BioMedical
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DARK SPOT SERUM

The Willows Office Park, Unit H3,
c/o Simon Vermooten & Farm Roads, Die Wilgers, Pretoria, South Africa
+27 12 809 2856 | info@biomedicalemporium.com

www.biomedicalemporium.com

COSMECEUTICAL SIGNIFICANCE

Hyperpigmentation occurs due to an increase in pigment within the skin. It is most commonly caused by an excess of melanin, but can also result from the accumulation of other substances, such as hemosiderin, amyloid, or certain drug deposits. Where excessive pigmentation is caused by melanin, the colour of pigmentation can signify the severity of melanin deposition. Excessive melanin deposition within the dermis can present a brown appearance, whereas deeper melanin deposition generates a grey or blue appearance. Different factors play a role in the production and expression of melanin in the skin, such as exposure to UV radiation, genetic predisposition, and melanocyte size leading to a difference in the amount of melanin produced per cell. Disorders of hyperpigmentation, including post-inflammatory hyperpigmentation, can cause dermal deviation such as freckles, age spots and acne scars. The appearance and formation of these pigmentary dermal deviations can be improved by including skin nutrients in a daily skincare routine, such as retinol, niacinamide, ellagic acid, vitamin E and liquorice extract.

Topical retinol improves the cell turnover of epidermal keratinocytes and promotes a decrease in melanosome transfer and a rapid loss of melanin via epidermopoiesis. Topical retinol controls cell

differentiation to restore a healthy dermal barrier. Retinoid-induced changes in the SC and the permeability barrier may also facilitate the penetration of depigmenting agents in the epidermis and increase their bioavailability, leading to increased depigmentation. In addition, several *in vitro* studies demonstrate that cis and trans-retinoic acid inhibit UVB-stimulated melanogenesis concerning tyrosinase activity and melanin synthesis. Topical retinol likely modulates epidermal melanin count via a direct action on melanocytes and epidermal keratinocytes.

Vitamin B3, also known as niacinamide or nicotinamide, can also reduce hyperpigmentation, as it interferes with the interaction between keratinocytes and melanocytes, inhibiting melanogenesis and the transfer of melanosomes from melanocytes to the keratinocytes. Studies have shown that niacinamide can significantly reduce dermal pigmentation. It was reported that 44% of niacinamide-treated areas showed a good to excellent reduction in pigmentation, compared to 55% with hydroquinone treatment. Moreover, side effects such as erythema, pruritis, and burning were less frequent and milder with the application of niacinamide compared to hydroquinone (18% vs. 29%). This is attributed to niacinamide decreasing cutaneous pigmentation by suppressing the transfer of melanosomes from melanocytes to keratinocytes.

Ellagic acid, a natural phenol antioxidant, can be found in different fruits, vegetables, and nuts. Ellagic acid is described as a copper iron chelator from the

tyrosinase enzyme's active site and was reported to inhibit melanogenesis in melanocytes. With its copper ions chelating ability, ellagic acid dose-dependently and noncompetitively inhibits tyrosinase activity in melanocytes. Research reported the capacity of ellagic acid to alleviate inflammatory responses in atopic dermatitis skin lesions in keratinocytes via the suppression of the pro-inflammatory mediator expression which can also potentially reduce inflammation associated with hyperpigmentation.

Vitamin E is a fat-soluble compound naturally found in fruits, vegetables (such as nuts, mangoes, and kiwis), and vegetable oils (like olive oil, avocado oil, and sunflower oil). It aids in maintaining healthy skin functions in both the dermis and epidermis and is a trusted dermatologic antioxidant due to its photo-protective effect on the skin. Vitamin E acts as an antioxidant against free radicals generated by UV exposure. Hence, skin damage such as erythema, oedema, and sunburns can be reduced by applying vitamin E topically prior to UV exposure. Vitamin E application can help prevent skin cancers and protect against photo-aging by reducing wrinkles and improving skin elasticity, structure, and softness. Depigmentation is facilitated by vitamin E through lipid peroxidation of melanocyte membranes, which enhances intracellular glutathione content which in turn will inhibit tyrosinase.

Liquorice extract (*Glycyrrhiza glabra*) can act as an effective pigment-lightening agent. It contains

bioactive components such as glabridin, licochalcone A, and isoliquiritin that effectively inhibit tyrosinase to combat pigmentation. Literature reports that topical application of liquorice extract can aid in reducing inflammation. Interestingly, the anti-oxidant potential of liquorice extract was also reported as capable of preserving cosmetic formulations, signifying its superior anti-oxidative capacity as a valuable pigmentation corrector included in the BioMedical Emporium Dark Spot Serum.

In conclusion, various topical agents such as retinol, vitamin B3, ellagic acid, vitamin E, and liquorice extract offer significant benefits in the management of hyperpigmentation. Retinol improves epidermal cell turnover and facilitates the penetration and bioavailability of depigmenting agents. Vitamin B3 interferes with the transfer of melanosomes, reducing pigmentation with fewer side effects compared to hydroquinone. Ellagic acid inhibits melanogenesis and reduces inflammation associated with hyperpigmentation. Vitamin E provides antioxidant protection against UV damage and supports skin health, while liquorice extract effectively inhibits tyrosinase and reduces inflammation. These agents, through their unique mechanisms, collectively offer promising strategies for the treatment and prevention of hyperpigmentation, highlighting their importance in dermatologic and cosmetic applications, such as Biomedical Emporium Dark Spot Serum.

THE CLINICAL POTENTIAL OF RETINOL

Even Complexion and Brightening Therapy

Cosmeceutical features: ↑ epidermal thickness, ↑ skin texture, ↑ overall youthful complexion, ↑ appearance of pigmented lesions

Physiology: ↑ epidermal keratinocyte proliferation, ↑ endothelial cell growth, ↑ c-Jun

Assists in the improvement of skin hyper-pigmentation

Cosmeceutical features: ↑ appearance of pigmented lesions, ↑ overall youthful complexion, ↑ skin texture

Physiology: ↓ tyrosinase, ↓ melanin synthesis, ↑ skin cell turnover, ↑ exfoliation of pigmented cells, ↓ post-inflammatory hyperpigmentation, ↑ collagen

Promotes skin smoothness

Cosmeceutical features: ↑ epidermal thickness, ↑ skin texture, ↑ overall youthful complexion, ↑ wrinkle appearance, ↓ fine line formation

Physiology: ↑ Type I collagen, ↑ fibronectin, ↑ tropoelastin, ↑ TGF-β/Smad pathway, ↑ TGF-β1 mRNA expression, ↓ inhibitory Smad7, ↑ CTGF/CCN2, ↑ TGF-β/CTGF pathway, ↓ CCN1 gene expression, ↓ TGF-β/CTGF pathway, ↑ MMP, ↑ ECM production, ↑ epidermal keratinocytes, ↑ c-Jun

Supports a radiant skin appearance

Cosmeceutical features: ↑ epidermal thickness, ↑ skin texture, ↑ overall youthful complexion, ↑ appearance of pigmented lesions

Physiology: ↑ epidermal keratinocyte proliferation, ↑ endothelial cell growth, ↑ c-Jun

THE CLINICAL POTENTIAL OF NIACINAMIDE

Even Complexion and Brightening Therapy

Cosmeceutical features:
↑ lightening of cutaneous pigmentation, ↑ even skin tone, ↑ skin radiance

Physiology: ↓ tyrosinase directly, ↓ PAR-2, ↓ melanosome transfer from melanocytes to keratinocytes, ↑ expression of differentiated type keratin K1, ↑ antiglycation

Assists in the improvement of skin hyper-pigmentation

Cosmeceutical features:
↑ lightening of cutaneous pigmentation, ↑ even skin tone

Physiology: ↓ tyrosinase directly, ↓ PAR-2, ↓ melanosome transfer from melanocytes to keratinocytes, ↑ expression of differentiated type keratin K1, ↑ antiglycation

Promotes skin smoothness

Cosmeceutical features:
↑ skin texture, ↑ skin thickness, ↑ wrinkle appearance, ↓ fine line formation

Physiology: ↓ excess dermal GAGs, ↑ collagen synthesis, ↑ ceramides, ↑ intercellular lipids, ↑ SPT mRNA

Supports a radiant skin appearance

Cosmeceutical features:
↑ lightening of cutaneous pigmentation, ↑ even skin tone, ↑ skin radiance

Physiology: ↓ tyrosinase directly, ↓ PAR-2, ↓ melanosome transfer from melanocytes to keratinocytes, ↑ expression of differentiated type keratin K1, ↑ antiglycation

THE CLINICAL POTENTIAL OF ELLAGIC ACID

Even Complexion and Brightening Therapy

Cosmeceutical features:
↑ lightening of cutaneous pigmentation, ↑ even skin tone, ↑ skin radiance

Physiology: ↓ UVA-induced ROS generation, ↓ DNA damage, ↓ apoptosis, ↓ tyrosinase activity, ↓ MCIR expression, ↓ α-MSH, ↑ ERK, ↓ JNK, ↓ MITF, ↑ intracellular LC3-I to LC3-II conversion, ↑ p62/SQSTM1 expression, ↓ ATG4B, ↓PI3K, ↓ mTOR, ↑ Beclin-1/Bcl-2 dysregulation, ↑ NQO-1, ↑ γ-GCLC, ↑ HO-1, ↓ pCREB, ↓ CREB, ↓ MITF, ↓ TRP-1/-2, ↓ ROS-mediated POMC/α-MSH

Assists in the improvement of skin hyper-pigmentation

Cosmeceutical features:
↑ lightening of cutaneous pigmentation, ↑ even skin tone, ↑ skin radiance

Physiology: ↓ UVA-induced ROS generation, ↓ DNA damage, ↓ apoptosis, ↓ tyrosinase activity, ↓ MCIR expression, ↓ α-MSH, ↑ ERK, ↓ JNK, ↓ MITF, ↑ intracellular LC3-I to LC3-II conversion, ↑ p62/SQSTM1 expression, ↓ ATG4B, ↓PI3K, ↓ mTOR, ↑ Beclin-1/Bcl-2 dysregulation, ↑ NQO-1, ↑ γ-GCLC, ↑ HO-1, ↓ pCREB, ↓ CREB, ↓ MITF, ↓ TRP-1/-2, ↓ ROS-mediated POMC/α-MSH

Promotes skin smoothness

Cosmeceutical features:
↓ swelling, ↑ skin texture

Physiology: ↓ IL-1β, ↓ IL-6, ↓ IL-8, ↓ TNF, ↑ IL-10, ↑ Nrf2 pathway, ↓ phosphorylation of JAK2, STAT 1 and STAT3, ↓ phosphorylation of Akt

Supports a radiant skin appearance

Cosmeceutical features:
↓ swelling, ↑ skin texture, ↑ skin radiance

Physiology: ↓ IL-1β, ↓ IL-6, ↓ IL-8, ↓ TNF, ↑ IL-10, ↑ Nrf2 pathway

THE CLINICAL POTENTIAL OF TOCOPHEROL ACETATE

Even Complexion and Brightening Therapy

Cosmeceutical features:
↓ pigmentation

Physiology: ↓ UVB-mediated COX-2 induction, ↓ peroxynitrite production, ↓ lipid peroxidation, ↓ ROS

Assists in the improvement of skin hyper-pigmentation

Cosmeceutical features:
↓ pigmentation

Physiology: ↓ UVB-mediated COX-2 induction, ↓ peroxynitrite production, ↓ lipid peroxidation, ↓ ROS

Promotes skin smoothness

Cosmeceutical features:
↓ dermal dryness, ↑ skin texture, ↑ wrinkle appearance, ↓ fine line formation, ↑ skin texture

Physiology: ↓ MMP-1, ↓ collagen degradation, ↑ keratinocyte production, ↑ fibroblast viability

Supports a radiant skin appearance

Cosmeceutical features:
↓ dermal dryness, ↑ skin texture

Physiology: ↑ keratinocyte production, ↑ fibroblast viability

THE CLINICAL POTENTIAL OF LIQUORICE EXTRACT

Even Complexion and Brightening Therapy

Cosmeceutical features: ↓ pigmentation, ↑ skin whitening, ↑ protection against pigmentation

Physiology: ↓ tyrosinase, ↓ melanin, ↓ PTP1B, ↓ MITF, ↓ cAMP-CREB pathway, ↓ MAPK/ERK pathway, ↓ ERK

Assists in the improvement of skin hyper-pigmentation

Cosmeceutical features: ↓ pigmentation, ↑ skin whitening, ↑ protection against pigmentation

Physiology: ↑ Nrf2/ARE, ↓ PGE2, ↓ tyrosinase, ↓ melanin, ↓ PTP1B, ↓ MITF, ↓ cAMP-CREB pathway, ↓ MAPK/ERK pathway, ↓ ERK

Promotes skin smoothness

Cosmeceutical features: ↓ depth of wrinkles, ↑ dermal thickness, ↓ swelling, ↑ skin texture

Physiology: ↓ MMP-2, ↑ collagen, ↓ ROS, ↓ elastase, ↑ superoxide scavenger activity, ↓ MMP-1, ↓ MMP-9, ↓ NF-kB, ↓ MAPK, ↓ AP-1, ↓ microsomal lipid peroxidation

Supports a radiant skin appearance

Cosmeceutical features: ↑ delays ageing, ↑ dermal brightening, ↑ overall healthy skin appearance

Physiology: ↓ MMP-2, ↑ collagen, ↓ ROS, ↓ elastase, ↑ superoxide scavenger activity, ↓ MMP-1, ↓ MMP-9, ↓ NF-kB, ↓ MAPK, ↓ AP-1, ↓ microsomal lipid peroxidation, ↑ Nrf2/ARE, ↓ PGE2

Table 1: Classification and clinical significance of ingredients included in the BioMedical Emporium Dark Spot Serum

INGREDIENT	CLASSIFICATION	REASON FOR INCLUSION
Retinol	Vitamin A derivate	Reduces hyperpigmentation, improves epithelisation of the skin, improves the appearance of fine lines and wrinkles and helps to normalise the physiology of the epidermis and retain skin moisture
Niacinamide	Water soluble vitamin, antioxidant	Lightening effect, photo-protective and improves barrier protective function of the skin
Ellagic Acid	Phenol, antioxidant	Skin whitening, reduces hyperpigmentation, anti-inflammatory, protective role in UV radiation-induced oxidative stress, anti-photo-aging properties and anti-melanogenic agent.
Vitamin E (Tocopherol Acetate)	Lipid soluble vitamin, antioxidant	Reduces lipid peroxidation, photo protecting and improves skin moisturisation
Liquorice extract	Glycyrrhiza glabra root extract, antioxidant	Reduces pigmentation, limits free radical formation, skin lightening, reduces lipid peroxidation, limits wrinkle formation and anti-photo ageing agent

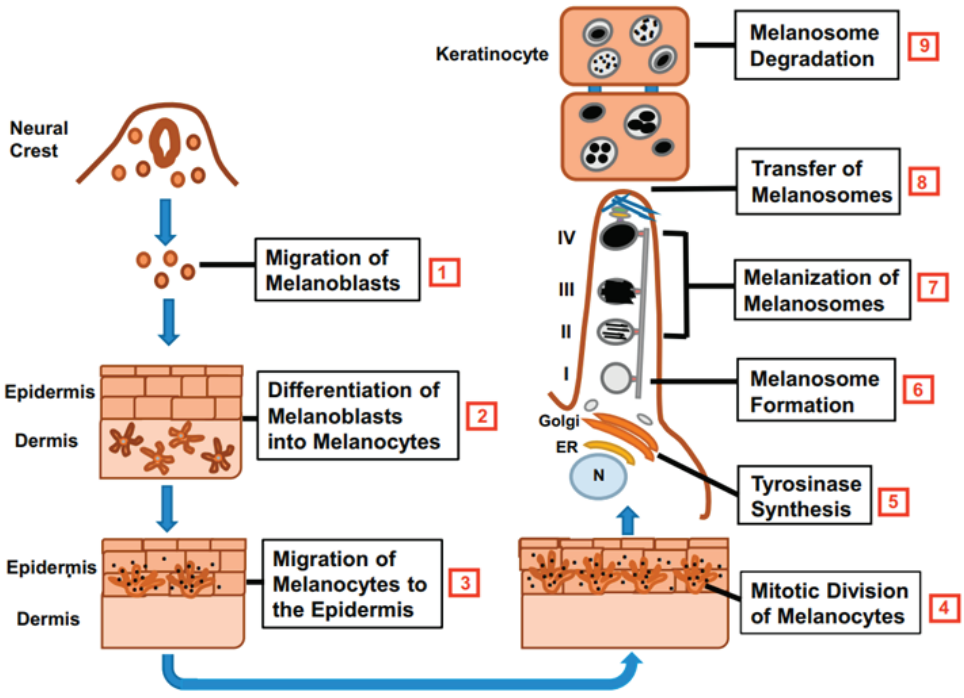

Figure 1. Stages in melanocyte development, melanosome formation and melanization, and melanin transfer to keratinocytes (Lambert *et al.*, 2019).

ABBREVIATIONS

Akt:	protein kinase B
AP-1:	activator protein 1
ARE:	antioxidant responsive element
ATG4B:	autophagy related 4B cysteine peptidase
Bcl:	B-cell lymphoma
cAMP:	cyclic adenosine monophosphate
CCN:	cellular communication network factor
c-Jun:	Jun-Proto-Oncogene
COX-2:	cyclooxygenase-2
CREB:	cAMP-responsive element binding protein
CTGF:	connective tissue growth factor
DNA:	deoxyribonucleic acid
ECM:	extracellular matrix
ERK:	extracellular signal-regulated protein kinase
IL:	interleukin
JAK:	janus kinase
JNK:	c-Jun N-terminal kinase
LC3:	microtubule-associated protein light chain
MAPK:	mitogen-activated protein kinase
MCIR:	melanocortin-1 receptor
MITF:	microphthalmia-associated transcription factor
MMP:	matrix metalloproteinases
MTOR:	mammalian (or mechanistic) target of rapamycin
mRNA:	messenger Ribonucleic Acid

MSH:	-melanocyte stimulating hormone
NF-κB:	nuclear factor-κB
Nrf2:	nuclear factor erythroid 2-related factor 2
NQO:	dehydrogenase [quinone] a serine
P62/ SQSTM1:	protein sequestosome 1
PAR:	poly (adenosine diphosphate ribose) polymerase
PCREB:	phosphorylated cAMP-responsive element binding protein
PGE2:	prostaglandin E2
PI3K:	phosphoinositide-3-kinase–protein kinase B
POMC:	pro-opiomelanocortin
PTP1B:	protein tyrosine phosphatase 1B
ROS:	reactive oxygen species
SC:	stratum corneum
Smad:	suppressor of mothers against decapentaplegic
Smad7:	suppressor of mothers against decapentaplegic homolog 7
SPT:	single particle tracking
STAT:	signal transducer and activator of transcription
SQSTM1:	sequestosome 1
TGF:	transforming growth factor
TNF:	tumor necrosis factor
TRP:	tyrosinase-related protein
UVA:	ultraviolet A radiation
UVB:	ultraviolet B radiation
UV:	ultraviolet

WARNINGS

Inappropriate or excessive use of topical retinol can lead to potential side effects. These generally include skin dryness, redness, and peeling, which can cause discomfort. However, typically these side effects diminish over time as the skin adjusts. Therefore, lower doses of retinol can be applied until the skin tolerability improves. Whereafter, the concentration of retinol can be increased. Please note: Biomedical Emporium Dark Spot Serum contains Vitamin A-related compounds, which contribute to daily intake of Vitamin A. Sun Alert: Vitamin A-containing products may cause photosensitivity and increase sensitivity to sunburn, be certain to apply adequate sunscreen protection while using Biomedical Emporium Dark Spot Serum.

Rarely contact allergy resulting from ellagic acid application has been reported. Patch testing by applying a small amount of the BioMedical Emporium Dark Spot Serum should be performed to test for delayed-type hypersensitivity.

Side effects from the topical application of niacinamide are minor and rare. Reported side effects include mild burning, pruritis, and erythema.

However, these side effects tend to improve with continued use.

Vitamin E and its derivatives are widely used in many cosmetic and dermatologic products, in general, literature reporting side effects such as allergic or irritant skin reactions are rare.

Rarely contact allergy to topical liquorice extract application has been reported. Patch testing by applying a small amount of the BioMedical Emporium Dark Spot Serum should be performed to test for delayed-type hypersensitivity.

STORAGE INSTRUCTIONS

This product is packed in an airless, opaque container, providing protection from oxygen exposure and ambient light. Store at or below 25°C.

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The Willows Office Park, Unit H3, c/o Simon Vermooten
& Farm Roads, Die Wilgers, Pretoria, South Africa
+27 12 809 2856
info@biomedicalemporium.com
www.biomedicalemporium.com