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**NEW ASPECTS OF MELASMA**
RECENT PROGRESS IN UNDERSTANDING PATHOPHYSIOLOGY OF MELASMA IN IMPLICATIONS FOR NEW TREATMENT STRATEGIES

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**HYPERPIGMENTATION**

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Scientific data & in vitro study

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ACLARANSE contains Gatuline, Arbutin, Nonapeptide-1, Retinol Palmitate, antioxidants among others.

SKIN TONE MULTI-CORRECTOR

REDUCES THE APPEARANCE OF PIGMENT IRREGULARITIES

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Skin colour is basically due to a complex combination of various dermal and epidermal pigments.

Melanin is certainly the most interesting one but the resulting basic skin colour is also due to the presence of oxygenated haemoglobin (in arteries), to deoxygenated haemoglobin (in veins), to deposits of various pigments such as carotenoids and other exogenous or endogen pigments.

Epidermis basal layer melanocytes synthesize skin main pigment: melanin. It gives the skin its basic genetically driven colour and also is the major pigment to blame in case of hyperpigmentations secondary to relatively excessive sun exposure or inflammatory processes.

There is a significant variation in melanocyte concentrations, between different body areas on one single human but if we compare the concentration of melanocytes in the same area, dark- and light-skinned humans have analogous numbers of melanocytes.

The difference is that melanosomes, organelles containing melanin, are larger, more abundant, more widely dispersed into melanocyte cytoplasm and contain a higher melanin concentration in dark compared to light skin.

What happens inside of melanocyte [the cascade of chemical events from Tyrosine up to melanin, the stock of melanosome up to the melanocyte external cell membrane, the bilayer phospholipids membrane fusion processes necessary for exocytosis] is of equal importance to what happens outside of melanocytes, since every melanocyte is directly connected to an average 40 keratinocytes (epidermal melanization unit), able to actively receive the pigments liberated by melanocytes and bring it to the skin surface. Membrane fusion processes are here also of significant importance and keratinocytes seem to have genetic skills to properly distribute melanin in relation with cell genotype. Amazingly, keratinocytes cocultured with different types of melanocytes give rise to a melanosome allocation pattern characteristic of its own genetic. Light skin keratinocyte cocultured with dark skin melanocyte give rise to a light skin melanin distribution in keratinocyte and vice versa. Furthermore, it seems that keratinocytes are able to control melanocyte dendritogen-

Melanin (Greek: μέλας - melas, “black, dark”) is a broad term for a group of natural pigments found in most organisms (arachnids are one of the few groups in which it has not been detected). Melanin is produced by the oxidation of the amino acid tyrosine, followed by polymerization. The pigment is produced in a specialized group of cells known as melanocytes.

Evgeniya Ranneva dermatologist, PHD
Melanogenesis, depending on the neighboring situation. Melanocytes dendrites number and size widely depend on local events. Melanin is transferred to melanocytes in various ways: dendrites protrusions enter into keratinocyte [melanocytophagocytosis], membrane fusion processes between melanocyte and keratinocyte membranes and melanosome exocytosis [melanosomes are expelled out of melanocytes and secondarily captured by keratinocytes endocytosis]. Melanocytes not only send melanin to keratinocytes but also parts of its cytoplasm end membranes.

Many pigment exchanges happen into the skin since not only melanosomes do their own trip but also keratinocytes progressively are pushed up to the surface where they will die dry, allowing building stratum corneum, the ultimate skin protection layer.

Skin global color directly depends on the surface melanin concentration. As well, melanocytes are not fixed into basal layer: they have a migratory potential seen in scars repigmentation. Sun exposure induces an event cascade into melanocytes and keratinocytes. Even the number of melanocytes can increase secondarily to UV exposure, maybe due to a specific keratinocyte signal.

Melanin can be of "good" [eumelanin] or "bad" [phaeomelanin] quality: eumelanin is a stable molecule that correctly protects our skin, scavenging free radicals induced by UV photons energy transformation. Phaeomelanin offers a poor protection, adsorbs a reduced number of photos and is unstable: it breaks when transforming UV photons energy and liberates more free radicals than the photon itself. Therefore, sunlight exposure damages much faster light skins comparing to dark skins.

A last point would be to know - out of freckles, lentigines and other hereditary or secondary skin pathologies, - why some people have a very nice uniform face tanning or basic skin colour and other have a geographic style tanning colour. In other words, why some patients suffer melasma and other don’t. Basically, we meet three main explanations in our every day’s work. Very often the aetiology is hormonal: pigments appeared during pregnancy or after changing a contraceptive pill, in any case, more often in woman than in man and basically never before the onset of menstruation [menarche]. Often genetic plays a role: that’s the case when a mother comes with her sister and 3 children, everybody showing melasma. Sometimes hyperpigmentation is post-inflammatory: we have to face more and more laser induced pigmentation [and also scarring] that are quite hard to treat. In all the case, voluntary or involuntary sun exposure seems to be an important parameter and sun protection plus sun avoidance are mandatory for having good results.
Melasma is a common, acquired, circumscribed hypermelanosis of the face and occasionally of the neck and forearms, which significantly impacts the quality of life. Chloasma comes from the Greek term for “a green spot” and describes melasma during pregnancy or the “mask of pregnancy”.

Although it may affect any race, melasma is much more common in darker-skinned individuals (skin types IV to VI) (1). There are few prevalence studies on melasma, but there is evidence that the prevalence of this disorder differs among different ethnic groups. Melasma is more common in individuals of Hispanic, Oriental and Asian origin (2). The reported prevalence of melasma ranges from 8% among Latinas in the United States, to 30% in Southeastern Asian populations. Melasma is more prevalent in women, especially during their reproductive years, with the peak age between 20 and 30 years. It is rarely reported before puberty (3). Extra-facial melasma is more prevalent in postmenopausal women (4).

Etiology and pathogenesis
Etiopathogenesis of melasma is multifactorial and remains unclear. Genetic and hormonal factors and exposure to UV radiation are classical influencing factors. There are many other factors that may play a role in the etiology of melasma, such as ingredients in cosmetics, phototoxic and anti-seizure drugs, endocrine disorders (ie, ovarian or thyroid dysfunction), hepatic dysfunction, parasites, and nutritional deficiency. It is important to note that most cases of melasma in men and up to one third of cases in women are idiopathic (5).

Ultraviolet exposure is a major triggering and aggravating factor in the development of melasma, since it has a well known ability to stimulate proliferation of melanocytes, their migration, and melanogenesis(1). However, UV-induced hyperpigmentation usually recovers spontaneously, whereas melasma does not. Recently, Kim et al. detected down-regulation of the H19 gene on microarray analysis of hyperpigmented and normally pigmented skin in patients with melasma (6).

Melasma is commonly reported in women using estrogen-progesterone oral contraceptives, hormone replacement therapy for prevention of osteoporosis, and in men using hormone replacement therapy.
using estrogen derivatives for treatment of prostatic cancer (7). The mechanism of induction of melasma by estrogen may be related to the presence of estrogen receptors on the melanocytes that stimulate cells to produce more melanin (8, 9). One study of melasma in patients who had never been pregnant or used hormone therapy, reported increased serum concentrations of luteinizing hormone (10). Sawney and Anand found a high prevalence of chronic pelvic inflammatory disease in women with melasma (11). These findings may implicate mild ovarian dysfunction as a possible cause of idiopathic melasma.

However, many observations strongly suggest the role of genetic factors. Familial occurrence of melasma has been reported to vary from 20% to 70% in different studies (12). Characteristic clinical features of melasma are symmetry of hyperpigmentation and distribution related to trigeminal nerves, which suggest that the neural involvement may play a role in the pathogenesis of pigmentation. Bak et al. found higher levels of neural endopeptidase in melasma lesions and suggest that neuroactive molecules, including nerve growth factor, are critical factors for the pathogenesis of melasma (13).

It is still unclear why certain areas of the face are predisposed to develop melasma, while others are not. Besides neural factors and hormone receptors, blood vessels may play a role. Human melanocytes may respond to angiogenic factors because normal human melanocytes express functional receptors for vascular endothelial growth factor (VEGF) (14). In some types of melasma, a pronounced telangiectatic erythema confined to melasma-lesional skin has been observed. Furthermore, increased vascularity is one of the major histologic findings in melasma (15). These findings may explain the effects of localized microinjection of plasmin inhibitor tranexamic acid, and good therapeutic efficacy of vascular lasers in the treatment of melasma (16).

Pathology
Few studies have investigated the histologic alterations in melasma lesions. Compared to uninvolved skin, the areas of hyperpigmentation showed increased deposition of melanin in the epidermis and dermis, as well as enlarged intensely stained melanocytes with prominent dendrites (17).

Clinical presentation
Clinically, melasma presents as a symmetrically distributed macular pigmentation with irregular borders, which can vary in color ranging from a light to dark brown or brown-gray. Th number of hyperpigmented lesions may range from one single lesion to multiple patches located on the forehead, cheeks, dorsum of the nose, upper lip, chin, occasionally on the V-neck area and forearms. Pigmentation may be guttate or confetti-like, linear, or confluent evolves slowly over weeks or years. Th hyperpigmented patches often fade in winter and get worse in the summer.

According to the distribution of lesions, there are three clinical patterns of melasma: centrofacial (65%), malar (20%), and mandibular (15%). The centrofacial pattern involves the forehead, cheeks, upper lip, nose, and chin; the malar pattern involves the cheeks and nose, and mandibular the ramus of the mandible (18) (Figure 1).

Wood’s lamp (320–400 nm) is used to determine the depth of melanin in the skin. Wood’s light may also serve as a prognostic guide in the treatment of melasma, as the epidermal type of melasma is more likely to respond favorably to topical depigmenting agents. Common reasons for diagnostic failure are topical petrolatum and salicylic acid, lint and soap residues since these may fluoresce under Wood’s light (19). Based on Wood’s light examination, Sanchez et al. (20) classified melasma into four major clinical types, that show good correlation with the depth of melanin pigments:

1. Epidermal melasma is light brown; its color contrast is enhanced by Wood’s light examination.
2. Dermal melasma is brown or bluishgray by visible light; under Wood’s light this type expresses less distinct borders, with no enhancement of pigmentation.
3. Mixed melasma is dark-brown; enhancement of pigmentation is present under Wood’s light in some areas, but not in all.
4. Indeterminate or inapparent melasma is found in individuals with dark-brown skin.
Wood’s light does not localize the pigment. Since dermal melanin deposition may be unrecognized under Wood’s light, diagnosis and treatment of patients with apparent epidermal melasma is still difficult [21].

Clinical outcome measures

The Melasma Area and Severity Index (MASI) is a common outcome measure, used to assess melasma patients. The severity of melasma in each of the four regions (forehead, right malar region, left malar region and chin) is assessed based on three variables: percentage of the total area involved (A), darkness (D), and homogeneity (H) [22]. Melasma has a significant negative impact on patients’ health related quality of life (QoL), and severely affects social life, emotional well-being, and physical health [23]. Several instruments have been developed to evaluate QoL in melasma patients. Such instruments need to undergo translation, validation and cultural adaptation [24].

Diagnosis

The diagnosis is clinical and an effort must be made with every patient to detect the individual risk factors and triggers. However, a number of other conditions can mimic melasma (Table 1).

Therapeutical approaches

The aim of melasma treatment is to eliminate already existing pigmentation and to block de novo pigmentation. Numerous treatment options are currently available for melasma. Th choice of treatment options of their combination depends mainly on the type of melasma, eff eces of prior treatments, and expectations of the patient [25]. New regimens aim to shorten and simplify the treatment. Difficulties in treatment of melasma arise from the following:

1. Melasma is often recalcitrant to treatment
2. High tendency for recurrence/reappearance
3. Risk of adverse events
4. Successful treatment requires long term patient compliance, because therapeutic effects usually become evident after 1-2 months
5. Treatment costs

Protection from sun exposure

Melanocytes in melasma are easily stimulated not only by UVB, but also but UVA and visible radiation. In order to maintain good treatment results and to prevent recurrences, one must make major lifestyle changes. Sunbathing is absolutely contraindicated, as a few minutes of sunbathing can reverse the benefit of months of therapy. Sunscreens must be applied daily, during and after the treatment, throughout the sunny months of the year for an indefinite period [18]. Sunscreens are crucial for sun protection, so the use of mineral sunscreens containing titanium dioxide or zinc oxide, with a sun protection factor (SPF) of 30 or higher, is mandatory.

Bleaching agents

Skin lightening or skin bleaching is the practice of using chemical substances in order to lighten the skin color or provide an even toned complexion. Bleaching agents act at various levels of melanin production in the skin, many of which act as competitive tyrosinase inhibitors, the key enzyme in melanogenesis. Others inhibit the maturation of this enzyme or the transport of melanosomes from melanocytes to the surrounding keratinocytes [26]. The most important medical indications for the use of lightening agents are melasma and postinflammatory hyperpigmentation, but also depigmenting conditions, like vitiligo.

There are three different categories of bleaching agents: phenolic compounds, non-phenolic compounds, and combination formulas [27]. Some herbal extracts, flavonoids, coumarins and other derivatives are well known hypopigmenting agents (Table 2). Their classification is difficult, due to a great number of products and various mechanisms of action [28]. In clinical practice, reflectance chromameters measure not only the skin color, and ultraviolet (UV)-induced pigmentation, but the bleaching effect of depigmenting agents.

### Table 1: Differential diagnosis of melasma

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Differentiating Signs/Symptoms</th>
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<tr>
<td>Post inflammatory hyperpigmentation</td>
<td>Distribution of the eruption, history of inflammation</td>
</tr>
<tr>
<td>Cosmetic dermatitis (Riehl’s melanosis)</td>
<td>Reddish-brown pigmentation, reticulate pattern</td>
</tr>
<tr>
<td>Poikiloderma of Civatte</td>
<td>Reddish-brown, reticulate pattern, atrophy, telangiectasias</td>
</tr>
<tr>
<td>Distribution (anterior neck, sparing of submental region)</td>
<td></td>
</tr>
<tr>
<td>Hori’s nevus</td>
<td>Blush-gray pigmentation, distribution of macules</td>
</tr>
<tr>
<td>Drug induced facial pigmentation*</td>
<td>Phenothiazines, tetracyclines, phenytoin, antimalarials</td>
</tr>
<tr>
<td>Actinic lichen planus:</td>
<td>Papular lesions, histology</td>
</tr>
</tbody>
</table>

*Hyperpigmentation is reversible but may take up to one year for complete resolution after stopping the drug.

Hydroquinone (HQ)

Hydroquinone (C6H6O2) is the most commonly used bleaching agent and the gold standard for melasma treatment. HQ inhibits the conversion of 3,4-dihydroxyphenylalanine (DOPA) to melanin by tyrosinase inhibition, and it also inhibits RNA and DNA synthesis in melanocytic cells, and degrades melanosomes [27]. Since 2001, HQ has been banned in the European Unit (EU) as an ingredient in cosmetics [29]. The EU decision was based on its mid-term side effects, mainly exogenous ochronosis and leukoderma-en-confetti [30]. During the past decade, concerns over the safety of HQ have increased. Its use has been connected with toxicity and mutagenicity, and an increased incidence of exogenous ochronosis [31]. Although animal studies demonstrated its toxicity and/or mutagenic effects, these have not been proven in humans [32]. In 2009, the Food and
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Best Results

Before | After
---|---

**Treatment:** Unideep
**Daily Care:** Blending Bleaching Cream, Melablock-HSP® SPF 50+

**Treatment:** Easy TCA® (Pixel Peel)
**Daily Care:** Blending Bleaching Cream, Melablock-HSP® SPF 50+

---

**Treatment:** Lip & Eyelid
**Daily Care:** IPLase Mask®, Melablock-HSP® SPF 50+ Actilift® / Nutritive Cream Vit. A-C-E Lipoic Complex

---

CLEANSER
Cleansing foam suitable for all skin types

VIT. E ANTI-OXYDANT
Anti-aging moisturizing cream

NUTRITIVE CREAM
VIT. A-C-E LIPOIC COMPLEX

MELABLOCK-HSP SPF 50+/SPF 30
Allow gradual tanning and lower the risk of pigmentation marks

BLENDING BLEACHING CREAM
Whitening, anti-oxidant
are temporary and they resolve upon discontinuation of HQ. These side-effects include irritant and rarely allergic contact dermatitis and bic acid 0.1% as preservative. Side-effects of HQ mostly reversibly inhibit tyrosinase activity and may also interfere with mitochondrial oxidoreductase activity. Azelaic acid does not appear to affect normal melanocytes, but has an antiproliferative effect on abnormal melanocytes. AzA has antibacterial and anti-keratinizing activities. At 10–20% concentration, twice-daily application may treat melasma with minimal side effects; most patients report a mild but transient irritation of the skin at the beginning of treatment. A recent study suggests that 20% azelaic acid cream applied twice daily may be more effective than hydroquinone 4% in reducing mild melasma [30].

Kojic acid
Kojic acid is a fungal metabolite that inhibits catecholate activity of tyrosinase, used in a 1–4% cream base, alone or in combination with tretinoin, HQ, and/or corticosteroids. Although kojic acid alone is less effective than HQ 2%, (36) in combination with glycolic acid 10% and HQ 2%, it seems to have a synergistic action [37].

L-ascorbic acid (vitamin C)
Several forms of topical vitamin C are used to treat melasma in 5 to 10% concentrations and can be formulated with other depigmenting agents, such as HQ. Other advantages of vitamin C include antioxidant effects and photo protective properties. The weakness of ascorbic acid is its chemical instability and the hydrophilic nature limits its skin penetration. Magnesium ascorbyl phosphate, ascorbyl palmitate and sodium ascorbyl phosphate are stable derivatives of ascorbic acid. Iontophoresis has been used to promote percutaneous absorption of vitamin C into the skin [38].

Drug Agency (FDA) renewed its call for additional studies on the safety of HQ. The request for evaluation focuses on uncovering the risks of skin disorders, cancer, and genetic mutations from HQ exposure in humans [33].

However, HQ over 2% can only be prescribed from a doctor’s office. The effectiveness of HQ is related to the concentration of the preparation, to the vehicle used and the chemical stability of the product. Concentrations of HQ vary from 2% to as high as 10%. Several formulations are commonly prescribed by dermatologists, in order to reach the desired HQ concentration. HQ is easily oxidized, therefore, antioxidants such as 0.1% sodium bisulphate and 0.1% ascorbic acid should be used [33]. The following formula can be prescribed: HQ 3-10% in hydroalcoholic solution (equal parts of propyl-ene glycol and absolute ethanol) or hydrophilic ointment or HQ 3-10% in hydroalcoholic solution (equal parts of propyl-
edium ascorbyl phosphate are stable derivatives of ascorbic acid.

Combination formulas
The skin lightening effects of HQ can be enhanced by adding various topical agents such as tretinoin and corticosteroids (Table 3). Tretinoin accelerates cell turnover, and facilitates epidermal penetration of HQ, moreover, it suppresses steroid atrophy, and prevents HQ oxidation. Corticosteroids suppress melanin production, and eliminate the irritation caused by HQ and tretinoin [34].

Azeleic acid is a naturally occurring byproduct of the metabolism of Pityrosporum ovale and is associated with hypomelanosis seen in tinea versicolor. In vitro, azelaic acid reversibly inhibits tyrosinase activity and may also interfere

## Table 2: Treatment options for melasma

<table>
<thead>
<tr>
<th>Category</th>
<th>Bleaching agent</th>
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<tbody>
<tr>
<td>Phenolic compounds</td>
<td>Hydroquinone (HQ)</td>
</tr>
<tr>
<td></td>
<td>4-hydroxyanisole ([Mequinol])</td>
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<tr>
<td></td>
<td>N-acetyl-4-Scystaminylghenol (4-S-CAP)</td>
</tr>
<tr>
<td>Nonphenolic Compounds</td>
<td>Azelaic acid (AzA)</td>
</tr>
<tr>
<td></td>
<td>Topical Retinoids</td>
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<tr>
<td></td>
<td>L-ascorbic Acid (vit.C)</td>
</tr>
<tr>
<td></td>
<td>Kojic acid</td>
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<tr>
<td>Chemical peels</td>
<td>Alpha-hydroxy acids (AHAs)</td>
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<tr>
<td></td>
<td>Beta-hydroxy acid (BHA)</td>
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<tr>
<td></td>
<td>Jessner’s original and modified solutions</td>
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<tr>
<td>Device-Based Therapies</td>
<td>Trichloroacetic acid</td>
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<tr>
<td></td>
<td>Intense pulsed light</td>
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<tr>
<td></td>
<td>Lasers</td>
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<tr>
<td></td>
<td>Microdermabrasion</td>
</tr>
<tr>
<td>Plant extracts/active agents</td>
<td>Arbutin, licorice extract, aloesin, oreganin, soy, green tea orchid extracts, coumoric acid, ellagic acid, liquiritin, genisteic acid, hesperedin, licorice, niacinamide, yeast derivatives</td>
</tr>
<tr>
<td>Others</td>
<td>Mercury, indomethacin, ZnS04, topical corticosteroids</td>
</tr>
</tbody>
</table>

Topical retinoids
Topical retinoids stimulate the cell turnover and promote rapid loss of melanin via epidermopoeisis. Retinoid-induced changes in the stratum corneum facilitate the penetration of depigmenting agents in the epidermis, leading to increased depigmentation [39].

Tretinoin used at 0.05 – 0.1% concentrations, applied once nightly, can be effective as monotherapy, but requires 20 to 40-week treatment periods. The most common adverse effects include burning, erythema and scaling. Retinoid dermatitis may itself lead to postinflammatory hyperpigmentation, especially in dark-skinned individuals [40].

Adapalene 0.1% was found to be a safe and effective monotherapy in the treatment of epidermal melasma with a lower potential for skin-irritation compared to tretinoin [41]. A study confirms that the efficiency of tretinoin 1% peelings is similar to glycolic acid 70%, with very rare side-effects [42].

Chemical peels
Superficial chemical peeling agents are beneficial in the management of epidermal melasma and may be used in combination with other forms of melasma treatment. The peel solution is selected according to patient’s needs, skin type and sensitivities. Because of their superficial action, superficial peels can be used in nearly all skin types [41]. Medium-depth peels may be an alternative treatment in refractory cases of severe melasma. All types of chemical
peels, but mainly alpha-hydroxy acids, beta-hydroxy acid, salicylic acid, Jessner’s original and modifi solutions, and trichloracetic acid are used alone or in combination with other depigmenting agents. It has to be emphasized that the response of melasma to chemical peels is rather unpredict-able and there is a tendency for changes in pigmentation after chemical peel, especially in dark skinned individuals. Chemical peeling remains as an alternative modality for pa-tients with melasma (34).

Laser and light therapies
Based on actual evidence, laser and light therapies show the best response in light-skinned patients, and are consid-ered as third-line agents. Post inflammatory hyperpigmen-tation remains the most important side eff Recurrences are common and are seen in up to 50% (1).

Melanosomes are the primary target of the laser-induced damage, and melanin is the main chromophore. Therefore it is important to choose wavelengths between 630 nm and 1100 nm which are preferentially absorbed by melanin, and pulse duration between 40 ns and 750 ns (43).

Epidermal melasma can be treated with ablative lasers, such as carbon dioxide (CO2) laser and erbium (Er):YAG laser. Non-ablative, 1,550 nm fractional laser therapy has been reported to improve melasma (1). Q-switched (QS) lasers deliver their energy in nanosec-ond pulses, hence they selectively target melanosomes. The 1064 nm QS-Nd:YAG is the most widely used laser for melasma. The number of treatments varies from 5 to 10 at 1-week intervals. Encouraging results have been observed in the treatment of the dermal-type melasma by using a novel 694-nm QS ruby fractional laser (44).

Melasma treatment with pulsed dye laser and the newer antiangiogenic lasers [copper bromide laser] is based on the theory that melasma occurs due to the interaction be-tween cutaneous vasculature and melanocytes. These la-sers can be used in patients with melasma and pronounced telengiectasia (43).

A combination of lasers can be beneficial for dermal melas-ma. Ablative lasers remove the epidermis; this can be fol-lowed by the use of the Q switched pigment selective laser which reaches deeper layers of the dermis (dermal mela-

| Table 3. The most commonly used combination formulas |
| Formula | Comment |
| Kligman’s and Willis formula* | Depigmentation begins within 3 weeks after the twice daily application used for a maximum of 5-7 weeks |
|_pathak’s formula (2% HQ, 0.05-0.1% tretinoin) | By omitting steroids it has been suggested that they should be added only if irritation from HQ or tretinoin is observed |
| Westerholz’s formula** | The formula leads to significant bleaching within 4 to 8 weeks acetone |
| Katsambas’s formula*** (HQ 4%, tretinoin 0.05%, hydrocortisone acetate 1%) | The formulation should be dispensed in a 25-ml volume, in a dark-colored bottle with an airight screw cap and it should be kept in a refrigerator at 2-4°C |

* Formulation is preserved by antioxidants, and therefore should never be more that 30 days old; HQ, hydroquinone; **; The mode of action of N-acetylcystein may be attributed to the intercellular increase of glutathione concentration that stimulates phytoestrogen instead of melanin synthesis; *** By lowering the concentration of tretinoin and the use of a non-fluorinated steroid, the aim is to minimize the irritation caused by tretinoin and eliminate local steroid side-effects |

In recent years, the skin whitening industry has used complex mixtures of ingredients that target different mechanismsliketyrosinase expression, transfer of melanosomes, antioxidant and anti-inflammatory effects. Different commercially available whitening products contain various natural (glutathione; leukocyte extracts), particular-ly herbal ingredients, although information on some formula-tions is not always clear (51). Paper mulberry (Broussonetia kazinoki); Mitracarpus (Mitracar-pus hirtus) - the active ingredi-ent is harounoside; Bearberry (Arctostaphylos uva-ursi) - the active ingredient is arbutin; Yellow dock (Rumex crispus); Licorice root (Glycyrrhiza glabra) - the active ingredient is glabridin; Yohimbe (Pausinystalia Yohimbe); Cang Zhu (At-racylodes lancea), Bai Xian Pi (Dictamnus albus); Hu Zhang (Fallopia japonica); Gao Ben (Liguricium rhizome); Chuanxiong (Rhizoma ligustici); and Fang Feng (Radix sileris also Radix ledebouriella). Table 4 shows melasma therapies, and level of evidence according to Rendon et al. (52).
SKIN TECH PHARMA GROUP | Research & Publications

References


The Skin Tech Pharma Group thanks to author for the possibility to reprint the article

Increasing security of AHA peels

Neutralizer Versicolor

200 mL tube

Extending Skin Tech® Hydroxy Acids peeling line
ACLARANSE
SKIN TONE IMPROVES AFTER 4 WEEKS OF APPLICATION

Skin testing by Scanner & analyser BS-3200
Investigation continues
Hyperpigmentation treatment is hard, long and complex.

This basic knowledge will help us to understand how to treat pigment problems using peelings and how to enhance and maintain results when peelings have given results.

Globally, we treat melasma in two steps: first step consists in eliminating the existing stock of epidermal or dermal melanin. Second step consists in avoiding excess melanin resynthesis and transfer.

First step:
to get rid of the stock, using chemical peelings.

Peeling solution selection is important since we should select a minimally active peeling solution: the one that will give good result without inducing post inflammatory hyperpigmentation. That’s the point: to work deep enough but not too deep. From here, another question arises: how can we determine if melanin is located in the epidermis, into the dermis or into both?

Clinical exam can be of little help: lighter brown pigmentation is usually more superficial than blue or dark brown ones; stretching the skin will lighten a superficial pigmentation and have no effect on a deep one.

Wood lamp is interesting since it makes appear darker superficial pigmentation and lighter deeper melanin. Nevertheless, in case of mixed pigmentation, the skin appears darker after wood’s light reflexion on superficial keratinocytes melanin and this hides the deeper melanin. That’s a good way to build ourselves our patient’s deception since the performed treatment will not work as fast as scheduled if we assumed that the pigments were located in superficial skin layers.

It is easy to inform the patient about these clinical and wood lamp exams tricks. I usually make clear to him that the only real way to know how the treatment will work is to perform the first two peeling sessions since it is often after peel that we can understand what was the depth of pigment: superficial, epidermal melasma disappears or is dramatically enhanced after one peel session only. Mixed melasma looks lighter after few peeling sessions but does not disappear completely. Deeply located melanin shows nearly no change, even after few peeling sessions. From here, we will be able to foresee results and schedule eventual deeper and or different treatments.

That is the reason why we prefer to use Skin Tech® Easy TCA® peeling in melasma treatment. Easy TCA® (ETCA) is a trichloroacetic acid (TCA) peeling made of a peeling solution and a post peel mask. Peeling solution is made of TCA®, alpha hydroxy acids (AHA), saponines and antioxidants. One plus of this specific peeling technique is that the peeling solution has to be applied in a progressive multicoat way, allowing stopping application exactly when the needed depth has been reached. The right depth, which is the one we decided to reach, will therefore never be over passed. A second and important benefit of the use of ETCA comes from the "post peel mask" (PPM) activity which is not a neutralizer but a fast and strong anti-inflammatory topical treatment that is able to remove the post peel inflammation in few minutes and hence to strongly limit the risk of post inflammatory hyperpigmentation (PIH).

In case of melasma, Blending Bleaching cream (BnB) morning and evening on the whole face has to be associated to Melablock HSP (Heat SHock Protein), SPF.
In case of acne, Purifying cream or Purigel will take the place of BnB; in case of ageing, after 45 years old, DHEA Phyto will stimulate skin metabolism. In case of smoking or life in polluted cities, Re Nutriv ACE Lipoc complex will catch free radicals. Recent ageing will be treated by association with B Phase Addiction (a serum combining 3 highly concentrated botulinic toxin like oligopeptides and a fibroblast Growth Factor (FGF). Simple hydration will be achieved using Vit E antioxidant cream.

**ETCA application for superficial pigmentation: basal layer peeling**

ETCA basic protocol is used as described above. Peeling sessions will be repeated once a week, 4 times. Blending Bleaching cream 2x/day and Melablock HSP, SPF 50 if the patient is living in a very sunny country or SPF 25 if the sun index is low.

After 4 peeling sessions and at least a total of 10 weeks of daily BnB and Melablock HSP, result will usually be definitive if abnormal pigmentation was secondary to post inflammatory inflammation (and if inflammation is definitively over) or to actually stabilized hormonal changes (pregnancy is finished or contraceptive pill has been substituted by an other mean). Genetic melasma could reappear as fast as the skin is exposed to the sun, obliging these patients to a very long sun avoidance and daily application of BnB and Melablock HSP. In any case, the natural patient’s skin colour is evenly restored and the patient should stay cautious about sun exposure since sun rays are stronger than any classical hyperpigmentation treatment and could induce a new abnormal pigmentation in case of sun burning.

**ETCA application for deeper pigmentation: basal layer peeling associated with local papillary dermis peel.**

A basal membrane disruption could be one responsible of dermal pigment location, allowing melanocytes to deliver the melanin as “bombs” falling into the dermis and not as usually: “balloons” climbing inside of the epidermis using the dendrites speedway. Dermal melanin is picked up by phagocytary cells having a quite long life duration. It induces usually darker or blue pigmentations. Moreover, deep pigment can come from hyperactivity of deeply located epidermal melanocytes, in the bottom of epidermal papillae or in pilosebaceous units.

In this case, the first coats of ETCA should be applied exactly on the pigmented areas and application repeated until inducing locally a cloudy frosting. After obtaining a local cloudy frosting, ETCA will be applied as a basic protocol on the whole face to get frosting points. ETCA will also be applied again over the cloudy frosting area, inducing a pink white nearly uniform frosting, locally on pigment area. Using this tip, hyperpigmented area are treated up to papillary dermis when the rest of the face benefits of a basal layer peeling.

PPM will carefully be applied on the deeply treated areas since the inflammatory reaction will be locally stronger. As daily care, the patient will apply BnB twice a day on the melasma area.

Cloudy frosting is a sign of “Grenz Zone” peel, pink white even frosting is a sign of papillary dermis peeling. In both cases, inflammation resulting of this depth is stronger and possibly could induce a PIH on very sensitive skins. We therefore recommend to associate to BnB and Melablock HSP, the daily use of IPLASE Mask.

**How to repeat peeling will depend on the skin reaction after the first ETCA session. We basically face two situations.**

---

**PEELING APPLICATION**

*Easy TCA® is usually applied with circular movements, using the cotton buds (called "the applicators") included in the kit.*

**1. APPLICATION OF THE FIRST LAYER**

- Divide the face in 7 different areas (see the graph below). Soak the applicators into the peeling solution, spin them dry on the edge of the container in order to eliminate an eventual excess of solution and apply on the first area using regular circular movements; repeat this process for each area. Let this first layer dry completely and check “the result”.

  "The result" is not a volumetric notion (milliliters) or a temporal concept (minutes) but rather a clinical sign:
  - Erythema signs peeling depth 3/7 (intraepidermal).
  - Frosting points sign peeling depth 3/7 (basal layer).
  - Frosting clouds sign peeling depth 4/7 (Grenz zone).

  If the desired frosting was obtained with the first layer, apply immediately the right amount of “Skin Tech® Post Peel Mask” on the treated skin (see dosing card in kit).
  
  If the desired frosting has not been obtained with the first layer, reapply the Easy TCA® solution on the face, as described below.

**2. APPLICATION OF POSSIBLE FOLLOWING LAYERS**

- Divide the face in 3 different areas (frontal and lateral areas: see the graph on the left) and apply the peeling solution using circular movements. Let this second layer dry and check “the result” (see above). Repeat if necessary the application (divide the face in three different areas) leaving each layer dry, until obtaining the needed frosting.

  The “clinical sign” corresponds to the achieved depth (depth of frost, white spots or white clouds). Then, we consider that it is the “end of the peeling”.

  At this time, apply the right amount of “Skin Tech® Post Peel Mask” (see dosing card).

**APPLICATION OF THE "SKIN TECH® POST PEEL MASK"**

Apply the cream “Skin Tech® Post Peel Mask” in the amount determined by the dosing card of the kit. The “Skin Tech® Post Peel Mask” stops pain, erythema, swelling and heat of the skin in a few seconds, and the risk of side effects is drastically limited.
1- The most positive reaction shows a melasma disappearance after the first session. In this case, next 3 ETCA sessions will be done with frost- ing points as end points. No more need for local deeper frosting. Daily care (BnB) and sun avoidance/protection (Melablock HSP) will be carefully continued during 6 to 12 months.

2- A less positive reaction is a simple melasma lightening. In this case, the next ETCA sessions should be performed the same way as the first one: local papillary dermis peel, associated to full face basal layer peel, on a weekly basis. This means that if melasma lightens after the second locally deep ETCA, then the 3rd and 4th session will be simply done as a basic protocol. One coat of a strong corticoid cream can be applied immediately after the PPM, locally, on the resisting melasma area, to cut off some excessive inflammatory reactions. Evidently, tremendous care will be taken about any UV contact, BnB will be applied 2 or 3 times/day and iPLASE will be added to the daily regimen.

3- A negative but fortunately rare reaction shows no difference at all or a melasma stress with worsening. In this case we have 4 possibilities.

First, Hydroquinone (up to 6%) can carefully be added to our daily care regimen if there is no risk of pregnancy or ochronosis.

Second, we could simply advise the patient to temporarily stop peelings but go on with daily care (BnB, Melablock) and sun avoidance during 6 weeks, then resume peelings treatments.

Forth: deeper peelings can be done and the question that immediately arises is: which one? My experience showed me that, if an ETCA deeper application did not work perfectly, any other deeper TCA peeling might also be efficient. More, deeper TCA peel would easily induce PIH.

Deeper peeling option passes therefore through phenol peel that has a clear blocking effect on excess of melanin synthesis but can be applied only on phototypes Fitzpatrick 1 to 4 only.

Second step:
to avoid stock rebuilding

This step is quite simple and totally mandatory: melasma virtually always comes back when adapted daily care and behaviour are not correctly understood.

1- Avoiding sun rays do not only mean not to lie down on the beach without sun protection. Avoiding sun rays is a full new behaviour for the patient. Give your back to the sun, never your face, use covering hat, sun glasses. Avoiding UV will avoid melanocyte stimulation and melanin synthesis.

2- Sun protection cream. Even water resisting high factor sun protection creams have to be applied at 9 am, 12 am and 3 pm. The tickier the coat, the best the protection. Patient is naturally limited by the white aspect of thick coat of physical sun screens but... could we have a white coat of physical sun protection (zinc oxide type) on melasma, then would we have long term good results. Physical shields molecules, in nanosomes eventually could massively penetrate the body and induce damage. That’s a pity, since these nanosomes are not whitely visible on the skin.

Sun protection creams will lower the UV impact on the skin and limit melanin synthesis.

3- I will use the term of metabolic creams to describe creams acting on the chemical cascade of events transforming tyrosine in the polymer of melanin

BIBLIOGRAPHY
Gregory S Barsh  What Controls Variation in Human Skin Color? Published online 2003 October 13. doi: 10.1371/journal.pbio.0000027
Melasma treatment

<table>
<thead>
<tr>
<th>Control of pigmentation</th>
<th>Recommended application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 EASY TCA® Superficial / medium peeling</td>
<td>1st Easy TCA Classic / Pain Control sessions</td>
</tr>
<tr>
<td>Removes actual pigment stock</td>
<td>2nd</td>
</tr>
<tr>
<td>1 / week</td>
<td>3rd</td>
</tr>
<tr>
<td>4 sessions</td>
<td>4th</td>
</tr>
</tbody>
</table>

BLENDING BLEACHING CREAM Daily care

Implements skin condition in pre-/post-treatment period

1st daily application: morning
2nd daily application: evening

MELABLOCK-HSP® SPF 50+

Optimal sun protection

Anti UVA/UVB
Anti oxidant HSP stimulator

Avoid sun
i.e: 9.00 - 12.00 - 15.00 h

LIGHTENING

Blending Bleaching Cream

Daily care · Anti-oxidant

Active ingredients:
- Tyrosinase inhibitors complex (Morus Alba, Kojic Dipalmitate, Licorice extracts, Urea, Arbutin, Glabridine, Liquiritine, Mulberroside F)
- Tocopheryl Acetate
- Glycyrrhiza Glabra Y Root extract
- Retinyl Palmitate
- Allantoin

Indications:
Prevention and/or treatment of hyperpigmentations. Also very efficient before and/or after laser treatments, peelings, dermabrasions and depilation. Slows down skin oxidation and free radical activity, and help to keep skin smooth and fair.

Presentation:
Sachet containing 2 mL
Tube containing 50 mL

PRESENTATION
GET A REAL HELP with MELASMA

PHOTOTYPES 1-3

1st PEEL
ETCA* GZ* on melasma + BL* rest of face + DC*
1 week

2nd PEEL
Before peel, check if
Worse
ETCA* BL* Full face + DC* + Hq*
1 week
Stable
ETCA* GZ* on melasma + BL* rest of face + DC* + Hq*
1 week
Better / Cured
ETCA* BL* Full face + DC*

3rd PEEL
Before peel, check if
Worse
SUSPEND PEELS
Stable
ETCA* GZ* on melasma + BL* rest of face + DC* + Hq*
1 week
Better / Cured
ETCA* BL* Full face + DC*

4th PEEL
Before peel, check if
Worse
SUSPEND PEELS
Stable
Last ETCA* BL* Full face + DC*: 3-12 months
Better / Cured
ETCA* BL* Full face + DC* + DC

*ETCA: Easy TCA - *BL: Basal Layer - Frosting points - *GZ: Grenz Zone - Frosting Clouds exactly on melasma -

Please download this chart from our website:
**MELEASMA CHART**

**PHOTOTYPES 4-6**

1st PEEL

ETCA* BL* Full face

1 week

2nd PEEL

**Before peel, check if**

Better / Cured

ETCA* BL* Full face + DC*

1 week

Stable

ETCA* BL* Full face + DC*

Worse

ETCA* BL* Full face + DC* + Hq*

3rd PEEL

**Before peel, check if**

Better / Cured

ETCA* BL* Full face + Daily care

Stable

ETCA* BL* Full face Hq*+DC*

Worse

SUSPEND PEELS

4th PEEL

**Before peel, check if**

Better / Cured

Last ETCA* BL* Full face + DC*: 6-12 months

Stable

SUSPEND PEELS

Worse

**PRE PEEL: CONDITIONING**

3-4 weeks

- Blending Bleaching Cream 2 times a day
- Hydroquinone 3% 3 times a day
- Melablock HSP SPF 50+ 9am - 12am - 3pm

**MELABLOCK-HSP**

SPF 50+ or 30
(9am 12am 3pm)

6-8 weeks

then PEEL AGAIN

According To Phototype

**www.skintech.info/melasmachart**

*Hq*: Hydroquinone 6% 2x/Day to be mixed 50/50 with Blending Bleaching immediately before applying

*DC*: Daily Care
Melasma is considered as a common physiological skin change during pregnancy (Elling and Powell, 1997; Muallem and Rubeiz, 2006; Sodhi and Sausker, 1988), and as an undesirable cutaneous effect of oral contraceptives (Foldes, 1988). Epidemiological data revealed the occurrence of melasma in 14.5–56% of pregnant women and in 11.3–46% of individuals who used oral contraceptives in different countries, including Singapore (Goh and Dlova, 1999), Iran, Tunisian (Guinot et al., 2010), India (Achar and Rathi, 2011; KrupaShankar et al., 2014), and Brazil (Handel et al., 2014b; Tamega Ade et al., 2013).

With respect to female sex hormones, estrogens and progestenes have been implicated in the development of melasma. The activities of estrogens and progestenes- terones are mediated by specific receptors expressed in human skin, including the estrogen receptors (ERs) ER- alpha/ER-beta and progesterone receptors (PRs), respectively (Pelletier and Ren, 2004; Thornton, 2002). Conflicting results regarding the effects of these hormones, particularly progestones, have been obtained. Melasma has been reported as an adverse reaction of contraceptives containing the synthetic progestin levonorgestrel, and the expression of PR proteins is increased in hyperpigmented skin in melasma (Jang et al., 2010; Tamega Ade et al., 2015), suggesting that progestrone plays a role in the development of melasma. Conversely, the prevention of melasma by progestrone components in oral contraceptives has been suggested based on findings that progestrone reduces proliferation without significant effects on tyrosinate activity, counteracting the stimulatory effects of estrogen in cultured melanocytes (Wiedemann et al., 2009).

Certain factors which could alter the sex hormone metabolism, including interindividual variation in the enzymes (Orme et al., 1989), may contribute to generate the conflicting result. Other cellular and para-crine regulatory factors have been also suggested to be involved in estrogen responses (Ing and Tornesi, 1997), which may require a careful research design and an analysis of the result for in vitro studies.

Immunohistochemistry revealed increased ER expression in the affected skin (Lieberman and Moy, 2008), although significant immunohistochemical expression of ER-beta has been presented in melasma-affected dermis, but not in epidermis (Jang et al., 2010). Increased ER expression indicates a potential role of estrogen in melasma. Estrogens are considered to stimulate melanogenesis in cultured human melanocytes by inducing synthesis of melanogenic enzymes such as tyrosinase, TRP-1, TRP-2, and MITF (Jian et al., 2011; Kim et al., 2012). Melanocytes express ERs (Jee et al., 1994; Kim et al., 2012), which are involved in estrogen-induced melanogenesis, because the inhibition of ER by its antagonist leads to reduction in melanogenesis (Kim et al., 2012).

In addition, estrogen-induced melanogenesis could be associated with the activation of the cAMP- PKA pathway, because estrogens enhance cAMP levels and upregulation of tyrosinase and MITF attenuation by blocking the PKA pathway, which has previously been reported (Jian et al., 2011).
Early aging, melasma

Patient age/sex: 41/Female
Area, pathology: face, early aging, melasma
Type of treatment: nappage injections of Reparestim Whitening TD
Average number/frequency of sessions: 5 ml/session, once per week 5 sessions total
Daily home care: Blendig Bleaching cream 2 times per day, Melablock HSP SPF 30 (at 9:00h - 12:00h - 15:00h) 3 times a day
Combination treatment:-
Comments: very good improvement of skin condition and melasma

References
To get all the references, please contact SkinTech Pharma Group Scientific Department at www.skintechpharmagroup.com

MECHANISM INVOLVED IN ESTROGEN-INDUCED MELANOGENESIS AND PDZK1 ROLE IN MELASMA

By binding to ERs, estrogen enhances cAMP levels and upregulates CREB, MITF, and tyrosinase family protein expression, with the involvement of the PKA pathway. (B) PDZK1 could facilitate the estrogen action by interaction with other proteins including ion exchangers, resulting in the stimulation of melanogenesis and melanosome transfer in melasma patients (ER, estrogen receptor; PKA, protein kinase A; CREB, cAMP responsive-element-binding protein; CBP, CREB-binding protein; MITF, microphthalmia-associated transcription factor; TYR, tyrosinase; TRP, tyrosinase-related protein; PDZK1, PDZ domain protein kidney 1; NHE, sodium–hydrogen exchanger; CFTR, cystic fibrosis transmembrane conductance regulator).
Localized keratosis & Lentiginosis

**TREATMENT RECOMMENDATION**
Two weeks before treatment, the patient should start applying Skin Tech® Blending Bleaching Cream on the area to be treated.

On the end of procedure post-peel mask applied must be kept on until the next day. The patient must not wash the treated area on the evening of the peel.

The next day, the patient must cleanse face with special Skin Tech® Cleanser.

A few days after the peel, scabs will form on the area treated by Only Touch. This is perfectly normal and the patient should not worry. The scabs will heal within +/- 10 days. The patient must not pick at them or scratch them and he/she should keep the treated area well hydrated.

The patient must protect skin from the UVA/UVB with Melablock-HSP® SPF 30 or Melablock-HSP® SPF 50+.

**TO OPTIMIZE PEELING RESULTS**
DHEA-Phyto cream optimizes the result of anti-aging treatment, apply it twice a day.

Nutritive Cream can be used for a complementary anti-aging treatment, great for smokers.

Blending Bleaching Cream helps even out the complexion on the skin.

---

**Hands rejuvenation protocol**

<table>
<thead>
<tr>
<th>Excellent results Before/after</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONLY TOUCH Focal deep peeling</td>
<td>Removes actual pigment stock</td>
<td>Local application (Ø&lt;1cm)</td>
<td>Together with 1st and 4th Easy TCA®</td>
<td></td>
</tr>
<tr>
<td>EASY TCA® Superficial/medium peeling</td>
<td>Epidermal &amp; dermal remodelation</td>
<td>Once / 2 weeks</td>
<td>4 sessions</td>
<td></td>
</tr>
<tr>
<td>DHEA-PHYTO Anti-aging daily care</td>
<td>Optimizes results of anti-aging treatment</td>
<td>1st daily application: morning</td>
<td>2nd daily application: evening</td>
<td></td>
</tr>
</tbody>
</table>

**Recommended application**

1. **DHEA PHYTO morning**
   - NUTRITIVE CREAM VIT. A-C-E LIPIOIC COMPLEX evening
   - Sun protection: MELABLOCK-HSP SPF 50+

2. **ONLY TOUCH** should not be used for areas > 1 cm Ø
MELABLOCK-HSP®, SPF 50+ has successfully passed the “Study for the evaluation of the Sun Protection Factor (SPF)” according to the international method COLIPA. Melablock-HSP® SPF 50+ widely exceeds the SPF 60 standard recommendation.

**Gradual tanning**
Protection against erythema
allowing progressive sun tanning and preventing PIH
SPF 50+ protects against 98% UVA and UVB.

**Sunscreen & filters**
Sunscreen: reflects UVA and UVB
back to the sky: they do not reach keratinocytes
Micronized Titanium Dioxide: unique light-scattering and UV reflecting properties.
Extremely stable compound. Non irritative, non toxic, non mutagenic.

Filters: absorb UVA and UVB
before they reach keratinocytes
Blend of stable chemical sun filters absorbing photons that could pass through sunscreen.

**HSP activation**
Anti- free radicals
Skin proteins protection (HSP)
Activation of the natural synthesis of Heat Shock Proteins which defends the skin against protein destruction and thermal cell lysis which occur after a increase in temperature of just a few degrees.

**Fighting free radicals**
Tocopheryl acetate, a stable vitamin E derivative and an excellent free radicals scavenger.
Vitamin E accelerates burns healing, limits the duration of post UV erytheme and protects SOD (Superoxide Dismutase), that neutralizes superoxide radicals.

**NON TOXIC · NON ALLERGIZING**
**PHOTOCHEMICALLY STABLE**
Paba free · Paraben free
Oxybenzone free
Not sticky texture
Readily absorbed
CASE REPORT
Products: Easy TCA® Classic, Blending Bleaching, Melablock HSP SPF 50+

Before        After

Patient age/sex: 27/Male
Area, pathology: face, freckles
Type of treatment: Easy TCA® Classic peeling
Average volume/frequency/sessions: one Easy TCA® Classic/week, total 2 peelings.
Daily home care: Blending Bleaching cream, 2 times per day 4 weeks
Combination treatment: -
Comments: Improvement of the freckles and better skin quality

CASE REPORT
Products: Easy TCA® Classic, Blending Bleaching cream, Melablock HSP SPF 30

Before        After

Patient age/sex: 36/Female
Area, pathology: face
Type of treatment: Easy TCA® Classic peeling
Average volume/frequency/sessions: ETCA 1 peel/week. 4 peels total.
Daily home care: Blending Bleaching cream, Melablock HSP SPF 30 (at 9:00h - 12:00h - 15:00h).
Combination treatment: Blending Bleaching cream combined with hydroquinone 5% one time per night 2 months
Comments: Improvement and maintenance of melasma and skin condition
CASE REPORT

Products: Easy TCA® Classic, Blending Bleaching cream, Melablock HSP SPF 30

Before

After

Patient age/sex: 49/Female
Area, pathology: face
Type of treatment: Easy TCA® Classic peeling
Average volume/frequency/sessions: ETCA 1 peel/week. 4 peels total,
Daily home care: Blending Bleaching cream, Melablock HSP SPF 30 (at 9:00h - 12:00h - 15:00h) Patient continued home care during 5 months post peeling.
Combination treatment: botulinic toxin
Comments: Improvement and maintenance of melasma and skin condition (even 5 months after completing one course of ETCA)

CASE REPORT

Products: Easy TCA® Pain Control, IPLase, Atrofillin, Melablock HSP SPF 50+

Before

After

Patient age/sex: 64/Female
Area, pathology: neck, decolletage
Type of treatment: Easy TCA® Pain Control Peeling
Average number/frequency of sessions: 1 treatment/ 2 weeks, total 2 peelings
Daily home care: IPLase cream, 2x/day, Melablock HSP SPF 50+ (09:00h, 12:00h, 15:00h)
Combination treatment: Skin Tech® Cleanser every morning, Atrofillin 2x/day, total 8 weeks
Comments: Visible skin rejuvenation, improvement of skin elasticity, color and turgor
RRS® HA WHITENING

Skin sun damage - Melasma & Chloasma
Skin whitening effect - Skin color injectable regulation

RRS® HA WHITENING is a product specially formulated as a resorbable dermal implant for sun damaged, photo-aged skins, since the filling effect of Hyaluronic Acid is assisted by the whitening modulating effect.

Area: face / neck & decolletage
Average volume/session: 3 ml / area
Type of injection: micro dermal papule
Frequency: 1 session / week (1 protocol = 4-6 sessions average)
Recommended number of sessions: repeat protocol as necessary

Combination with other aesthetic treatments:
- Botulinum toxin: two weeks before RRS® injection
- Filler: time is not important, can be injected in one treatment
- Peeling: RRS® can be injected immediately before TCA peelings
- Lasers: RRS® injection can be done immediately before
- Excellderm® Pro after RRS® injections: synergetic action

Area of pigmentation ≤ 3 ml
Distance between injection points (0.5 cm)
0.05 mL / Injection point

box of 2 vials / 6 vials containing 3 ml (0.10 Fl.oz.)
PRODUCT DESCRIPTION

RRS® HA Whitening must be used under appropriate aseptic conditions in an authorized clinic on healthy, disinfected skin.

Before the treatment the physician should inform the patient about:
- indications and effects
- possibilities of the side effects (pain, redness, ecchymosis, stinging sensations and swelling, local inflammation, usually disappearing in 24 hours)
- check allergy test
Sensitive skins may benefit from application of an anaesthetic cream prior to the treatment.
Recommended to have a consent signed by the patient.

After the treatment
Avoid: extreme temperatures, Saunas - Hammam; direct exposure to sun or UV.
From next day make-up can be used.

Contraindications
Allergy to any of the ingredients. Patients presenting any skin alteration, skin disease, infections or sequelae of streptococcal infections. Patients taking immunosuppressants, undergoing cortical therapy, with autoimmune disease history, patients with uncompensated diabetes, acute joint rheumatics, repetitive angina, and endocarditis.

*No studies are available for use during pregnancy and breastfeeding or in case of treatment on children or minors under 18.

MORE INFORMATION IN RRS-INJECT.COM/MEDINET

RRS® HA Whitening
Hyaluronic Acid, non crossed link, associated to:
- Whitening agents: Arbutin, Aminoethylphosphinic Acid, Retinyl Palmitate, Morus Alba extract, Oxyresveratrol, Licorice extract, Malic Acid, Vit C.
- Flavonoids: Glabridin, Glycyrrhetinic Acid, Glycyrrhizin, Glyasperin C, Glabrene, etc.
- Vitamins: Vit B5, Vit E, Vit A, Vit C.
- Antioxidants: Ascorbic Acid, Alpha Tocopheryl Acetate, Oxyresveratrol, Moracin, Glabridin, etc.
- AHA: Malic Acid, Lactic Acid.
- βHA: Salicylic Acid
- Glycosides: Mulberroside A, Mulberroside B, Mulberroside F
- Polyphenols: Moracin, Morusin, Alabafuran, Mulberrofuranc
- Triterpenoids: Ursolic acid, Betulinic Acid
- Trace elements: Ca, Cr, Co, P, Mg, K, Si.
- Amino acid: Serine

Depths of intradermal and subdermal injections

Correct depth of RRS® HA Whitening injection

- < 0.2 cm
- ≤ 0.2 - 0.4 cm
- ≤ 0.2 - 1 cm
- ≤ 1.5 - 3 cm
Due to many side effects that aforementioned induce, another therapeutic modality can be used in everyday practice: intralesional localized microinjections of RRS® HA Whitening.

RRS® HA Whitening has several properties that are useful for treatment of melasma: skin whitening property or the ability to inhibit melanogenesis, anti-inflammatory property and antioxidant property. It dramatically reduces pigmentation and is one of the safest skin whitening modalities.

The injectable procedure RRS® HA Whitening is safe, easy to do, comfortable, and it can be done all year long without the possibility to induce post-inflammatory reaction including hyperpigmentation.

A broad-spectrum sunscreen with a minimum SPF of 30 is needed for patients experiencing melasma. The reactivity of skin prone to hyperpigmentation and melasma is exacerbated by UV-induced inflammation. Therefore, choosing an SPF combined with Bleanding & Bleaching Cream which is abundant in melanogenesis inhibitors and antioxidants can provide additional treatment and pigment suppression along with necessary UV protection. All sunscreens must be applied 30 minutes before sun exposure and reapplied every 3 hours, or after swimming or perspiring, for maximum protection.

Based on my experience, I suggest that the intralesional localized microinjections of RRS® HA Whitening can be used as a potentially new, effective, and safe therapeutic modality for the treatment of melasma. Appropriate maintenance therapy should be used to avoid relapse of melasma.

Tyrosinase is a well-known key enzyme in melanin biosynthesis. Indeed, it catalyzes two distinct sequential reactions in melanin biosynthesis: the hydroxylation of tyrosine to DOPA followed by the oxidation of DOPA to dopaquinone. For years now, researchers have been looking for new tyrosinase inhibitors because of their potential use as hypopigmenting agents. Nowadays, a variety of creams sold as hypopigmenting agents are available on the market. The most commonly used hypopigmenting agent is hydroquinone that was demonstrated to be cytotoxic and genotoxic when use for long period of time. Therefore, new cosmetic creams demonstrating to be safe and to efficiently inhibit tyrosinase activity are expected on the market. Common alternative to hydroquinone is the well known kojic acid.

In the present study, the inhibitory effects Aclaranse and Blending Bleaching creams on mushroom tyrosinase activity were evaluated. Both cream showed inhibitory effects against mushroom tyrosinase, with Aclaranse and Blending Bleaching exhibiting an IC50 values of 3,36 µg/ml and 5,68 µg/ml respectively. When compared to kojic acid (IC50 value of 12,04 µg/ml), Aclaranse demonstrated to be 3,5 more efficient than kojic acid, whereas Blending Bleaching cream 2 times more effective in inhibiting mushroom tyrosinase activity.

These results demonstrate that Aclaranse and Blending Bleaching effectively inhibit the activity of the enzyme tyrosinase in vitro, which confirms skin whitening effect already observed with patients.

Dr. Nenad Stankovic, Serbia

Skin Tech Pharma Group Scientific Department
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### Box of 6 vials
- **Transdermal solution**

### ACTION
- Melanogenesis inhibition
- Anti tyrosinase effect
- Dopachrome Tautomerase inhibition
- Melanine polymerization inhibition
- Catecholase inhibition
- Hydroquinone precursor
- Transformation of eumelanin
- O-quinone reductor
- Anti inflammatory

### ACTIVE INGREDIENTS
- Bearberry (Arbutin)
- Albatin
- Murus alba
- Licorice extracts
- Kojic acid (Aspergillus)
- Ascorbyl phosp. Na
- Ethoxy-diglycol

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### Box of 6 vials
- **Injectable class III**

### Antioxidant effect

### ACTION
- Antioxidant defense

### ACTIVE INGREDIENTS
- Tocopherol acetate
- Ascorbyl phosp. Na
- Kojic acid (Aspergillus)
- Bearberry (Arbutine)

---

### Bottle 50 mL cream
- **Daily care**

### Whitening effect
- Smooth skin colour

### ACTION
- Enhance skin elasticity

### ACTIVE INGREDIENTS
- Hyaluronic acid
- Diopanthenol
- Retinol palmitate
- Lactic acid
- Bearberry (Arbutine)

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**MEDICAL COMMENTS | 29**
Patients with melasma usually present with irregular patches of darkened skin on the cheeks, forehead, upper lip, nose, and chin. Melasma has always been very challenging to treat for multiple reasons including the presence of melanin at varying depths in the epidermis and dermis. Because chemical peels remove melanin and improve skin tone and texture, they are commonly used in treating this condition. More superficial and more limited involvement melasma is often more responsive to treatment. Data from small studies suggest that melasma improvement occurs more rapidly when peels are combined with medical therapy. Several peels have been studied (SA, LHA, GA, TCA, tretinoin and resorcinol, retinoic acid and Jessner’s), although Glycolic Acid (GA) is currently most popular.

In a study by Javaheri et al, peeling was performed upon 15 Indian females with melasma, using 50% glycolic acid, once-monthly for 3 months. An improvement in Melasma Area Severity Index (MASI) score was observed in 91% of patients (P < 0.01). A better response was seen in patients with epidermal melasma, compared to those with mixed melasma (P < 0.05) 2.

Kalla et al did a comparative study of 55%-75% GA versus 10%-15% trichloroacetic acid (TCA) peels in 100 patients with recalcitrant melasma. The peels were conducted at 15-day intervals in both groups. It was seen that the response to TCA was rapid, and produced better results than GA. However, relapse was more common in the TCA group (25%) than in the GA group (5.9%) 3.

In a comparative study of 10%-20% TCA versus 20%-35% GA peels for the treatment of melasma, similar improvement was seen with both peels. However, the GA peel was seen to be associated with fewer side effects than the TCA peel, and gave the added benefit of facial rejuvenation 4.

In addition, Sharquie et al reported improvements of lactic acid in the Melasma Area and Severity Index (MASI) Sharquie et al. studied 20 Iraqi patients (SPT IV) with melasma treated with pure lactic acid (92%, pH 3.5) every 3 weeks until the desired response was achieved (range two to six sessions). All 12 patients who completed the study showed a statistically significant improvement in MASI (by 56%) with no side-effects reported 5. The following year, Sharquie et al. compared full-strength lactic acid (92%, pH 3.5) with Jessner’s solution, applied every 3 weeks until the desired response was achieved (range two to five sessions), in a split-face trial of 30 Iraqi patients with melasma (mostly SPT IV). In the 24 patients who completed the study, both treatments showed statistically significant improvements in MASI, with equal effectiveness when comparing both groups, and no side-effects reported 6.

Lim JT showed that the addition of 2% kojic acid to a gel further improves melasma. Forty Chinese women with epidermal melasma were treated with 2% kojic acid in a gel containing 10% glycolic acid and 2% hydroquinone on one half of the face. The other half was treated with the same application but without kojic acid. The side receiving the kojic acid showed better improvement in melasma (60% vs 47.5%), and the 2 patients with complete clearance of melasma, it was on the side where kojic acid was used. Side-effects include redness, stinging, and exfoliation. These were seen on both sides of the face, and they settled by the third week 7.

Cotellessa C and colleagues evaluated the efficacy of glycolic acid associated with kojic acid in the treatment of cutaneous hyperpigmentations. Twenty patients with diffuse melasma were treated with a solution composed of 50% glycolic acid and 10% kojic acid. Complete regression of diffuse melasma was observed in 6 of 20 patients (30%), a partial regression in 12 of 20 patients (60%), and no regression in 2 of 20 patients (10%). Based on these findings, this peeling can be considered effective in the treatment of cutaneous hyperpigmentations 8.

Draelos ZD evaluated kojic acid and glycolic acid (concentrations were not published) as an alternative skin lightening agents with efficacy comparable to hydroquinone but with a better safety profile. This double-blind study examined the skin lightening ability of a topical formulation containing kojic acid, emblica extract, and glycolic acid compared with prescription generic hydroquinone cream 4%. Eighty multi-ethnic participants with mild to moderate facial dyschromia were randomly assigned to evaluate product efficacy, tolerability, and safety. Study results demonstrated efficacy parity between the study product and hydroquinone 4%. Thus this novel skin lightening preparation is an alternative to hydroquinone 4% for participants with mild to moderate facial dyschromia 9.
Another work studied glycolic acid 5% combined with either 4% hydroquinone or 4% kojic acid. Although none of the patients was completely cleared, both combinations proved equally effective, with reduction of pigmentation in 51% of patients; dramatic results were noted in 28% of patients treated with GA/kojic acid and in 21% treated with GA/HQ, concluding that both GA/kojic acid GA/hydroquinone topical skin care products are highly effective in reducing the pigment in melasma patients.

The efficacy and safety of Jessner’s solution was compared with 30% salicylic acid as superficial chemical peeling agents in treating epidermal melasma in Asian skin. Sixty patients with epidermal melasma were randomly divided into two groups, and treated with Jessner’s solution or with 30% salicylic acid. Baseline Melasma Area Severity Index (MASI) score and adverse effects were recorded bi-weekly. Treatment was stopped at 12 weeks and patients were followed-up at 4 weekly intervals for further 12 weeks. Results showed that difference in baseline, treatment end and follow-up end MASI scores was not significant between the two. On the other hand, within group analysis of difference between pre and posttreatment MASI score was highly significant in both groups (p<0.0001), indicating that both treatments are equally effective. In addition, adverse effects were mild and comparable in both groups.

Doses currently used for the peeling

The concentrations of glycolic, lactic, citric, salicylic and kojic acids present in "Easy Droxy Versicolor Peel" are in the range of concentrations currently recommended in the literature.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Doses from literature</th>
<th>Doses in “Easy Droxy Versicolor Peel”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolic Acid</td>
<td>8 – 75%</td>
<td>34%</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>8 – 92%</td>
<td>12%</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>4 – 25%</td>
<td>10%</td>
</tr>
<tr>
<td>Kojic Acid</td>
<td>2 – 10%</td>
<td>4%</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>2 – 30%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Medical publications report that melasma treatment is among the main indications concerning alpha hydroxy acids (AHAs), salicylic acid and kojic acid. Chemical peels removes melanin and improve skin tone and texture. Glycolic, lactic, salicylic and kojic acids peels are commonly and efficiently used in treating melasma. In addition, there are huge numbers of studies that show the safety and efficacy of combining hydroxy acids.
Bibliography for the article of Dr. Rodrigo Arroyo

Lentiginosis

Trichloroacetic Acid (TCA) is effective in treating solar lentigines: the concentration of the TCA is chosen depending on the assumed depth of the lentigo. Relatively superficial lentigines are easily treated with Easy TCA®. Lentigines of medium depth respond to Unideep®. Lentigines originating from the deepest dermal papillae and embedded deep in the dermis only respond to very concentrated TCA (Only Touch®), or even phenol (Lip & Eyelid® formula), applied locally and combined with Easy TCA® (or Unideep®) to even out the results and treat the smaller subclinical lesions. It should be noted that a TCA peel, even to the papillary dermis, does not always treat lentigines definitively and that several peels to the papillary dermis may be necessary for long-term results.

Freckles

Freckles are small, clearly delimited, benign pigmented macules that appear on areas of sun-exposed skin in patients with a light skin phototype. They are never present at birth, but can start to appear from the age of 3 years, and there is an autosomal dominant pattern of genetic transmission. They result from melanocyte hypertrophy, although not from an increase in melanocyte numbers. In the basal and suprabasal layers, more melanin is synthesized and transferred between the melanocytes and keratinocytes. This increased melanin synthesis could result from melanocyte clones that have mutated following UV exposure. The structure of the epidermis remains normal, apart from the parabasal keratinocytes, which contain more melanin in relation to the neighboring unpigmented cells.

A peel to the basal layer lightens the freckles, sometimes only temporarily. A peel to the Grenz zone removes many freckles and lightens others. A peel to the papillary or reticular dermis gets rid of freckles altogether.

Post-inflammatory hyperpigmentation and berloque dermatitis

Post-inflammatory hyperpigmentation (PIH) and berloque dermatitis usually respond well to TCA; they can be treated in the same way as melasma, but have a better prognosis as the original trauma disappears after treatment, unlike melasma, which often persists or recurs.

Berloque dermatitis is an acquired hypermelanosis resulting from contact photodermatitis caused by a sensitizing agent (perfume or metal in jewelry). Berloque, or berlock, dermatitis gets its [misspelled] name from the French word ‘breloque’ meaning a trinket or charm that is attached to a bracelet. These charms are often of poor quality and cause contact allergies in the shape of the trinket itself.
What does mean GMP?
Good manufacturing practice (GMP) are the practices required in order to conform to the guidelines recommended for manufacture and sale of food, drug products, and active pharmaceutical products.

What does mean cosmetic product or medical device? What is the main difference?

• COSMETIC PRODUCT
According to REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT Cosmetic product means any substance or mixture intended:
- to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to clean, perfum (or correct body odours), change the appearance, protect or keep in good condition

• MEDICAL DEVICE
According to COUNCiL DirECtiVE 93/42/EEC concerning Medical Devices, the medical device means any instrument, appliance, material, whether used alone or in combination, including the software necessary for its proper application intended to be used for human beings for:
- diagnosis, prevention, monitoring, treatment or alleviation of disease
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

These guidelines provide minimum requirements that a pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public.

Good manufacturing practices, along with good agricultural practices, good laboratory practices and good clinical practices, are overseen by regulatory agencies in the United States, Canada, Europe, China, and other countries.

LEARN MORE ABOUT PRODUCT
regulatory status of products become very important for aesthetic medicine practitioners
RRS® and SKIN TECH® peelings are medical devices. What make them different from other existing products?

RRS® and SKIN TECH® products are originally formulated, safe and effective. From period 2011-2013 RRS® and SKIN TECH® peelings were evaluated thoroughly and obtained CE mark. CE marking process contains:

1. Determination of device classification (I, IIa, IIb, III)
2. Implementation Quality Management System (QMS) in accordance with ISO 13485 standard.
3. Preparing a Technical File that provides detailed information about medical device MDD 93/42/EEC.
4. Successfully pass audit by a third party accredited by European authorities to audit medical device companies and products.
5. Receive a Declaration of Conformity, a legally binding document prepared by the manufacturer stating that the device is in compliance with the applicable Directive.
6. Regularly pass clinical evaluation.

Conclusion

Process for manufacture and follow up for the CE mark products are very strict which guarantee high quality and grants to the doctors and their customers maximum security and efficacy.
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- **RRS® HA Whitening**
- **RRS® HA Strimatrix**
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- **XL Hair®**
- **RRS® HA Eyes**
- **RRS® Silisorg**
- **RRS® Silisorg HA**
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**New injectable solution for melasma treatment**