

MECHANISTIC FACTS AND REVERSAL OPTIONS OF IMMATURE HAIRGRAYING

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ABSTRACT

Hair serves as a great esthetic tool and means of nonverbal communication. Hair length, color and style can significantly alter the physical appearance and self-perception of a person and thus alter his/her body image. Graying of hair is usually a manifestation of the ageing process. Premature Hair Graying (PHG) is defined as graying of hair before the age of 20 years in Whites, 25 years in Asians and 30 years in Africans. Knowledge on premature hair graying (PHG) is coupled with major concept of partial or complete loss of melanogenesis that leads to the production of pheomelanin as well as eumelanin.

KEYWORDS: Premature Hair Graying, melanogenesis, pheomelanin, tyrosinase related protein 2.

INTRODUCTION

Youngness and general well-being are indicated by healthy hair. Hair is a fantastic visual aid and nonverbal communication system. Among primates, humans are exceptional in that our scalp hair is extremely dense, long, and highly pigmented. The physical appearance and self-perception of an individual can be greatly influenced by their hair length, color, and style, which in turn can change that person's body image.

The aging process is typically indicated by graying hair. Depending on race, the typical age at which hair starts to gray is 34 to 44 years old; by the time they are 50 years old, 50% of men and women are thought to be gray. Graying of the hair before the ages of twenty for White people, twenty-five for Asian people, and thirty for African people is known as premature hair graying, or PHG.^[1] While most Asians start to go gray in their late 30s, North Indians start to go gray earlier than their South Indian counterparts. Given the essential role that hair plays in social communication, premature graying of the hair has a detrimental impact on a person's look, self-esteem, and socio-cultural acceptance. It is frequently seen as an indication of aging and declining health.

Knowledge on premature hair graying (PHG) is coupled with major concept of partial or complete loss of melanogenesis that leads to the production of pheomelanin as well as eumelanin. The studies conducted in this league identify multiple factors acting alone or in combination leading to PHG.^[2] These factors include environmental factors

such as physical [ultraviolet (UV) rays, smoking, lifestyle, stress, nutrition]; chemical (cosmetics and hair care products); and biological (autoimmune diseases). Some of the worth mentioning facts include the varied pattern of PHG over the scalp among men and women, sensitivity to environmental stress, roughness of hair, etc. All these differences are associated with the increased production of reactive oxygen species (ROS) and decreased Bcl2 and TRP2 (tyrosinase related protein 2) gene expression.^[3-5] However, the baseline phenomenon is poorly understood leading to the problem in extent of treatment available. The temporary approaches currently available in market are like temporary/permanent dyes, cosmetic products, dietary, and herbal components; however, none of the method have existing evidence and assurance for permanent cure or even reversal of PHG. Thus, generation of a safe, effective, easy to use product with minimum side effects is the need of the situation.

Melanocytes are present in two compartments of the hair follicle: in the anagen hair bulb, where they transfer pigment to cells that will form the hair cortex, and in the outer root sheath (ORS).

However, recent studies suggest that gray hair follicles lack melanocytes in the hair bulb while retaining those in the ORS. Under stimulation from radiation or cytokines, the ORS melanocytes may be stimulated to migrate and differentiate to naturally repigmented graying hair follicles.^[18]

The process of hair pigmentation includes the melanogenic activity of follicular melanocytes, the transfer of melanin granules into keratinocytes and the formation of pigmented hair shafts. The two chief melanins present in human hair are the "eumelanins" (brown/black pigment) and "pheomelanin" (red/yellow pigment). Melanin is synthesized through an enzymatic reaction catalyzed by tyrosinase (TYR), dihydroxyphenylalanine (DOPA) chrome tautomerase [DCT], and tyrosinase related protein1 (TRP1) on the substrate tyrosine to produce the final product. The membrane glycoprotein TYR catalyzes the conversion of tyrosine to DOPA which consequently oxidizes DOPA to form DOPA quinone.^[20]

Diversity of hair color arises mostly from the quantity and ratio of the brown-black eumelanin and the yellow-red pheomelanin. In gray hair, the pigmentary unit becomes fuzzy, the melanocytes become few and rounded. During anagen, there is a marked reduction in the number of melanocytes in the hair follicles through autophagolysosomal degeneration leading to pigment loss. This is thought to be central in the pathogenesis of graying.

Defective melanosomal transfer to cortical keratinocytes or melanin incontinence due to melanocyte degeneration contribute to graying. Degenerative changes within the hair follicle are associated with an increase in dendritic cells in the hair follicle.^[19]

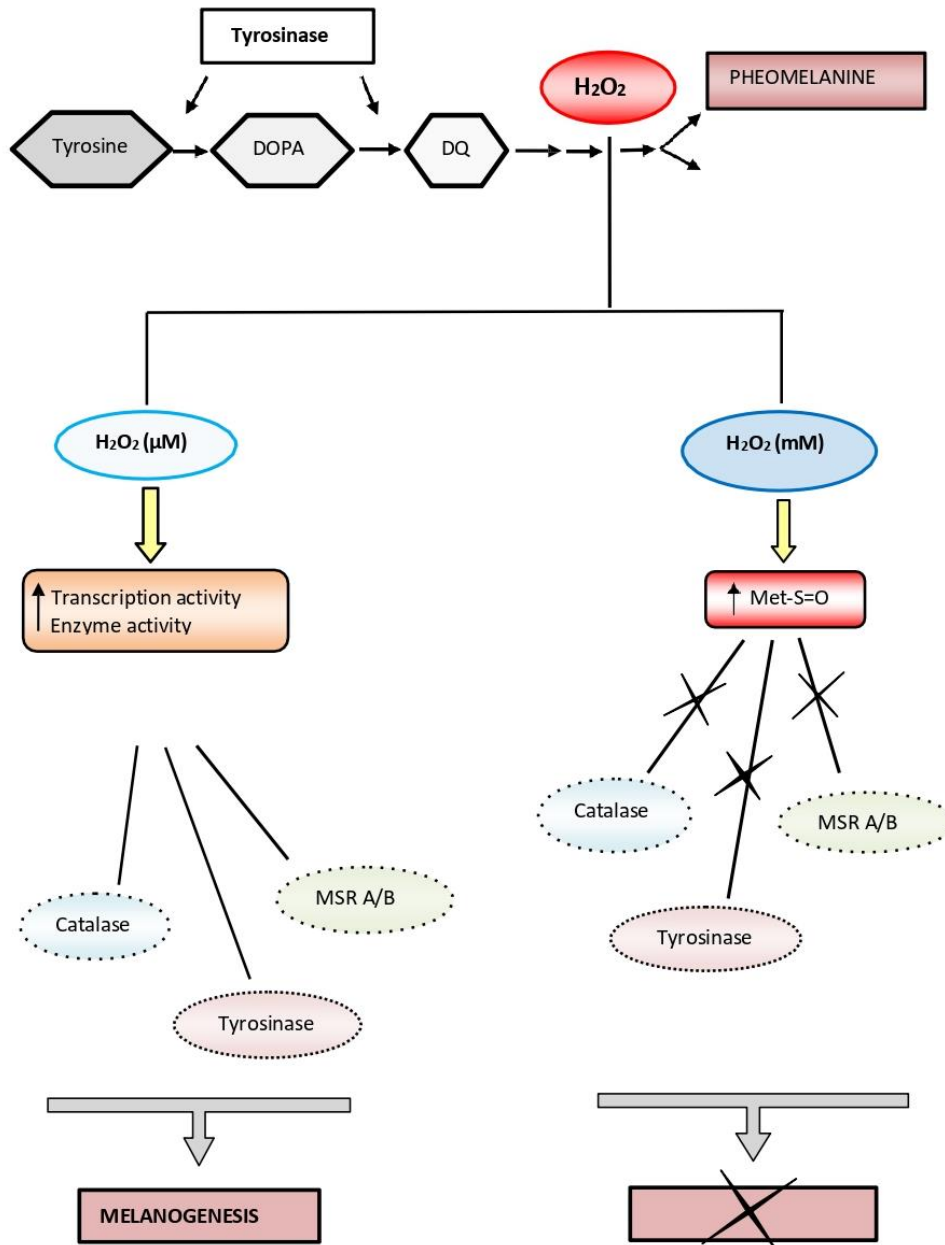
PATHOGENESIS & RISK FACTORS PATHOGENESIS OF PHG

Hair graying or loss of pigment production within hair shafts is the evident sign of aging. Multiple mechanisms acting at diverse levels and follicular locations contribute to hair graying varying from loss of melanocyte stem cells, unbalanced differentiation, defects of migration, apoptosis of melanocytes, and machinery malfunction or loss.^[20,29]

Reactive oxygen species (ROS), the highly reactive molecules of unpaired electrons, are efficient to bind to different entities present in a cell, that is, lipids, proteins, and DNA. During active growth phase, i.e., anagen phase there is active melanogenesis in the hair follicle. This involves hydroxylation of tyrosine and oxidation of dihydroxyphenylalanine to melanin causing enormous accumulative oxidative stress. Generation of H₂O₂ has been attributed to its intrinsic release

from the melanogenesis pathway. → Ultimately yielding apoptosis of hair follicle melanocytes (HFMs) and DNA damage. Decline of melanogenesis is associated with loss of tyrosinase activity which affects in turn the rate-limiting step in melanogenesis.

The mechanism of protection is dependent on reduction and neutralization of free radicals. However, with the increasing age, there is linear decrease in the endogenous defense mechanisms and this imbalance results in harm to cellular structures because of the system's disability to detoxify the reactive intermediates and thus presumably resulting in the aging phenotype.^[30]



Under normal conditions, whenever there is augmentation of ROS levels, the multitude of endogenous defense mechanisms such as anti-oxidative enzymes [glutathione peroxidase (GPx), catalase, SOD] and nonenzymatic molecules (ubiquinone, vitamin C, vitamin E) also increases. Theories for the gradual loss of pigmentation include exhaustion of enzymes involved in melanogenesis, impaired DNA repair, and loss of telomerase, antioxidant mechanisms, and

antiapoptotic signals including the reduction in number of stem cell factor. Vacuolation in hair bulb melanocytes has been ascribed to oxidative stress.^[30,31]

Recent studies have focused on the imperative role of ROS especially in process of PHG at various stages such as melanogenesis, hair pigmentation, melanocyte transfer, stem cell maintenance, and gene expression (BCL-2, TRP1, TRP2) in humans.^[19,20]

RISK FACTORS

1. Water Quality and Pollution

A polluted environment is one of the biggest reasons causes grey hair at young age. The toxin and pollutants in the environment produce free radicals that damage the melanin increasing the rate of ageing of your hair. Apart from deficiency of important nutrients like melanin, the quality of water that we use to wash our hair or drink also badly affects the hair quality and growth. High chlorine or iron containing water also causes early grey hair.^[22]

2. Sedentary lifestyle

The factors like daily routine, personal, familial, social, professional environment of the individual, and relationship with others, if in excess, will certainly have distress and can negatively influence growth and nutrition of the cells leading to their premature exhaustion.^[20]

3. Stressful and Anxious Life

Yes, its scientifically proven, stress and anxiety has major role in graying your hair before right age. If you are anxious and live with a certain kind of tension all the time, it will accelerate your genetic density that will also affect hair color.^[22]

4. Smoking and Alcohol Intake

The mechanism for PHG via smoking is also linked to generation of huge amounts of ROS, thus leading to premature damage to hair follicles.^[24]

Actually, smoking constricts blood vessels, which reduces the flow of blood into hair follicles causing the hair loss. Moreover, toxins in cigarettes can damage parts of your body including your hair follicles, causing graying of hair.^[22]

5. Chemical hair dyes and hair products

Chemical hair dyes and hair products, even shampoos, can contribute to premature hair graying. Many of these products contain harmful ingredients that decrease melanin.

Hair colorants containing hydrogen peroxide as the oxidant.^[25] The hydrogen peroxide has a dual function of oxidizing and decolorizing melanin in hair which lightens the underlying hair color and oxidizing the dye precursors to form synthetic color. The damage species formed during hair coloring with these products includes the perhydroxyl anion (HOO-) and Reactive oxygen species (ROS) such as hydroxyl radicals (HO).^[26]

Excessive use of products that bleach hair, Toxins and chemicals used in hair styling products will also eventually cause it to turn white and hair dyes can also damage the natural colour of hair and onset early graying. Premature graying also occurs due to use of harsh chemicals in artificial straightening of hair in salons.

Ultraviolet radiation (UV) is a key external initiator for the oxidative stress in skin and hairs and is one of the main reasons associated with PHG. The UVA has the ability to induce biochemical damage which causes color changes in hair whereas UVB induces protein loss which is responsible for external morphological deterioration to the cuticle of hair shafts. The mode of action of UV is linked to the increased production of ROS which further brings out mitochondrial as well as cytosolic DNA damage. The impact of this photo degradation also complies with the cysteine (rich in hair cuticle) which is more vulnerable at a wavelength of 254-350 nm.^[27]

6. Genetic or Parental Grayed Early

If your parents or grandparents experienced the early graying of hair, then there is huge chances you will also face the same situation in your life. Actually, our body also grows and shows similar symptoms that it gains from our parents or grandparents genes. Similarly, graying of hair in early age is another indications shows you got such deficiencies from your progenitor.^[22]

7. Lack of Nutrition like Vitamin B-12

Vitamin B12 and iron have been revealed to facilitate stabilization of the early anagen phase of hair follicle and pigmentation.^[28] Vitamin B-12 needs for healthy red blood cells that carry oxygen to cells in your body and its deficiency weaken hair cells affects melanin production.^[22] Copper and iron deficiency also can cause graying of hair.^[19] A newer study of young Indian population reported lesser serum levels of ferritin, calcium, and Vitamin D3 levels in subjects prone to PGH.^[19]

8. Hormonal Imbalance or Medical Condition

Hormonal changes in the body also have major impact on pigmentation of your hair. Decreased thyroid hormones cause premature graying, alopecia, and changes in hair morphology.^[19]

Actually due to hormonal Imbalance the hair color loses its texture, density, and color with the time being which usually starts after the age of 30. Similarly, owing to certain medical conditions, loss of pigment in your hair starts.^[22]

- Insufficient neuroendocrine stimulation of hair follicle melanogenesis by locally synthesized agents, such as adrenocorticotrophic hormone, α -MSH and β -endorphin, has also been hypothesized as a possible mechanism for hair graying.^[19]
- Progeroid syndromes with defective repair of DNA and Vitiligo are more sensitive to oxidative stress. ROS damage to melanocytes leads to ectopic differentiation of stem cells and apoptosis of differentiated melanocytes.^[19]
- Certain chemotherapeutic drugs and antimalarials are thought to inhibit the receptor tyrosine kinase c-kit found in melanocytes reducing melanogenesis. Chloroquine preferentially reduces pheomelanin production by unknown mechanism.^[19]
- Administration of certain drugs including chloroquine, mephenesin, phenylthiourea, triparanol, fluorobutyrophenone, dixyrazine, the epidermal growth factor receptor inhibitor imatinib and interferon - alpha, and use of certain chemicals (medicated oils) and topically applied agents like dithranol, chrysarobin, resorcin, prostaglandin F 2 alpha (PGF 2 alpha) analogs.^[18]

NEWER THERAPEUTIC APPROACHES AYURVEDIC PERSPECTIVE ON PGH

According to traditional Ayurveda, the three doshas (bodily forces) - Vata, Pitta, and Kapha regulate your body activity. Based upon nature, geography, environment and genetics, each individual has a unique mixture of Tridoshas,

whose balance is called as the innate 'Prakriti' of that individual. Any imbalance occurring in these three dosha levels results in diseases.

In ayurveda the hair (kesha or roma) is the waste (mala) of Asthi Dhatu. Hence, anything detrimental to asthi dhatu will be harmful to the hair. When the skin and the hair are exposed to the wind, it causes aggravation of vata dosha, resulting in dryness. Depletion of Asthi dhatu and sweat causes hair loss. Health of hair depends upon the health of the skin and the bones. The oleation of hair is received from kapha dosha, softness from pitta dosha and black colour due to vata dosha. The nourishment of hair depends entirely upon the rasadhatu. Derangement in rasa dhatu causes hair fall and premature graying. As a whole, the health of hair depends upon rasa and asthi dhatus and all the three doshas. Optimum majja and medo dhatus keep the hair oily.^[32]

In ayurvedic system of medicine Premature graying of hair is described as "Akala Palitya" means graying of hairs before 30 years of age (Tarunastage), which is categorized under Kshudra Rogas, caused by excess of Ushnaguna of pitta.^[33]

According to Ayurveda, greying hair is a pure Pitta disorder that occurs due to the vitiation of Pitta dosha (biohumor related to fire and water). This is why people of the Pitta constitution tend to start graying earlier than others. Excessive Pitta in the sebaceous glands which reside at the hair roots, called folliculitis can also result in hair loss and graying prematurely.^[34]

"The Bhrajaka pitta, a sub-type of Pitta, is responsible for the color and complexion of your skin and hair. It is attributed to melanocytes that produce melanin pigment, which is responsible for the natural color of your hair. Imbalance in Bhrajaka Pitta causes insufficient melanin production, which in turn results in premature greying".^[35]

But apart from being a primarily Pitta problem, the sage Vagbhata classified palitya according to the doshic dominancy.

Vata dosha: Hairs develop split ends; brittle, dry and rough in texture; color appears shimmery and transparent like water.

Pittadosha: Scalp shows signs of burning; hairs have a yellowish tinge Kapha dosha: Hairs are thick, long and exceptionally white in color.^[34]

Generally, the production of melanin in the follicles decreases with growing age and the hair starts turning grey from mid-thirties (Kala Janya Palitya). In some cases, the early occurrence of grey hair is caused by the genetics of an individual. In such cases, it is not possible to reverse the process of hair greying.^[35]

However, when your melanin production is ceased at a younger age by interim Pitta aggravation in the body, you can absolutely reverse your premature grey hair through natural Ayurvedic techniques and lifestyle changes that pacify excess Pitta and bring your body into a balanced state.^[35]

1.1 Causes of Palitya

There are four main reasons. First one is dietary (Aharaja), second one is life style (viharaja), third one is psychological (mansik) & fourth one is other reason or unknown (adibalpravritta).^[33]

Tab 7.1: Causes of Palitya.

Sr. No	Etiological Factors	
1.	Aharaja(dietary)	Excess intake of pungent (katu), sour (amla), salt (lavana), pungent (tikshna), hot (ushna), light (laghu), mustard (sarshapa), linseed (atasi), green vegetable (harita shaka), fish(matsya), goat (aja), sheep (avika), curd (dadhi), takra (butter milk), kurchika, water of curd (mastu), suravikara (type of sour alcohol) and amla phala (sour fruits), etc. Deficiency of Iron, Copper, vitamin B12, Calcium & VitaminD3. ^[36]
2.	Viharaja (Environmental and life style)	Over indulgence in physical exercise & over exertion, awakening during night (raatrijagarana), excessive exposure to sunlight (atiatapasevan), use of smoking & dust particle (atirajo and dhumasevan), intake of vitiated air (dushitvayusevan), excess exercise (ativyayama) and fast (upvasa) may cause the palitya. ^[33]
3.	Manasika (Psychological)	Certain psychological factors like anger (Krodha), grief (shoka), afraid (bhaya) and mental stress (maansika shrama) vitiate the pitta dosha causes palitya & other paittik diseases. ^[33]
4.	Other reason or Unknown (adibalapravrta)	May occur alone as an autosomal dominant condition or in association with various autoimmune or premature aging syndromes. ^[33]

1.2 Roopa (Lakshanas): Palitya Lakshan

- Gradual change in colour of hair from black to white.
- Palitya due to vitiated Vata dominance - hair appear blackish grey and rough.
- Palitya due to vitiated Kapha dominance - hair appear white and shining.
- Due to Pitta - hair has yellowish tinge and burning sensation of scalp.^[37]

1.3 Samprapti of Palitya^[33]

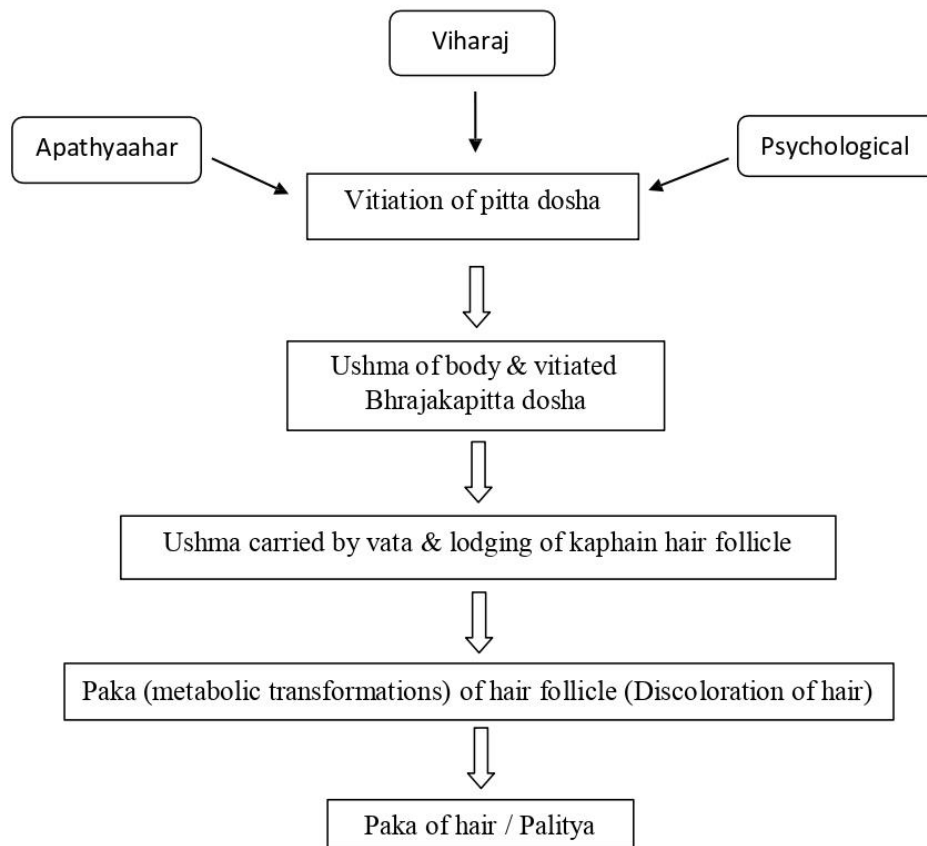


Fig. 6.1: Samprapti (Pathogenesis) of Palitya.

1.4 Herbs used in PGH^[34]

1. Bhringraj

This herb is also called Kesharaj or 'King of Hair' and is one of the best natural remedies for grey hair treatment. Dry some fresh leaves. Boil some dried leaves of this herb in coconut oil and rest it rest for anywhere between a week to 10 days. Once ready, filter the oil and bottle in a dark-colored bottle. Bhringaraj powder can be added to hair packs to retain color, reduce hair loss and promote hair growth.^[34,50]

2. Amla

Known for its high Vitamin C content, amla or Indian gooseberry is an excellent Ayurvedic treatment for white hair. One can make potent hair oil by boiling dried pieces of amla and curry leaves in coconut oil. Cool and bottle this oil in an amber-colored glass bottle. Use this as massage oil twice weekly. One can also use amla to prevent premature graying of hairs by drinking 30ml of fresh amla juice or eating the fruit daily. Amla powder is an excellent addition to hair masks. Make your own herbal shampoo by mixing equal parts of reetha (soapnut), amla and shikakai (acacia concinna). Use this to wash your hair instead of a shampoo loaded with chemicals.

3. Henna

Henna is the best treatment for grey hair because of its coloring and conditioning properties. Soak henna in an iron pot overnight and make a deep conditioning hair mask by combining eggs, curd and other herbs for gray hair.

4. Sesame

Usually used as oil for head massage, sesame or til is an excellent way to reduce gray hair naturally. The seeds can be consumed after dry roasting them. White sesame seeds have higher iron content than the black variety, which contain more calcium.

5. Onion

Pyaz or onion can answer how to stop gray hair with its rich sulfur content. Used while cooking, onion is a powerful home treatment for hair loss and premature graying. Apply the juice of an onion to your hair and scalp to arrest gray hair or mix it in with an all-natural oil of your choice.

6. Brahmi

One of the best herbs for graying hair if your hair turning gray due to stress. This brain and nerve tonic is used in Ayurveda as a tranquilizer. Massage your hair and scalp with brahmi oil to keep Pitta at bay or use the powder in a cooling hair masks.

1.5 Diet approach^[34]

- External therapies will be effective only when one observes an Ayurvedic diet for gray hair. As far as possible, one should only take milk and avoid sour things like yogurt. Salt should also be avoided. Pungent, hot and spicy foods are on the no-no list.
- Adding Vitamins B9 and B12, copper, selenium and folic acid are essential ways in which can you reverse grey hair with diet.
- Stay away from refined foods such as white sugar and white flour (maida).
- Nuts and seeds make for healthy and tasty snacks that can also reverse grays.

- Foods like grains, meat and soy that are rich in protein helps in the production of melanin.

1.6 Lifestyle approach^[34]

- One should sleep well at night and go to bed by 10:00 p.m.
- They should be free from worry, anxiety and passion.
- If suffering from cold and sinusitis, prompt and careful treatment should be given.
- Hot water should never be used for washing the hair. Cool water should always be used for bathing. It helps tone the scalp and refreshes the nervous system.
- Regular massages with sesame oil, castor oil or cow butter twice a week will give your hairs a deeper color due to increased circulation.
- It is advisable to keep the hair and scalp clean by washing with a mild, natural shampoo.
- Ensure that your digestion is in top condition as is your liver as poor digestion and a sluggish liver can make your hair go gray.

1.7 Treatment protocol of Palitya^[36]

Table 6.2: Treatment protocol of Palitya.

Sr. No	Treatment	Procedure
1	Sodhana (Purification)	<ul style="list-style-type: none"> • Vamana (medicated vomiting) • Virechana (medicated purgation) • Nasya karma of elimination type (nasal medication) • Raktamokshana (bloodletting)
2	Samana (Palliative)	<ul style="list-style-type: none"> • Shiro dhara (pouring oil on head) with Bhringraj taila, Neeli taila, etc. • Shiro pichu (cloth dipped in oil kept on head) with above said oils. • Shiro basti (oil is kept on head with an apparatus) with above said oils. • Shiro lepa (application of medicated paste overhead)
3	Rasayana (Rejuvenation)	<ul style="list-style-type: none"> • Shirobhyanga (oil massage to head) as a daily routine prevents premature graying of hair. • Internal usages of medicaments like, Bhrungarajadi rasayana, Siddhamakaradhawa, Vasantakusumakara, Naradiya lakshmvilas rasa, Narasimha Rasayana, etc.
4	Preventive	<ul style="list-style-type: none"> • Rasayana therapy with above said formulations. • Avoiding the etiological factors. • Intake of wholesome dietetics with Pitta dosha balancing & keshya (hair nourishing) properties.

HAIR DYEING: A SOLUTION FOR PHG

The assessment of the impact of PHG on “quality of life” has highlighted “the need of medical care” as important criteria considering the group of population affected. (T)

Hair is commonly colored with synthetic dyes to enhance its appearance or as a fashion statement. History has highlighted hair coloration as one of the oldest acts of adornment, reflecting a perennial dissatisfaction with natural hair color.³⁸ (O) Dyes, the most common cosmetic product, are used by both men and women worldwide for coverage of colored or gray hair. The concept of dyes (henna) came into existence during Ancient Egyptian times; however, nowadays hair dyes are in an imperative stage of development and new discoveries are being made including synthetic dyes. One of the important observations came into light that gray hair fails to hold a temporary or permanent hair color because of

underlying substructure of hair fibers.^[39,20] (T)

1.8 Non oxidative dyes

The non-oxidative dyes are temporary or semi-permanent dyes cannot penetrate in the hair cortex and have affinity to bind to keratin/cuticle. The temporary dyes are based on high molecular weight, anionic compounds while the semi-permanent dyes have low molar mass, cationic compounds.^[18]

1.9 Oxidative dyes

The oxidative dyes included semi-permanent and permanent dyes which are based on the complex reactions happening between precursors (reaction modifiers) and oxidizing agent. The advantage of using oxidative dyes over Non-oxidative dyes is long-lasting stay (more than 20 washes) and ease of application; however, 100% coverage of the hair is not possible.^[20]

1.10 Risk factors associated with dyes

There are two types of risk factors associated with dyes.^[20]

1. Allergic reactions
2. Incidence of tumors

The effect is dependent on the dye permanence, color, number of uses, type of dye, etc. Since the dyes are applied directly on scalp skin, they can lead to allergic reactions ranging from acute to severe. Various studies have supported the above-mentioned fact. Another study conducted by same group reported para-phenylenediamine (PPD) as a potent allergen since most of the people were treated with antihistamines. A study in mouse model showed that permanent hair dyes are made up of mixture of ingredients and may also result in inflammatory reactions such as increased interleukin-1 α (IL-1 α) production resulting in irritation.^[40]

EMERGING RESEARCH WORK

Despite concerns regarding the possible toxicity of commercially available hair dyes, their usage continues to grow, and the lack of modern approaches makes this branch of cosmetics every interesting target for novel and rapidly rising nonmaterial-based approaches.

1.11 Preparation of Polydopamine Coating as a Multifunctional Hair dye

The research work reports a PDA-based hair dye that achieved PDA deposition on hair surfaces using CuSO₄/H₂O₂ as a trigger. This method afforded comparable results and faster reaction times (5 min) than those of commercial permanent hair dyes.^[41]

A rapid and effective PDA-based method for dyeing human hair was developed. PDA coatings produced by copper ions and hydrogen peroxide achieved a significant black color on human hair, similar to what is achieved with commercial hair dyes. Moreover, this treatment could be accomplished in 5 min, which is faster than what are possible with commercial products. Owing to the inherent adhesive nature of PDA, we demonstrated that this PDA-based hair dye shows strong adhesion, as it fades only slightly in 30 washes with shampoo.^[41]



The PDA coating on the hair surface enhanced its thermal insulation performance, which might increase the level of comfort.

In addition, the PDA-based hair dyes exhibited remarkable antibacterial performance, due to the involvement of copper ions, which might prevent bacterial dermatitis on scalp and enhance the quality of daily life.

This report provides a rapid, multifunctional PDA based hair dye, which is critical for developing hair dyes based on novel nanomaterials and has high practicality and potential marketability. Taken together, these results demonstrate that the PDA based hair dyes are comparable to commercial hair dyes and exhibit some superior characteristics, such as enhanced thermal insulation and antibacterial performances. We expect this PDA-based hair dyeing method to be extended to other practical applications, including energy storage materials or sensing devices.^[41]

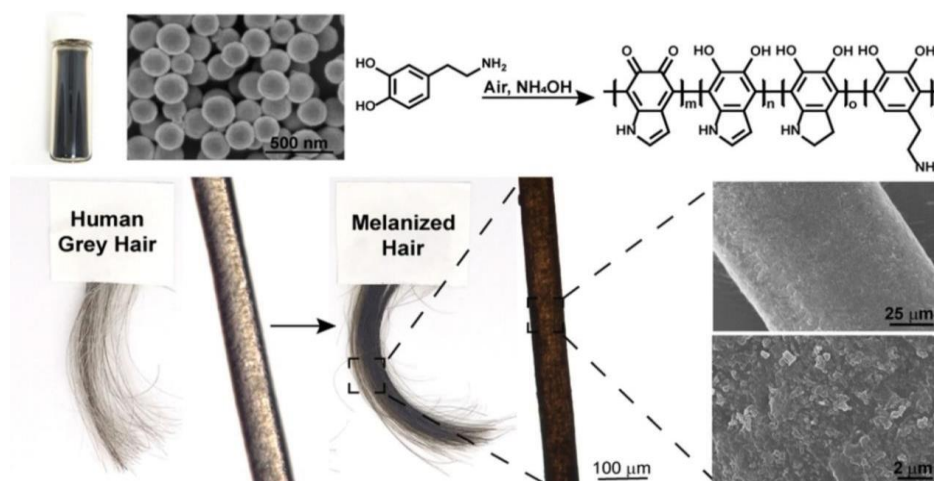
1.12 Human Hair Pigmentation via Synthetic Melanin

Human hair dyeing using synthetic melanin has been explored only very recently, and the reported protocols required high concentrations of potentially toxic heavy metals such as copper and iron as chelators, as well as very strong oxidative conditions, which may not be suitable for wide spread use in at-home or in salon applications.^[41]

The current research work supposed that the efficient deposition of synthetic melanin on human hair without the need for metal chelators or strong oxidants to generate not only black/brown, but also orange/gold colorations from blond hair. These different colors can be achieved by tuning reaction conditions such as temperature and that effective hair dyeing can be achieved using milder conditions compared to those previously employed for polydopamine coatings. Moreover, these conditions are similar or even milder than those employed in conventional hair dyeing protocols. In addition, blond and naturally red, brown, and gray hair, as well as hair previously dyed with a very bright commercial dye, was successfully colored to dark brown/black using this method.^[44]

These results suggest that this novel, inexpensive, mild and versatile approach to generate nature-inspired hair pigmentation opens new opportunities for melanin-based hair dyes, so far limited by the reaction conditions employed, and has the potential to replace classical, harsh hair dyes currently common in the cosmetic industry.^[44]

Very recently, some of the oxidation reactions have been used to deposit polydopamine on human hair. Reactions employing $\text{CuSO}_4/\text{H}_2\text{O}_2$ were particularly successful as this method catalyzes both polydopamine deposition and hair binding via metal interaction.^[41]



However, as previously anticipated, these harsh conditions limit the translation of synthetic melanin into a competitive hair dye. For biocompatibility, the auto-oxidation of dopamine in air is the most interesting and gentle approach for generating polydopamine (PDA) coatings or nanoparticles. This oxidation is spontaneous when carried out under alkaline conditions ($\text{pH} > 7.5$) using naturally ambient oxygen, making this method mild, inexpensive, and scalable.^[42,43] When added to an alkaline solution, the polymerization of DA begins immediately and is accompanied by a color change from clear and colorless, to pale brown, and finally to dark brown and black (PDA).^[44]

Self-oxidation of dopamine is the most promising approach for melanin deposition on human hair since the use of air as an oxidant makes this method not only mild, but also extremely inexpensive and scalable. Trisbuffer ($\text{pH} 8.5$) and NaOH are reagents used extensively for successful dopamine oxidation. Ammonium hydroxide is an attractive choice as this base is commonly used in current hair dyeing protocols. Although some modern hair dye formulations are ammonia free, where ammonia is generally replaced by less volatile/odorous ethanolamine and its derivatives, these alternatives can still create adverse reactions. The use of bases in conventional hair dyeing protocols is generally needed to swell the hair cuticle, thereby allowing dye penetration into the hair.^[44]

2. Future solutions

2.1. Use of herbal medicines

An *in vivo* study in mouse model using both oral administration and topical administration of *Polygonum multiflorum*, a Chinese medicine, could completely reverse the hair decolorization induced by H_2O_2 . The test group showed outstanding black hair having highest content of total melanin, MC1R, α -MSH, and TYR which are critical factors for melanin production.^[45]

2.2. Use of safe dyes

A recent study in the United States of America has come up with database that is efficient in performing “cheminformatics” using computed physicochemical properties of different hair dye substances such as hydrophobicity, number of hydrogen bond acceptors, and topography. This information can also be used to check the mutagenicity, skin sensitization future for synthesis of “allergy free dyes”.^[46]

2.3. Use of stem cell approach

Melanogenically active melanocytes express full set of melanin biosynthesis enzymes and proteins; thus, diagnosis of expression of these proteins at gene level (stem cell) can be an alternative permanent approach to treat PHG.⁴⁷ Another

approach in similar league could be exploitation of neural-crest–derived stem cells to differentiate into functional melanocytes in order to restore pigmentation of gray hair.^[48]

2.4. Use of laser

During combined treatment of a male patient for hair loss with 1,927-nm fractionated thulium laser energy, topical application of keratinocyte growth factor (KGF), and intra-perifollicular polydeoxyribonucleotide (PRDN) injections, eventual decrease in number of gray hair was observed. The mechanism behind this effect is linked to anti-oxidative effects of PRDN and KGF. However, the results of the study are confined to an individual and need to be validated on larger population.^[49]

2.5. Use of topical applications

The entities having protective effect against UVA/UVB such as methane, nanoparticles or rich in peptides, amino acids, and peaproteins can be an alternate approach; however, more work needs to be done.

2.6. Use of drugs

An incidental finding has been reported in case of drugs wherein the patients suffering from psoriasis, vitiligo, and multiple myeloma of varied age groups, that is, adult to elderly showed repigmentation of gray hairs with drugs such as cyclosporine, lenalidomide, and defibrotide. However, further studies using new generation of the drugs with less side effects, cross-reactivity, and better understanding of mode of action need to be explored which might become the choice of treatment for PHG.^[20]

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