

Suppression of SLC7A11-Mediated Inhibition of Dendritic Cell Efferocytosis Underlies the Wound-Healing Effects of Ginsenoside Rg5

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ABSTRACT

Ginsenoside Rg5 represents a scarce ginsenoside recognized for its ability to lower blood glucose levels in diabetic mice. The present investigation aimed to examine the influence of ginsenoside Rg5 on cutaneous wound repair in *Lepr^{db/db}* mutant (db/db) mice on a C57BL/KsJ genetic background and to clarify the associated molecular pathways. Experiments were conducted using seven-week-old male C57BL/6J mice, SLC7A11-knockout (KO) animals, their corresponding littermate wild-type (WT) controls, and db/db mice in both in vivo and ex vivo settings. Oral delivery of ginsenoside Rg5 by gavage to db/db mice substantially lowered the quantity of apoptotic cells within the wound bed and promoted faster skin wound closure. Exposure to 50 μ M ginsenoside Rg5 roughly doubled the efferocytic capacity of bone marrow-derived dendritic cells (BMDCs) isolated from db/db mice. The compound also decreased NF- κ B p65 and SLC7A11 levels in the injured skin of db/db mice in a concentration-dependent fashion. Ginsenoside Rg5 bound directly to SLC7A11, thereby inhibiting cystine import and glutamate export in BMDCs from both db/db and SLC7A11-WT mice, whereas no such inhibition occurred in cells from SLC7A11-KO mice. Within BMDCs and conventional type 1 dendritic cells (cDC1s), ginsenoside Rg5 decreased intracellular glycogen reserves while stimulating anaerobic glycolysis. Pretreatment with the glycogen phosphorylase inhibitor CP-91149 largely prevented ginsenoside Rg5 from enhancing efferocytosis. Ginsenoside Rg5 downregulates SLC7A11 expression and directly interferes with its transporter activity through physical interaction. Together, these actions counteract the suppressive influence of SLC7A11 on anaerobic glycolysis, a metabolic pathway that powers dendritic cell efferocytosis. Thus, ginsenoside Rg5 emerges as a potential supportive therapeutic option for managing impaired wound repair in conditions such as diabetic foot ulcers.

Keywords: Ginsenoside Rg5, SLC7A11, Diabetes, Wound healing

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Introduction

Patients with type 1 or type 2 diabetes mellitus (T1DM and T2DM) frequently experience persistent non-healing wounds that elevate infection risk and markedly diminish quality of life [1]. Successful resolution of skin injuries relies on efficient removal of apoptotic cells by phagocytes (a mechanism termed efferocytosis) at the wound site [2]. Prolonged inflammatory states in wounded skin are closely associated with deficiencies in efferocytic clearance [3-5].

Multiple immune cell populations, such as T cells, macrophages, neutrophils, and dendritic cells, jointly regulate the local microenvironment in the skin [6, 7]. Both tissue-resident and recruited dendritic cells, macrophages, and neutrophils serve as phagocytes in cutaneous tissue, contributing significantly to the wound-healing cascade [8-10]. Recent evidence indicates that the cystine/glutamate antiporter SLC7A11 functions as a key negative

modulator of efferocytosis in diabetic wounds, acting predominantly through dendritic cells rather than macrophages [8]. Pharmacological suppression of SLC7A11 activity substantially improves wound closure rates in diabetic mouse models [8].

Ginsenosides comprise the primary pharmacologically active compounds derived from **Panax ginseng** Meyer. Earlier reports have documented the anti-inflammatory and wound-healing benefits of several ginsenosides, including Rg1 [11], Rg3 [12], and Rh2 [13]. Ginsenoside Rg5, a less abundant variant, exhibits pronounced hypoglycemic properties that alleviate insulin resistance and support mitochondrial function in diabetic mice [14, 15]. In both *Lepr*^{db/db} (db/db) and high-fat diet combined with streptozotocin-induced diabetic models, ginsenoside Rg5 attenuates NF- κ B p65 expression and activation in liver and kidney tissues [14, 16]. Comparable inhibitory effects have been observed in human keratinocytes and macrophages [17]. NF- κ B p65 is known to transcriptionally upregulate SLC7A11 [18, 19]. Additionally, ginsenoside Rg5 has been proposed as a beneficial anti-aging constituent in red ginseng extracts for dermatological applications [20]. Drawing upon these observations, we postulated that ginsenoside Rg5 could exert beneficial effects on diabetic wound healing, potentially by influencing SLC7A11-regulated efferocytosis in dendritic cells.

This study therefore aimed to assess the therapeutic potential of ginsenoside Rg5 in promoting skin wound repair using the db/db mouse model. SLC7A11-knockout (KO) mice were further employed to evaluate the involvement of SLC7A11 in ginsenoside Rg5-mediated modulation of dendritic cell efferocytosis.

Materials and Methods

Animal study

Seven-week-old male C57BL/6J, SLC7A11-KO, corresponding littermate wild-type (WT), and db/db mice (C57BL/KsJ background) were acquired from Cyagen Biosciences (Suzhou, China). All animals were maintained in a specific pathogen-free environment and housed in cages containing two or three mice each. Experimental protocols were reviewed and approved by the Animal Care and Use Committee of Sichuan Provincial People's Hospital and Chengdu Jinruijie Biotechnology Service Center, China (Approval no. 202207006), and conducted in compliance with institutional guidelines for laboratory animal care and use. Following a one-week adaptation period, C57BL/6J or db/db diabetic mice ($n = 6$ per group) were given either the vehicle control (0.5% (w/v) CMC-Na) or ginsenoside Rg5 (prepared at 1.0 mg/mL in 0.5% (w/v) CMC-Na, administered at 20 or 80 mg/kg/day) once daily for one week through oral gavage prior to the induction of wounds.

Full-thickness skin wounds were created as detailed in an earlier publication [21]. Briefly, mice were anesthetized with isoflurane, after which the dorsal fur was removed. Circular wounds were produced with 8-mm biopsy punches. Wound dimensions (major diameter A and minor diameter B) were recorded every other day using a digital caliper. Wound surface area (S) was determined according to the equation: $S = (A \times B \times \pi)/4$. On day 4 after wounding, tissue samples from selected mice were harvested following euthanasia via carbon dioxide (CO₂) inhalation. Specimens were fixed, paraffin-embedded, sectioned, and then stained with hematoxylin and eosin (H&E) or processed for immunofluorescent (IF) detection of cleaved caspase-3 (1:500, #9661, Cell Signaling Technology, Danvers, MA, USA).

Primary cell cultures

Bone marrow-derived dendritic cells (BMDCs) were differentiated from bone marrow cells isolated from the femurs and tibias of 8- to 12-week-old db/db, SLC7A11-WT, or SLC7A11-KO mice. Progenitor cells were cultured for 10–12 days in medium containing granulocyte-macrophage colony-stimulating factor (GM-CSF) using the protocol established by Lutz *et al.* [22]. Bone marrow-derived macrophages (BMDMs) were prepared according to a previously reported method employing both macrophage colony-stimulating factor (M-CSF) and GM-CSF [23]. Following differentiation, BMDC identity was confirmed by flow cytometry with FITC anti-mouse MHC-II (11-5321-82, Thermo Fisher Scientific, Waltham, MA, USA) and BV786 anti-mouse CD11c (cat#563735, BD Biosciences, Franklin Lakes, NJ, USA). BMDMs were verified using PerCP/Cy5.5 anti-mouse F4/80 (cat#123127, Biolegend, Dedham, MA, USA) and BV510 anti-mouse CD11b (cat#101245, Biolegend). Ginsenoside Rg5, erastin, cytochalasin D, and CP-91149 were obtained from MedChemExpress (Monmouth Junction, NJ, USA).

Reverse transcription-quantitative real-time PCR (RT-qPCR)

Total RNA was converted to complementary DNA (cDNA) through reverse transcription. Real-time quantitative PCR assays were carried out on an ABI PRISM 7900HT Sequence Detection System with SYBR Green Master Mix (Applied Biosystems, Bedford, MA, USA). Relative gene expression levels were normalized to PPIA and determined using the $2^{-\Delta\Delta CT}$ calculation method. Primer sequences employed were: mouse SLC7A11 forward 5'-CTTTGTTGCCCTCTCCTGCTTC-3', reverse 5'-CAGAGGAGTGTGCTTGTGGACA-3'; mouse PPIA forward 5'-CATACAGGTCCTGGCATCTTGTC-3', reverse 5'-AGACCACATGCTTGCCATCCAG-3'.

Data retrieved from the human protein atlas

Single-cell level RNA expression profiles of SLC7A11 in normal human skin were accessed from the Human Protein Atlas database (<https://www.proteinatlas.org/>) [24, 25].

Western blotting

Western blotting experiments followed a previously described procedure [26]. Wound skin tissues were homogenized in lysis buffer containing protease and phosphatase inhibitor cocktails (MilliporeSigma, St. Louis, MI, USA). Equal amounts of total protein (20 µg) were separated by 10% SDS-PAGE and electrotransferred onto polyvinylidene difluoride membranes (MilliporeSigma). Membranes were washed, blocked, and incubated overnight at 4 °C with appropriately diluted primary antibodies. After extensive washing, membranes were incubated for 1 h at room temperature with horseradish peroxidase-conjugated (HRP) anti-rabbit IgG secondary antibody (Proteintech, Wuhan, China). Chemiluminescent signals were generated using ECL reagent (BeyoECL Star, Beyotime, Shanghai, China) and captured with a Tanon 4600 imaging system (Tanon, Shanghai, China). Primary antibodies used included: anti-NF-κB p65 (1:1000, 10745-1-AP, Proteintech), anti-IκBα (1:5000, 10268-1-AP, Proteintech), anti-SLC7A11 (1:1000, 26864-1-AP, Proteintech), anti-β-actin (1:10000, 66009-1-Ig, Proteintech), and anti-Histone H3 (1:2000, 17168-1-AP, Proteintech).

Determination of cystine uptake and glutamate release

Assessment of sodium-independent cystine uptake relied on the sodium nitroprusside method reported earlier [27]. In summary, 5×10^5 BMDs were plated in 6-well dishes and subsequently exposed to ginsenoside Rg5 (10 µM or 50 µM) over a 48-hour period. Following treatment, the cells underwent washing steps, were placed in cystine-specific uptake medium, and then received 1 µM L-cystine, with incubation continuing for 1 hour at 37°C. Thereafter, 500 µl of buffer from each well was retrieved and spun down by centrifugation. A 400 µl aliquot of the clarified supernatant was combined with 100 µl of 20% sodium nitroprusside reagent prior to reading absorbance values at 521 nm. Glutamate levels in the collected media were quantified employing a Nova BioProfile 100 Plus Analyzer (Nova Biomedical, Waltham, MA, USA). Both cystine and glutamate amounts were derived after correction for background signals from acellular control wells and adjusted according to the cell density determined for each sample.

Evaluation of in vitro engulfment by flow cytometry and cell sorting

Phagocytic uptake of apoptotic cells was examined using a previously validated efferocytosis protocol [28]. Jurkat T cells represent a convenient model system for such studies owing to their rapid expansion, uniform apoptotic response, high reproducibility, and overall experimental practicality [8, 29-31]. In practice, human Jurkat cells received 254-nm UV irradiation for 15 minutes and were allowed to undergo apoptosis during a subsequent 4-hour incubation at 37 °C under 5% CO₂. Successful apoptosis induction was validated by Annexin V-7AAD labeling (cat#559763, BD Biosciences) and flow cytometric detection. The apoptotic targets were then stained with 1 µM CypHer5E (GE Healthcare, PA15401) for 30 minutes. Mouse BMDMs, BMDs, cDC1s, or cDC2s were first seeded into 24-well plates. Selected dendritic cell populations were pretreated for 2 hours with either erastin (10 µM) or ginsenoside Rg5 (10 or 50 µM). These cells were next combined with the fluorescently labeled apoptotic Jurkat cells at a 1:5 ratio and co-incubated for an additional 2 hours. After this period, the mixed populations were harvested, subjected to three washes with cold PBS, and prepared in FACS buffer. Dendritic cells received staining with FITC anti-mouse MHC-II (11-5321-82, Thermo Fisher Scientific) plus BV786 anti-mouse CD11c (cat#563735, BD Biosciences), while BMDMs were labeled with PerCP/Cy5.5 anti-mouse F4/80 (cat#123127) and BV510 anti-mouse CD11b (cat#101245, Biolegend) at 1:200 dilution for 30 minutes at 4°C. Samples were acquired on a BD FACS Canto II cytometer, with subsequent analysis conducted via NovoExpress

software (v1.5.4, Agilent Technologies, Santa Clara, CA, USA). Efferocytosis efficiency was quantified by calculating the percentage of CypHer5E-positive cells within the respective marker-defined populations: for dendritic cells, CypHer5E⁺ events among CD11c⁺/MHC-II⁺ cells; for BMDMs, CypHer5E⁺ events among CD11b⁺/F4/80⁺ cells.

Primary cDC1 and cDC2 populations were purified from mouse spleen cell suspensions generated according to an established procedure [8]. Spleens were mechanically and enzymatically dissociated, followed by erythrocyte depletion with RBC lysis buffer (cat#420301, Biolegend). Target dendritic cell subsets were sorted by flow cytometry utilizing BV650 anti-mouse/rat XCR1 (cat#148220, Biolegend) and APC anti-mouse CD172a (cat#144013, Biolegend) on a BD FACSAria II instrument.

Molecular docking studies

The molecular structure of ginsenoside Rg5 was prepared in mol file format. The cryo-EM coordinates for the SLC7A11/SLC3A2 complex (<https://www.rcsb.org/structure/7P9U>) were obtained and divided into distinct files corresponding to each subunit. Docking calculations were executed through the CB-Dock online platform (<http://clab.labshare.cn/cb-dock/php/index.php>) [32].

Cellular thermal shift assay (CETSA)

The CETSA procedure followed a method documented in prior literature [33]. BMDCs were first collected and lysed in PBS-based buffer. The resulting lysates were treated with DMSO vehicle (1%), Rg5 (50 μ M), or erastin (10 μ M) and held at room temperature for 30 minutes. Treated samples were then divided into separate tubes and heated across a temperature gradient (42 °C to 67 °C) for 5 minutes each. After brief centrifugation, the soluble protein fractions were subjected to western blot analysis to monitor SLC7A11 levels.

Surface plasmon resonance binding analysis

Interaction affinities of ginsenoside Rg5 toward recombinant SLC7A11, SLC2A1, SLC7A5, and SLC16A1 proteins were measured on a Biacore T200 platform (GE Healthcare, Pittsburgh, PA, USA) with CM5 sensor chips using established amine-coupling approaches [34]. Proteins were covalently attached to the carboxylated dextran surface at pH 4.0. Serial dilutions of ginsenoside Rg5 prepared in HBS-P⁺ running buffer (pH 7.4, 0.05% Tween20) were injected across the immobilized proteins, and binding responses were recorded. Sensorgram data were processed and evaluated using BIAevaluation 3.2 software (Cytiva, Marlborough, MA, USA) to derive kinetic parameters and calculate the dissociation constant K_D .

Determination of glycogen content

Glycogen levels were assessed employing a Glycogen Assay Kit (ab65620, Abcam, Cambridge, UK).

Metabolic profiling via seahorse platform

Real-time extracellular acidification rate (ECAR) was monitored in BMDCs with the Seahorse XFe96 Analyzer (Agilent Technologies). Briefly, 5×10^4 cells per well were plated onto Seahorse 96-well tissue culture plates (Agilent Technologies) and cultured overnight. Cells were pretreated for 2 h with 10 μ M erastin or 50 μ M ginsenoside Rg5 immediately prior to the assay. The medium was replaced with unbuffered, glucose-free DMEM containing 2 mM glutamine. Experiments were conducted using the Seahorse XF Glycolysis Stress Test Kit (103020-100, Agilent Technologies) per the supplier's protocol, with final values normalized to total cell numbers.

Data analysis and statistics

All quantitative results are expressed as the mean $\pm$ standard deviation (SD). Group differences were evaluated by one-way ANOVA combined with Tukey post hoc tests for multiple comparisons, or by unpaired Welch's t-test when comparing only two groups. Analyses were carried out in GraphPad Prism 8.1.0 (GraphPad Software, La Jolla, CA, USA), with statistical significance defined as $P < 0.05$.

Results and Discussion

Therapeutic effect of ginsenoside rg5 on cutaneous wound closure in diabetic mice

Owing to its established ability to reduce hyperglycemia and counteract insulin resistance in diabetic models [14, 15], ginsenoside Rg5 (**Figure 1a**) was investigated for potential benefits on wound repair in leptin receptor-deficient db/db mice versus lean C57BL/6J controls. This db/db strain recapitulates core features of human type 2 diabetes, such as obesity accompanied by elevated blood glucose. The overall study protocol is depicted schematically in **Figure 1b**. Mice received daily oral doses of vehicle or ginsenoside Rg5 (20 or 80 mg/kg) for one week prior to surgical wounding (**Figure 1b**). Excisional wounds in db/db animals exhibited markedly slower closure rates than those in C57BL/6J mice. Administration of ginsenoside Rg5 nevertheless produced substantial improvements in healing kinetics across both strains (**Figures 1c, 1d**). In db/db mice given the 80 mg/kg dose, time to 50% wound closure was shortened by approximately two days relative to the vehicle group (**Figures 1e, 1f**).

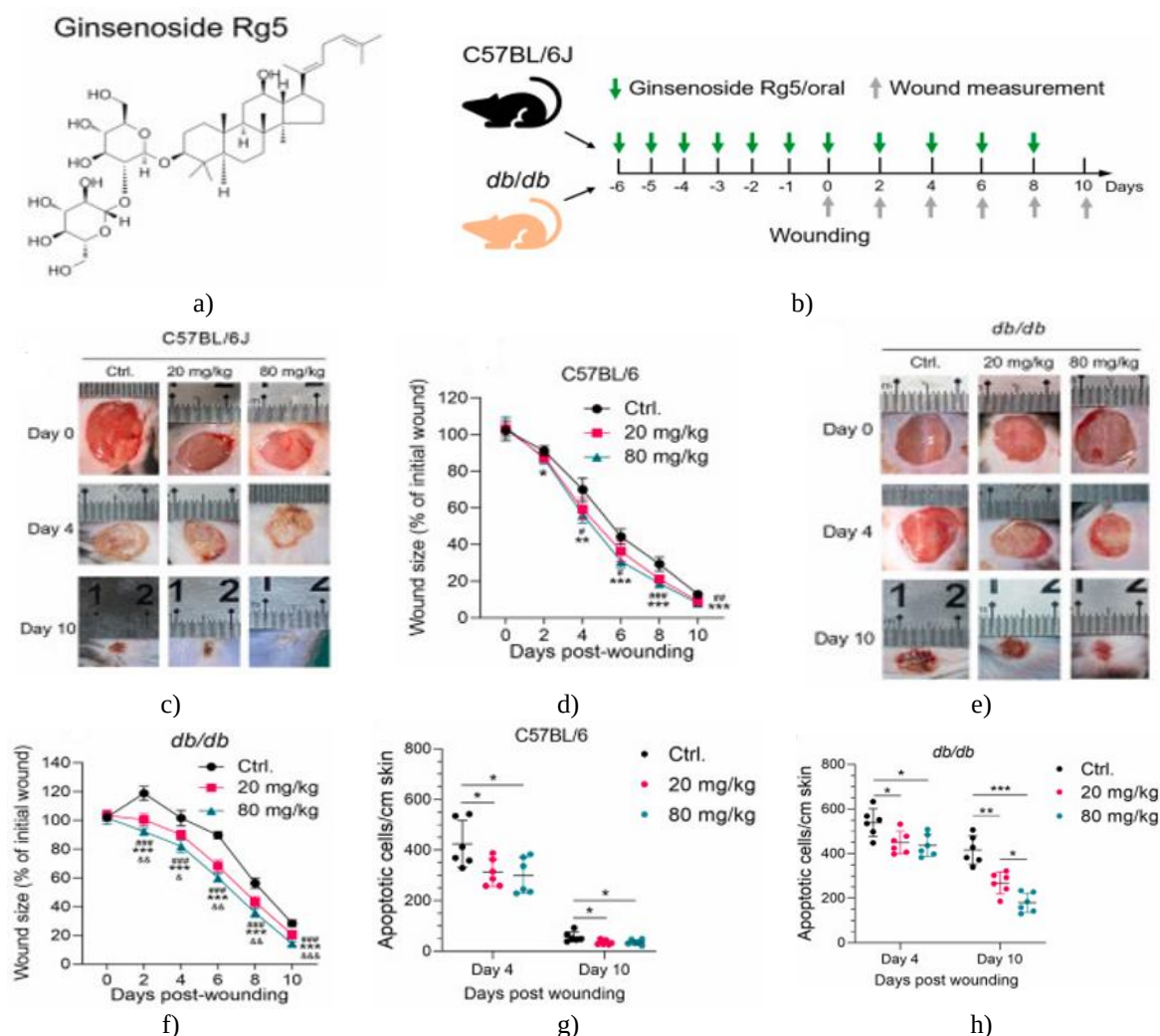


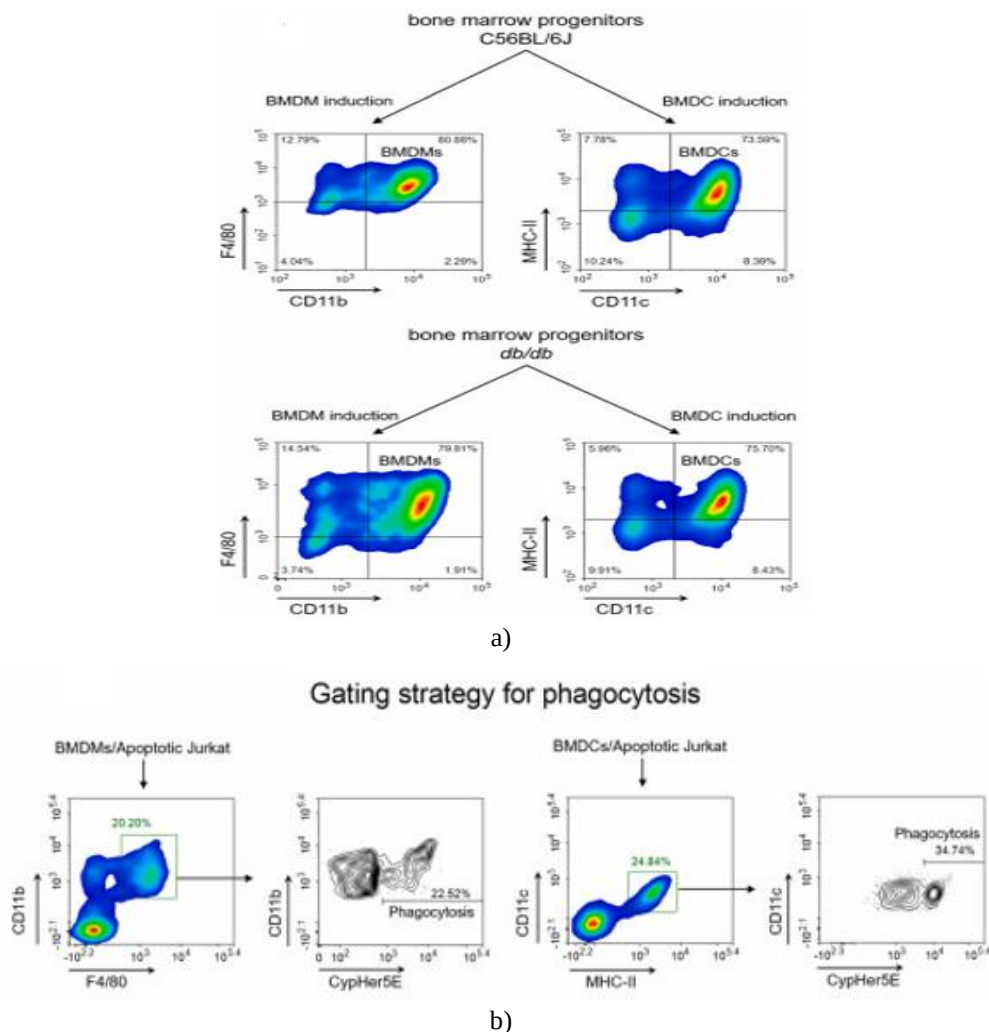
Figure 1. Therapeutic effect of ginsenoside Rg5 on cutaneous wound closure in diabetic mice. (a) Chemical structure of ginsenoside Rg5. (b) Schematic representation of the study timeline. (c–f) Representative wound images taken at serial time points (c and e) and corresponding quantitative closure profiles for C57BL/6J (C–D) and db/db (e–f) mice treated with vehicle or ginsenoside Rg5 over days 0–10 ($n = 6$ animals per group). Findings are representative of three independent replicates. (g–h) Apoptotic cell counts (cleaved caspase-3-positive) per cm of wounded skin tissue from C57BL/6J (g) and db/db (h) mice on day 4 after injury following vehicle or ginsenoside Rg5 treatment ($n = 3$). One-way ANOVA with Tukey multiple comparison tests was performed. #, comparison between 20 mg/kg and control groups; *, comparison between 80 mg/kg and control groups; &, comparison between 20 mg/kg and 80 mg/kg groups; *, # and &, $p < 0.01$; **, ### and &&, $p < 0.01$; ***, ### and &&&, $p < 0.001$.

Accumulation of uncleared apoptotic cells within wounds sustains chronic inflammation and impairs timely repair [35]. To explore this mechanism, immunofluorescence staining was applied to detect apoptotic cells and cleaved

caspase-3-positive cells in wound sections. Ginsenoside Rg5 treatment resulted in a clear reduction of apoptotic cell burden in the injured tissue of both mouse strains, manifested as lower numbers of persistent cleaved caspase-3-positive cells (**Figures 1g and 1h**). In vehicle-treated C57BL/6J mice, apoptotic cell density averaged around 400 per cm (mean $\pm$ SD, $424 \pm 93/\text{cm}$) at day 4 post-wounding and declined to approximately 60 per cm (mean $\pm$ SD, $57 \pm 20/\text{cm}$) by day 10 (**Figure 1g**). These counts decreased further to 300 ± 72 and 35 ± 10 per cm, respectively, in the 80 mg/kg ginsenoside Rg5 cohort (**Figure 1g**). Vehicle-treated db/db mice showed 539 ± 63 apoptotic cells per cm on day 4 and 416 ± 64 per cm on day 10 (**Figure 1h**). Corresponding values in the 80 mg/kg treatment group were reduced to 437 ± 50 and 179 ± 44 per cm (**Figure 1h**).

Augmentation of efferocytosis in bone marrow-derived dendritic cells by ginsenoside Rg5 under diabetic conditions

The notable decrease in residual apoptotic cells suggested involvement of enhanced efferocytosis. Since macrophages and dendritic cells function as the primary professional phagocytes [2], BMDMs and BMDCs were generated from bone marrow of C57BL/6J and db/db mice. Successful differentiation was confirmed via flow cytometry using lineage-specific markers (F4/80/CD11b for macrophages; MHC-II/CD11c for dendritic cells) (**Figure 2a**). Phagocytic capacity was then tested by co-culture with CypHer5E-labeled apoptotic cells (5:1 ratio, 2 h incubation), followed by flow cytometric measurement of CypHer5E uptake within gated CD11b⁺ F4/80⁺ BMDMs and CD11c⁺ MHC-II⁺ BMDCs (**Figure 2b**). Cells isolated from db/db mice demonstrated impaired efferocytosis compared with wild-type counterparts (**Figure 2c**). Ginsenoside Rg5 exposure restored this function in diabetic-derived cells, particularly in the BMDC fraction (**Figure 2d**). A 50 μM concentration of ginsenoside Rg5 nearly doubled efferocytic activity in db/db BMDCs, while showing no stimulatory effect on the phagocytosis of live cells (**Figure 2d**). These observations shifted the focus of subsequent work to the regulatory actions of ginsenoside Rg5 specifically on BMDCs.



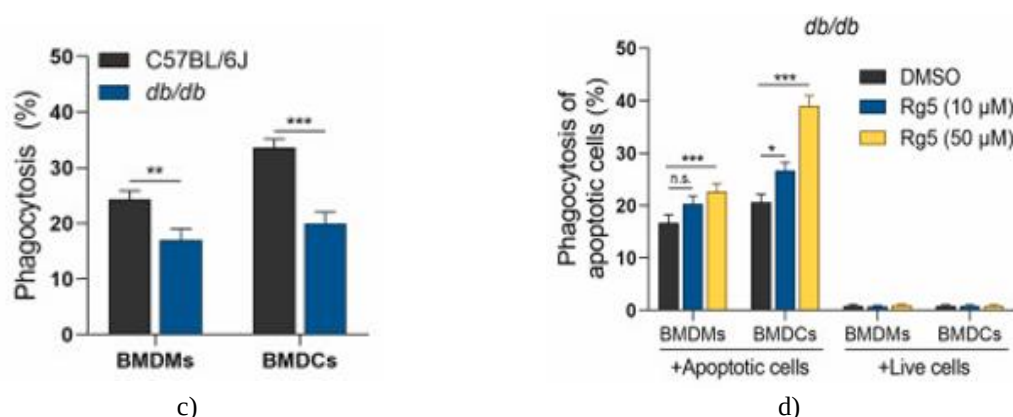
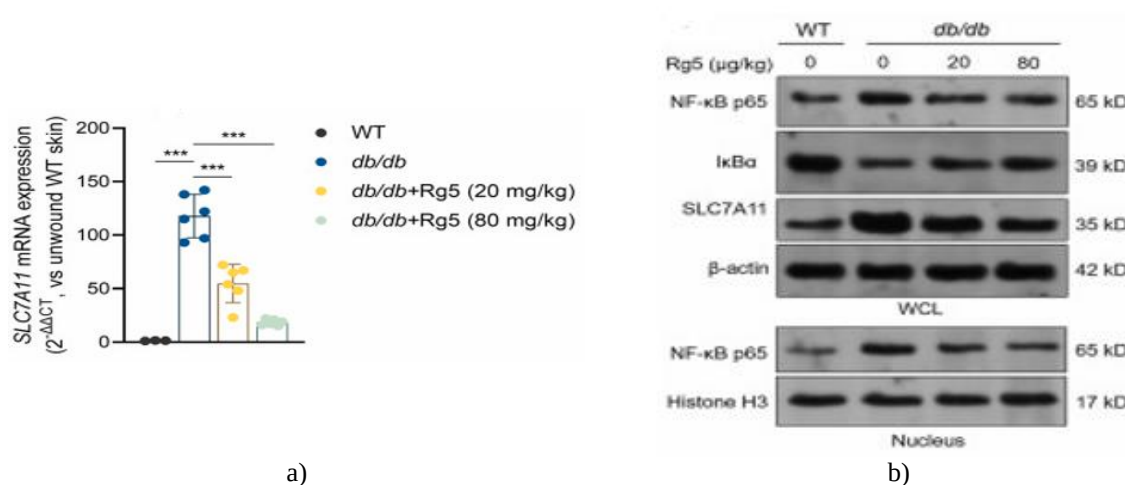


Figure 2. Augmentation of efferocytosis in bone marrow-derived dendritic cells (BMDCs) by ginsenoside Rg5 under diabetic conditions. (a) Representative flow cytometric confirmation of BMDM and BMDC differentiation from bone marrow progenitors of C57BL/6J and db/db mice based on macrophage (F4/80, CD11b) and dendritic cell (MHC-II, CD11c) marker expression. (b) Gating strategy used to quantify phagocytic events. BMDMs and BMDCs were incubated with CypHer5E-labeled apoptotic or viable Jurkat cells at a 5:1 ratio for 2 h, after which the proportion of CypHer5E-positive events was determined within the respective marker-positive populations by flow cytometry. (c) Quantitative comparison of efferocytic performance between cells derived from C57BL/6J and db/db mice. (e) Modulation of efferocytosis in BMDMs and BMDCs from db/db mice following ginsenoside Rg5 treatment. Data derive from at least three independent experiments, each performed in triplicate, and are shown as mean $\pm$ SD. One-way ANOVA with Tukey multiple comparison tests was performed. *, $p < 0.01$; **, $p < 0.01$; ***, $p < 0.001$; n.s., not significant.

Suppression of SLC7A11 expression in db/db mouse BMDCs by ginsenoside Rg5

Earlier work reported an approximately 200-fold increase in SLC7A11 expression within db/db mouse wounds relative to those in wild-type C57BL/6J animals [8]. Consistent with this finding, our models displayed strong induction of SLC7A11 (**Figure 3a**). Subsequent experiments assessed the impact of ginsenoside Rg5 on this transporter. The compound produced a robust downregulation of SLC7A11 at both transcript and protein levels in db/db wounds on day 4 after injury, bringing expression closer to that observed in normoglycemic C57BL/6J controls (**Figures 3a, 3b and 3e**). Concurrently, ginsenoside Rg5 reduced overall NF- κ B p65 abundance and recovered I κ B α levels in injured skin tissue in a manner dependent on dose (**Figures 3b and 3d**). It also blocked p65 translocation into the nucleus (**Figures 3b and 3f**). Examination of publicly available single-cell RNA-seq profiles from healthy human skin (Human Protein Atlas) indicated that SLC7A11 is primarily expressed by Langerhans cells (a unique macrophage-dendritic cell hybrid), macrophages, and B cells (**Figure 3g**).



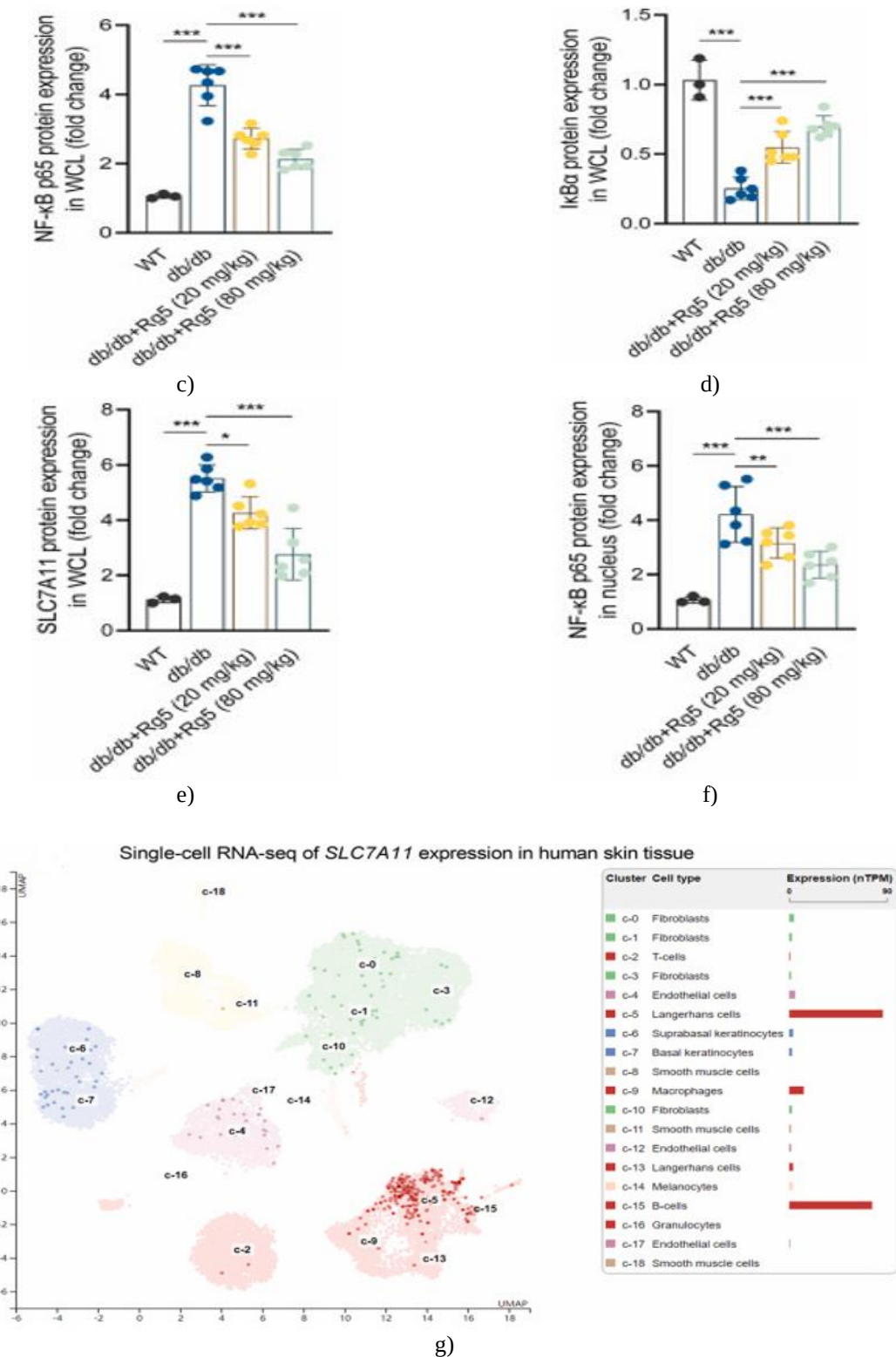
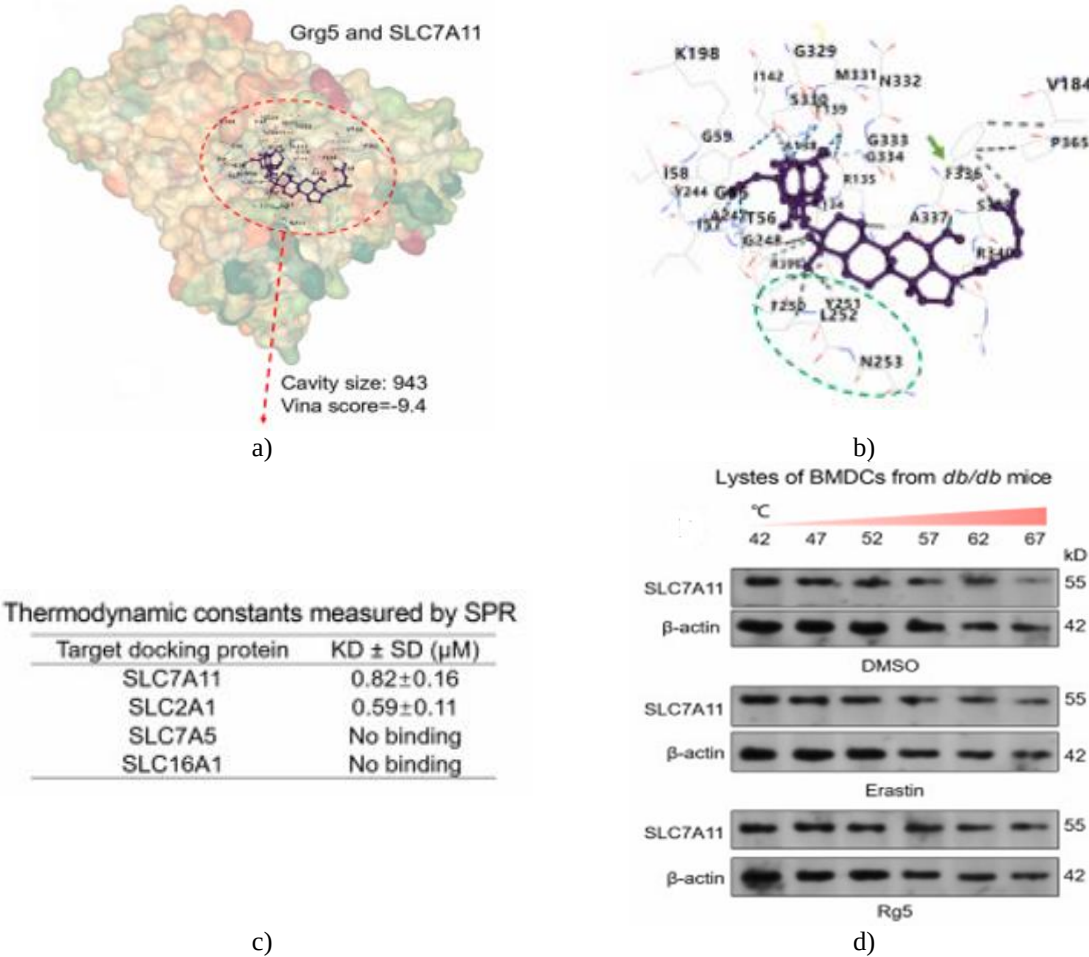


Figure 3. Suppression of SLC7A11 expression in db/db mouse BMDCs by ginsenoside Rg5. (a) SLC7A11 mRNA levels measured by qRT-PCR in skin extracts from unwounded wild-type controls (n = 3) and day-4 wounded db/db mice (n = 6 per group) receiving vehicle or ginsenoside Rg5 (20 or 80 mg/kg). (b–f) Western blot images (b) and densitometric quantification (c–f) of NF- κ B pathway components and SLC7A11 in whole-cell lysates (WCL) or nuclear fractions prepared from skin of unwounded wild-type (n = 3) and wounded db/db mice (n = 6 per group) treated with vehicle or ginsenoside Rg5 (20 or 80 mg/kg). (g) UMAP visualization (left) and corresponding bar graph (right) of SLC7A11 transcript distribution across cell populations in normal human skin at single-cell resolution. Individual cells are represented as dots in the UMAP. The bar graph indicates normalized transcript expression (nTPM) per cluster. Data sourced from

Human Protein Atlas version 21 (<https://www.proteinatlas.org/ENSG00000151012-SLC7A11/single+cell+type/skin>). Values represent mean $\pm$ SD. One-way ANOVA with Tukey multiple comparison tests was performed. **, $p < 0.01$; ***, $p < 0.001$.

High-affinity interaction of ginsenoside Rg5 with SLC7A11 and resulting inhibition of Cystine/Glutamate exchange

Several ginsenosides are known to engage with and utilize members of the solute carrier family [36-38]. Molecular docking was therefore performed to model potential contacts between ginsenoside Rg5 and SLC7A11 (**Figures 4a, 4b**). The top-ranked conformation exhibited a strong binding energy (Vina score of -9.4 kcal/mol). Ginsenoside Rg5 was predicted to occupy the intracellular vestibule of SLC7A11, mirroring the binding mode of the established inhibitor erastin [39]. Residues Q191, F254, and F336 play critical roles in cystine transport mediated by this transporter [39]. Within the simulated complex, ginsenoside Rg5 formed a direct interaction with F336 (**Figure 4b**, green arrows) and engaged neighboring residues around F254 (F250, Y251, L252, N253) (**Figure 4b**, green circle). Given that SLC7A11-driven cystine import inhibits efferocytosis [8], binding studies were extended to additional SLC transporters linked to phagocytic regulation (SLC7A11, SLC2A1, SLC7A5, SLC16A1) [8, 29]. SPR analysis verified potent direct binding of ginsenoside Rg5 to SLC7A11 ($K_D = 0.82 \pm 0.16$ μ M) and SLC2A1 ($K_D = 0.59 \pm 0.11$ μ M) (**Figure 4c**). CETSA further showed that ginsenoside Rg5 stabilized SLC7A11 protein against thermal denaturation in db/db BMDCs, without affecting the control protein β -actin (**Figures 4d, 4f**).



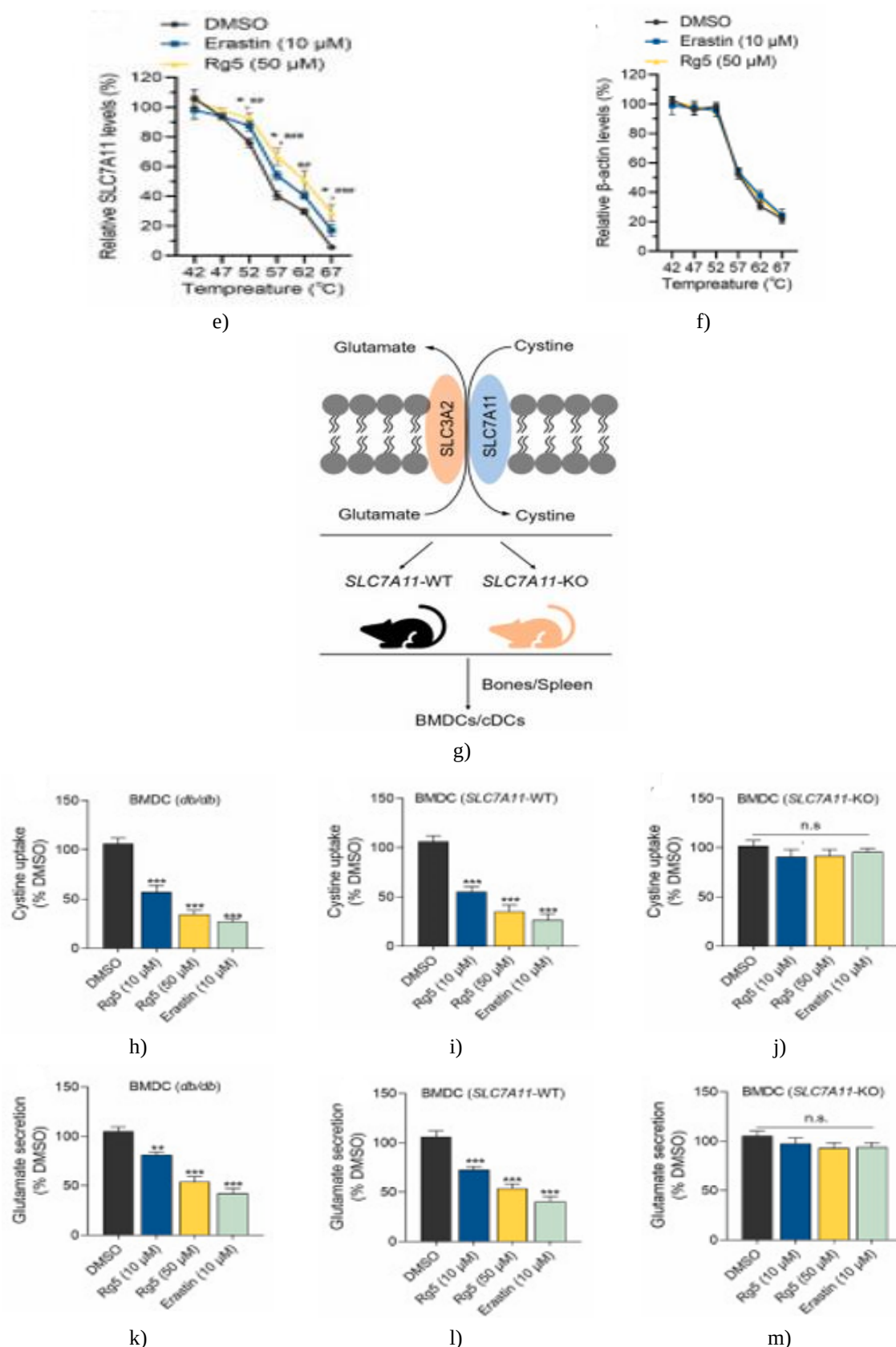


Figure 4. High-affinity interaction of ginsenoside Rg5 with SLC7A11 and resulting inhibition of cystine/glutamate exchange. (a–b) Computational prediction of ginsenoside Rg5 docking site within SLC7A11. Residue numbering follows the SLC7A11 sequence, with expanded view of contacts in panel B. (c) Binding parameters obtained by SPR for ginsenoside Rg5 against selected immobilized SLC family proteins (SLC7A11, SLC2A1, SLC7A5, SLC16A1). (d–f) CETSA immunoblots (d) and quantification (e–f)

using lysates from db/db BMDCs incubated with DMSO (1%), 50 μ M ginsenoside Rg5, or 10 μ M erastin. β -actin acted as negative control. *, comparison between DMSO and erastin; #, comparison between DMSO and ginsenoside Rg5. (g) Diagram illustrating SLC7A11 antiporter function and the mouse strains utilized. (h–m) Cystine uptake (h–j) and glutamate export (k–m) measured in BMDCs from db/db, SLC7A11-WT, and SLC7A11-KO mice after 2 h pretreatment with ginsenoside Rg5 (10 or 50 μ M) or erastin (10 μ M). Mean $\pm$ SD, n = 3. One-way ANOVA with Tukey's post hoc tests. *p < 0.05; *** and ###, p < 0.01; *** and ###, p < 0.001.

We then evaluated functional consequences by measuring cystine uptake and glutamate release in BMDCs from db/db, SLC7A11-KO, and SLC7A11-WT mice (**Figure 4g**). Ginsenoside Rg5, like erastin, attenuated both cystine influx and glutamate efflux in cells from db/db and SLC7A11-WT mice (**Figures 4h and 4i–4l**). Importantly, these effects were completely lost in SLC7A11-KO BMDCs (**Figures 4j and 4m**).

Promotion of dendritic cell efferocytosis by ginsenoside Rg5

Exposure to ginsenoside Rg5 markedly increased efferocytic activity in BMDCs isolated from SLC7A11-WT mice, matching the potency of erastin (**Figure 5a**). This improvement depended on intact actin cytoskeleton dynamics, as it was fully prevented by cytochalasin D (CytoD) (**Figure 5a**). BMDCs from SLC7A11-KO mice showed only marginal enhancement following ginsenoside Rg5 treatment (**Figure 5a**). To address possible discrepancies between cultured BMDCs and primary conventional dendritic cells (cDCs) arising from distinct transcriptional programs [40, 41], splenic cDCs were purified by cell sorting from SLC7A11-WT and SLC7A11-KO animals (**Figure 5b**). Ginsenoside Rg5 selectively augmented apoptotic cell uptake by cDC1s from SLC7A11-WT mice (**Figure 5c**), with no comparable effect on cDC2s (**Figures 5c and 5d**). A non-significant trend toward increased phagocytosis was noted in cDC1s from SLC7A11-KO mice after ginsenoside Rg5 exposure (**Figure 5c**).

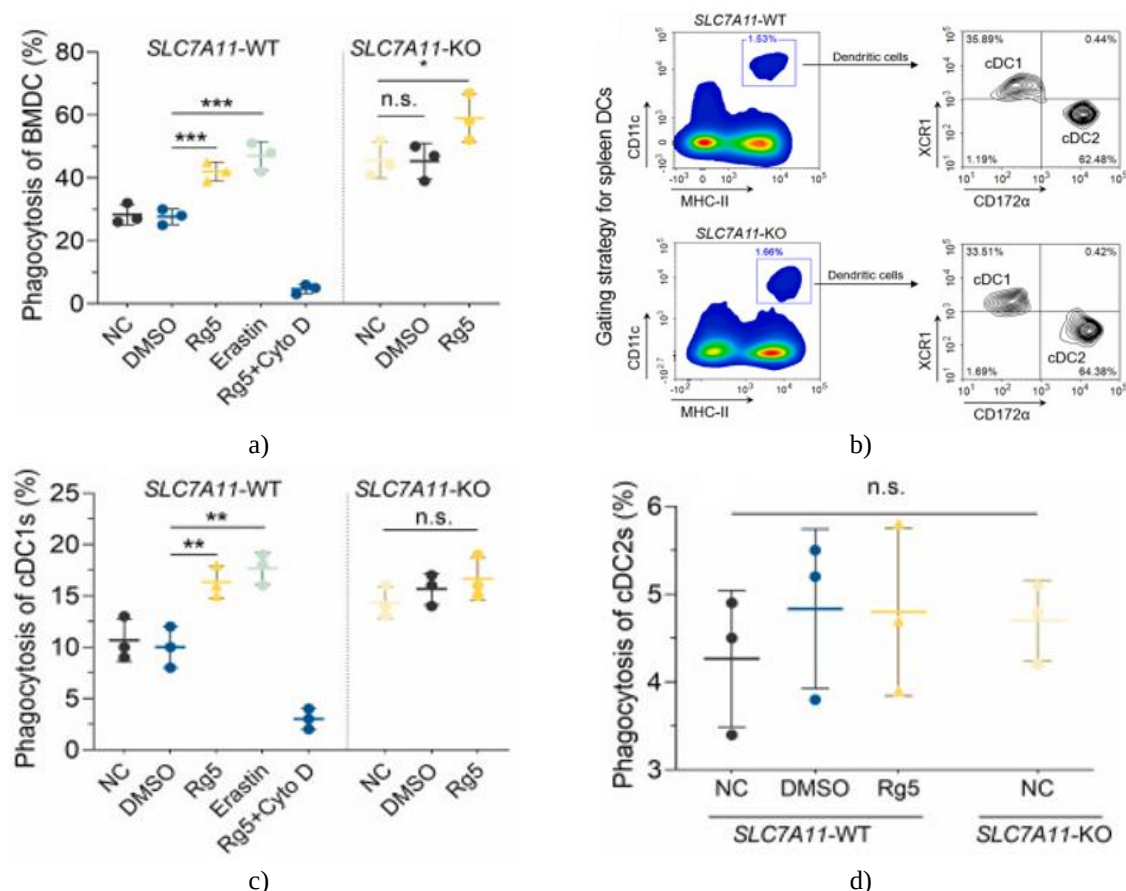
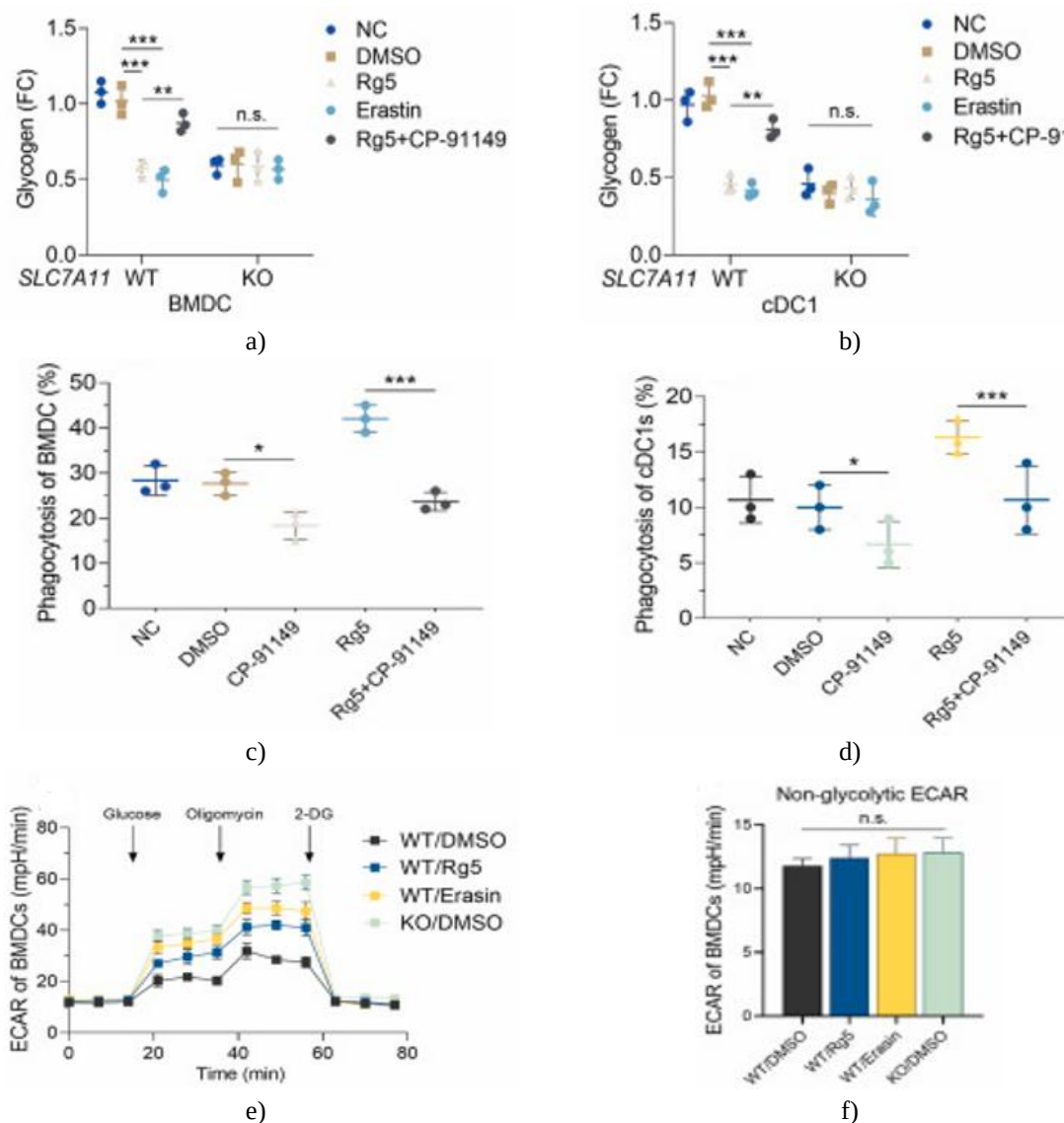


Figure 5. Promotion of dendritic cell efferocytosis by ginsenoside Rg5. (a) Efferocytosis by BMDCs from SLC7A11-KO or SLC7A11-WT mice following 50 μ M ginsenoside Rg5 treatment (2 h). Uptake was quantified using CypHer5E-labeled apoptotic Jurkat cells at a 1:5 ratio. Erastin was included as positive

control. (b) Flow cytometry gating used to isolate cDCs from spleens of 8-week-old SLC7A11-KO or SLC7A11-WT mice. (c–d) Phagocytic activity of sorted cDC1 (c) and cDC2 (d) subsets toward apoptotic and viable Jurkat cells after 4 h incubation, with or without prior exposure to ginsenoside Rg5 or erastin. Data from three biological replicates. One-way ANOVA with Tukey multiple comparison tests. *, $p < 0.01$; **, $p < 0.01$; ***, $p < 0.001$; n.s., not significant.

Ginsenoside Rg5 enhances dendritic cell efferocytosis by facilitating SLC7A11-dependent anaerobic glycolysis
Inhibition of SLC7A11 has been shown to promote dendritic cell efferocytosis through stimulation of glycogen breakdown [8]. Treatment with ginsenoside Rg5 lowered intracellular glycogen stores in both BMDCs and cDC1s isolated from SLC7A11-WT mice, whereas no such reduction occurred in cells from SLC7A11-KO animals (**Figures 6a and 6b**). Co-administration of the glycogen phosphorylase inhibitor CP-91149 prevented this glycogen depletion in ginsenoside Rg5-treated BMDCs and cDC1s (**Figures 6a and 6b**). Moreover, CP-91149 markedly attenuated the ginsenoside Rg5-induced increase in efferocytic activity (**Figures 6c and 6d**). These observations indicate that glycogenolysis triggered by ginsenoside Rg5 constitutes a primary mechanism underlying improved dendritic cell efferocytosis.



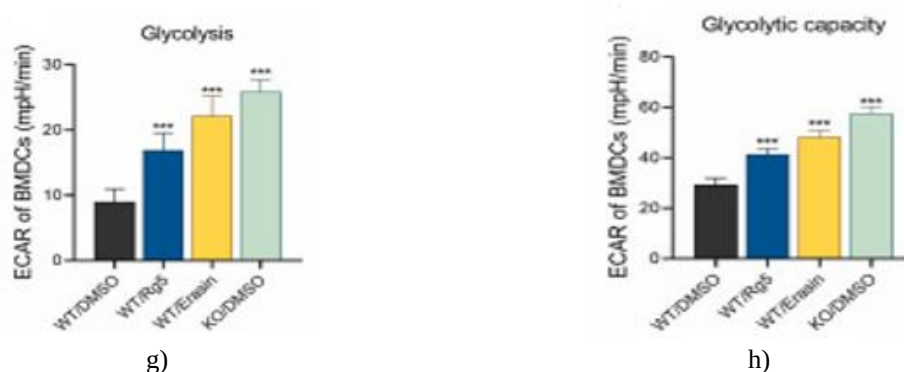


Figure 6. Ginsenoside Rg5 enhances dendritic cell efferocytosis by facilitating SLC7A11-dependent anaerobic glycolysis. (a–d) Intracellular glycogen content (a–b) and efferocytic activity (c–d) in BMDCs (a, c) or cDC1s (b, d) from SLC7A11-WT or SLC7A11-KO mice following treatment with DMSO, ginsenoside Rg5, erastin, or the combination of ginsenoside Rg5 and CP-91149. (e–h) Real-time ECAR measurements in BMDCs from SLC7A11-WT (WT) or SLC7A11-KO (KO) mice under the indicated treatments. Sequential additions of glucose, oligomycin, and 2-deoxyglucose (2-DG) were performed. Derived parameters included non-glycolytic ECAR (prior to glucose injection) (f), glycolytic rate (post-glucose increment above baseline) (g), and glycolytic capacity (peak ECAR following oligomycin) (h). Data are presented as mean $\pm$ SD ($n = 3$ per group). One-way ANOVA with Tukey multiple comparison tests was used to determine statistical significance. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; n.s., not significant.

To further confirm the impact of ginsenoside Rg5 on anaerobic glycolysis in dendritic cells, a glycolysis stress test was performed on BMDCs from SLC7A11-WT and SLC7A11-KO mice with or without ginsenoside Rg5 pretreatment using the Seahorse XFe96 Analyzer. Glucose, oligomycin, and 2-deoxyglucose (2-DG) were injected sequentially. Non-glycolytic ECAR (measured before glucose addition) remained comparable across all treatment groups (**Figures 6e and 6f**). Both ginsenoside Rg5 and erastin elevated basal glycolysis in SLC7A11-WT BMDCs (**Figures 6e and 6g**). In addition, cells from SLC7A11-WT mice treated with either compound displayed greater glycolytic capacity, as indicated by the maximum ECAR achieved after oligomycin-mediated inhibition of oxidative phosphorylation (**Figures 6e and 6h**).

Persistent, non-healing wounds represent a frequent and serious complication of diabetes, substantially elevating the likelihood of infection and tissue necrosis. Therapeutic options remain constrained, largely because the underlying disease mechanisms are incompletely understood [42]. Recent investigations have highlighted the importance of efficient efferocytosis in supporting timely wound repair [43, 44]. Impaired clearance of apoptotic cells by macrophages and dendritic cells within wounded skin leads to their accumulation and drives sustained inflammation [8, 9, 44]. In the present work, oral administration of ginsenoside Rg5 to db/db mice effectively reduced apoptotic cell numbers in wounds and accelerated cutaneous healing. Notably, 50 μ M ginsenoside Rg5 approximately doubled the efferocytic capacity of db/db-derived BMDCs. Collectively, these results indicate that ginsenoside Rg5 promotes wound closure at least partly by stimulating dendritic cell-mediated efferocytosis.

Ginsenoside Rg5 is recognized for its ability to attenuate NF- κ B p65 expression and activity across various cell types, including human keratinocytes and macrophages [14, 16, 17]. As NF- κ B p65 functions as a transcriptional activator of SLC7A11 [18, 19], and SLC7A11 itself restrains dendritic cell efferocytosis [8], this pathway is highly relevant. The current study verified that ginsenoside Rg5 dose-dependently lowered both NF- κ B p65 and SLC7A11 levels in db/db wounds. SLC7A11 expression can additionally be upregulated by nuclear factor erythroid-2-related factor 2 (NRF2) and phosphorylated signal transducer and activator of transcription 3 (p-STAT3) [45, 46]. Since ginsenoside Rg5 also inhibits NRF2 and STAT3 [47, 48], these actions likely contribute to the observed transcriptional repression of SLC7A11 in injured tissue.

Certain ginsenosides are capable of direct interaction with SLC family transporters, thereby modulating their activity. Examples include ginsenoside Rg3 binding to SLC2A1 [34] and ginsenoside Rd engaging SLC5A1 [38]. Here, integrated molecular docking, SPR, and CETSA approaches demonstrated that ginsenoside Rg5 physically associates with SLC7A11 in a configuration resembling that of erastin. Erastin is thought to occupy the extracellular region of SLC7A11, inducing structural shifts that block cystine transport [39]. Similarly, ginsenoside Rg5 is predicted to contact multiple critical residues involved in cystine uptake, such as F250, Y251,

L252, N253, and F336 [39]. Decreased cystine import coupled with increased glutamate release following SLC7A11 blockade promotes intracellular ROS accumulation, which in turn supports dendritic cell efferocytosis [8]. Ginsenoside Rg5 strongly inhibited cystine uptake and glutamate secretion in BMDCs from db/db and SLC7A11-WT mice, but not from SLC7A11-KO mice. These data support the conclusion that ginsenoside Rg5 binds SLC7A11 and impairs its antiporter function. Thus, the compound appears to enhance dendritic cell efferocytosis through dual mechanisms: transcriptional downregulation of SLC7A11 and direct inhibition of its cystine/glutamate exchange activity. Definitive confirmation of specific residue interactions will require targeted mutagenesis experiments.

Aerobic glycolysis is essential for initiating and sustaining efferocytosis [29]. Dendritic cells maintain substantial intracellular glycogen reserves. SLC7A11 inhibition augments anaerobic glycolysis, thereby providing metabolic fuel for efferocytosis [8]. In both BMDCs and cDC1s, ginsenoside Rg5 depleted glycogen stores and boosted anaerobic glycolysis. Pharmacologic blockade of glycogen phosphorylase with CP-91149 essentially eliminated the pro-efferocytic benefit of ginsenoside Rg5. These findings suggest that ginsenoside Rg5 relieves SLC7A11-mediated suppression of glycolysis, thereby promoting dendritic cell efferocytosis.

Although ginsenoside Rg5 also improved efferocytosis in db/db BMDMs (**Figure 2d**), additional SLC7A11-independent pathways may contribute to its overall wound-healing effects. The compound additionally reduced NF- κ B p65 accumulation. Prior evidence indicates that Sprouty2 (Spry2) inhibition can enhance macrophage efferocytosis partly by limiting NF- κ B p65 phosphorylation [49]. Glycogenolysis may not be the sole metabolic contributor. Beyond SLC7A11, SPR data identified SLC2A1 as another potential binding partner for ginsenoside Rg5. Efferocytosis activates a coordinated SLC transporter program that favors glucose uptake and aerobic glycolysis, driven by SLC2A1 and accompanied by downregulation of oxidative phosphorylation [29]. Hence, ginsenoside Rg5 may further support efferocytosis by modulating metabolic reprogramming. Elucidation of these additional mechanisms warrants further investigation.

Conclusion

In summary, ginsenoside Rg5 downregulates SLC7A11 expression and directly inhibits its transporter activity through physical interaction. These actions counteract the inhibitory influence of SLC7A11 on glycolysis, thereby supplying the necessary metabolic support for dendritic cell efferocytosis. Consequently, ginsenoside Rg5 represents a promising adjunctive therapeutic candidate for impaired wound healing conditions, such as diabetic foot ulcers.

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