

REGU®-FADE

*The most effective
solution for noticeable
brighter skin*

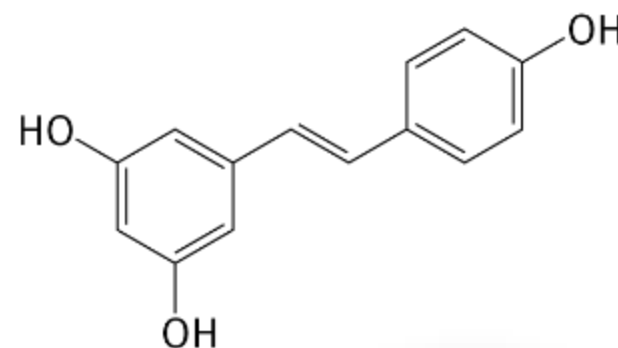


Personal Care & Aroma **Bioactives** Technical & Performance Ingredients UV Filters Aroma Ingredients



What is Resveratrol and where is it found?

Resveratrol is a powerful antioxidant, a polyphenol found in nature in small amounts, most notably in red wine



Peanuts
($<0.1\%$)



Grapes & Wine
($<0.02\%$)

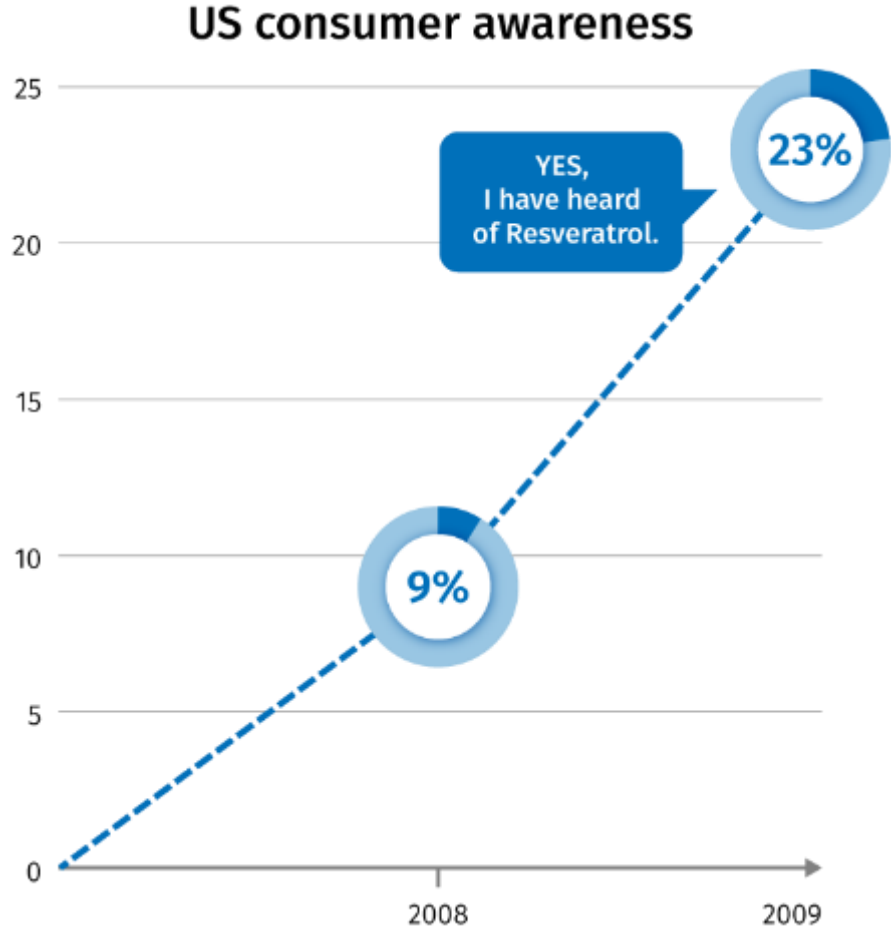
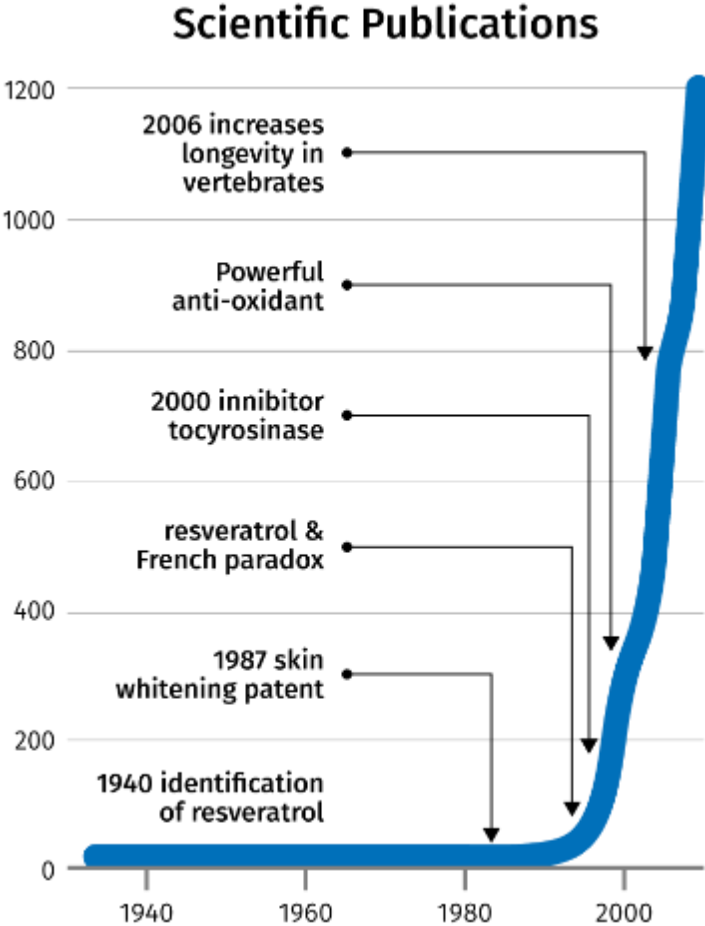


Polygonum cuspidatum
"Knotweed" ($<0.3\%$)



Mulberries

Resveratrol: Science and consumer awareness are building up rapidly



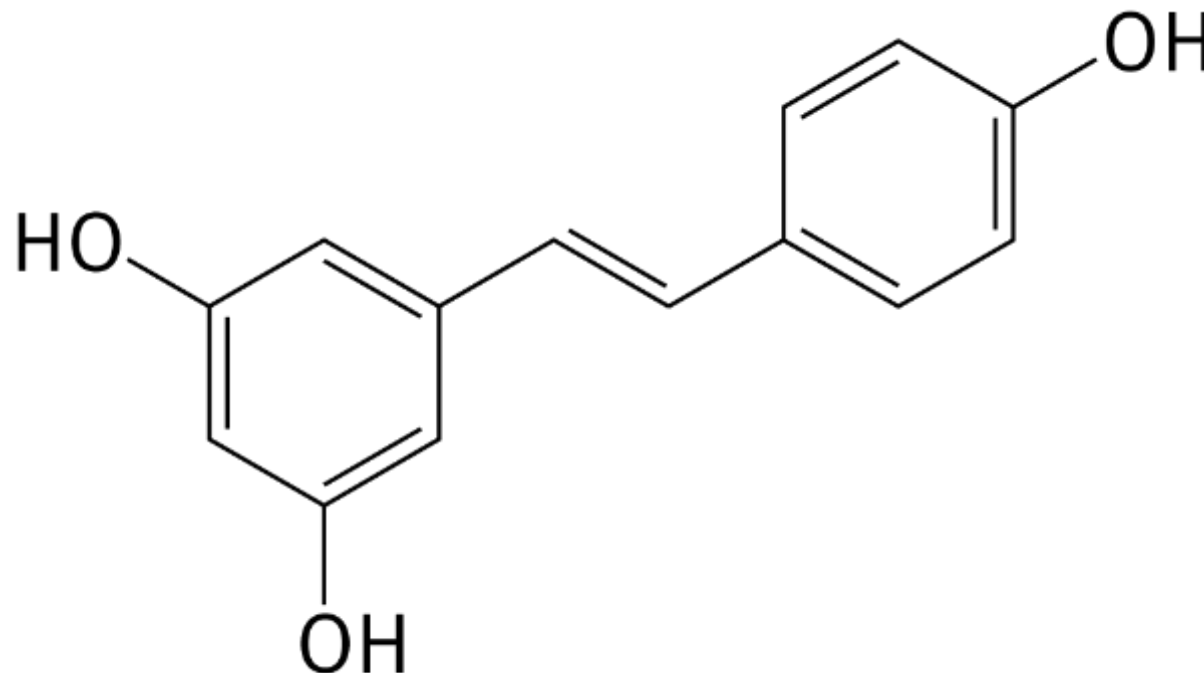
Resveratrol: Radical scavenging and anti oxidative properties



Resveratrol exhibited stronger anti radical activity than kaempferol and is more efficient than α -tocopherol

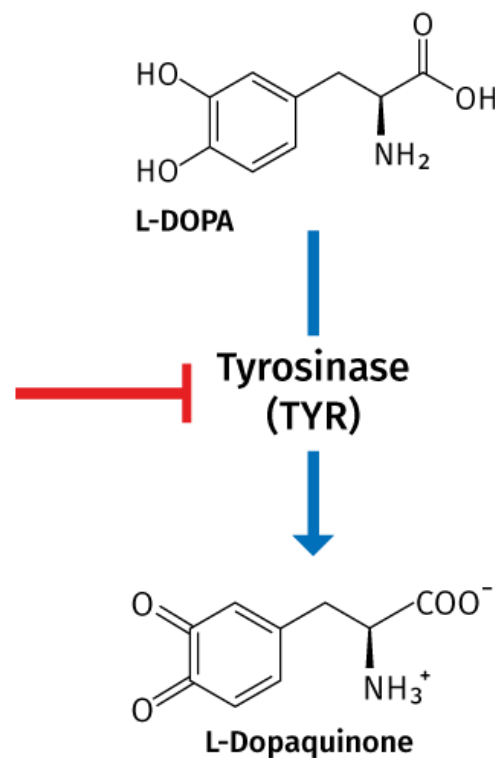
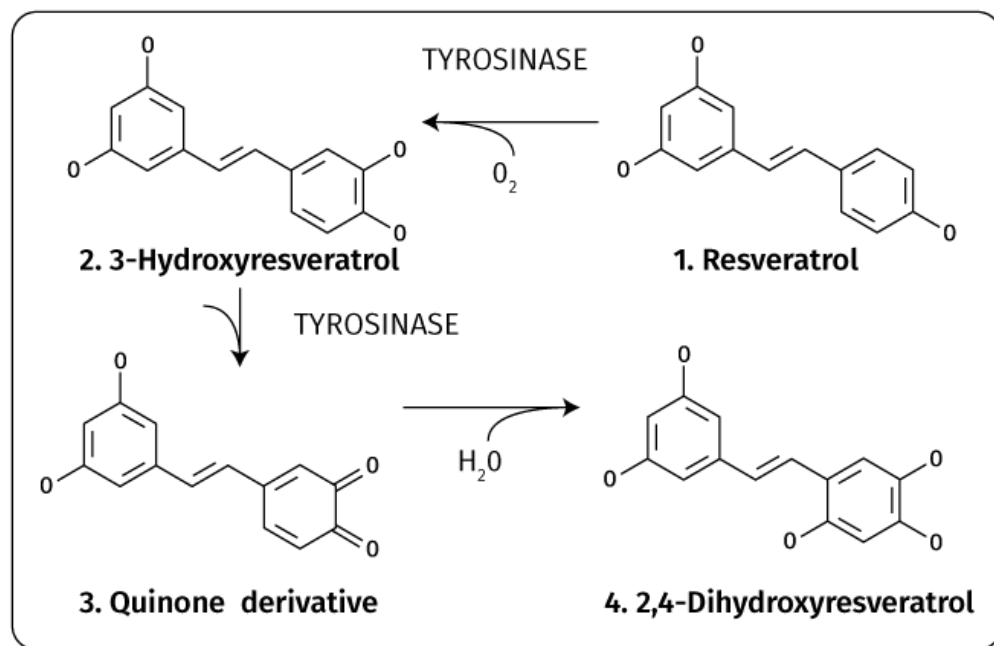


Resveratrol was found to be stronger anti oxidant than catechin and kaempferol



Resveratrol: Inhibitor to Tyrosinase

Bernard P. and Berton J.-Y., IJoCS, 22, 219-226 (2000)

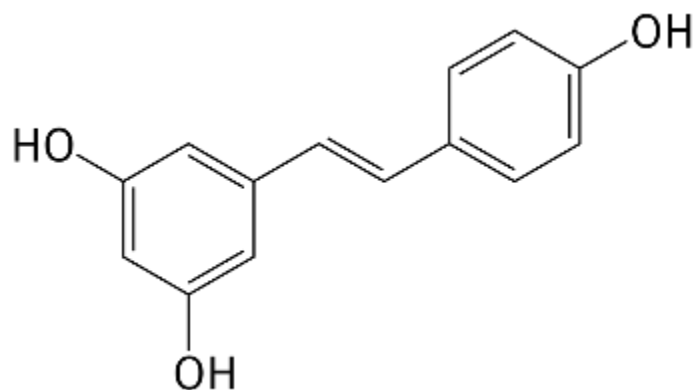


What is REGU[®]-FADE?

Nature-identical, pure, substantiated

Why REGU[®]-FADE?

- ✓ Fast, visible results (14 days)
- ✓ Multi target mechanism
- ✓ Strong scientific substantiation
- ✓ Two Clinical studies with significant results
- ✓ Complete safety dossier
- ✓ High consumer awareness for resveratrol
- ✓ Registered in China
- ✓ Appealing stories: red wine, life-extending, french paradox



> 99% trans-Resveratrol

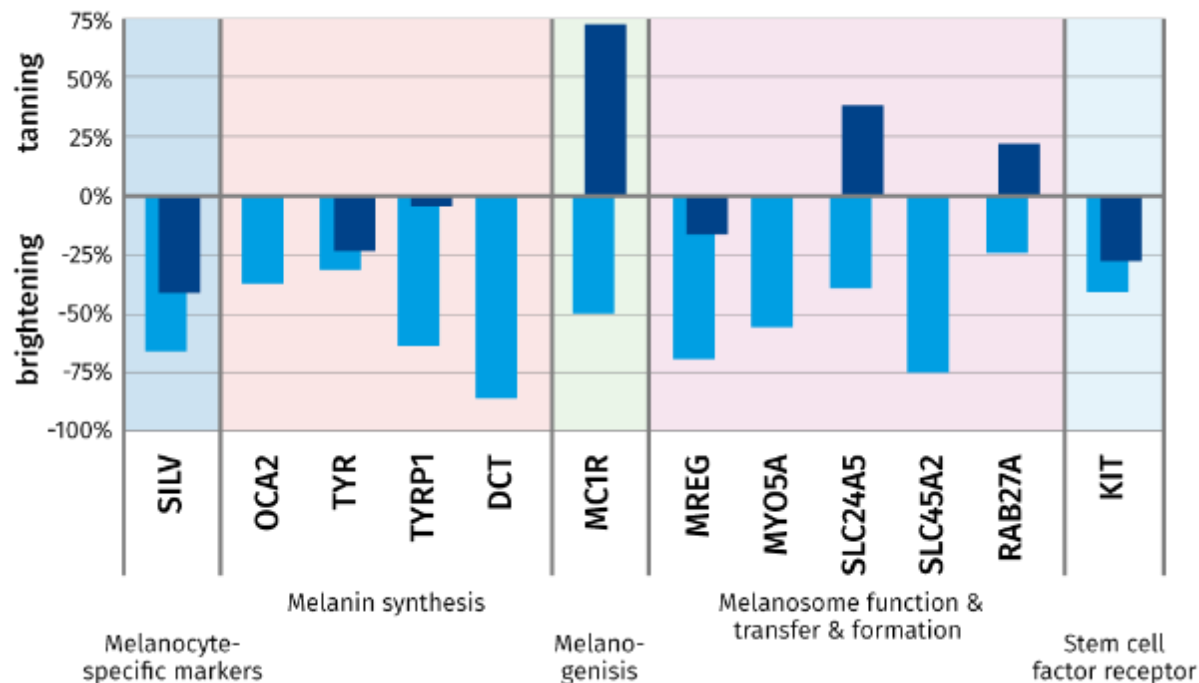
Why a nature-identical form?

- ✓ Free from pesticides
- ✓ Free from emodin
- ✓ Does not contain cis-form
- ✓ Organic synthesis vs. solvent extraction from low yield plants
- ✓ Consistent supply

REGU[®]-FADE: Multi target mechanism

Efficacy: in vitro - Gene expression (PCR array)

REGU[®]-FADE vs Ascorbyl Glucoside



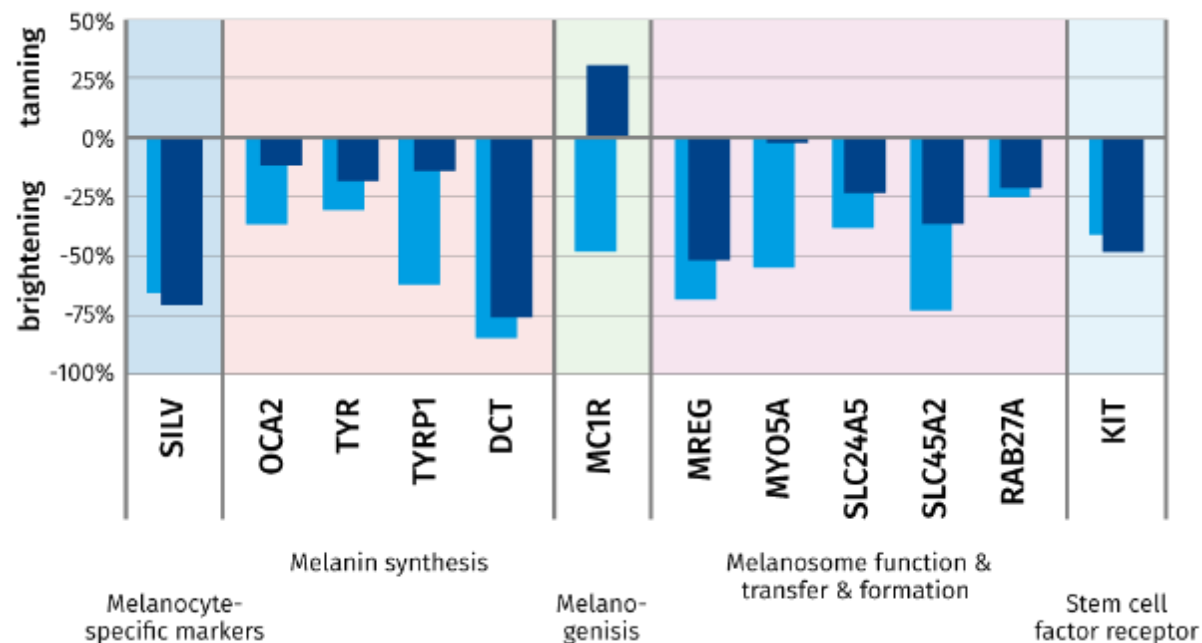
- Tissue
Human Melanocytes
- Treatment
88μM REGU[®]-FADE
1180μM Ascorbyl Glucoside
- Timepoint
72h

0.002% REGU[®]-FADE downregulates the expression of key genes involved in the pigmentation process

REGU[®]-FADE: Multi target mechanism

Efficacy: *in vitro* - Gene expression (PCR array)

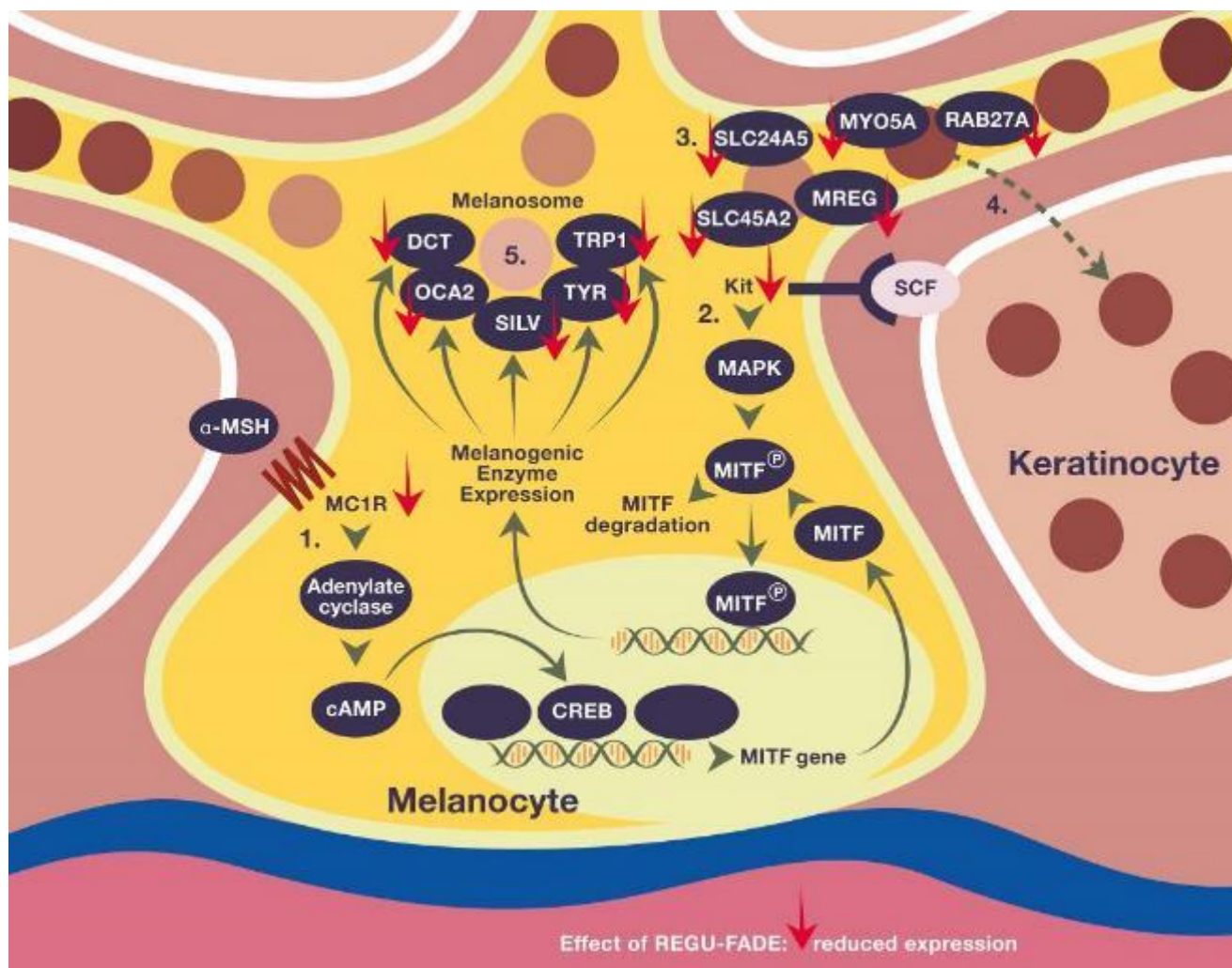
REGU[®]-FADE vs cis-Resveratrol



- Tissue
Human Melanocytes
- Treatment
88μM REGU[®]-FADE
88μM cis-Resveratrol
- Timepoint
72h

REGU[®]-FADE is more effective than cis-Resveratrol

REGU[®]-FADE: Multi target mechanism



1) α - MSH signaling

REGU[®]-FADE downregulates the MCR1 (α - MSH receptor) expression level, leading to decreased expression of MITF-regulated genes such as SILV, TYR (tyrosinase), TRP1, DCT, OCA2 which reduces melanin synthesis.

2) KIT signaling

REGU[®]-FADE decreases KIT (=stem cell factor receptor) gene expression which additionally reduces melanin synthesis.

3) Melanosome function & maturation

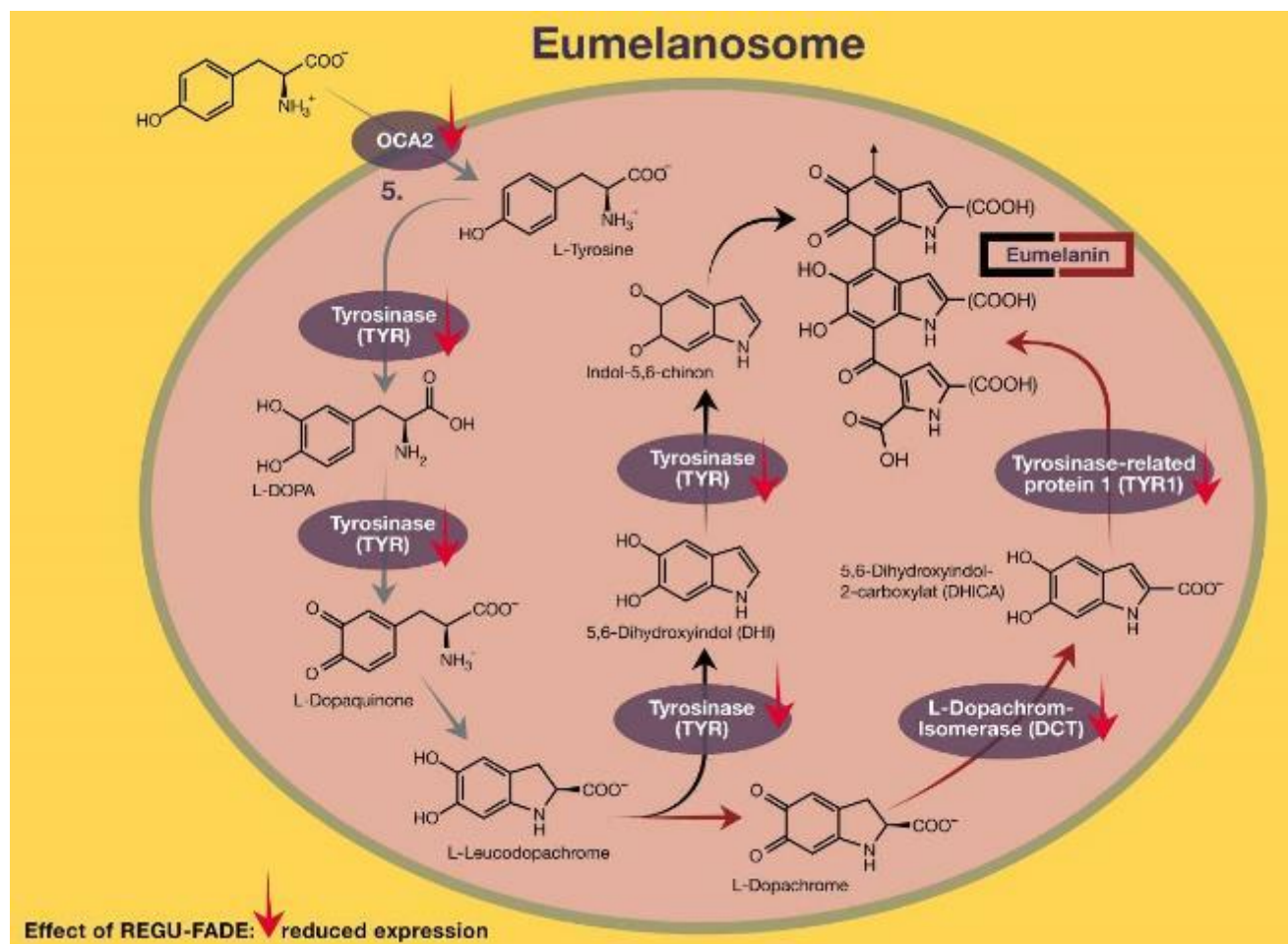
REGU[®]-FADE also affects the function and maturation of melanosomes by reduction of SLC24A5 and SLC45A2 gene expression levels.

4) Melanosome transport

REGU[®]-FADE attenuates melanosome transport within melanocytes, shown by the reduction of the MYO5A and MREG gene expression levels as well as the melanosome transport to keratinocytes, shown by the reduction of RAB 27A gene expression levels.

5) Melanin synthesis

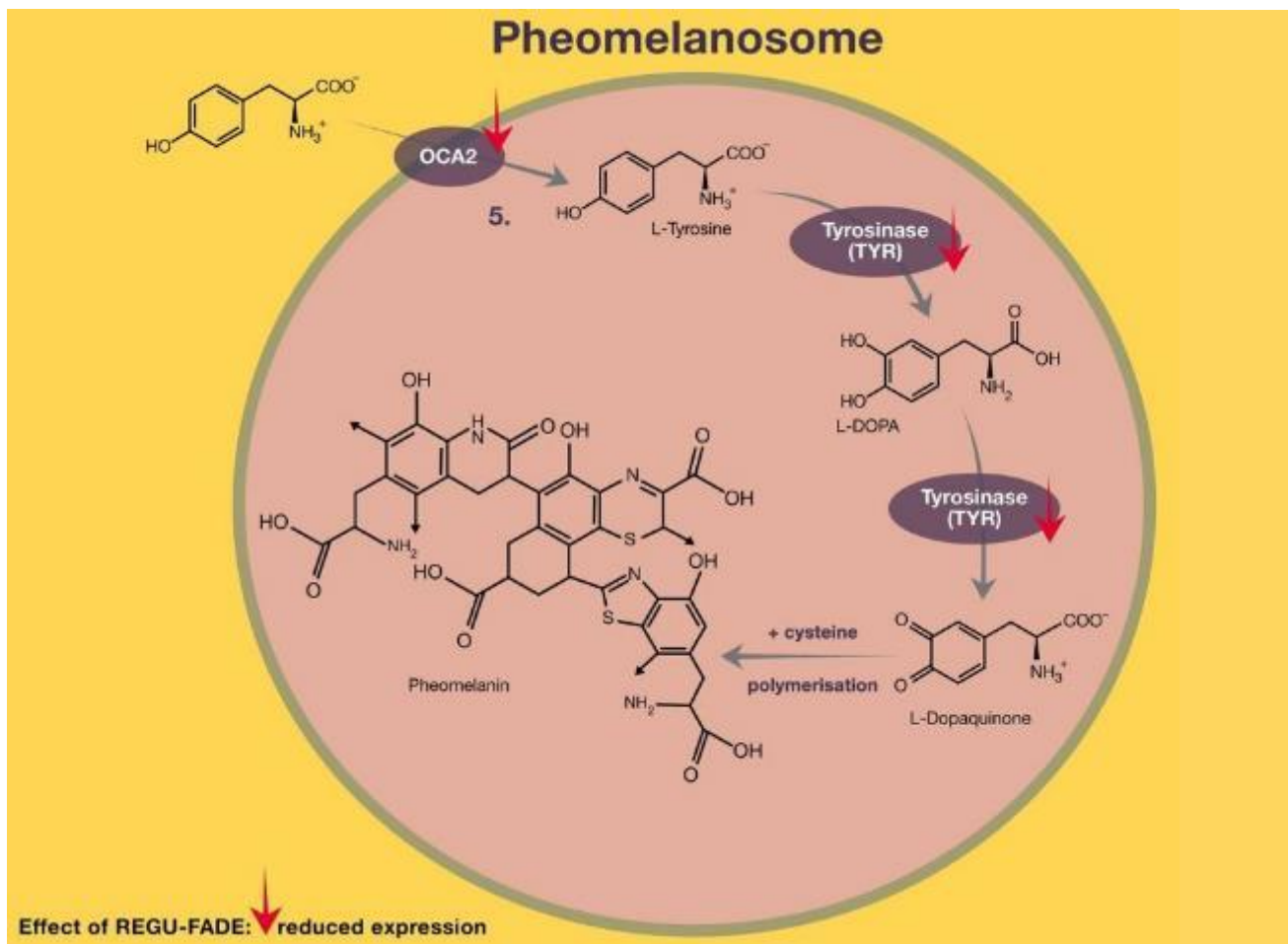
REGU[®]-FADE: Multi target mechanism



5) Eumelanin synthesis

REGU[®]-FADE reduces the conversion of tyrosine into eumelanin at various points, shown by the downregulation of OCA2, TYR (tyrosinase), DCT and TYR1 gene expression levels

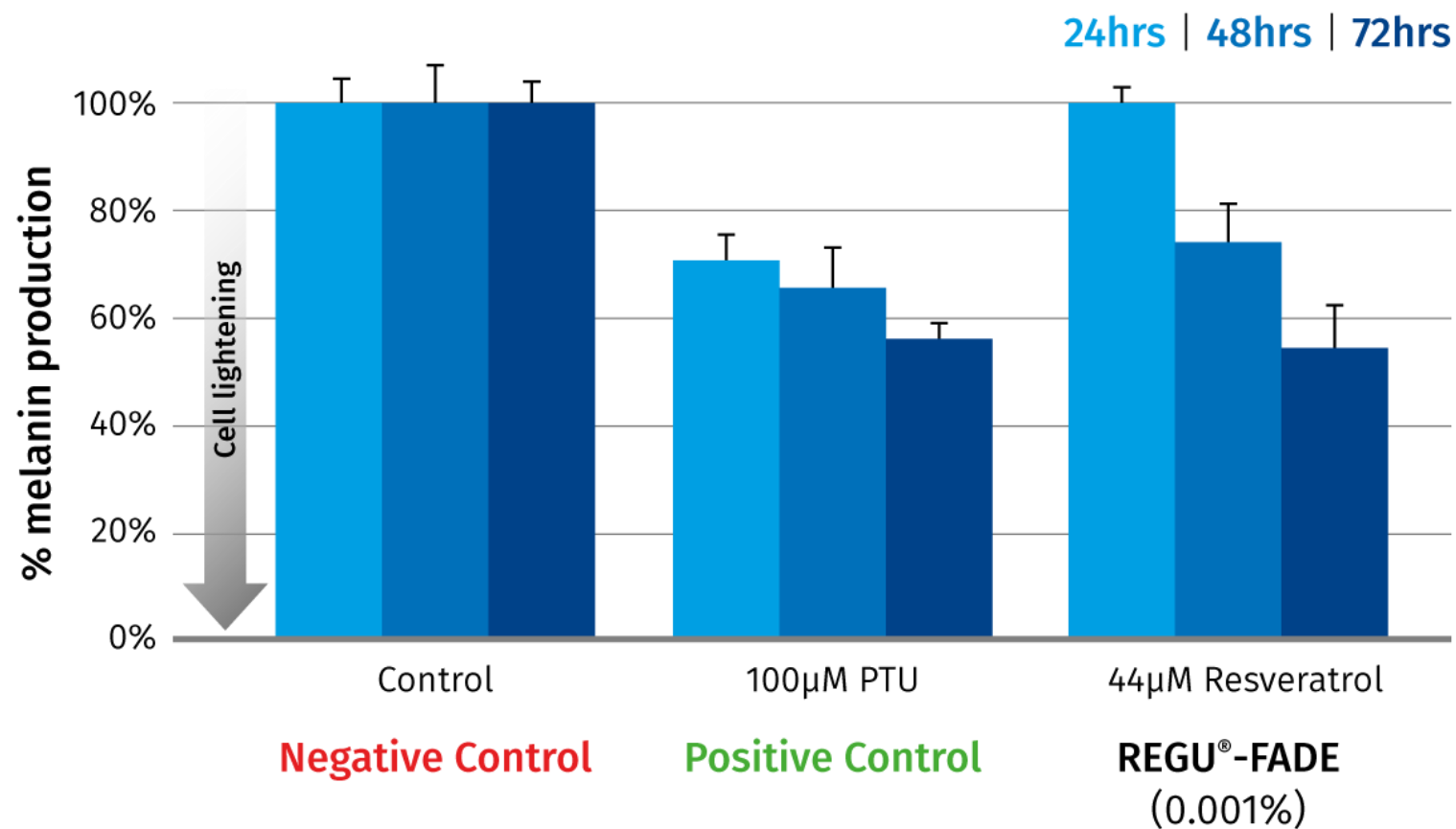
REGU[®]-FADE: Multi target mechanism



5) Pheomelanin synthesis

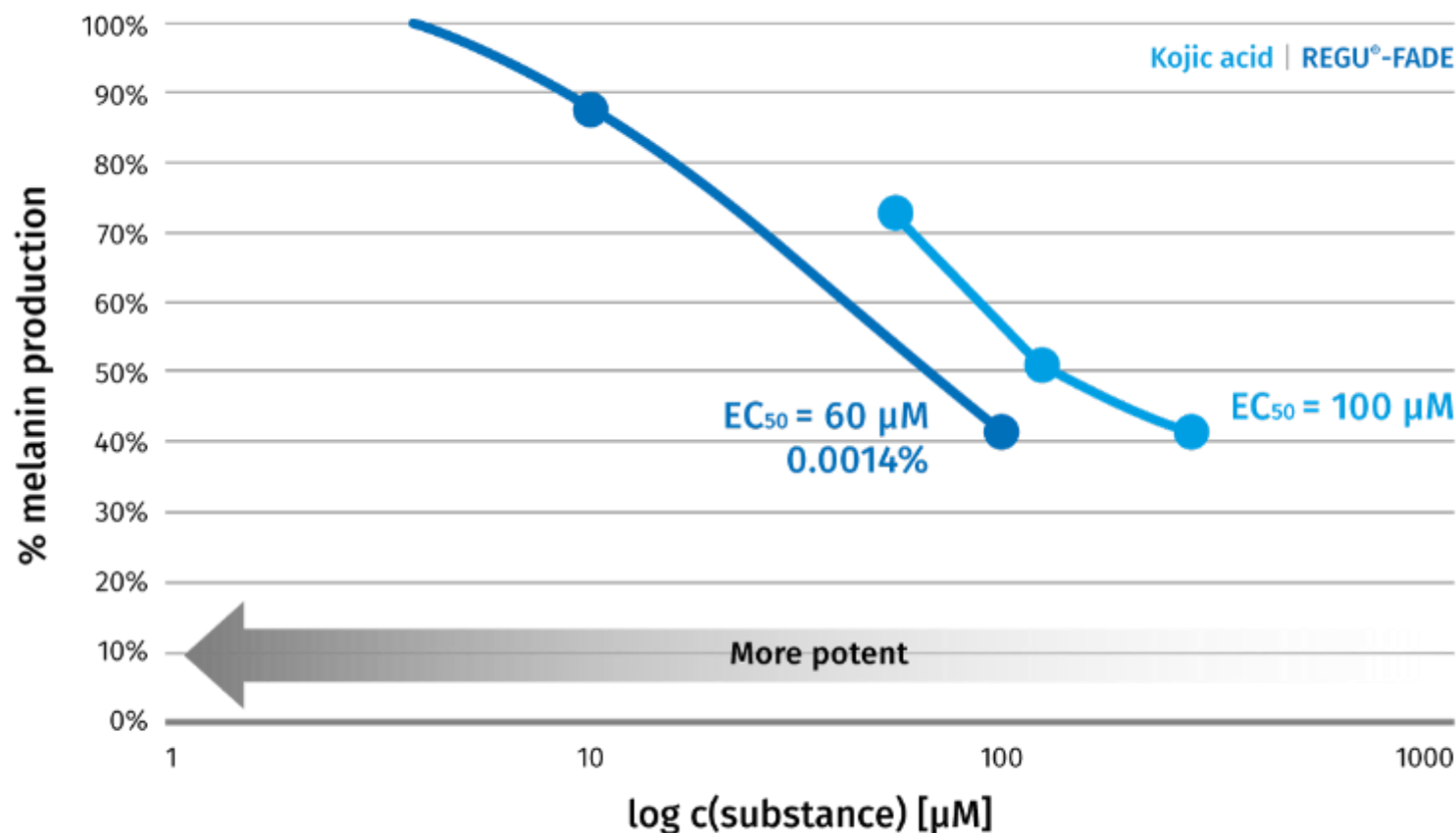
REGU[®]-FADE reduces the conversion of tyrosine into pheomelanin at various points, shown by the downregulation of OCA2 and TYR (tyrosinase) gene expression levels.

Efficacy: *in vitro* – Melanin Assay in B16F10 Cells



0.001% REGU®-FADE
reduces melanin
production by 50% in
B16F10 Melanin Assay

Efficacy: *in vitro* on Normal Human Melanocytes

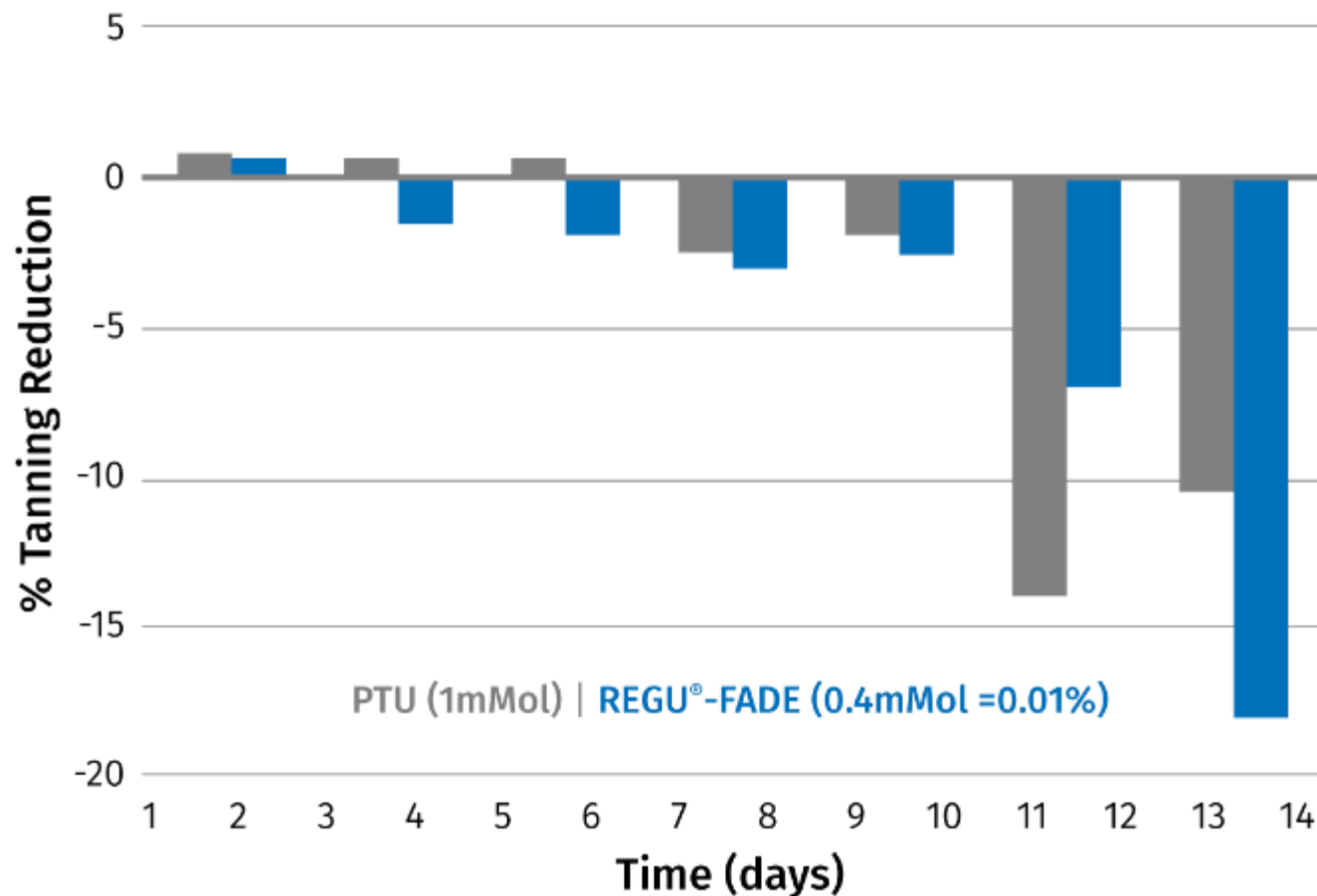


Performed at BIOalternatives

REGU®-FADE
performs better
than Kojic acid

- Tissue
Normal Human
Melanocytes
- Treatment
REGU®-FADE
Kojic acid

Efficacy: *in vitro* – Skin brightening in 3D-human reconstituted epidermis



REGU®-FADE performs excellent after 14 days in 3D - human reconstituted epidermis



before



after 14 days

Efficacy:

in vivo – long term study



Double-blind placebo controlled study with 53 Indian volunteers performed by CLAIMS (India)



Study duration: 90 days



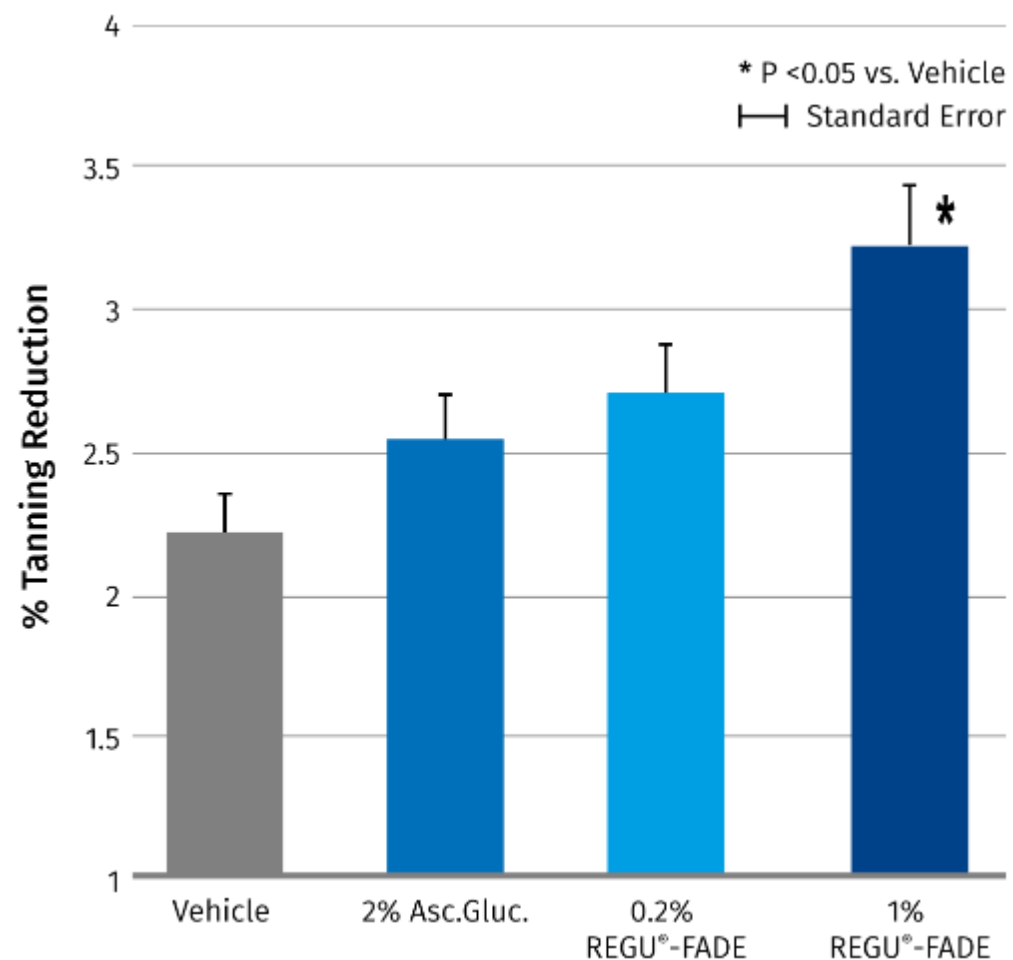
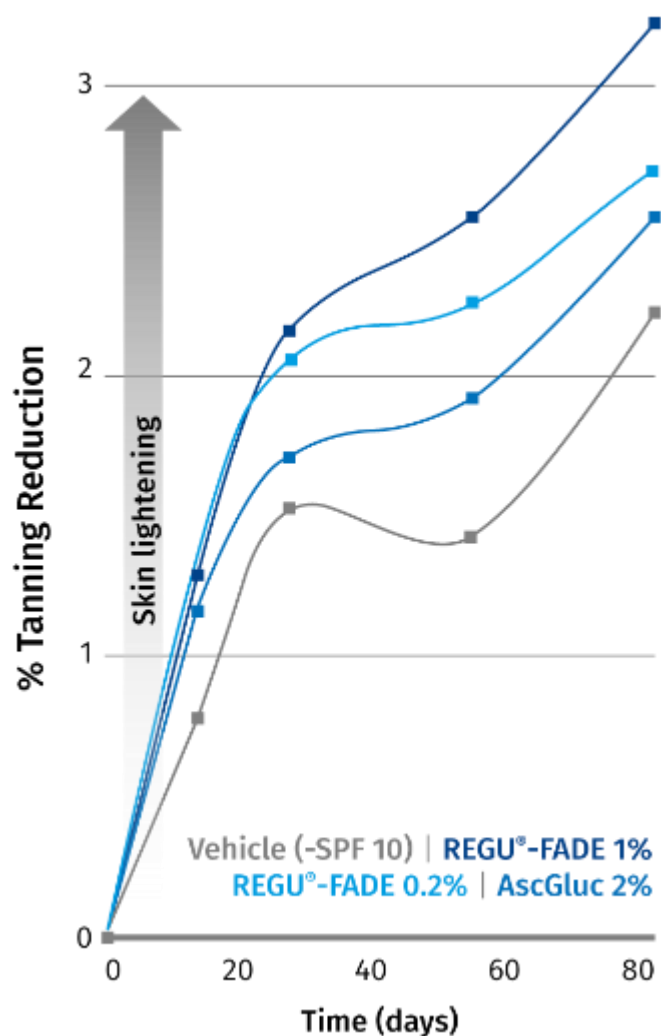
Per test area a cream (SPF ~10) + test substance (0.2% REGU[®]-FADE, 1% REGU[®]-FADE, 2% Ascorbylglucoside, Placebo) was applied twice daily on the volar forearms.



Colorimetric measurements were performed after 2 and 4 weeks, 2 and 3 months (ITA[°] value's define the degree of skin pigmentation)



Efficacy: *in vivo* – long term study



Visible and significant skin brightening with 1% REGU®-FADE

REGU[®]-FADE: *in vivo* short term study



A double-blind placebo controlled study performed by proDERM (Germany) was performed with 12 Caucasian volunteers.



Per test area creams (1% REGU[®]-FADE, 2% Ascorbyl Glucoside, Placebo) were applied 3 times per day on their volar forearms



Study duration: 14 days

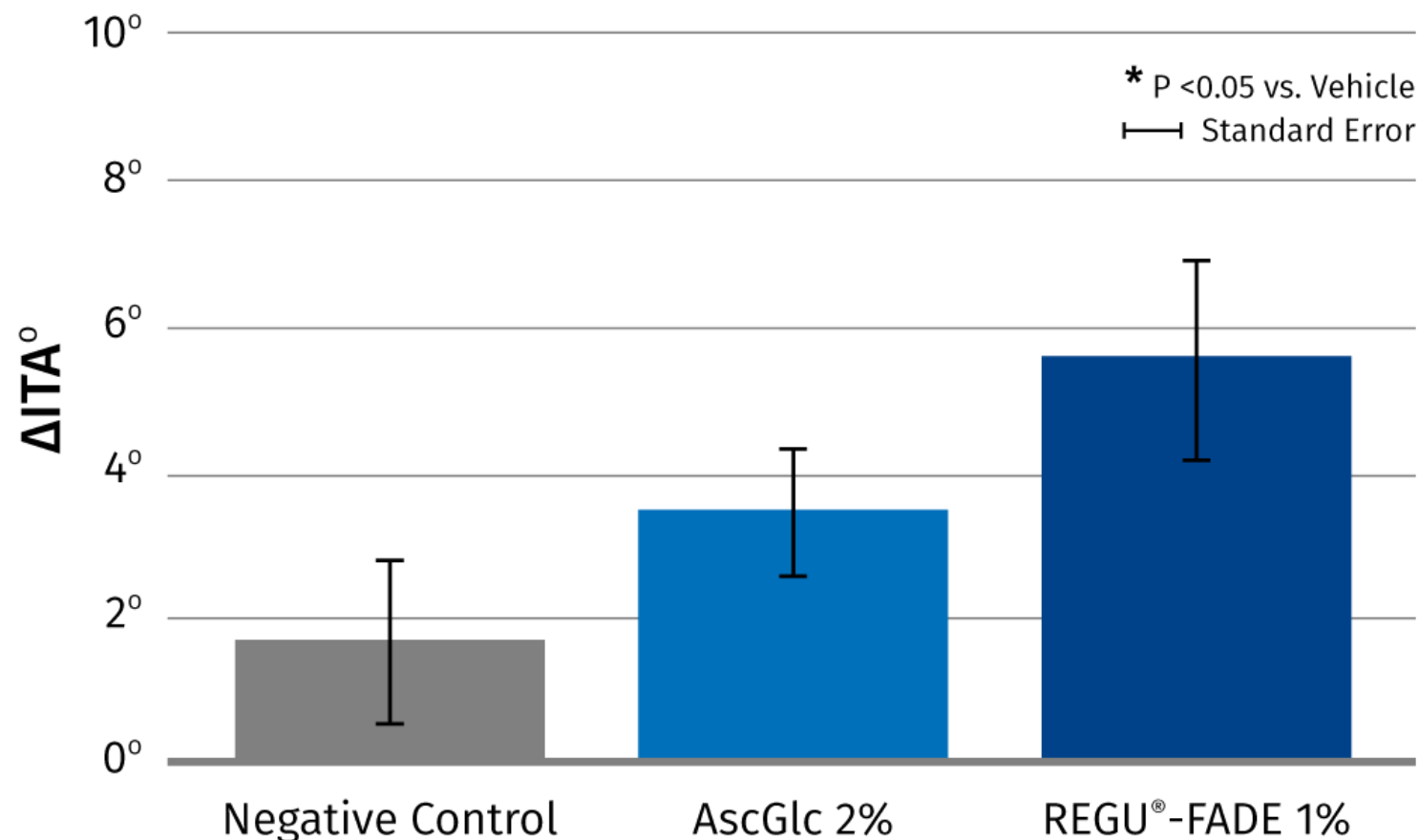


Colorimetric measurements were performed after 14 days



REGU[®]-FADE: *in vivo* short term study

ΔITA° of >3 can be distinguished visually



Fast-acting:
Visible and significant
results in only 2 weeks!

REGU[®]-FADE - Properties

General properties:

- ✓ Off-white to light brown
 - ✓ Practically odorless
 - ✓ Preservative-free
 - ✓ Thermostable
-
- Sensitive to light
 - Almost insoluble in water (23 mg/l) and in lipophilic components



A broad range of suitable solubilizers for REGU[®]-FADE was identified to produce stable formulations.*



REGU[®]-FADE – Formulation Guidelines

- **Cosmetic application**
 - REGU[®]-FADE can be used for different kinds of products like O/W, W/O or Si/W formulations, toners, as well as in gel formulations
 - Skin brightening facial and body care products
 - Anti-age spot creams and serums
 - Anti-aging skin care products for more even skin tone
- **Suggested concentration**
Up to 1 % REGU[®]-FADE in cosmetic formulations
- **INCI name**
Resveratrol



REGU[®]-FADE – Formulation Guidelines

- Additional information
 - Optimal pH range from 3 to 6.5 in formulations
 - Exposure of the final formulations to direct sun light should be avoided (use opaque packaging)
 - The addition of UV filters is recommended for day care products



REGU®-FADE

Intensive Skin Tone Corrector

Phase	Ingredients	INCI Name	% w/w
A	Imwitor 372 P Schuppen	Glyceryl Stearate Citrate	2.00
	Lanette 16	Cetyl Alcohol	1.00
	Lipocire Na 10 Pastilles	Hydrogenated Coco Glycerides	1.00
	Finsolv TN	C12-15 Alkyl Benzoate	4.00
	Dow Corning 200 Fluid 100 cs	Dimethicone	2.00
	Tegosoft M	Isopropyl Myristate	6.00
	da-Tocopheryl Acetate	Tocopheryl Acetate	0.20
B	Keltrol CG-T	Xanthan Gum	0.15
	Pemulen TR-1	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.30
	Water dem.	Aqua	72.33
C	REGU®-FADE	Resveratrol	1.00
	Dow Corning 190 Surf.	PEG/PPG-18/18 Dimethicone	4.00
	1,2-Propanediol	Propylene Glycol	5.00
D	Preservative	q.s.	
	Triethanolamine (T.E.A.)	Triethanolamine	0.22

100250-301

Contains

1% REGU®-FADE

Solubilizer:

4% PEG/PPG – 18/18
Dimethicone

Solvent:

5% Propylene Glycol

Example formulation with high content of **REGU®-FADE** without any cristal formation or discoloration after 3 months storage at RT, 4°C, and 43°C.

REGU[®]-FADE

Multi-active Brightening Cream

Phase	Ingredients	INCI Name	% w/w
A	Isopropyl Myristate	Isopropyl Myristate	2.00
	Myritol 318	Caprylic/Capric Triglyceride	5.00
	Fitoderm	Squalane	1.50
	Preservative	q.s.	
	Novemer EC-1	Acrylates/Acrylamide Copolymer Mineral Oil & Polysorbate-85	1.00
B	D-PANTHENOL 75L	Panthenol	2.00
	Carbopol Ultrez 21	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.20
	Water dem.	Aqua	86.40
C	Cremophor RH 40	PEG-40 Hydrogenated Castor Oil	1.00
	REGU[®]-FADE	Resveratrol	0.10
D	Triethanolamine (T.E.A)	Triethanolamine	0.20

100250-269

Contains

0.1 % REGU[®]-FADE
+ 2.0 % Panthenol

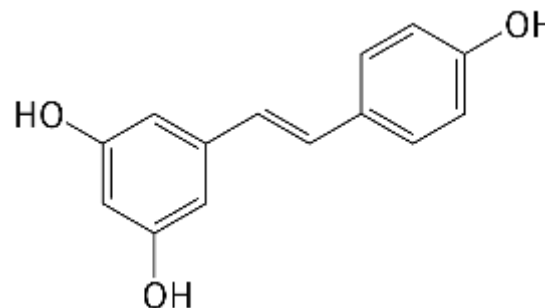
Solubilizer:

1% PEG-40 Hydrogenated
Castor Oil

Example formulation with
high water content without
any cristall formation or
discoloration after 3 months
storage at RT, 4°C, and 43°C.

REGU[®]-FADE – Summary

- The most effective solution for noticeably brighter skin
 - Visibly brighter skin in 2 weeks
 - Nature-identical pure trans-resveratrol for more effectiveness and even skin brightening
 - Multi-target mechanism
- Clinically proven in 2 studies
- Broad range of supporting preclinical studies
- Nature-identical pure resveratrol
- With full safety documentation
- Extensive formulation guidelines
- Registered in China



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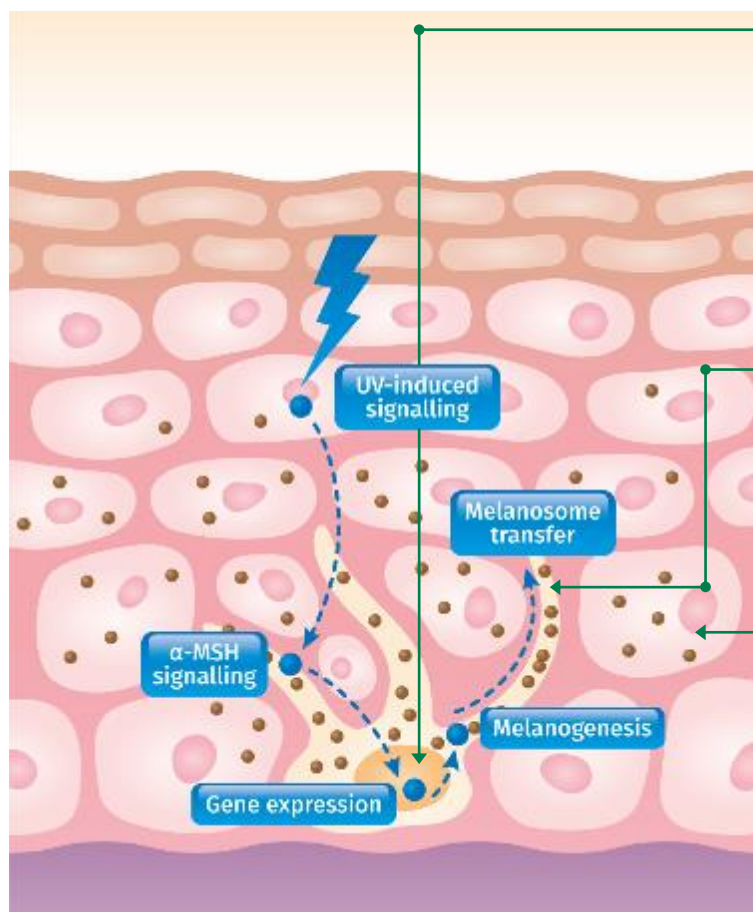
Disclaimer Formulation Guideline

This information is for illustration purposes only and based upon our current knowledge and experience at the time of printing. We do not make any representation or warranty of any kind, express or implied, including merchantability or fitness for a particular use, with respect to such information or its application. Use of this information is at your discretion and risk. Nothing herein relieves you from carrying out your own suitability determinations and tests. You are responsible for observing all laws and regulations relevant to your products, uses or processes. We do not assume any liability in connection with your product and its use. The foregoing information and suggestions are also provided without warranty of non-infringement as to the intellectual property rights of third parties, and shall not be construed as any inducement to infringe the rights of third parties.

Back-up REGU[®]-FADE



Safe Skin Brightening is Inhibition of Tanning



Melanocytes

- part of the basal cell layer of the epidermis
- form long, finger-like dendrites which reach to neighboring keratinocytes
- create enzymes (e.g. tyrosinase) and the amino acid tyrosine

Melanosome

- is an organelle (specialized subunit within a cell) containing melanin
- converts tyrosine into Eumelanin (brown – black) and Pheomelanin (yellow – red)
- migrates upward into the dendrites and are taken up by keratinocytes

Effective skin brightening requires to attenuate the melanin production cascade at multiple points.

Resveratrol content in wines

Variety	mg/L
Pinot noir	3.1
Cabernet sauvignon	1.8
Cabernet franc	2.0
White wines	1.0

Creasy et al., 1998



Resveratrol The French Paradox



French Paradox and Resveratrol associated since the late 90s.



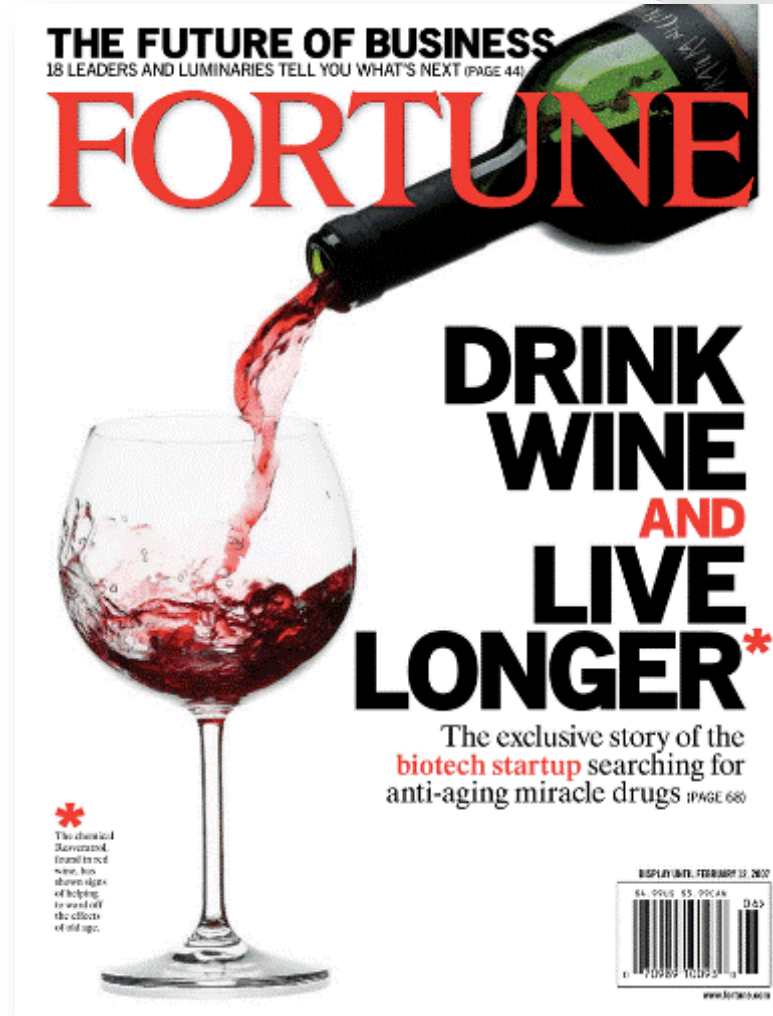
The French exhibit an astonishing low incidence of heart disease (42% lower than Americans) while consuming one of the highest fat diets in the world.



They are also famous for their soft spot for good red wine in modest but regular quantities.



The regular consumption of red wine has been found to correlate with a reduced risk of coronary heart disease.



Melanogenesis associated genes

GENES	FUNCTIONS
SILV	melanosome marker on transcript and protein level
OCA2	transmembrane transport
TYR	provides instructions for making tyrosinase
TYRP1	stabilizes tyrosinase protein and modulates its catalytic activity
DCT	regulates eumelanin
MC1R	• activated by α-msh • controls the melanogenesis
MYO5A	melanosome transport
MREG	melanosome formation and transport
SLC24A5	melanosome function and maturation
SLC45A2	melanosome function
RAB27A	transfer of melanin to keratinocytes
KIT	• stem cell factor receptor • involves in the process of proliferation • differentiation and activity of melanocytes • triggers mitf mediated gene expression



Melanogenesis associated genes in hyperpigmented skin

Melanogenesis associated genes: e.g. TYRP1 (tyrosinase-related protein 1), DCT (dopachrome tautomerase), Pmel-17 (SILV protein), MITF (microphthalmia-associated transcription factor) are all increased in actinic lentigos.

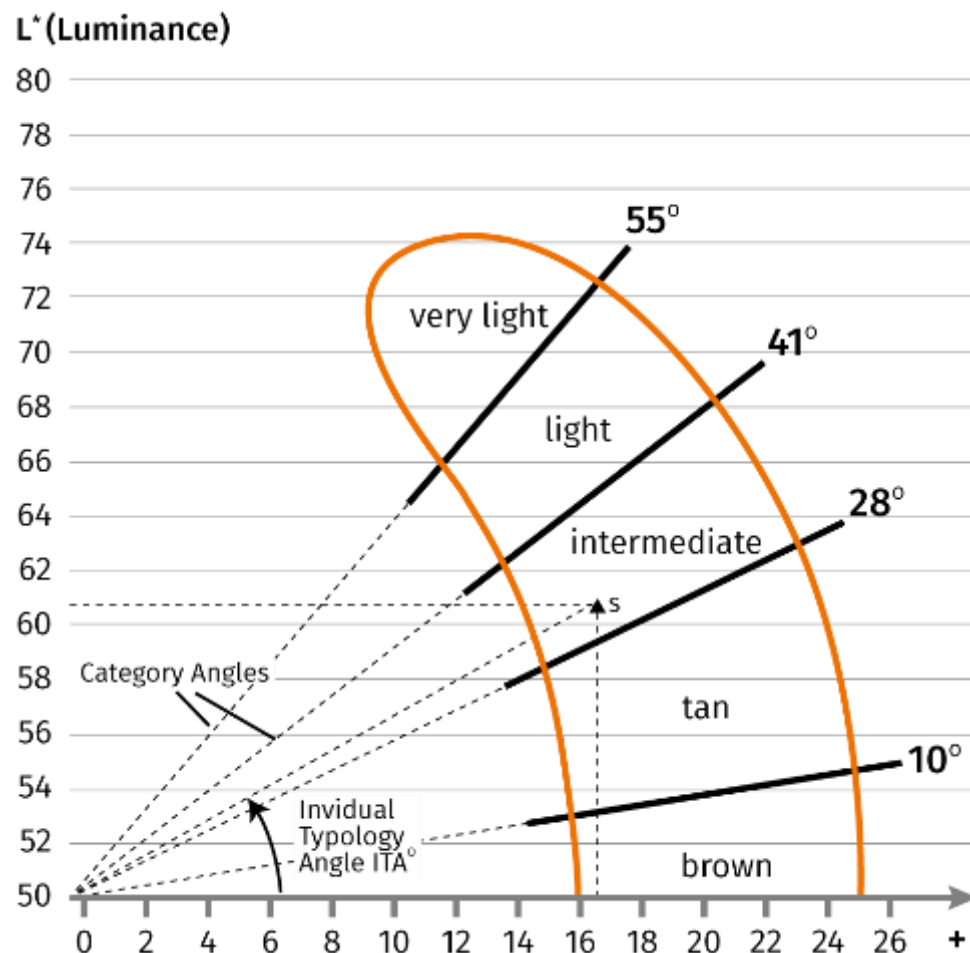
There is also a role for stem cell factor (SCF) in hyperpigmentation (solar lentigos in particular)

Latest Insights into Skin Hyperpigmentation - review
Jean-Paul Ortonne¹ and Donald L. Bissett;
Journal of Investigative Dermatology Symposium Proceedings (2008) 13, 10–14; doi:10.1038/jidsymp.2008.7



ITA°: Individual Typology Angle

(defines the degree of skin pigmentation)



SKIN COLOUR TYPING

CIE-L*a*b (1976) COLOUR SPACE
Plane L*Λ*b
(Chardon 1990)

Individual Typology Angle:

$ITA^\circ = (\text{ArcTan}((L^*-50)/b^*)) \times 180 / 3.1415$
(when ArcTan calculated in radians)

ITA° = 12° 26°

L: Luminance (dark – light)

a: green to red spectrum

b: blue to yellow spectrum

The higher L parameter and the ITA are, the lighter the skin

L: 55	L: 55
a: 9.3	a: 9.3
b: 28	b: 10

Efficacy: performed by CLAIMS

(India) study formulation

PHASE	Ingredients	INCI Name	% w/w	Supplier
A	PARSOL® 1789	Butyl Methoxydibenzoylmethane (Avobenzone; USAN)	2.00	100288
	PARSOL® 340	Octocrylene (Octocrilene; USAN)	6.00	100288
	Imwitor 372 P Schuppen	Glyceryl Stearate Citrate	2.00	100398
	Lanette O	Cetearyl Alcohol	1.50	100396
	Lipocire Na 10 Pastilles	Hydrogenated Coco-Glycerides	1.00	100413
	REGU®-FADE	Resveratrol	0.20	100288
	Finsolv TN	C12-15 Alkyl Bezoate	7.00	100472
	Myritol PC	Propylene Glycol Dicaprylate/Dicaprate	5.00	100396
	d-alpha Tocopheryl Acetate	Tocopheryl Acetate	0.20	100288
B	Keltrol CG-T	Xanthan Gum	0.15	100400
	Pemulen TR-1	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.30	100435
	Dow Corning 190 Surfactant	PEG/PPG-18/18 Dimethicone	4.00	100404
	1,2-Propanediol	Propylene Glycol	5.00	100134
	Water dem.	Aqua	62.63	0
D	Phenonip	Phenoxyethanol & Methylparaben & Ethylparaben & Butylparaben & Propylparaben & Isobutylparaben	0.80	100394
	Triethanolamine (T.E.A.)	Triethanolamine	0.22	100134
	Ethanol	Alcohol	2.00	100230

100250-100/001

REGU®-FADE: performed by PRODERM

(GERMANY) study formulation

PHASE	Ingredients	INCI Name	% w/w	Supplier
A	Imwitor 372 P Schuppen	Glyceryl Stearate Citrate	2.00	100398
	Lanette O	Cetearyl Alcohol	1.50	100396
	Lipocire Na 10 Pastilles	Hydrogenated Coco-Glycerides	1.00	100413
	Finsolv TN	C12-15 Alkyl Benzoate	7.00	100472
	Myritol PC	Propylene Glycol Disaprylate/Dicaprate	5.00	100396
	d-alpha Tocopheryl Acetate	Tocopheryl Acetate	0.20	100288
	Tegosoft M	Isopropyl Myristate	8.00	100415
B	Keltrol CG-T	Xanthan Gum	0.15	100400
	Pemulen TR-1	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.30	100435
	Water dem.	Aqua	63.83	0
C	Dow Corning 190 Surfactant	PEG/PPG-18/18 Dimethicone	4.00	100404
	1,2-Propanediol	Propylene Glycol	5.00	100134
	REGU®-FADE	Resveratrol	1.00	100288
D	Phenonip	Phenoxyethanol & Methylparaben & Ethylparaben & Butylparaben & Propylparaben & Isobutylparaben	0.80	100394
	Triethanolamine (T.E.A.)	Triethanolamine	0.22	100134

100250-187/001

BRIGHT SCIENCE. BRIGHTER LIVING.™