor water solubility (<0.1 mg/ml) and low transdermal bioavailability of free NH, ensuring efficient cellular uptake and sustained release. This is consistent with previous findings that nanoliposomes and other lipid-based nanocarriers significantly improve the solubility, permeability, and photoprotective efficacy of poorly soluble flavonoids[20-21].

Thus, the combination of NH's intrinsic UV-absorbing and antioxidant properties with the enhanced bioavailability provided by nanoliposome encapsulation results in superior inhibition of UVB-induced cell death, apoptosis, and senescence. These findings strongly suggest that NH-Liposomes represent a promising strategy for the prevention and treatment of UVB-induced skin photodamage and photoaging.

Conclusion

In summary, NH-liposomes effectively protect HaCaT cells from UVB-induced photodamage by significantly improving cell viability and reducing both apoptosis and senescence in a dose-dependent manner, highlighting their potential as a natural nanocarrier-based anti-photoaging agent.

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aeration and pumping equipment can decrease electricity consumption and carbon emissions. The combination of the reactor HRT and the filtration unit is adjusted to accommodate the varying aquaculture densities across different regions. For example, in aquaculture areas where the tailwater exhibits high phosphorus concentrations, a calcium-based adsorption layer may be incorporated. In cases where the tailwater contains elevated levels of suspended solids, a microfiltration unit with a pore size of no more than 50 μm can be employed as a pretreatment step to extend the operational lifespan of the core equipment. Additionally, chemical flocculation sludge, which is rich in nitrogen and phosphorus, can be processed through anaerobic digestion to produce slow-release organic fertilizer, subsequently returned to the agricultural system. The purified tailwater can thus be recycled within a closed-loop system, thereby reducing water resource consumption[8].

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