Supplementary Material

Epigenetic Skin Aging and Its Reversal to Improve Skin Longevity across Ethnicities and Phototypes Using a Dihydromyricetin-Containing Serum: Results from a Prospective, Single-Cohort Study

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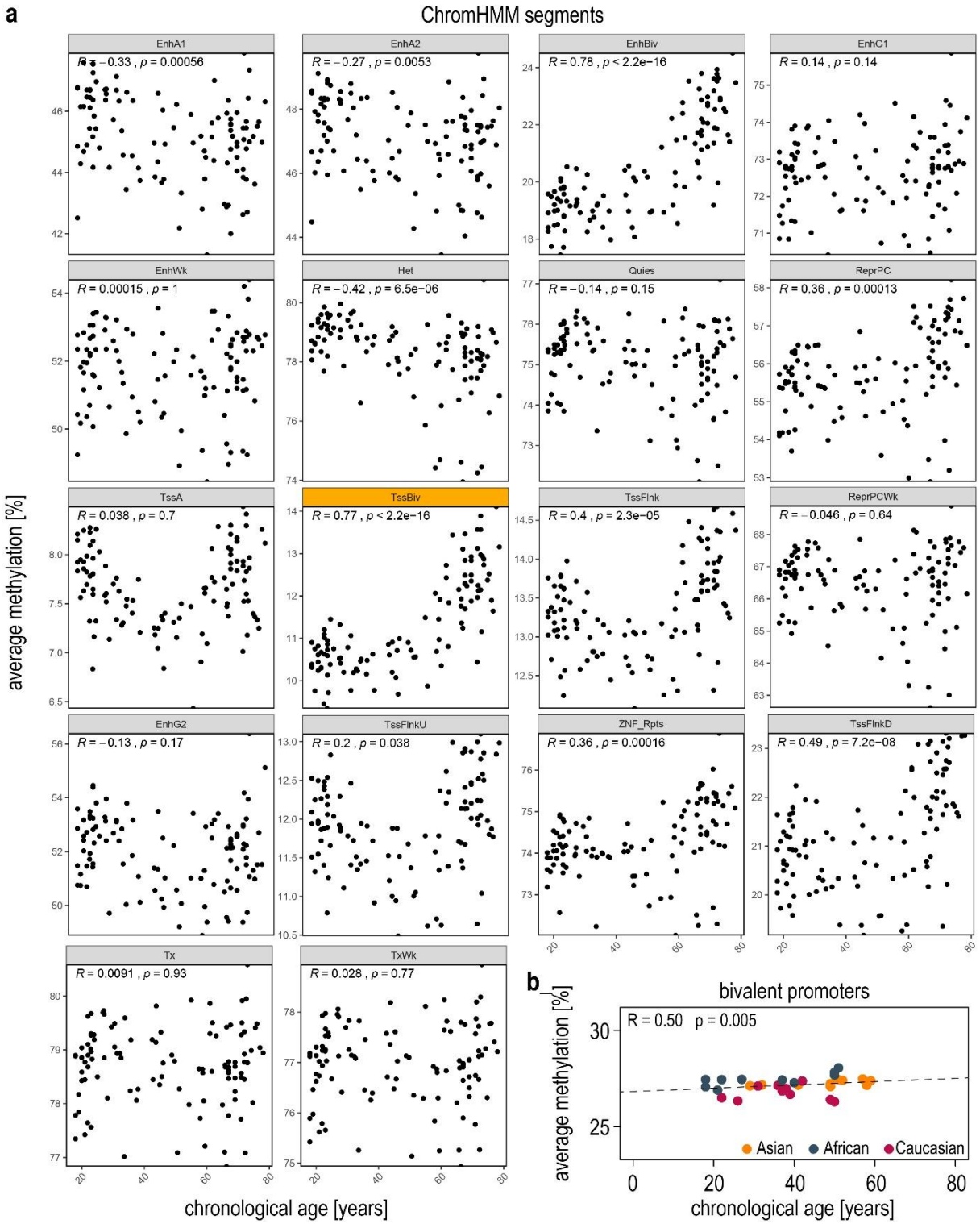
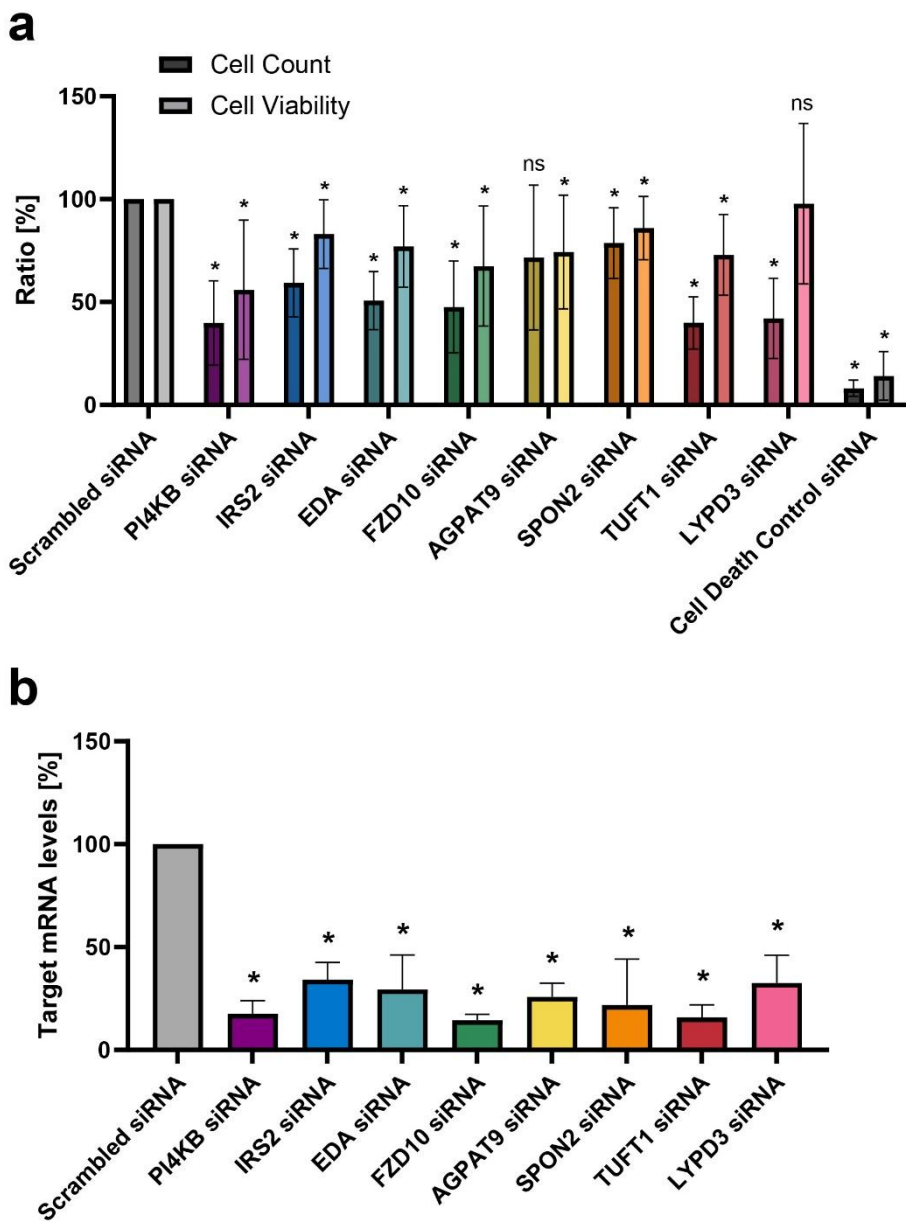
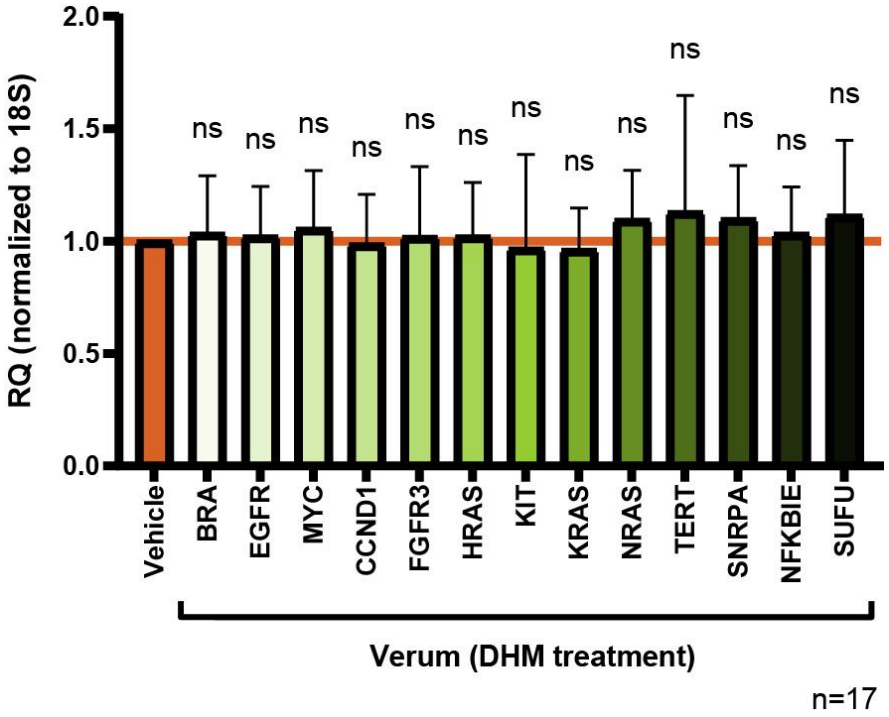
Supplementary Figures



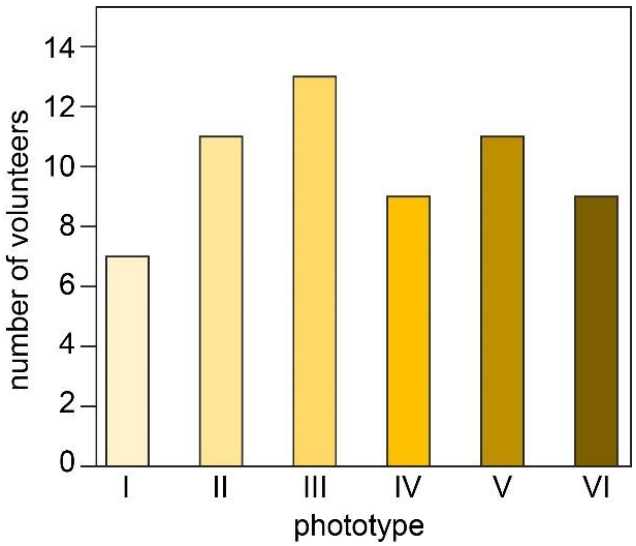
Supplementary Figure S1: Age-dependent DNA hypermethylation is enriched in bivalent promoters, which is associated with gene silencing (39), and is conserved across ethnicities. **(a)** ChromHMM segmentation of a published epidermis methylation dataset from epidermis samples of 108 female Caucasian donors aged 18-78 years (6). A robust and highly significant (R=0.77, p<2.2e-16) hypermethylation effect was observed for bivalent promoters (TssBiv = bivalent transcription start side; yellow box). **(b)** Average methylation levels of the bivalent promoter subset from 30 female multi-ethnic donors (1,787 probes, 27k array). The positive correlation (R=0.50) of the methylation level with donor age is highly significant (p<0.01).



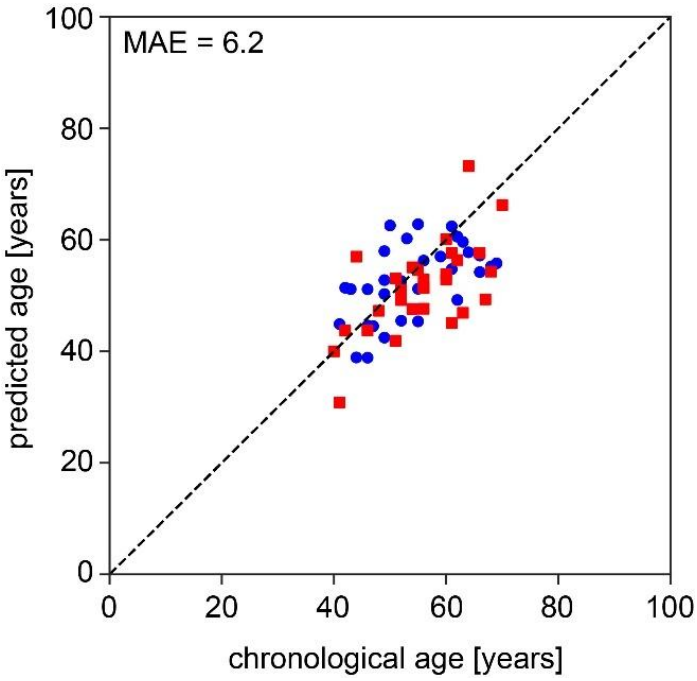
Supplementary Figure S2: SiRNA knockdown experiments in keratinocytes revealed that several of selected marker genes known for age-related epigenetic silencing *in vivo* contribute to cell viability and proliferation suggesting their relevance for cell´s longevity **(a)** Cell count (PI stain) and cell viability (esterases activity) three days after siRNA transfection (n=9) normalized to scrambled siRNA. Results are depicted as mean +/- SD. * $p<0.05$ (Wilcoxon signed-rank test). **(b)** Knock-down efficacy. Messenger RNA levels were analyzed 48h after siRNA transfection (n=3) and normalized to scrambled siRNA. Results are depicted as mean +/- SD. * $p<0.05$ (one sample t-test).



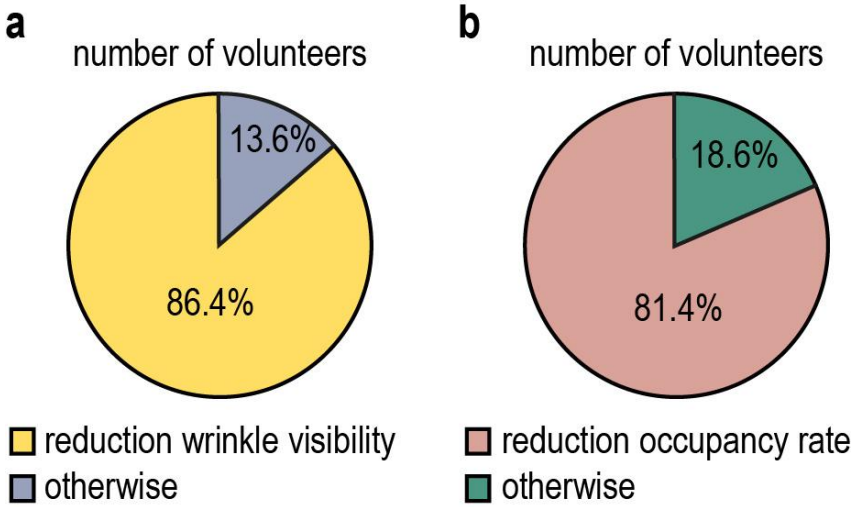
Supplementary Figure S3: Expression of skin-related oncogenes *in vivo* after topical application of DHM for 8 weeks compared to vehicle. Samples were taken from (12).



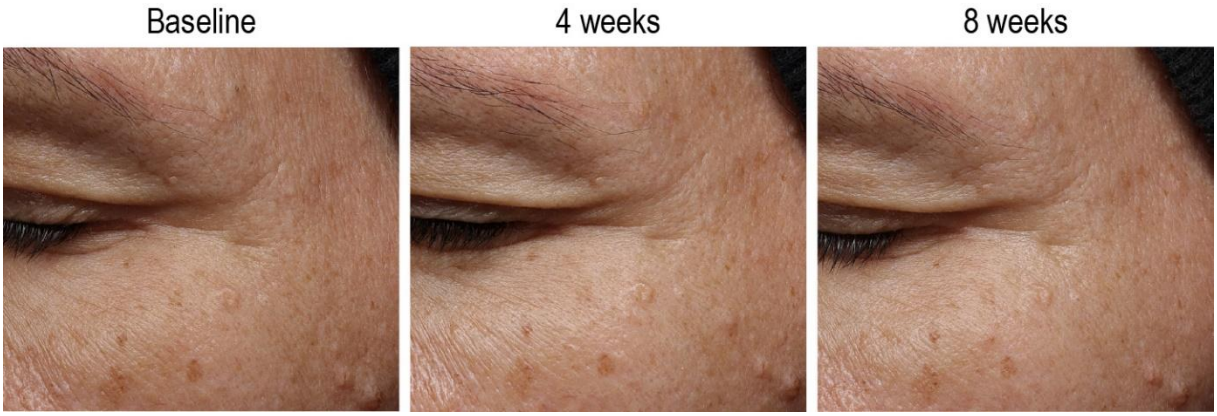
Supplementary Figure S4: Number of volunteers per phototype I – VI from the product-use study.



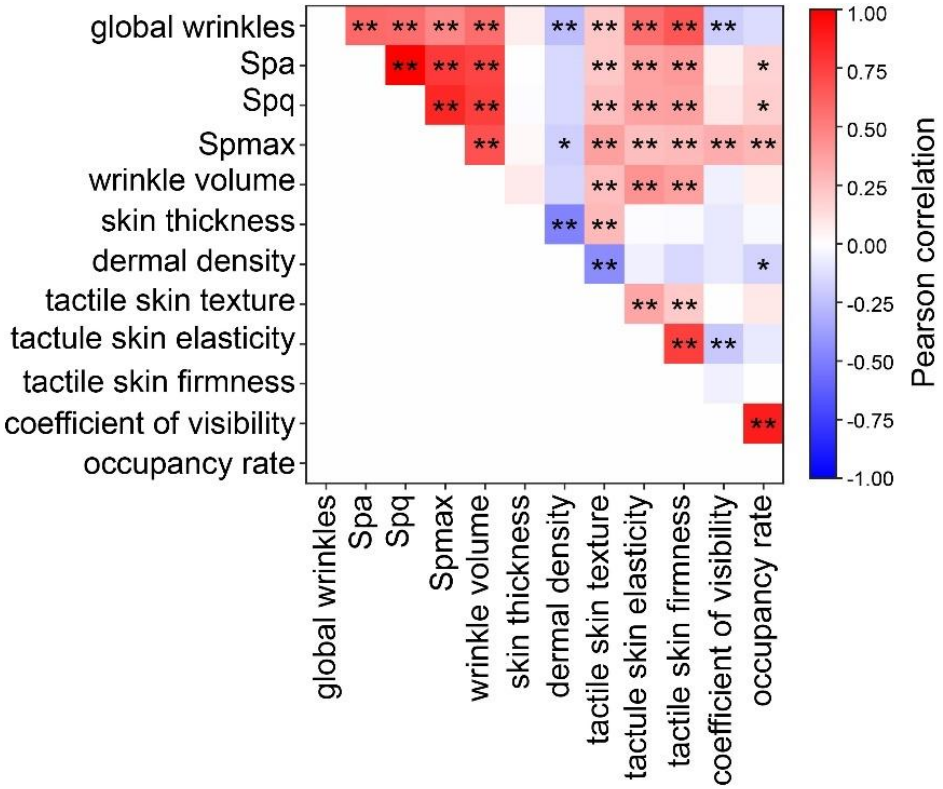
Supplementary Figure S5: Comparison of chronological age and DNA methylation age for phototype I – III (blue points; n=31) and phototype IV – VI (red rectangles; n=29) before topical application of DHM-containing serum. Predictions are not biased towards phototypes indicating that the applied epigenetic age clock is robust across different skin types. MAE = mean absolute error.



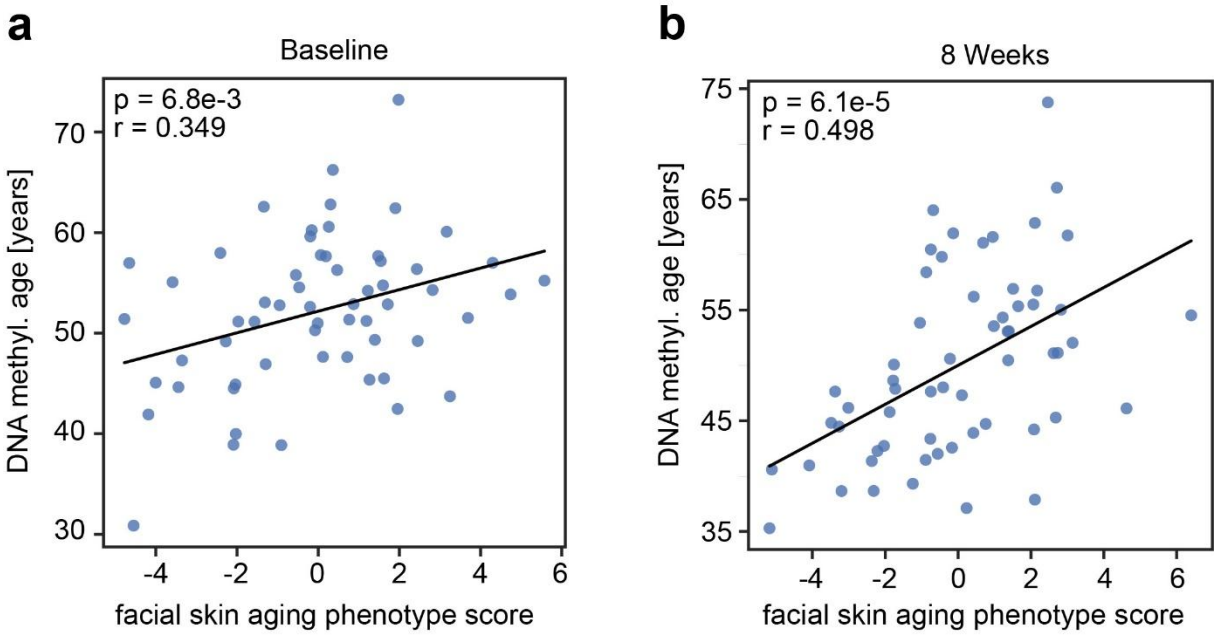
Supplementary Figure S6: Fraction of volunteers with improvement in wrinkle parameters **(a)** wrinkle visibility and **(b)** occupancy rate after DHM serum treatment for 8 weeks.



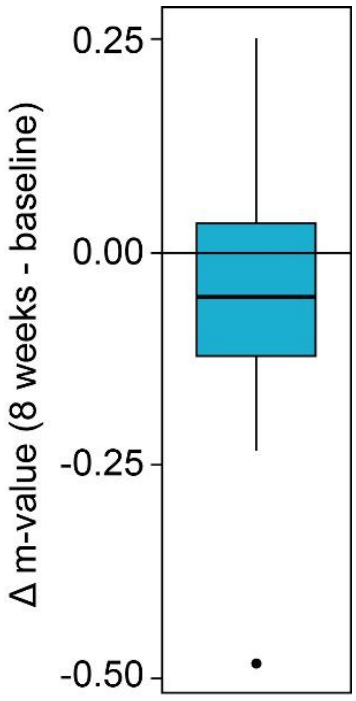
Supplementary Figure S7: Wrinkle measurements via high resolution images depicting average case (see Supplementary Methods for details).



Supplementary Figure S8: Pearson correlation of the measured clinical skin structure parameters among each other. Direction of correlation is color coded (blue = negative; red = positive) whereas color intensity reflects the strength of correlation. * p<0.1. ** p<0.05. Spa = arithmetic mean roughness; Spq = root mean square roughness; Spmax = maximum wrinkle depth.



Supplementary Figure S9: Facial skin aging phenotype score significantly ($p<0.01$) correlates with biological age before **(a)** and after 8 weeks **(b)** topical application of DHM-containing serum twice a day.



Supplementary Figure S10: Hypomethylation after 8 weeks application of DHM-containing serum of 34 age-dependent hypermethylated CpGs annotated to bivalent promoters and enhancers of epigenetically silenced genes in mature skin (Supplementary Table S8). This aligns with the observed gene reactivation (12), as hypermethylation of these regions is associated with gene silencing (39).

Supplementary Tables

Supplementary Table S1: Details of non-Caucasian tape samples from the pilot study with the intention to cover a broad range of phototype, ethnicity, and age to support generalizability of the obtained results. F = female; M = male.

#	Gender	Country	Ethnic background	Phototype	Donor age	Age pred.
1	F	Equador	Caucasian/mixed	III	24.8	33.6
2	M	India	Mixed	V	26.0	32.1
3	F	China	Asian	IV	26.5	27.5
4	F	South Korea	Asian	IV	28.0	33.5
5	F	India	Mixed	IV	28.1	32.7
6	F	China	Asian	III	29.0	30.4
7	M	China	Asian	III	29.9	34.1
8	M	Mexico	Caucasian/mixed	IV	33.5	41.4
9	F	India	Mixed	IV-V	33.7	37.5
10	F	Madagascar	African/mixed	V	37.3	35.4
11	M	Brazil	Caucasian/mixed	III	39.5	40.9
12	M	Morocco	Mixed	IV-V	42.8	38.7
13	M	China	Asian	III	46.8	47.4
14	F	Cuba	African/mixed	VI	56.2	52.4
15	F	Thailand	Asian	IV	56.9	38.1
16	F	Peru	Caucasian/mixed	IV	64.0	61.2
17	M	Eritrea	African	V	69.3	54.9

Supplementary Table S2: Details of the subjects form the product-use study. To support generalizability of the obtained results, the cohort was designed to be diverse in phototype, ethnicity, and age. F = female; M = male.

#	Gender	Phototype	Donor age	#	Gender	Phototype	Donor age
1	F	I	50	31	F	III	41
2	F	I	55	32	F	IV	40
3	F	I	59	33	M	IV	60
4	F	I	64	34	F	IV	51
5	F	I	55	35	F	IV	52
6	F	I	46	36	F	IV	67
7	F	I	53	37	F	IV	64
8	F	II	52	38	M	IV	42
9	F	II	46	39	F	IV	44
10	F	II	62	40	F	IV	41
11	F	II	69	41	F	V	61
12	F	II	44	42	F	V	56
13	F	II	47	43	F	V	60
14	F	II	42	44	F	V	60

15	F	II	61	45	M	V	56
16	F	II	56	46	F	V	66
17	F	II	49	47	F	V	56
18	F	II	52	48	F	V	48
19	F	III	55	49	F	V	62
20	F	III	43	50	F	V	70
21	M	III	49	51	F	V	58
22	M	III	66	52	M	VI	46
23	F	III	49	53	F	VI	51
24	F	III	66	54	F	VI	54
25	F	III	63	55	F	VI	55
26	F	III	68	56	F	VI	52
27	F	III	61	57	F	VI	61
28	F	III	62	58	F	VI	63
29	F	III	46	59	F	VI	68
30	F	III	49	60	F	VI	54

Supplementary Table S3: The correlation between the biological age reduction and the amount of used sunscreen corrected for DHM-containing serum was not significant (p=0.29) and showed a slightly negative (R=-0.14, Pearson correlation) trend indicating that sunscreen use can be excluded as cofounding factor for the observed biological age reduction. * time point = 4 weeks.

factor X	**factor Y**	**corrected for factor Z**	**partial correlation $\rho_{XY \cdot Z}$**	**p-value**
Δ biological age	Δ Eucerin® epigenetic serum*	Δ SPF product*	0.25	0.05
	Δ SPF product*	Δ Eucerin® epigenetic serum*	-0.14	0.29

Supplementary Table S4: The correlation between the biological age reduction and the amount of used sunscreen not corrected for DHM-containing serum was not significant (p=0.61) and showed a slightly negative (R=-0.07, Pearson correlation) trend indicating that the observed biological age reduction is not associated with a SPF-related effect. * time point = 4 weeks.

factor X	**factor Y**	**correlation ρ_{XY}**	**p-value**
Δ biological age	Δ Eucerin® epigenetic serum*	0.22	0.09
	Δ SPF product*	-0.07	0.61

Supplementary Table S5: Summary of self-grading results after 4 weeks and 8 weeks topical application of DHM-containing serum 2-times daily complementing the objective and molecular findings and thus reinforcing clinical relevance. Percentage improvement to baseline in visual and tactile parameters of skin aging assessed by the volunteers themselves. ↑ indicates an increase in the score which equals an improvement of the parameter (score range [1-10], with 1 = "bad" and 10 = "good"). Significance is depicted as *** p<0.001 (pairwise Wilcoxon signed-rank test).

Parameter	Δ(T4w – baseline)	Improvement % to baseline	Δ(T8w - baseline)	Improvement % to baseline
Wrinkles (Global)	1.8↑	29.2 (***)	2.6↑	40.0 (***)
Texture (Tactile)	2.0↑	33.3 (***)	2.5↑	36.7 (***)
Skin Elasticity (Visual)	1.5↑	26.7 (***)	2.1↑	36.7 (***)
Skin Firmness (Visual)	1.7↑	20.0 (***)	2.6↑	45.0 (***)
Skin Sagging (Visual)	1.7↑	22.5 (***)	2.3↑	33.3 (***)
Signs of neck aging (Visual)	1.6↑	25.0 (***)	2.4↑	41.4 (***)
Facial Plumpness/Volume (Visual)	2.1↑	40.0 (***)	2.9↑	50.0 (***)

Supplementary Table S6: Summary of self-assessment results of 60 volunteers answering the below listed statements after 4 weeks and 8 weeks topical application of DHM-containing serum 2-times daily thereby providing complementary support of the objective and molecular findings and reinforcing clinical relevance. Volunteers had three options to answer the statement: "yes", "no" and "do not know".

Statement	After 4 weeks		After 8 weeks	
	Yes (2)	No (1)	Yes (2)	No (1)
The product reduced my wrinkles	80.0% (48)	20.0% (12)	85.0% (51)	15.0% (9)
The product reduced my fine lines	86.7% (52)	13.3% (8)	93.3% (56)	6.7% (4)
The product minimized and softened my wrinkles and fine lines	95.0% (57)	5.0% (3)	100.0% (60)	0.0% (0)
The product improved my overall appearance	95.0% (57)	5.0% (3)	98.3% (59)	1.7% (1)
The product improved my skin texture	98.3% (59)	1.7% (1)	100.0% (60)	0.0% (0)
The product refined the elasticity of my skin	93.3% (56)	6.7% (4)	95.0% (57)	5.0% (3)
I feel my skin firmer	91.7% (55)	8.3% (5)	95.0% (57)	5.0% (3)
I feel my skin denser	85.0% (51)	15.0% (9)	91.7% (55)	8.3% (5)
I feel the contour of my face more visible	81.7% (49)	18.3% (11)	86.7% (52)	13.3% (8)
The product improved the aging signs of my face	90.0% (54)	10.0% (6)	95.0% (57)	5.0% (3)
I feel my face more plumped	85.0% (51)	15.0% (9)	93.3% (56)	6.7% (4)
I feel younger	86.7% (52)	13.3% (8)	93.3% (56)	6.7% (4)
It is ideal for my skin type and tone	98.3% (59)	1.7% (1)	100.0% (60)	0.0% (0)
It is the best anti-wrinkles product I have used	91.7% (55)	8.3% (5)	93.3% (56)	6.7% (4)
My skin feels moisturized and soft	98.3% (59)	1.7% (1)	100.0% (60)	0.0% (0)
My skin feels revitalized and rejuvenated	93.3% (56)	6.7% (4)	98.3% (59)	1.7% (1)
My skin feels more even	96.7% (58)	3.3% (2)	98.3% (59)	1.7% (1)
My neck skin feels smoother and softer	91.7% (55)	8.3% (5)	90.0% (54)	10.0% (6)
My neck skin feels firmer	80.0% (48)	20% (12)	88.3% (53)	11.7% (7)
I feel like this texture is ideal for my skin	95.0% (57)	5.0% (3)	98.3% (59)	1.7% (1)

Supplementary Table S7: Summary of the results from 60 volunteers of the “quality of life” questionnaire after 8 weeks topical application of DHM-containing serum 2-times daily supporting the objective and molecular findings and hence their clinical relevance. Significance is depicted as *** p<0.001 (pairwise Wilcoxon signed-rank test).

Quality of life self-assessment questionnaire (statements)	Percentage improvement to Baseline	
	4 weeks	8 weeks
In the previous week, my skin appearance gave me the impression of being attractive	66.7 (***)	100 (***)
Looking back over the past week, my skin appearance gave me confidence in social life, leisure, and activities	75.0 (***)	100 (***)
Considering the previous week, I was at peace with myself and my skin	83.3 (***)	100 (***)
Total Score	56.3 (***)	79.2 (***)

Supplementary Table S8: 34 age-dependent hypermethylated CpGs annotated to bivalent promoters and enhancers of epigenetically silenced genes in mature skin (Falckenhayn et al. 2024).

CpG	Genesymbol	CpG	Genesymbol
cg01155039	AMN	cg03687345	SPON2
cg02811627	AMN	cg12024828	SPON2
cg07435445	AMN	cg14652131	SPON2
cg09540471	AMN	cg22757391	SPON2
cg11038340	AMN	cg23339454	SPON2
cg24810305	AMN	cg02500231	NOS1
cg25017060	AMN	cg03538436	NOS1
cg00239870	CH25H	cg04529785	NOS1
cg02022481	CH25H	cg04883903	NOS1
cg07899729	CH25H	cg04899175	NOS1
cg19984146	CH25H	cg18243853	NOS1
cg23410627	CH25H	cg18834729	NOS1
cg23967742	CH25H	cg21273407	NOS1
cg24919790	CH25H		
cg27018185	CH25H		
cg02214745	FZD10		
cg09048530	FZD10		
cg13755349	FZD10		
cg19694010	FZD10		
cg21386611	FZD10		
cg22813950	FZD10		

Supplementary Table S9: Details of suction blister samples used for the analysis of expression levels of skin-related oncogenes *in vivo* after topical application of DHM for 8 weeks compared to vehicle. Samples were taken from (12). Results are shown in Supplementary Figure S3. F = female.

#	Gender	Ethnic background	Phototype	Donor age
1	F	Caucasian	III	51
2	F	Caucasian	II	51
3	F	Caucasian	II	62
4	F	Caucasian	III	52
5	F	Caucasian	II	61
6	F	Caucasian	II	63
7	F	Caucasian	II	63
8	F	Caucasian	II	59
9	F	Caucasian	II	64
10	F	Caucasian	II	62
11	F	Caucasian	I	56
12	F	Caucasian	III	57
13	F	Caucasian	II	56
14	F	Caucasian	II	53
15	F	Caucasian	II	54
16	F	Caucasian	III	65
17	F	Caucasian	II	64

Supplementary Methods

Investigation of DNA hypermethylation across ethnicities

We divided the keratinocyte genome into 17 functionally distinct segments. We then determined the methylation levels in each of the 17 segments for the published 450k epidermis methylation dataset from 108 female Caucasian donors aged 18-78 years (6). 34 age-dependent hypermethylated CpGs in bivalent promoters and enhancers could be annotated to a set of marker genes (Supplementary Table S1) that has been described to be epigenetically silenced in aged Caucasian skin (12).

In the next step, we investigated whether age-dependent DNA hypermethylation of bivalent promoters is detectable in other ethnicities. To this end, we determined the average methylation levels of 1,787 probes from bivalent promoters that were available from the published dataset of epidermis samples from African, Asian and Caucasian donors (13).

Volunteers

All volunteers were in general good health condition. Exclusion criteria for the product-use study were pregnancy, breastfeeding, systemic diseases e.g., diabetes mellitus or immune insufficiency, inflammatory such as psoriasis or atopic dermatitis and current use of the following topical or systemic medications: corticosteroids, immunosuppressant and anti-histaminic drugs. All volunteers displayed intact skin on test site prior sampling.

Measurement of clinical and self-perception skin structure parameters

A multimodal methodological framework was employed to comprehensively assess efficacy at 4 and 8 weeks timepoints in comparison to baseline. For qualification of wrinkle visibility and occupancy rate, VISIA® CR was used and standardized, high-resolution facial images were captured. For providing objective metrics of surface roughness, including SPq (root mean square roughness), SPa (arithmetic mean roughness) and volume PRIMOS® CR 300 was applied and three-dimensional profilometry of the periorbital area skin surface on the right, left and front sides of the subject’s face were generated. To measure dermal echogenicity, a

surrogate of dermal density, DermaLab® Ultrasound, a 20 MHz high-resolution probe, was employed. Images were acquired from the malar region on one randomized side of the face, where denser structures have a higher echogenicity and are represented by red/white colors, while less dense structures with lower echogenicity are represented by the colors green/black. Additionally, an expert clinical grader, blinded to time points, performed standardized tactile and visual evaluations of facial and cervical skin aging markers. Finally, each volunteer performed visual and tactile self-grading of facial skin condition and self-assessment validating their improvements perception with questionnaire assessing level of agreement, also addressing quality of life parameters for each timepoint describe above. The Self-Assessment by the study subjects is performed by following the “Standard Guide for Sensory Claim Substantiation” (ASTM E 1958-06, 2006) and the quality-of-life questionnaire was from Beiersdorf AG.

Epidermal tape stripping

After cleansing the temple or the forehead area respectively using 100% ethanol, an adhesive tape strip was affixed to the designated area. For the pilot study, the published TapeLift protocol by Rodriguez-Paredes et al. (2026) was used. For the product-use study, the only difference was the application of Opsite Flexifix tape (Smith & Nephew). Consistent pressure was applied for 5–10 seconds before the strip was gently removed using clean forceps and placed into a sterile 50-mL Falcon tube. This procedure was carried out four times on the same skin site and the four strips were collected in the same tube and stored at -80°C.

Training of the 23k epidermis clock

The training of the 23k epidermis clock was performed as described previously (14), with following exceptions: the intersect of probes from 27k and 450k BeadChip arrays (Illumina) were used for clock training. As training dataset, publicly available DNA methylation data from epidermal samples (6) were applied. Furthermore, cross-validation was performed using mean squared error (MSE) as measure for predictive accuracy.

In vitro knock-down experiments

SiRNA-mediated gene knockdown experiments were performed with human primary epidermal keratinocytes isolated from skin biopsies obtained from nine different donors (18–43 years) as described previously (40). After isolation, keratinocytes were seeded in 96 well plates at a density of 2.500 cells/well and cultured in KGM-Gold (Lonza) for 24 h. In the following, siRNA transfection was conducted using Lipofectamine RNAiMAX (Invitrogen) according to manufacturer's protocol (final concentrations: 5 nM siRNA, 1µl/ml Lipofectamine RNAiMAX). After 24 h of transfection, the medium was changed to the appropriate growth medium KGM-Gold. One siRNA (Qiagen) was used per target gene [PI4KB (Hs_PIK4CB_5), IRS2 (Hs_IRS2_5), EDA (Hs_EDA_7), FZD10 (Hs_FZD10_1), AGPAT9 (Hs_MAG1_1), SPON2 (Hs_SPON2_3), TUFT1 (Hs_TUFT1_5), LYPD3 (Hs_LYPD3_3)]. The following siRNAs (Qiagen) were used as negative and positive controls: AllStars Negative Control siRNA (Scrambled siRNA), AllStars Hs Cell Death siRNA.

For analysis of knockdown efficiency on RNA level cells were harvested 48 h after transfection. Total RNA was extracted using the RNeasy Mini Kit (Qiagen) according to the manufacturer's protocol. After reverse transcription using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems), gene expression was detected using the 7900HT Fast-Real-Time PCR System (Applied Biosystems). Ct values were normalized to endogenous housekeeping gene GAPDH and gene expression fold changes were calculated via the $2^{-\Delta\Delta Ct}$ method. FAM labelled TaqMan Assays for the qRT-PCR (Applied Biosystems) were as follows: PI4KB (Hs00356327_m1), IRS2 (Hs00275843_s1), EDA (Hs03025596_s1), FZD10 (Hs04999826_s1), AGPAT9 (Hs00262010_m1), SPON2 (Hs00202813_m1), TUFT1 (Hs00360629_m1), LYPD3 (Hs01012111_m1), GAPDH (Hs99999905_m1).

To analyze the knockdown effect on cell viability and cell count, cells were harvested 72 h after transfection. Cell viability was determined by measuring endogenous esterases activity. Briefly, cells were washed with 1xPBS and incubated for 15 min at 37°C and 5% CO_2 with 100 µl/well of a fluorescein diacetate (FDA, Sigma) solution (15 µg/ml FDA in 1xPBS). Fluorescence was

determined at 517 nm using the microplate reader infinite M200 (Tecan). After FDA measurement, cells were fixed with 4% formaldehyde solution (Sigma) for 15 min at room temperature, washed with PBS and stained with 5 µg/ml Hoechst 33342 (Invitrogen). The cell nuclei were then counted using the ImageXpress Pico Imaging System (Molecular Devices).

In vivo gene expression analysis

As previously described (12), the inner forearm skin of 17 female volunteers (51–64 years of age, see Supplementary Table S9 for details) was treated for eight weeks with a topical oil-in-water (o/w) emulsion containing 0.15% DHM (w/w) or a vehicle control. Following the treatment period, suction blisters were generated to collect samples for RNA extraction as described previously (41). The expression levels of 13 selected oncogenes were analyzed using quantitative real-time PCR (qRT-PCR). To this end, total RNA of suction blister roofs was isolated using the RNeasy Fibrous Tissue Mini Kit (Qiagen) according to the manufacturer's protocol. After reverse transcription using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems) gene expression was detected using Real-Time TaqMan PCR (QuantStudio 7 Pro, Applied Biosystems). Ct values were normalized to endogenous housekeeping gene 18sRNA and gene expression fold changes were calculated via the $2^{-\Delta\Delta Ct}$ method.

Calculation of facial skin aging phenotype score

First, the pairwise Pearson correlation for all 12 clinical skin parameters was conducted (Supplementary Fig. S8). Based on the correlation analysis representative measurements were selected to avoid overrepresentations of single aspects of the skin aging phenotype: expert-assessed scores of global wrinkles, tactile skin firmness and tactile skin texture as well as the instrumentally measured occupancy rate. Z-score normalization of the selected parameters was performed to ensure equal weighting into the final score. Finally, the facial skin aging phenotype score is the sum of the normalized parameters (see formula 1) where a

high score corresponds to a mature skin phenotype and a low score to a juvenile skin phenotype.

$$facial\ skin\ aging\ phenotype\ score_i = \sum_{f \in F}^{F} \frac{x_{fi} - mean(X_f)}{std(X_f)}$$

Formula 1: facial skin aging phenotype score; i = volunteer i; F = collection of selected factors; x_{fi} = value of factor f for volunteer i; X_f = values of factor f for all volunteers

Supplementary References

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