Original Article

Avicenna Journal of Medical Biotechnology
Volume 18, Issue 1, 61-68
https://doi.org/10.18502/ajmb.v18i1.21049

Sophoraflavanone G in Nano-Niosomal Form: Implications for Bacterial Inhibition, Biofilm Disruption, and Cancer Suppression

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Received: 13 Jan 2025
Accepted: 13 Nov 2025

Abstract

Background: Sophoraflavanone G, SG, is a flavonoid compound found in Sophora species with various biological properties, including antibacterial, anticancer, antibiofilm activities. However, this compound shows limited solubility in water, which reduces its bioavailability and hinders its practical application. To overcome this barrier, SG nano-niosomal form was prepared.

Methods: In the current study, a nano-niosomal form of SG was prepared using cholesterol (Chol) and Tween 20. Antibacterial and antibiofilm activities were assessed by disc and well diffusion and biofilm assays, respectively, while anticancer specificity was evaluated by MTT on KB and L929 cell lines.

Results: Disc and well diffusion assays showed a reduction in planktonic antibacterial activity of niosomal SG compared with free SG, whereas biofilm assays improved antibiofilm effects; MTT assays indicated reduced cytotoxicity toward L929 cells with retained activity against KB cancer cells, suggesting improved anticancer specificity.

Conclusion: While niosomal formulation decreased SG's activity against planktonic bacteria, it enhanced antibiofilm effects and improved anticancer specificity by reducing toxicity to normal cells, making niosomal SG a promising candidate for cancer-directed therapeutic applications despite limited antimicrobial gains.

Keywords: Anti-bacterial agents, Anticancer agents, Anti-infective agents, Niosomes, Sophoraflavanone G

To cite this article: Teymouri M, Khayyer R, Iranshahy M, Salarinia R, Zarghami Moghaddam P, Mohammdi A, *et al*. Sophoraflavanone G in Nano-Niosomal Form: Implications for Bacterial Inhibition, Biofilm Disruption, and Cancer Suppression. Avicenna J Med Biotech 2026;18(1): 61-68.

Introduction

Sophoraflavanone G (5,7,2',4'-tetrahydroxy-8-lavandulylflavanone, SG) is a prenylated flavonoid compound extracted from the roots of Sophora species. This bioactive agent exhibits a multifaceted profile, including antimicrobial, radical scavenging, anti-inflammatory, and anticancer properties. The prenylation of SG has significantly improved its biological activity by enhancing lipophilicity and promoting affinity for the cellular membrane of both eukaryotic and prokaryotic cells, in addition to interaction with cellular components [1]. Consequently, SG accumulates in various tissues due to this modification [2]. Also, studies have suggested promising results of SG on Oral Squamous Cell Carcinoma (OSCC) and oral bacterial flora. However, this compound is highly hydrophobic and exhibits poor solubility in aqueous biological media, limiting its absorption and effective delivery *in vivo*.

To address this, a nanoformulated form of SG could improve its bioavailability, especially in the oral environment [3,4]. This limitation hinders the full therapeutic

potential of SG. To overcome this issue, nanoparticle forms of SG are used to improve bioavailability, increase absorption, and reduce toxicity in non-tumor cells [5].

Among researchers, attention has turned to niosomes—a promising class of lipid-based nanocarriers [6]. These nanocarriers have demonstrated remarkable efficiency in enhancing drug payload stability in both *in vitro* and *in vivo* settings. Specifically, niosomal formulations of bioactive agents have been associated with improved bioavailability, leading to enhanced antibacterial, antifungal, anticancer, and antibiofilm effects [7]. Biodegradability, biocompatibility, non-toxicity, and encapsulation of a large amount of material in a relatively small volume are among the advantages of using niosomes as a suitable carrier for drug delivery [8]. Niosomes are uniformly dispersed formulations containing high concentrations of nonionic detergents, such as polysorbates [9]. Polysorbates, due to their large polar heads, can solubilize lipophilic compounds such as SG. For example, Tween 20 has a hydrophilic polar head due to the presence of hydroxyl (OH) groups, which can attract water molecules. In many cases, cholesterol and its derivatives are used to prepare niosomes. Cholesterol is uncharged and used to produce stable formulations. Cholesterol prevents the precipitation of the formulation and the sudden release of the drug. In the biological environment, *i.e*., cells, 40% of cholesterol is present, which provides stability to the cell membrane [7].

In light of SG's high hydrophobicity and its low bioavailability, it is important to establish more applicable delivery systems like niosome which is an amphiphilic and flexible drug carrier. Accordingly, the current investigation focuses on developing a nano-niosomal formulation of SG. By addressing its poor aqueous solubility, it was attempted to improve SG's dispersion in biological media, thereby improving its bioavailability and therapeutic efficacy [10].

Materials and Methods

SG separation and purification

The roots (1,400 *g*) of the herbaceous plant *Sophora pachycarpa* (voucher number: 13275), preserved in the herbarium room of the School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, were air-dried in darkness and finely ground using an electric grinder. The resulting herbal powder was subjected to maceration with 4 *L* of acetone solvent. The supernatant was then concentrated *via* vacuum evaporation using a rotary evaporator at ambient temperature to remove the solvent. This maceration and evaporation process was repeated three times. The final dry extract (35.56 *g*) was further purified by silica gel column chromatography (230-400 mesh, no. 377635, 5 *cm* width, Sigma-Aldrich) pre-equilibrated with petroleum ether. A gradient of petroleum ether/acetate was applied, starting from 1000 *ml*/0 *ml* and increasing to 500 *ml*/500 *ml* in 50 *ml* increments. Subsequently, a second gradient of acetate/methanol was used, ranging from 1000 *ml*/0 *ml* to 500 *ml*/500 *ml* with 250 *ml* increments.

The fractionated components were collected in separate 200 beakers. Finally, the solvents were evaporated, and the resulting powder was freeze-dried to eliminate residual solvent traces.

Subsequently, the fraction containing SG was identified using Thin-Layer Chromatography (TLC) against the standard SG (Sigma-Aldrich). The TLC process was carried out using the same solvent in which the fraction was initially collected, *i.e*., petroleum ether/ethyl acetate 5.5/4.5 *v/v*. Various colored bands, including the SG, became visible under UV irradiation (256 *nm*) following the application of vanillin sulfuric acid reagent (100 *g/dl* in 95% ethanol) spray and heat treatment at 110°*C*.

Next, the identified fraction containing SG was further purified using preparative-TLC. A 20×20 *cm* PTLC silica gel plate was preheated at 110°*C* for 30 *min*. The fraction, in powdered form, was dissolved in a small amount of acetone and applied to the TLC plate. The mobile phase consisted of a petroleum ether/ethyl acetate mixture (4/6 *v/v*). The region corresponding to the SG band was then scraped off, removed, and dissolved in acetone to yield a purified SG solution.

SG chemical structure characterization

The chemical structure of SG was determined using one-dimensional ^{1}H-NMR spectroscopy with the aid of MestReNova (Mestrelab Mnova 15).

SG nanoformulation

The preparation of SG nano-niosomes was accomplished using the reverse-phase evaporation method, employing a solvent mixture of ethanol and deionized water. In brief, stock solutions of cholesterol, SG, and Tween 20 in ethanol were combined in a specific Molar ratio of 70:28:18 to form a final 25.91 *mg/ml* ethanol solution. This ethanol phase was then mixed with deionized water in a 1:9 volume ratio and subjected to 60 *Hz* sonication (Elmasonic ultrasound, Germany) at 80°*C* for 30 *min* to eliminate the ethanol phase. After sonication, the remaining ethanol and water were evaporated using the vacuum-equipped evaporator and subsequently lyophilized in a freeze-dryer. The resulting lyophilized powder was then reconstituted in a hot saline solution at an SG concentration of 8.5 *mg/ml* to yield lipid-based SG nano-niosome formulation.

Physicochemical characterization of SG niosomes

The liposome size distribution and Polydispersity Index (PDI) were measured using dynamic light scattering (DLS, Zetasizer Nano-ZS; Malvern, UK).

To quantify the amount of SG encapsulated within the niosomes, the niosomes were first dissolved in acetonitrile. This solution was then passed through a reverse-phase C18 HPLC column (250 *mm*×4.6 *mm*, either Alltech or Shiseido Capcell Pak) using the Lach-

rom Elite HPLC system from Shimadzu [11]. The mobile phase, a mixture of acetonitrile and water, was initially set at 30% acetonitrile and gradually increased to 100% over a period of 10 *min*. The flow rate was maintained at 0.1 *ml/min* at a temperature of 50°*C*. Following this, the area Under the Curve (AUC) of the resulting peaks was compared with the AUCs from the SG standard curve to determine the amount of encapsulated SG. The initial concentration of SG employed in the niosomal formulation, relative to the encapsulated SG following niosome formation, was quantified and reported as a percentage, representing the Encapsulation Efficiency (EE%) of the preparation.

Antimicrobial activity of niosomal SG

The antimicrobial properties of the niosomal SG were evaluated using three methods: disk diffusion, well diffusion, and biofilm formation. The pathogens tested for antimicrobial activity included *Streptococcus mutans (S. mutans)* ATCC 25175, *Staphylococcus aureus (S. aureus)* ATCC 6538, and *Candida albicans (C. albicans)* ATCC 14053. In addition to niosomal SG (50 μl), the agents tested for their antimicrobial activity were non-niosomal SG (50 μl) suspended in DMSO, ciprofloxacin (50 μl, 0.3%), and nystatin (50 μl, 1×10^5 *units/ml*).

For the disk-diffusion assay, 30 *ml* of freshly autoclaved, Tryptic Soy Agar, TSA (40.0 *g/L*) was poured into individual petri dishes under sterile conditions and allowed to cool at room temperature. A sample of the pathogens, with turbidity equivalent to 0.5 McFarland standards, was then collected from the microbial suspension using a sterile loop and streaked across the agar. Subsequently, 6.4 *mm* blank paper discs (Padtan Teb Co., Iran) were coated with the agents and left to dry for 30 *min* under sterile conditions. The discs were then flipped and placed on the petri dishes, which were incubated at 35°*C* for 48 *hr* to allow bacterial colonization. The inhibition zones (2r, *mm*) were finally measured using a ruler.

The well-diffusion test followed the same steps as the disk-diffusion assay, with the exception of creating a well in the agar using a Pasteur pipette (6 *mm* width) and filling it with 50 μl of each reagent.

Antibiofilm activity of niosomal SG

The antibiofilm efficacy of various agents, including niosomal SG, was evaluated using a microtiter assay [12]. In brief, a 96-well culture plate was prepared by dispensing 150 μl of TSA growth medium and microbial species, calibrated to a turbidity equivalent to 0.5 McFarland. Subsequently, 100 μl of the agents (niosomal SG, non-niosomal SG, PBS) were introduced into the wells. Control wells were established without either microbial species (negative control) or the agents (positive control). The plate was then incubated at 37°*C* for 24 *hr*.

Post-incubation, the medium and planktonic species were carefully removed and the wells were thoroughly rinsed with normal saline, three times. The now empty wells were treated with 200 μl methanol to stabilize the biofilm population. After 15 *min*, the contents of the wells were discarded and the plate was dried at room temperature. For staining, 200 μl of 2% crystal violet was added to each well for 5 *min*. Then, the excess dye was completely washed off with a gentle stream of water and the microplate was dried at room temperature. Lastly, contents of the well were dissolved by adding 200 μl of 33% *v/v* acetic acid, and the absorbance was quantified at 630 *nm* using a Multiskan Plus plate reader (Labsystems).

The cut-off value for Optical Density (ODc) [13] was determined based on the absorbance value of the negative control, calculated using the formula:

ODc=average OD of negative control+3×SD of negative control

The biofilm activity was then classified based on the absorbance as follows:

Absorbance ≤ODc indicates no biofilm activity

ODc <Absorbance ≤2×ODc indicates weak biofilm activity

2×ODc <Absorbance ≤4×ODc indicates medium biofilm activity

Absorbance >4×ODc indicates strong biofilm activity.

Antiproliferative activity of niosomal SG

The cytotoxic activity of the niosomal and non-niosomal SG was assessed in cancer KB cells (CRL-3596 ™, Pasteur Institute, Iran) and normal L929 cells (CCL-1 ™, Pasteur Institute, Iran) using the MTT assay. Briefly, 4×10^4 viable KB cells and 1×0^4 L929 cells were dispensed to a flat-bottomed 96-well plate and incubated at 37°*C*. After 24 *hr*, the cells were treated with niosomal and non-niosomal SG within the range of 0.015 *mg/ml* –1 *mg/ml* for 24- and 48-*hr* incubation periods at 37°*C*. For control, some wells were left either without cells (positive control) or without reagent treatment (negative control). Subsequently, the medium was replaced with fresh RPMI-1640 culture medium (Sigma-Aldrich) supplemented with 20 μl MTT solution (5 *mg/ml*) -3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide–and incubated for a further 4 *hr*. Finally, the medium was washed away extensively with normal saline, the formazan dye was dissolved in 0.2 *ml*/well DMSO, and the absorbance was measured at 550 *nm* using the ELISA reader.

Subsequently, the antiproliferative activity of the niosomal and non-niosomal SG was determined for each SG concentration using the following formula:

Antiproliferative activity=(OD550 *nm* of negative control–OD550 *nm* of reagent)×100/(OD550 *nm* of negative control–OD550 *nm* of positive control).

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 6 (GraphPad Software, San Diego, CA) at a significance level of 0.05. One-way ANOVA was employed followed by the Bonferroni's multiple com-

parisons test to determine significant differences between the treatment groups.

Results

SG chemical structure characteristics

The ^{1}H NMR spectrum (A) along with the chemical structure (B) of SG were characterized by ^{1}H NMR (Supplementary 1). Based on ^{1}H NMR spectrum the following hydrogen shifts were observed: Hydrogen at Carbon 2 (H2) that appeared as a doublet of doublets (dd) at 5.67 *ppm* with coupling constants of 13.2 *Hz* and 7.2 *Hz*; central and equatorial Hydrogen at Carbon 3 (H3) that were observed at 3.0 *ppm* and 2.79 *ppm*, respectively, with coupling constants of 13.2 *Hz*, 2.17 *Hz*, and 2.7 *Hz*. Methyl groups attached to carbons 9", 10", and 4" exhibit chemical shifts of 1.50 *ppm*, 1.58 ppm, and 1.68 *ppm*, respectively. The hydrogen attached to the hydroxyl group at position 5 forms a hydrogen bond with the carbonyl group. Its sharp singlet peak appears weak due to its position between several electronegative groups. The peak is observed at 12.2 *ppm*. Hydrogen at Carbon 6 (H6) appeared as a sharp singlet at 6.05 *ppm*. Methylene Hydrogens (H5") showed two peaks, corresponding to the methylene hydrogens, appeared as a doublet of doublets at 4.56 *ppm* and 4.64 *ppm*. Ring B Hydrogens (H3", H5", and H6') exhibited chemical shifts of H3" 6.5 *ppm*; H5" 6.46 *ppm*; H6" 7.4 *ppm*. For a more detailed overview, refer to the complete data in supplementary 2.

Physicochemical characteristics of niosomal SG

Figure 1 depicts the size distribution of niosomal SG with an average size of 115 *nm*. The first quartile of the particles exhibited a size distribution of <90 *nm* and third quartile displayed a size distribution of <164 *nm*. Overall, the majority (95%) of the particles displayed a size distribution of <209 *nm*. The PDI of the particles varied between 0.18-0.22 (of three independent niosomal preparations) with zeta potential, ranging from -10 to -20 *mV*. Regarding SG loading, the SG contained 4.75 *mg* SG/*ml* niosomal formulation, corresponding to EE of 56% of the initial amount of SG used.

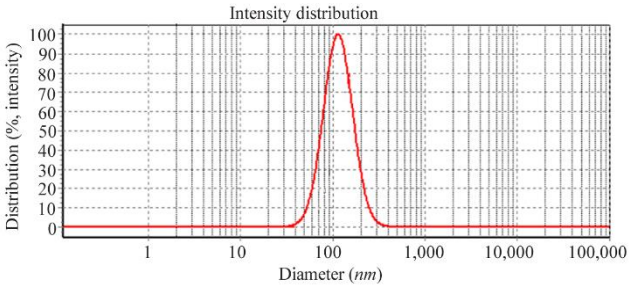

Figure 1. Size distribution graph of niosomal SG.

Antimicrobial properties of niosomal SG

Figure 2 presents the results of the inhibition zones around the discs and wells treated with various reagents, while Figure 3 illustrates biofilm formation in the treated wells. It was observed that non-niosomal SG exhibited superior antimicrobial activity compared to niosomal SG.

The most substantial inhibition zones were associated with the reference antibiotics, specifically ciprof-

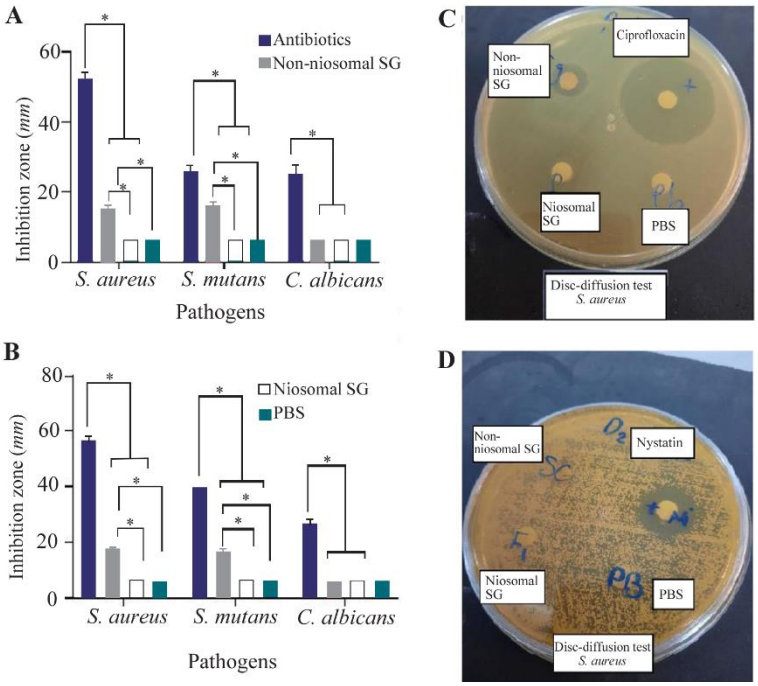

Figure 2. Antimicrobial activity of non-niosomal and niosomal SG. A and B indicate the quantitative results for disc- and well-diffusion tests. C and D represent the results of disc-diffusion tests for *S. mutans* and *C. albicans* in the plates, repsctively.
* Indicates p-value <0.05. Data are shown as mean ± SD (n=8).

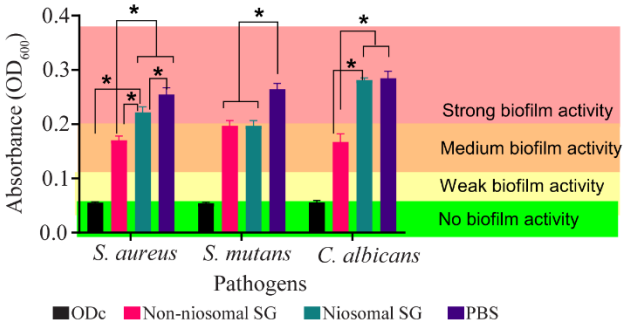

Figure 3. Biofilm activity of wells treated with non-niosomal and niosomal SG.
* Indicates p-value <0.05. Data are shown as mean ± SD (n=8).

loxacin for bacteria and nystatin for *C. albicans* (Figures 2A and B). The inhibition zone exceeded 50 *mm* for *S. aureus*, while for *S. mutans* and *C. albicans*, it was approximately 25 *mm* around the discs. In contrast, the inhibition zone for non-niosomal SG was less than 20 *mm* for the bacteria and was negligible (6 *mm*) for *C. albicans* (Figures 2A and B) when compared to PBS. A similar pattern was observed around the wells. Niosomal SG did not exhibit any significant antibacterial or antifungal activity compared to PBS. Similar results could be seen in the disc-diffusion plats for *S. aureus* and *S. mutans* (Figures 2C and D).

The diminished antimicrobial efficacy of niosomal SG was evident in its limited capacity to inhibit biofilm formation. Wells treated with niosomal SG exhibited strong biofilm activity, indicating insufficient suppression of microbial colonization. In contrast, non-niosomal SG demonstrated moderate biofilm activity against *S. aureus* and *C. albicans*, suggesting a partial inhibitory effects on biofilm development (Figure 3).

Antiproliferative properties of niosomal SG

Figure 4 presents the dose-response graph for both non-niosomal and niosomal SG in the cancerous KB (A) and normal L929 cell lines (B). While niosomal SG showed only a marginal increase in the inhibition of cell proliferation in normal L929 cells, it exhibited a significant difference in the KB cells when compared to non-niosomal SG.

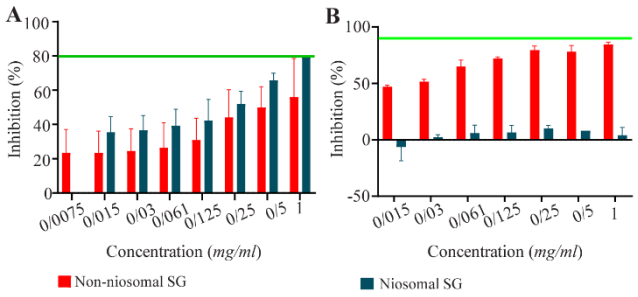

Figure 4. Antiproliferative activity of non-niosomal and niosomal SG. A and B indicate cancer KB and normal L929 cells. Data are shown as mean ± SD (n=8).

Discussion

This study delved into the potential of niosomal formulation to enhance the efficacy of the prenylated flavonoid, SG. Given the high hydrophobicity and poor water solubility of SG, it was finely dispersed using either DMSO supplementation or niosomal formulation for its biological activity assessment.

Numerous studies have underscored the role of niosomal formulations in unlocking and reintroducing the beneficial properties of highly hydrophobic herbal compounds. These compounds would otherwise precipitate in biological media, resulting in significantly low bioavailability. For instance, Agarwal *et al* [14] utilized a niosomal system comprising non-ionic surfactant span 60 and cholesterol to create a well-dispersed suspension of Morusin, another prenylated flavonoid. Similarly, Murugesan *et al* [15] used a comparable niosomal system for the dietary polyphenols quercetin and resveratrol. Without the niosome, the water solubility of these compounds is considerably lower than their effective biologically-active concentrations–the solubility of quercetin and resveratrol is 0.01 *mg/ml* and 0.05 *mg/ml*, respectively [16,17].

Through the niosomal formulation, we attained a high loading concentration of 4.75 *mg/ml*, adequate to trigger antimicrobial activity. However, the niosomal SG did not exhibit any antibacterial activity or fungal growth inhibition (Figure 2), and only marginal antibiofilm activity was observed for *S. mutans* (Figure 3).

In contrast, non-niosomal SG demonstrated some antibacterial (Figure 2) and antibiofilm activity (Figure 3). The absence of a DMSO control group in this study limits the interpretation of these results. The observed effects could be attributed to either the synergistic antimicrobial activity of DMSO or its enhanced penetration and availability. Previous studies have highlighted the antimicrobial activity of DMSO across a broad spectrum of bacteria and fungi [18,19], and its ability to penetrate deeply into tissues affected by dental infections [20]. Thus, it appears that niosomal SG may not be suitable for dental hygiene in terms of controlling bacterial and fungal growth.

Turning to the anticancer potential of niosomal SG, intriguing and promising findings were uncovered. Niosomal SG slightly enhanced its ability to inhibit cell growth in the KB cell line and showed strong protection against cell damage in normal L929 cells (Figure 4). KB is a human epithelial cell originally derived from a patient with epidermal carcinoma of the mouth and L929 is a fibroblast cell; therefore, it appears that niosomal formulation enhanced cancer-specific cytotoxicity for oral malignancies.

The anticancer activity of SG aligns with previous literature. Huang *et al* [21] reported the antiproliferative effect of SG on human leukemia HL-60 cells and the triple-negative breast cancer MDA-MB-231 cells. In the present study, both niosomal and non-niosomal SG exhibited antiproliferative activity against cancer KB

cells, while only the niosomal SG exhibited no toxicity against the normal L929 cells, suggesting that niosomal SG delivers SG at non-toxic concentrations to normal cell lines.

Conclusion

This study evaluated the biological activity of SG encapsulated in a niosomal system, comprising cholesterol and tween 20. SG is a biologically active compound but unstable in the biological environment, which causes to precipitate rapidly in the aqueous environment and become unavailable. Encapsulation of SG in niosomes resulted in the formation of a stable SG suspension in the aqueous media at nanoscale, mostly in the range of 100 to 200 *nm*. It appeared that the niosomal system somewhat obscured the antimicrobial activity of SG when compared to that of non-niosomal SG dissolved in DMSO. It is plausible that a niosomal formulation with elevated concentrations of tween 20 or substitution with alternative ionic detergents could enhance the antimicrobial activity of SG, a prospect worth exploring. Despite this, the niosomal formulation provided valuable insights, indicating SG might be effectively utilized as a highly selective formulation in the treatment of gingival cancers, while SG may not be a potent antimicrobial agent. The use of a nano-niosomal form of SG has the potential for targeted elimination of cancer cells in clinics, while reducing the toxicity of SG. This could position niosomal SG as a suitable therapeutic candidate, especially in the cancer treatment.

Acknowledgement

The authors would like to thank the Vice President for Research and Technology of North Khorasan University of Medical Sciences for their financial support (Project No. 4000195). The study has been approved by the Ethics Committee of North Khorasan University of Medical Sciences (IR.NKUMS.REC.1400.163).

Conflict of Interest

The authors declare no competing interests.

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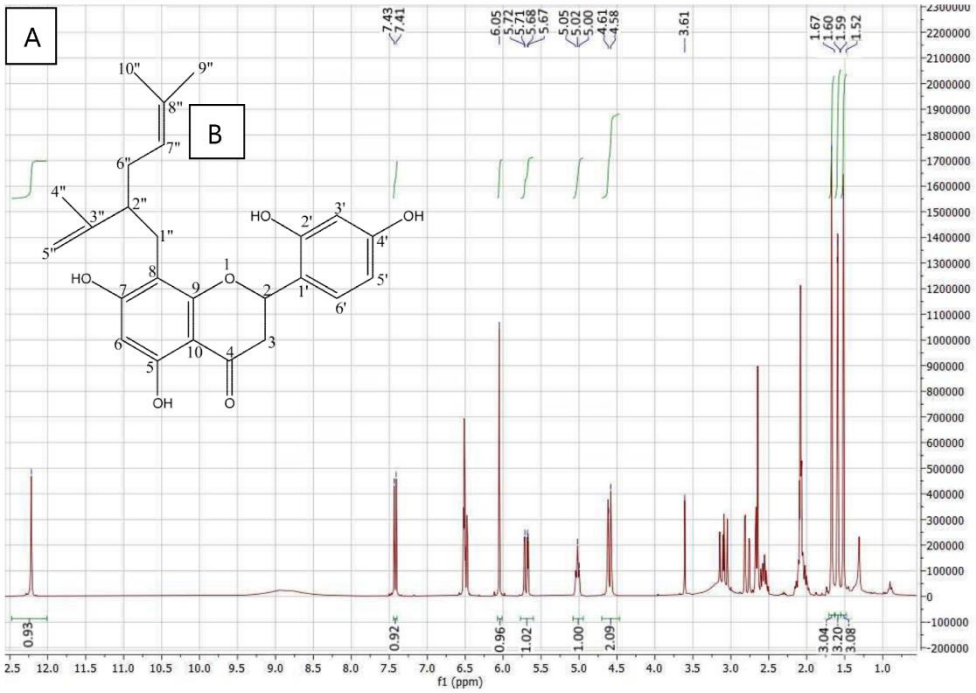

Supplementary 1. ^{1}H NMR spectrum (A) and associated chemical structure (B) of SG ^{1}H NMR (DMSO-d6, 400 MHz): 12.1(s, 5-OH), 7.4(1H, d, J=8.4 Hz, H-6′), 6.5(1H, d, J=2.3 Hz, H-3′), 6.46(1H, dd, J=8.4, 2.5 Hz, H-5′), 6.05(1H, s, H-6), 5.68(1H, dd, J=2.8, 13.3 Hz, H-2), 4.89(1H, t, J=6.8 Hz, H-4″), 4.55(1H, brs), 4.47(1H, brs), 3.1(1H, dd, J=13.3, 17.2 Hz, H-3a), 2.62(1H, dd, J=2.9, 17.2Hz, H-3b), 2.4(3H, m), 1.9(2H, m), 1.56(3H, s), 1.52(3H, s), 1.43(3H, s).

Supplementary 2. ^{1}H NMR chemical shifts of different H attached to carbons

H/C no.	H- NMR (*ppm, Hz*)	H/C no.	H- NMR (*ppm, Hz*)
2	5.67 (H, dd; 13.2; 2.7)	2”	2.58 (1 H, m)
3 ax, eq	3.0 (1 H, dd; 13.2; 2.17), 2.79 (1 H; dd; 2.7)	4”	1.67 (3 H, S)
6	6.05 (1 H, s)	5”	4.56; 4.61 (2 H, brs)
3’	6.5 (1 H; d; 2.2 *Hz*)	6”	2.05 (2 H, m)
5’	6.46 (1 H; dd; 8.3; 2.2)	7”	5.01 (1 H, brt)
6’	7.4 (1 H, dd; 8.2)	9”	1.50 (3 H, s)
1” a,b	2.64 (1 H, dd; 1.2); 2.66 (1 H, d; 2.3)	10”	1.58 (3 H, s)