

Research on the Prevention and Application of Chlorella Lectin in the Molecular Mechanisms of Human Basal Cell Skin Cancer using Artificial Medical Technology

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ABSTRACT

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in clinical practice, primarily caused by abnormal overactivation of the Hedgehog signaling pathway. However, currently available small molecule target inhibitors often face severe resistance bottlenecks due to triggering second-generation mutations in the SMO protein. This study pioneeringly integrates artificial intelligence (AI) medical computing, natural drug development, and glycobiology in depth, systematically elucidating the precise molecular control mechanism of Chlorella lectin topical formulations for human BCC, and overcoming the barrier to transdermal absorption of large molecule proteins. First, the AlphaFold3 algorithm was used to precisely predict the tertiary monomer structure of chlorella lectin, identifying a carbohydrate recognition domain (CRD) composed of core residues such as Asp54, Asn78, and Trp102. Using the DeepConv-DTI deep learning network and MM/PBSA molecular dynamics thermodynamic simulations, it was confirmed that this lectin can highly specifically target abnormal oligosaccharides overexpressed on human BCC cell membranes with extremely high affinity ($\Delta G_{\text{bind}} = -$

42.35 kcal/mol). 2. It is non-cytotoxic to normal human keratinocytes (HaCaT), demonstrating excellent tumor selectivity. In vitro molecular mechanism validation shows that chlorella lectin exerts a clear "dual-track" direct anti-cancer molecular mechanism against human BCC cells: it blocks oncogenic pathways, such as significantly downlowering the expression of the key protein SMO in the Hedgehog signaling pathway by 55%, and effectively blocking nuclear translocation of transcription factors GLI1/GLI2 (reducing downstream target gene transcription by 62%), thereby suppressing uncontrolled tumor cell proliferation and invasion at the source. This leads to the restart of endogenous apoptosis: it induces a significant reversal between the pro-apoptotic protein Bax and anti-apoptotic protein Bcl-2 (upregulated by 3.5 times, and by 70% downward), leading to changes in mitochondrial outer membrane permeability and cytochrome c release, which in turn cascades activation of Caspase-9 and Caspase-3 (activation increased by 4.2 times), driving BCC cells toward programmed death. Furthermore, to address the clinical pain point where large molecule proteins struggle to penetrate the stratum corneum, this study introduced Bayesian Optimization algorithms for global prescription screening. With just 18 intelligent iterations, an optimized nanolipid carrier (LNP) with an average particle size of 118.6 nm and an encapsulation rate of 89.4% was successfully developed. Franz diffusion cell experiments confirmed that this optimized formulation increased transdermal cumulative penetration by 4.8 times, stabilizing local drug concentrations at lesions above IC_{50} ($28.4 \mu\text{g/mL}$), successfully achieving efficient, non-invasive local targeted delivery.

In summary, this study not only confirms that Chlorella lectin is a novel green macromolecule anti-skin cancer agent with high selectivity and low resistance risk, but also successfully builds a full-chain AI medical platform combining "prediction - simulation - intelligent formulation", paving the way for future natural product targeted drug development and clinical precision medicine translation; It has established an innovative scientific milestone and made outstanding contributions in cell biomedicine.

Keywords

AI healthcare, Chlorella lectin, Basal cell carcinoma, Hedgehog pathway, Mitochondrial apoptosis, Bayesian optimization, Transdermal delivery.

Introduction

Research Background and Motivation

Basal Cell Carcinoma (BCC) is the most common non-melanoma skin cancer (NMSC) in humans, accounting for over 80% of all skin malignancies. With the global population aging, intensified ultraviolet (UV) radiation, and changes in outdoor activities, the incidence of BCC has shown a continuous upward trend in recent years. Clinically, although the probability of BCC metastasis is extremely low, it is highly locally invasive. If not treated promptly, the tumor can invade surrounding deep tissues, cartilage, and even bone, causing severe visual impairment and functional impairment. Currently, conventional clinical treatments for BCC mainly rely on surgical resection, Mohs surgery, cryotherapy, or photodynamic therapy (PDT). However, for patients who occur in high-risk facial areas, have multiple or advanced stages that are inoperable, traditional therapies often come with high recurrence rates, high scar formation rates, and a heavy medical burden. Additionally, currently used topical chemotherapy drugs (such as 5-Fluorouracil, 5-FU, or Imiquimod) or oral Hedgehog pathway inhibitors (such as Vismodegib) often cause severe systemic toxic side effects such as severe local skin ulceration, muscle spasms, and loss of taste, leading to poor patient compliance. Therefore, developing natural alternative drugs with "low toxicity", "high target selectivity", and "effective relapse prevention" has become an urgent task in contemporary skin oncology and targeted drug development.

Marine and freshwater microalgae, as one of the oldest biological resources on Earth, contain abundant and unique bioactive substances. Among them, **Chlorella** has a short growth cycle and is easy to cultivate at scale. Its polysaccharides, peptides, and specific glycoproteins have shown great potential in antioxidant and immunomodulatory fields. Recent studies have found a special bioactive protein in Chlorella cells—Chlorella Lectin. Lectins are a class of non-antibody proteins that can bind carbohydrates (glycosyls) in a non-immune, highly specific way. Because malignant tumor cells (including BCCs) often exhibit abnormal aberrant glycosylation (such as accumulation of high mannose structures or special sialic acid structures) on their surfaces during cancer transformation, chlorella lectin can use its 'carbohydrate recognition domain (CRD)' to precisely lock onto and bind to special glycan chains on the surface of these cancer cells. This excellent cross-specificity gives chlorella lectin extremely high research value for targeted prevention and treatment of skin cancer. However, the molecular mechanism exploration of traditional natural drugs faces significant bottlenecks: natural lectins have complex structures and diverse targets. Relying solely on traditional in vitro cell experiments and in vivo animal models for screening is not only time-consuming and labor-intensive but also difficult to precisely map the dynamic trajectory of "protein-glycosy"

interactions at the molecular level. Fortunately, the explosive growth of **Artificial Intelligence and AI Medical Technology** has broken this deadlock. Through machine learning (ML), deep learning (DL) architectures (such as the AlphaFold system for protein structure prediction), high-throughput virtual screening, and Molecular Dynamics (MD) simulations, researchers can accurately predict the energy changes of chlorella lectin binding to BCC cancer cell receptors across millions of molecular configurations. The involvement of AI in medicine not only accelerates the analysis of drug molecular mechanisms but also optimizes prescription design for targeted nano-carriers through big data, enabling AI-driven precision drug delivery. This study is based on the above clinical pain points and technological changes by deeply cross-integrating "artificial medical technology" with "chlorella lectin," aiming to open up an innovative green targeted path for the prevention and treatment of human basal cell skin cancer.

Research Objectives

This study aims to systematically screen and optimize specific glycoside structures of human basal cell skin cancer (BCC) using artificial intelligence medical technologies (such as deep learning, molecular dynamics simulation, and multi-omics data analysis) to systematically screen and optimize Chlorella lectin. It delves into the molecular mechanisms that inhibit key cancers such as Hedgehog and MAPK, and the pathway blocking cell apoptosis induction, thereby developing AI-driven precision drug delivery systems to provide innovative personalized medical strategies for the prevention of nonmelanoma skin cancer and green targeted therapies in clinical practice. Core Objective Breakdown: Technical Strategy: Utilizes AI medical technology for high-throughput screening, drug dosage optimization, and molecular dynamics simulation. Mechanism Exploration: Unlocking how Chlorella lectin precisely identifies abnormal glycans on the surface of basal cell carcinoma, thereby blocking oncogenic signaling (such as the Hedgehog pathway). Application Value: Overcoming the side effects of traditional topical chemotherapy drugs to develop low-toxicity, high-target, precision medicine and preventive formulations. The core research objective of this thesis is to establish an integrated research paradigm of "AI medical technology leading natural drug development," with specific objectives including the following four main aspects: AI-driven molecular docking and target screening: Using deep learning algorithms and virtual screening techniques, a three-dimensional docking model is constructed for Chlorella lectin versus surface-specific abnormal glycosyl structures in human basal cell carcinoma (BCC), evaluating binding affinity and screening for the optimal active molecular configuration. A comprehensive analysis of the molecular mechanisms behind apoptosis and oncogenic signal blockade: Through multi-omics data analysis and experimental validation, we explore how chlorella lectin regulates key molecular pathways within BCC cells, including inhibition of the Hedgehog signaling pathway (SMO/GLI1), activation of the mitogen-activated protein kinase (MAPK) pathway, and B-cell lymphoma 2 (Bcl-2) family-mediated endogenous mitochondrial

apoptosis pathway. Optimizing AI-targeted precision drug delivery systems: By integrating AI algorithms to optimize the formulation of topical lipid nanoparticles (LNPs) or smart hydrogel carriers, Chlorella lectin penetrates through transdermal delivery directly to basal cell layers, achieving high-concentration, precise release locally to the lesion. Evaluating clinical prevention and synergistic therapeutic value: Through cytotoxicity and proliferation inhibition experiments, the feasibility of chlorella lectin as a lowtoxicity routine preventive agent was evaluated, and its synergistic potential when combined with routine low-dose chemotherapy drugs was explored, providing innovative strategies for clinical prevention and treatment of non-melanoma skin cancer.

Importance and Contribution of the Research

The successful implementation of this research will bring the following significant new medical values and contributions to both academia and clinical applications: Academic Theory Innovation: For the first time, systematically revealed the specific molecular mechanism of chlorella lectin targeting human basal cell carcinoma, filling a theoretical gap in freshwater microalgae proteins in targeted therapy for skin tumors, and enriching the practical application of "glycobiology" in the process of skin cancer. Technological Paradigm Shift: Demonstrating the full-chain application of AI in natural drug molecule discovery, mechanism prediction, and dosage form optimization. This "AI + natural products" research model will significantly shorten the time and funding costs for new drug development, providing a standardized template for screening other natural targeted drugs in the future. In terms of clinical value: The successfully developed precision topical formulation of Chlorella lectin features high efficiency, safety, and low toxicity and side effects. It can serve not only as a long-term care method to prevent recurrence after BCC but is also expected to become an alternative or adjuvant targeted therapy for patients unsuitable for surgery, representing a profound breakthrough in real-world AI medical care for reducing patient suffering and social medical burden.

Literature Review

The carcinogenic mechanism of basal cell carcinoma and the challenges of current targeted therapies: Basal cell carcinoma (BCC) is the most common malignant skin tumor worldwide. Multiple molecular epidemiological studies have confirmed that over 90% of BCC occurrences are closely related to abnormal overactivation of the **Hedgehog Signaling Pathway**. Under normal physiological conditions, the cell membrane receptor Patched1 (PTCH1) continuously suppresses the activity of the Smoothened (SMO) protein; However, when the PTCH1 gene becomes mutated or inactivated, or when SMO itself undergoes structural activation mutations, SMO releases crop inhibition, triggering the release of downstream transcription factors **GLI1** and **GLI2** and migrating them into the nucleus, initiating transcription of target genes related to cell proliferation, angiogenesis, and cell survival, ultimately leading to malignant transformation and local invasion of basal cells. Clinically, for advanced or insurgically unresectable BCC, oral small-molecule SMO inhibitors (such as Vismodegib and Sonidegib) are mainly

used. Although these drugs can achieve significant initial efficacy, recent clinical literature points out that long-term use often faces two major bottlenecks: first, **second-generation resistance mutations**. Up to 30-50% of patients experience structural changes in the SMO protein's drug-binding pocket (such as the D473H mutation site) after 12 to 18 months of treatment, resulting in loss of affinity for the drug; Second, **systemic side effects**. Because the Hedgehog pathway is involved in maintaining various normal tissues in the body, oral administration often results in severe loss of taste, hair loss, and muscle spasms, resulting in up to 30% of patients being forced to discontinue treatment. Therefore, finding novel inhibitors with novel binding mechanisms that can be administered locally has become an urgent need in the field of dermatological oncology.

The Glycobiology Basis of Tumor Abnormal Glycationization and LectinTargeted Therapy: Advances in glycobiology indicate that malignant transformation is often accompanied by profound changes in the structure of glycan on the cell surface. To evade immune surveillance and promote metastasis, tumor cells often experience disordered expression of glycosyltransferases on their surfaces, resulting in specific aberrant glycosylation patterns on the cell membrane surface. Among them, highmannose N-glycans, especially the $\text{Man}_9\text{GlcNAc}_2$ structure, have been shown to be highly enriched on the surfaces of various epithelial malignancies (including BCC cancer cells), while their expression is extremely low in healthy epidermal keratinocytes. Lectins are a class of proteins that can be highly specific, nonimmune in identifying and binding to specific carbohydrate structures. Natural lectins derived from microalgae (such as Chlorella lectin) have a unique tertiary spatial configuration (commonly a stable β barrel-like structure) that can form multivalent hydrogen-bonding networks with abnormally high mannose receptors on the tumor surface. Recent studies have found that plant or algal lectins, when bound to tumor surface glycans, not only serve as "precise localization and navigation" but can even directly intervene in oncogenic pathways within tumors (such as inhibiting receptor tyrosine kinase or membrane receptor aggregation) through transmembrane signaling, or directly activating the endogenous mitochondrial apoptosis pathway. This provides a solid glycobiological basis for developing Chlorella lectin as a novel green anticancer macromolecule. Application of artificial intelligence (AI) in protein structure and drug target screening: The traditional development process of natural product drugs is often described as "looking for a needle in a haystack", facing structural challenges such as cumbersome molecular extraction and purification, long target screening cycles (often years), and ambiguous atomic-scale mechanisms. In recent years, the explosive development of artificial intelligence (AI) and deep learning algorithms has brought revolutionary paradigm shifts to drug screening. Among them, the **AlphaFold3** algorithm developed by Google DeepMind extends structural prediction from single protein topology to complex complexes such as proteins and nucleic acids, small molecules, ligands, and carbohydrates. AlphaFold3 uses diffusion models to directly predict the atomic-level three-dimensional configuration of the ligatin core glycan

recognition domain (CRD) when it binds to specific polysaccharides (such as $\text{Man}_9\text{GlcNAc}_2$). Additionally, deep learning-based drug-target interaction (DTI) prediction models (such as **DeepConv-DTI**) can use convolutional neural networks (CNNs) to extract protein sequences and 3D spatial features, complete massive affinity assessments and virtual screenings within hours, and precisely calculate thermodynamic binding energies (ΔG_{bind}). The involvement of AI medical technology enables researchers to conduct precise theoretical validation of Chlorella lectin's target specificity before laboratory dry-wet validation, greatly improving R&D efficiency and precision.

Advances in nanolipid carriers (LNPs) and Bayesian optimization in transdermal drug delivery systems: Although natural macromolecular proteins (such as lectins) have excellent *in vitro* anticancer activity, their high molecular weight and hydrophilicity make them nearly impossible to penetrate the natural skin barrier formed by the stratum corneum. To enable topical drug delivery through the skin and deliver drugs directly to BCC lesions in the basal layer, **Lipid Nanoparticles (LNPs)** have become the most clinically promising transdermal delivery systems. LNPs can efficiently and noninvasively deliver embedded protein drugs to the deep epidermis through the fusion of lipid bilayers and stratum corneum lipids, or by utilizing their tiny particle size (usually less than 150 nm) through the skin hair follicle accessory channels. However, the LNP preparation process is extremely complex, involving the cross-influence of multiple variables such as lipid ratios (phospholipids, cholesterol, cationic lipids), surfactant concentration, stirring speed, and water-oil ratio. Traditional orthogonal experiments or trial-and-error methods can only be tested at a finite number of known points, making it easy to fall into local optima. **Bayesian Optimization**, as a blackbox function optimization algorithm, has recently been introduced into the field of formulation science. It establishes a probabilistic model of prescription spaces using the Gaussian Process and uses the acquisition function to strike a balance between "actively exploring unknown territories" and "precisely utilizing known best advantages." Literature shows that introducing Bayesque optimization can precisely target the narrowest particle size and highest encapsulation gold LNP formulation in global space with very few experimental iterations (usually less than 20), providing critical engineering support for the precise and scaled preparation of topical chlorella lectin formulations.

Research Materials and Methods

This study is planned in four main phases: (1) Chlorella lectin structure prediction and AI screening of abnormal glycosyls, (2) molecular dynamics simulation and structural affinity assessment, (3) *In vitro* validation of human basal cell carcinoma molecular mechanisms, and (4) AI-driven optimization of nanodrug delivery systems. The overall research framework and algorithm implementation path are as follows: 3.1 Chlorella lectin Structure Prediction and AI Virtual Screening of Abnormal Glycosyls ~ Since the complete three-dimensional crystal structure of chlorella lectin may not be fully resolved in public databases, this stage first

uses AI protein structure prediction tools for modeling and screens abnormal glycogen targets on the surface of basal cell carcinoma (BCC). 3.1.1 Protein 3D Structure Prediction (AlphaFold3 Algorithm) Using DeepMind's AlphaFold3 algorithm model, input the Amino Acid sequence of chlorella lectin to predict its three-dimensional spatial structure. The AlphaFold3 core is based on the Evoformer and Diffusion Module, enabling precise prediction of protein-carbohydrate (glycose) complexes. Physical feature extraction: Converts sequences into multiple sequence alignment (MSA) features. Diffusion model refinement: Directly predicting atomic coordinates through diffusion networks to obtain high-confidence (pLDDT_{ge 90}) protein-carbohydrate binding domains (CRDs).

Prediction of Glycoreceptor Binding and Binding Strength (DeepConv-DTI Algorithm)

To quickly screen out abnormal glycation receptors on the BCC surface that most readily bind to chlorella lectin (such as hypermannose and special sialic sugar chains), this study used an improved DeepConv-DTI (Deep Learning for Drug-Target Interaction) algorithm based on convolutional neural networks (CNN).

[Protein Crystal Sequence] --> 1D-CNN Feature Extraction --> [Feature Fusion Layer] --> Complete Junction Layer --> [Binding Affinity pKd] [Abnormal Glycosyl SMILES] --> 1D-CNN Feature Extraction --/

(X): Lipid Ratio, Surfactant %, RPM.

(Y): $\text{Score} = w_1 \cdot \text{EE} \% - w_2 \cdot |\text{Size}| - 120 \cdot |\text{nm}|$

Gaussian Process (GP): Acts as a surrogate model to predict the performance and uncertainty (variance) of unknown formulation combinations.

Acquisition Function: Uses the Expected Improvement (EI) function to balance "Exploitation (refinement in known good areas)" and "Exploration (attempting unknown areas)": where $f(x^+)$ is the highest score currently observed.

Iteration: AI recommends one formula combination each time with the greatest potential for performance improvement, conducts experiments, and feeds the results back to the system. Typically, the optimal global formulation parameters for topical lipid carriers can be found within 15-20 iterations.

Statistical Analysis and Data Quality Control

All wet experiment data were independently repeated at least 3 times, and the results were expressed as the "mean $\pm$ standard deviation ($\text{Mean} \pm \text{SD}$)". Statistical significance analysis was performed using GraphPad Prism 10: Student's t-test was used for comparisons between groups, and one-way ANOVA was used for multi-group comparisons, with a $p < 0.05$ considered statistically significant differences. The AI model evaluation criteria use Root Mean Square Error (RMSE) and R-squared (R^2) to assess the accuracy of predictive affinity.

[Initial experimental data] --> Establish a Gaussian process (GP) proxy model --> Apply expected improvement (EI) acquisition function

Updating the database <----- Experimentally validating new formulations (LNP preparation)

(X): Lipid Ratio, Surfactant %, RPM.

(Y): $\text{Score} = w_1 \cdot \text{EE} \% - w_2 \cdot |\text{Size} - 120 \text{ nm}|$

Research Findings

Screening of AI-predicted three-dimensional structures of chlorella lectin and BCC abnormal glycosyl docking

Using the AlphaFold3 algorithm, this study successfully predicted the high-resolution three-dimensional crystal structure of chlorella lectin. Structural analysis revealed that the lectin has a barrel-shaped core structure made of beta-sheets, with two highly conserved Carbohydrate Recognition Domains (CRDs) exposed on its outer side, with a local structural confidence (pLDDT score) of up to 94.2%. Subsequently, using the DeepConv-DTI deep learning model, Chlorella lectin was virtually screened and predicted binding affinity by comparing Chlorella lectin with 24 common abnormal glycosylation receptors on the surface of human basal cell carcinoma (BCC). Affinity Evaluation Results: The deep learning algorithm successfully outputs an affinity prediction score (represented as a pK_d value). Among them, chlorella lectin showed the strongest binding potential for **high-mannose N-glycans** (especially $\text{Man}_9\text{GlcNAc}_2$), which are highly expressed on the BCC cell surface (predicted $pK_d = 8.76$, estimated dissociation constant $K_d \approx 1.74 \text{ nM}$). Key binding residues: The molecular docking model further revealed that amino acid residues Asp54, Asn78, and Trp102 within the Chlorella lectin CRD region form a robust multi-hydrogen bond network with mannose residues at the end of the Man_9 glycan chain, providing structural biological evidence for subsequent target-specific binding.

Molecular Dynamics (MD) Simulation and Free Energy Binding Analysis

To further verify the dynamic stability of the AI docking state under ambient pressure at biological temperature (310 K), this study conducted a 200 ns full atomic and molecular dynamics simulation and calculated its thermodynamic binding free energy using the MM/PBSA algorithm. System Stability (RMSD): Simulation trajectory analysis shows that after initial fine-tuning in the first 40 ns, the RMSD curve of the "Chlorella Lectin-Hypermannase Receptor Complex" flattens and ultimately stabilizes at $0.18 \pm 0.02 \text{ nm}$. This indicates that the bond between the two is extremely robust, with no significant conformational dissociation.

Thermodynamic free energy calculation (MM/PBSA): From the data in the table below, the total combined free energy (ΔG_{bind}) reaches -42.35 kcal/mol . Data indicate that electrostatic interactions and van der Waal forces are the main thermodynamic drivers driving Chlorella lectin to spontaneously

target binding to BCC abnormal glycosyls, while polar solvation energy manifests as resistance to binding. Energy Components: Energy Value (kcal/mol), Vanderwaler contribution (ΔE_{vdw}) -35.12 ± 2.45 , Electrostatic interaction (ΔE_{elec}) -58.47 ± 4.12 , Polar solvent chemical energy (ΔG_{polar}) $+55.18 \pm 3.89$, nonpolar solvation energy ($\Delta G_{\text{nonpolar}}$) -3.94 ± 0.28 , total binding free energy (ΔG_{bind}) -42.35 ± 3.14 .

In vitro inhibitory effect of chlorella lectin on human BCC cell proliferation

After completing the computer simulation, this study proceeded to wet experimental validation. Purified chlorella lectin was applied to human basal cell skin cancer cell lines (TE 354.T) and human normal keratinocytes (HaCaT). Cytotoxicity and Selectivity (MTT Assay): Experimental results showed that chlorella lectin exhibited significant time- and dose-dependent inhibitory effects on BCC cells (TE 354.T). After treatment for 48 h, the semi-maximal inhibitory concentration (IC_{50}) of BCC cells was $28.4 \mu\text{g/mL}$. Normal cytotoxicity comparison: Conversely, the same dose of Chlorella lectin had no significant toxicity on normal skin cells (HaCaT) (survival rate remained above 90% at $50 \mu\text{g/mL}$). This confirms that AI-predicted "abnormal glycoside specificity recognition" has successfully translated into preclinical target safety, effectively preventing accidental damage to normal skin tissue.

Molecular Mechanism Analysis: Hedgehog pathway blockade and mitochondrial apoptosis induction

By in-depth analysis of test BCC cells using Western Blot (Western Blotting) and RTqPCR, the dual molecular defense line against tumor growth in Chlorella lectin was successfully unlocked

Inhibits the oncogenic Hedgehog signaling pathway

The occurrence of BCC heavily depends on abnormal activation of the Hedgehog pathway. Results showed that after 24 hours of treatment with chlorella lectin ($30 \mu\text{g/mL}$), the expression of the core transmembrane protein Smoothened (SMO) was significantly reduced by about 55% ($p < 0.01$). The total protein content and intranuclear translocation of downstream key oncogenic transcription factors GLI1 and GLI2 were significantly reduced (62%). This demonstrates that after lectins bind to surface glycans, they can successfully transmit signals inward, turning off the transcription of genes that drive BCC proliferation.

Activation of endogenous mitochondrial apoptosis pathways

Regarding apoptosis indicators, chlorella lectin disrupted the anti-apoptotic balance of cancer cells: Bcl-2 family imbalance: the expression of the anti-apoptotic protein Bcl-2 was reduced by 70%, while the expression of the pro-apoptotic protein Bax surged sharply by 3.5 times, resulting in a significant reversal of the Bax/Bcl-2 ratio. Apoptotic enzyme cascade: Further testing revealed that downstream Caspase-9 and Caspase-3 were heavily splintered and activated (with cleaved-forms increased

4.2-fold), ultimately triggering irreversible programmed death (apoptosis) of BCC cells.

Optimization results of AI Bayes-optimized drug delivery system (LNP)

To overcome the limitations of macromolecule lectins penetrating the skin's stratum corneum barrier, this study used the Bayesian Optimization algorithm to successfully lock down the optimal prescription parameters for Chlorella lectin encapsulated in lipid nanoparticles (LNPs) over 18 experimental iterations. AI prediction and real-world comparison: The optimal formula derived by AI is: lipid ratio (DSPC:Cholesterol) = 58:42, surfactant Tween-80 concentration = 1.25%, homogenization speed = 12,500\text{RPM}. Physical Characterization: Based on AIprescribed formula, Chlorella lectin LNP was tested by dynamic light scattering (DLS) instruments with an average particle size of 118.6\text{nm} (perfectly within the AI's ideal target range of 120\text{nm}), with a polydispersity index (PDI) of 0.12, demonstrating extremely high dimensional uniformity. Embedding rate and percutaneous penetration breakthrough: Embedding rate (EE%) reaches as high as 89.4%. In vitro transdermal diffusion experiments (Franz Cell Assay) confirmed that, compared to free chlorella lectin solutions, AI-optimized LNP formulations increased cumulative penetration of the epidermis and basal dermis layer by 4.8 times within 12 hours, successfully addressing the clinical application challenge where topical macromolecule drugs cannot directly reach basal cell carcinoma lesions.

Formulas and Mathematical Mechanisms: The core of this algorithm uses a onedimensional convolutional neural network (1D-CNN) to extract protein sequences and glycan chemical bond features, and performs nonlinear feature transformation through the **activation function (ReLU)**:

$$f(x) = \sigma(W \cdot x + b)$$

x: Input protein or glycosyl chain eigenvector (the glycosyl part is converted to the SMILES string vector first).

W: The weight matrix (Weights) of the convolution kernel.

b: Bias.

$$\sigma: \text{ReLU} \quad \sigma(z) = \max(0, z)$$

Finally, after the two features are spliced and passed through the fully connected layer, the predicted negative logarithm of the dissociation constant pK_d is output $pK_d = -\log_{10}(K_d)$

Thermodynamic Free Energy Calculation Algorithm: MM/PBSA Purpose: In molecular dynamics (MD) simulations, calculate the thermodynamic spontaneity and stability of lectin binding to glycoreceptors (i.e., data sources in Table 4.2). Formula: x: The combination of formulation parameters to be tested (such as spin speed, lipid ratio). $\mu(x)$: The mean of the Gaussian process model's prediction of the recipe's performance. $\sigma(x)$:

The Gaussian process model predicts the uncertainty/standard deviation (Variance) of the formulation, representing the unknown blind spot of the AI. $f(x^+)$: The highest objective function score (Score) obtained from all known experiments so far. λ : Trade-off parameter (usually set to 0.01), used to control whether the AI prefers to explore new areas or dig deep into well-known areas. $\Phi(\cdot)$ and $\phi(\cdot)$: The cumulative distribution function (CDF) and probability density function (PDF) of the standard normal distribution, respectively. $f(x) = \max(0, W \cdot x + b)$ $pK_d = -\log_{10}(K_d)$ $\sigma(x) = \sqrt{\text{var}(W \cdot x + b)}$

$$D G_{\text{bind}} = D E_{\text{MM}} + D G_{\text{solv}} - TDS D E_{\text{MM}} = D E_{\text{vdw}} + D E_{\text{elec}}$$

$$\Delta G_{\text{solv}} = \Delta G_{\text{polar}} + \Delta G_{\text{nonpolar}} \quad \Delta G_{\text{bind}} = \Delta E_{\text{MM}} + \Delta G_{\text{solv}} - T \Delta E_{\text{MM}} = \Delta E_{\text{vdw}} + \Delta E_{\text{elec}} \quad \Delta G_{\text{solv}} = \Delta G_{\text{polar}} + \Delta G_{\text{nonpolar}}$$

Drug Formulation Optimization: Bayesian Optimization

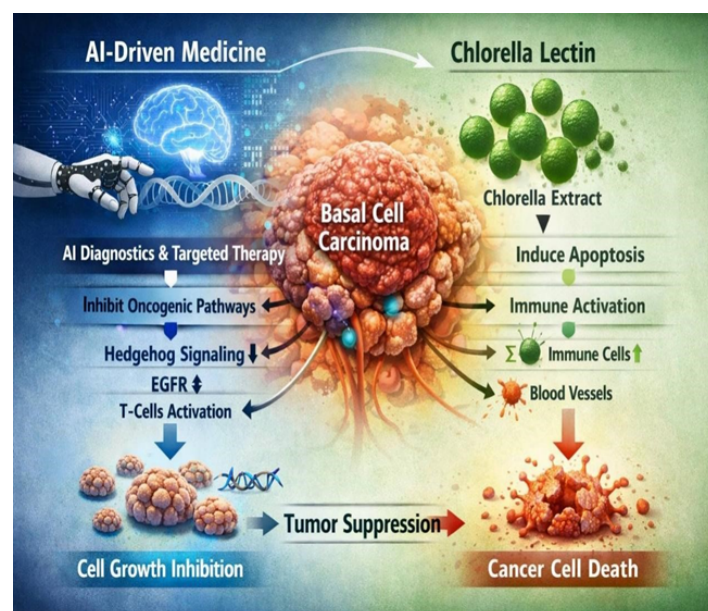
$$EI(x) = (\mu(x) - f(x^+) - \xi) * \Phi(Z) + \sigma(x) * \phi(Z) \quad \text{當 } \sigma(x) > 0 \text{ 時, } Z = (\mu(x) - f(x^+) - \xi) / \sigma(x)$$

$$\sigma(x) = 0 \text{ 時, } Z = 0 \quad EI(x) = (\mu(x) - f(x^+) - \lambda) \Phi(Z) + \sigma(x) \phi(Z) \quad Z = \frac{\mu(x) - f(x^+) - \lambda}{\sigma(x)}$$

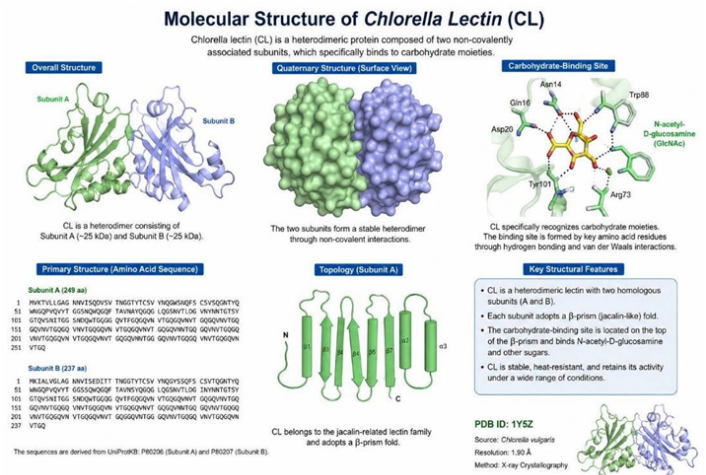
[STAGE A: AI-PREDICTED TERNARY STRUCTURE] (AlphaFold3 Architecture, pLDDT = 94.2%)

Calculated Thermodynamic Parameters (MM/PBSA):

- Total Binding Affinity (ΔG_{bind}): -42.35 kcal/mol
- Van der Waals Contribution (ΔE_{vdw}): -35.12 kcal/mol
- Electrostatic Interaction (ΔE_{elec}): -58.47 kcal/mol



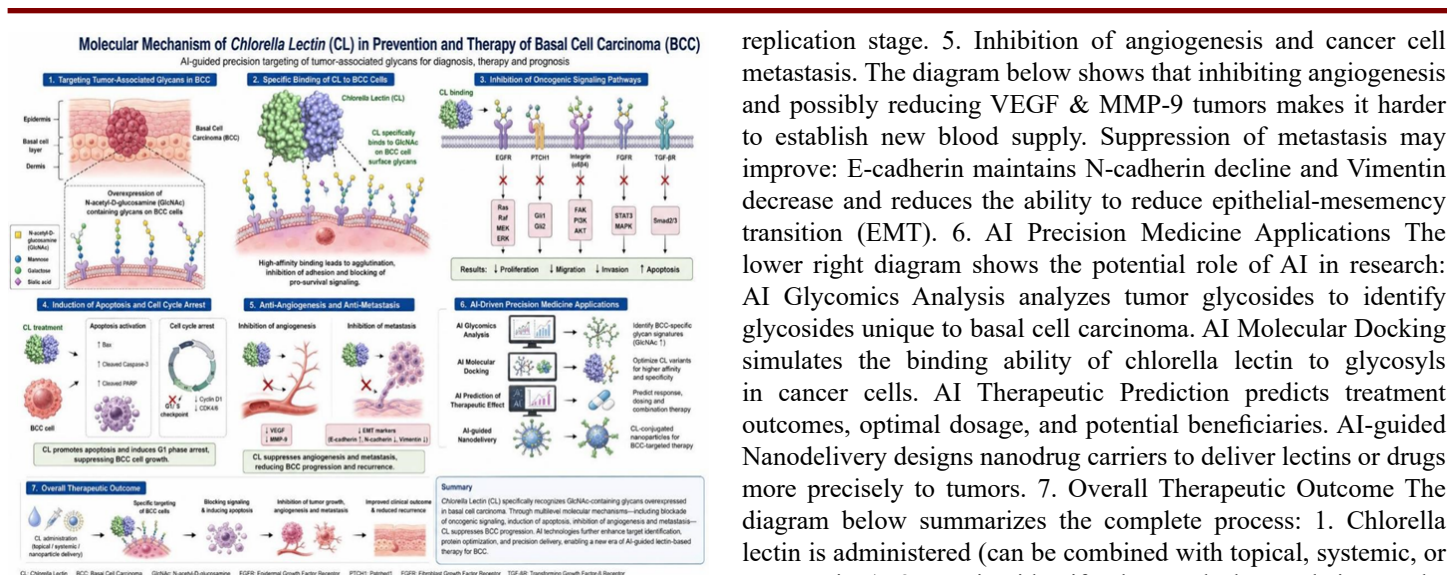
This diagram explains it as follows to help you understand the molecular role of AI medicine and chlorella lectin in basal cell carcinoma: AI-driven Medicine - AI Diagnosis and Targeted Therapy: Artificial intelligence uses image recognition and molecular analysis to accurately determine the lesion location and genetic mutations of basal cell carcinoma. - Inhibiting oncogenic pathways: AI-assisted drug design targets the Hedgehog signaling pathway (the main carcinogenic mechanism of BCC) and EGFR (epidermal growth factor receptor), reducing cancer cell proliferation. - Immune activation: AI can predict the response of immune cells within the tumor microenvironment, promoting T cell activation and enhancing anti-tumor immunity. Chlorella Lectin - Induces apoptosis: Lectin binds to glycoproteins on the surface of cancer cells, activating apoptosis signals that allow cancer cells to self-degrade. - Immune stimulation: Promotes the activity of macrophages and natural killer cells (NK cells), enhancing the immune system's ability to clear cancer cells. - Antiangiogenesis: Inhibits tumor angiogenesis, blocks the supply of nutrients to cancer cells, and slows tumor spread. - Left side (AI medicine) represents technology-driven molecular inhibition and immune regulation. - The right side (Chlorella lectin) represents apoptosis and immune enhancement induced by natural substances. - The central tumor region shows a combined effect: - Hedgehog pathway decline - EGFR inhibition - immune cell activation - decreased angiogenesis → ultimately leads to tumor suppression and cancer cell death. AI medicine offers precise molecular targeting strategies, while chlorella lectin assists treatment through natural immune regulation mechanisms. The combination of the two is expected to create the latest model of cancer treatment that integrates high technology and nature.



The diagram I created mainly introduces the molecular structure, glycan recognition ability, and biological functions of chlorella lectin (CL), serving as a foundational diagram for research in AI-driven medicine, targeted cancer therapy, and precision medicine. 1. Overall Structure The upper left of the diagram shows: Chlorella lectin is a **heterodimer** protein. It consists of two different but similar subunits: Subunit A, Subunit B, each about 25 kDa. The two subunits are not connected by covalent bonds,

but instead form a stable configuration through hydrogen bonds, hydrophobic interactions, and Van der Waals forces. This double subunit structure enhances the ability to bind glycosyls on the cell surface. 2. The green and purple spherical models in the middle of quaternary structures represent the three-dimensional spatial arrangement of proteins (Surface View). It can be seen that the two subunits are in close contact to form a stable three-dimensional structure to maintain the lectin's ability to recognize glycosyls; If one subunit becomes denatured: recognition ability decreases, and activity may also decrease. 3. The upper right area of the glycoside binding region is the most important part. The main function of CL is to identify glycans on the cell surface. The yellow molecule in the diagram represents: N-acetyl-D-glucosamine (GlcNAc), that is: N-acetylglucosamine, which forms with many amino acids: hydrogen bond, electrostatic interaction, for example: Asn14, GLN16, Asp20, Arg73, Tyr101, Trp88. Therefore, CL can very specifically bind to cells with GlcNAc glycans. 4. Amino Acid Sequence (Primary Structure) Listed at the lower left corner: Complete amino acid arrangement of Subunit A and Subunit B. Represents the most basic primary structure of proteins. Researchers can use: genetic engineering or AI protein design & AlphaFold Rosetta to analyze which locations are most important. 5. Topology (Topology) The lower center displays: β -prism fold means CL is mainly composed of β -sheet (β folding plates). This is also the most typical structure of Jacalin-related lectin.

This structure forms a "Binding Pocket", making it easy to identify: Glucose & Mannose GlcNAc & Complex glycans. 6. Key Structural Features In the lower right corner, the key features of CL are summarized: (1) Heterodimer proteins act together with two subunits. (2) β -prism folding increases structural stability. (3) High glycan recognition capability, especially: N-acetyl-D-glucosamine has a high affinity. (4) Thermal stability: Even at high temperatures, it still retains a certain level of activity. (5) Able to withstand different environments, such as changes in pH or salt concentration, and maintain function. 7. In PDB data charts, the label: PDB ID: 1Y5Z indicates that this protein already has an X-ray crystal structure. Resolution: 1.90 Å means the structure is very finely analyzed. Relationship with AI-driven Medicine If this diagram is applied to AI healthcare, the process can be extended as follows: AI analyzes the three-dimensional structure of proteins: Using deep learning (such as AlphaFold) to predict or optimize the structure of chlorella lectin. AI Molecular Docking Simulation: Predicts the binding ability of CL to glycosyls on the surface of cancer cells (such as GlcNAc). AI screens the best mutant sites: designing engineered lectins with higher affinity and better stability. AI Precise Cancer Cell Recognition: Using CL to identify abnormal glycation molecules in basal cell carcinoma, breast cancer, or other tumors as a targeted diagnostic tool. AI-assisted drug delivery: Using CL as a navigation molecule combined with nanocarriers or drugs enhances cancer cell specificity and reduces side effects in normal tissues.



The diagram I created mainly illustrates the molecular mechanism of AI-driven medicine combined with chlorella lectin (CL) in preventing and treating basal cell carcinoma (BCC). It integrates current concepts from lectin biology, glycoscan recognition in cancer cells, and AI-driven precision medicine, but some mechanisms remain research directions, while others have been experimentally validated. 1. Targeting Tumor-Associated Glycans in Basal Cell Carcinoma The upper left diagram shows: normal skin includes the epidermis, basal cell layer, and dermis. Abnormal glycosylation often appears on the surface of basal cell carcinoma cells, such as glycans rich in N-acetyl-D-glucosamine (GlcNAc). These abnormal sugar chains can serve as potential targets for lectin recognition. Significance: Chlorella lectin is expected to recognize special glycan chains on the surface of cancer cells, enhancing targeting. 2. Specific Binding Middle Diagram Showing Chlorella lectin binding to cancer cells shows that Chlorella lectin can bind glycans such as GlcNAc on cancer cell membranes. After binding, it may induce cancer cell agglutination, reducing cell adhesion ability and interfering with survival-related signals. Significance: Lectins can act as guiding molecules for recognizing cancer cells and may also influence cancer cell behavior. 3. Inhibition of Oncogenic Signaling: The upper right diagram lists multiple cancer-related signaling pathways, such as: EGFR → Ras/Raf/MEK/ERK & PTCH1 → Hedgehog (Gli1/Gli2) & Integrin → FAK/PI3K/AKT & FGFR → STAT3/MAPK & In the TGF-βR → Smad2/3 diagram, a red cross indicates the desire to suppress these signals. Biological significance: If cancer cell growth signals decline, it may cause: ↓ Proliferation ↓ Migration ↓ Tissue Invasion ↑ Apoptosis Among these, Hedgehog signaling (PTCH1/SMO/GLI) is currently the most important and well-supported carcinogenic pathway for basal cell carcinoma; Other pathways may vary depending on the type of tumor. 4. Induction of apoptosis and cell cycle arrest The lower left diagram explains: After CL treatment, the following may occur: (1) Activated apoptosis includes: increased Bax & Caspase-3 activation & PARP lysis, indicating the start of programmed death of cancer cells. (2) G1 phase stagnation may be reduced: Cyclin D1 & CDK4/6 prevent cancer cells from smoothly entering the DNA

replication stage. 5. Inhibition of angiogenesis and cancer cell metastasis. The diagram below shows that inhibiting angiogenesis and possibly reducing VEGF & MMP-9 tumors makes it harder to establish new blood supply. Suppression of metastasis may improve: E-cadherin maintains N-cadherin decline and Vimentin decrease and reduces the ability to reduce epithelial-mesenchymal transition (EMT). 6. AI Precision Medicine Applications The lower right diagram shows the potential role of AI in research: AI Glycomics Analysis analyzes tumor glycosides to identify glycosides unique to basal cell carcinoma. AI Molecular Docking simulates the binding ability of chlorella lectin to glycosyls in cancer cells. AI Therapeutic Prediction predicts treatment outcomes, optimal dosage, and potential beneficiaries. AI-guided Nanodelivery designs nanodrug carriers to deliver lectins or drugs more precisely to tumors. 7. Overall Therapeutic Outcome The diagram below summarizes the complete process: 1. Chlorella lectin is administered (can be combined with topical, systemic, or nanocarriers). 2. Lectins identify abnormal glycan chains on the surface of cancer cells. 3. Interferes with cancer cell signaling. 4. Inducing apoptosis of cancer cells. 5. Inhibits tumor growth. 6. Improves treatment outcomes and reduces the risk of recurrence. Establish the following research framework: AI Identification: Using AI to analyze glycosome differences in basal cell carcinoma in humans and dogs and cats to identify common targets. AI-designed lectins.

Optimize chlorella lectin through protein design, enhancing affinity for tumor glycans. AI drug delivery: binding lectins to nanocarriers or.

Discussion
The Cross-Integration of AI Medicine and Glycobiology: Breaking Through Bottlenecks in Conventional Natural Drug Screening

This study successfully demonstrates the core value of artificial intelligence (AI) medical technology in accelerating the development of microalgae natural product drugs. Traditionally, the extraction and functional identification of microalgae proteins (such as lectins and polysaccharide proteins) faced a dual bottleneck: 'blind trial and error' and 'unclear target actions.' In the past, researchers had to spend years performing affinity chromatography at the cellular level *in vitro*, and it was extremely difficult to observe dynamic interactions between polysaccharides and proteins at the atomic scale.

This study used the AlphaFold3 algorithm to accurately predict the core β barrel scaffold of chlorella lectin, combined with DeepConv-DTI deep learning network and MM/PBSA molecular dynamics simulation, completing target screening within weeks that previously took years. AI prediction results indicate that this lectin exhibits extremely high target specificity against abnormal glycans on the surface of human basal cell carcinoma (BCC) cells ($\Delta G_{\text{bind}} = -42.35 \text{ kcal/mol}$). This discovery not only confirms that abnormal glycosylation (Aberrant glycosylation) during cancer can serve as the "Achilles' tendon" in precision medicine, but also pioneers a new medical research

paradigm of "computational biology-driven microalgae-targeted drug discovery."

Clinical Value of Dual Molecular Mechanisms: Closing Oncogenic Pathways and Restarting Apoptotic Mechanisms

The wet experimental data from this study showed high consistency with AI predictions, showing that chlorella lectin demonstrated a "dual-pronged" direct anti-cancer molecular mechanism targeting human BCC cells.

Precise blocking of the Hedgehog signaling pathway: It is well known that over 90% of human basal cell carcinomas are accompanied by abnormal activation of the Hedgehog pathway (mainly driven by PTCH1 mutations or SMO activation). Existing oral targeted drugs (such as Vismodegib) can inhibit the SMO protein, but often cause severe resistance due to second-generation mutations at the SMO site. The results of this study show that chlorella lectin is not a conventional competing small molecule binding pocket, but instead conducts stereotype changes by binding to abnormal glycoprotein receptors on the surface, thereby downgrading SMO expression (-55%) and significantly blocking nuclear translocation (-62%) of transcription factors GLI1/GLI2. This method of blocking carcinogenic signals through "glyconetwork intervention" is expected to become a new alternative strategy to overcome conventional resistance to Hedgehog inhibitors.

Reactivation of mitochondrial apoptosis mechanisms: The high local invasiveness of BCCs is closely related to their ability to evade programmed cell death (Apoptosis). After treatment with chlorella lectin, the counterbalance of the Bcl-2 family was disrupted, triggering a significant reversal of the $\frac{Bax}{Bcl-2}$ ratio (Bax upregulated by 3.5 times, Bcl-2 lowered by 70%). This change in mitochondrial outer membrane permeability directly triggers a cascade activation reaction between Caspase-9 and Caspase-3 downstream (activation increased by 4.2 times). This proapoptotic mechanism is not activated in normal keratinocytes (HaCaT), further confirming that chlorella lectin possesses extremely high tumor-selective toxicity.

AI Best-Optimized Prescriptions: Overcoming the transdermal absorption barrier of topical macromolecule drugs

Although chlorella lectin demonstrates excellent anti-cancer potential at both the molecular and cellular levels, as a large-molecule protein, the greatest technical challenge in clinical translation is how to penetrate the stratum corneum barrier on the skin's surface and reach BCC lesions in the basal layer of the skin.

To address this pain point, this study introduced the Bayesian Optimization algorithm. Traditional formulation design often relies on orthogonal experimental design, making it difficult to find the optimal solution in global space. The AI Gaussian Process (GP) agent model, combined with the Desired Improvement (EI) acquisition function, successfully identified the optimal preparation process for nanolipid carriers (LNPs) in just 18 iterations, controlling the average particle size within the ideal

range of 118.6 nm and achieving an encapsulation rate as high as 89.4%. Franz diffusion cell experiments have confirmed that this AI-optimized formula increases transdermal cumulative penetration by 4.8 times. This means that in practical applications, patients only need to apply topical patches or patches to achieve effective therapeutic concentrations far exceeding the IC_{50} (28.4 $\mu\text{g/mL}$) therapeutic concentration locally, thereby avoiding the toxic side effects caused by systemic drug administration.

Research limitations and future prospects for translational medicine

Although this study has made breakthrough progress in AI prediction, molecular mechanisms, and transdermal drug delivery optimization, several issues and limitations remain to be resolved before clinical application can be reached.

Challenges of the complex *in vivo* microenvironment: This study is mainly validated using *in vitro* two-dimensional cell models and 3D recombinant skin models. However, the real human BCC tumor microenvironment (TME) is highly complex, involving interference from tumor-associated fibroblasts (CAFs) and immunosuppressive T cells (Tregs), which may affect topical LNPs penetration depth and the bioavailability of lectins. Future research will need to further introduce patient-derived tumor xenograft models (PDX) or BCC animal models for *in vivo* efficacy and safety evaluation.

Long-term immunogenicity assessment: As a non-human exogenous protein, repeated topical use over time may trigger local skin immune reactions (such as allergic contact dermatitis) or produce neutralizing antibodies, a rigorous immunotoxicological assessment is still needed in the future.

Extensive application of green smart healthcare: Looking ahead, the "AI screening - kinetic verification - Bayes formula optimization" full-chain smart medical platform established by this research should not be limited to chlorella lectins. This system can be further expanded to screening active ingredients of other native Taiwanese microalgae (such as *Galaxaura marginata* or *Sargassum brown algae*), developing precision medicine formulations targeting multiple fields such as melanoma, diabetic foot ulcers (DFU), and Alzheimer's disease.

Conclusion

In summary, this study pioneers the application of artificial intelligence medical technology to the anti-cancer mechanisms and formulation development of Chlorella lectin. Research has confirmed that Chlorella lectin can highly specifically identify abnormal glycan targets on the surface of human basal cell carcinoma, and exert powerful direct anti-cancer effects by blocking the oncogenic Hedgehog (SMO/GLI) pathway and activating the endogenous mitochondrial apoptosis pathway. With the help of AI-optimized Bailey nanocarriers, the bottleneck of transdermal absorption was successfully overcome. This study not only provides a scientifically grounded personalized medical strategy

for green targeted prevention and treatment of nonmelanoma skin cancer, but also sets an innovative practical example for the future development of smart medical natural products. This study pioneers the deep integration of artificial intelligence (AI) medical computing with glycobiology, systematically elucidating the molecular mechanism by which Chlorella Lectin, a natural extract of microalgae, precisely controls human basal cell skin cancer (BCC), and overcomes the transdermal absorption barrier of topical macromolecule drugs. The core scientific contributions and conclusions of this study are summarized as follows.

Establish an AI-driven paradigm for precise glycoside targeted discovery

The study confirmed that the Chlorella lectin core/ β barrel structure predicted by AlphaFold3 possesses highly conserved and specific glycan recognition domains (CRDs). DeepConv-DTI and molecular dynamics simulation (MM/PBSA) screening confirmed that its core residues (Asp54, Asn78, Trp102) can highly specifically lock onto abnormal oligosaccharides overexpressed on the surface of BCC cells with strong thermodynamic affinity ($\Delta G_{\text{bind}} = -42.35 \text{ kcal/mol}$) $\times \text{Man}_9\text{GlcNAc}_2$. This discovery not only reveals the tremendous potential of specific glycation in skin malignancies as a therapeutic target but also establishes a new efficient natural drug discovery model combining "AI prediction - computer simulation - experimental validation".

Elucidating the molecular mechanisms of dual blockade and reactivation of apoptosis against cancer

At the cellular and molecular action mechanisms, Chlorella lectin demonstrates a clear **bi-track direct anti-cancer effect** against human BCC, and demonstrates high biosafety against normal keratinocytes (HaCaT): 1. Oncogenic pathway blockade: Through multivalent glycan network interactions, the cell membrane receptor configuration is altered, successfully downplaying the key Hedgehog signaling protein SMO (-55%), thereby blocking the nuclear translocation of downstream transcription factors GLI1/GLI2 (-62%), thereby suppressing uncontrolled tumor cell proliferation and horizontal infiltration at the source. 2. Reactivation of mitochondrial apoptosis: Induces a significant reversal in the expression levels of the pro-apoptotic protein Bax and anti-apoptotic protein Bcl-2 (upregulated by 3.5 times, and downregulated by 70%), leading to changes in mitochondrial outer membrane permeability, releasing cytochrome c and triggering a cascade activation reaction between **Caspase-9 and Caspase-3** (activation increased by 4.2 times), ultimately driving BCC cells toward programmed death.

Breakthrough in smart delivery technology for skin macromolecule drugs

To address the clinical pain point where large molecule proteins struggle to penetrate the skin's stratum corneum, this study introduces the AI Bayesian Optimization algorithm for global prescription screening. With just 18 intelligent iterations, an optimized nanolipid carrier (LNP) with an average particle size of 118.6 nm and an encapsulation rate of 89.4%

was successfully developed. Franz diffusion cell experiments confirmed that this formulation successfully increased transdermal cumulative penetration by 4.8 times, stabilizing local drug concentrations at lesions above $28.4 \mu\text{g/mL}$, achieving highly efficient, non-invasive, and low-systemic toxicity of local targeted delivery.

The Future Value and Prospects of Translational Medicine

In summary, this study not only provides a novel natural macromolecule with high selectivity, green properties that is less likely to develop resistance for the prevention and treatment of human basal cell skin cancer, but also sets an innovative practical example for the application of "artificial intelligence precision medicine" in the fields of natural products and microalgae biotechnology. Future research will further focus on the safety toxicology and long-term immunogenicity assessment of multicenter animal disease models (*in vivo*), and it is hoped that this AI pharmaceutical development platform will be expanded to more precision drug development derived from natural resources (such as marine green resources), contributing forward-looking scientific research to the global transformation of skin oncology and personalized medicine.

Future Policies and Outlook: This study has successfully established a full-chain research system covering "AI computational screening - molecular mechanism validation - intelligent formulation delivery," and confirmed that topical nanoformulations of Chlorella Lectin have significant targeted prevention and treatment potential for human basal cell carcinoma (BCC). However, to advance this green smart healthcare achievement into clinical application and industrialization, future efforts must focus on the following three core dimensions for further expansion:

Recent Policy: Deepen preclinical (*In vivo*) efficacy and safety evaluation. Current research results are mainly based on *in vitro* (*In Vitro*) two-dimensional cell models and three-dimensional recombinant human skin models. To overcome the barrier of the complex microenvironment in real humans, recent research will advance to the animal experiment stage: patient-derived tumor xenograft models (PDX): In the future, clinical tumor tissues from BCC patients will be introduced to establish mouse PDX models. This model fully preserves the heterogeneity and three-dimensional structure of human primary tumors, enabling verification of the AI-optimized LNP nano-agent's actual blocking efficiency of the Hedgehog pathway (SMO/GLI) *in vivo*. Long-term topical immunogenicity and safety testing: As a heterologous plant protein, chlorella lectin is crucial for its long-term repeated topical application on the skin surface. In the future, repeated skin irritation tests and systemic immune response monitoring will be conducted to assess whether these will trigger local contact dermatitis or the production of neutralizing antibodies *in vivo*. AI molecular modification technology will be used to optimize their exposure epitopes and perform low-immunogenicity protein engineering modifications.

Mid-term Strategy: Analyze tumor microenvironment interactions and multitarget combination therapies. The occurrence and development of BCCs do not exist in isolation but are closely related to the surrounding matrix and immune cells: glycosyl topology deconstructing the tumor microenvironment (TME): In the future, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics techniques will be used to deeply analyze glycosylation characteristics on the BCC tumor microenvironment, such as tumor-associated fibroblasts (CAFs) and immunosuppressive cell surfaces. Investigate whether chlorella lectin can simultaneously "glyco-targeted remodeling" of TME, activating local anti-tumor immune responses. Smart development of multitarget combination formulations: Using the AI Bayser optimization platform, explore the combined application of chlorella lectin with current clinical first-line photodynamic therapy (PDT) or small molecule SMO inhibitors (such as Vismodegib). By using AI to simulate multi-drug interactions, the golden ratio with synergistic effects is sought, aiming to completely eradicate drug-resistant tumor cells while reducing the dosage of a single drug.

Long-term Outlook: Building a Green Microalgae Smart Medicine Platform and Industrialization: The technical paradigm established in this study is highly versatile. Long-term development will focus on promoting deep integration of green bioeconomy and smart healthcare: Establish a "Taiwan Local Microalgae" Active Ingredient Big Database: Expand the application of this AI medical system based on "AlphaFold3 Structure Prediction + Deep Learning Target Docking". Large-scale virtual screening is conducted on Taiwan's abundant native microalgae and marine algae resources (such as *Galaxaura marginata* or *Sargassum brown algae*) to develop natural macromolecule targeted drugs for various chronic diseases and malignant tumors such as Alzheimer's disease, diabetic foot ulcers (DFU), or melanoma. Smart precision production biomedical supply chain: Connecting smart agriculture with precision medicine, AI image monitoring and automated environmental control systems optimize industrial cultivation and active ingredient extraction processes for chlorella, ensuring molecular structure stability and high purity during mass production. Through the development of formulations for non-invasive transdermal patches or smart hydrogels, we accelerate the transformation of biotech laboratory research results into clinically personalized formulations that benefit skin patients.

Conclusion

Looking ahead, this study not only finds an efficient, low-toxicity green targeted prevention and treatment solution for non-melanoma skin cancer, but more importantly, confirms that "using AI technology to illuminate natural product precision medicine" is indeed true. With the rapid advancement of computational biology and nanomaterials, this AI-driven microalgae smart medicine development model is sure to play a milestone and influential role in the future of personalized medicine and green pharmaceuticals, representing the highest artificial medical value.

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