

Emblica™

**A new safe skin lightener
with multifunctional attributes**

**Dr. Ratan K. Chaudhuri, Francois Marchio,
EM Industries , New York, USA**

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Updated 2/26/02

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What is Emblica™ ?

- ⊕ A Multifunctional Natural Antioxidant
- ⊕ Isolated from *Phyllanthus emblica* fruit (edible)
 - ⊕ One of the key medicinal plants in Ayurvedic system (Science of Life) of medicine
 - ⊕ Standardized extract
- ⊕ Key active ingredients
 - ⊕ Emblicanin A & Emblicanin B
- ⊕ Patent protected product composition (US 6,124,268)
- ⊕ INCI name: *Phyllanthus emblica* fruit extract



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Product Highlights

- ⊕ Pro-oxidation free natural antioxidant
 - ⊕ Broad-spectrum activity
 - ⊕ Chelator for iron & copper
 - Eliminates transition metal-induced oxidative damage
- ⊕ Excellent ingredient for age-defying products
 - ⊕ Inhibits collagenase activity
 - ⊕ Stimulates non-collagenic proteins
 - ⊕ Reduces & repairs UV-induced skin damage (clinical)
- ⊕ Excellent skin lightening agent
 - ⊕ Comparative clinical studies with commercial products
- ⊕ Excellent safety profile

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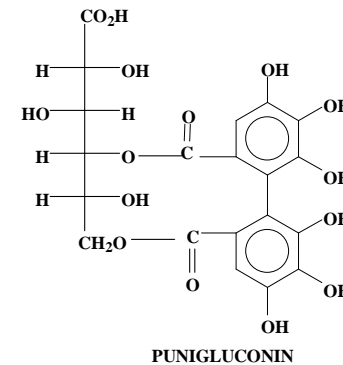
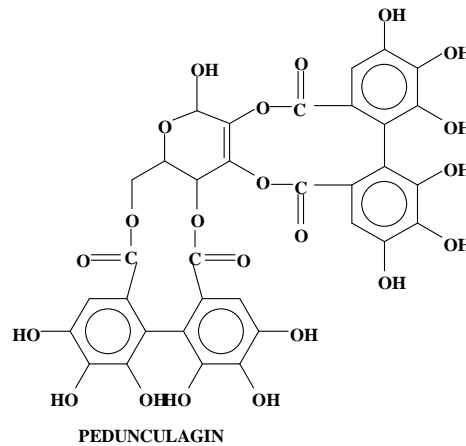
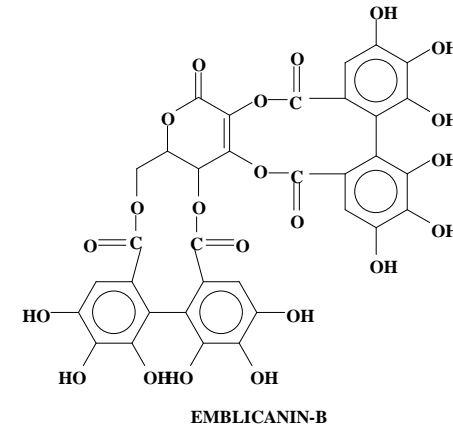
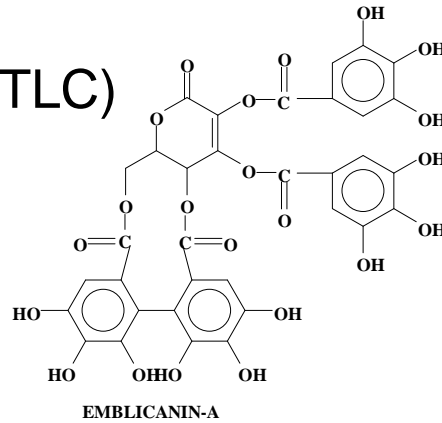
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Key ingredients in Emblica™

Standardized (HPLC/HPTLC)

- Hydrolyzable tannins
➤ 50% min
- Water-soluble fraction
➤ 80% min
- Lipid-soluble fraction
➤ 20% max



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Sources of iron & copper in skin

- ⊕ UV-light causes release of iron from iron-storage protein ferritin
 - ⊕ **UV-B induced formation of superoxide radical and its attack to ferritin** [Masaki et al, (1995) *Biochem.Biophys.Res.Commun.*, 206, 474-479]
 - ⊕ **UV-A induced degradation of iron** [Pourzand et al, (1999) *Proc.Natl.Acad.Sci.*, 96, 6751-6756]
 - ⊕ **Elevated levels of iron in sun-exposed body sites** [Bissett & McBride, (1992) *J.Soc.Cosmet.Chem.* 43, 215-217]
- ⊕ Sweat also contains iron & copper
 - ⊕ **Shown by taking samples from athletes immediately after exercise** [Gutteridge et al, (1985) *Clin.Chim.Acta*, 267-273]
- ⊕ Water

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Fenton chemistry

⊕ Requires iron and H₂O₂

- ⊕ $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Intermediate complex (es)}$
 $\rightarrow \text{Fe}^{3+} + \text{OH}^\bullet + \text{OH}^-$ (Very fast reaction)
- ⊕ $\text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Intermediate complex (es)}$
 $\rightarrow \text{Fe}^{2+} + \text{O}_2^{\bullet-} + 2\text{H}^+$ (slow reaction)

⊕ Requires Fe³⁺ chelates and H₂O₂

- ⊕ $\text{Fe}^{3+}\text{-EDTA} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+}\text{-EDTA} + \text{O}_2^{\bullet-} + 2\text{H}^+$

⊕ Requires iron(or copper), H₂O₂ & an antioxidant

- ⊕ $\text{Fe}^{3+} + \text{ascorbate} \rightarrow \text{Fe}^{2+} + \text{ascorbate}^\bullet$
 $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow [\text{intermediate complex(es)}]$
 $\rightarrow \text{Fe}^{3+} + \text{HO}^\bullet + \text{HO}^-$

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What is the solution?

⊕ Possibilities

- ⊕ Alteration of oxidation potential of iron to disfavor reaction with hydrogen peroxide
- ⊕ Blocking the available coordination sites on the iron to avoid attachment of H_2O_2

⊕ Ideal solution

- ⊕ A product having both
 - ☐ Chelating functionality
 - ☐ Antioxidant functionality
 - ☐ Separated from each other

⊕ Does this product exist?

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Chelating Property: Azide-induced UV spectral analysis

⊕ Methodology

⊕ Reference:

- E. Graf, J.R. Mahoney, R.G. Byrant and J.W. Eaton, *J.Biol. Chem.*, 259, 3620-3624 (1984).
- A.E. Martell, R. Gustafson & S. Charberek, *In Advances in Catalysis*, IX (A. Farakas, ed.), 319-329 (1957)

- ⊕ Add NaN_3 solution (50, 100, 200, 500 nM) to Fe^{3+} -antioxidant solution [Fe^{3+} , 1 mM; Antioxidant, 5.0 mM; Tris buffer, 50 mM, pH 7.4]
- ⊕ Carry out UV spectral analysis with and without sodium azide; Note azide-induced shift
 - Azide-induced shift indicates free coordination site in Fe^{3+} -Chelate; Making room for oxo-ferryl radical formation; Cause of pro-oxidant effect at low concentrations.

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UV spectral data of Fe³⁺-chelators: free/dissociable iron-coordination site

Chelators	Absorption maxima of complex (λ_{\max} in nm)	
	With Fe ³⁺	N ₃ Induced shift
EDTA	241, 283	241, 283, 410
EMBLICA _{TM}	241, 294, 353, 377	241, 294, 353, 377
PAOx (Pine antioxidant)	241, 294, 353, 384	241, 294, 353, 400, 440
Vitamin C	238, 268	241, 266, 295
GAOx (Grape antioxidant)	247, 295, 353, 396	247, 295, 353, 415, 430
Gree Tea antioxidant	240, 272, 324, 390	240, 277, 325, 390
Gallic Acid	247, 295, 337	247, 295, 353, 412

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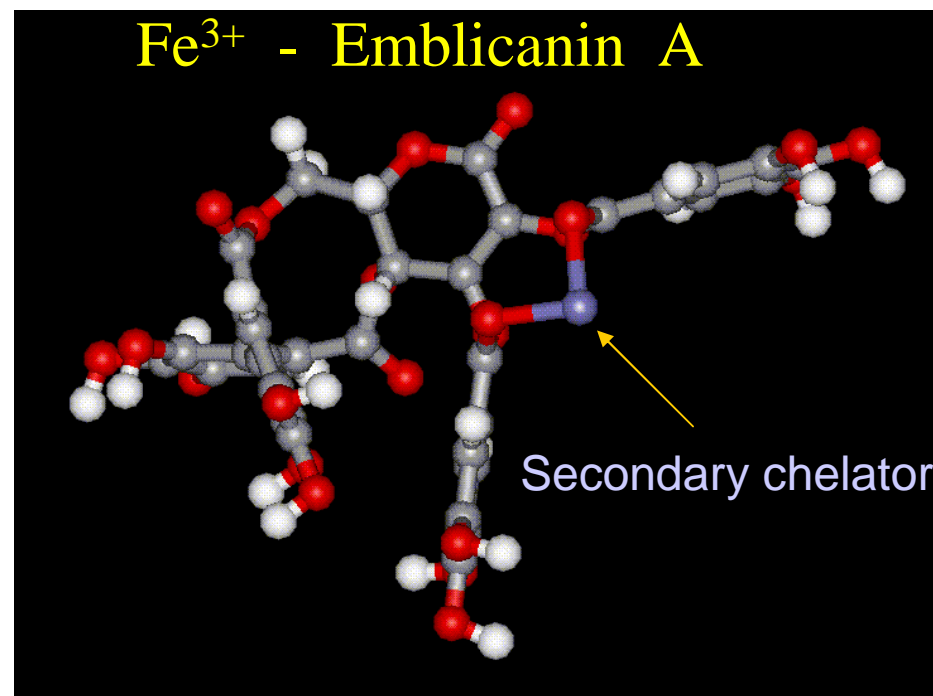
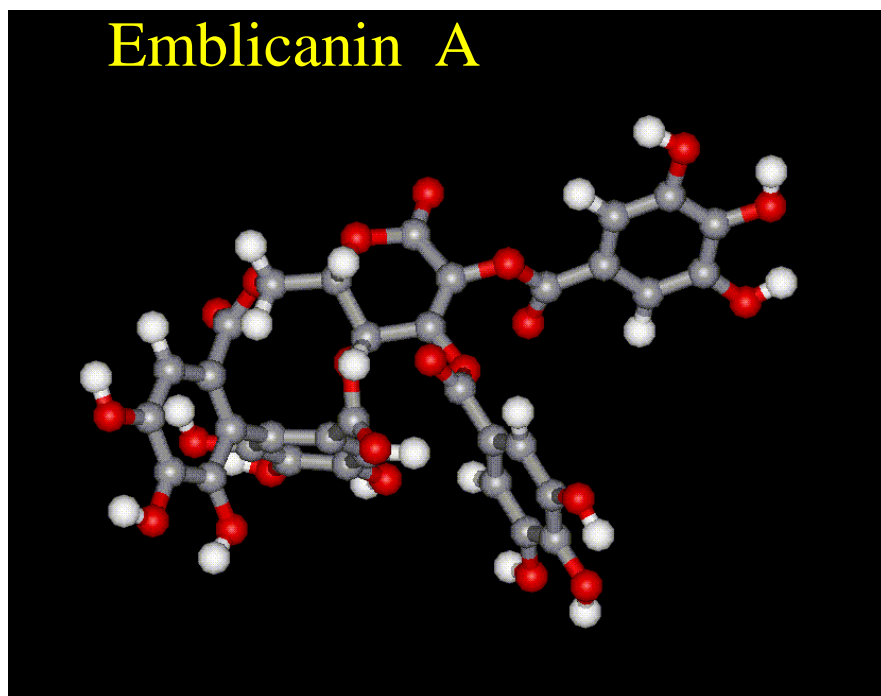
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Emblicanin A binding with Fe³⁺: A highly flexible chelator



Gaussian 98 with Semi-Empirical AM1 / 6-31G basis set

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Deoxyribose test - Rate constants of hydroxyl radical generation

⊕ Methodology

⊕ References

■ B. Halliwell, J.M.C. Gutteridge & O.I. Aruoma, *Anal. Biochem.*, 165, 215-219 (1987)

■ O. Auroma, *Methods in Enzymology*, 233, 57-66 (1994)

⊕ Add antioxidant to a solution [Fe^{3+} -EDTA, 0.3 mM; H_2O_2 , 33.6 mM, Deoxyribose, 33.6 mM; Phosphate buffer (pH 7.4)]

⊕ After 1 h at 37 C, add thiobarbituric acid (TBA, 1% w/v) and trichloroacetic acid (2.8% wv) and heat solutions for 20 min at 90 C. Measure at 532 nm.

■ Formation of hydroxyl radical; Degradation of deoxyribose; Generation of malonaldehyde; Formation of pink color adduct with TBA

⊕ Efficiency in hydroxyl radical prevention shows iron binding ability

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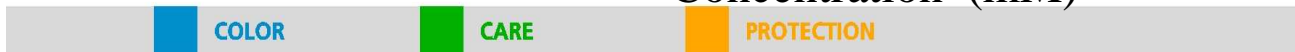
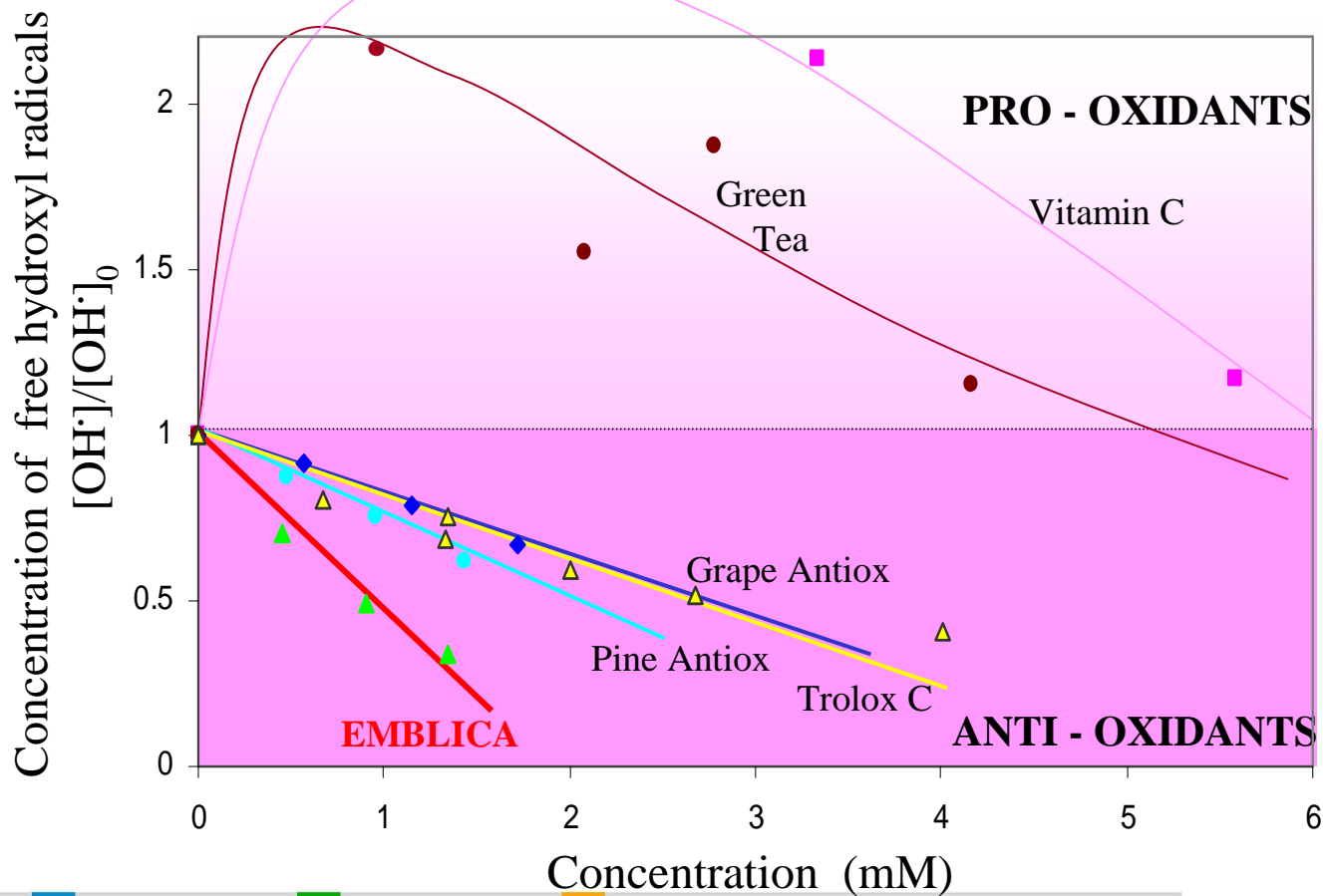
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Deoxyribose test: Hydroxyl radical prevention by iron chelators

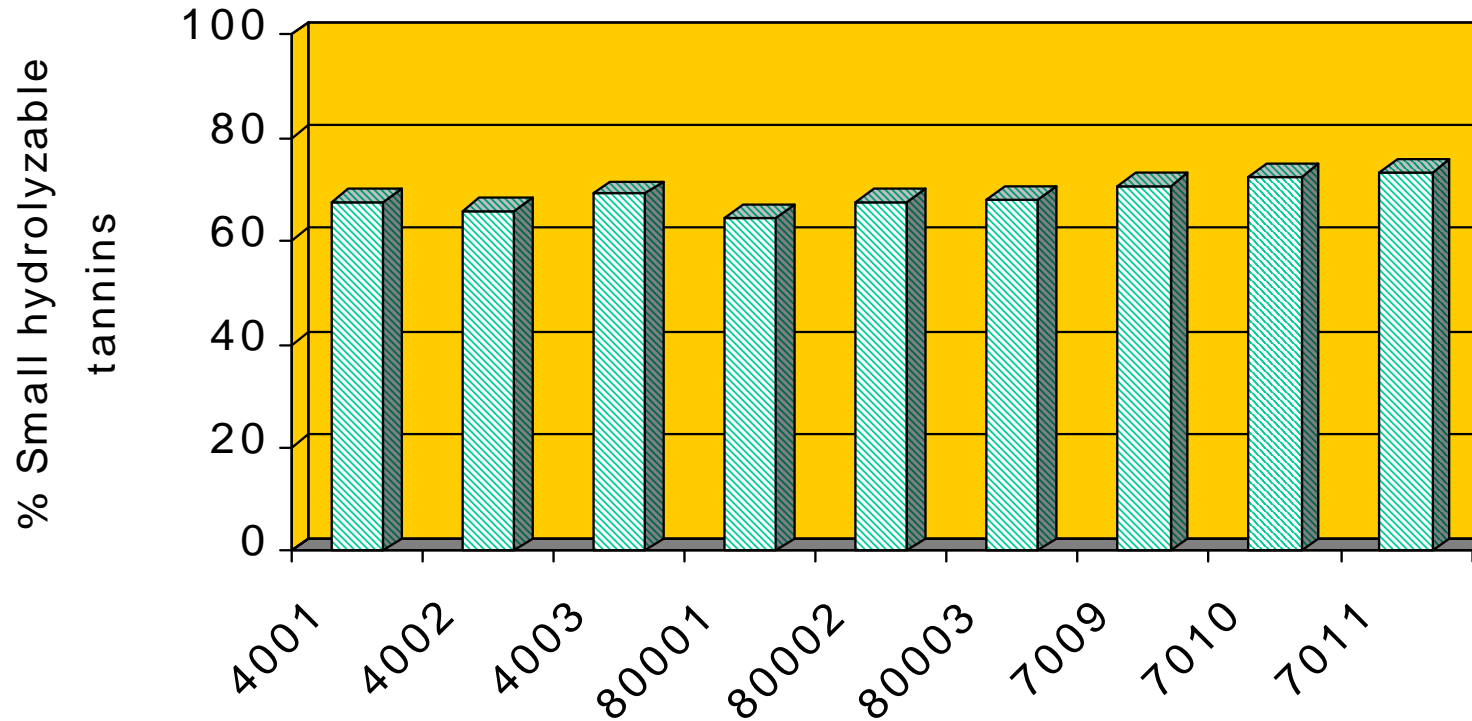


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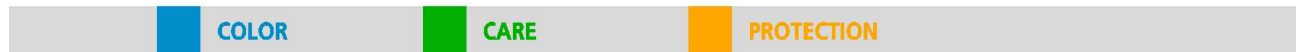
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Emblica™: Product consistency (chemical composition)



Different batches of EMBLICA (1999-2001)



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Emblica™: Product safety

- ⊕ Repeat insult patch test (Human, 100 subjects)
 - ⊕ Non-primary irritant & non-photosensitizer
 - ⊕ No adverse effects or unexpected reactions observed
- ⊕ Phototoxicity test (Human, 20 subjects)
 - ⊕ Non-phototoxic
 - ⊕ No adverse effects or unexpected reactions observed
- ⊕ In-vitro cytotoxicity test (Human skin fibroblast cells)
 - ⊕ Non-cytotoxic

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Existing skin lighteners: An overview

⊕ Hydroquinone

- ⊕ Banned in Europe, Toxicity problems, OTC drug in the US

⊕ Arbutin

- ⊕ β -D-glucoside of hydroquinone, Expects similar toxicity problems as that of hydroquinone, Hydrolytic instability

⊕ Kojic Acid

- ⊕ Tumorigenic (mice), Fast skin penetration, Induce allergic contact dermatitis, Unstable in aqueous base

⊕ Magnesium ascorbyl phosphate (MAP)

- ⊕ Pro-oxidant, pH limitation (>7.0)

⊕ Numerous plant extracts

- ⊕ Active principle(s) unknown, Not well standardized, Instability

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Protocol for in-vitro inhibition of melanin synthesis

⊕ Cell Type

- ⊕ Human skin melanocyte and keratinocyte cell lines
 - ▢ Used 1:3 ratios of melanocytes/keratinocytes co-culture

⊕ Method

- ⊕ Incubate in the presence of product in culture medium without serum (McCOY, Gibco) for 48 hrs
- ⊕ Discard supernatant and treat with 1N NaOH (10% DMSO) for cell-lysis.
- ⊕ Centrifuge and collect supernatant (contains melanin)
- ⊕ Read the absorption at λ_{\max} 470 nm
- ⊕ Calculate % melanin inhibition by comparing the optical density of product vs control

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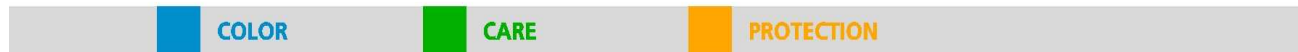
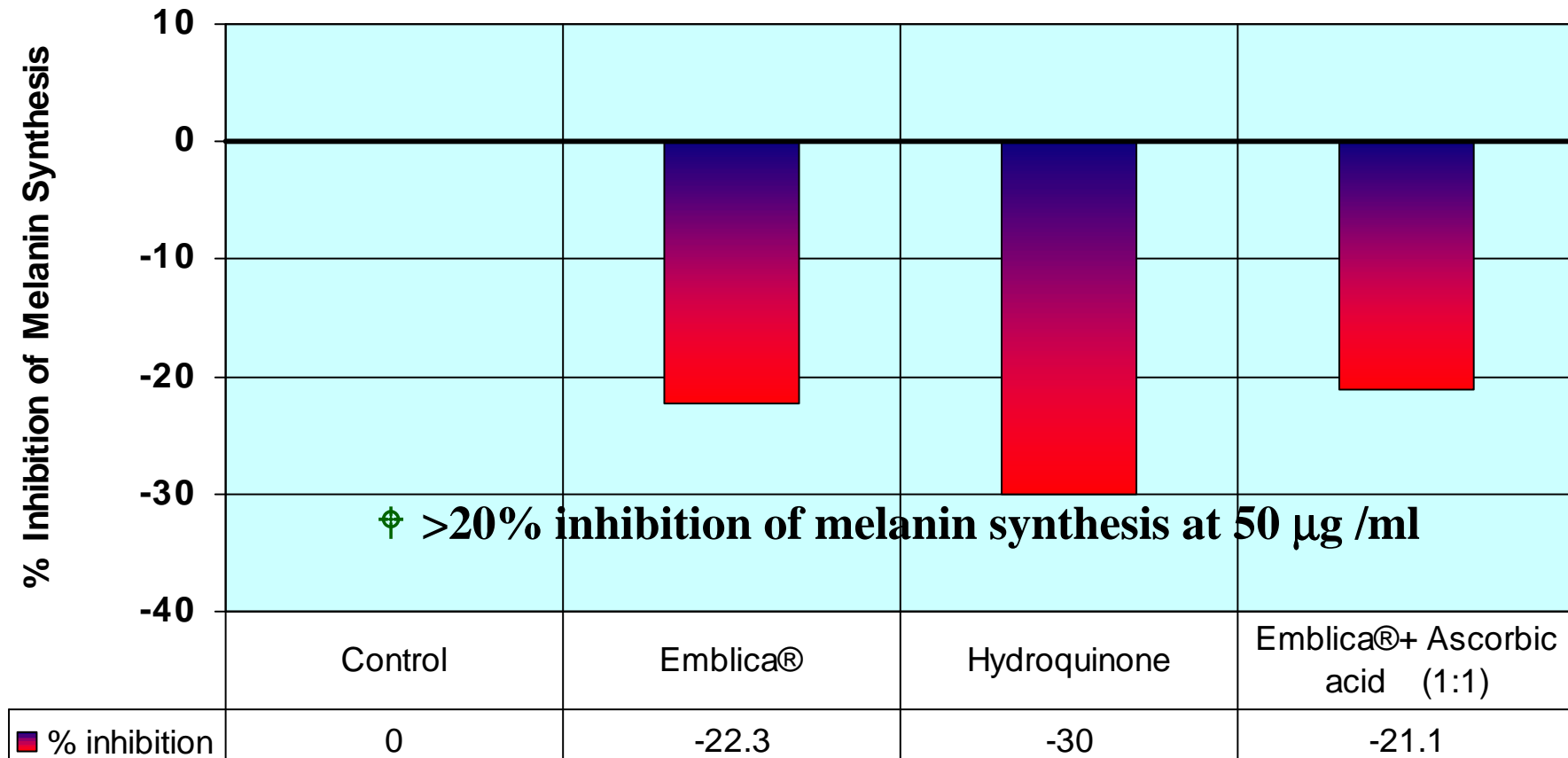
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Inhibition of melanin synthesis in human skin melanocytes/keratinocytes co-culture



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Clinical study protocol for skin lightening 2% Emblica™ vs 2% Hydroquinone

- ✦ **Human volunteers** - Hispanic (13) & Asian (13)
 - ✦ Skin type III (burns moderately / tans gradually) and IV (burns minimally / always tans well)
 - ✦ Defined by Fitzpatrick phototype scale
- ✦ **Study Schedule** - January 30 to April 24, 2001 (12 weeks)
- ✦ **Test sites** - Upper arms, left & right
- ✦ **Test substances** - 2% Emblica™ & 2% Hydroquinone cremes
- ✦ **Application frequency** - 0.05 ml twice a day
- ✦ **Results** - Represented using the individual typology angle (COLIPA SPF test method); Measured by chromametric measurement
- ✦ **Work done by** - Consumer Product Testing Co., NJ, USA

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Individual typology angle (ITA)

$$ITA^{\circ} = [\text{Arc Tangent } ((L^*-50)/b^*)] 180 / 3.1416$$

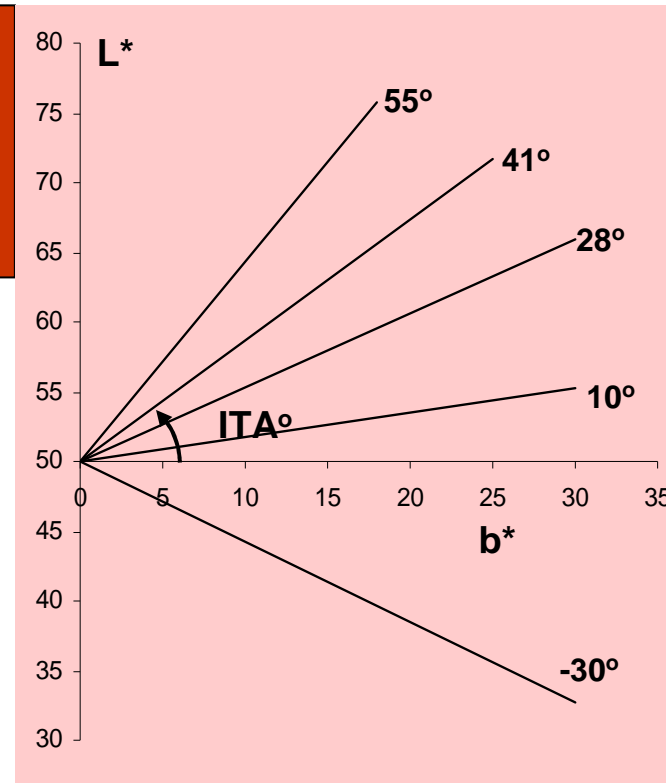
L* value - Lightness

a* value - color in red-green axis

b* value - Color in blue-yellow axis

ITA⁰ Skin Color

> 55	Very Light
41 to 55	Light
28 to 41	Intermediate
10 to 28	Tan
- 30 to 10	Brown
< - 30	Black



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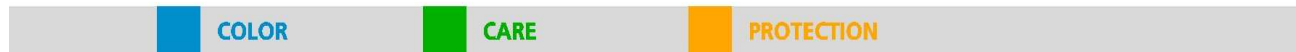
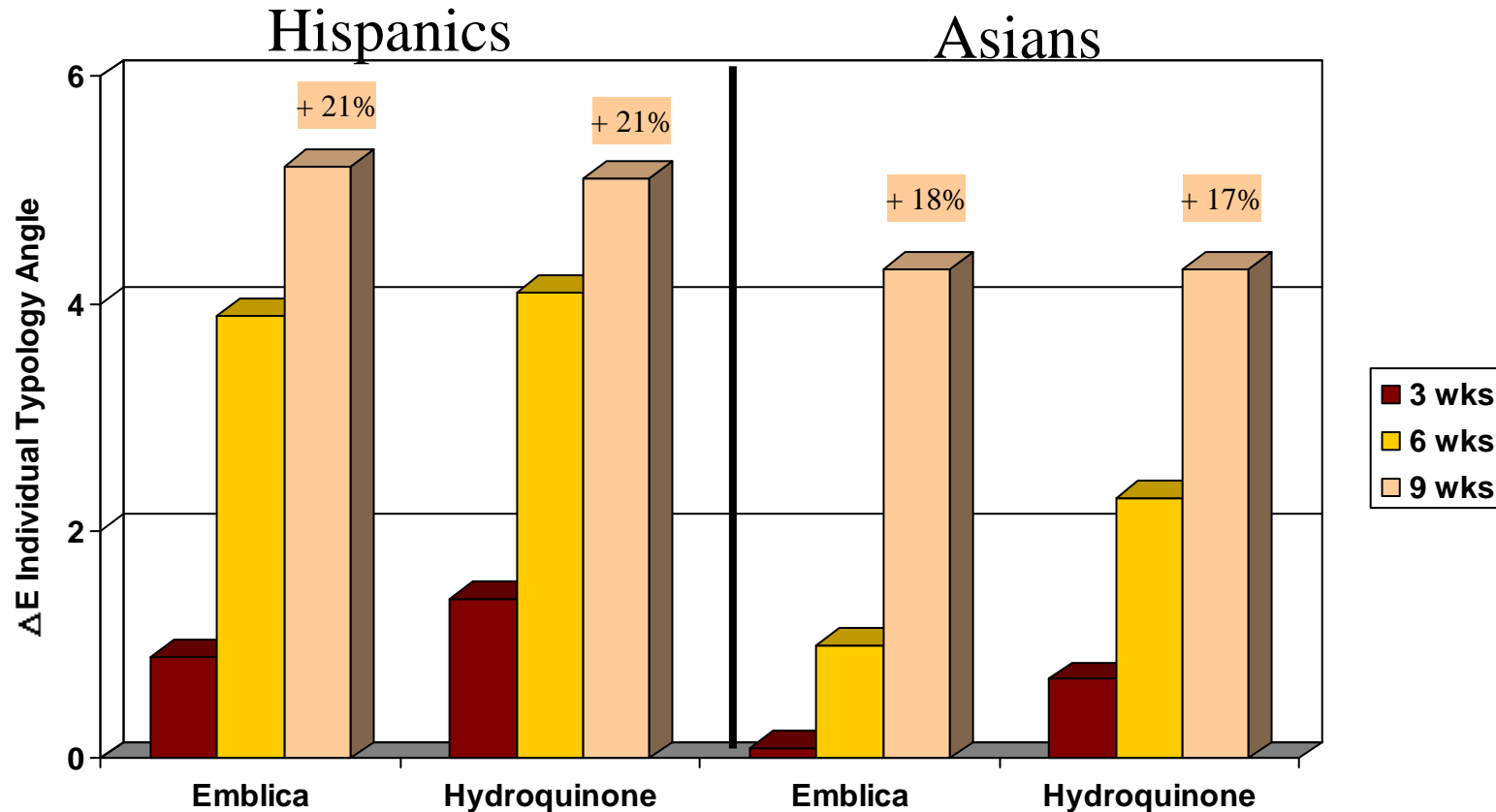
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Clinical study results for skin lightening: Change in ITA degree (from day 0 to day 90)



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Clinical study results for skin lightening with and without Emblica™

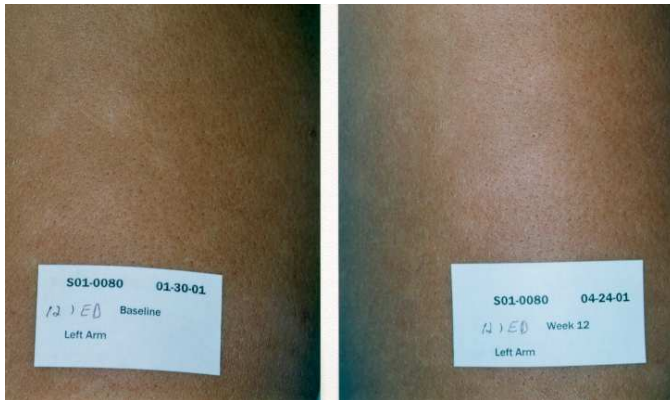
Baseline

after 12-weeks

Baseline

after 12-weeks

#1



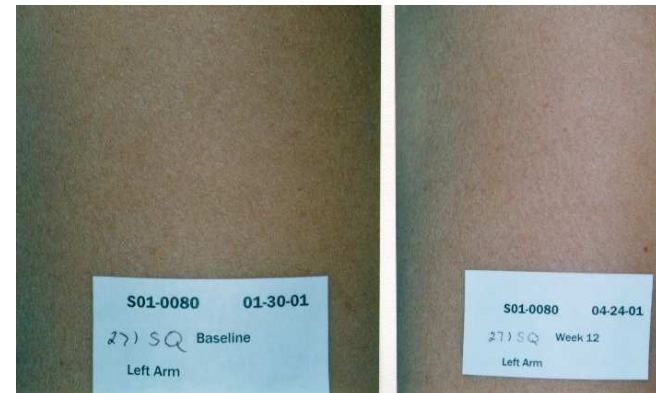
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#3



#4



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Formulation used for clinical testing (Emblica™)

Formulation # EUS 17-99 (2% Emblica)		
<i>INCI name</i>	<i>Trade Name/Supplier</i>	<i>% w/w</i>
Phase A		
Water (demineralized)		58.70
Na2 EDTA		0.05
Propylene Glycol		5.00
Phase B		
PEG-6 Stearate and Ceteth-20 and Glyceryl Stearate and Steareth-20	Tefose 2561/Gattefosse	10.00
Glyceryl Stearate and PEG-100 Stearate	Arlacel 165/Uniqema	6.00
Stearyl alcohol	Lanette 18/Cognis	3.00
Dimethicone	Dow Corning 200 Fluid, 50cst/Dow Corning	4.00
Phase C		
Water (demineralized)		10.00
Phyllanthus emblica fruit extract	Emblica cascading antioxidant	2.00
Phase D		
Triethanolamine		0.25
Phase E		
Phenoxyethanol and Isopropylparaben and Isobutylparaben and Butylparaben	Liquapar PE/ ISP	1.00
Total		100.00

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Formulation used for clinical testing (Hydroquinone)

Formulation # EUS 17-97 (2% Hydroquinone)		
<i>INCI name</i>	<i>Trade Name/Supplier</i>	<i>% w/w</i>
Phase A		
Water (demineralized)		68.75
Na2 EDTA		0.05
Propylene Glycol		5.00
Phase B		
PEG-6 Stearate and Ceteth-20 and Glyceryl Stearate and Steareth-20	Tefose 2561/Gattefosse	10.00
Glyceryl Stearate and PEG-100 Stearate	Arlacel 165/Uniqema	6.00
Stearyl alcohol	Lanette 18/Cognis	3.00
Dimethicone	Dow Corning 200 Fluid, 50cst/Dow Corning	4.00
Phase C		
Sodium metabissulfite		0.15
Ascorbic acid	L(+)-Ascorbic acid USP/ EM Inds.	0.05
Hydroquinone	Hydroquinone USP/Eastman	2.00
Phase D		
Phenoxyethanol and Isopropylparaben and Isobutylparaben and Butylparaben	Liquapar PE/ ISP	1.00
Total		100.00

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Clinical study protocol for skin lightening 1% Emblica™ vs 3% MAP

- ✦ **Human volunteers** - Asians (16)
 - ✦ Skin type III (burns moderately / tans gradually) and IV (burns minimally / always tans well)
 - ✦ Defined by Fitzpatrick phototype scale
- ✦ **Study Schedule** - October 1 to December 24, 2001 (12 weeks)
- ✦ **Test sites** - Upper arms, left & right
- ✦ **Test substances** - 1% Emblica™ & 3% MAP cremes
- ✦ **Application frequency** - 0.05 ml twice a day
- ✦ **Results** - Represented using the individual typology angle (COLIPA SPF test method); Measured by chromometric measurement
- ✦ **Work done by** - Consumer Product Testing Co., NJ, USA

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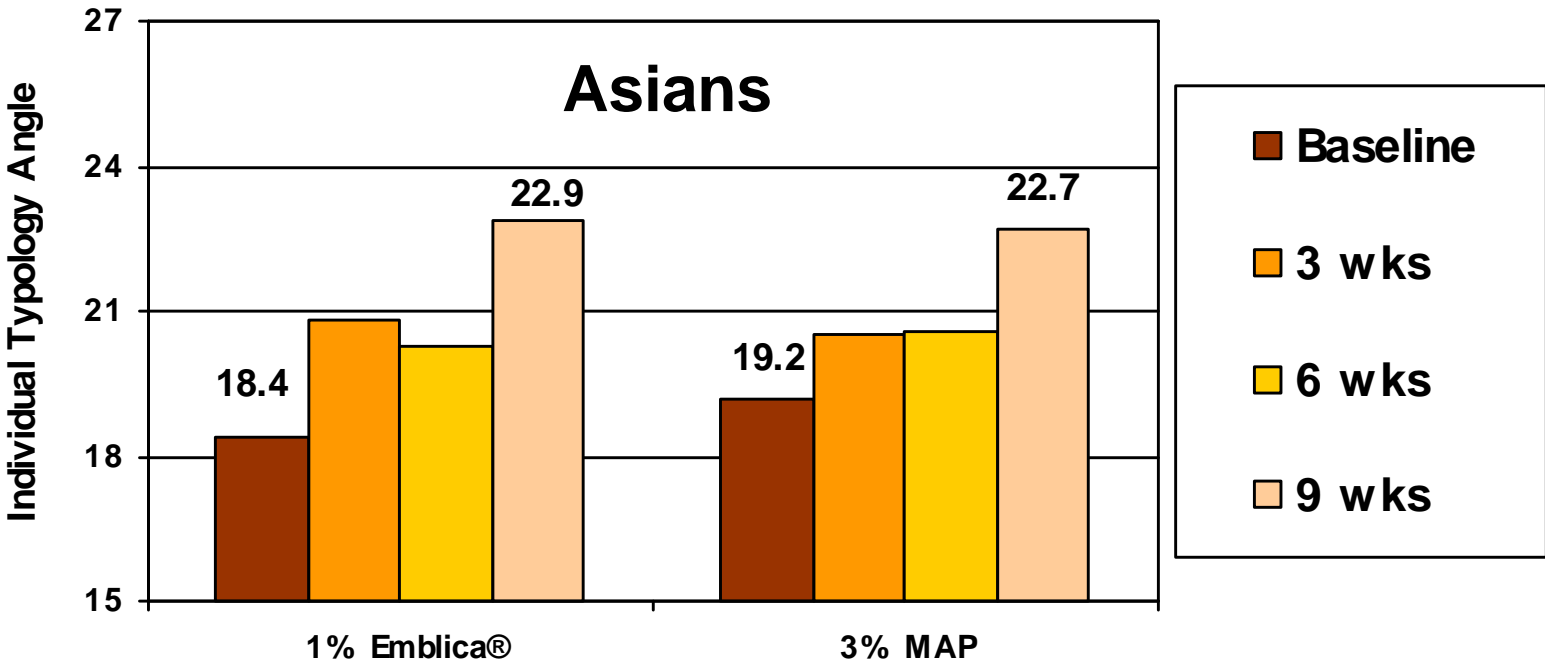
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Clinical study results for skin lightening

1% Emblica™ compares well with 3% MAP



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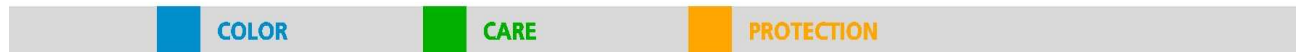
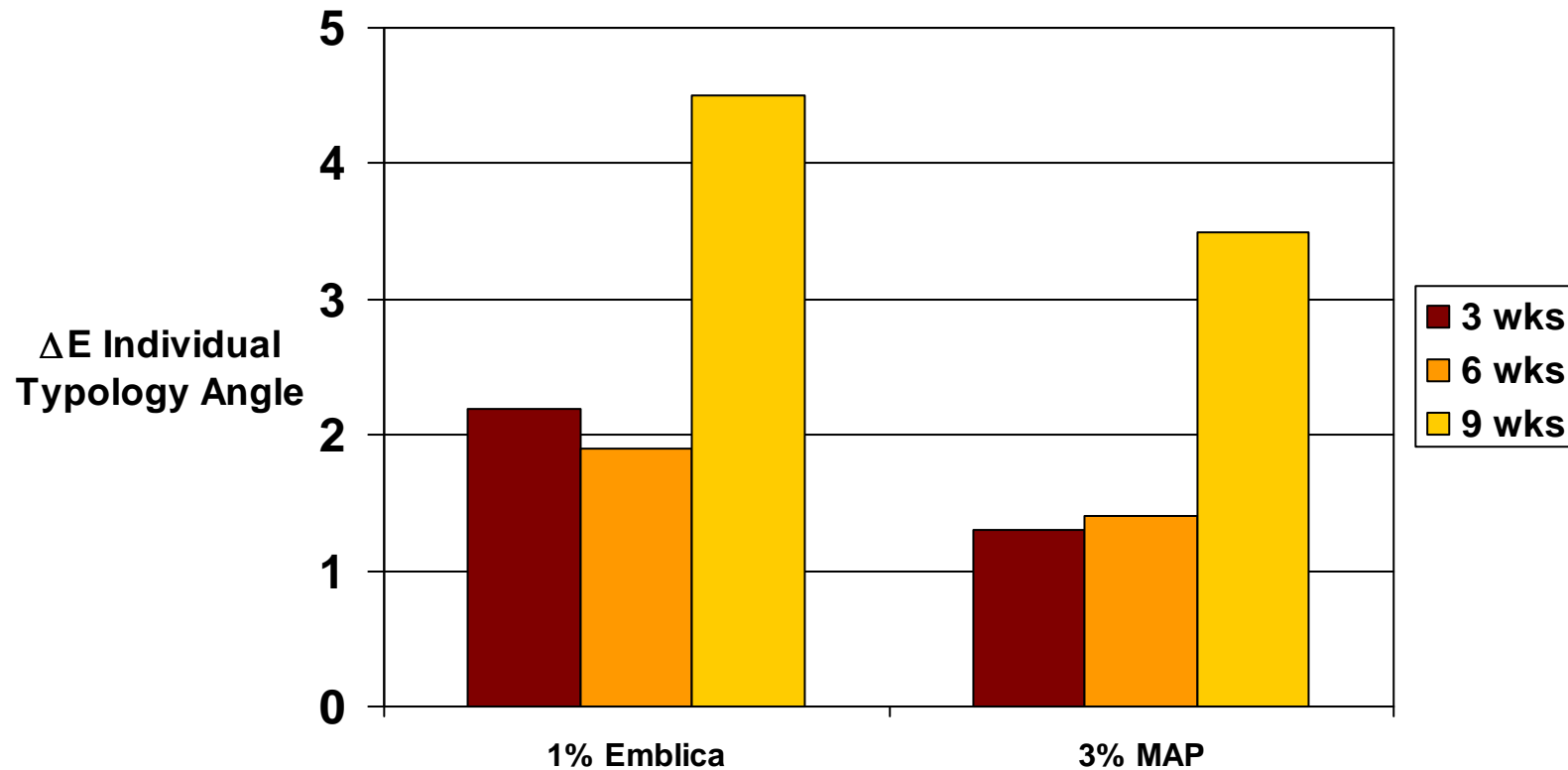
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Clinical study results for skin lightening: Change in ITA degree



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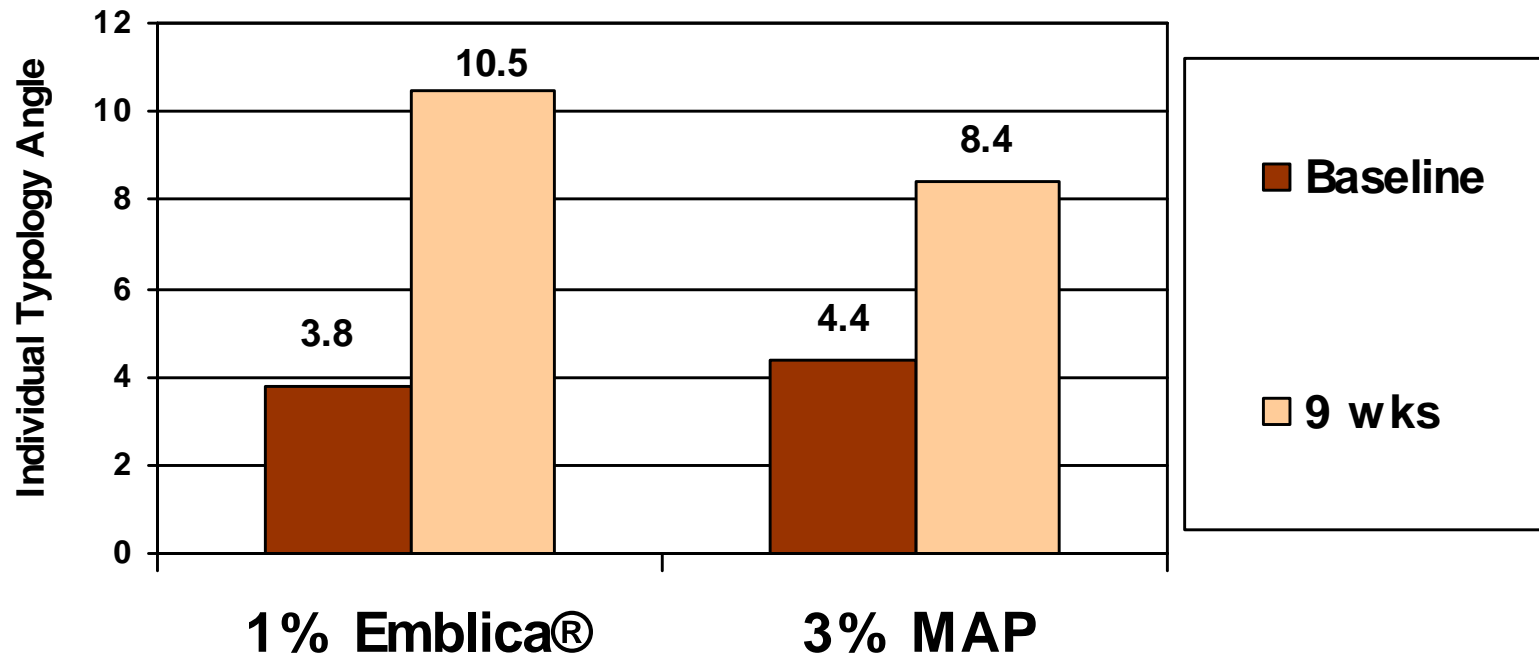
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Clinical study results for skin lightening

For the 9 Asian volunteers having $ITA^0 < +20$

1% Emblica™ superior to 3% MAP



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Clinical study: Reduction in UV-induced pigmentation

- ✦ **Human volunteers** - Eleven / Ten
- ✦ **Test sites** - Subject's back, 4x2.5 cm area
- ✦ **Test substances** - 0.2 and 0.5% levels (cremes)
- ✦ **Application frequency** - 2 mg/cm² once a day
- ✦ **Results** - Represented using the individual typology angle (COLIPA SPF test method); Measured by chromametric measurement; Calculated E ITA⁰ by subtracting treated site with untreated irradiated control.
- ✦ **Protocol A (protection)**- Apply product for 8 days & then induce pigmentation by UV light; Compare untreated irradiated control vs the site with product
- ✦ **Protocol B (repair)** - Induce pigmentation by UV light; Apply product; Compare untreated irradiated control vs the site with product
- ✦ **Work done by** - Consumer Product Testing Co., NJ, USA

COLOR

CARE

PROTECTION

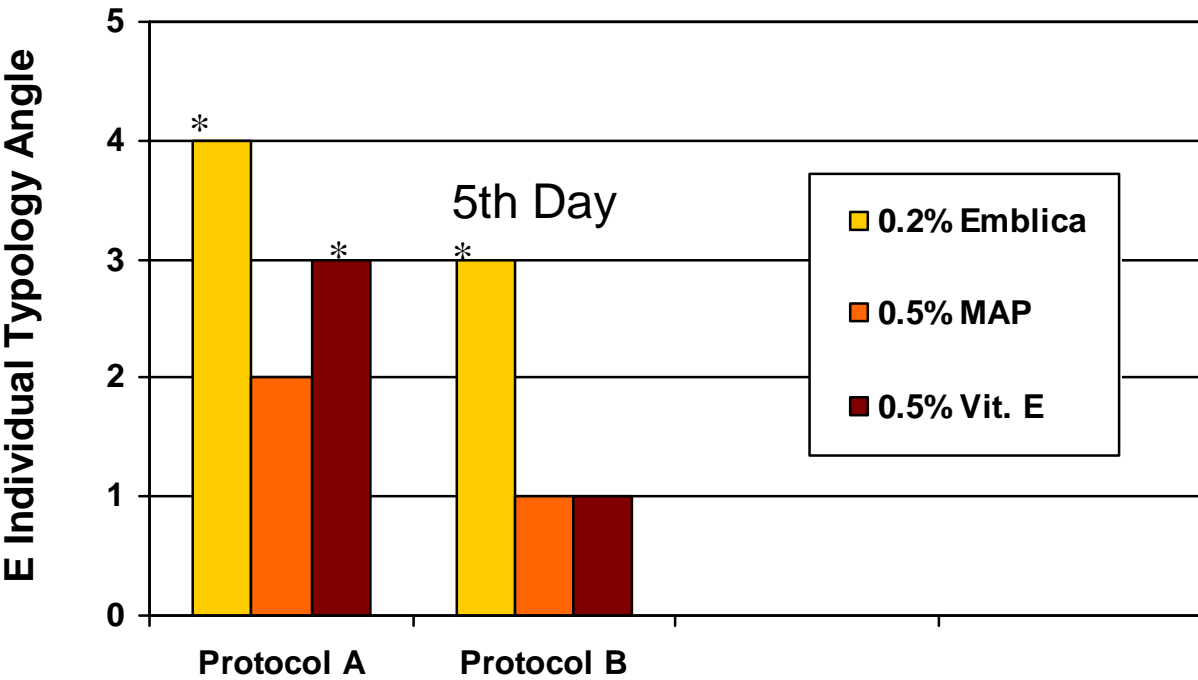
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Phone: 914-345-66 07 · Fax: 914-785-58 04 · www.emindustries.com · e-mail: rona@emindustries.com

Clinical study results: Reduction in UV-induced pigmentation



Protocol A: Protection / Protocol B: Repair
*Statistically significant results: Two-tailed $p < 0.05$

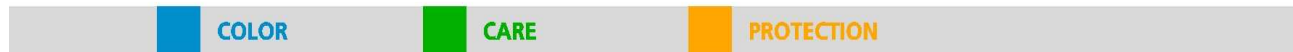
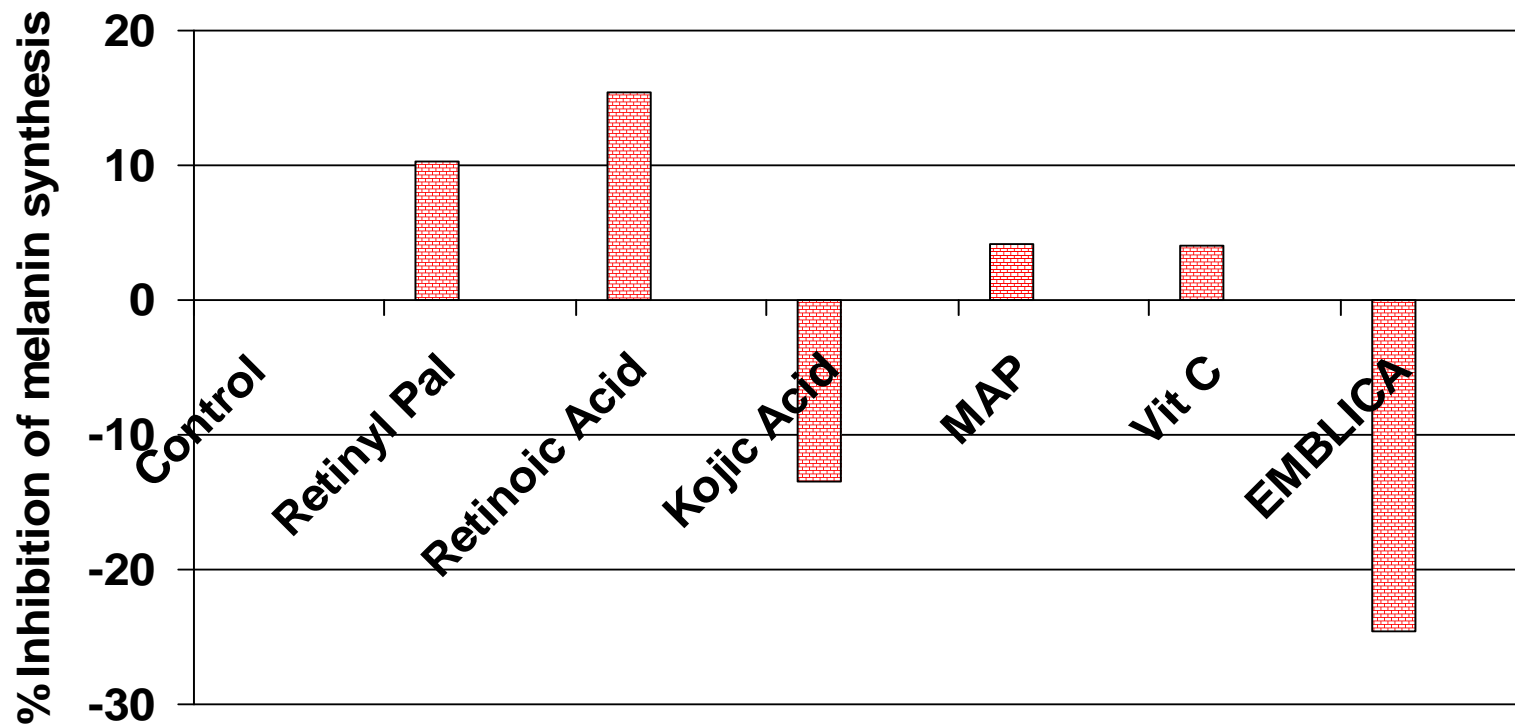


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Effects on human skin melanocytes culture

‡ >25% inhibition of melanin synthesis at 100 µg/ml vs control; Far superior than other skin whiteners (Texinfine)



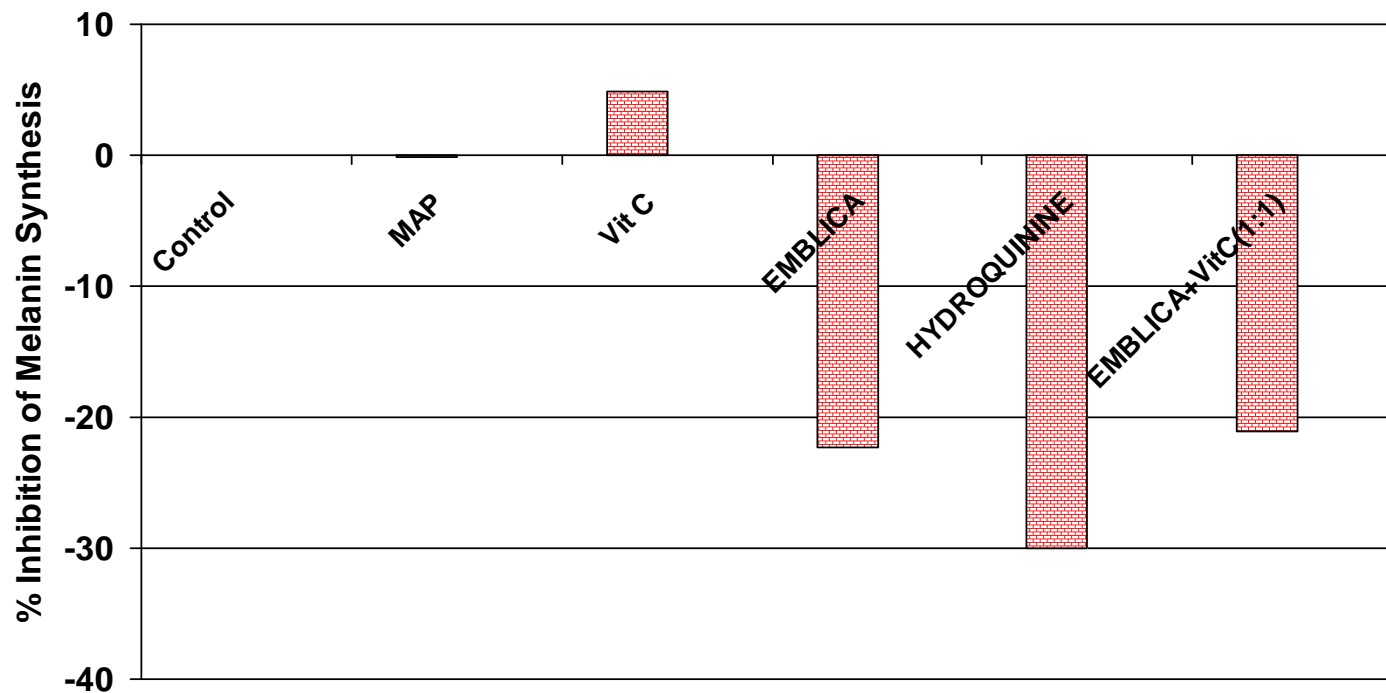
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Effects on human skin melanocytes/keratinocytes co-culture

⊕ >20% inhibition of melanin synthesis at 50 µg/ml (Texinfine)



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In-vivo skin whitening protocol

- ⊕ Human volunteers - Hispanic (13) & Asian (13)
 - ⊕ Skin type III (burns moderately/tans gradually) and IV (burns minimally/always tans well)
 - ⊕ Defined by Fitzpatrick phototype scale
- ⊕ Test sites - Upper arms, left & right
- ⊕ Test substances - 2% Emblica™ & 2% Hydroquinone as cremes
- ⊕ Application frequency - 0.05 ml twice a day
- ⊕ Time of Duration - 12-weeks
- ⊕ Results - Represented using the individual typology angle (COLIPA SPF test method)
- ⊕ Work done by - Consumer Product Testing Co., NJ, USA

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Formulation guidelines

- ⊕ Recommended use level: 0.5 to 2%
 - ⊕ Preferred 1-2% as a skin lightener
 - ⊕ Requires fragrance and color adjustment > 0.5% use level
- ⊕ Use nonionic or anionic emulsifiers for making emulsions
 - ⊕ Maintain acidic pH (6 or below)
 - ▢ Remains in the phenolic form; Works as an antioxidant
 - ▢ Provides stabilization to Emblica™
 - ▢ Improved color of the finished products at or below pH 5.5
- ⊕ Add Emblica as a suspension in water to the formulation
- ⊕ May need chelating agent, such as, EDTA (0.05%)
 - ⊕ Provides synergistic effect for chelation
- ⊕ Suggested thickeners
 - ⊕ Xanthan gum, Carbomers, Cellulose ethers
- ⊕ Avoid prolong heating and exposure to sunlight
 - ⊕ Causes darkening of the product

COLOR

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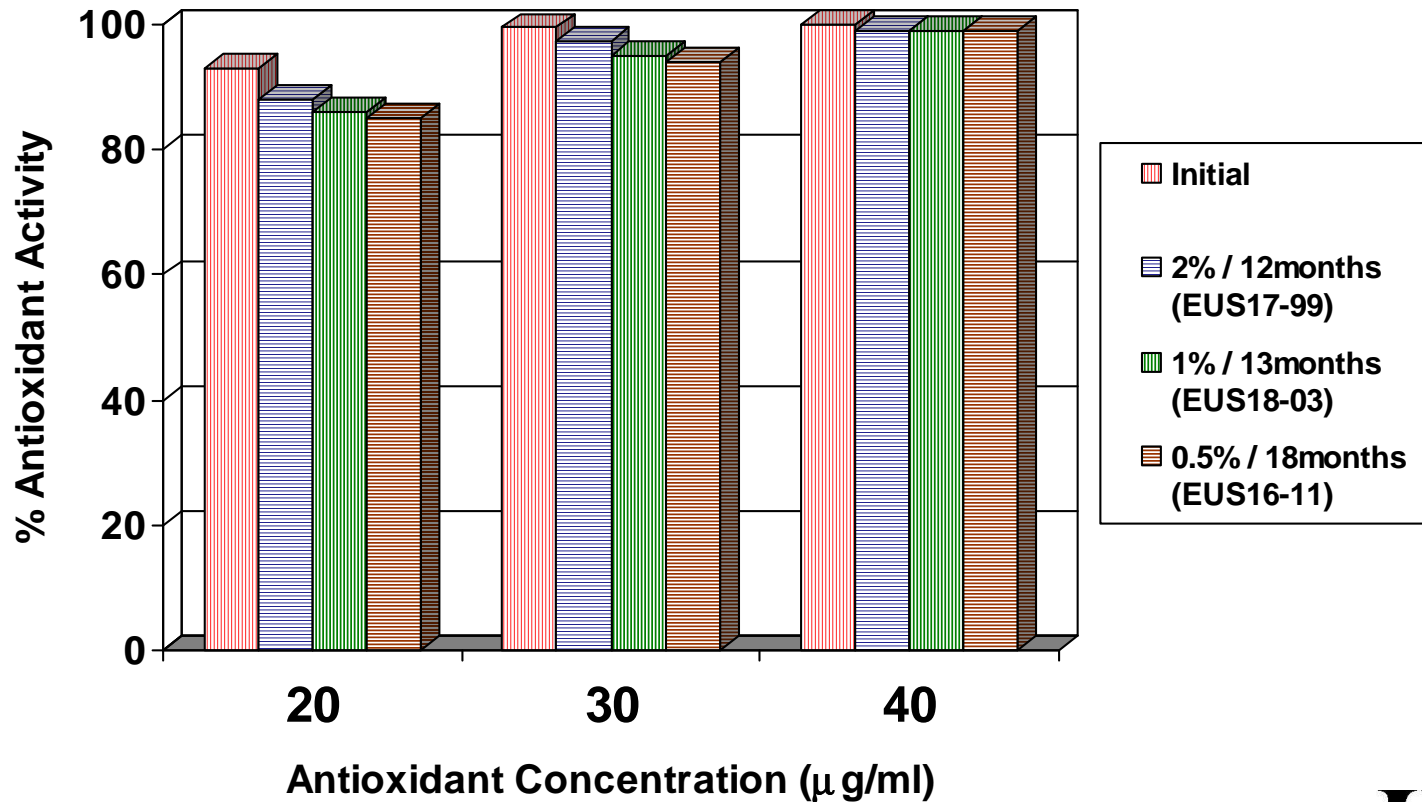
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Formulation stability of Emblica™ containing products (DPPH test)

Loss of activity: < 5% in 12 to 18 months



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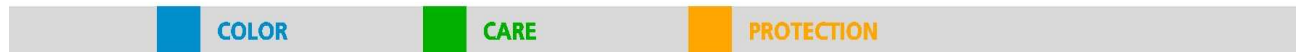
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Comparison of benefits

Criteria	Emblica	MAP	Hydroquinone
pH	Acidic +++	Basic - -	Acidic ++
Stability	++++	++	- requires sodium metabisulfite
Safety	++++	++++	- - -
Efficacy	+++	+	+++
Origin	Natural +++	Synthetic ++	Synthetic



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Summary

⊕ **Extremely efficient and cost effective skin lightening agent**

- ⊕ Proven by in-vitro & clinical studies

⊕ **Excellent safety profile - Edible fruit**

- ⊕ Some of the existing products have major toxicity problems

⊕ **Well-defined material**

- ⊕ Identified active principle(s)

- ⊕ Standardized product

⊕ **Excellent product stability**

- ⊕ Aqueous & formulated products

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