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A *Passiflora edulis* Fruit Extract with an Increase in Vitamin D3 Level in Skin Epidermis: In Silico and In Vitro Research

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Abstract

Vitamin D3 deficiency is a common concern in dermatology and aging, yet its topical supplementation is restricted in the EU, and direct precursors are unstable. Stimulating the skin's endogenous vitamin D3 biosynthesis using phytochemicals represents a promising alternative. This research reveals the potential of a natural *Passiflora edulis* (passion fruit) extract to stimulate vitamin D3 synthesis in the skin epidermis. An in silico screening of phytochemicals using molecular docking and Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) analysis was performed to identify compounds with affinity for the vitamin D receptor (VDR) and lathosterol oxidase, a key enzyme in the vitamin D3 biosynthesis pathway. While several flavonoids showed high predicted vitamin D receptor affinity, genistein, which has been reported to occur in *P. edulis* fruit extracts, exhibited favorable docking scores and was predicted to interact with the active site of lathosterol oxidase. Subsequent in vitro experiments on HaCaT keratinocytes and an ex vivo human skin model demonstrated that the *P. edulis* extract significantly increased vitamin D3 amount, both under UVB irradiation and, notably, in its absence. The *P. edulis* extract significantly increased vitamin D3 level in HaCaT keratinocytes by up to 274.04% without UVB exposure and demonstrated a synergistic effect with UVB, enhancing production by a further 61.41% compared to UVB alone ($p < 0.001$). In the ex vivo model, the extract alone increased vitamin D3 levels by 153.31%, and its combination with UVB resulted in a 54.82% higher yield compared to the UVB control ($p < 0.01$). These findings highlight the promising potential of *P. edulis* fruit extract as a natural cosmeceutical ingredient for enhancing cutaneous vitamin D3 synthesis, offering a novel approach to supporting skin health through dermatocosmetics.

Keywords: vitamin D3; skin health; Passiflora edulis extract; lathosterol oxidase; vitamin D receptor; UVB stimulation

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1. Introduction

Vitamin D3 is a fat-soluble vitamin that is involved in many important biological processes in the body, including regulating calcium metabolism and bone mineralization [1]. In addition, vitamin D3 has anti-inflammatory and immunomodulatory properties [2] along with its role in cancer prevention [3,4]. 1,25-dihydroxyvitamin D, the active form of vitamin D, plays a key role in the skin, regulating keratinocyte growth and differentiation,

contributing to epidermal barrier formation, controlling the hair follicle growth cycle, and suppressing oncogenic signaling pathways [5].

Vitamin D3 enters the body through food or is synthesized in the skin from 7-dehydrocholesterol (7-DHC) under the UVB rays of sunlight (290–315 nm) [6]. Ultraviolet irradiation of 7-DHC promotes photochemical cleavage of the steroid B-ring between C9 and C10 atoms, resulting in the formation of provitamin D3. It undergoes further molecular isomerization and chemical transformation into natural vitamin D3 (cholecalciferol), an inactive form that immediately enters the bloodstream for further modification by the liver and kidney systems [7]. In the liver, vitamin D3 undergoes hydroxylation at the C25 position under the action of D-25-hydroxylase, resulting in the formation of 25-hydroxyvitamin D3 (calcidol), which is a precursor to the active form [8]. The subsequent activation step occurs in the proximal tubular cells of the nephron, where 25-hydroxyvitamin D-1α-hydroxylase acts to form 1,25-dihydroxyvitamin D (1,25(OH)2D3, also known as calcitriol), the most active form of vitamin D3 [9]. This active form is responsible for most of the biological effects of vitamin D3 in the body, which are mediated by its binding to vitamin D receptors (VDR). These receptors belong to the family of nuclear receptors and are expressed in many cells, including osteoblasts, immune cells, dermal fibroblasts and keratinocytes of skin and other tissues [10,11].

Although vitamin D3 is found in a wide range of animal and plant products, the primary source of vitamin D3 in the body is its synthesis in the skin under the influence of UVB radiation [12]. The efficiency of vitamin D3 production in skin depends on many factors including season, time of day, age, skin tone related to the melanin level, area of open body surface, use of sunscreens, latitude (the higher is latitude, the longer is distance passed by ultraviolet rays to the Earth surface, the greater is absorption by ozone layer) [13,14]. It is known that some mammals and birds can synthesize vitamin D without sunlight, but humans absolutely need long-term UVB exposure to produce a sufficient amount of vitamin D3 for the whole body [15,16]. Because of this, vitamin D3 deficiency is observed in almost half of the world's population, especially in Nordic regions that are far from the equator and have limited sunny days in the year [17]. Low vitamin D levels not only have a negative systemic effect on the body, but can influence dermatological diseases as an aggravating factor in atopic dermatitis and psoriasis, since its deficiency negatively affects the barrier function of the skin and weakens the local immune response to any pathogens [18,19].

This issue could be addressed using cosmetic products designed to supplement vitamin D3 or to stimulate its local production in the skin. Vitamin D3 itself cannot be used in EU cosmetic products because it is considered a medicinal product with clear pharmacological activity when taken in its active form (No. 335 in Annex II of Regulation (EC) No. 1223/2009) [20,21]. When cosmetic products are applied topically to the skin, it is impossible to control the vitamin D3 concentrations consumed, which poses a risk of uncontrolled absorption, overdose, and systemic effects, including hormonal effects on the body [22,23]. However, vitamin D3 precursors, such as 7-DHC, are approved for addition in beauty products according to the actual EU regulation [24]. 7-DHC is a direct precursor that is converted into provitamin D3 under UVB radiation (Figure 1) [25]. High susceptibility to light and oxygen degradation makes 7-DHC very unstable in cosmeceutical formulations. When exposed to light outside the skin, 7-DHC easily converts into inactive compounds such as pyrocalciferol and lumisterol, rather than its precursor vitamin D3 [26]. Lathosterol, the second immediate precursor of vitamin D, appears to be a more stable compound and may therefore be used in cosmetic formulations [27].

The use of natural vitamin precursors in cosmetics, which can be converted by the skin into their active vitamin forms to support natural biosynthesis processes, is a fairly popular

approach [28]. Instead of adding chemically synthesized substances, preference is often given to their natural enhancers, mainly of plant origin [28–30]. Various phytochemicals have been shown to affect vitamin D3 receptors and metabolism [31–34]. Furthermore, many of these compounds, particularly flavonoids, are known for their anti-inflammatory, antioxidant, and immunomodulatory properties, which potentially allow them to synergistically enhance the vitamin D3-mediated beneficial effects [35–38]. Due to their complex composition, flavonoid-rich natural extracts may comprehensively support vitamin D3 activity in the skin, addressing its functions through multiple complementary pathways. Moreover, vitamin D3 and its hydroxylated derivatives, such as 1a,25$(OH)_2$-vitamin D3, are found in plants of the *Solanaceae*, *Cucurbitaceae*, *Fabaceae*, and *Poaceae* families [39]. 7-DHC is also found in many *Solanaceae* and serves as a direct precursor for cholesterol biosynthesis [40].

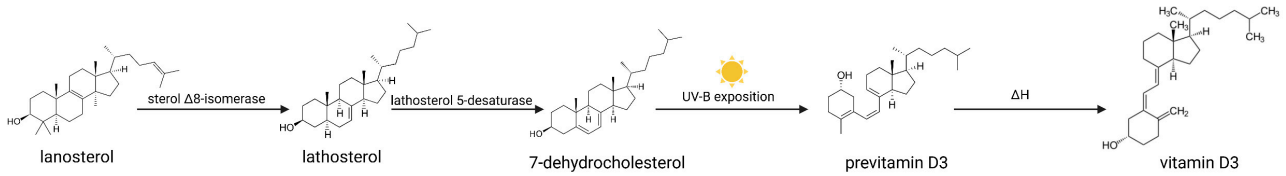


Figure 1. Vitamin D3 precursors and skin enzymes are responsible for their biochemical modifications.

The study was designed as a sequential investigation. First, an exploratory in silico screening was performed on a diverse set of fifteen phytochemicals commonly found in cosmetic botanicals and reported to possess bioactivity relevant to skin health or vitamin D biology. The objective of this initial step was to identify promising molecular candidates capable of interacting with key targets in the vitamin D3 biosynthesis pathway—VDR and the enzyme lathosterol-5-desaturase, which catalyzes a rate-limiting step in the 7-dehydrocholesterol biosynthesis pathway. Based on this screening, genistein emerged as a high-affinity hit for both targets, guiding our selection of *P. edulis* as a botanical source reported to contain this phytochemical.

Moreover, passion fruit (*Passiflora edulis*) is known to contain numerous bioactive compounds with antioxidant and anti-inflammatory properties [41]. Recent studies suggest the components of *P. edulis* may have significant potential for cosmetic applications [42]. For example, passion fruit seed extract is used in concealers as a sun-protecting agent [43]. It is also reported that the polyphenol and flavonoid compounds found in passion fruit peel, due to their antioxidant properties, can be used in anti-aging cosmetics [44].

However, the potential of *P. edulis* phytocomplex to modulate cutaneous vitamin D3 metabolism has not been systematically investigated. To experimentally validate these in silico findings and explore the underexamined potential of this botanical, the non-cytotoxic concentrations of a standardized *P. edulis* extract were determined, and its biological activity was validated using in vitro models (HaCaT keratinocytes) and an ex vivo human skin explant system to quantify its effect on vitamin D3 level, both independently and in combination with UVB irradiation.

2. Materials and Methods

2.1. In Silico Screening of Passiflora edulis Phytochemicals with Responsible Targets in Vitamin D3 Synthesis

The protein structure of VDR (PDB ID: 4ITF) was retrieved in PDB format from the Protein Data Bank (PDB), and the lathosterol-oxidase structure was obtained from AlphaFold v.2 [45]. The crystal structures of proteins were utilized to generate three-dimensional models for molecular docking studies. Prior to docking, each protein structure was preprocessed by removing crystallographic water molecules, eliminating redundant

polypeptide chains, and adding polar hydrogens and partial atomic charges. The resulting models were saved in PDB format for subsequent in silico analyses.

Molecular docking simulations were performed using DiffDock v.1.1.3 [46], with ursolic acid, caffeic acid, chlorogenic acid, ellagic acid, apigenin, epigallocatechin-3-gallate, ferulic acid, gallic acid, genistein, kaempferol, luteolin, naringenin, quercetin, resveratrol and rosmarinic acid detected in *Passiflora edulis* fruits as ligands [47–53]. To validate the docking protocol, the native co-crystallized ligand of each protein was redocked, yielding a root mean square deviation (RMSD) of less than 2.0 Å, confirming the reliability of the methodology. During docking, the ligand was treated as fully flexible, while the protein receptor was held rigid.

For the prediction of active pocket in VDR and lathosterol-oxidase, PasserRank v.1was utilized [54]. Binding affinities were subsequently estimated using GNINA 1.0 v.1.3.2 [55]. All computational analyses were carried out on a workstation equipped with an Intel Core i7-12700U CPU (2.3 GHz), an NVIDIA RTX 4090 GPU, 64 GB of RAM, and a 64-bit Windows 11 operating system. Structural comparisons among the selected compounds were performed based on Tanimoto similarity coefficients calculated relative to the target molecules. Molecular fingerprints were generated using the RDKit cheminformatics toolkit [56], specifically employing Morgan (circular) fingerprints with a radius of 2 and 2048 bits. The Tanimoto coefficient, defined as the ratio of the number of bits set in both fingerprints to the number of bits set in either fingerprint, was used as a quantitative measure of structural similarity.

2.2. Performing Molecular Dynamics and MM/PBSA Analysis

The highest-scoring docking poses of genistein were further refined through molecular dynamics (MD) simulations using GROMACS v.2023.1 [57] with MPI support. Each protein–ligand complex was set up for MD simulation employing the CHARMM36 force field [58] for the protein and CGenFF parameters [59] for the ligand. The systems were embedded in a cubic solvent box filled with TIP3P water molecules [60], ensuring a minimum padding of 1.0 nm between the protein surface and the box edges. System neutrality was achieved by introducing counterions.

Initial geometry optimization was carried out via the steepest descent algorithm, followed by equilibration in the NVT ensemble (100 ps) and then in the NPT ensemble (100 ps). A production MD trajectory was generated for 20 ns under NPT conditions at 298.15 K and 1 bar, with temperature and pressure regulated by the Nosé–Hoover thermostat [61] and the Parrinello–Rahman barostat [62], respectively. Coordinates were recorded every 10 ps for downstream analyses.

Binding free energies were estimated using the MM/PBSA approach [63] as implemented in gmx_MMPBSA v.1.6.4 [64]. The calculation was based on the final 10 ns of each production trajectory, sampling frames at 100 ps intervals. The Poisson–Boltzmann (PB) implicit solvation model was used with a grid spacing of 0.5 Å and an ionic strength of 0.1 M [65].

2.3. Substances and Materials

Passiflora edulis (passion fruit) extract (INCI: Aqua, Glycerin, *Passiflora edulis* (passion fruit) extract, Citric acid, Potassium sorbate, Sodium benzoate) containing 40% of extractive phytochemicals was obtained from GRUMANT LLC (Veliky Novgorod, Russian Federation). This extract has a pH of 4.0–6.0, a refractive index of 1.3200–1.4400, a faint characteristic odor and a yellowish color.

2.4. Evaluation of Cytotoxicity of Passiflora edulis Fruit Extract

HaCaT keratinocyte cells were seeded in 75 cm^2 flasks (Corning, Glendale, CA, USA), cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 5% fetal

bovine serum, and maintained at 37 °C in a humidified atmosphere containing 5% CO_2. After reaching confluence, cells were harvested and seeded into 96-well plates (Corning, Glendale, CA, USA) at a density of 1×10^4 cells/well for the cytotoxicity assay, and into 6-well plates at a density of 2×10^5 cells/well for the bioactivity assay and subsequent quantification of vitamin D3.

Cell viability was determined by a colorimetric method using MTT dye [3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyltetrazolium; Sigma, St. Lous, MO, USA] [66]. For the assay, the product was prepared in culture medium with 3% Tween 20 (Sigma, St. Lous, MO, USA) and added to the 96-well plate at a serial dilution in the range of 100.00 to 0.003 mg/mL using the dilution factor of 3.16. The human keratinocytes culture was incubated for a period of 48 h. MTT was then added to the culture at a concentration of 5 mg/mL (30 µL/well) and incubated for an additional 4 h. The contents of the well were removed, and 100 µL of isopropanol was added for the purpose of solubilizing the formazan crystals formed by viable cells. The absorbance of each well was determined at 570 nm in a Multiskan GO monochromator (Thermo Fisher Scientific, Vantaa, Finland). Cell viability was expressed as a percentage and calculated according to the equation:

$$Cell\ viability,\ \% = \frac{OD_{PA}}{OD_{NC}} \times 100\%$$

where OD_{PA}—absorbance of cells incubated with the sample, OD_{NC}—control absorbance.

2.5. In Vitro Evaluation of Vitamin D3 Synthesis in Human Keratinocyte Culture

HaCaT keratinocytes were incubated with standardized *P. edulis* fruit extract at three non-cytotoxic concentrations selected based on the cytotoxicity assay (Section 3.2) of 10.01, 3.17 and 1.00 mg/mL, representing the highest concentration maintaining cell viability and two subsequent serial dilutions (≈3.16-fold) to assess a potential dose–response relationship, at 37 °C for 72 h. Some keratinocyte cultures were also exposed to 50 mJ/cm^2 of UVB radiation [67], using a Handisol UVB irradiation device (National Biological Corporation, Twinsburg, OH, USA), to compare irradiated and non-irradiated cultures treated with the extract. Cells were maintained in contact with the test sample for 72 h. Then, the supernatant was collected for quantification of the synthesized vitamin D3. Vitamin D3 levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, Houston, TX, USA, Cat. No. E-EL-0014) according to the manufacturer's instructions. Absorbance was measured at 450 nm using a Multiskan GO microplate reader (Thermo Fisher Scientific).

2.6. Ex Vivo Evaluation of Vitamin D3 Synthesis in Human Skin Explants

After the surgical procedure, skin anatomical pieces originating from one healthy subject, a 36-year-old female, phototype (Fitzpatrick) II, were collected in plastic vials containing 0.9% saline and kept in refrigeration for up to 24 h. Ethics committee approval for the research project with the use of ex vivo samples was granted by Universidade São Francisco-SP Ethics Committee (Opinion number: 5.503.565 of 1 July 2022).

Skin fragments of approximately 1.5 cm^2 were carefully weighed and incubated in Dulbecco's modified Eagle's medium containing 4.5 g/L glucose (Thermo Fisher Scientific Inc., Waltham, MA, USA), supplemented with 10% fetal bovine serum (Thermo Fisher) and 1% penicillin/streptomycin/amphotericin (Lonza Walkerville Inc., Salisbury, MD, USA) to maintain viability. Each fragment was then treated with 1% of the liquid *P. edulis* extract, applied at a concentration of 20–30 mg/cm^2 [68].

Immediately after *P. edulis* extract product application, the treated fragments were exposed to UVB radiation at a dose of 350 mJ/cm^2 [69] using the Handisol device (National

Biological Corporation, Twinsburg, OH, USA). Each UVB exposure lasted approximately 15 min to deliver the target dose of 350 mJ/cm^2. This procedure was conducted to evaluate the effects of *P. edulis* extract by comparing irradiated and non-irradiated fragments subjected to the same treatment. The treatment and UVB exposure cycle were performed once daily for three consecutive days, resulting in a cumulative UVB dose of 1050 mJ/cm^2 over the experimental period.

Concentrations of vitamin D3 were measured in the supernatant by ELISA, according to the protocol on the datasheet provided by the supplier, using a commercially available kit (Elabscience). The 450 nm absorbance was read in the Multiskan GO monochromator (Thermo Fisher Scientific).

2.7. Synergy Analysis Using the Bliss Independence Model

To evaluate whether the combination of UVB irradiation and the *P. edulis* extract acted synergistically, the interaction was quantified using the Bliss independence model, which is appropriate when the mechanisms of the combined agents are unknown or assumed to be independent.

The response of each treatment condition (R) was first normalized to the basal control:

$$E = \frac{R - R_{basal}}{R_{basal}}$$

For two treatments A (*P. edulis*) and B (UVB), the Bliss-expected combined effect was calculated as:

$$E_{AB}^{Bliss} = E_A + E_B - E_A E_B$$

Synergy was defined as the difference between the observed combination effect and the Bliss-expected value:

$$Synergy = E_{observed} - E_{AB}^{Bliss}$$

Positive values indicate synergistic interaction.

2.8. Statistical Analysis

Statistical analyses were performed using GraphPad Prism software (version 8.4.3, GraphPad Software, San Diego, CA, USA). All experiments were conducted in at least three independent replicates, and data are presented as mean ± standard deviation (SD). Comparisons among multiple groups were performed using one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test. For comparisons between irradiated and non-irradiated conditions, an unpaired Student's *t*-test was applied when appropriate. Differences were considered statistically significant when $p < 0.05$.

3. Results and Discussion

3.1. Molecular Screening of Passiflora edulis Phytochemicals with Vitamin D3 Molecular Targets

Various phytochemicals are widely used in dermatocosmetics, and many of them show potential for modulating vitamin D3 metabolism, in particular through interaction with VDR [34,70–72]. To test this hypothesis, the affinity of fifteen plant-derived compounds, selected based on literature reports of their biological activity, relevance to skin physiology, and potential involvement in vitamin D-related pathways, was assessed toward VDR using molecular docking. The in silico analysis indicated that several of these compounds are predicted to interact with the receptor (Table 1).

A separate task was searching for phytochemicals capable of directly influencing vitamin D3 biosynthesis in the skin. The enzyme lathosterol oxidase (lathosterol-5-desaturase), which catalyzes one of the key stages in the biosynthetic pathway of lathosterol conversion

to vitamin D3, was selected as the key target for further in vitro research [73]. Among all the ligands tested, only genistein showed significant binding to the active site of this enzyme (Table 2).

Table 1. Predicted affinity of selected phytochemicals to the VDR.

Phytochemicals in *Passiflora edulis* Fruits	Reference	Affinity, kal/mol	Diffdock Score of Top-1 Position
Caffeic acid	[47]	−7.09	−2.04
Chlorogenic acid	[47]	−5.50	0.21
Ellagic acid	[48]	−6.33	−1.06
Ursolic acid	[49]	5.30	−0.32
Apigenin	[50]	−7.68	−4.98
Epigallocatechin-3-gallate	[51]	−8.58	−6.56
Ferulic acid	[47]	−7.19	0.14
Gallic acid	[53]	−6.39	−2.36
Genistein	[52]	−9.73	0.42
Kaempferol	[50]	−8.21	0.57
Luteolin	[50]	−10.67	−4.39
Naringenin	[54]	−7.57	−1.05
Quercetin	[47]	−8.70	0.35
Resveratrol	[54]	−9.17	−0.82
Rosmarinic acid	[51]	−11.28	−0.35

Table 2. Affinity of selected phytochemicals to lathosterol-5-oxidase.

Phytochemicals in *Passiflora edulis* Fruits	Reference	Affinity, kal/mol	Diffdock Score of Top-1 Position
Caffeic acid	[47]	−3.76	−1.03
Chlorogenic acid	[47]	−5.46	−0.77
Ellagic acid	[48]	−6.80	−2.01
Ursolic acid	[49]	−4.63	−1.32
Apigenin	[50]	−6.80	−5.61
Epigallocatechin-3-gallate	[51]	−5.60	−9.36
Ferulic acid	[47]	−7.20	0.72
Gallic acid	[53]	−5.70	−3.53
Genistein	[52]	−8.60	0.53
Kaempferol	[50]	−7.20	0.01
Luteolin	[50]	−10.10	−7.01
Naringenin	[54]	−6.98	−0.23
Quercetin	[47]	−7.98	0.31
Resveratrol	[54]	−9.00	−0.95
Rosmarinic acid	[51]	−11.00	−1.86

Molecular docking analysis suggested that genistein may bind favorably to both protein targets, as indicated by its binding affinity and DiffDock score [46,74]. In each case, the ligand is situated within the key interaction pocket, as predicted by the PasserRank algorithm [54] and visualized in the 3D structural models (Figure 2A,B). These findings support the potential inhibitory activity of genistein against the D3 receptor and lathosterol oxidase.

The molecular docking provides only an initial estimate of binding affinity and is inherently limited by the inaccuracies of scoring functions in reliably predicting true binding free energies [75]. For further validation, the docking position of genistein (Diffdock-confidence score equal 0.40 and 0.05), we used MM/PBSA analysis based on the Poisson–Boltzmann method, which yielded binding free energies of -6.03 ± 1.05 kcal/mol for VDR and -5.56 ± 0.81 kcal/mol. Analysis of the MD trajectories indicated that paeoniflorin remained stably positioned within the corresponding docking binding site throughout

the simulation (Figure 3). This demonstrates the stability of genistein in interaction with both proteins.

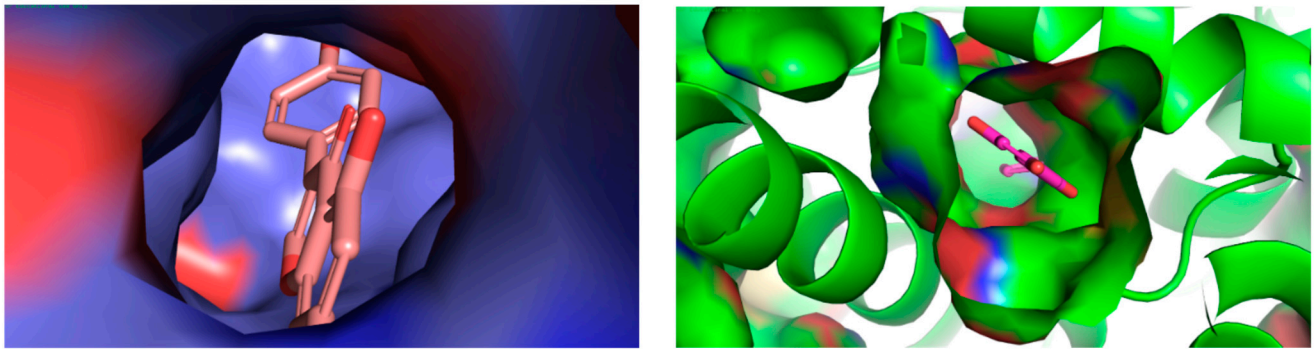


Figure 2. Best position of genistein: (**A**) in VDR interaction pocket (pink), active pocket colored red-blue color; (**B**) in lathosterol-oxidase interaction pocket (magenta), active pocket colored green-red color.

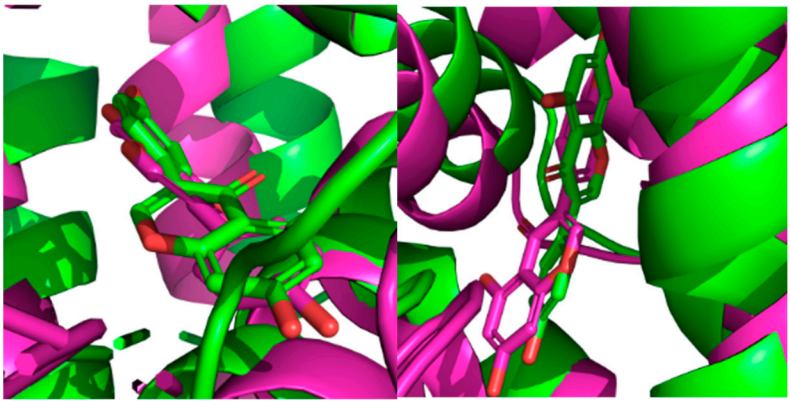


Figure 3. Comparison of positions of genistein after MD: (**A**) in VDR interaction pocket; (**B**) in lathosterol-oxidase interaction pocket. Green color represents the docking position corresponding to target crystal structures, magenta represents the position of genistein and target stable positions after MD.

Resulted position of genistein into the ligand-binding domain (LBD) of the Vitamin D Receptor (VDR) revealed 12 residue-level interactions, comprising hydrophobic contacts with LEU233 and TRP286, and van der Waals contacts with TYR143, ASP144, PHE150, TYR236, SER237, ARG274, SER278, TRP286, CYS288, and VAL300. The identified residues are well-established constituents of the VDR ligand-binding pocket (LBP): TYR143, SER237, ARG274, SER278, and TRP286 have been consistently described as key structural determinants of ligand recognition in the VDR LBD, forming the hydrophobic channel that accommodates the steroidal scaffold of the natural ligand 1,25-dihydroxyvitamin D_3 (calcitriol). In particular, TRP286 is an absolutely critical residue for ligand binding and VDR transactivation, as demonstrated by site-directed mutagenesis studies. The van der Waals contact with ARG274 and SER237—residues classically involved in hydrogen bonding with the 1α- and 25-hydroxyl groups of calcitriol—without formation of direct hydrogen bonds, suggests that genistein partially mimics the binding geometry of the natural ligand while lacking full polar engagement. This interaction pattern is consistent with previously reported binding behavior of dietary flavonoids, including quercetin, which similarly engages ARG274, SER278, and TRP286 via hydrophobic and van der Waals contacts rather

than canonical H-bonds. The hydrophobic contact with TRP286 may further stabilize the flavonoid A/C ring system within the nonpolar core of the LBP. These findings suggest that genistein acts as a partial VDR modulator, consistent with its reported ability to cooperate with $1,25(OH)_2D_3$ in upregulating VDR protein stability and modulating vitamin D signaling in prostate cancer cells [34,76–79].

According to the literature, genistein is found in the peel and fruit of *Passiflora edulis* [41]. Therefore, *P. edulis* extract was selected as a promising plant-based substance for further in vitro and ex vivo studies to experimentally test its ability to enhance vitamin D3 synthesis in the skin epidermal cells.

3.2. Determination of Non-Cytotoxic Concentrations of Passiflora edulis Extract

As illustrated in Figure 4, *P. edulis* fruit extract demonstrated a non-cytotoxic concentration range starting from 10.01 mg/mL. This concentration, along with the subsequent dilutions (3.17 mg/mL and 1.00 mg/mL), was selected to assess the impact of the extract on vitamin D3 levels in human keratinocytes. The evaluation of non-cytotoxic concentrations was further validated after 48 h of incubation using the MTT method, which confirmed that the extract did not adversely affect cell viability at the tested concentrations.

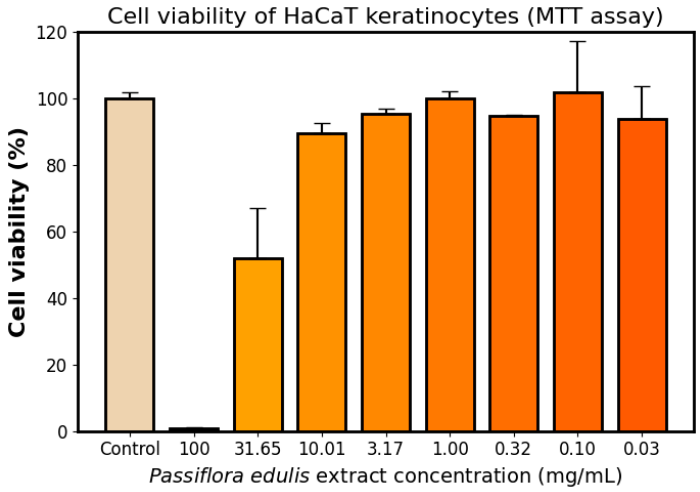


Figure 4. Cell viability of HaCaT human keratinocytes after exposure to increasing concentrations of *Passiflora edulis* fruit extract, determined by the MTT assay. Results are expressed as a percentage of viable cells relative to untreated control and presented as mean ± SD (n = 3).

The results indicate that *P. edulis* extract at the specified concentrations was suitable for further investigation regarding its potential role in modulating vitamin D3 levels in human keratinocytes. The non-cytotoxic nature of the extract at these concentrations provided a safe range for exploring its biological effects, particularly in the context of vitamin D3 metabolism and its implications for skin health. The findings indicate that *P. edulis* extract is non-cytotoxic to human keratinocytes at concentrations up to 10.01 mg/mL and can therefore be safely used in further studies on vitamin D3 determination.

3.3. Quantification of Vitamin D3 Amount in Human Keratinocytes In Vitro

It was demonstrated that *P. edulis* extract significantly increases vitamin D3 levels detected by ELISA in human keratinocytes even without short-term and long-term UVB exposure, as shown in Figure 5. In HaCaT cells treated with *P. edulis* extract at concentrations of 10.01, 3.17, and 1.00 mg/mL, an increase in vitamin D3 of 274.04% ($p < 0.001$), 151.22% ($p < 0.01$), and 125.86% ($p < 0.05$), respectively, was observed compared to the baseline control without UVB exposure.

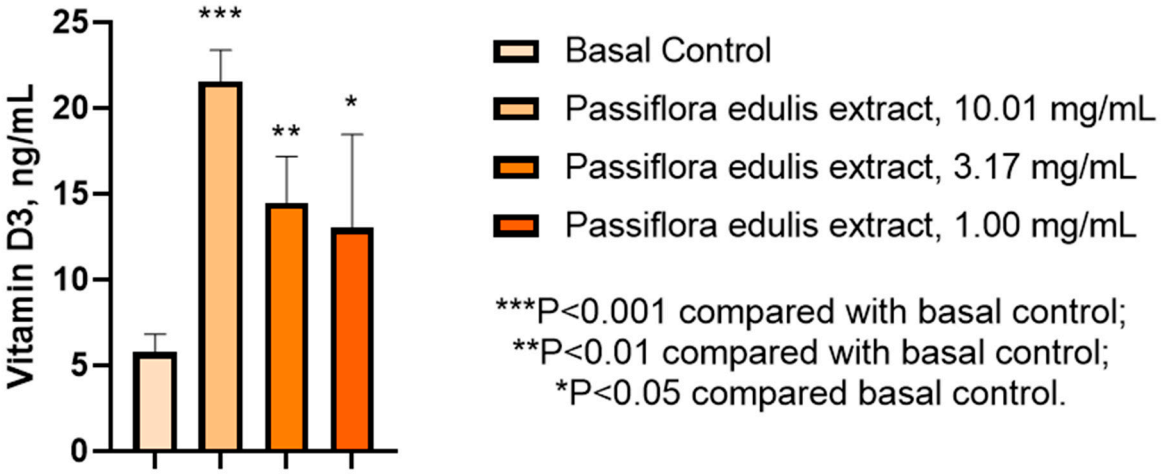


Figure 5. Vitamin D3 levels in skin epidermal cells by treatment of *P. edulis* extract without UVB radiation.

As expected, exposure to UVB radiation led to a significant increase in vitamin D3 to 146.00% compared to the basal control ($p < 0.01$) (Figure 6). At the same time, in HaCaT cells treated with *P. edulis* extract at concentrations of 10.01 and 3.17 mg/mL, vitamin D3 levels increased to 61.41% ($p < 0.001$) and 45.82% ($p < 0.05$), respectively, compared to the positive UVB control. Thus, *P. edulis* extract not only increases the level of vitamin D3 in skin cells but also has a synergistic effect in combination with the UVB radiation.

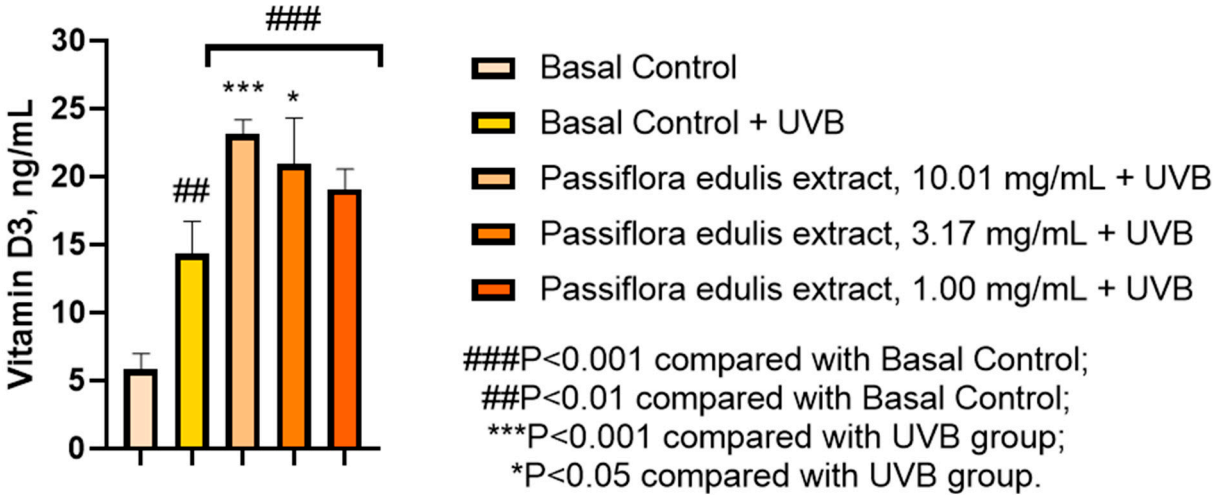


Figure 6. Vitamin D3 levels in skin epidermal cells by treatment of *P. edulis* extract under UVB radiation.

The observed results suggest a potential increase in detected vitamin D levels in skin keratinocytes treated with *P. edulis* extract even in the absence of UVB radiation, indicating the possibility of alternative or indirect mechanisms that require further investigation. To date, it is known that such processes are possible in subterranean mammals, fish, and some birds, but the exact mechanism remains unclear [16,80]. As a promising hypothesis, an alternative enzymatic pathway may be activated in human keratinocytes, leading to vitamin D synthesis even in the absence of UVB light, but further comprehensive research is needed to clarify this idea. Apparently, a lathosterol analog from *P. edulis* extract serves as an additional substrate for the enzyme lathosterol 5-desaturase (SC5D), leading to an increase in the pool of 7-DHC in skin keratinocytes [81]. This increased pool of 7-DHC is a ready precursor for further photolysis under the action of UVB and, possibly, for non-photochemical conversion in dark conditions.

The *P. edulis* extract increased the measured response in a dose-dependent manner. When UVB irradiation was combined with the extract, the fixed response substantially exceeded the Bliss-predicted additive effect at all tested concentrations. For the highest extract concentration (10 mg/mL), the observed fractional effect was 3.01, whereas the Bliss-expected value was 0.15, resulting in a synergy score of +2.86. Similarly strong synergy was observed at 3.17 mg/mL (+1.88) and 1.00 mg/mL (+1.43). These results demonstrate that UVB and the *P. edulis* extract interact positively in increasing the vitamin D3 level, with the combination producing synergetic effects for further therapy. However, ELISA reflects immunoreactivity rather than direct physicochemical quantification, and the potential interference from sample components, particularly plant-derived compounds, cannot be fully excluded.

Since molecular docking analysis predicted that phytochemicals from *P. edulis* fruits can interact with VDR, it was assumed that receptor-mediated regulation of gene expression might happen through potent VDR activation [82] This activation can lead to increased expression of genes critical for vitamin D3 synthesis, primarily the gene encoding the SC5D enzyme. Thus, *P. edulis* extract can have a complex effect on enhancing vitamin D3 production in skin keratinocytes, which opens new prospects for its use in cosmeceuticals and therapeutics after clinical research of safety and general therapeutic potential in comparison with supplement treatment.

3.4. Pre-Clinical Quantification of Vitamin D3 Amount in Human Skin Explants Ex Vivo

As presented in Figure 7, the quantification of vitamin D3 in human skin explants ex vivo with or without UVB radiation following treatment with *P. edulis* extract was accurately conducted. As anticipated, exposure to UVB radiation resulted in a significant increase in vitamin D3 amount by 139.09% compared to the basal control ($p < 0.01$). Compared to basal control, the treatment with the *P. edulis* extract without UVB radiation resulted in a significant increase in vitamin D3 amount by 153.31% ($p < 0.01$). The *P. edulis* extract combined with UVB radiation demonstrated synergistic impacts, showing an increase of 54.82% in vitamin D3 level compared to the UVB control ($p < 0.01$). If comparing both *P. edulis* extract treatments, the one associated with UVB radiation resulted in a vitamin D3 quantification of 46.13% higher than the one without UVB.

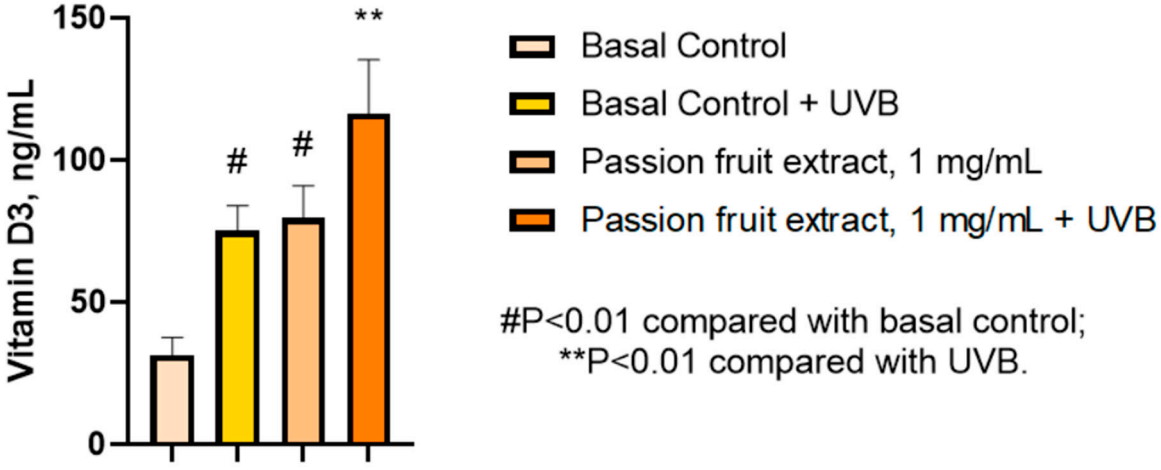


Figure 7. Effects of the *P. edulis* extract on vitamin D3 in human ex vivo after UVB radiation exposure. Data represent the mean ± SD of 3 biological replicates (ANOVA, Bonferroni).

These findings supported the promising therapeutic potential of *P. edulis* extract to increase vitamin D3 levels, especially when combined with UVB radiation on skin explants. While the extract alone significantly increased D3 levels, its association with UVB further

amplified this effect. An experiment conducted on ex vivo human skin fragments allows us to reproduce and evaluate the effectiveness of *P. edulis* extract in conditions that are as close to real skin physiology. In the skin, keratinocytes do not exist in isolation but interact closely with other cells and components of the extracellular matrix [83]. The ex vivo experiment shows that *P. edulis* extract increases vitamin D3 amount not only in single-cell models but also in whole tissue, considering the depth of penetration into the epidermis when applied topically. This consideration confirms the high potential of *P. edulis* extract as an active substance for increasing vitamin D3 levels in the skin when included in cosmeceutical products.

When taken orally, vitamin D is not always fully delivered to the skin. Topical vitamin D precursors provide a targeted effect on the skin and induce local synthesis directly in keratinocytes. This not only eliminates the risk of systemic side effects from vitamin D overdose, but also helps maintain its most important functions in the skin [5].

For people living in the Nordic regions with low insolation, working indoors or in polar night conditions, cosmetics with *P. edulis* extract can be a reliable tool for maintaining local skin homeostasis of vitamin D3 all year long. Perhaps, cosmeceuticals containing *P. edulis* fruit extract can also serve as a component of comprehensive sun protection. By increasing the pool of 7-DHC, they prepare the skin for the effective and safe synthesis of sufficient vitamin D even with short-term and moderate UVB exposure, while minimizing the risks of excessive and harmful sun exposure. In addition, *P. edulis* fruit extract has some sun protection activity (sun protection factor of 8.39 in vitro), due to the presence of UV-absorbing phenolic compounds such as quercetin and kaempferol [84]. Moreover, it has been shown that the use of sunscreen can reduce vitamin D3 production in the skin, which means the body needs an additional source of it. *P. edulis* fruit extract could be a solution to this problem, providing a comprehensive effect on both vitamin D3 production and UVB protection [85].

Due to the anti-inflammatory, immunomodulatory, and pro-differentiating properties of vitamin D3, topical products with *P. edulis* extract also have therapeutic potential for certain skin conditions. For example, psoriasis therapy includes the topical use of vitamin D analogs [86]. Since atopic dermatitis is associated with impaired skin barrier function and immune imbalance, stimulating local vitamin D3 production may help correct it by enhancing the skin's protective properties and modulating the inflammatory response [87]. In acne and seborrhea, whose pathogenesis is largely due to impaired keratinocyte proliferation and differentiation, the use of passion fruit extract can help normalize cell renewal and reduce hyperkeratinization of the follicle ostia [88,89].

Despite promising results, further clinical research is required to fully establish the efficacy and safety of *P. edulis* extract in cosmetic and topical pharmaceutical applications, both in healthy individuals and in patients with skin disorders, in comparison with currently approved therapies and oral vitamin D3 supplementation. Additionally, fundamental research on molecular mechanisms involved in increasing vitamin D production and biological pathways is still needed to reveal the theoretical hypothesis about alternative biochemical pathways.

4. Conclusions

In this study, the ability of *P. edulis* fruit extract to effectively increase vitamin D3 levels in skin epidermal cells was demonstrated for the first time. In silico analysis has shown that genistein is a promising candidate with high affinity for lathosterol-5-oxidase and the VDR. *P. edulis*, which has been reported in the literature to contain this compound, was selected as a promising botanical candidate for further experimental evaluation. Experiments confirmed that *P. edulis* extract significantly increases vitamin D3 amount both in human

keratinocyte cultures in vitro and in human skin models ex vivo. This effect is observed even in the absence of UVB irradiation. In addition, a synergistic effect of the extract in combination with UVB radiation has been identified, suggesting a complex effect on the vitamin D3 synthesis pathway in the skin.

The ability to increase vitamin D levels in the skin makes *P. edulis* fruit extract enriched by phytochemicals a promising approach for the next generation of cosmetics and pharmaceutics aimed not only at correcting but also preventing a wide range of dermatological conditions. Nevertheless, additional studies of stability in formulations, mechanism of action, dermatological tolerance in the products, and general clinical research of vitamin D3 level according to the worldwide regulation and authorized treatment lines are needed to fully confirm the beneficial effects of boosters in skin.

5. Patents

Results of this research have been part of the patent applications related to EP 25171835.

Author Contributions: E.P.: Conceptualization, Data curation, Formal Analysis, Methodology, Investigation, Project administration, Software, Validation, Visualization, Writing—original draft, Writing—review and editing. E.I.: Data curation, Formal Analysis, Investigation, Software, Validation, Visualization, Writing—original draft. V.F.: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review and editing. B.d.F.C., G.F., A.L.T.A.P., S.E.: Methodology, Investigation, Supervision, Validation, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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Abbreviations

The following abbreviations are used in this manuscript:

7-DHC	7-dehydrocholesterol
VDR	vitamin D receptor
SC5D	lathosterol 5-desaturase
1,25(OH)2D3	1,25-dihydroxyvitamin D
MM	Molecular Mechanics
PBSA	Poisson–Boltzmann Surface Area
MD	Molecular Dynamics
RMSD	Root mean square deviation

PDB	Protein Data Bank
NVT	Constant Number of Particles, Volume, and Temperature
NPT	Constant Number of Particles, Pressure, and Temperature

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