Chapter 1
Cosmetic products

1.1. Depigmenting and lightening agents

1.1.1. Targets in the skin

As mentioned previously, true depigmenting (bleaching) agents include substances that inhibit melanogenesis. Some act as competitive tyrosinase inhibitors, some 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 the same time.

Exfoliating products can help lighten and even out the overall skin tone. Their purpose is to speed up the desquamation of melanin-overloaded corneocytes. Thus, 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 considering peels in general, salicylic acid, which refer to beta-hydroxy acids, is not recommended on low-sebum skin.

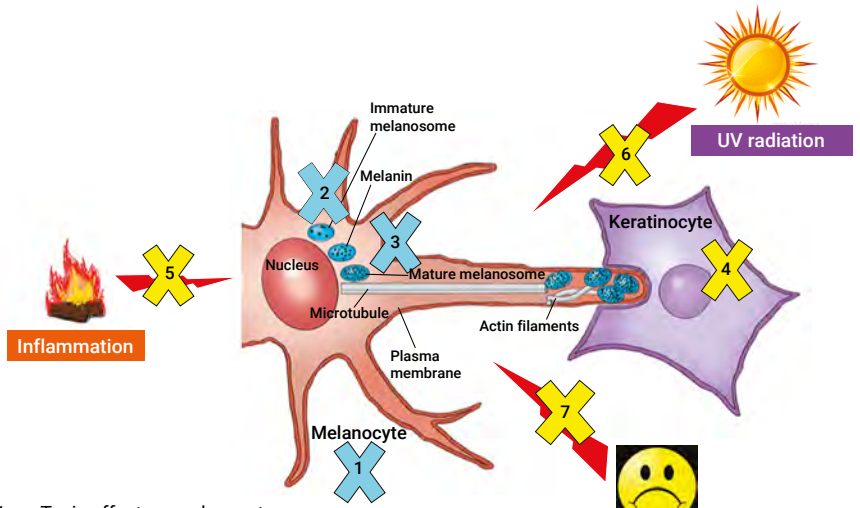
According to the mechanism of action, all currently known depigmenting agents can be divided into two main groups:

1. **Toxic (non-specific):** Usually damage and kill melanocytes/keratinocytes and destroy the mature melanin. Almost all

long-known bleaching agents traditionally used in dermatology belong to this group. For example, mercury and phenol compounds, hydroquinone, and 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 the depigmentation methods that, while effective, are dangerous to the health of the skin and the body, giving preference to modern means and a comprehensive approach. The targets for skin lightening and approaches to pigmentation control are outlined in **Fig. III-1-1** and **III-1-2**.



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

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

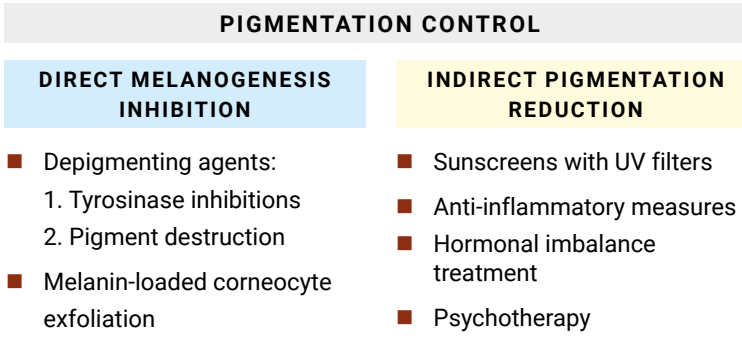


Figure III-1-2. An integrated approach to effective pigmentation control

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 included in the table because they are mixtures of different substances, but they are discussed later when each substance is analyzed separately. **The more targets we involve in our treatment program, the better the chance of achieving the desired result!**

1.1.2. Obsolete and dangerous substances

The substances discussed in this section were previously routinely used for skin whitening. Although they are now banned due to toxicity, they can still be found on the market and thus deserve due attention in this book.

Mercury

In modern medicine, mercury is not considered 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 is rarely a subject of scientific research, but 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

Table III-1-1. The most common ingredients in formulations used for treating 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 conducive to the melanocyte activity reduction)	
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 accelerating corneocyte exfoliation)	
Exfoliating	• Alpha hydroxy acids (AHAs) • Salicylic acid • Retinol

"disarming" because mercury ions non-selectivly inhibit all antioxidant systems designed to protect melanocytes from free-radical "explosion." Another hypothesis for their mode of action implicates 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. As a result, reports of mercury intoxication continue to appear in academic publications (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 in cosmetics is banned in most countries.

Hydroquinone

Hydroquinone, also related to phenolic compounds, is one of the most widely recognized inhibitors of melanogenesis owing to

its ability to markedly reduce tyrosinase activity due to its 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 use duration — a combination known as the Kligman formula.

With prolonged hydroquinone use, 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.

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 based on 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 tumor incidence. 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 rarely occurs in Europe and the United States, as hydroquinone is used extensively in Asian and African countries, ochronosis has become a serious problem in these populations. 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