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Review

THE CHEMISTRY MECHANISM OF HAIR DYES

***Arzu YILDIRIM*[1] *Belinda DEMİR*[1] *Berfin AK İZGİ*[1] *Büşra Nur ERKOL*[1] *Çağla ÖZSU*[1] *Gülşah EŞLİK AYDEMİR*[1] *Mine MUSTAFAOĞLU*[1] *Murat KIZIL*[1] *Nubar AYHAN*[1] *Sevil EMEN*[1]* ***

[1]Lila Cosmetics, Diyarbakır, Turkey, 21010
*Corresponding Author: ar-ge@lilafix.com

Abstract: *One of the oldest and most well-known cosmetics, hair color has been used by numerous ancient cultures throughout history on both men and women. It involves treating hair with various chemical compounds for changing hair color. According to how long they remain in the hair, these products are primarily divided into two categories: temporary and permanent. This classification is consistent with the types of active substances used in the dyeing process as well as the dyeing method itself, which are referred to as non-oxidative and oxidative hair dye products, respectively. Permanent hair dyes often consist of active chemicals that are not dyed but are oxidized to provide the desired color. As a result, the phrase "oxidative hair dye" was emerged. The precursor part and coupler part are the two main ingredients in formulations for oxidative hair dyes. Quinonediimine intermediates are momentary compounds that are generated when combined with hydrogen peroxide (developer). As a result, the coupler agent and these compounds interact to form the appropriate hair dye molecule. Notably, the entire dyeing process requires both an alkaline medium and an oxidizing agent, often hydrogen peroxide, to ensure that the staining agents reach the cuticle widely. This review's objective is to provide information about hair dye formulations and mechanisms of action as well as repairing damaged hair and new applications.*

Key words: *Hair dyes; temporary; semipermanent; permanent; chemical mechanism*

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1. Introduction

Since the dawn of human civilisation, people have used vegetable and animal fats in cosmetics and other items [1,2]. It is well known that both men and women frequently utilize a combination of natural materials, such as original hair color changes with chemical dye application [3,4]. Colors are crucial to human existence. Previously, dyes were used for clothing coloring, cosmetics, medicine, and a variety of other uses, but recently, due to biodegradability and environmental concerns, the usage of natural dyes has grown significantly [5]. Hair dyes are currently in a crucial stage of development, and substantial advancements are being made in the discovery and use of numerous new synthetic dyes.

The oxidation behavior of dyes falls under two categories. These can be divided into two groups: oxidative and non-oxidative hair dyes [6]. Some hair dyes are referred to as "non-oxidative" dyes because they produce color without the use of oxidation chemicals. Contrarily, oxidative hair colors feature oxygen release in their formula and make up about 90% of the hair dyes on the market today. The oxygen that is produced helps to oxidize the dye substance, start the reaction process, and also provide the desired color in the hair [7]. For cream and lotion-based hair dyes, a variety of oxidizing agents are available. These agents are also employed in liquid form, with hydrogen peroxide serving as the finest illustration. The reaction mechanism greatly depends on the concentration of the oxidizing agent. Faster color integration and reaction mechanism are provided by higher concentrations [8].

Numerous people utilize hair cosmetics, which alter the hair's structural characteristics [9]. It alters the hair's protein composition and structure while also changing the physical characteristics of the hair. Long polyhedral hair strands are encased in cuticle cells. Cortical cells are arranged structurally in it. The majority of the mechanical properties of the hair are determined by the cortical layer [10]. The usual structure of the hair shaft must be altered chemically in order for the hair to change color when dyed. This allows color pigments to enter the hair and provides a coloring process [11].

When hair colors are applied continuously, the hair strands are repeatedly exposed to the dye, which makes them more sensitive. Therefore, even if you've colored your hair before, it could be difficult to do so again without experiencing difficulties. Some hair colors can give sensitive people adverse reactions that result in skin discomfort and hair loss [12]. Before applying the color, the user must adhere to the user’s instructions. Before using the hair dye, the consumer is required to carefully follow the user instructions each time. This reduces the likelihood of allergic reactions in the user.

2. Hair Biology and Chemistry

The term "hair" refers generally to the cluster of hairs on a person's scalp. A human embryo's skin begins to develop hair follicles during the eighth and twelfth weeks of gestation as the epidermis invades the dermis. A hair fiber's 50-100 μm in diameter serves both defensive and aesthetic purposes. The skin's hair follicles create hair, which is a highly keratinized tissue. Dermal stem cells in hair follicles modify the kind of hair and renew the dermal sheath and dermal papilla [13].

The three distinct components of the hair's composition are as follows: the medulla, which is the innermost layer of the hair shaft and is made of an amorphous, soft, greasy substance. The nourishing part necessary for hair growth is found within the cuticle, a thin protective outer layer. The main component of the hair, the cortex, is highly keratinized and is made up of cells that resemble scales that are layered one over the other, measuring roughly 60 micrometers long and 6 micrometers wide Long keratin chains in the cortex give the hair its elasticity, suppleness, and resistance [14,15]. A lipid- and protein-rich intercellular cement holds the cortex's cells together. Each cell is made up of bundles called macrofibrils, which are composed of microfibrils and lie in the direction of the hair length. (Fig 1).

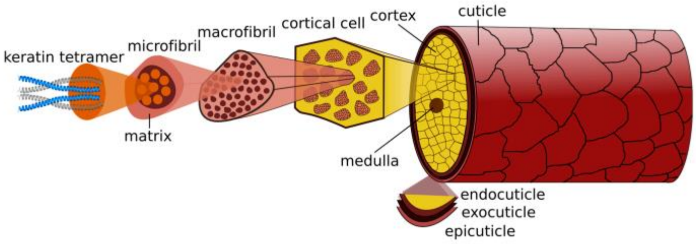


Figure 1. An illustration of a hair strand in cross-section. Adapted from ref. [15].

Human hair is composed of proteins called keratins. The family of fibrous structural proteins includes the complex natural composites known as keratins, which have varied morphological structures. As the cells develop and create the hair fiber, keratin, which is present in the cells during hair creation, crystallizes. The majority of the time, the hair surface contains a negative charge because keratin, which makes up the majority of the hair fiber, has an acidic isoelectric point. The molecular weight of keratins ranges from 40 to 70 kDa. Alpha-keratins are primarily in the α-helical conformation and are found in tissues like hair, nails, and claws of animals, including humans [14].

Alpha keratins come in type I and type II varieties. Human hair keratins are typically Type I keratins, bigger (50 to 60 kDa), neutral to slightly basic (pI range: 6.5-7.5), and larger than other keratins (50 to 60 kDa). The most notable variation is in the quantity of cysteine and glycine residues. The increased amount of cystine in human hair keratin, which converts to a higher amount of disulfide bonds, results in a tougher and more robust structure with good mechanical, thermal, and chemical properties.

All keratin forms, however, contain a lot of aspartic and glutamic acid residues, which explains why these proteins are relatively acidic. For proteins' structural stability to be maintained, water is a crucial component. As a result, while considering the physical and aesthetic qualities of hair, the water content is a crucial factor.

The amount of lipids and pH of the hair both affect how much water is absorbed. With an average amount of 4% by weight of the fiber, hair lipids are dispersed throughout the hair fiber. Cholesterol, cholesterol esters, cholesterol sulfate, free fatty acids, triglycerides, paraffins, squalene, and ceramides make up the majority of lipids. 18-MEA, which is a crucial part of exogenous lipids and is covalently attached to the cuticle surface, when this lipid is absent, the sensory sense of the hair is affected, leading to dry hair or difficulty combing, as it acts as a lubricant to reduce friction between hair fibers. Inorganic elements can also be found in hair, though they typically make up less than 1% of the total composition [15].

The most prevalent are metalloids (Hg, Cd, Pb, As, and Se), other metals (Ca, Zn, Fe, Mn), alkaline earth elements (K and Na), and alkaline earth metals (Mg, Ca, and Sr) (Si). & P) If the scalp is lengthy, hair can reveal long-term information about drug use and toxin exposure over the course of months or even years. The connections between and within the protein chains are what keep the keratins' macromolecular structure stable and hold it all together.

From stronger contacts like hydrogen bonds, Coulomb interactions, Van der Waals forces, and hydrophobic interactions to weaker ones like covalent bonds like disulfide bonds and isopeptide cross-links, these interactions span the entire chemical spectrum. Reactive groups must be present in the fiber for these interactions to occur, but they must also be present due to the fiber's shape and molecular structure. Although weak and quickly disrupted by water, hydrogen bonds are the most prevalent in hair, and interchain hydrogen bonding along the polypeptide chain is crucial for the integrity of the -keratin structure. Coulombic interactions are rather stable in an aqueous media due to the high amount of acidic and basic side chains but are easily broken by acids or alkalis.

All along the keratin, nonpolar groups interact hydrophobically. Keratin's stability depends on disulfide bonds. A bridge between two chains or two sections of the same chain is created when two adjacent cysteines link together to produce cystine. The majority of chemical alterations in the hair and the resulting change in its physicochemical qualities are caused by these bonds' vulnerability to reduction and oxidation [14,15].

Changes in disulfide bonds are a negative side effect of some other cosmetic procedures, including oxidative hair coloring, bleaching, and hair damage. In both situations, redox chemical reactions have an inadvertent or intentional impact on the physicochemical characteristics of the hair. There are 18 methyleicosanoic acid-based covalently linked lipids that attach to proteins in the cuticle cells' outer layer. Involved in the penetration of substances into the fibers, including the breakdown of the cell membrane complex by persistent waves, sunlight, hair bleaches, and cyclic elongation stresses, they contribute to the surface characteristics of the fibers.

3. Pigmentation of Hair

The quantity and distribution of melanosomes in the cuticle, cortex, and medulla determine the color of hair. Vesicular organelles called melanosomes hold the melanin pigments eumelanin (brown to black) or pheomelanin (yellow or red). The density, location, and relative amounts of various melanin granules might vary depending on the age of the person and the stage of hair growth [16, 17]. The colour variations between hair strands collected from the same person are shown in Figure 2. These two hair strands were taken from a person's top of the head; however, it is obvious that they differ in terms of color, diameter, and medullation. Researchers examining genotype-phenotype connections can obtain a quantitative color assessment by spectrophotometric measurement, chemical analysis, and microscopic examination [18].

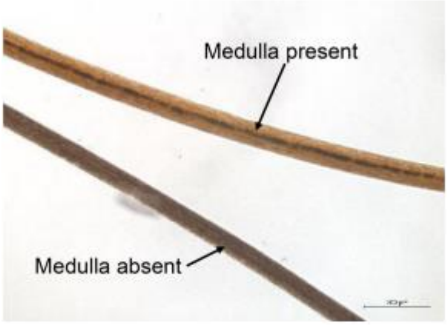


Figure 2. Two hairs from the same person are shown in a photomicrograph with different colour and medulla presence/absence. Adapted from ref. [18].

Studies on hair color employ handheld spectrophotometers to classify the various hair hues and examine mass hair samples [19, 20]. Blond, red, brown, and dark brown/black hairs can all be classified quantitatively using spectrophotometry, although there are detection limits that make it impossible to study a single hair strand [21]. Examining melanin and the genes responsible for various phenotypes using reflection spectrophotometry can provide quantitative information about hair color. This kind of study might be constrained, though, by the quantity of hair and the differences in the sample hair used for such investigations [22].

It is possible to investigate hair color and composition at the chemical level quantitatively by analyzing the kind and quantity of melanin in hair. It has been demonstrated that there is a correlation between the hair color and the amount of melanin in the hair when the melanin in the hair is chemically examined with the High-Performance Liquid Chromatography instrument [23]. Pheomelanin, although it cannot be seen, the ratio of eumelanin to eumelanin can be established chemically. It should be noted that brown to dark hair consistently has a pheomelanin content of 11–17% [24].

In order to take advantage of and interpret the numerous procedures available, it would be more acceptable to combine multiple techniques in studies on hair color and melanin. Investigating the superstructure of the hair, hair pigmentation, color, and shape, and linking chemical and genetic data are all advantages of this sort of integrated study [25]. This combined approach will also result in a more precise approach when examining the variations in hair pigment hue.

Using natural or synthetic hair dye, such as henna, indigo, strawberry, and other herbs, it is possible to temporarily alter the color of hair. Changes in hair pigmentation can be temporary or semi-permanent by coating the hair cuticle or introducing color molecules to the hair cuticle. Additionally, more lasting alterations in hair color are made possible by the color molecules' penetration of the deeper cortical layer. An essential component is hydrogen peroxide, which penetrates the cortical layer, oxidizes melanin, and eliminates color. The cuticle is opened by high pH (alkaline) substances like ammonia, allowing the dye to penetrate the cortex and bond to the keratin. The cuticle is closed by substances with a pH between 4 and 5.5, which helps the new desired color permeate the hair [26, 27].

4. Hair Dyes

According to the chemistry involved, modern commercial hair coloring products can be simply separated into two primary groups: the oxidative process and the nonoxidative process. Semipermanent hair dyes are included in the nonoxidative category. Oxidative dyeing products are classified into two subcategories: permanent hair dyes, and demipermanent hair dyes, which lighten hair less and cause colors to fade over time.

4.1. Non-oxidizing Hair Dyes

Hair coloring is a widely popular process, particularly among ladies. Temporary, semi-permanent, demipermanent and permanent hair colors are categorized according to their color resistance. Based on colored molecules, the first two dye classes (Table 1). Semi-permanent dyes can somewhat penetrate the hair cortex; therefore, the color permanence may resist up to six washes, in contrast to temporary dyes, which affect hair by accumulating on the cuticles [12].

Table 1. Contemporary hair dyes' classification and ingredients. Adapted from ref. [28].

Dyes category	Hair coloring process	Composition	Hair coloring type
Temporary	Non-oxidative	Water-soluble acidic and basic dyes containing azo or anthraquinone groups	Build up on hair
Semi-permanent	Non-oxidative	Azo groups, anthraquinones, triphenylmethanes and nitro derivatives as chromophores.	Ionic interactions or Van der Waals forces
Permanent	Oxidative	Precursor, binder and oxidizer	Hair penetration

4.2. Temporary (Non-Oxidative) Hair Dyes

Because the dye cannot penetrate the cortex, non-oxidative temporary hair dyes have a shorter lasting period on the hair fiber and start to wash out of the hair after the first shampoo. Because of its heavy molecular structure, it leaves deposits on the hair's surface.

Due to the fact that this kind of dye cannot bleach the hair, it is only used to add new nuances to the existing color of the hair. Once the color is at least one shade lighter than the original hair color, these dyes are ready for use. If the hair was born black, the color is not immediately apparent [29].

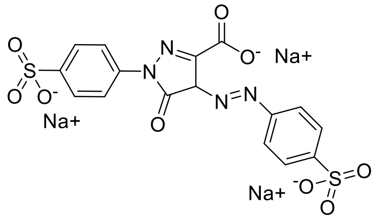
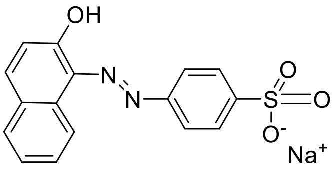
The color appears better on white, blond, or bleached hair because the original color of the hair strand allows the appearance of the new color applied. Temporary dyes work by building up in the hair strands and can colour hair that contains up to 15% white hair fiber. These colors have acidic characteristics. Typically, they have a large molar mass. Their effects on the hair are gone after the first wash since they exhibit anionic qualities, act with maximal water solubility, and penetrate the hair very minimally [30]. These colors function in aqueous solutions with a pH range of 2.5 to 4.0. Generally, no metal salts are used in their use (Table 3) [31].

Table 2. A few samples and reflections of temporary dye pigments.Adapted from ref [30].

Pearl Name	Ci Number	Cas Number	Color/Reflection
Acid yellow 23	CI19140	1934-21-0	Yellow

Acid Orange No. 7	CI15510	633-96-5	Orange
Acid Yellow No. 1	CI10316	846-70-8	Yellow

Table 3. A selection of anionic dyes with their structural and molecular formulations that are used in semi-permanent hair coloring. Adapted from ref [12].

Acid Yellow 23	Acid Orange 7
	

Because extra dye molecules are rapidly removed by shampooing, higher concentrations of temporary color pigments should be used in temporary hair dyes to produce the desired color on the hair without exceeding the usage limit [29].

Because it is impossible to achieve the necessary tones with a single pigment, temporary dyes typically require at least two or five pigments in order to achieve the ideal hair color. Some types mix four to five colours to obtain red, brown, and black tones, and some types utilize two pigments to conceal the whiteness of the hair. Temporary non-oxidative dyes are stronger stains and have higher dye concentrations between 0.1% and 2.0% (w/w).

4.3. Semi-Permanent (Non-Oxidative) Hair Dye

The term "semi-permanent hair dye" refers to colors that can permanently change hair color without the use of hydrogen peroxide for up to 4 to 6 shampoos [29].

These hair colours have a strong affinity for the keratin in hair. These dyes have a low molar mass and are basic cationic dyes. Because of their straightforward application, semi-permanent hair dyes do not contain oxidation processes. After waiting for 10 to 40 minutes, they are rinsed out of the hair and dried. Nitroaniline, nitrophenylenediamines, nitroaminophenols, azoic compounds, and anthraquinone compounds are the general categories for semi-permanent colorants (Table 4) [32].

Semi-permanent hair dye products have higher wash resistance than temporary dyes because the semi-permanent dye molecules are in a form that can be applied with other oxygen-release agents without hydrogen peroxide or alkali solution. Robbins and Crawford only examined the diffusion pattern of semi-permanent color and found that weak Van der Waals bonds are formed in the semi-permanent coloring mechanism [29].

Table 4. A few illustrations of cationic semi-permanent hair color. Adapted from ref. [12, 33].

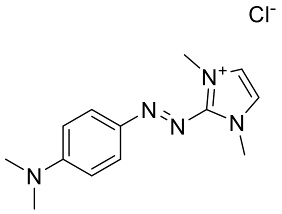
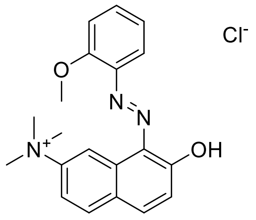
Name	Color/Reflection
2-Nitro-P-Phenylenediamine	Rejection
Basic Blue No.99	blue
Basic Yellow No.57	yellow

Given the high affinity of both dye families for hair, another type of product is that it might be essential to combine nitro aniline dyes with basic or acidic dyes, which offer a better color outcome and improved wash resistance. Nitro anilines are extremely polar compounds with mono, di, or tri nuclear rings that are made up of a neutral aromatic amine or anthraquinone derivatives. These colors are held by flimsy Van der Waals connections and spread throughout the hair fiber. Larger molecules with three aromatic rings are expelled from the hair more slowly than smaller mononuclear molecules under the same circumstances.

The cationic molecules' identical sizes provide the hair a uniform permanence that promotes even color replication and washing resistance. In other words, during this procedure, all colours from the hair are washed away simultaneously (Table 5) [12].

Ionic bonds between the positive areas of the dye molecule and the negative sites on the hair fiber make cationic dyes more resistant to washing than nitro anilines, they are particularly useful for treating damaged hair [34].

Table 5. Cationic dyes used in various semi-permanent hair dyes, including their structural and molecular compositions. Adapted from ref [12].

Basic Red 51	**Basic Red 76**
	

4.4. Semi-Permanent Hair Dyes

Hemi-Cyanin is the abbreviation for "HC Dyes" in semi-permanent hair dye. These Hemi-Cyanine dyes, sometimes referred to as Nitro dyes, are a secondary source of amines. HC dyes are direct dyes because they belong to the semi-permanent dye class, but they are not direct dye color indicators (Fig 3). These HC dyes can be combined with oxidative dyes or used independently. These dyes have low molar extinction coefficients (approximately 10,000 L mol^{-1} cm^{-1}). For better color results, use more of it in general (Table 6) [35].

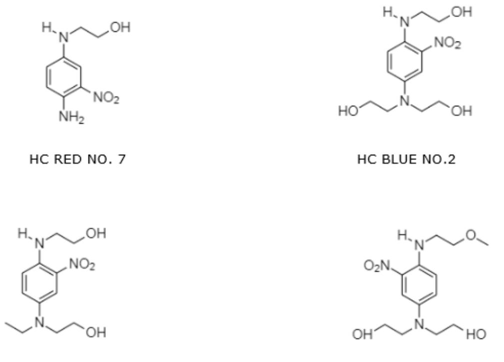

HC RED NO. 7
HC BLUE NO.2
HC BLUE NO.12
HC BLUE NO.11

Figure 3. The Most Popular HC Dyes. Adapted from ref [35].

Table 6. Some HC Dyes containing secondary amine group. Adapted from ref [35].

Dye	**Contains A Secondary Amin Group**	**Maximum Concentration Allowed %**
HC Blue NO.16	+	No Limited

HC Yellow No.4	+	1.5

4.5. The Effect of pH on the physical properties of the hair structure

One of the variables that fundamentally affects the physical characteristics of the hair structure is pH. The outer layer of the hair develops pores as a result of acidic pH dyes, and the hair strands become positively charged. On the other hand, when negative charges are present and the pH is basic, the fibers swell and produce more holes [32].

As a result, a change in pH can affect how colors are distributed in the hair fiber's outer and interior layers. Ballarin, Galli, and Morigi (2007) described the Basic Red 76 pigment's state and the staining process, which took 30 minutes. In this situation, he noticed that the color deposited more on the hair surface at basic pH values compared to acid pH values. pH regulation is a crucial component of color stability. For instance, to produce a pH of 9.0, a weak base like monoethanolamine must be added, and to reduce the pH to 6.0, a weak acid like 10% citric acid solution must be used [32].

This results in the creation of a buffer system that preserves the pH of the finished product during the course of its shelf life. [36]

4.6. Oxidative (Permanent) Hair Dyes

Because this category offers better permanent dyeing efficacy, resistance to shampoo washes, and resistance to other environmental elements including drying, friction, light, and others, permanent hair dyes are frequently used [37]. This category receives any colour and covers up to 100% of grey hair strands, accounting for around 80% of commercial hair dyes [38]. Additionally, the combination of the oxidizing chemicals and the ammonia hydroxide allows for the creation of both dark and light natural hair colors. In the presence of an oxidizing agent, color production occurs upon combination and involves intricate interactions between precursors [12].

Precursors can be divided into two groups: couplers or reaction modifiers and oxidation basis [12, 39]. The reaction takes place in an alkaline environment that encourages the cuticles to open, allowing the molecules of the dyes to enter the cortex. The oxidizing agent allows the reaction to start in the cortex, which produces a colorful complex with a large molar mass and prevents formed molecules leaving from hair. The cuticles also participate in the process, and the first washes remove the molecules [40, 41].

An aromatic amine with ortho or para substitutions (hydroxy or amino) as coupling bases, reaction modifiers, an alkalizing material, and an oxidizing agent are the four primary components needed for redox reactions, which are used to make permanent dyes.

Three essential elements are needed for permanent hair coloring. The primary intermediate, oxidation base, or developer is an o- or p-substituted (hydroxy or amino) aromatic amine (by analogy with color photography). p-phenylenediamine (Fig 4), p-aminophenol (Fig 5), and their derivatives are examples of primary intermediates [12, 39].

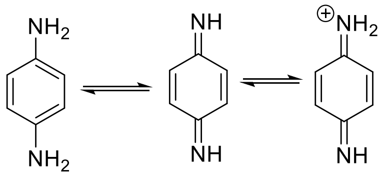


Figure 4. Formula structural for p-phenylenediamine (PPD).

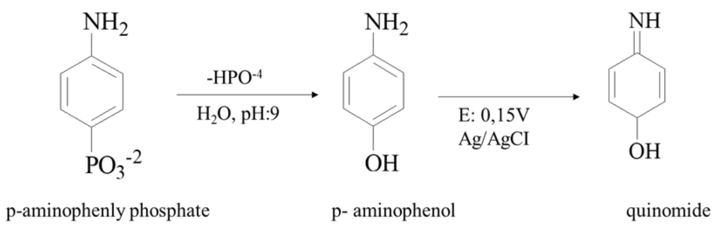


Figure 5. The structural formula of p-aminophenol (PPD).

The coupler, the second component, is often an aromatic compound with electron-donating groups organized in a meta-to-meta arrangement. Examples of such compounds include m-phenylenediamines, resorcinol, naphthols, and their derivatives (Table 8). When combined with the primary intermediates and an oxidant, these chemicals, which by themselves do not create noticeable hues by oxidation, can change color. According to the color produced in the fiber with the primary intermediates, couplers are divided into three groups: yellow-green, red, and blue. The third component is an alkali, typically ammonia, and an oxidant, nearly always hydrogen peroxide (although ambient oxygen can be used under some circumstances) [42].

To promote the right pH level for the start of the oxidation reaction, alkalizing substances must be added throughout the hair colouring process. Ammonia, in the form of ammonium hydroxide, monoethanolamine, and sodium silicate, when the formulation comprises water, are the most often employed alkalizing substances (powder) [12].

To delay the interaction between bases and reaction modifiers and to stop the reaction from starting in the packaging tube during storage, reducing agents are added to formulations of oxidative dyes. Sodium metabisulfite is one of the compounds most frequently utilized for such purposes (MBS) [12].

Antioxidants are required to stop the reaction from starting before the actual oxidant is added. It is advised to employ a water-soluble antioxidant since adjusting bases and reaction modifiers may start an oxidative process that could affect the product's final color. Erythorbic acid is one of the compounds that is most frequently utilized for this purpose (AEB). Additionally, it is advised to add an oil-soluble antioxidant when using an emulsion as a carrier for hair dyes in order to prevent wax from turning yellow and bases and reaction modifiers from oxidizing. The most often utilized chemical is t-butylquinone (TBQ) [36].

Sodium persulfate is used when the vehicle is a powder, while hydrogen peroxide is used when the vehicle is water. Because the peroxides are so unstable, stabilizers such sodium stannate and pentasodium pentetate must be used. They are typically used as an emulsion, or "creamy hydrogen peroxide." [36].

4.6.1 Mechanism of Action

Precursors and peroxide diffuse into the hair shaft, where chemical processes lead to the creation of color. The p-benzoquinone imines/diimines, which are reactive intermediates in color synthesis, are created when hydrogen peroxide oxidizes the dye precursors. The intermediates and couplers, which are both relatively stable to hydrogen peroxide, quickly react to form dinuclear, trinuclear, or polynuclear colorant molecules [43] (Fig 6).

The size of these molecules prevents them from escaping the hair structure. In oxidative hair dyeing formulations, hydrogen peroxide also acts as a bleaching agent for the hair's natural pigment. The precursors and direct dyes present in the dyeing solution, the pH of the dyeing solution, and the length of time the dyeing solution was in contact with the hair all affect the color creation (shades).

Couplers prevent the formation of self-coupling compounds like Bandrowski's base, which are the major reaction products produced by precursor and coupler combinations. The kinetics of reaction products production have not been observed to be impacted by the additional ingredients contained in the formulas of contemporary commercial hair dyes, including direct dyes like HC Yellow 2 and 2-Amino-6-chloro-4-nitrophenol. In addition, no new reaction products were discovered beyond those that were predictable [43].

A study using three couplers (2-methylresorcinol, 4-amino-2-hydroxytoluene, and p-toluenediamine) and three precursors (1-hydroxyethyl-4,5-diaminopyrazole, aminophenol, and 2,4-diaminophenoxyethanol) in a hair dye formulation showed that the oxidative coupling reaction products agreed with theoretical expectations based on the reaction kinetics and that the chemistry in the formulation is dominated by the fastest coupling reactions [43] (Fig 6).

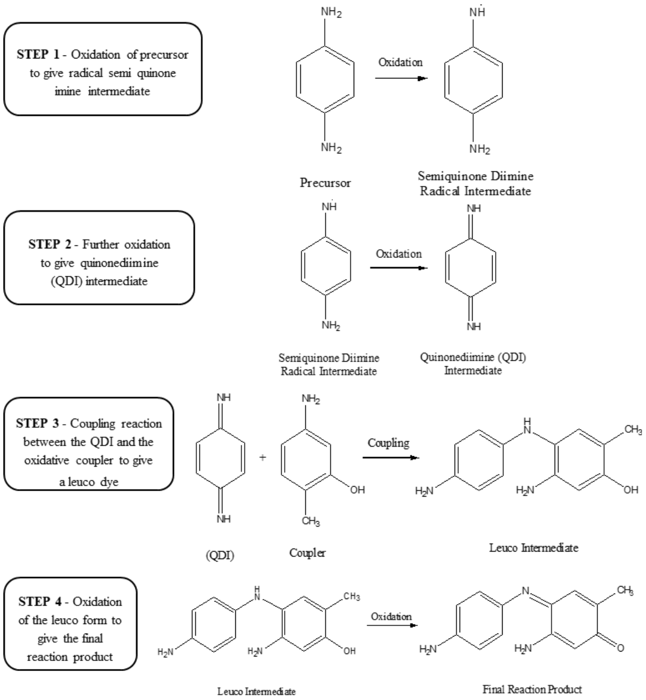


Figure 6. Proposed mechanism of oxidative hair dye formation. Adapted from ref. [43].

5. Repairing Damaged Hair

Hair can become damaged by a variety of things in daily life. In addition to problems including sun exposure, air pollution, improper product usage, hair dye, high styling temperatures, combing, drying, and even gathering hair can harm skin and hair strands. Depending on the amount of damage, mending products must be used to lessen all these negative effects or to treat damaged hair. Different shampoos, conditioners, and serums that contain lipids and protein can replace the elements that have been removed from the structure of healthy hair. For instance, Lee et al. (2022) examined the impact of applying a rinse-off conditioner made with argan and camellia oil on bleach-damaged hair. It has been demonstrated that using a conditioner with argan or camellia oil while washing can protect bleached hair from breakage, boost tensile strength, and lower protein leakage to pre-bleaching levels [44].

This had a stronger impact on conditioner with argan oil, and it was found that argan oil also lengthened the duration that color stayed in the hair. Studies were done on bleached hair to determine the specific effects of each of the four fatty acids (stearic acid, palmitic acid, oleic acid, and linoleic acid) used in the formulation of the rinse-off conditioners (Fig 7) [44]. The rinse-off conditioner made with palmitic acid had the best results in repairing the surface characteristics of the hair and retaining the color, whereas the conditioner made with oleic acid had the worst results when these effects were studied. Additionally, it has been found that conditioners designed with linoleic acid first, then palmitic acid, and finally stearic acid, boost the tensile strength of the hair. Currently, it is believed that the high palmitic acid and linoleic acid concentration in argan oil's composition is what contributes to color protection [44].

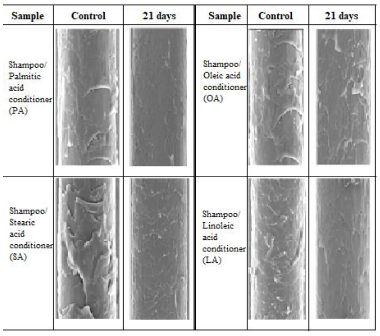


Figure 7. SEM images of bleached hair treated with rinse-off conditioner formulated with four different fatty acids. Adapted from ref. [44].

Morita et al. (2010) synthesized mannosylerythritol lipids (MELs) from pseudozyma based on the effects of lipids on hair restoration and the advantages of glycolipids for the hair cuticle. The tensile strength of damaged hair was shown to be much higher after treatment with these biosurfactants, MEL-A (122.0 13.5 gf/p), MEL-B (119.4 7.6 gf/p), and ceramide (100.7 15.9 gf/p), than it was after treatment with lauryl glycoside (96.7 12.7 gf/p) alone. The mean friction coefficient of damaged hair was shown to be conserved by MEL-A (0.108 0.002), MEL-B (0.107 0.003), and ceramide (0.111 0.003), but it was increased by lauryl glucoside treatment (0.126 0.003). In contrast to lauryl glucoside (0.204 0.002), it was discovered that MEL-A (0.129 0.002), MEL-B (0.176 0.003), and ceramide (0.164 0.002) all prevented the rise in hair bending stiffness. These findings reveal that MELs can efficiently repair hair fibers in place of 18-methyleicosanoic acid. They also demonstrate their potential for improving the smoothness and elasticity of hair strands [45, 46].

In addition to the lipids' healing power, proteins, one of the hair's structural constituents and present in high concentrations in the hair, are known to have a significant part in the health of damaged hair. Transglutaminase (TG) enzyme is now employed in the restoration of protein-based materials like silk, wool, and hair. The reaction between the -hydroxyamide group on the glutamic acid residue and the -amino group on the lysine residue, which results in the formation of crosslinking between proteins or peptides, is catalyzed by the TG enzyme, a commonly used enzyme preparation (Fig 8). In order to repair hair, Xiao et al. (2021) created keratin repair solution (KRS), TG enzyme repair solution (TGRS), and a combination of keratin-TG enzyme repair solution (TG-KRS), all of which were based on the information above and the fact that hair is primarily made of keratin and contains similar lysine and glutamic acid residues. The combination of TG-KRS produced the best results in smoothing the damaged hair's surface using AFM pictures, it was determined (Fig 9). It demonstrates that the application of the TG-KRS combined repair solution to damaged hair induces a significant amount of keratin or keratin peptides to cross-link into those places under the control of the TG enzyme or by protein disulfide bond recombination [47].

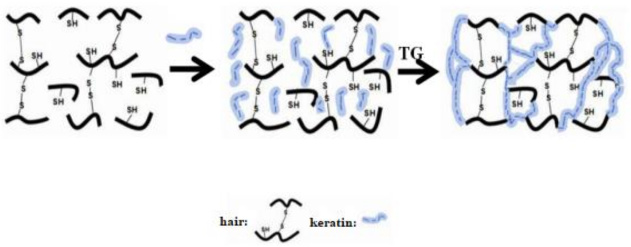


Figure 8. Hair repair mechanism with the combination of keratin and TG enzyme. Adapted from ref. [47].

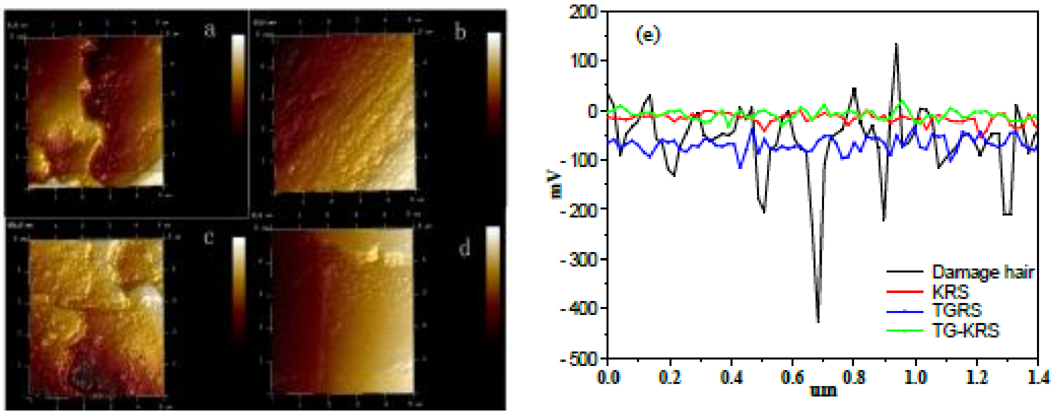


Figure 9. AFM images of (a) damaged hair, (b) KRS, (c) TGRS, and (d) TG-KRS, and (e) surface roughness graph. Adapted from ref. [47].

Another study looked at the effects of five different pentapeptide types with varied amino acid sequences on hair restoration. The STTSS (Ser-Thr-Thr-Ser-Ser), LIILL (Leu-Ile-Ile-Leu-Leu), CMMCC (Cys-Met-Met-Cys-Cys), DEEDD (Asp-Glu-Glu-Asp-Asp), and RKKRR (Arg-Lys-Lys-Arg-Arg) peptides were synthesized by Kang et al. (2020) (53). After being exposed to the fluorescent dye 5(6)-carboxytetramethyl-rhodamine, succinimidylester (5(6)-TAMRA), it was shown that these peptides bound to TAMRA. Due to their extra carboxyl or amine groups, DEEDD and RKKRR showed increased binding affinity to the hair in damaged hair treated with pentapeptide alone or pentapeptides containing crosslinking agents such 1-ethyl-3-(3-imethylaminopropyl) carbodiimide (EDC) and polymeric carbodiimide (PCI). By increasing the number of bonds in the hair by the carbodiimide coupling process, the hair was strengthened. With the exception of DEEDD, which can reach the innermost part of the hair, all peptides have been determined to have hair repair ratios that are appropriate for average fluorescence yield (Fig 10). The polymerizations within the peptide and between the peptide-hair might be claimed to perhaps aid in hair healing for DEEDD and RKKRR [48].

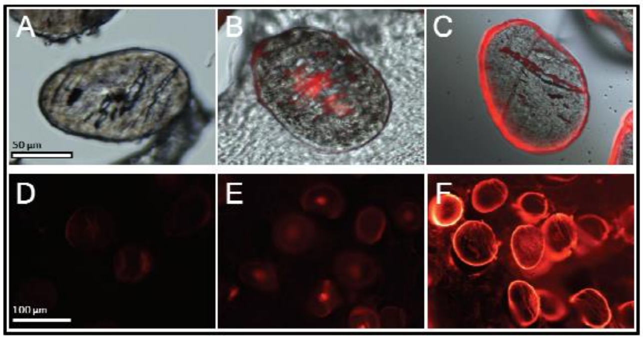


Figure 10. Representative fluorescent microscope images (400 X, 200 X) of hair treated with (A, D) TAMRA-STTSS, (B, E) TAMRA-DEEDD treated and (C, F) TAMRA-RKKRR treated hair after EDC solutions. Adapted from ref. [48].

Antioxidants, immunocosmetics, nanoparticles, as well as lipids and amino acids that can penetrate the hair shaft, are known to be employed in hair cosmetic products. According to Fernandez et al. (2012), rice and artichoke natural antioxidants were employed to prevent UV-induced chemical and physical harm. While the larger molecular weight peptides produced a protective layer to stop tryptophan from degrading and discoloring, the low molecular weight peptides of the rice formulation increased the mechanical qualities of the cortex by permeating the hair. The hydroxycinnamic characteristic of the artichoke formulation, on the other hand, has been demonstrated to improve the integrity of the hair fiber and exhibit better antioxidant qualities, greatly reducing lipid peroxidation and protein degradation of the hair. Both formulations have been demonstrated to be effective at lessening the negative effects of UV [49].

The impact of immunocosmetic use on removing hair damage was assessed in a different study. Human hair was used as the antigen to produce an egg yolk antibody, which was then used to make a hair care product. The anti-hair antibody formed from egg yolk, according to the present invention, has remarkable effects including elasticity, smoothness, gloss, hair renewal, moisturizing even in dry conditions, and a permanence that does not vanish even with repeated washes [50].

Nanotechnology's applications in cosmetic products have become more varied as a result of the technology's evolving and increasing effects. The nanostructured lipid carriers (NLCs) and NLCs loaded with vitamin E’s (Vit E-NLCs) influences on the prevention of hair damage and discolouration induced by UV radiation and heat impacts were examined using cutting-edge nanotechnology. Using a process called high-pressure homogenization, NLCs and Vit E-NLCs were created. It was noted that creams containing Blank-NLCs (NLC's cream) and Vit E-NLCs (Vit E-cream) NLC's were protectively effective. On hair exposed to heat and UV radiation, both NLC creams have offered surface smoothness comparable to that of unharmed hair and the least amount of color loss as compared to other treatments. It was understood that, when compared to Blank-NLCs, the cream containing antioxidant Vit-E showed reduced protein loss and a greater photoprotective action against hair discolouration, but it had no additional effect for heat protection [51].

We can see from this information and the research that has been done that the damage to the hair can be reversed with the right kind of treatment. In order to restore damaged hair strands, proper maintenance and the use of products with suitable ingredients are essential considerations. The therapies of the future are emerging as a beacon of hope for the cosmetic industry as well as in every other industry thanks to science's unrelenting advancement.

6. Patch Test for Toxicity, Allergic Effect, and Hyperoxidative Hair Colors

Hair colors are primarily divided into two categories: oxidative and non-oxidative colors. The group of non-oxidative hair dyes includes temporary and semi-permanent colors that do not remain in the hair permanently and create dye accumulation; the dye does not penetrate the cortex and instead just interacts with the hair cuticles. Deep penetration of the hair shaft by chemicals is necessary to achieve permanent color. The cuticles must be opened for this.

Ammonia and other alkaline solutions are frequently employed for this purpose. In addition to opening the hair fibers, this alkaline solution makes the hair expand, which facilitates easier colour absorption. The next step is to mix these monomers with binding compounds and polymerize them using an oxidizing agent (like hydrogen peroxide). Due to this, colorful complexes are created that are too big to spread back out from the hair shaft [12].

Recently, studies on the chemistry and types of hair dyes have been conducted [52]. These are the several types of hair dyes: (Fig 11).

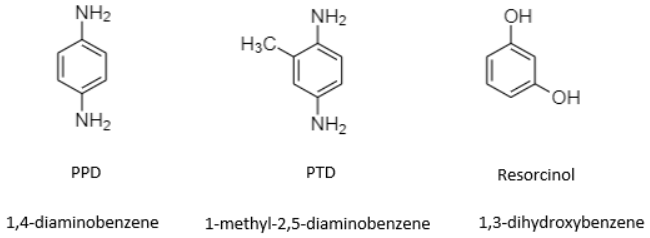


Figure 11. Paraphenylenediamine (PPD), paratoluendiamine (PTD), and resorcinol (binder): primary oxidative hair dye intermediates [52].

Similar compounds are still present in the majority of hair dyes today, despite the fact that their compositions have changed since the day they were originally produced. Depending on the type of metal and its concentration, or the extent of its harmful effects, it can cause a variety of health issues when consumed, including skin damage, allergic reactions, disorders of the tissue or organs, and occasionally even death [53].

The majority of the time, permanent hair dyes are linked to health hazards. These products often include binding molecules, oxidizing agents, primary intermediates, such as p-phenylenediamine (PPD), alkalizing agents, such as ammonia, and oxidizing agents, such as hydrogen peroxide (e.g. resorcinol). The other chemicals in the product stimulate a chemical reaction inside the hair shaft to generate color molecules, and the alkalizing agent aids in the product's penetration of the hair shaft's outer layer [54].

A common issue for hair colorists worldwide is allergic contact dermatitis (ACD), which is brought on by hair dyes [55, 56].

7. Acute Toxicity of PPD - Contact Allergy and Dermatitis

When a person is exposed to the same allergen again after being sensitized to it, they develop allergic contact dermatitis (ACD). T-cell (cellular-type) immunity mediates the hypersensitive reaction, which is of the delayed kind. Even while individual immune responses and clinical manifestations differ depending on the allergen, it typically worsens until itchy, eczematous-like sores develop at the point of contact [57].

PPD products like permanent hair dye, black henna, and permanent eyelashes have been linked to contact allergy and eczema. It encompasses symptoms including erythema multiforme, hyperpigmentation, lichenification, blepharoconjunctivitis, systemic contact allergy, and dermatitis syndromes [56, 58].

A colorless substance called p-phenylenediamine is used mostly in black hair dyes and is oxidizable by hydrogen peroxide. When PPD is administered to the skin, complications might range from contact dermatitis to allergic responses [59, 60]. PPD is permitted at hair dye quantities of up to 0.5% by the European Parliament and the Union of the European Commission. The harmful effects become more pronounced when this concentration is exceeded [61].

A hypersensitive response to chemicals that come into touch with the skin is known as allergic contact dermatitis (ACD). To find the allergens that induce ACD, a patch test is utilized [62].

7.1. Patch Test

Patch testing; sometimes known as allergic contact dermatitis; is a skin examination performed to identify eczema (contact eczema). Allergic eczema that appears 48–96 hours after frequent contact with an allergic person is known as allergic contact dermatitis (ACD), a type-IV hypersensitivity reaction to chemicals in touch with the skin [62].

A diagnostic technique for identifying allergies that can cause disease is patch testing. Patch testing is a crucial and secure technique for identifying allergic contact eczema [63].

7.1.1 Application

On the back, allergens formulated in pure vaseline are applied. The upper portion of the back is covered with tape. An alcohol wipe is used to clean the back's skin if it is oily or sweaty. The patient should be advised not to bathe, perspire, or perform any physical activity that would cause the bands to separate because the attached test will stay on the back for 48 hours. One week prior to the test, creams applied to the back should be stopped, and anti-allergic or cortisone-containing medications should not be taken due to their potential to stifle the reaction. A doctor should record the bands' placements with a pencil after 48 hours and do an evaluation after at least 30 minutes. A doctor should reevaluate the test site at 72 and 96 hours due to late-reactive allergens (Table 7) [63].

Table 7. Patch Test Interpretation and Evaluation. Adapted from ref. [63]

	Evaluation	**Clinical Comment**
IR	Irritation	Contact Allergies
+++	Vesiculobullous and/And Ulcerative Reaction	Allergic Contact Dermatitis (Definite)
++	Vesiculobullous, Erythema and Infiltration	Allergic Contact Dermatitis
+	Edema, Erythema and Infiltration	Contact Allergies
0	No Reaction	No Contact Allergies
+/-	Mild Erythema	Suspicious Reaction

The last 48 hours are when irritant effects are most notable. Lesions that are clearly outlined and barely infiltrating are present here. It has been documented that erythematous and follicular irritant reactions might manifest as papules, pustules, bullae, and necrosis. Another common observation is the emergence of wrinkled skin that is restricted to the region of the applied substance. After the test strips were removed from the skin, the majority of irritating reactions quickly subsided [64].

8. Conclusion

We have tracked changes in the past few decades about the interactions between the physical and chemical characteristics of the structure of the hair and the mechanisms underlying the hair-coloring process. The development of existing dye precursors and new technologies is aided by extensive knowledge of the makeup of the hair fiber, particularly the chemical composition of its outer layer and the factors influencing the dye diffusion pathways and process kinetics.

The oxidative treatment will continue to work best in an optimal form due to widespread technological advancements that do not appear to slow down in the near future, a considerable number of novel dye precursors patented over the years, and some examples of commercial success. Additionally, addressing worries about toxicological problems linked to commercial permanent hair-dying technology based on the oxidative process, originating from Hofmann's discovery about 150 years ago, has received a lot of attention [34].

This issue was addressed by Im et al. (2017) using a mordant staining-type method in which iron (II) sulfate and "synthetic melanin" (i.e. polydopamine (PDA)) oxidized via oxidative self-coupling of dopamine (DA) are applied combined [65]. According to Gao et al. (2019), by covering the hair with polydopamine, oxidative self-coupling of dopamine enhanced by copper (II) sulfate and peroxide provided quick and effective coloring [66]. According to Battistella et al. (2020), in situ polymerization and deposition of polydopamine nanoparticles on the surface of the hair can produce permanent coloration [67].

One of the key priorities in the beauty and care sector is ensuring the safety of hair dyes and all cosmetic products. Consumers should feel assured of the safety of today's hair dye formulas based on the considerable safety data that is already accessible. To give customers, clients, and hairdressers a higher degree of confidence and certainty, hair dye makers are also continuing their studies into safety. It is crucial to inform consumers and hairdressers about the potential hazards of hair dyes, increase collaboration with experts (dermatologists), and reduce risk in order to fulfill the consistently high consumer demand for hair coloring products. There are already controls in place to safeguard vulnerable people [68].

9. New Applications

Oxidative coloring first rose to commercial popularity over a century ago, and it still reigns supreme in the professional and retail hair dye industries today. The popularity of oxidative hair dying is a result of its quick and inexpensive means of achieving long-lasting coloration [69].

Additionally, the entry of new dye precursors will likely be restricted to those for which there is unambiguous proof of a commercial return on investment due to the costs associated with the licensing procedure of new formulation ingredients as demanded by social norms and legislation. Systems that support natural, biotechnological, or semi-synthetic hair repigmentation may benefit from the fast-evolving genetics and growing understanding of the molecular basis of hair pigmentation [34].

Synthetic methods that are influenced by biology are gaining popularity [70]. Important research has been done in this regard on polydopamine (PDA)-based techniques for coloring human hair [66].

According to research by Battistella et al. (2020), optimal conditions for PDA coating can be combined with the oxidation of dopamine utilizing oxygen in the air to produce a protective and colored layer in the hair coating [70].

Sun et al. (2021) were able to collect polydopamine groups on the hair surface through metal chelation and hydrogen bond adsorption by oxidizing dopamine to polydopamine, an imitation of human eumelanin [71].

Gao et al. (2019) obtained the black color faster (within 5 minutes) than was feasible with commercial items using PDA coatings made from copper ions and hydrogen peroxide [66].

The findings demonstrate the potential of these innovative, simple, and efficient techniques for biomaterial-based hair cosmetics, and more crucially, they show that built systems behave similarly to natural materials [67].

The scientific community has become interested in natural dyes for use in a number of conventional and recently found application disciplines since they are typically believed to be non-toxic, affordable, renewable, and sustainable resources with minimum environmental impact [72]. Although the efficient use of colorants generated from natural sources has seen substantial technological advancement in recent years, there are still some technical obstacles that must be removed in all parts of natural dye application before these technologies can be put to use. Due to the great range of natural dye sources, it is currently difficult to develop extraction and application procedures and construct cost-effective processes [73].

Nanotechnology researchers have created natural and non-harmful hair surface engineering techniques to create hair coloring formulations that no longer rely on chemical reactions but rather only on physical forces acting at a very close distance thanks to recently published scientific papers and patents [73]. Long-lasting hair dyes using carbon nanotubes, which have volumizing and damage-prevention benefits, are among these works. The hair dye business will undoubtedly continue to pay attention to this amazing advancement in nanotechnology [74].

Considering the subject heading of the European Green Deal, which is the new growth strategy of the EU, which includes the main objectives such as ending the dependence on the use of resources for economic growth, "Innovative, Systemic Zero Pollution Solutions Against the Negative Effects of Persistent and Mobile Chemicals on Human Health, Environment and Nature" [75], the most important result is undoubtedly the following: *"The cost is not the only important issue, it is very important to apply alternative test methods for safety and toxicity, and also to be environmentally friendly".*

Ethical Statements

The author declares that this document does not require an ethics committee approval or any special permission. Our study does not cause any harm to the environment.

Conflict of interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

A. Y: writing-review and editing
B.D: writing-review and editing
B.A: writing-review and editing
B.N.E: writing-review and editing
Ç.Ö: writing-review and editing
G.E.A: writing-review and editing
M.M: writing-review and editing
M.K: writing-review and editing
N.A: writing-review and editing
S.E: writing-review and editing
All authors have read, reviewed the results and agreed to the final published version of the manuscript.

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