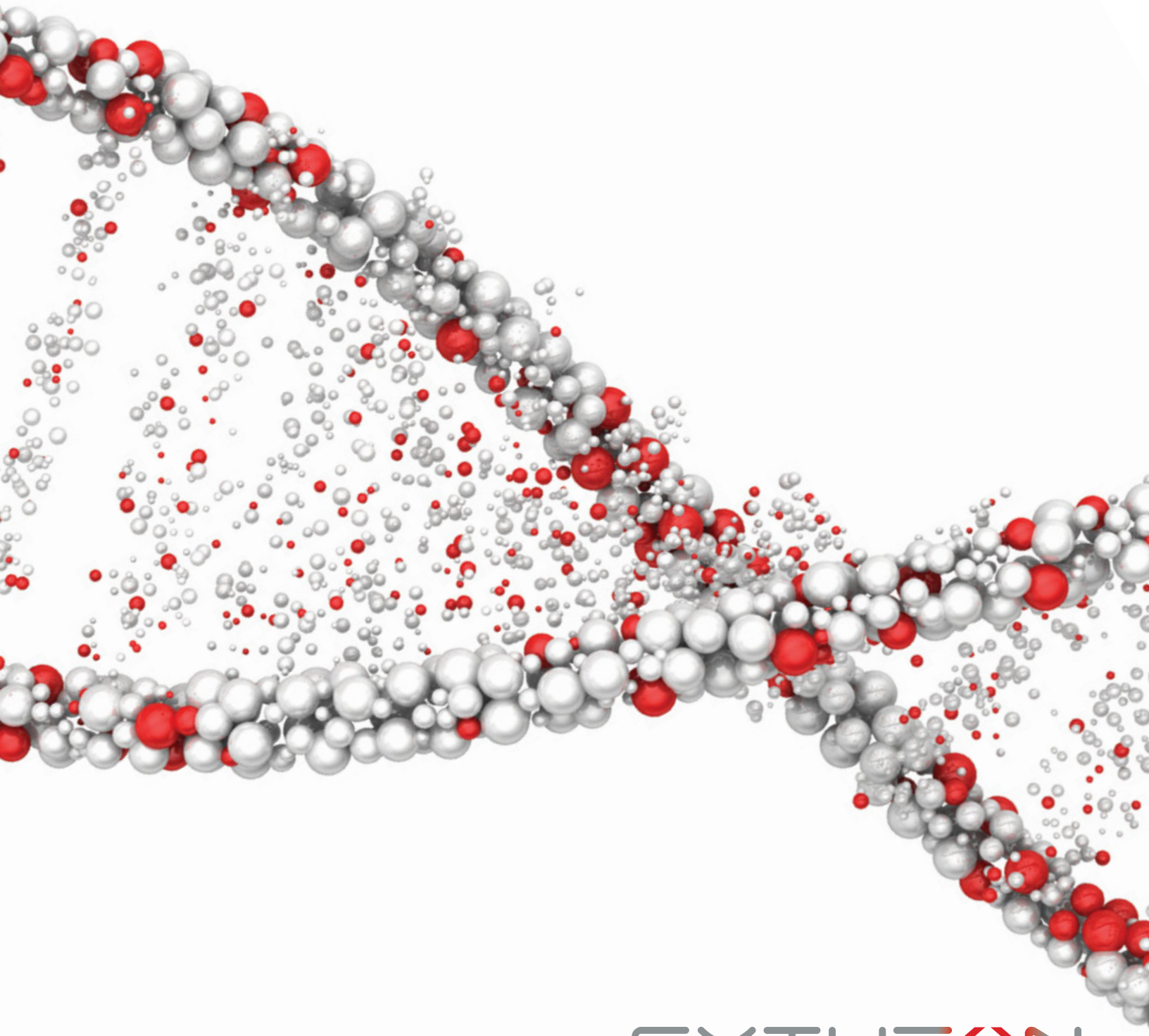
Synovea® HR | Asyntra® SL

The New Gold Standards in Skin Brightening & Even Toning



SYTHEON

...making innovation work

Synovea® HR | Asyntra® SL

Synovea® HR

Alkylresorcinols are amphiphilic phenolic lipids present in significant amount in the bran fractions of rye and other cereals. 4-Hexylresorcinol (HR) is the most studied and well-known alkylresorcinol, which has an 80-year history of use in food & pharmaceuticals. HR has a GRAS status and is considered to be safe and effective in use as an anti-browning dip for shrimp and fresh cut fruits.

Despite its long history of human use, it is only recently that its use and benefits as an active ingredient for skin care applications has been realized. In 2007, Sytheon introduced HR as a skin lightener/ even-toner under the trade name Synovea® HR. Its superb efficacy in this application is believed, in part, to arise from Sytheon's ability to attain highly purified HR (>99.5-99.9%) which is essentially free of resorcinol (a known skin irritant) and its intermediate hexanoylresorcinol. HR is now a sought after ingredient for developing skin brightening/even toning products. For a comprehensive overview on HR, please review publication #1.

Asyntra® SL

By adding Synovea® HR (Hexylresorcinol) and Synovea® EL (Ethyl Linoleate) to the skin-friendly emollient Caprylic/Capric Triglycerides Sytheon has created an elegant, easy-to-use and very cost-effective new synergistic skin lightening blend - Asyntra® SL. Ethyl Linoleate is a very good solubilizer for HR and is a stable form of Linoleic acid. Linoleic acid is an essential fatty acid, a precursor of ceramides and a major component of skin lipids. EL is clinically proven to lighten UV-induced skin pigmentation by accelerating post-translational proteolytic degradation of tyrosinase.

Product Information

Trade Name	Synovea® HR	Asyntra® SL
INCI Name	Hexylresorcinol	Caprylic/Capric Triglycerides and Hexylresorcinol and Ethyl Linoleate
CAS#	136-77-6	65381-09-1; 136-77-6; 85049-36-1
EC #	205-257-4	265-724-3; 205-257-4; 285-206-0
Appearance	White to pale yellow powder; May become soft lump	Clear yellow to yellowish brown liquid
Purity	Minimum 99% Hexylresorcinol	24-27% (w/w) of Hexylresorcinol
Solubility	>20% solubility in a wide range of hydrophobic emollients and solubilizers, HydraSynol™ DOI, low molecular weight glycols; do not use Ethanol	Highly miscible with a wide range of hydrophobic emollients and solubilizers
Use Level & Formulation pH	0.5 to 1%; < 6.0	1.5 to 4%; < 6.0
Storage	Store in original, sealed container at +10 to +30 °C; avoid light, heat & moisture	Store in original, sealed container at +10 to +30 °C; avoid prolong exposure to light & heat
Regulatory	Globally approved	Globally approved

Human Skin Tolerances

Synovea® HR

Safety assessment based on MOS value: 1% Synovea® HR was found to be safe for topical application (MOS = 548) compared to 1% Kojic Acid (MOS = 88). MOS value 100 and above is considered to be safe. MOS calculated for a face product at 1% use level.

Human Repeat Insult Patch Test to assess Allergenicity/Skin irritation/Skin sensitization: (1, 2 and 5% in corn oil); Synovea® HR is found to be a non-primary irritant and a non-primary sensitizer.

Chamber Scarification Test to assess Skin-irritating propensities: (0.1% and 0.5% in petrolatum) on scarified skin: Synovea® HR is found to have low irritating potential and compares well with saline control.

Asyntra® SL

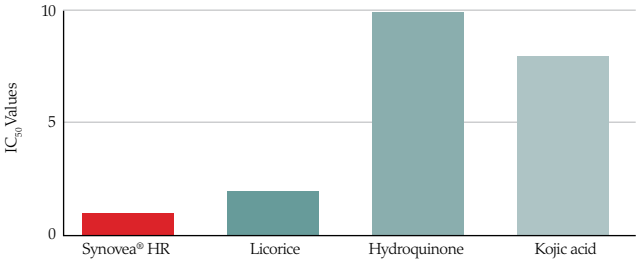
Human Repeat Insult Patch Test to assess Allergenicity/Skin irritation/Skin sensitization: (10% in corn oil); Asyntra® SL is found to be a non-primary irritant and non-primary sensitizer.

In-vitro Enzyme Inhibitory Activity: Synovea® HR vs Key Skin Lighteners

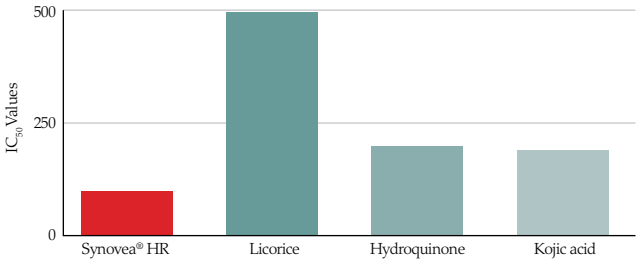
Protocol:

- **Enzymes –** Mushroom tyrosinase & Horeseradish peroxidase
- **Substrates –** Tyrosine & L DOPA
- **Test substances –** Dissolved in Ethanol & further diluted with water
- **Measurements –** Spectrophotometric; Scan speed - 1200 nm/min; Spectral range - 370 to 700 nm
- **Quantification of performance –** Concentration needed to reduce the enzyme activity by 50% (IC_{50})

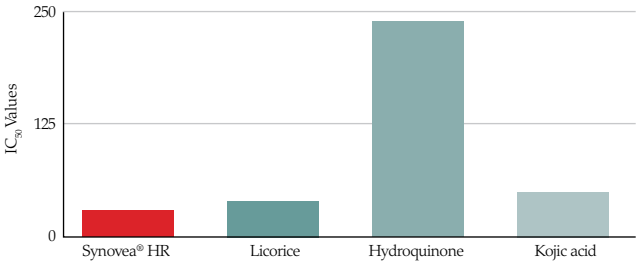
Tyrosine + Tyrosinase → DOPA



DOPA + Peroxidase/H_2O_2 → DOPAchrome



DOPA + Tyrosinase → DOPAchrome

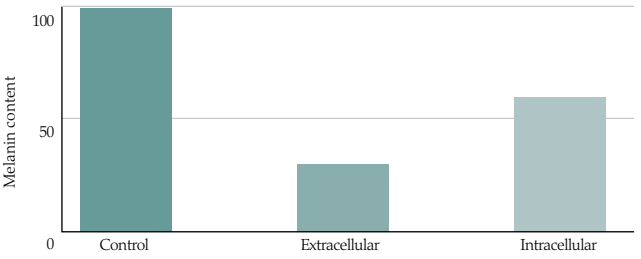


Synovea® HR provides the most effective melanin inhibitory (in-vitro) activity vs key commercial skin lighteners.

In-vitro Melanin Inhibitory Activity of Synovea® HR and Asyntra® SL

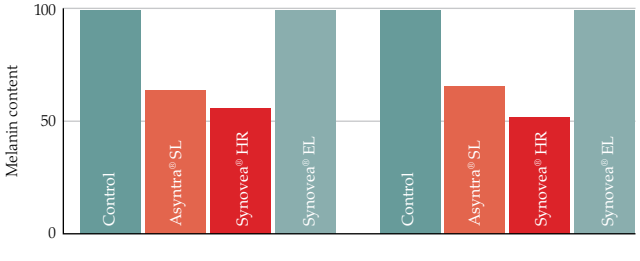
Protocol:

- **Cells –** B16 melanocytes
- **Incubation time –** 72 hrs.
- **Test substances –** Synovea HR® & Asyntra® SL
- **Quantification of performance –** Estimation of extracellular and intracellular melanin of test substances vs. control



Synovea® HR 10 µg/ml

Extracellular melanin | Intracellular melanin



Use level 10 µg/ml

Asyntra® SL contains 2.5 µg/ml Synovea® HR + 2.5 µg/ml Synovea® EL

Synovea® HR reduces extracellular melanin by 75% and intracellular melanin by 36%

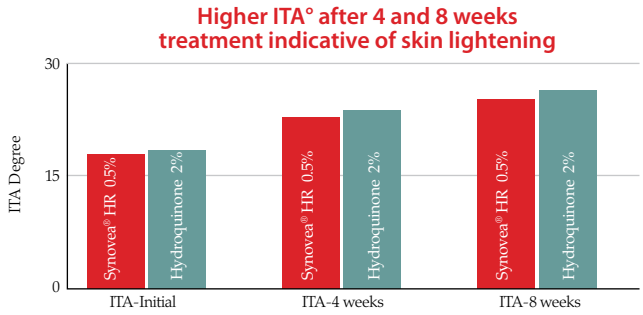
Asyntra® SL reduces extracellular melanin by 40% and intracellular melanin by 35%

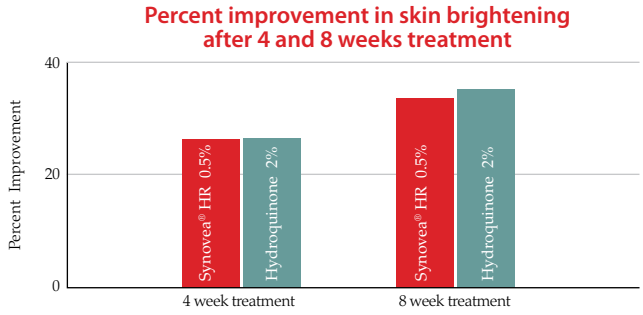
Skin Lightening Clinical Study: Synovea® HR vs. Hydroquinone

Protocol:

- **Volunteers –** Asian, Caucasion, Hispanic and African American - 13 subjects (ITA° ranging from 7 to 31)
- **Study duration –** 8 weeks
- **Test sites –** Left and right arms
- **Test substances –** 0.5% Synovea® HR lotion vs 2% Hydroquinone lotion
- **Application frequency –** Twice a day
- **Quantification of performance –** Chromometric measurement; ΔE was calculated by subtracting ITA° of the treated site from that of the average baseline (first day of the study)

Skin lightening effectiveness of 0.5% Synovea® HR compares well with 2% Hydroquinone. In fact, Synovea® HR is four-times more effective than Hydroquinone.



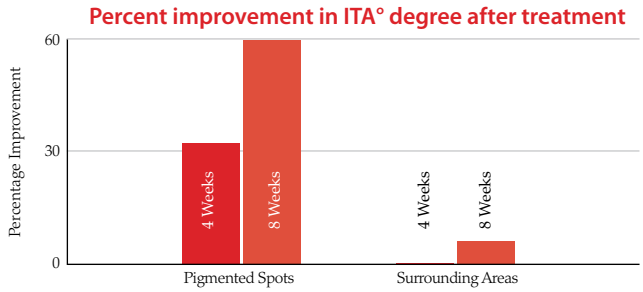


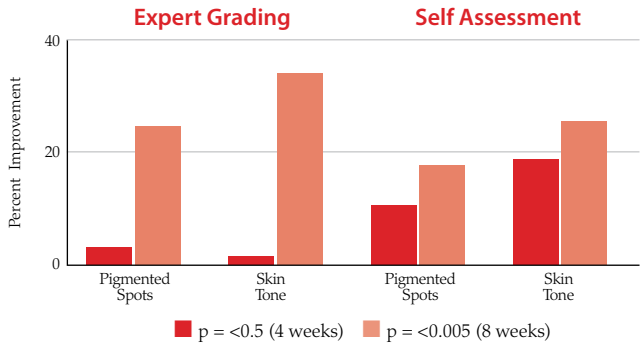
Hyperpigmentation Control Clinical Study with Synovea® HR

Protocol:

- **Volunteers –** 18; Asian (7), caucasian (10) and Hispanic (1)
- **Study duration –** 8 weeks
- **Test sites –** Hand
- **Test substances –** 1% Synovea® HR lotion
- **Application frequency –** Twice a day entire hand, (no sunscreen applied)
- **Quantification of performance –** Comparative ITA° before and after treatment & expert grading (scale 0 to 4), Skin tone, Pigmented spots

Synovea® HR provides significant pigmentation reduction without affecting the surrounding areas

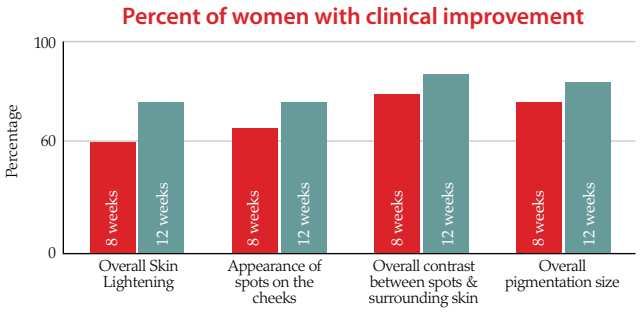




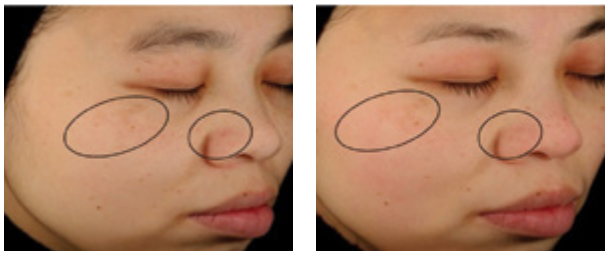
Synovea® HR Reduces Skin Hyperpigmentation in Chinese Subjects

Protocol:

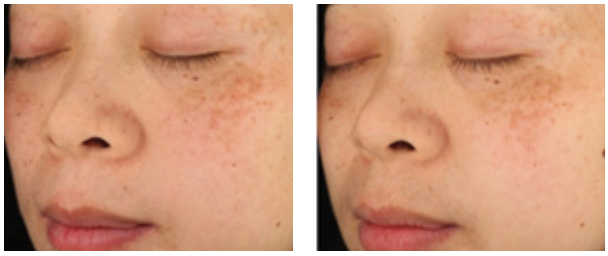
- **Volunteers –** Chinese; 32 with Synovea HR and 31 with control aged 30 to 40 yrs.
- **Study duration –** 12 weeks; double blind, vehicle controlled and randomized
- **Test sites –** Face
- **Test substances –** Synovea HR lotion vs control without HR
- **Application frequency –** Twice a day
- **Quantification of performance –** Digital imaging and clinical assessments – appearance of spots, skin lightening, contrast between spots & surrounding skin; pigmentation size, even toning, radiance & intensity of pigments



Data obtained from: YK Won et al., Clinical Efficacy and Safety of 4-hexyl-1,3-phenylenediol for improving Skin Hyperpigmentation, *Arch Dermatol Res*, 306(5):455-465, 2014



Baseline | After 12-week treatment



Baseline | After 12-week treatment

Synovea® HR Reduces Skin Hyperpigmentation in African Subjects

Protocol:

- **Volunteers –** African, 20 subjects aged 31 to 51 yrs.
- **Study duration –** 8 weeks
- **Test sites –** Face
- **Test substances –** Cream A: 0.75% Synovea HR + 2.5% Niacinamide and SPF 30 lotion & Cream B: 1% Synovea HR + 3% Niacinamide
- **Application frequency –** Cream A during the day and Cream B during the night
- **Quantification of performance –** Measurement of ITA° before and after treatment, subjective assessment by the volunteers and photography

Comparison of ITA° before and after 8 weeks of product application showed 20% improvement for hyperpigmented spots vs. 14% for the surrounding areas. Significant improvement seen in skin clarity, complexion, pigmented spots and hydration after 4 and 8 weeks of daily application; 89% volunteers would like to continue using the product irrespective of pricing.

Volunteer 9

Baseline | After 8-week treatment

Volunteer 17

Baseline | After 8-week treatment

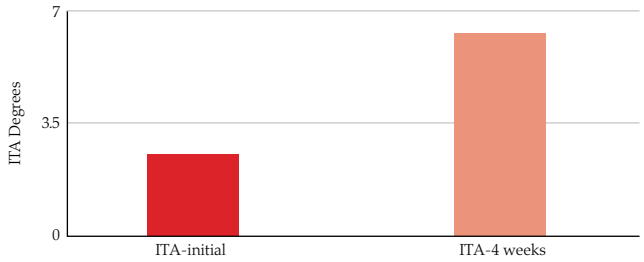
Skin Lightening Clinical Study with Asyntra® SL

Protocol:

- **Volunteers –** Hispanics and African American
- **Test sites –** Face
- **Product –** 2% Asyntra® SL lotion (no sunscreen)
- **Application frequency –** Twice a day
- **Study duration –** 4 weeks
- **Quantification of performance –** Measurement of ITA° before and after treatment

Asyntra® SL provides statistically significant ($p < 0.05$) skin lightening within 4 weeks treatment

Higher ITA° after treatment indicative of skin lightening



Skin Protective Properties of Synovea® HR

Cell Protection
Up-regulating Glutathione, Glutathione peroxidase & Glutathione reductase

DNA Protection
Providing long-term protection of DNA; No DNA degradation under UV-light

DNA Repair
Inhibiting DNA damage and improving DNA repair via NFκB pathway

Protein Protection
Protecting Collagen and other proteins by reducing Glycation

Inhibition of NFκB Activity

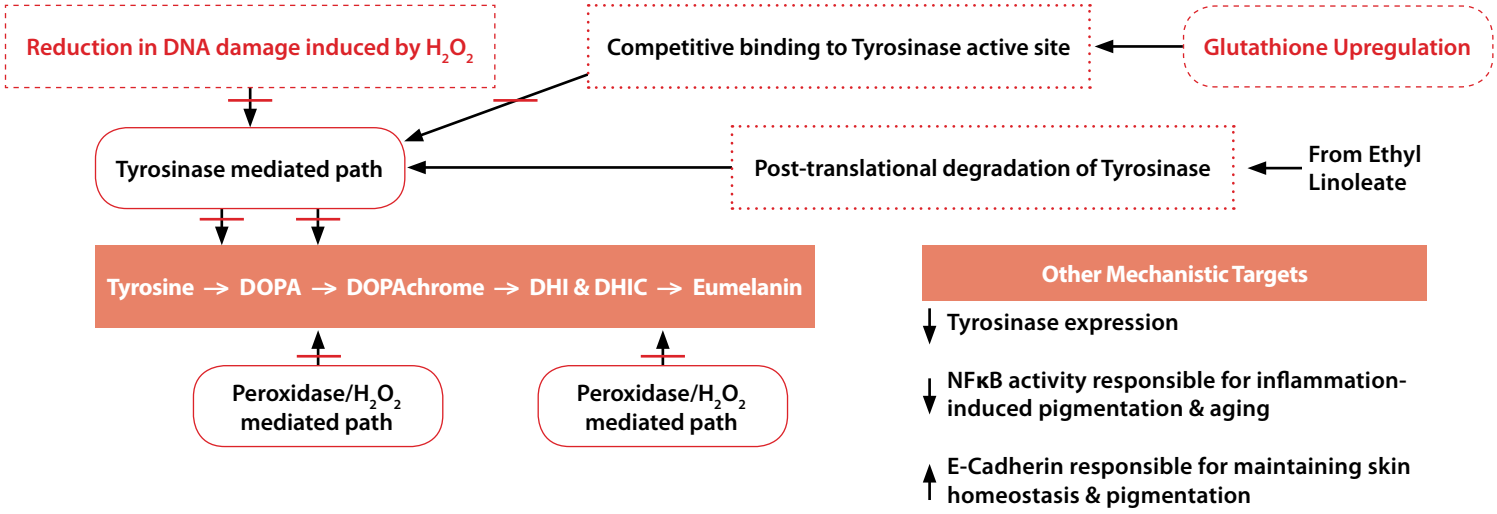
NFκB is a pleiotropic transcription factor which is present in almost all cell types and is a major mediator of inflammation. Inhibition of NFκB activation suppresses inflammation. **Synovea® HR is found to be 8 and 16-fold more effective than Resveratrol and Curcumin, respectively.**

Reference: J Yang et al., Food Chemistry, 160:338-345, 2014

Compound	Amount Required to Inhibit NFκB activity by >90%
Synovea® HR	6.25 µg/ml
Resveratrol	50 µg/ml
Curcumin	100 µg/ml

Synovea® HR and Asyntra® SL Inhibiting Multiple Sites in the Melanogenesis Pathway

Ethyl Linoleate in Asynta® SL is involved in post translational degradation of Tyrosinase. All other sites in the melanogenesis pathway are inhibited by Synovea® HR. Synovea® HR is modulating at least eight sites in the melanogenesis pathway.



Suggested Synergists / Additives for Improving Skin Lightening / Even Toning Effects

Synergist/ Additive	Rationale / Mechanism	Use level
Niacinamide **INCI: Niacinamide**	Inhibits transfer of melanin from melanocytes to keratinocytes; multiple skin benefits	1-2%
N-Acetyl glucosamine **INCI: Acetyl glucosamine**	Inhibits glucosidation step of Tyrosinase (active form); multiple skin benefits	1%
Synastol® TC **INCI: Terminalia chebula fruit extract**	Strong peroxidase inhibitor, Glycation inhibitor & reversal; Broad-spectrum antioxidant & anti-inflammatory; multiple skin benefits	0.5%
Sytenol® A **INCI: Bakuchiol**	Works by modulating α-MSH pathway & stimulating E-Cadherin; The first true alternative to retinol without having the negatives of retinol; multiple skin benefits	0.5%

Synovea® HR: A True Multi-functional Skin Lightening/Even Toning Active with Outstanding Safety Record

Safe and effective skin lightener/even toner

- 80+ years history of human use; edible
- Clinically proven to be four times more effective than hydroquinone
- Clinically proven to work for normal and hyper-pigmented skin & all races

Skin protection provided by

- Protecting DNA damage & repairing damaged DNA by inhibiting NFκB
- Stimulating glutathione to protect cells
- Reducing glycation to protect protein
- Reducing inflammation by inhibiting NFκB

Anti-aging benefits provided by

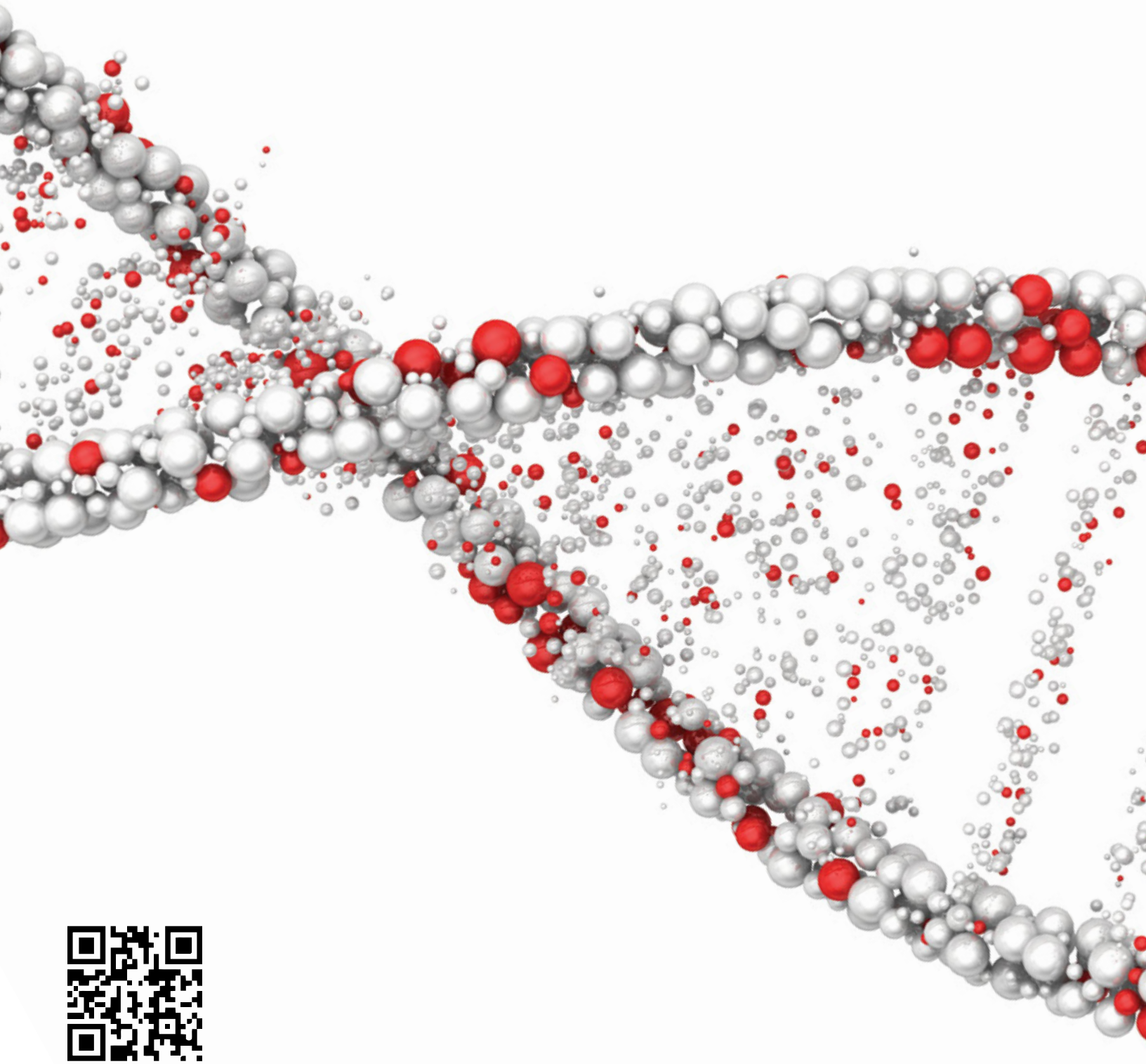
- Stimulating collagen & elastin
- Clinically proven to reduce multiple signs of aging

Can be used alone or in combination with other cosmetic active ingredients utilizing its

- Skin lightening
- Skin protection
- Anti-aging properties

Key References

1. RK Chaudhuri, Hexylresorcinol: Providing Skin Benefits by Modulating Multiple Molecular Targets, In Cosmeceuticals and Active Cosmetics, 3rd Edition, Eds. Raja K Sivamani, Jared Jagdeo, Peter Elsner, Howard I Maibach, Francis & Taylor, Boca Raton, Chapter 7, pp 73-83, 2015
2. S Tucker-Samaras, M Kizoulis, S Kaur, M Southall, J Fantasia, 4-Hexyl-1,3-phenylenediol, an NF-kB inhibitor, improves photodamaged skin and clinical signs of ageing in a double-blinded, randomised controlled trial, Brit J Dermatol, 173(1):218-226, 2015
3. YK Won, CJ Loy, M Randhawa, MD Southall, Clinical Efficacy and Safety of 4-hexyl-1,3-phenylenediol for Improving Skin Hyperpigmentation, Arch Dermatol Res, 306(5):455-465, 2014
4. S Kaur, T Oddos, S Tucker-Samaras, MD Southall, Regulation of DNA Repair Process by the Pro-inflammatory NFκB Pathway, Intech, Chapter 8, http://dx.doi.org/10.5772/54341, 2013
5. RK Chaudhuri, Effective Skin Lightening with Skin Protective Properties, Personal Care, 39-44, 2010



Sytheon Ltd.
315 Wootton Street, Boonton, NJ 07005, USA
www.sytheonltd.com • info@sytheonltd.com
Tel.: +1 973.988.1075

Sytheon SARL
72/74 Avenue Edouard Vaillant, 92100 Boulogne Billancourt, France
www.sytheonltd.com • sytheon@sytheonltd.com
Tel.: +33 (0)1.4110.8182

Disclaimer
The information given and the recommendations made herein are based on our research and literature search and are believed to be accurate but no guarantee of their accuracy is made. This information is intended to be helpful, but no warranty is expressed or implied as to the results obtained from use in the formulation, procedure or products suggested herein. Neither is any permission or recommendation to practice any invention covered by patent either expressed or implied.