

Research Article

Glucuronyl Glucosyloleanolate, an AI-Discovered Saponin: From Melanocyte Assays to Clinical Skin Lightening-Brightening in a Multi-Ethnic Panel

Yannick Quesnel^{1,*} , Michael Gold² 

¹Research and Development, Kokuma SRL, Gosselies, Belgium

²Gold Skin Care Center, Tennessee Clinical Research Center, Nashville, United States

Abstract

Most of the depigmenting active ingredients currently in use work by inhibiting the catalytic activity of tyrosinase, and several of them are now subject to increasingly stringent regulatory and tolerance requirements. Glucuronylglucosyloleanolate (GGO), a natural triterpene saponin, was identified from public compound databases using an AI-based discovery platform combining in-silico predictions, physchem parameters and market requirements; and was subsequently subjected to a series of stepwise experiments. In normal human epidermal melanocytes, GGO reduced melanin production by up to 86% at a concentration of 2 µg/mL without any loss of viability; in one benchmark, it scored ahead of hydroquinone, kojic acid, niacinamide and tranexamic acid on melanin reduction. An in vitro assay on melanocyte tyrosinase showed no inhibition between 0.3 and 100 µM, indicating that the compound acts on enzyme expression rather than catalysis, and that it may also interfere with melanosome transfer. In UV-stimulated human explants, melanin content decreased by 45% and tyrosinase expression was reduced by a factor of 2.4 compared with controls, whilst tissue integrity was preserved. Safety was assessed at three levels: a 48-hour semi-occlusive patch test with the pure compound on 12 volunteers yielded an average irritation index of 0.00; the validated GARD®skin test revealed no sensitizing potential up to 0.4 g/L; and a repeated-challenge test in humans (HRIPT), carried out on over 100 volunteers at a concentration ten times higher than the clinical dose, did not result in any irritant or allergic reactions. Clinical efficacy was assessed in a randomized, single-blind, placebo-controlled trial, in which 60 volunteers, stratified according to Fitzpatrick phototype, applied 0.01% GGO or a placebo twice daily for 84 days. The individual typology angle increased significantly from day 21 onwards and continued to rise until day 84, reaching 11% in phototype III, 14% in phototype IV and 24% in phototype V, with no plateau observed at the end of the study. Hyperpigmented spots responded earlier and more rapidly than the surrounding skin, lightening approximately 34% faster to achieve a 17% reduction in patch intensity by day 84 and a measurable reduction in contrast compared with the adjacent skin. GGO therefore reduces the expression of enzymes involved in melanogenesis, a mechanism distinct from that of ingredients currently on the market, while also restricting pigment distribution, an effect reported in the literature. GGO achieves clinically significant depigmentation of both the overall complexion and localized hyperpigmentation at a concentration of 0.01%, making it far more potent than all competing products.

Keywords

Hyperpigmentation, Melanogenesis, Triterpene Saponin, Oleanolic Acid, Skin Lightening, Tyrosinase Expression, Multitarget Ligand, Clinical Trial

*Correspondence: Yannick Quesnel (yannick.quesnel@kokuma.tech)

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1. Introduction

Saponins are amphiphilic glycosides in which a steroid or triterpene aglycone carries one or more sugar chains [1]. The combination of a hydrophobic core with hydrophilic substituents gives these molecules their surfactant behavior and, in plants, a defensive role: they deter herbivores through bitterness and show antifungal and antibacterial activity [2, 3]. Those same properties have been put to industrial use in detergents, food emulsifiers, agricultural biopesticides and vaccine adjuvants [4-7]. In Asian pharmacopoeias, saponin-rich species such as *Panax ginseng*, *Astragalus membranaceus* and *Glycyrrhiza uralensis* have been prescribed for centuries to support immunity, endurance and recovery, well before their chemistry was understood [8].

Skin lightening, by contrast, is an area where the available chemistry has changed very little. The global market exceeds ten billion United States dollars and grows at 6 to 8% per year, sustained by aesthetic preference, cultural factors and social media. It is split between a regulated segment built on a handful of mild actives, chiefly ascorbic acid, niacinamide and tranexamic acid, and an unregulated segment in which mercury salts, high-dose hydroquinone, corticosteroids and injectable glutathione circulate freely [9]. Adverse outcomes from the second segment range from cutaneous atrophy, acne and exogenous ochronosis to hepatic, renal and neurological injury, together with an elevated skin cancer risk [10]. Where regulatory oversight is weak, this has become a public health matter rather than a cosmetic one, and the shortage of actives that are simultaneously effective, well tolerated and defensible on a regulatory basis is the practical reason for it.

Saponins have attracted some attention in this context, but the few identified so far as depigmenting agents remain poorly supported. Steroid saponins such as Ginsenosides Rb2 [11] and Rg3 [12] are active in vitro only, and triterpenoid saponin-rich licorice extracts require 10-40% in the final product to work in vivo [13]. Their effect, long attributed to glycyrrhizin, is now credited to glabridin and its resorcinol moiety [14], confirmed as a tyrosinase inhibitor only against the fungal enzyme [15], which does not transfer reliably to human tyrosinase [16].

Machine learning is increasingly used upstream of experimental screening to narrow large chemical libraries down to a handful of testable candidates. Ligand-based models combined with molecular docking have recently selected tyrosinase inhibitors from natural product libraries that outperformed arbutin in vitro [16], and active-learning pipelines achieve comparable results at a fraction of the computational cost [17]. However, such models are only as broad as their training set: built on compounds annotated against a single known target, they explore chemical space rather than mechanistic space, and are unlikely to surface a mode of action that has not already been described.

Glucuronyl glucosyloleanolate (GGO), a saponin, was

identified as a depigmenting candidate through a proprietary decision tree in which computational screening precedes experimental confirmation. Candidates are ranked in silico, then filtered through functional assays on human melanocytes, then through irradiated human skin explants, and only the survivors reach human testing (Figure 1). The *in-silico* and *ex-vivo* stages of that cascade have been described separately [18]. The present work brings together the full experimental record for GGO: melanogenesis and cytotoxicity in cultured melanocytes, a head-to-head comparison with the marketed actives listed above, a cell-free tyrosinase assay designed to test whether the compound acts on the enzyme itself, the *ex vivo* explant data, and the three human studies that followed, namely a patch test, a human repeated insult patch test (HRIPT) and an 84-day randomized clinical trial in a multi-ethnic panel.

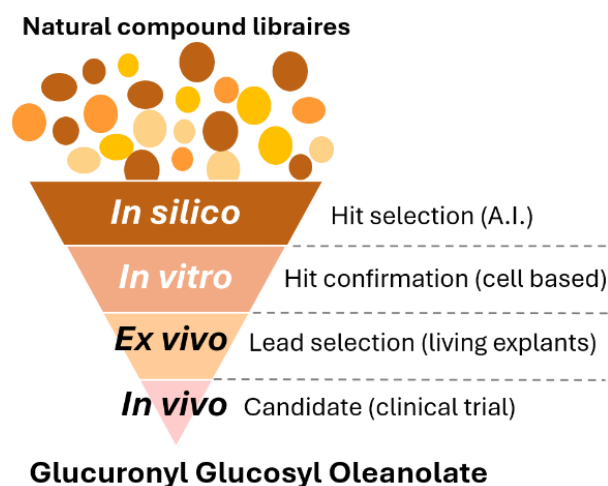


Figure 1. Screening cascade used to select GGO, from computational ranking through cell-based and explant assays to human studies.

2. Materials and Methods

2.1. Test Compound and Reference Actives

GGO was supplied by Kokuma SRL at a purity above 98%. Lipoic acid served as the internal positive control in the melanocyte assays. Tranexamic acid, niacinamide, hydroquinone and kojic acid were sourced as analytical-grade material and used as benchmark actives. Kojic acid also served as the reference inhibitor in the cell-free tyrosinase assay.

2.2. Melanogenesis in Normal Human Epidermal Melanocytes

Normal human epidermal melanocytes of moderate pigmentation (NHEM-MP) were grown at 37 °C under 5% carbon

dioxide in Dermalife basal medium supplemented with Dermalife M LifeFactors and in M254 basal medium supplemented with phorbol-ester-free HMGS-2. Cells at passage 11 were used for melanin synthesis and cells at passage 12 for the preliminary cytotoxicity screen.

Melanocytes were plated in 24-well plates and left to attach for 24 hours. Culture medium was then exchanged for assay medium containing GGO, lipoic acid at 5 µg/ml or nothing at all, and the cells were pre-incubated for a further 24 hours. Fresh assay medium of the same composition was then applied together with the inducer, a mixture of L-tyrosine and alpha-melanocyte-stimulating hormone. Incubation continued for nine days, with treatment and stimulation renewed on days 2 and 6. An unstimulated well was carried in parallel at every time point. All conditions were run in triplicate.

At the end of the incubation the monolayers were lysed in 0.5 normal sodium hydroxide and the released melanin was read at 405 nm. Melanin was quantified against a standard curve of exogenous melanin covering 0.39 to 100 µg/ml.

2.3. Benchmarking Against Marketed Depigmenting Actives

The comparison run used the same cell type and culture conditions, with passage 12 for cytotoxicity and passage 13 for melanin synthesis. The melanocytes were stimulated with L-tyrosine (300 µM) and the compounds were tested at their maximum tolerated concentration (kojic acid, hydroquinone) or their maximum effective concentration where safe (GGO, niacinamide, tranexamic acid), as previously determined by a cytotoxicity test (see below). Plating, 24-hour pre-incubation, nine-day incubation and triplicate design were, as described in Section 2.2, with treatments renewed on days 1 and 5.

Cytotoxicity was screened after 24, 48, 72 and 96 hours of exposure using the WST-8 reduction assay together with microscopic examination of cell morphology. WST-8 is reduced to a water-soluble orange formazan by mitochondrial succinate dehydrogenase in proportion to the number of metabolically active cells; absorbance was read at 450 nm on an Agilent BioTek reader. Viability was expressed as the ratio of sample to control absorbance. Melanin was extracted and quantified as in Section 2.2.

2.4. Cell-Free Tyrosinase Assay

Melanocyte lysate was prepared by culturing NHEM for three weeks with medium renewal every three to four days, detaching the cells with trypsin, neutralizing with fetal calf serum, centrifuging and storing the pellets at minus 80 °C. On the day of the assay the pellets were lysed in phosphate-buffered saline containing 1% Triton X-100. Tyrosinase activity of the lysate was calibrated against mushroom tyrosinase using L-3,4-dihydroxyphenylalanine (L-DOPA) as substrate and normalized to 100 units per ml.

GGO at 0.3, 1, 3, 10, 30 and 100 µM, or kojic acid at five

concentrations from 0.0625 to 1 mM, was pre-incubated with the enzyme for 10 minutes on ice. L-DOPA was then added to a final concentration of 2 mM and the plates were held at 37 °C for one hour before reading absorbance at 540 nm on a Versamax reader (Molecular Devices). A parallel series without substrate was run in single wells at every concentration so that optical interference from the test compounds could be subtracted. All other conditions were run in triplicate.

2.5. Ex Vivo Study on Ultraviolet-Irradiated Human Skin

Sixteen NativeSkin models of 11 mm diameter were produced from a single donor, a 48-year-old woman of phototype III with a body mass index of 24 kg/m². Models were maintained at 37 °C under 5% carbon dioxide and maximum humidity for seven days, with one ml of standard NativeSkin medium renewed daily.

GGO was added to the medium from day 0 to day 6 at 80 ng/ml, 0.4 µg/ml and 2 µg/ml, and was maintained in the medium throughout culture and irradiation. On days 1 to 6 the models received 25 mJ/cm² of ultraviolet B and 2.25 J/cm² of ultraviolet A in an Opsytec Dr. Gröbe BS-02 chamber. Silicone rings protected the matrix during exposure and were removed afterwards; medium was renewed after each irradiation. Models were unmolded on day 0 for the untreated control and on day 7 for all other conditions, repunched to remove the area shielded by the ring, halved, fixed in 10% buffered formalin and embedded in paraffin.

Sections of 5 µm were used for Fontana-Masson staining of melanin, anti-tyrosinase immunofluorescence and hematoxylin and eosin staining. Whole-slide scans at 20-fold magnification were used for quantification and representative fields were recorded at 40-fold magnification. Fontana-Masson quantification returned mean staining intensity and positive spot area for the whole epidermis and for the basal layer where melanocytes reside. Tyrosinase quantification returned mean fluorescence intensity and the percentage of positive cells in the epidermis. Both were performed by Quantacell (Montpellier, France). Hematoxylin and eosin sections were read for structural integrity and viability.

2.6. Patch Test

The patch test was run under dermatological supervision in line with the Declaration of Helsinki, after approval by an independent ethics committee and written informed consent from every participant. Pure GGO was applied to the scapular region of 12 volunteers, seven women and five men aged 20 to 70, under a semi-occlusive patch with filter paper for 48 hours. A physician graded erythema and oedema at patch removal on a standardised scale from 0 for no reaction to 3 for vivid erythema spreading beyond the test area or marked oedema with vesicles. The mean irritation index (MII) was the primary endpoint.

2.7. Human Repeated Insult Patch Test

The HRIPT was conducted in accordance with the Declaration of Helsinki, ICH E6 (R3), Regulation (EU) 536/2014, the Colipa guidelines and Romanian good clinical practice regulations, after ethics committee approval and written informed consent. The objective was to detect delayed contact sensitization under maximized exposure: GGO was diluted to 0.1% by weight in mineral oil, ten times the concentration used in the clinical trial.

108 healthy adults were enrolled and 101 completed the challenge phase (Table 6). 7 volunteers withdrew from the study before it was completed for personal reasons unrelated to the study. Nine semi-occlusive patches were applied to the upper back over three weeks for the induction phase. After a two-week rest, a single challenge patch was applied both to the induction site and to a previously untreated site, with water as negative control. Skin reactions, subjective discomfort and any allergic response were graded at every visit using the International Contact Dermatitis Research Group (ICDRG) scale.

2.8. Clinical Trial

The clinical study was randomized, single-blind and placebo-controlled, supervised by a dermatologist and conducted according to good clinical practice (CPMP, July 1996), French law 2004-806 of 9 August 2004 and the Declaration of Helsinki. Written informed consent was obtained before enrolment.

Sixty volunteers were randomized into two arms of 30. Group A received a cream containing 0.01% GGO and group B the same base without the active. Each arm contained 10 participants of African or North African origin (phototype IV to V), 10 of Asian origin (phototype III to IV) and 10 of Caucasian origin (phototype III). Product was applied to the face twice daily after the morning and evening cleansing routine for 84 days. Every participant applied an SPF 50+ sunscreen (Avène) during daylight hours throughout, so that ultraviolet exposure would not confound the measurements.

Assessments were made at day 0, day 21, day 56 and day 84. Skin color was measured as the individual typology angle (ITA) with a CR400 chromameter (Konica Minolta), and hy-

perpigmented spots were quantified on standardized two-dimensional facial photographs acquired with the VISIA imaging system. Spot readings and adjacent skin readings were taken from the same images so that the two kinetics could be compared within the same subject.

The results were presented as the change in Individual Typology Angle over time (ITA) rather than absolute values, as baseline skin tones vary among volunteers, thereby allowing each subject to serve as their own control and ensuring that depigmenting efficacy is measured independently of initial pigmentation.

2.9. Statistical Analysis

Raw absorbance and melanin data were processed in Microsoft Excel. Intergroup comparisons in the cell and enzyme assays used the two-tailed unpaired Student t-test, with the caveat that formal interpretation requires $n \geq 5$; with n equal to 3 the p values are reported for guidance only. Ex vivo data were plotted in GraphPad Prism and analyzed by one-way analysis of variance. The standard error of the mean was calculated as the standard deviation divided by the square root of the sample size. Significance thresholds are reported as ns for p above 0.05, one asterisk for 0.01 to 0.05, two asterisks for 0.001 to 0.01 and three asterisks for p below 0.001.

3. Results

3.1. GGO Suppresses Melanin Synthesis in Cultured Melanocytes

Stimulation with L-tyrosine and alpha-melanocyte-stimulating hormone raised melanin content from 8.0 to 22.3 $\mu\text{g/ml}$ over nine days, so the unstimulated baseline sat at 36% of the stimulated control (Table 1). GGO reduced pigment in a concentration-dependent manner over three orders of magnitude. At 80 ng/ml the effect was absent. At 0.4 $\mu\text{g/ml}$ melanin fell to 69% of the stimulated control, and at 2 $\mu\text{g/ml}$ to 14%, an 86% reduction that also brought the cultures below their own unstimulated baseline. Lipoic acid at 5 $\mu\text{g/ml}$, used as internal control, gave 23%. Triplicate values were tightly grouped at every concentration, with standard errors at or below 0.2 $\mu\text{g/ml}$.

Table 1. Melanin content of NHEM stimulated with L-tyrosine and alpha-melanocyte-stimulating hormone after nine days of treatment.

Condition	Concentration ($\mu\text{g/ml}$)	Melanin, ($\mu\text{g/mL}$)	% of stimulated control	SEM%	p
Unstimulated control		8.0	36	1	***
Stimulated control		22.3	100	2	-
Lipoic acid	5	5.1	23	0	***
GGO	0.080	21.7	97	1	ns

Condition	Concentration (µg/ml)	Melanin, (µg/mL)	% of stimulated control	SEM%	p
GGO	0.4	15.5	69	1	***
GGO	2	3.2	14	0	***

3.2. Comparison With Marketed Depigmenting Actives

Viability was screened first so that pigment readings could be interpreted against a known tolerance window (Table 2). GGO left melanocyte viability essentially untouched from 0.46 to 37 µM and produced only a mild decline at 111 µM, where morphology became borderline. Niacinamide and tranexamic acid were similarly well tolerated across their ranges. Kojic acid began to erode viability above 37 µM, reaching 71% at 333 µM. Hydroquinone behaved very differently: viability rose slightly at low concentrations, then collapsed to 3% at 37 µM and 7% at 111 µM, with morphology scored as abnormal from 12 µM upwards.

Table 2. Melanocyte viability after exposure to GGO and to four marketed depigmenting actives. Values are means of three wells expressed as% of untreated control.

Active	Concentration range tested (µM)	Viability across the range (%)
GGO	0.46 to 111	101 to 91
Tranexamic acid	0.137 to 333	101 to 90

Active	Concentration range tested (µM)	Viability across the range (%)
Niacinamide	4.1 to 1000	91 to 104
Hydroquinone	0.46 to 37	115 to 2
Kojic acid	1.4 to 333	101 to 71

Melanin content was then measured under tyrosine stimulation alone (Table 3) for all the compounds tested, in triplicate, so that their efficacy could be compared directly in this *in vitro* assay. This weaker stimulus produced a smaller dynamic range than the assay in Section 3.1, the unstimulated control sitting at 61% rather than 36%, which compresses the apparent size of every treatment effect. GGO reached 78% of the stimulated control at 17 µM and 77% at 50 µM, both significant. The four benchmark actives clustered between 83 and 97%. Tranexamic acid produced no significant change at any concentration up to 10 mM. Niacinamide reached 83% at 28 µM but lost the effect at 1 mM. Hydroquinone and kojic acid gave 86 and 85% at their best-performing concentrations, 1 and 100 µM respectively. Read on a molar basis, GGO therefore delivered the largest pigment reduction of the series while sitting three orders of magnitude above tranexamic acid and one to two orders above niacinamide and kojic acid.

Table 3. Melanin content of NHEM stimulated with 300 µM L-tyrosine, comparing GGO with four marketed actives.

Active	Concentration	Melanin (SEM) µg/mL	% of stimulated control	p
Unstimulated control	-	6.0 (0.1)	61	***
Stimulated control	-	9.8 (0.2)	100	-
Lipoic acid	5 µg/mL	4.2 (0.2)	43	***
GGO	2.5 µM	10.5 (0.6)	107	ns
GGO	5.6 µM	8.7 (0.4)	89	ns
GGO	17 µM	7.7 (0.2)	78	**
GGO	50 µM	7.5 (0.3)	77	**
Tranexamic acid	1.1 mM	9.5 (0.2)	97	ns
Tranexamic acid	3.3 mM	8.9 (0.3)	91	ns
Tranexamic acid	10 mM	9.3 (0.4)	94	ns
Niacinamide	9 µM	8.3 (0.3)	84	**

Active	Concentration	Melanin (SEM) µg/mL	% of stimulated control	p
Niacinamide	28 µM	8.2 (0.2)	83	**
Niacinamide	1 mM	9.1 (0.3)	93	ns
Hydroquinone	0.4 µM	9.0 (0.2)	92	*
Hydroquinone	1 µM	8.4 (0.2)	86	**
Hydroquinone	4 µM	8.5 (0.3)	86	*
Kojic acid	33 µM	8.0 (0.2)	89	*
Kojic acid	100 µM	7.6 (0.2)	85	*
Kojic acid	333 µM	7.8 (0.4)	87	**

3.3. GGO Does Not Inhibit Tyrosinase Catalysis

The cell-free assay was run to establish whether the pigment reduction observed in melanocytes could be explained by direct enzyme inhibition. Kojic acid behaved as expected, with activity falling from 100% at 0.0625 mM to 87, 70, 42 and 22% at 0.125, 0.25, 0.5 and 1 mM (Table 4). GGO gave no inhibition whatsoever across a 333-fold concentration range: activity stayed between 97 and 103% of control from 0.3 to 100 µM, with no concentration reaching significance. Optical interference controls were flat across the series, so the absence of effect is not a reading artefact. GGO reduces melanin in living melanocytes without touching the catalytic activity of the enzyme that produces it.

Table 4. Tyrosinase activity of melanocyte lysate after pre-incubation with kojic acid or GGO, measured by L-DOPA oxidation at 540 nm and corrected for optical interference.

Com-pound	Concentra-tion (µM)	Activ-ity ^b	SEM	% of control	P
Control	-	0.424	0.004	100	-
KA ^a	62.5	0.422	0.002	100	ns
KA	125	0.370	0.006	87	**
KA	250	0.299	0.005	70	***
KA	500	0.180	0.004	42	***
KA	1,000	0.093	0.001	22	***
GGO	0.3	0.437	0.003	103	ns
GGO	1	0.420	0.004	99	ns
GGO	3	0.414	0.005	98	ns

Com-pound	Concentra-tion (µM)	Activ-ity ^b	SEM	% of control	P
GGO	10	0.411	0.005	97	ns
GGO	30	0.411	0.006	97	ns
GGO	100	0.421	0.003	99	ns

^a KA: Kojic Acid. ^b by measure of the optical density at 540nm

3.4. GGO Lowers Tyrosinase Expression in Irradiated Skin Explants

Six days of combined ultraviolet A and B exposure produced a clear increase in Fontana-Masson signal in the NativeSkin models, concentrated in the basal layer of the epidermis, although focal melanin-rich areas were also present in the untreated controls. Adding GGO to the culture medium reduced the ultraviolet-induced melanin signal, and quantification confirmed a consistent downward trend across the three concentrations.

Immunofluorescence gave a sharper picture (Figure 2, Table 5). Tyrosinase-positive cells represented 4.6% of the epidermis in untreated models and 31.1% after irradiation, a significant induction distributed through the basal and suprabasal layers. All three GGO concentrations brought this figure back down, to 17.1% at 2 µg/ml, 16.8% at 0.4 µg/ml and 13.0% at 80 ng/ml. Mean fluorescence intensity followed the same direction, from 7238 in irradiated controls to between 6258 and 6516 in treated models. The reduction reached statistical significance at the low-concentration condition. Between-explant variability was substantial, which is expected with a single donor and three replicates per condition, and it is the reason the concentration ranking should not be over-interpreted.

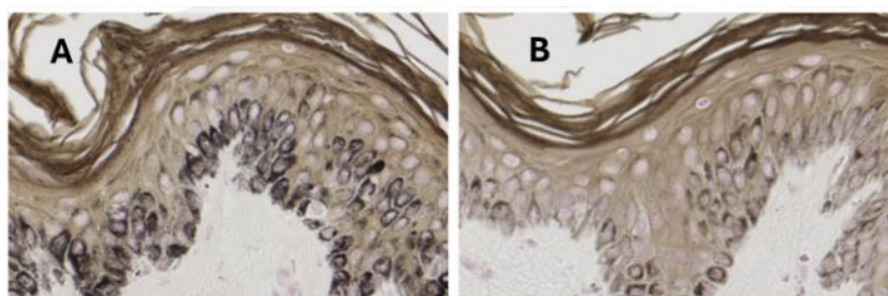


Figure 2. Representative histological images (Fontana-Masson staining) of UV-irradiated human skin explants showing melanin distribution. Panel A: UV irradiation alone (positive control). Panel B: UV irradiation with systemic GGO treatment. GGO substantially reduced melanin accumulation in the epidermis.

Haematoxylin and eosin sections showed intact, viable tissue at day 0. After seven days the irradiated models were histologically comparable to untreated controls apart from a few pyknotic cells, confirming that the ultraviolet dose was sub-cytotoxic and that melanogenesis was not being measured against a background of tissue damage. Models exposed to ultraviolet light and treated with GGO showed no sign of toxicity or loss of viability relative to irradiated untreated models.

Table 5. Tyrosinase expression in NativeSkin explants after six days of ultraviolet A and B exposure, quantified by anti-tyrosinase immunofluorescence on whole-slide scans (three explants per condition).

Condition	Mean fluorescence intensity	Positive cells, mean (%)
Untreated	4859	4.6
UV alone	7238	31.1
UV plus GGO 2	6258	17.1

Condition	Mean fluorescence intensity	Positive cells, mean (%)
µg/mL		
UV plus GGO 0.4 µg/mL	6516	16.8
UV plus GGO 80 ng/mL	6289	13.0

3.5. Primary Skin Tolerance

Forty-eight hours of semi-occlusive contact with pure GGO produced neither erythema nor oedema in any of the 12 volunteers, across phototypes I to IV and ages from 27 to 68. Every individual score was zero and the mean irritation index was therefore zero, well below the threshold for a non-irritant classification (Table 6). No participant reported discomfort during or after the exposure.

Table 6. Composition of the panels used in the two tolerance studies and the reactions recorded.

Study	Panel	Sex ^a / Age ^b	Phototypes	Reactions recorded
Patch test, pure GGO	12 enrolled, 12 evaluable	7F, 5M, 27 to 68y	I to IV	None; MII = 0
HRIPT, 0.1% GGO in mineral oil	108 enrolled, 101 evaluable	91F, 10M 32 to 70y	I (1%), II (24%), III (67%), IV (8%)	None at induction or challenge

^a F: female, M: male. ^b y: years

3.6. Absence of Sensitisation Under Maximised Exposure

Nine repeated semi-occlusive applications of GGO at 0.1% over three weeks produced no erythema and no complemen-

tary observation in any of the 102 subjects entering the induction phase (Table 7). At challenge, a single application to both the induction site and a virgin site in 101 subjects produced no reaction of any kind, and no response that could be assessed according to the established criteria was recorded. Under these conditions, at ten times the concentration used clinically, GGO is neither an irritant nor a sensitizer. The result supports

a hypoallergenic claim, with the usual reservation that a panel of this size cannot exclude rare sensitization events in very large populations.

Table 7. Reactions recorded during the induction and challenge phases of the HRIPT.

Phase	Reaction type	Description	Reactive subjects (n, %)
Induction	E: erythema	None	0, 0
Induction	M: complementary observation	None	0, 0
Challenge	E: erythema	None	0, 0
Challenge	M: complementary observation	None	0, 0
Challenge	A: ICDRG scale	None	0, 0

3.7. Clinical Efficacy Over 84 Days

Skin tone lightened steadily in every ethnic subgroup of the treated arm over the 84-day application period (Figures 3 & 4). Pigmentation fell by 10% in Asian participants, 14% in Caucasian and North African participants and 24% in Black

participants by day 84. The curves had not flattened at study end in any subgroup, so the plateau of the response lies beyond the observation window, and longer application would be expected to add further effect. Restricting the analysis to the fair phototypes III and IV in the Caucasian and Asian subgroups gave 17% spot lightening at day 84, again without a plateau.



Figure 3. Representative VISIA imaging showing lightening and brightening evolution over time following twice-daily application of GGO at 0.01% for 84 days. Progressive homogenization of skin tone and lightening of hyperpigmented spots are evident. Images were captured at Days 0, 21, 56, and 84.

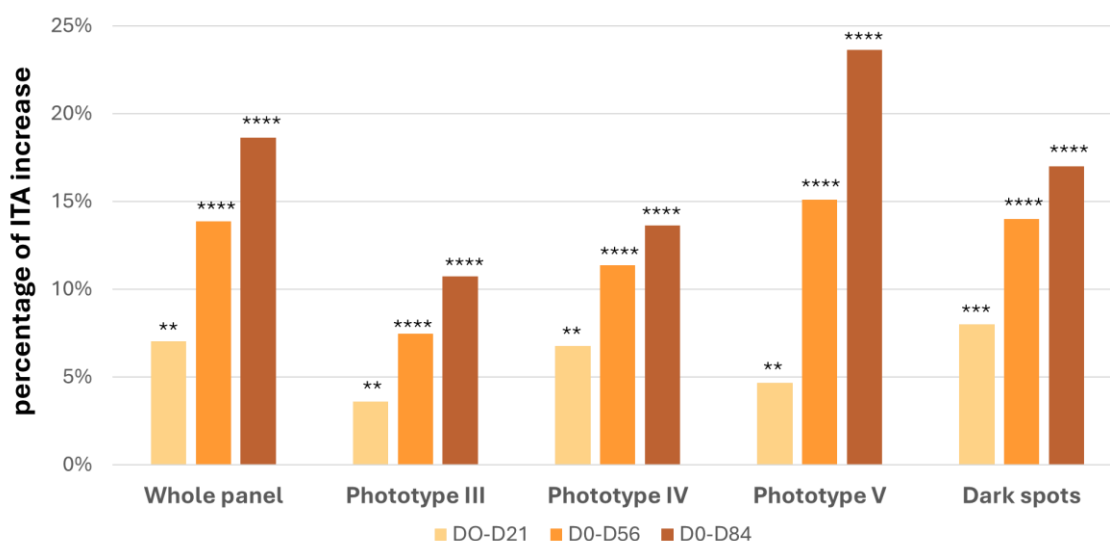


Figure 4. Change in ITA for overall skin tone and for hyperpigmented spots over 84 days of twice-daily application, compared with placebo.

The more informative observation concerns the relative kinetics of the two compartments (Figure 5). Spots lightened significantly from day 21, earlier than overall skin tone, and continued to separate from the surrounding skin thereafter, ending roughly 34% ahead of it. Because the visibility of a pigmented lesion depends on its contrast against adjacent skin

rather than on its absolute darkness, this differential translates directly into visible fading. Several volunteers finished the study with spots that had become difficult to locate. Most depigmenting actives act on melanocytes indiscriminately and lighten lesion and background together, which improves the photograph without improving the appearance; the behavior

recorded here is the opposite.

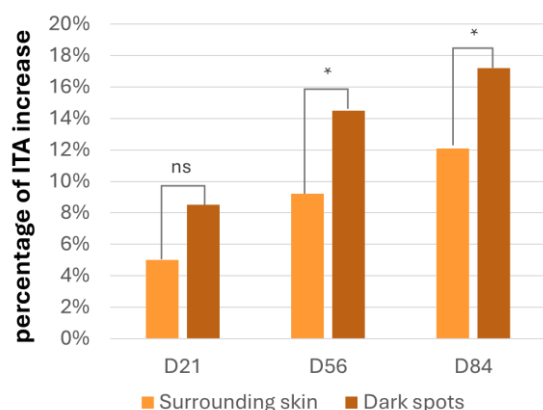


Figure 5. Comparative ITA change in hyperpigmented spots and in the surrounding skin of the same subjects.

4. Discussion

4.1. A Multitarget Approach to Pigment Control

Actives that engage several mechanisms converging on one

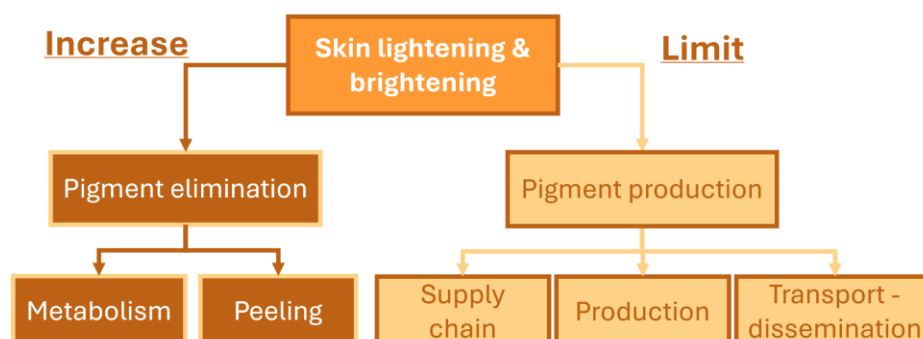


Figure 6. Points of intervention available for controlling cutaneous pigmentation.

GGO acts on the last two. The explant immunostaining reported in Section 3.4, together with the tyrosinase, TRP1 and TRP2 data described separately [18], shows that the compound lowers the expression of the melanogenic enzymes. The cell-free assay in Section 3.3 shows just as clearly that it does not inhibit their catalytic activity: no measurable effect from 0.3 to 100 μ M, in an assay where kojic acid loses three-quarters of the enzyme activity at 1 mM. Acting on expression rather than catalysis is unusual among depigmenting ingredients and is what allows the compound to work at concentrations where a competitive inhibitor would be inert. Separately, GGO interferes with NF-kappa-B signalling [24], a pathway implicated in melanosome transfer to keratinocytes, which

physiological endpoint have an obvious advantage over single-mechanism molecules, and the argument is the same one that produced the multitarget-directed ligand concept in medicinal chemistry [19]. Rather than optimizing affinity for a single protein, an MTDL exploits the redundancy of interconnected pathways: partial modulation at several points can produce the same net effect as full blockade at one, at a lower concentration per mechanism and with a correspondingly wider safety margin [20].

Cutaneous pigmentation offers four points of intervention (Figure 6). Epidermal turnover can be accelerated so that pigment is shed faster, which is how ascorbic acid, tocopherol and the organic acids used in exfoliating preparations contribute [21]. Substrate supply can be limited, either by dietary restriction of L-tyrosine or by reactive species that intercept biosynthetic intermediates, the mechanism attributed to glutathione [22] and to 2-mercaptosuccinyl glycine [23]. Production can be blocked, which is what hydroquinone, kojic acid, alpha-arbutin, tranexamic acid and Thiamidol do by inhibiting tyrosinase catalysis, and several of these now face tightening regulatory scrutiny. Finally, transport can be interrupted: melanin packaged into melanosomes moves from basal melanocytes into keratinocytes through dendritic contacts, and interfering with that transfer limits the spread of pigment through the epidermis independently of how much is made.

places a second mechanism at the transport step. Niacinamide [25] and Rhododendrol [26] are held to act at that same step, which makes the comparison in Table 3 a reasonable one.

The combination of reduced enzyme expression and restricted melanosome transfer is what a multitarget profile looks like in this therapeutic area [27], and the quantitative record across the cascade is consistent with it: 86% less melanin in melanocytes, up to 45% less in irradiated explants [18], and up to 24% tone reduction with 17% spot fading in vivo. What makes those figures notable is the concentration at which they were obtained. Table 8 sets the clinical use level of GGO against the usual loading of the marketed actives; the gap is two to three orders of magnitude.

Table 8. Principal depigmenting actives, their mechanism and their typical loading in a finished topical product.

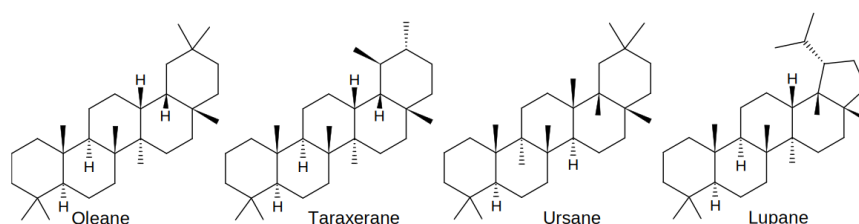
Active	Mechanism	Point of intervention	Typical loading
Hydroquinone	Tyrosinase inhibition	Production	1 to 5%
Kojic acid	Tyrosinase inhibition	Production	1%
Niacinamide	Melanosome transfer	Transport	up to 20%
Alpha-arbutin	Tyrosinase inhibition	Production	0.5%
Tranexamic acid	Tyrosinase inhibition	Production	5%
Thiamidol	Tyrosinase inhibition	Production	0.5%
2-MNG	Reactive species	Supply	0.5%
GGO	Tyrosinase expression and melanosome transfer	Production and transport	0.01%

Tolerance follows the same pattern. Explant histology stayed intact throughout the exposure, which is not a trivial observation given that several tyrosinase inhibitors compromise tissue integrity in comparable models, and the human data leave little ambiguity: a mean irritation index of zero with the pure compound and no reaction at all in more than one hundred subjects at ten times the use level.

4.2. GGO Within the Saponin Family

Triterpene saponins are usually classified by the skeleton of their aglycone, and four cores account for most of them: oleanane, taraxerane, ursane and lupane [28]. These triterpene saponins share a closely related pentacyclic triterpene core (Figure 7), the differences between them amounting to the position of one or two methyl groups and, in the case of lupane, to a

five-membered E ring bearing an isopropenyl side chain rather than a six-membered one. The diversity of the family therefore comes less from the aglycone than from its decoration: the nature of the oxygenated functions carried by the skeleton, and above all the number, identity and anchoring position of the sugar units, typically a glycosidic linkage at C-3, an ester linkage at the C-28 carboxyl, or both. Oleanolic acid, the oleanane representative, was the starting point here for reasons that were as much practical as biological. It has been reported in more than two thousand plant species, which makes it one of the most widely distributed triterpenes in the plant kingdom, and several of those species accumulate it at concentrations high enough for extraction at a commercially defensible cost. Cheap, abundant starting material is what allows glycosylation chemistry to be explored at all.

**Figure 7.** The four principal triterpenoid cores found in plant saponins.

Oleanolic acid itself has low toxicity and a broad documented activity profile spanning anticancer [29], antiviral [30], antibacterial [31], hepatoprotective [32], neuroprotective [33], antidiabetic [34], anti-obesity [35], antioxidant [36] and anti-inflammatory [37] effects. As a glycosylated derivative, GGO inherits much of this. Published work places it in oncology, through PI3K/Akt, PKC- α -ERK1/2, TLR4/NF- κ B and Wnt/ β -catenin signalling with downstream effects on

MMP2, MMP9 and caspase-3 [38]; in diabetes, through FFAR1 activation [39]; in inflammation, through the JAK/STAT pathway [40]; and in fibrosis [41]. Within dermatology specifically, GGO has been credited with anti-inflammatory activity through reactive oxygen species reduction [42], wound healing through FFAR1 activation [43], cytoprotection through the Fas/FasL pathway [44], anti-ageing activ-

ity through improved autophagy and mitophagy [45] and photoprotection through MAPK/AP-1 modulation [46] (Figure 8).

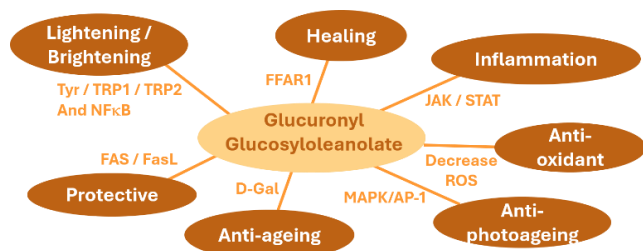


Figure 8. Cutaneous effects of GGO reported in the literature and demonstrated in the present work.

This matters for formulation practice rather than for the depigmentation claim. An active that also carries anti-inflammatory and antioxidant activity is well suited to melasma and post-inflammatory hyperpigmentation, where inflammation is part of the pathogenesis rather than an incidental finding. It is worth being explicit that the dermatological activities listed above come from published studies on GGO in other contexts and were not measured in the present work; they define a research agenda, not a claim.

4.3. One Molecule Against a Combination of Ingredients

Cosmetic formulation usually reaches multitarget behavior by combining actives, and the practice has costs. Co-formulated ingredients can interact pharmacokinetically, compete for the same penetration routes, destabilize one another and contribute additively to irritation [47]. Each addition also multiplies the regulatory and stability work required. A single molecule that carries two mechanisms provides the same convergence within one safety profile and one set of stability data [48].

There is a wider point about the field. Innovation in pigment control has largely consisted of reformulating a small inventory of molecules that every manufacturer can access, which limits how far any product can differentiate itself on substance. The result described here came from a discovery route rather than a formulation route, and it is that route, not the individual compound, that the data validate most directly.

4.4. Limitations

Several constraints on interpretation should be stated. The two melanocyte runs used different stimuli, tyrosine with alpha-melanocyte-stimulating hormone in one and tyrosine alone in the other, so the percentages in Table 1 and Table 3 are not interchangeable and the benchmark comparison is internally valid but not transferable to the first run. All cell and

enzyme conditions were run in triplicate, below the n of 5 that the statistical treatment requires, so the p values in Tables 1, 3 and 4 are indicative. The ex vivo assay used explants from a single donor of phototype III, which constrains generalization across phototypes at that stage of the cascade. The clinical trial was single-blind rather than double-blind, ran for 84 days without a post-treatment follow-up, and contained 10 participants per ethnic subgroup per arm, which is adequate for the pooled analysis but thin for subgroup comparison. Finally, the trial recruited volunteers with pigmentation spots rather than patients with a diagnosed pigmentary disorder; the melasma and post-inflammatory hyperpigmentation applications suggested by these results still require dedicated clinical study.

5. Conclusions

Glucuronyl glucosyloleanolate reduces melanin production and limits its distribution through the epidermis, and it does so without inhibiting tyrosinase catalysis. That combination separates it mechanistically from the actives currently available for pigment control, most of which target the enzyme directly.

The experimental record supports the claim at every level at which it was tested. Cultured melanocytes lost 86% of their melanin at 2 $\mu\text{g/ml}$ with no loss of viability. Irradiated human skin explants showed the proportion of tyrosinase-positive epidermal cells fall from 31% to between 13 and 17%, with histology unchanged 48 hours of contact with the pure compound produced a mean irritation index of zero in 12 volunteers, and a repeated insult protocol at ten times the clinical concentration produced no reaction in more than one hundred. Over 84 days of twice-daily use at 0.01%, skin tone lightened by 10 to 24% depending on ethnic origin and hyperpigmented spots faded roughly a third faster than the skin around them, with no sign that the response had reached its ceiling.

Two features are worth carrying forward. The first is the use level: 0.01% is two to three orders of magnitude below what the established actives require, which has consequences for formulation cost, sensory quality and toxicological margin. The second is the preferential response of spots over background skin, which is what determines whether a lesion becomes less visible rather than merely lighter, and which is uncommon among depigmenting ingredients.

The work also validates the screening cascade that produced the compound. A decision tree combining computational ranking with staged experimental filtering identified a candidate that survived every subsequent test, and the same route is now being applied to other endpoints. For GGO specifically, the priorities are a controlled trial in melasma, a longer study to locate the plateau that was not reached at day 84, and dedicated assessment of the anti-ageing and antioxidant activities that the literature attributes to the molecule.

Abbreviations

GGO	Glucuronyl Glucosyloleanolate
HRIPT	Human Repeated Insult Patch Test
ICDRG	International Contact Dermatitis Research Group
ITA	Individual Typology Angle
L-DOPA	L-3,4-dihydroxyphenylalanine
MII	Mean Irritation Index
MTDL	Multitarget-directed Ligand
NHEM	Normal Human Epidermal Melanocytes
OD	Optical Density
SEM	Standard Error of the Mean
TRP	Tyrosinase-related Protein
UV	Ultraviolet

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Author Contributions

Yannick Quesnel: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft

Michael Gold: Investigation, Supervision, Validation, Writing – review & editing

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Data Availability Statement

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request. Access to individual clinical trial data may be requested in writing from the corresponding author and will be granted subject to applicable data protection legislation.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography



Yannick Quesnel is co-founder of Kokuma, a Belgian biotech dedicated to skin physiology and to the applications that derive from it, and founder of Inchinn Therapeutics, a Belgian biotech working on central nervous system disorders, principally neurodegenerative diseases, and oncology. He has more than 25 years of experience across chemistry, biopharma and biotech, built on a detailed working knowledge of physiological pathways. He has led chemistry teams in global companies and in biotech and previously held the position of chemistry director at a major pharmaceutical company. His work centers on drug discovery and on the applications that follow from it. He has filed more than 25 patent applications in the pharmaceutical and cosmetic fields.



Michael Gold is the founder and medical director of Gold Skin Care Center, Advanced Aesthetics Medical Spa, The Laser & Rejuvenation Center, and Tennessee Clinical Research Center in Nashville, TN. He is a board-certified dermatologist and dermatologic surgeon and oversees the various facets of the center's operations - a combination of medical and surgical dermatology, cosmetic dermatology, aesthetic services and research endeavors which began in 1990. Dr. Gold has earned worldwide recognition for providing patients with leading-edge technological advances in dermatology and aesthetic skin care. He plays an integral role in the development of new pharmaceutical products and medical devices through his clinical research, and presents the results regularly at national and international dermatology and cosmetic meetings. Dr. Gold has authored over 300 published scientific articles, 28 textbook chapters, and has edited 2 textbooks on Photodynamic Therapy

Research Field

Yannick Quesnel: central nervous system and oncology drug discovery; new pharmaceutical products research; skin biology; novel biological mechanisms for cosmetic applications, New ingredients in depigmentation, brightening, and melanin boosting.

Michael Gold: technological research in dermatology; technological research in aesthetic skin care; dermatology surgery; development of new pharmaceutical products development of new medical devices.