Chapter 1
Cosmetic products

1.1. Depigmentanting and lightening agents

1.1.1. Targets in the skin

As mentioned, true depigmenting (bleaching) agents include substances that inhibit melanogenesis. Some act as competitive tyrosinase inhibitors, others block the synthesis of this enzyme, and others prevent the transfer of melanosomes from melanocytes to neighboring keratinocytes. However, most «work» on several fronts at once.

Exfoliating products can help lighten and even out your overall skin tone. Their purpose is to speed up the desquamation process of melanin-overloaded root cells. And if they simultaneously reduce melanin synthesis, new corneocytes will have less pigment and the skin will become lighter.

Retinol-based cosmetics and superficial chemical peels (hydroxy acids, keratolytic and enzymatic peels) are lightening products. It is currently not recommended to use medium-depth and deep peels to treat pigmentation lesions because aggressive skin damage can provoke pigmentation. When using peels to lighten skin with post-inflammatory pigmentation or ethnic skin, anti-inflammatory drugs must be used, and significant skin irritation must be avoided. Also, when referring to peels in general, salicylic peels, which refer to beta-hydroxy acids, are not recommended on low-sebum skin.

According to the mechanism of action, all currently known depigmenting agents can be divided into two main groups:

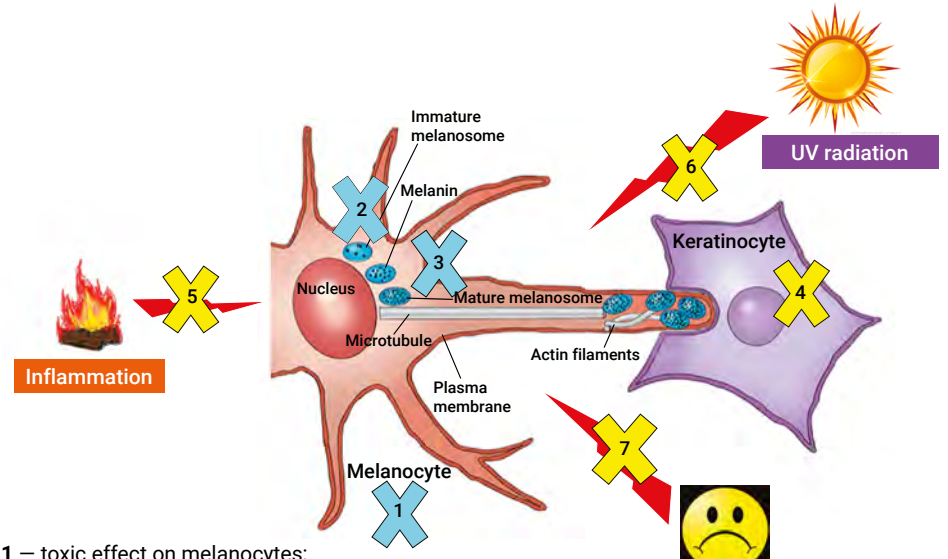
1) **toxic (nonspecific)** — usually cause damage and death of melanocytes/keratinocytes and destruction of the finished melanin pigment. Almost all long-known and traditionally used in dermatology bleaching agents belong to this group. For example, mercury and phenol

compounds, hydroquinone, azelaic acid can also have similar properties.

2) **selective (specific)** — selectively inhibit either the activity of enzymes involved in melanogenesis or cell receptors perceiving the signal to enhance melanin synthesis. This group includes bleaching agents of the latest generation.

Currently, trends are increasingly moving away from albeit effective but dangerous to the health of the skin and the body as whole depigmentation methods, betting on modern means and a comprehensive approach.

Fig. III-1-1 presents the targets for skin lightening and lists the methods of action on them, while **Fig. III-1-2** outlines the main causes of pigmentation. **Table III-1-1** lists the major groups of substances that are found in products used to correct pigmentation, both pharmaceutical and cosmetic. Plant extracts are not listed in the table because they are mixtures of different



1 — toxic effect on melanocytes;
2 — inhibition of tyrosinase;
3 — inhibition of melanin oxidation and packaging into melanosomes;
4 — exfoliation of corneocytes;
5 — anti-inflammatory agents;
6 — sunscreens with UV filters;
7 — medical treatment, psychotherapy

Fig. III-1-1. Targets and aesthetic tools for skin lightening: 1–3 (blue) — direct melanogenesis inhibition; 4–7 (yellow) — indirect pigmentation reduction

PIGMENTATION CONTROL

DIRECT MELANOGENESIS INHIBITION

- Depigmenting agents:
  1) tyrosinase inhibitions;
  2) pigmnt destruction
- Melanin-loaded corneocytes exfoliation

INDIRECT PIGMENTATION REDUCTION

- Sunscreens with UV filters
- Anti-inflammatory measures
- Hormonal imbalance treatment
- Psychotherapy

Fig. III-1-2. An integrated approach for pigmentation control

Table III-1-1. The most common ingredients in formulations to treat pigmentation

MAIN (BUT NOT THE ONLY) TARGET	SUBSTANCES
Inhibition of melanogenesis at different stages (true depigmenting substances)	
Cytotoxic effect	• Hydroquinone • Azelaic acid
Inhibits the synthesis of the amino acid tyrosine from precursors	• N-acetylglycosamine
Tyrosinase inhibition	• Hydroquinone • Arbutin • Kojic acid • Cinnamic acid
Inhibition of melanosome transfer to keratinocytes	• Soybean enzymes • Niacinamide
Reducing agents (prevent oxidative processes, in the course of which ready melanin is produced)	• Ascorbic acid
Melanosome destruction	• Hydrogen peroxide • Lignin peroxidase
Prevention of melanogenesis or reduction of its intensity (substances that create conditions to reduce the activity of melanocytes)	
Binding of metal ions of variable valence (copper, iron), which are initiators of free-radical chain reactions	• EDTA • Azelaic acid • Phytic acid
Reducing inflammation	• Antioxidants (e.g., plant polyphenols)
Elimination of the consequences of increased melanogenesis (substances that reduce the amount of pigment by accelerated exfoliation of corneocytes)	
Exfoliating	• Alpha hydroxy acids (AHAs) • Salicylic acid • Retinol

substances, but they are discussed later when each substance is discussed separately.**The more targets we involve in our treatment program, the better the chances of achieving the desired result!**

1.1.2. Obsolete and dangerous

Let's name substances that used to be used for skin whitening that are now banned due to toxicity. Unfortunately, despite the ban, they can still be found on the market.

Mercury

In modern medicine, mercury is not used as a medicinal substance because it is a toxic metal with many proven negative effects. However, it has been used for centuries to whiten skin, and unfortunately, it is still used in some countries.

The whitening mechanism of mercury ions remains unstudied, although there is sufficient, albeit indirect, evidence that mercury causes severe oxidative stress at the melanocyte level. So, the toxic effect of mercury on melanocytes can be rightly called «disarming» because mercury ions nonspecifically inhibit all antioxidant systems designed to protect melanocytes from free-radical «explosion.» Another hypothesis is tyrosinase inhibition.

The problem is that mercury from bleaching products can be absorbed through the skin and accumulate in various organs, causing marked nephro- and neurotoxic effects. A separate problem is that cosmetic products with mercury have been used primarily not to correct pitting hyperpigmentation but to lighten skin tone in general by residents of southern countries. Mercury use is now officially banned due to its toxic effects, but unfortunately, mercury-containing products are still being used by dark-skinned people, mostly in developing countries. Reports of mercury intoxication continue to appear in respected publications in 2020 (Kuehn B., 2020).

Phenol compounds

The depigmenting effect of phenolic compounds was first noted in workers who wore rubber gloves impregnated with benzoic hydroquinone ester to protect their hands from oxidation. Numerous phenol derivatives, such as cresol, hydroquinone, and benzoic hydroquinone ester, have a similar effect.

The mechanism of phenols' action is associated with free radicals of these compounds — semiquinones, formed on the enzyme tyrosinase. Due to subsequent reactions, they give rise to a whole family of reactive oxygen species with «killing potential» against melanocytes and keratinocytes. It is very important that the stability of semiquinone radicals (i.e., their ability to «rotate» in the redox cycle for a long time and efficiently) entirely determines the positive result of whitening. It is fundamentally important that semiquinone radicals of phenols can also be formed spontaneously, without the participation of the tyrosinase enzyme, especially in an acidic environment. However, in this case, their concentration is much lower than in the presence of the enzyme. Currently, the use of phenol as a cosmetic ingredient is banned in most countries, including Russia.

Hydroquinone

Hydroquinone, also related to phenolic compounds, is considered one of the most recognized inhibitors of melanogenesis due to the ability to markedly reduce tyrosinase activity due to structural similarity with melanin precursors, «framing» itself under the action of the enzyme (Parvez S. et al., 2006; Deri B. et al., 2016). In addition, hydroquinone exhibits selective toxicity to melanocytes, damages melanosomes, and reversibly inhibits DNA and RNA synthesis (Penney K.B. et al., 1984). Semiquinone radicals released by the interaction of hydroquinone with tyrosinase have a damaging effect. The higher the concentration of hydroquinone in bleaching agents, the stronger its effect on melanocytes, but the higher the probability of free radical damage to skin cells. Moreover, as the dose increases, other skin cells can also be damaged.

Hydroquinone is combined with tretinoin and/or glycolic acid (due to its exfoliating action, they improve the penetration of hydroquinone) and corticosteroids (reduction of inflammation) to increase effectiveness and reduce the concentration and time of use — a combination known as the Kligman formula.

Allergic and contact dermatitis, cataracts, post-inflammatory hyperpigmentation, hypopigmentation of adjacent normal skin, loss of skin elasticity, nail pigmentation, and impaired wound healing may occur with prolonged hydroquinone use.

Since hydroquinone penetrates well through the skin and can be absorbed into the blood, it should not be used during pregnancy and lactation. There is also evidence, although obtained in animals and by oral and injected intake, of carcinogenicity, nephrotoxicity, and effects on the reproductive system in

rats. Topical use of the compound in rodents has been associated with increased skin tumors. However, there are no clear data on similar effects in humans (McGregor D., 2007).

People with dark skin who use hydroquinone frequently and regularly over a long period may develop a rare complication, ochronosis. Although this condition infrequently occurs in Europe and the United States, in Asian and African countries, hydroquinone is used extensively, and ochronosis has become a serious problem. Hydroquinone inhibits the activity of homogentisic acid oxidase, a metabolite of tyrosine. Normally, it is rapidly destroyed, but with prolonged blockade of the enzyme that oxidizes it, homogentisic acid can accumulate in the dermal layer and polymerize to form a yellowish pigment. The first sign of ochronosis is coarsening and darkening of the skin in the areas treated with hydroquinone. Histological examination reveals yellow granules in the intercellular substance of the dermis (**ochronosis** — from the word «ochre»). In advanced ochronosis cases, skin atrophy and degeneration of elastin fibers occur because the pigment is deposited in and around them. There is also evidence of ochronosis of the eyes with long-term use of hydroquinone cream, including in the periorbital area (Hollick E.J. et al., 2019).

Since 2001, the use of cosmetics with hydroquinone has been completely restricted in the European Union. The use of hydroquinone in cosmetics has also been banned in Japan, Australia, and some African countries. The US FDA proposed banning over-the-counter cosmetic products with hydroquinone in 2006, but it is still not approved, although restrictions have been introduced. For example, in over-the-counter products, the maximum concentration of hydroquinone cannot exceed 2%, while in prescription products, it is 4%. Although hydroquinone is still actively used by consumers, most experts are gradually moving away from its use.

1.1.3. Active substances in modern topical pigmentation correctors

Let's take a closer look at the most common active ingredients in today's topical pigmentation-treating products.

Azelaic acid

Azelaic acid (1,7-heptandicarboxylic acid) is well-known to dermatologists as a treatment for acne. Studies have shown it is a weak direct inhibitor of