The Science of Hair Greying: Mechanisms, Causes, and Remedies

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Abstract: As healthy hair is a sign of general well-being and youth. As we can see, the current lifestyle is strongly affecting the pigmentation of hair and causing premature hair greying. As the obvious sign of premature hair greying is loss of pigment production and deposition within. Melanogenesis, a process in which melanin is produced and the enzymes involved are tyrosinase and L-3,4-dihydrooxyphenylalanine(DOPA)-oxidase. The melanogenesis occurs in anagen phase of hair cycle while in catagen phase hair follicle detaches from blood supply and in telogen phase the hair follicle is inactive i.e. in resting phase. A recent study suggests that bulge melanocytes stem cells (MSC) are the key cell for hair greying. The main cause of the hair greying is oxidative stress in hair follicle. There are many marketed products (synthetic and herbal) for the treatment of hair greying. It was suggested to use herbal products than synthetic products as herbal products is more beneficial than synthetic products.

Keywords: Hair, Hair cycle, Hair greying, Hair follicle, Oxidative stress, DOPA, Anti-greying products.

INTRODUCTION

Hair

Hair is part of the skin system and grows down into the second layer of skin called the dermis, where it is located in a structure called the hair follicle. [1] It is a filamentous biomaterial, which grows approximately 0.3mm/day or 6 inches/year, while the scalp sheds 100 hairs/day. Parts of hair-

- Hair follicle:

The follicle is the primary and club shaped structure from which hair can grow. The follicle may be network of blood vessels that provide nutrient to feed the hair and help it grow. It offer protection from cold and UV radiation, produce sebum. Follicle divided into three segments:

1. Infundibulum- It extends from the top of hair follicle to where the sebaceous gland open.
2. Isthmus- It extends from the infundibulum to where the arrector pili muscles attaches.
3. Inferior segments- The bottom of the bulb has a clump of vascularized loose connective tissue is called dermal papilla which is derived from mesenchyme. The papilla of the hair has lots of blood vessels and helps nourish hair for it to grow.[2]

- Hair shaft (hard part that sticks out above skin)

The hair shaft is divided into three zones:

1. Cuticle- The outermost layer which is made up of many thin cells that overlap like roof shingles.
2. Cortex- The middle layer and it has cell structures with keratin bundles that are shaped like rods.
3. Medulla- The innermost layer which is disorganized and open area at fiber's center.

Hair types:

a. Straigth hair
b. Wavy hair
c. Curly hair
d. Kinky hair

Figure 1: Types of hair

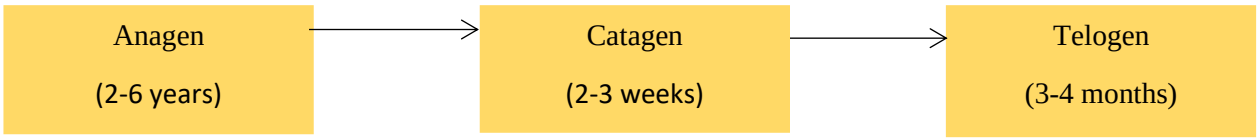
Hair growth cycle:

Hair development is a continuous cyclic process and all mature follicle go through a growth cycle consisting of growth (anagen), regression (catagen), rest(telogen),and shedding(exogen) phases. [1]

The duration of phases changes based on :

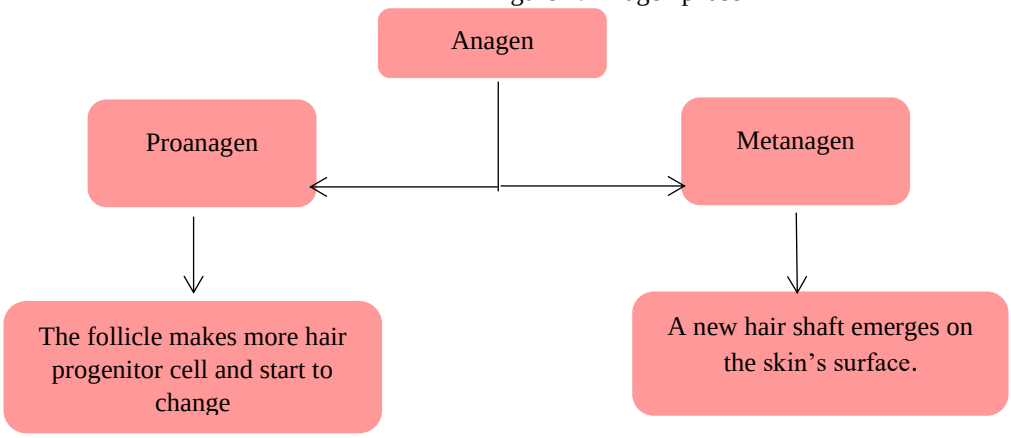
- Hair location
- Personal nutritional
- Hormonal status
- Age

This cycle can be divided into three phases:



In the anagen growth phase, the hair follicle changes shape to look like an onion and starts making hair. How long your hair grows depends on how long the anagen phase lasts, which is influenced by the cells at the base of the follicle growing and changing. Anagen typically lasts for 3-5 years, during which time follicles produce hair at a rate of around 1 cm per month.[1,3] This phase has two parts as follows:

Figure 2: Anagen phase



2. Catagen:

The catagen phase is the dynamic transition between anagen and telogen. This phase can last for two weeks. In includes apoptosis of epithelial cells in the bulb and outer root sheath (ORS), outermost epithelial layer. [4]

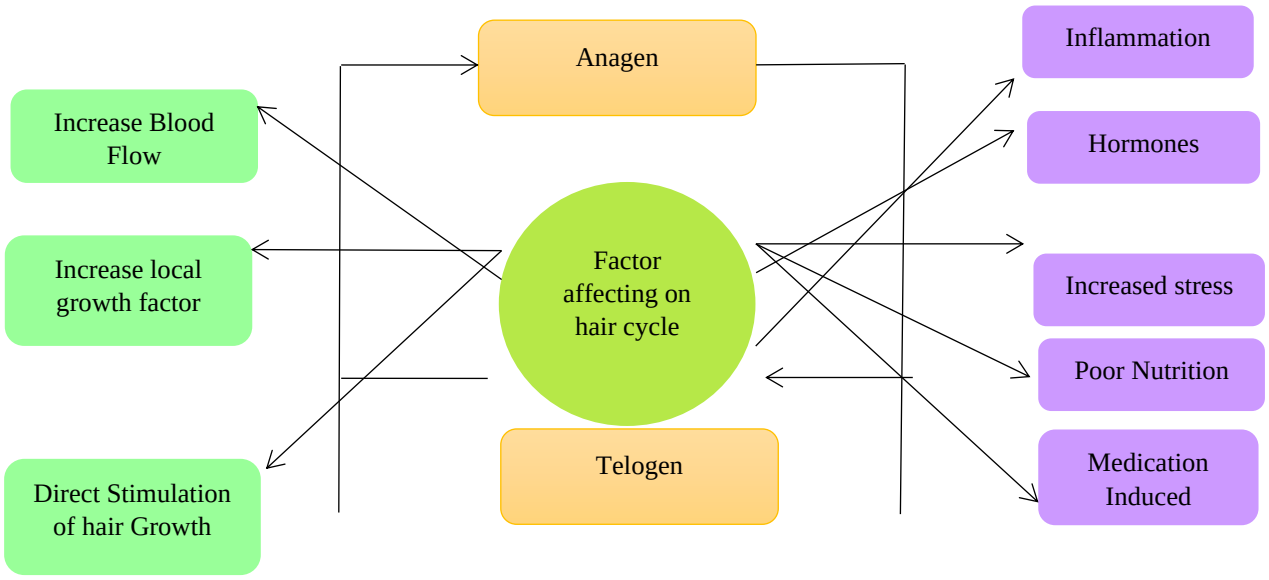
Figure 3: Catagen phase

In the catagen phase, the degeneration of hair follicles is tightly controlled, leading to many keratinocytes within the follicles beginning to undergo programmed cell death. At this point, melanin production in the hair follicles ceases, and melanin-producing cells in some follicles also start to undergo apoptosis. [5]

3. Telogen:

It is the resting phase of hair cycle in which the hair follicle is inactive and the hair shaft does not grow. In the telogen phase, the dermal papilla cells (DPCs) move to the lower section of the bulge, allowing them to directly engage with the stem cells there. These DPCs play a crucial role in activating the stem cells and starting new hair growth cycles. [1,5]

Figure 4: Telogen phase



Melanogenesis:

The production of melanin, also known as melanogenesis, is a process that it involves chemical reaction that relies on the enzyme tyrosinase and its L-3,4-dihydrooxyphenylalanine(DOPA)-oxidase activity. Melanogenesis occur in specialized lysosomal-related organelles termed melanosomes. The melanosomes with melanin are moved to the keratinocytes of the hair shaft using dendritic and filopodial processes. Research shows that melanin can either act as a scavenger against free radical or as an oxidant. Studies have shown that when there is a disruption in the balance between the anti-and pro-oxidant properties of melanin, it can lead to skin damage. Melanocytes become more vulnerable to oxidative stress, which can cause not only general damage from oxidation but also contribute to melanoma and the death of melanocyte cells.[6,7]

The human hair follicle contain two types of melanins: the black-brown pigment eumelanins mainly present in black and brown hair and the yellow and red pheomelanins in auburn and blonde hair. Pheomelanin increases the production reactive oxygen species (ROS) when exposed to ultraviolet (UV)-A and UVB rays in a lab setting. [6]

Signaling pathways in the regulation of mealanogenesis: [7]

- β-Catenin signaling pathway
- Melanocortin 1 receptor (MC1R) singnaling pathway
- Stem cell factor (SCF)/tyrosine kinase receptor(KIT) signaling system
- Endothelin recptor B (EDNRB) signaling system
- Phosphoinositide 3-kinase(PI3K) signaling pathway
- Transforming growth factor-β (TGF-β)

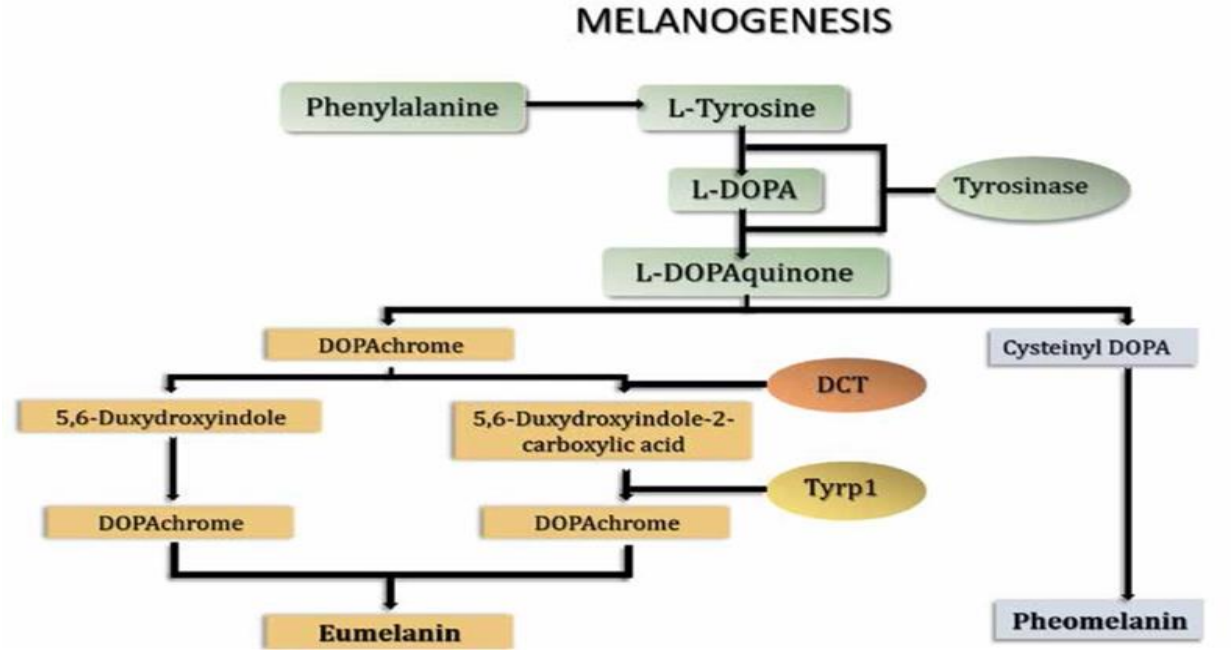
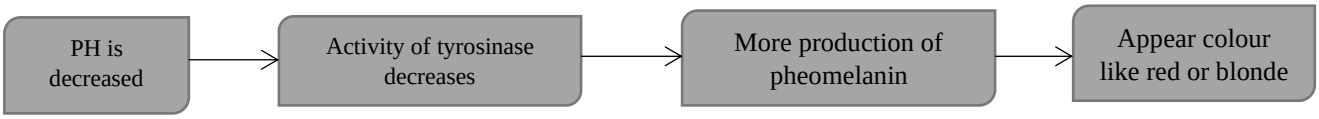


Figure 5: Pathway of melanogenesis

Hair pigmentation:

The hair pigmentation and hair cycle are inextricably linked. The hair cycle consists of phases of growth (anagen), regression(categen) and resting(telogen). In anagen III, the hair bulb melanocytes show the presence of tyrosinase and tyrosinase-related protein-1(TRP-1), along with DOPA-oxidase activity. Showing that some melanocytes in the hair follicle produce melanin. This melanocytes are active in producing enzyme like tyrosinase, TRP-1, and DOPA-oxidase. During the catagen or telogen phases, no detection is found, whereas PMEL-17 staining shows inactive melanocytes. Hair pigmentation is not present in these phases. Hair pigmentation takes place only during the growth phase of hair follicles, known as anagen, and at the beginning of the transition from anagen to catagen phase. [7] The PH and cysteine level of melanosomes affect the phenotype of hair, such as follows:



When a new hair growth cycle starts, special cells are called epithelial and melanocyte stem cells become active. They proliferate, differentiate and migrate together to produce a new hair follicle with a pigmented hair shaft.[7] It is multi-step process, several positive and negative regulators/factors regulate hair pigmentation such as: [8]

- Growth factors
- Cytokines
- Hormones
- Neuropeptides and neuro-transmitters
- Eicosanoids
- Cyclic nucleotides
- Nutrients
- Microelements
- Cation/anion

➢ Comparsion between pigmented and non-pigmented hair:[9]

Sr.No	Pigmented hair (Black)	Non-pigmented hair(White)
1.	This hair follicles are slowly grow in organ culture.	This hair follicles rapidly grow in organ culture.
2.	The growth and thickness of hair follicle are less.	The growth and thickness of hair follicle are significantly greater.
3.	In eyebrow, few short hairs are pigmented.	In eyebrow, few long hairs are non-pigmented.
4.	This hair shows presence of melanin.	This hair simply shows absence of melanin.

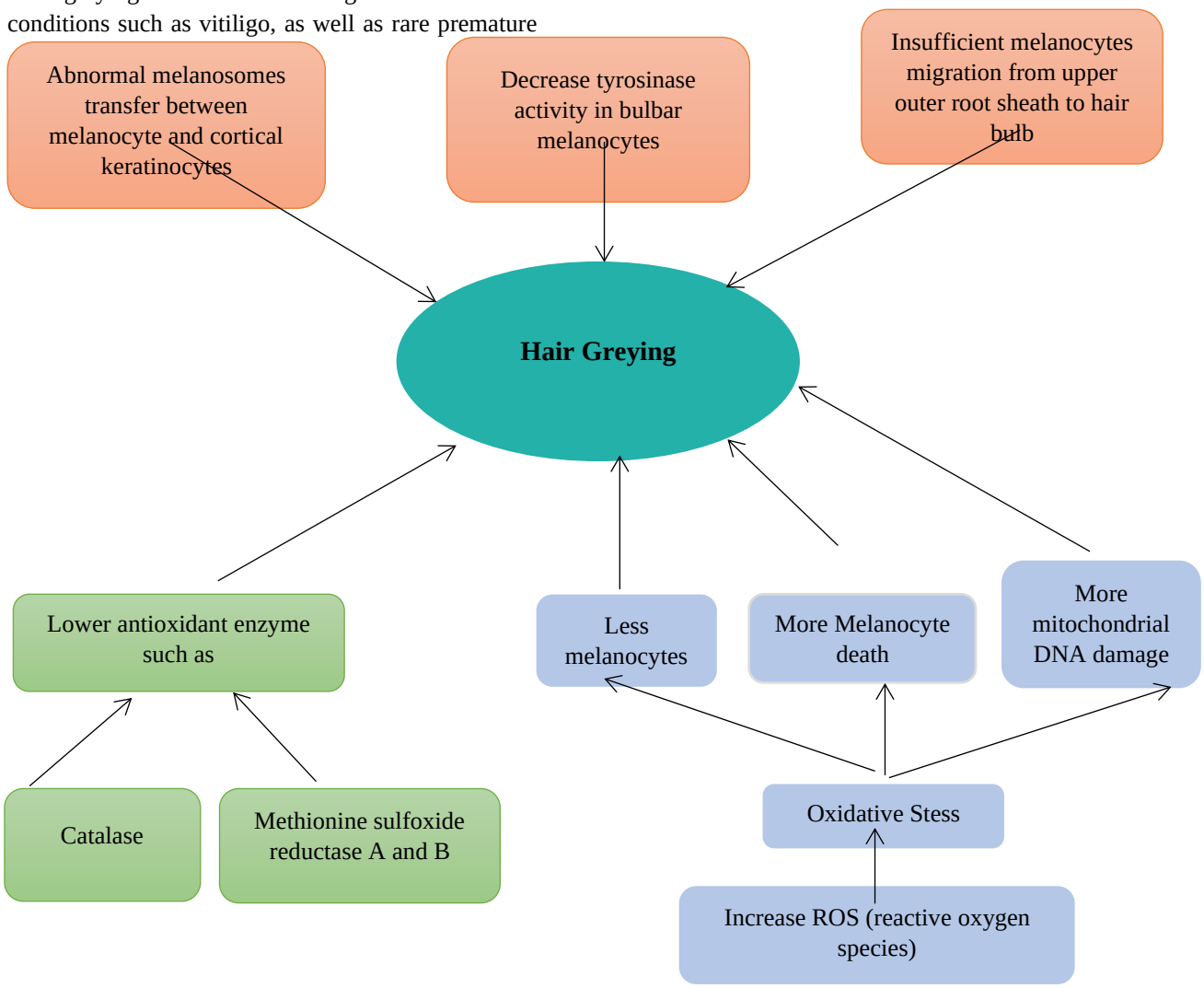
Hair Greying:

Canities, or the graying of hair, is a natural part of aging that happens to everyone, regardless of gender or ethnicity. The onset of graying can differ based on race and ethnicity. Hair graying is a natural occurrence that commonly happens as individuals grow older. According to the 50-50-50 rule, around half of the population will have roughly 50% gray hair by the age of 50. Premature graying of hair (PGH) is when hair turns gray before a person reaches 20 years old for Caucasians and before 30 years old for Blacks. White hair is primarily caused by the complete absence of melanin in the hair follicle. The term "gray hair" is used to describe a mixture of white non-pigmented hairs and pigmented hairs. [3,10,11]

Hair graying is linked to a range of autoimmune conditions such as vitiligo, as well as rare premature aging syndromes like Hutchinson-Gilford and Werner's syndrome. Additionally, it could indicate deficiencies in nutrition, particularly vitamins, and the consumption of medications like chloroquine. [10]

Hair greying mechanism:

Hair greying is a result of a decrease in melanocytes in the hair follicle due to disruptions in antioxidant mechanisms and the presence of anti-apoptotic factors. The excessive production of copper-zinc superoxide leads to this phenomenon. The production of hydrogen peroxide (H2O2) leads to oxidative damage, as reactive oxygen species (ROS) build up and create oxidative stress on bulbar melanocytes and the fast-growing hair bulb epithelium composed of keratinocytes. [9]



Factor affecting on hair greying:

The common causes of premature hair greying.

1. Genetic
2. Nutritional deficiencies
3. Stress
4. Vitiligo
5. Tuberous sclerosis
6. Medications
7. Thyroid disorder
8. Smoking

1. Genetics:

The makeup you inherit from your family can influence when you get white hair. If you see white hair early on, it's probably because your parents or grandparents also had grey or white hair they were young. You can't alter your genetics. However, if you are not happy with how your grey hair appears, you have the option to dye your hair. [19]

2. Nutritional deficiencies:

a) Minerals: like iron and copper. [18]
b) Vitamins: White hair at an early age can also indicate a vitamin B-12 deficiencies. This vitamin is essential for your body as it help with energy level and supports healthy hair growth and color. A deficiency in vitamin B-12 is linked to a medical condition known as pernicious anemia, where the body struggles to absorb an adequate amount of this essential vitamin. Vitamin B-12 is crucial for the formation of healthy red blood cells that transport oxygen to various cells in the body, including those in the hair. Insufficient levels of vitamin B-12 can lead to weakened hair cells and disrupt melanin production. [19]
c) Folic acid: zinc and calcium. [18]

3. Stress:

Stress is a common experience for individuals. According to a study conducted in 2013, there is a link between stress and a reduction in stem cells within the hair follicles of mice. Therefore, if you have observed an increase in the number of grey hairs, stress could be the underlying cause. This theory could also account for the accelerated aging or graying of certain world leaders during their time in office. [19]

Chronic stress can leads to:

- Sleep problems
- Anxiety
- Change in appetite
- High blood pressure

Formulation for hair greying treatment:

4. Vitiligo:

This is autoimmune disorder that causes melanocytes loss because the immune system "misfires" and attacks the scalp rather than an infection. This results in patches of lighter skin on the body. [18]

5. Tuberous sclerosis:

This is a rare genetic disorder that leads to the development of noncancerous growths in various organs such as the brain, heart, kidneys, eyes, lungs, and skin. Additionally, individuals with this condition may experience premature graying of hair. [18]

6. Medication:

Certain medications can cause early greying of hair:
Chloroquine (used in malaria)
Mephenesin (a muscle relaxant)
Phenylthiourea (used in DNA testing)
Triparanol (used to reduce cholesterol)
Dixyrazine (used to treat various psychiatric disorders)
Topical medication, such as Dithranol, Chrysarobin, and Benzocain-resorcinol (used for treatment of psoriasis) [18]

7. Thyroid disorders:

Thyroid issues like hyperthyroidism or hypothyroidism can lead to early grey hair due to hormonal changes. Your hair color can be affected by health of your thyroid. If your thyroid is too active or not active enough, it can lead to less melanin production in your body. [19]

8. Smoking:

Smoking cigarettes can lead to premature white hair. We already know that smoking can raise the chances of getting lung cancer and heart diseases. Long term smoking can do more than just harm your heart and lungs- it can also impact your hair. Due to smoking narrow blood vessels, leading to less blood reaching hair follicle and resulting in hair loss. Moreover, harmful substances in cigarettes can harm your body, including your hair follicles, causing premature hair greying. [19]

Table 1: Synthetic anti greying formulation

Sr.No.	Marketed product	Ingredients and their uses	Company
1.	Formen darkenal anti greying hair serum	▪ 2% Greyverse-increase melanin production in bulb and promotes better hair pigmentation ▪ Curry leaf extract-contain darkening agents, antioxidants and vitamin B complex ▪ Fenugreek extract-contain lecithin, anti-greying properties ▪ Sage extract-improve blood circulation in scalp	Formen
2.	Anti grey hair tablet	▪ Copper- delay the process of greying ▪ Green tea- stimulate hair growth ▪ Bioperine- slow premature greying ▪ Quercitine- produce natural hair color	Neofollics
3.	Grey escape tablet	▪ Biotin- boost growth of hair ▪ Copper-increase hair follicle size and inhibit follicle death ▪ Zinc-helps in hair tissue growth and repair ▪ Nettle root-helps in hair regrowth, hair loss and dandruff	Heyhair
4.	Hair darkening serum	▪ Arcolys-natural active ingredient that limits greying of hair ▪ Biotin-stimulates hair roots, improves hair health ▪ Arabica extract-increase the concentration of antioxidant ▪ Melano grey-stimulate melanin production	Masofta
5.	Charcoal grey semi permanent hair colour	▪ Propylene glycol, Cetearyl alcohol, Isodecyl oleate, Synthetic beeswax, Tridecane, Undecane, sodium hydroxide	2.Oh!

Drawbacks of synthetic formulation:

1. The synthetic hair serum causes scalp irritation, dullness and may affect the growth of hair.
2. The synthetic supplement causes gastrointestinal issues. It was observed that this supplement has rancid smell which causes allergic or adverse skin reaction such as itching, swelling, tongue and throat irritation.
3. By the use of synthetic hair color/dye products, following risks was observed such as hair fall, allergic reaction (redness, burning sensation), dandruff, contact dermatitis and cancer (due to presence of carcinogenic chemicals).
4. The orally administration of excessive zinc may causes diarrhea, abnormal cramps and vomiting.

Table 2: Herbal anti greying formulation

Sr. no.	Marketed product	Ingredients and their uses	Company
1.	Grey hair oil	▪ Brahmi- help to restore natural hair color ▪ Almond- help to nourish hair ▪ Amla- improve natural hair color ▪ Jojoba oil- help in increase hair growth ▪ Rosemary- help to prevent premature greying hair	Buddha natural
2.	Anti-grey hair shampoo	▪ Amla- stimulate melanin production ▪ Coconut oil- help to nourish both hair and scalp ▪ Bhringraj- prevent hair loss, dandruff and premature greying ▪ Reetha- hair shining, promotes growth, and works as an effective cleanser	Buddha natural
3.	Rice water hair serum	▪ Rice water- which help strengthen hair roots ▪ Arcolys- stimulates melanin synthesis restoring your natural hair color ▪ Fenugreek extract- incredible source of antioxidants that helps prevent gray hair	Nourish mantra

4.	Anti grey hair mist	▪ Rose- help to increase melanin in production ▪ Fenugreek- help to reduce premature greying efficiently ▪ Hibiscus- help to protect your scalp from sun damage ▪ Neem – help to strengthen and thicken hair	Buddha natural
5.	Anti grey hair tea	▪ Curry leaves- it prevents premature greying of hair ▪ Ashwagandha- helps support hair growth and hair strength ▪ Turmeric- helps boost hair shine and wellness ▪ Amla- promote hair growth	Teacurry

BENEFITS OF HERBAL FORMULATION

1. Herbal products can nourish and heal damaged or dry hair. They can also add shine and volume to hair.
2. Herbal products can help restore and regulate scalp health. They can also help balance scalp oil production.
3. Herbal products can help promote hair growth by improving blood circulation in the scalp.
4. Herbal products can help curb dandruff growth. Some herbal oils, like those containing neem and amla, have anti-fungal and anti-bacterial properties that can help eliminate dandruff.
5. Herbal products are less likely to irritate sensitive skin or scalp.
6. Herbal products are gentle on hair and won't strip it of its natural oils.
7. Herbal products are free form side effects and less harmful compared to synthetic products.

CONCLUSION

In summary, early greying of hair is mainly attributed to oxidative stress, which harms melanocytes and disrupts melanin production in hair follicles. This issue is closely associated with the hair growth cycle, particularly the anagen phase, which is vital for melanin formation. Moreover, bulge melanocyte stem cells (MSC) are essential for maintaining hair color, and their loss due to oxidative stress speeds up the greying process.

While there are both synthetic and herbal products available to tackle premature greying, herbal remedies are often favored for their antioxidant benefits and reduced likelihood of side effects compared to synthetic alternatives. Conversely, synthetic products can provide rapid cosmetic fixes like hair dyes, but they do not tackle the root causes of greying.

REFERENCE

[1] Hoover E, Alhajj M, Flores JL. Physiology, Hair. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.

[2] Lanjewar A, Maurya S, Sharma D, Gaur A, Review on Hair Problem and its Solution, Journal of Drug Delivery and Therapeutics. 2020; 10(3-s):322-329 DOI: http://dx.doi.org/10.22270/jddt.v10i3-s.4066

[3] Pandhi D, Khanna D. Premature graying of hair. Indian J Dermatol Venereol Leprol 2013;79:641-53.

[4] Laura Alonso, Elaine Fuchs. The hair cycle.J Cell Sci (2006) 119 (3): 391–393.DOI: https://doi.org/10.1242/jcs.02793

[5] Xiangyu LinXiangyu LinLiang ZhuLiang ZhuJing He Jing He.Morphogenesis, Growth Cycle and Molecular Regulation of Hair Follicles.Front. Cell Dev. Biol., 12 May 2022 Sec. Stem Cell Research Volume 10 - 2022 DOI: https://doi.org/10.3389/fcell.2022.899095

[6] M. Seiberg. Review Article Age-induced hair greying – the multiple effects of oxidative stress. International Journal of Cosmetic Science, 2013, 35, 532–538.DOI: 10.1111/ics.12090

[7] Feng Z, Qin Y, Jiang G. Reversing Gray Hair: Inspiring the Development of New Therapies Through Research on Hair Pigmentation and Repigmentation Progress. Int J Biol Sci 2023; 19(14):4588-4607. DOI: 10.7150/ijbs.86911

[8] D. J. Tobin. Human hair pigmentation – biological aspects. International Journal of Cosmetic ScienceVolume 30, Issue 4 p. 233-

257.DOI: https://doi.org/10.1111/j.1468-2494.2008.00456.x

[9] Seong Kyeong Jo, Ji Yeon Lee, Young Lee, Chang Deok Kim, Jeung-Hoon Lee, Young Ho Lee. Three Streams for the Mechanism of Hair Graying. Ann Dermatol. 2018 Jun 28;30(4):397–401. DOI: 10.5021/ad.2018.30.4.397

[10] Kyeong Jo, Ji Yeon Lee, Young Lee, Chang Deok Kim, Jeung-Hoon Lee, Young Ho Lee. Three Streams for the Mechanism of Hair Graying. Ann Dermatol Vol. 30, No. 4, 2018.DOI: https://doi.org/10.5021/ad.2018.30.4.397

[11] Anagha Bangalore Kumar, Huma Shamim, Umashankar Nagaraju. Premature Graying of Hair: Review with Updates.Int J Trichology. 2018 Sep-Oct;10(5):198–203.DOI: 10.4103/ijt.ijt_47_189.

[12] Nicole Natarelli, Nimrit Gahoonia and Raja K. Sivamani.Integrative and Mechanistic Approach to the Hair Growth Cycle and Hair Loss.J. Clin. Med. 2023, 12(3), 893.DOI: https://doi.org/10.3390/jcm12030893

[13] Nishimura EK, Granter SR, Fisher DE. Mechanisms of hair graying: incomplete melanocyte stem cell maintenance in the niche.Science. 2005; 307:720–724. DOI: 10.1126/science.1099593

[14] eiberg M. Keratinocyte-melanocyte interactions during melanosome transfer. Pigment Cell Res 2001;14:236-242

[15] Nagl W. Different growth rates of pigmented and white hair in the beard: differentiation vs. proliferation? Br J Dermatol 1995;132:94-97

[16] Choi HI, Choi GI, Kim EK, Choi YJ, Sohn KC, Lee Y, et al. Hair greying is associated with active hair growth. Br J Dermatol. 2011;165:1183–1189.DOI: 10.1111/j.1365-2133.2011.10625.x.

[17] Amelio, I., Lena, A. M., Bonanno, E., Melino, G., and Candi, E. (2013). miR-24 Affects Hair Follicle Morphogenesis Targeting Tcf-3. Cell. Death Dis. 4, e922. doi:10.1038/cddis.2013.426

[18] Available on: https://www.medicinenet.com/is_gray_hair_bad/article.htm

[19] Available on: https://www.healthline.com/health/white-hair