PREMATURE CANITIES: ETIOLOGY, PATHOGENESIS AND MANAGEMENT

S. Sobana[1], Dr. D. Senthil Rajan[1], L. Logeswari[1], J. Ramya[1], S. Reena[1], S. M. Neha[1]

Department of Pharmaceutics and Research, Swamy Vivekananda College of Pharmacy, Tiruchengode, Namakkal-637205, Tamil Nadu, India. (Affiliated to the Tamil Nadu Dr. M.G.R. Medical University), Chennai.

ABSTRACT:

Early greying of the hair, also known as premature canities, is a common dermatological disorder that causes severe psychological suffering in young people. It is caused by decreased melanocyte activity in hair follicles, which results in the loss of melanin pigment. Genetic susceptibility, oxidative stress, dietary inadequacies, autoimmune disorders, and environmental variables like smoking and pollution are all part of the complex etiology. Recent research emphasizes the pathophysiology of reactive oxygen species, melanocyte stem cell depletion, and poor melanogenesis. Management concentrates on addressing underlying deficits and lowering oxidative stress even though there is no known cure. Promising future directions are provided by emerging medicines, such as targeted molecular therapeutics, stem cell-based strategies, and antioxidant treatment. The goal of this study is to present a thorough summary of the biology, etiology, pathophysiology, clinical characteristics, and treatment of premature canities.

KEYWORDS:

Premature canities; Hair greying; Melanocyte; Melanogenesis; Oxidative stress; ROS; Melanin; Hair follicle; Genetics; Nutrition; Antioxidants; Stem cells.

1. INTRODUCTION:

Scientifically referred to as "canities," hair greying is a physiological phenomenon that is thought to be a component of chronological aging. In white people, physiological greying of the hair typically occurs at age 34.2 ± 9.6 years [1]. Asians are in their late 30s, Africans are in their mid-40s, and Caucasians are in their mid-30s. As a general rule, 50% of people have 50% Gray hair by the time they are 50 years old [2]. Due to its effects on aesthetics and social perception, this disorder not only modifies physical appearance but also has a substantial impact on self-esteem and social acceptance. One of the distinguishing characteristics is hair. of mammals and is essential in determining one's look and self-perception. Numerous factors contribute to the complicated etiologic of hair greying, including genetics, environmental exposures, and nutritional imbalances [3]. Weathering of the hair shaft and ageing of the hair follicle are the two main causes of greying hair. While ageing of the follicle is linked to a decrease in melanocyte activity, which results in decreased pigmentation and hair production, weathering is the gradual deterioration of hair fibres from root to tip [4]. While a great deal of

molecular research is still being done to understand the pathogenesis of premature canities, there is currently no viable medication and therapeutic alternatives are far from ideal. Despite the publication of new studies, therapy and prevention are still unclear due to the uneven effectiveness of several oral medicines [5]. Our physical appearance, as well as our sexual and social connections in society, are greatly influenced by the colour of our skin and hair. One characteristic that is typically associated with aging is hair greying. Literature has also shown a connection between an individual's age and increased greying of their hair. According to reports, smoking is significantly associated with grey hair in both sexes. For example, smoking with male baldness, as well as between men and women. 2-3 One study found a highly significant correlation between smoking and baldness or hair loss (p-value < 0.0001), while another study found that tobacco use has been linked to negative skin consequences that may potentially result in greying of the hair. The mechanism that causes baldness and how tobacco causes hair to become grey are still unknown. The melanin pigment's presence or absence mostly determines the colour of hair. There is very little information on the link between tobacco use or smoking and early hair greying. Therefore, the purpose of this study was to determine whether smoking could have an impact on baldness and hair greying. Thus, the study's goals are to: 1) determine the prevalence of baldness and grey hair in Lahore's male population; and 2) determine the relationship between smoking and baldness and greying of hair in men [6]. Although the loss of pigment in the hair shaft is thought to be the origin of greying hair, the precise etiologic of premature canities is yet unknown. The majority of patients have psychological issues related to their physical appearance since their grey hair appears earlier, making them feel self-conscious about their look. The purpose of the questionnaire is to evaluate the various aspects of a person's attitudes, feelings, and perceptions regarding their body or bodily parts.[7]

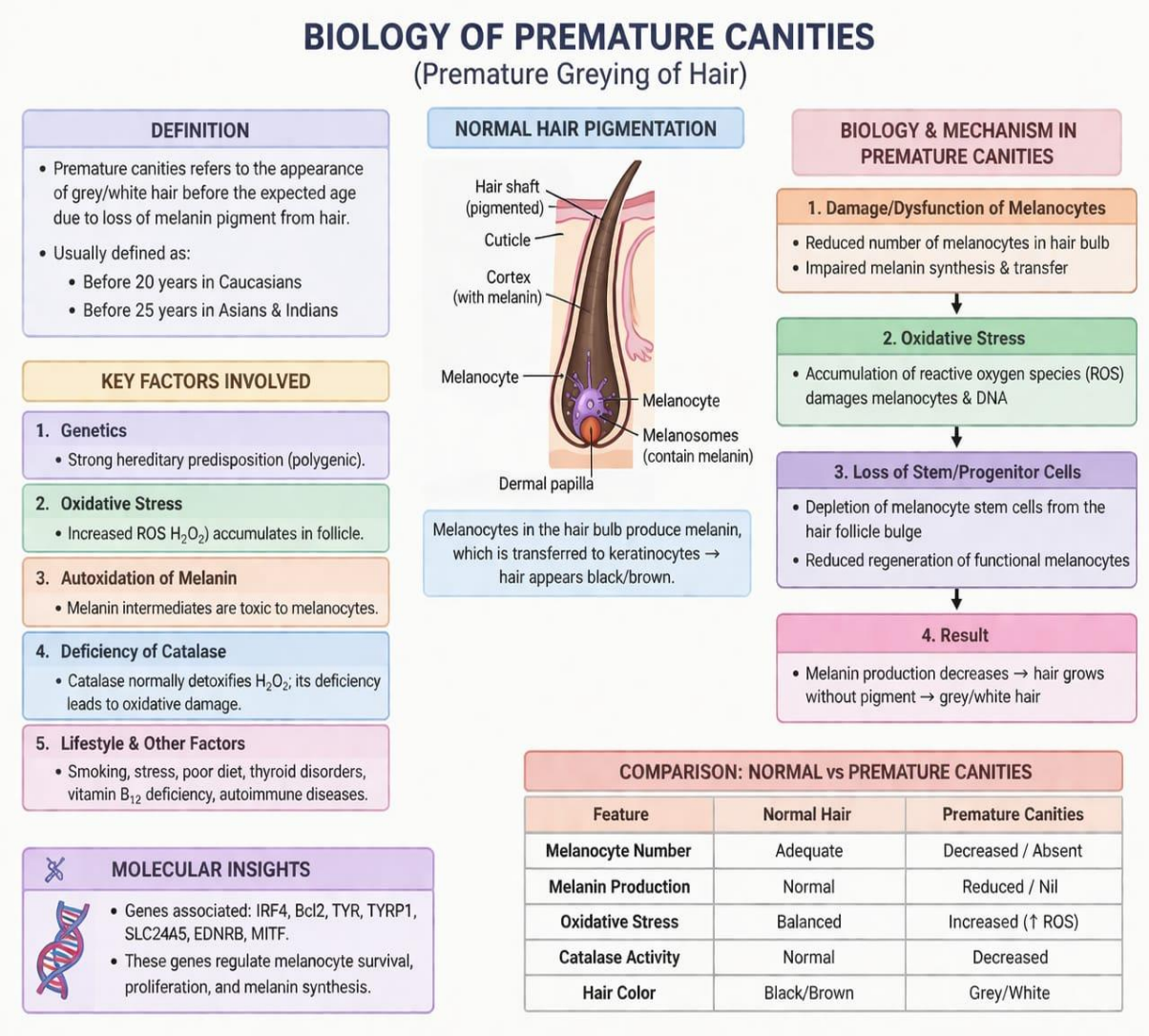
2. DEFINITION:

Hair greying, also known as canities, is a chronological aging process that affects people of all races and genders. The age at which people start to Gray depends on their race and ethnicity. Premature greying of hair is defined as occurring before the ages of 20 for white people, 25 for Asians, and 30 for Africans.[8]

3. BIOLOGY OF HAIR PIGMENTATION:

During development, immature melanoblasts from the neural crest move into the skin to produce melanocytes in the follicular and epidermal melanin units. The hair follicular melanin unit synthesis involves specialized cell types, molecular pathways, and cellular organelles. It resides within the immune-privileged proximal hair bulb influenced by DP (dermal papilla) fibroblasts. In the hair bulb, the ratio of melanocytes to keratinocytes is roughly 1:5, but the basal epidermal layer next to the DP retains a nearly equal 1:1 ratio. On the other hand, the ratio of the epidermal melanin unit is 1:36. In terms of size, dendritic organization, rough endoplasmic reticulum, Golgi activity, and the generation of bigger melanosomes, melanocytes in the hair bulb differ from those in the epidermis. Anagen usually lasts three to five years, during which time hair grows at a pace of about one centimetre every month. Early anagen is when immature melanocytes re-differentiate, most likely from a developing reservoir in the outer root sheath's top layer. Anagen III is when active melanogenesis starts, and tyrosinase activity starts to show. Anagen IV is when pigment transfer to cortical keratinocytes begins, and it continues through anagen V and VI. As a result, the hair shaft next to the scalp is still

unpigmented. Understanding melanocyte replenishment during the hair cycle, the role of melanocyte stem reservoirs, and the aging-related changes in pigmentation, including the loss of functional melanocytes contributing to the greying process, are all significantly impacted by this segregation of melanocyte subpopulations during skin development.[2] Hair colour usually starts off lightest in early childhood and progressively gets darker even before puberty sets in. Throughout adolescence and early adulthood, this darkening trend persists until it finally results in the appearance of canities or grey hair. This process is greatly influenced by hormones, especially oestrogens and androgens.[8] In terms of genetic significance, male history is more significant than maternal history, which advances our understanding of the inherited components of premature greying. The familial aspect of premature greying, which is demonstrated by correlations between afflicted family members and a thorough analysis of family history, emphasizes the importance of genetics in this condition. Twin-controlled studies have shown that up to 90% of the variability in hair greying can be related to hereditary variables, highlighting the importance of genetic predisposition. In terms of genetic significance, male history is more significant than maternal history, which advances our understanding of the inherited components of premature greying.[2]



4. EPIDEMIOLOGY OF PREMATURE CANITIES:

There is racial heterogeneity in the age at which canities appear because it depends more on an individual's genetics. The average age of onset is 43.9 ± 10.3 years for Negroes and 34 ± 9.6 years for Caucasians. Japanese men experience hair greying between the ages of 30 and 34, whereas Japanese women experience it between the ages of 35 and 39. Asians typically start to Gray in their late 30s, Africans in their mid-40s, and Caucasians in their mid-30s. Before the ages of 40 to 50, greying of the hair is considered rare in Bantus. Onset, however, may occur as late as the ninth decade or as early as the second decade. According to a recent study, by the time they are 50 years old, 6–23% of persons have 50% grey hair. Fair-haired people seem completely grey earlier, whereas dark-haired people show signs of greying more easily and earlier. The impact is equal for both sexes [1]. A total of 4840 students between the ages of 12 and 19 were examined for a variety of skin conditions, with a focus on premature hair greying. In 1241 students, a variety of skin issues were noted and addressed. There were sixty individuals (prevalence –1.2%) with early hair greying. The study group consisted of 35 patients who consented to additional research, whereas the control group consisted of 35 age and sex-matched controls. Of the 35 kids, 11.5% had light hair greying, 65.7% had significant hair greying, and 23% had severe hair greying. The average age of the subjects under study was 16.8 years, while the average age at which premature greying first appeared was 15 years. There was no sex preference, as indicated by the male to female ratio of 1:1.1. Every child had a moderate build and diet. 42.6% of patients had a parental history of premature greying, and 14.2% of patients had siblings involved. Interestingly, 8 (22.85%) of the individuals also exhibited vitiligo lesions in other body areas [9].

5. MATERIALS AND METHODS:

5.1 Design of the study:

The cross-sectional analytical method was used in this investigation this study’s main goal was to assess the relationship between premature canities and quality of life as well as the relationship between quality of life and age sex length of illness and severity of premature canities.

5.2 Sample size:

Between January 2017 and august 2017 177 participants63 of whom had premature canities and 114 of whom were healthy from two high schools and the university of Sumatera Utara medians faculty of medicine subjects between the ages of 15 and 25 who had both premature and non-premature canities the sequential sampling approach was used to collect samples.

5.3 Tools:

The quantity of grey hairs was calculated and a clinical examination of the hair was used to diagnose premature canities the relationship between premature canities and quality of life as the well as the relationship between quality of life and age sex length of illness and severity of

participants who suffered premature canities were evaluated using body image questionnaires big.

5.4 Participants:

Male and female participants with both premature and non-premature canities between the ages of 15 and 25 who were willing to participate in the study and sign an informed consent form met the inclusion criteria participants with poliosis hypo melanosis hair problem premature aging syndrome and premature canities with psychological disorders depression and anxiety were excluded.

5.5 Measurements:

Premature canities can be classified as mild less than 50 sheets of grey hair medium between 51 and 100 sheets of grey hair or severe more than 100 sheets of grey hair with at least five grey hairs a 15-item questionnaire based on body image questionnaires big was then administered to the chosen subjects in order to evaluate their quality of life the questions covered a number of criteria including self-image or body parts that are disliked or interfere with daily appearance feelings and emotions frequency and time spent on the conditions experienced personal and social relationships the ability to work or learn about the conditions experienced and actions that have been and will be done related to the conditions premature experienced each questions assessed domain contains five possible answers ranging from 0 to 8 including not disturbed sometimes disturbing and very disturbing higher scores indicate a reduction in living quality the overall score is determined by adding the answers to each question the patients quality of life is more disrupted the higher the score if the score is less than 24 the quality of life is considered good if it is more than 24 it is considered poor.

5.6 Analysis of data:

Based on each attribute the data were processed and analysed to determine the frequency distribution of quality of life in people with premature canities and non-canities the results were then displayed as a frequency distribution table the link between each variable was examined using the chi-square test with a significance level of p005 using spas statistical software.[6]

6. CAUSES OF PREMATURE CANITIES:

As we age the type of hair fibre continues to change adults have short usually pigmented vellus hair or fine pigmented intermediate hair with long terminal hair shafts but newborns and foetuses have unpigmented lanugo hair in a similar vein surface morphology varies with age especially as the size of the cuticular scale decreases melanocytes in hair bulbs have their maximum capacity for synthesis while they are young during the 45 years before grey hair appears an average scalp hair follicle receives 7 15 melanocyte replacements from an outside root sheath reservoir to the hair bulb the gradual loss of pigmentation associated with aging has been explained by a variety of ideas this includes telomerase loss antioxidant mechanisms antiapoptotic signals deoxyribonucleic acid DNA synthesis impairment and melanogenesis-related enzyme depletion in the end fewer melanosomes are integrated into the hair shafts cortical keratinocytes greying hair grows slowly at the rate of normal hair development as a result of melanocytes in the hair matrix region surrounding the dermal papilla ceasing to produce pigment not all hair bulbs reduce the amount of pigment incorporated into the growing

hair at the same time giving the scalp hair a salt and pepper pattern gender age of onset and smoking habits have all been found to influence the pattern of hair greying smokers are more likely to develop canities 6 in males the temporal area is affected first but in females the frontal area is the location of involvement is also influenced by the age of onset patients with early onset have involvement in the parietal and occipital areas whilst those with late onset have involvement in the frontal area.[2]

7. HAIR FOLLICULAR PIGMENTARY UNIT AND MELANOGENESIS:

The hair follicular represents a mini-organ functionally dependent on precisely coordinated interaction of keratinocytes and melanocytes in part regulated by fibroblasts of the dermal papilla These interactions are mediated by complex signalling pathways that regulate melanocyte proliferation, differentiation, and melanin synthesis. Disruption of this tightly controlled process can impair melanogenesis and reduce the transfer of pigment to keratinocytes. Consequently, decreased melanin production and incorporation into the hair shaft leads to progressive hair greying. [10] A specific functional system found in the follicle globe during the anagen synthesis stage of the hair cycle's growth is the hairy follicles pigment forming component. Melanocytes, matrix keratinocytes, and melanocyte stem cells make up the majority of it. These cells collaborate to create and integrate pigment into the developing hair shaft. Effective production of melanin and transport are made achievable by mature melanocytes, which are located above the papilla of and are still intimately linked to rapidly reproducing keratinocytes. blonde strands and tubular hair. During development, immature melanoblasts move from the neural crest into the skin, producing both epidermal and follicular melanocytes. Transient-amplifying melanocytes, the offspring of melanoblasts that develop in the epidermal layer, leave that compartment and enter the growing hair follicle as it develops. Depending on the intrafollicular compartment, melanocytes can either become or stay DOPAoxidase-positive cells (i.e., express active tyrosinase) or remain DOPA-oxidase-negative cells (i.e., fail to express tyrosinase or express an inactive tyrosinase). [6]

7.1 Structure of hair follicular pigmentary unit:

The hair follicular pigmentary unit (HFPU) is responsible for hair pigmentation and is located in the hair bulb region of the follicle. It consists of melanocytes, melanosomes, and matrix keratinocytes.

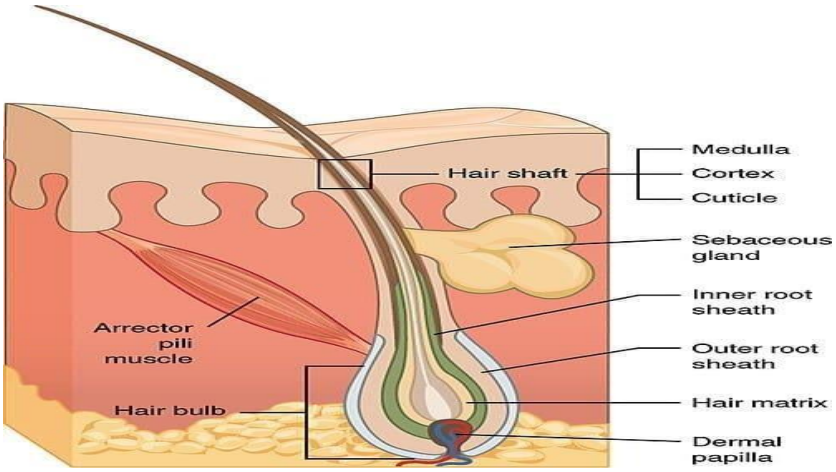


FIG:1 PIGMENTATION STRUCTURE

Melanocytes synthesize melanin pigment and transfer it to the surrounding matrix keratinocytes. These keratinocytes incorporate the pigment into the developing hair shaft as it grows. The activity of the pigmentary unit is closely associated with the hair growth cycle. Melanin production mainly occurs during the anagen phase, while during catagen and telogen phases melanocyte activity decreases or stops, leading to reduced pigmentation. hair follicular pigmentary unit is mainly located in the hair bulb region of the hair follicle. In this region, melanocytes are situated close to the dermal papilla and among the hair matrix cells. These melanocytes produce melanin pigment inside organelles called melanosomes.[11]

The hair follicle is a complex structure formed by an invagination of the epidermis into the dermis and contains several important components such as the hair shaft, inner root sheath, outer root sheath, sebaceous gland, arrector pili muscle, hair matrix, and dermal papilla. The hair shaft is composed of three layers namely the medulla, cortex, and cuticle which provide strength and protection to the hair. The sebaceous gland secretes sebum that lubricates the hair and skin, while the arrector pili muscle helps the hair stand upright during cold or emotional stimuli. The inner root sheath surrounds and guides the growing hair shaft, whereas the outer root sheath provides structural support and contains stem cells important for follicle regeneration. At the base of the follicle, the hair matrix contains rapidly dividing cells responsible for hair formation, and the dermal papilla supplies nutrients and regulatory signals necessary for hair growth and pigmentation. During the catagen and telogen phases of the hair cycle, melanocyte activity decreases or stops, leading to reduced pigmentation in the hair.[12]

7.2 Melanocyte biology in hair follicular:

Melanocytes are specialized pigment-producing cells responsible for hair pigmentation. They synthesize melanin in organelles called melanosomes from the amino acid tyrosine. The produced melanin is transferred to keratinocytes, which gives colour to the hair shaft. In hair follicles, melanocytes originate from melanocyte stem cells located mainly in the bulge region. During the anagen (growth) phase of the hair cycle, melanocytes actively produce melanin to pigment the growing hair. During the catagen phase, these melanocytes undergo apoptosis, and in the telogen phase they are absent until new melanocytes are regenerated from melanocyte stem cells in the next anagen phase.

Melanocyte stem cells are located in the bulge region of the hair follicle and remain in an undifferentiated and quiescent state during the telogen phase. These stem cells act as a reservoir that supplies new melanocytes during each hair growth cycle. When the anagen phase begins, melanocyte stem cells proliferate and differentiate into mature melanocytes that migrate to the hair matrix. These differentiated melanocytes produce melanin and transfer it to keratinocytes, which leads to pigmentation of the growing hair shaft.[13]

7.3 Melanogenesis process (melanin synthesis):

Melanogenesis is the biochemical process responsible for the production of melanin pigments that determine hair colour. This process occurs inside specialized organelles called melanosomes within melanocytes located in the hair follicle pigmentary unit. During the anagen (growth) phase of the hair cycle, melanocytes in the hair bulb actively synthesize melanin through enzymatic reactions involving key enzymes such as tyrosinase, which converts tyrosine into melanin intermediates. The synthesized is packaged into melanosomes

and transferred to nearby cortical keratinocytes of the growing hair shaft. As these keratinocytes differentiate and form the hair fibre, the incorporated melanin gives the hair its characteristic colour. Hair follicle melanogenesis is tightly coupled to the hair growth cycle and occurs mainly during the active growth phase, unlike epidermal melanogenesis which is continuous.[14] Melanogenesis is a multi-step biochemical process that occurs in melanocytes of the hair follicle during the anagen phase of the hair cycle. The process begins with the enzymatic oxidation of L-tyrosine catalysed by the enzyme tyrosinase (TYR), which is the rate limiting enzyme in melanin synthesis. Through a series of oxidation and polymerization reactions, L-tyrosine is converted into different types of melanin pigments such as eumelanin and pheomelanin. These pigments are synthesized inside specialized organelles called melanosomes. During melanogenesis, melanogenic genes including MITF, TYR, and SOX10 are up-regulated, which regulate the differentiation and activity of melanocytes. The produced melanin is then transferred to surrounding keratinocytes, contributing to pigmentation of the hair shaft and skin.[15]

8. TYPE OF MELANIN AND PIGMENT TRANFER:

8.1. Type of melanin:

EUMELANIN	PHEOMELANIN
•This pigment produces hair yellow or reddish hair colour. •it is the most melanin in or lighter hair dark hair.	•This pigment produces black or brown colour. •It is present in red abundant shades.

Hair follicle pigmentation mainly depends on two types of melanin pigment. The relative amount and combination of eumelanin and pheomelanin synthesized follicular melanocyte determines the final colour of the hair shaft.

8.2. Pigment transfer:

During the anagen phase of the hair cycle, melanocytes in the hair bulb actively synthesize melanin within organelles called melanosomes. These melanin granules are then transferred from melanocytes to the surrounding hair matrix keratinocytes. Melanosomes move through the dendritic processes of melanocytes and are delivered into keratinocytes that form the cortex and medulla of the hair shaft. The keratinocytes incorporate the pigment, leading to the formation of pigmented hair fibres. This coordinated interaction between melanocytes and keratinocytes forms the hair follicle pigmentary unit, which is responsible for hair coloration. [16]

8.3. Regulation:

Hair pigmentation is regulated by the interaction between hair follicle stem cells (HFSCs) and melanocyte stem cells (MCSCs) present in the hair follicle niche. During the hair growth cycle, melanocyte stem cells are activated in coordination with hair follicle stem cells and differentiate

into melanocytes that produce melanin pigment. These melanocytes transfer melanin to the developing hair shaft, thereby determining hair colour and providing protection against ultraviolet radiation.

The regulation of hair pigmentation is controlled by both intrinsic and extrinsic environmental factors. Intrinsic regulation occurs through signalling pathways and interactions within the hair follicle microenvironment. Extrinsic factors include signals from neighbouring cells, systemic hormonal influences, and external environmental stimuli. These factors influence whether melanocyte stem cells remain quiescent or become activated during the hair cycle. Proper coordination of these regulatory mechanisms is essential for maintaining normal hair pigmentation, while disturbances in these processes may lead to pigmentation disorders such as hair greying, vitiligo, or hair loss.[17]

9. AGING OF FOLLICULAR:

Aging of follicular melanin refers to the gradual decline in melanin production within the hair follicle with increasing age. This occurs due to the reduced activity and loss of melanocytes in the hair bulb, which are responsible for pigment synthesis. As the melanocyte reservoir becomes depleted and oxidative stress increases, melanin production decreases, leading to the appearance of grey or white hair. Tobin DJ, Paus R. Premature greying of hair.[18]

9.1melanocyte stem cell depletion:

In order to produce pigment-producing melanocytes, melanocyte stem cells (MCSCs) found in the hair follicle bulge are activated only during the hair development cycle. However, this equilibrium may be upset by the buildup of senescent cells as people age or experience cellular stress. A senescence-associated secretory phenotype (SASP) made up of cytokines and signalling molecules is released by senescent cells, changing the stem-cell niche in the area. By making stem cells, including melanocyte stem cells, senescent or non-proliferative, persistent senescence can diminish tissues' ability to regenerate. This ultimately leads to the depletion of the stem-cell pool. [19]. Melanocyte stem cell depletion can also occur due to defects in stem-cell maintenance mechanisms within the hair follicle niche. Proper regulation of signalling pathways such as Want, TGF-β, and Notch is essential for maintaining the self-renewal and survival of melanocyte stem cells. When these regulatory signals are disturbed, melanocyte stem cells may either undergo apoptosis or differentiate prematurely, leading to a gradual decline in the stem-cell population. In addition, repeated hair cycles and environmental stress factors can accelerate the exhaustion of melanocyte stem cells, thereby reducing their ability to replenish pigment-producing melanocytes. This progressive loss of melanocyte stem cells contributes significantly to hair depigmentation and the development of grey hair.[20]

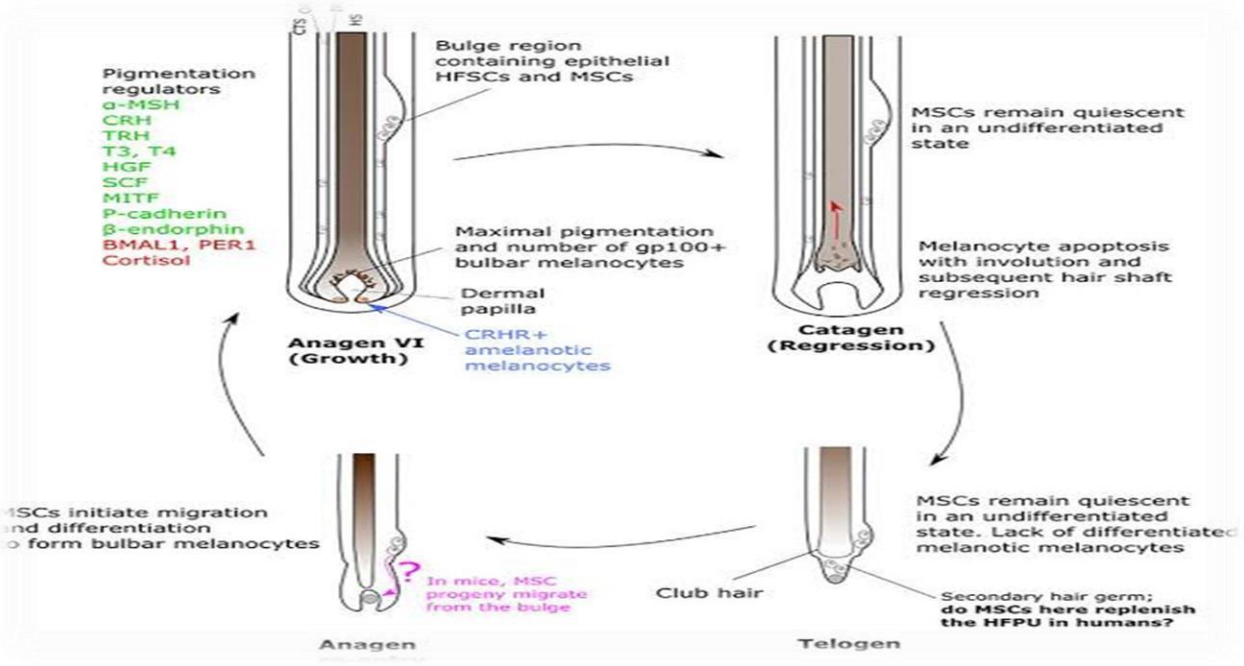
9.2 Decrease in melanocyte number and activity:

In psoriatic skin, melanocyte behaviour is altered due to the inflammatory environment. Although the number of melanocytes in lesional skin may increase, their normal melanogenic function can be disturbed. Pro-inflammatory cytokines present in psoriasis, such as TNF-α and IL-17, can suppress melanogenesis by reducing the activity of key enzymes like tyrosinase. This leads to decreased melanin production despite the presence of active melanocytes. As a result, changes in melanocyte activity and melanin synthesis may contribute to pigmentary

abnormalities such as hypopigmentation or hyperpigmentation after the resolution of psoriatic lesions.[21]

9.3 Reduced melanogenesis (melanin production):

suppress melanogenesis by regulating the expression and activity of melanogenesis-related proteins. Many plant compounds inhibit key enzymes and signalling pathways involved in



melanin synthesis, especially tyrosinase (TYR), which catalyses the initial steps of melanin production. Suppression of transcription factors such as MITF and its downstream genes (TYR, TYRP-1, TYRP-2) leads to decreased melanin synthesis in melanocytes. Certain plant extracts and compounds also inhibit signalling pathways including cAMP/CREB/MITF, MAPKs, AKT, and ERK pathways, resulting in reduced melanogenesis. For example, compounds such as arctigenin lower cellular cAMP levels, while linolenic and linoleic acids inhibit MC1R signalling, ultimately suppressing melanin production. Through these mechanisms, plant derived molecules demonstrate significant anti-melanogenic activity and may be useful in treating hyperpigmentation disorders.[22]

9.4 Oxidative stress and ROS damage:

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the cellular antioxidant defence system. When ROS levels exceed the capacity of antioxidant mechanisms oxidative stress develops and leads to cellular injury. Reactive oxygen species are highly reactive molecules that can interact with important cellular components. Excessive ROS accumulation damages lipids, proteins, and DNA, thereby altering their normal structure and function. This damage may disrupt cellular metabolism, signalling pathways and gene expression. ROS-induced damage also triggers lipid peroxidation in cellular membranes, protein oxidation, and DNA modifications such as strand breaks and mutations. These changes impair cell integrity and may lead to inflammation, mitochondrial dysfunction, and eventually cell death in skin and pigment-producing cells, prolonged

oxidative stress can damage organelles such as mitochondria and the endoplasmic reticulum, activating apoptotic pathways and increasing cellular vulnerability.[23]

9.5 structural changes in hair follicular pigmentary unit:

The hair growth cycle. At the beginning of the anagen phase, immature melanocytes located in hair follicle pigmentary unit undergoes marked structural and functional changes during the permanent portion of the hair follicle become activated, increase in volume, and enter mitotic activity. These cells migrate toward the hair bulb to repopulate the newly forming follicle. As anagen progresses, melanocytes proliferate actively and undergo morphological changes, including expansion of the Golgi apparatus and rough endoplasmic reticulum, which support melanosome biogenesis. Simultaneously, the size and number of melanosomes increase, and melanocytes develop a highly dendritic morphology. These dendritic processes facilitate the transfer of mature melanosomes to surrounding pre-cortical keratinocytes within the hair matrix. By the late anagen stage, melanocytes become fully differentiated and highly active in melanin synthesis. Toward the end of anagen, melanogenic activity declines, tyrosinase expression decreases, and melanocytes retract their dendrites as the follicle prepares for regression.[24]

10. ROLE OF REACTIVE OXYGEN SPECIES (ROS) IN PREMATURE CANITIES:

Reactive oxygen species (ROS) play an important role in the pathogenesis of premature greying of hair (premature canities). During the active growth phase of the hair follicle (anagen), melanocytes in the hair bulb synthesize melanin through oxidation reactions involving tyrosine and dihydroxyphenylalanine. This melanogenesis process naturally produces ROS as byproducts. When the production of ROS exceeds the capacity of the cellular antioxidant defence system, oxidative stress occurs, leading to damage of melanocytes in the hair follicle pigmentary unit. The accumulation of oxidative stress can impair melanocyte function, reduce melanin production, and eventually lead to degeneration or loss of melanocytes, which contributes to the development of grey hair at an early age [2]

10.1 Hydrogen peroxide (H202) accumulation in hair follicle:

Hydrogen peroxide (H_2O_2) accumulation within the hair follicle plays a crucial role in the process of hair graying. Under normal physiological conditions, antioxidant enzymes such as catalase break down hydrogen peroxide into water and oxygen, thereby preventing oxidative damage. However, in aging or stressed hair follicles, the activity of catalase and other antioxidant defence systems becomes significantly reduced. As a result, hydrogen peroxide accumulates within the hair follicle and hair shaft. This elevated H_2O_2 level induces oxidative stress and interferes with the normal function of melanocytes and melanogenic enzymes. In particular, hydrogen peroxide oxidizes methionine residues in tyrosinase, the key enzyme involved in melanin synthesis, thereby impairing its activity. The oxidative modification of tyrosinase and other cellular components ultimately leads to reduced melanin production and contributes to the progressive loss of hair pigmentation.[25]

10.2 Oxidative damage to melanocytes:

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the antioxidant defence capacity of the cell. Melanocytes are particularly vulnerable to oxidative damage because melanin synthesis involves several oxidation reactions that generate ROS such as superoxide anion and hydrogen peroxide. These reactive molecules can damage important cellular components including DNA, proteins, and lipids. Excessive ROS accumulation can lead to oxidative DNA damage and disrupt normal melanocyte function. Environmental factors such as ultraviolet radiation further increase ROS production and weaken antioxidant defence systems in melanocytes. Persistent oxidative stress may therefore contribute to melanocyte dysfunction, cell death, and the development of pigmentary disorders. (26). Melanocytes possess antioxidant defence systems such as catalase, superoxide dismutase (SOD), and glutathione to neutralize reactive oxygen species. However, when oxidative stress persists, these protective mechanisms become insufficient, resulting in increased cellular vulnerability. Reduced antioxidant enzyme activity can lead to the accumulation of hydrogen peroxide in melanocytes, which further enhances oxidative damage. Oxidative stress can also impair mitochondrial function and disturb cellular signalling pathways that regulate melanocyte survival and melanin production. Damage to mitochondria leads to decreased energy production and activation of apoptotic pathways. As a result, melanocytes may undergo degeneration or programmed cell death, which contributes to abnormalities in pigmentation and hair greying.[27]

10.3 Tyrosinase enzyme inactivation:

Tyrosinase is a copper-containing enzyme that catalyses the oxidation of phenols and catechol's during melanin synthesis. During its catalytic cycle, the enzyme exists in several oxidation states, including met-tyrosinase, deoxy-tyrosinase, and oxy-tyrosinase. Inactivation of tyrosinase occurs during the processing of catechol substrates in the monooxygenase reaction. This process leads to the reductive elimination of one of the copper ions from the active site, converting the active oxy-tyrosinase form into an inactive form known as dealt-tyrosinase. The loss or reduction of copper disrupts the catalytic activity of the enzyme, resulting in irreversible enzyme inactivation. Such inactivation is often described as suicide inactivation, because the enzyme becomes inactive while catalysing its own substrate. The mechanism is closely related to the oxidation of catechol's and the structural changes occurring in the active site during the catalytic cycle.[28] In addition, the inactivation of tyrosinase may also occur due to the accumulation of reaction intermediates produced during the oxidation of phenolic substrates. These intermediates can interact with the enzyme and cause structural modifications in the active site, which further reduces the catalytic efficiency of the enzyme. As a result, the enzyme gradually loses its ability to convert phenolic compounds into quinones during melanin formation. Environmental factors such as pH, temperature, and the presence of inhibitors can also influence the stability and activity of tyrosinase. Certain chemical compounds and natural inhibitors may bind to the enzyme and accelerate the inactivation process by disturbing the copper centre or altering the enzyme conformation. Therefore, tyrosinase inactivation plays an important role in regulating melanin synthesis and controlling enzymatic browning reactions. [29]

10.4. Melanocyte stem cell apoptosis/loss:

Melanocyte stem cells are maintained within the bulge region of the hair follicle and are responsible for generating differentiated melanocytes during the hair cycle. Proper maintenance of this stem cell population is essential for normal hair pigmentation. Disruption of regulatory signalling pathways can lead to apoptosis of melanocyte stem cells and depletion of the stem cell pool. For example, inhibition of the Notch signalling pathway results in melanocyte apoptosis and permanent loss of melanocyte stem cells, leading to hair greying.

Similarly, defects in survival factors such as Bcl-2 increase apoptosis of melanocyte stem cells, which reduces the stem cell population and impairs the regeneration of pigment-producing melanocytes. As a consequence, depletion of melanocyte stem cells contributes to loss of hair pigmentation and premature greying.[30]

11.ETIOPATHOGENESIS & PATHOMECHANISM:

Immune-mediated inflammatory diseases (IMIDs) develop due to a complex interaction between genetic susceptibility and environmental factors. These factors trigger abnormal activation of the immune system, leading to the release of pro-inflammatory cytokines and chronic inflammation. Persistent immune responses ultimately result in tissue damage and progression of the disease. The exact etiology of immune-mediated inflammatory diseases (IMIDs) is not completely understood, but current evidence suggests that these disorders arise from a complex interaction between genetic predisposition and environmental factors. Genetic studies, including genome-wide association analyses, have identified several susceptibility genes that are shared among different IMIDs as well as genes specific to individual diseases. Environmental influences such as smoking, diet, infections, drugs, stress, and geographical or social factors may act as triggers or modifiers of disease onset and progression. These factors can alter immune regulation and initiate abnormal immune responses in genetically susceptible individuals. The Patho mechanism of IMIDs involves dysregulation of both innate and adaptive immune responses, leading to persistent inflammation and tissue damage. Immune cells such as T lymphocytes, B lymphocytes, macrophages, and dendritic cells become activated and produce pro-inflammatory cytokines and chemokines. These mediators promote chronic inflammation and recruit additional immune cells to affected tissues. The resulting inflammatory cascade disrupts normal tissue structure and function, ultimately causing the clinical manifestations of the disease. Shared immune pathways among different IMIDs suggest that similar molecular mechanisms drive inflammation across multiple disorders, although disease-specific factors determine the exact pattern of tissue involvement.[31]

11.1 Oxidative stress and ROS accumulation:

The cellular antioxidant defence mechanism cannot keep up with the amount of oxygen species (ROS). ROS include very reactive chemicals that can harm biological components, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals. Overproduction of ROS can lead to DNA damage, protein oxidation, and lipid peroxidation, all of which can interfere with regular physiological processes. Because melanocytes naturally produce ROS during the melanogenesis process, oxidative stress plays a significant role in the etiopathogenesis of illness. ROS production can be further increased by environmental variables such UV light, toxins, and inflammation. Cellular malfunction and oxidative damage result from redox imbalance, which happens when ROS build up beyond antioxidant systems' ability to neutralize

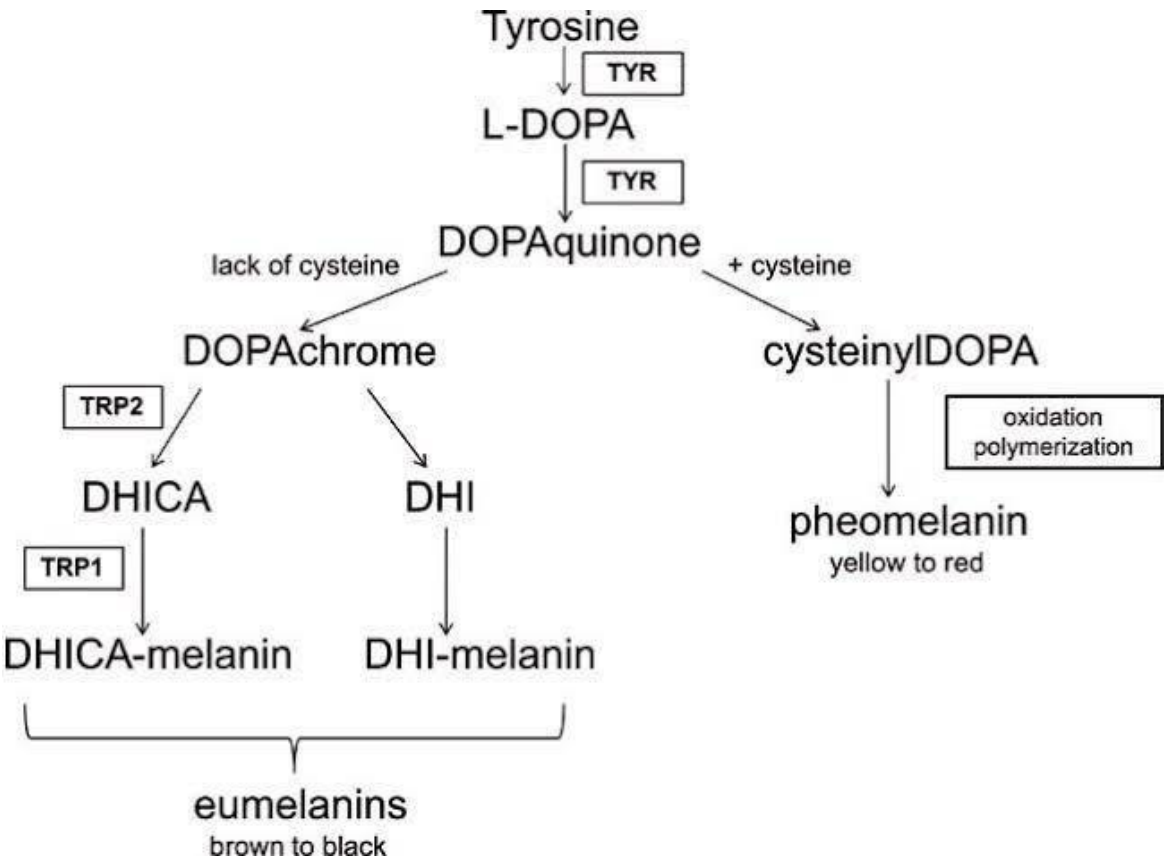
them. Long-term ROS buildup can damage mitochondria, interfere with metabolic processes, and cause melanocyte death. By impairing melanocyte survival and disrupting regular melanin formation, this oxidative damage adds to the Patho mechanism of pigmentary diseases.[32]

11.2 Impaired melanogenesis Mechan:

Impaired melanogenesis plays a central role in premature canities, characterized by a progressive decline or complete loss of melanin production in hair follicles. Normally, melanocytes located in the hair bulb synthesize melanin through the activity of key enzymes such as tyrosinase and transfer it to keratinocytes, which imparts colour to the hair shaft. In premature greying, this process becomes defective due to reduced melanogenic enzyme activity, leading to decreased melanin synthesis. Additionally, there is impaired transfer of melanosomes to cortical keratinocytes, resulting in inadequate pigment incorporation into the growing hair. Alterations in the melanosome microenvironment, including changes in pH and cysteine levels, further affect melanin production and may shift pigmentation toward lighter pheomelanin. Increased oxidative stress and accumulation of reactive oxygen species also damage melanocytes and interfere with normal melanogenesis. Together, these changes result in progressive depigmentation of hair, giving rise to grey or white hair.[33]

12. GENETIC AND MOLECULAR BASIS OF PREMATURE CANITIES:

Premature canities (premature hair greying) is a multifactorial condition in which genetic factors play a primary role, along with molecular alterations affecting melanocyte function. Studies indicate that a positive family history is one of the strongest predictors, suggesting a hereditary predisposition influencing the early onset of greying at the molecular level, premature greying results from impaired melanocyte activity within the hair follicle, leading to reduced melanin production. Genetic influences may affect pathways involved in oxidative stress regulation, melanocyte survival, and pigment synthesis. Alterations in signalling pathways and genes regulating melanogenesis contribute to early depletion or dysfunction of melanocytes, ultimately causing loss of hair pigmentation. Thus, the interaction between inherited genetic susceptibility and molecular changes in melanocyte biology forms the fundamental basis of premature canities.[34]



12.1 Melanogenesis regulatory gene alterations:

Hair pigmentation is strongly regulated by genes that control melanocyte function and melanin synthesis. Gene expression analysis comparing pigmented, grey, and white hair follicles has revealed significant alterations in melanogenesis-related genes. Several key genes involved in melanin synthesis and melanosome formation—such as TYR, TYRP1, PMEL, MLANA, KIT, and MET—were found to be downregulated in grey and white hair follicles compared to pigmented hair follicles. Genome-wide studies have also identified many differentially expressed genes associated with premature hair greying, including SLC45A2, GPR143, and OCA2, which are involved in melanosome biogenesis and pigment production. Reduced expression of these genes results in impaired melanin synthesis and decreased transfer of melanin to keratinocytes, leading to loss of hair pigmentation. Many of these melanogenesis related genes are transcriptionally regulated by MITF (microphthalmia-associated transcription factor), a key master regulator of melanocyte development and function. Reduced MITF activity leads to decreased expression of melanogenic enzymes and structural proteins necessary for melanin production. Consequently, alterations in melanogenesis regulatory genes disrupt melanin synthesis and contribute to the development of hair greying.[35]

12.2. Apoptosis and cellular senescence pathways:

Apoptosis and cellular senescence are two critical cellular responses to stress, particularly DNA damage, that help maintain tissue homeostasis. Apoptosis is a form of programmed cell death mediated through two main pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway. Both pathways ultimately activate caspases, which degrade cellular components and lead controlled cell elimination. In contrast, cellular senescence is a state of permanent cell cycle arrest, primarily regulated by the p53–p21 and p16–Rb pathways,

preventing the proliferation of damaged cells. Senescence acts as an alternative to apoptosis when cellular stress is not severe enough to trigger cell death. The decision between apoptosis and senescence depends on the severity and nature of cellular stress. Severe damage (e.g., high levels of DNA damage) typically induces apoptosis, whereas milder or chronic stress Favors senescence. Importantly, senescent cells often develop resistance to apoptosis through senescent cell anti-apoptotic pathways (SCAPs). These involve upregulation of anti-apoptotic proteins such as BCL-2, BCL-XL, and BCL-W, which enhance cell survival despite damage. This resistance allows senescent cells to persist and contribute to aging and disease. Therapeutically, targeting these survival pathways has led to the development of nonlytic drugs, which selectively induce apoptosis in senescent cells by inhibiting SCAPs, thereby restoring tissue function and reducing age-related pathologies.[36]

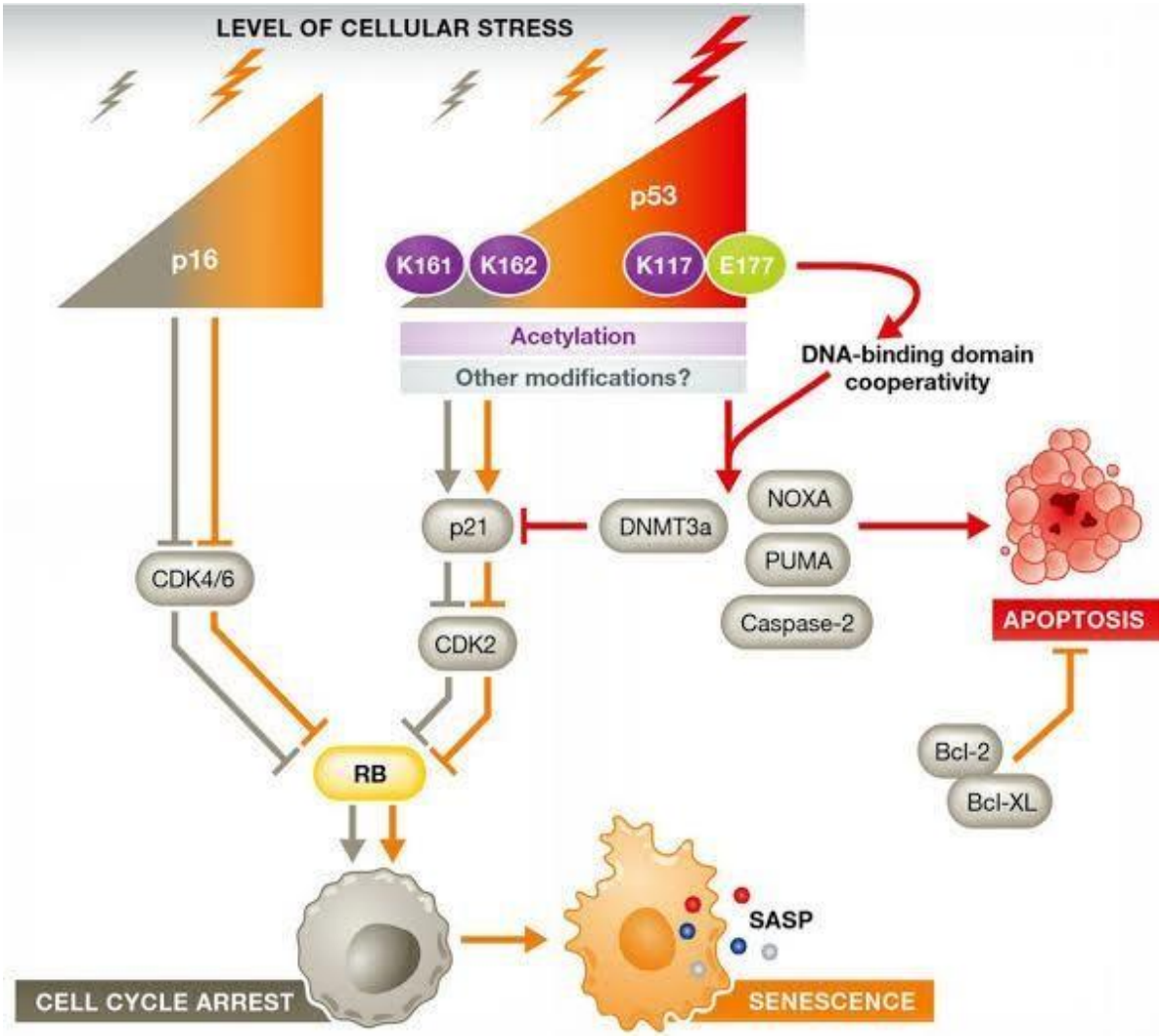
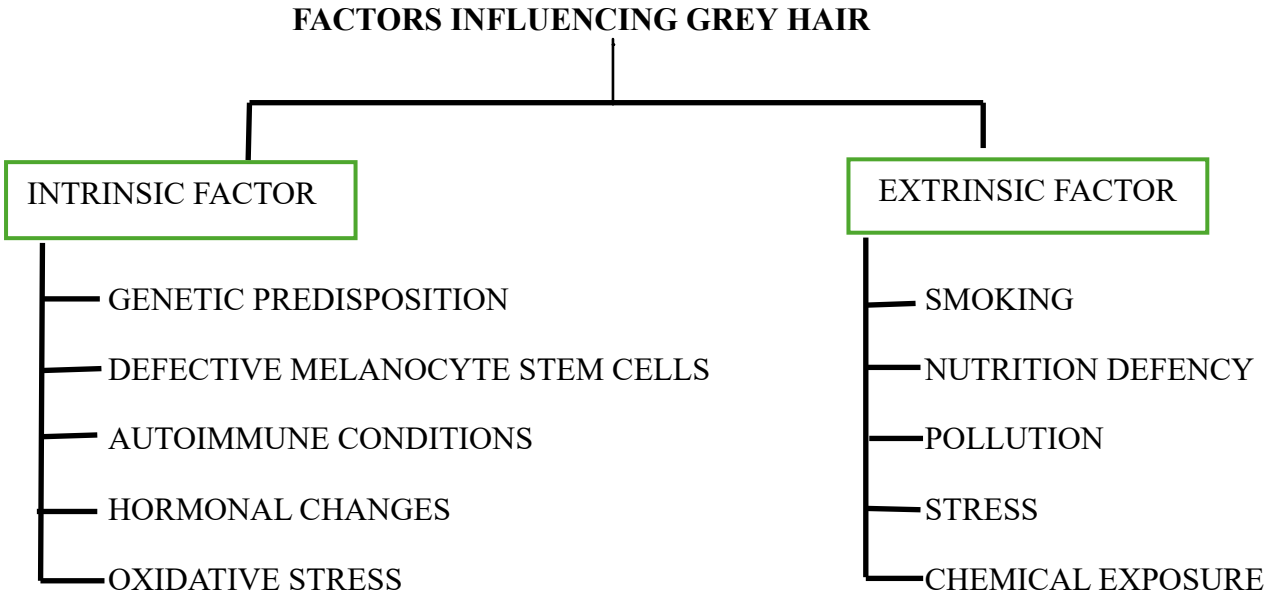


FIG:2 PATHWAY

13.INTRINSIC AND EXTRINSIC FACTORS ASSOCIATED WITH HAIR GREYING:

The loss of natural hair colour before the normal age is known as premature canities, or early greying. Genetics, health issues, and both internal and external events all have an impact. Hair colour is strongly associated with age perception, self-esteem, and social connections; therefore, it can have detrimental effects on psychosocial well-being in addition to physical changes. [1] Hair greying can be directly or indirectly caused by a variety due to the combined effect of both internal and external factors. Extrinsic variables are elements of life, for example, personal behaviours and outside impacts, whereas intrinsic elements include biological characteristics such as cellular and genetic components and physiological traits. The classification provided here is arbitrary because of the dynamic interaction and shared influence of numerous elements.[37]



13.1 Intrinsic:

13.1[1] Genetic disposition:

One of the main causes of premature hair greying is genetic predisposition. Numerous studies attest to the significant hereditary component of early canities, with a major role being played by family history, particularly paternal impact. Reduced pigmentation results from the downregulation of genes such as TYR, TYRP1, Pax3, and SOX10 that are involved in melanocyte activity and melanin formation. Early greying, uneven hair colour, and a shorter hair lifespan are the outcomes of this. [37,38,]

13.1 [2] Defective melanocyte stem cells:

Periodic cycles of hair pigmentation are maintained by melanocyte progenitor cells. In the vertebrate integumentary system, melanocytes—specialized dendritic cells—produce melanin, which determines colour. They transform amino acids into pigment inside melanosomes using certain enzymes. Coloured skin and hair are the result of these melanin-rich vesicles being moved to nearby epidermal cells via cytoplasmic extensions.[39] The forehead, vertex, occipital area, and sideburns are typically where hair greying begins. It happens when melanocyte stem cells and pigment cells in hair follicles are lost. This process can be

accelerated by stress, and the creation of melanin produces reactive oxygen species (ROS), which contribute to greying. By the age of 50, about half of persons have 50% grey hair (the "50/50/50 rule").[40]

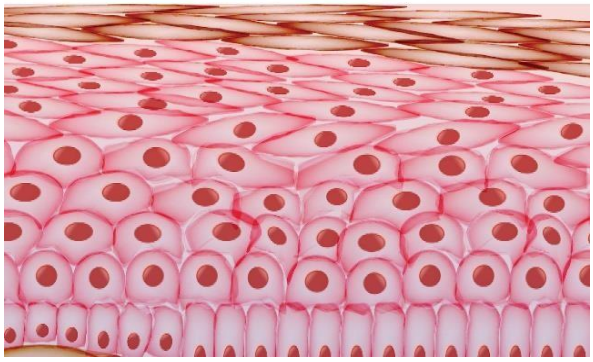


FIG 3: MELANOCYTE STEM CELL

13.2 Extrinsic factor:

13.2[1] Smoking:

Greying may be a sign of general health, according to recent research that relates smoking (though not causally) to early greying and hair loss. Smoking can hasten the aging process, which includes pigmentation loss. It is still debatable, though, whether greying is a predictor of illness, and if it is, it probably reflects underlying genetic variables.[6] Smoking damages hair follicles by exposing the body to harmful substances, lowering oxygen levels, and changing hormones. Because it increases oxidative stress and damages melanin-producing cells (melanocytes), it is a significant risk factor for premature greying. In a similar vein, extended UV exposure can cause early greying by initiating the same process.[41]

13.2[2] Nutritional deficiency:

Research on premature greying of the hair reveals different amounts of trace elements: some find lower levels of copper and higher levels of iron, while others find lowered levels of calcium, iron, and copper with unchanged levels of zinc. After taking oral iron supplements for five months, an 11-year-old kid with low ferritin and haemoglobin demonstrated a reversal of greying.[37]

Correcting vitamin shortages can reduce or reverse premature greying, according to scientific data. Key nutrients, their roles, and their dietary sources are compiled in the table. [41]

TABLE

NUTRIENT	EFFECT ON HAIR HEALTH	RECOMMENDED DOSAGE
biotin (vitamin h)	promotes collogen production and prevents hair loss	300 mcg daily
pantothenic (vitamin b5) acid	strengthens follicles, prevents greying	5-10 mg daily
copper	essential for melanin production	1.2mg daily
folic acid	supports keratin and melanin synthesis	400 mcg daily
selenium	enhances follicle stimulation and antioxidant	55 mcg daily

14. ROLE OF MICRONUTRIENTS IN HAIR PIGMENTATION:

Melanin, which is produced by melanocytes arising from the neural crest, determines the colour of hair. Eumelanin (black-brown) and pheomelanin (yellow-red) are the two pigments found in hair follicles that give hair its dark and lighter hues. This is a gene-regulated process. About 100,000 hair follicles make up a healthy scalp, and 90% of them are in the anagen (growth) phase. For healthy hair, these follicles need vital nutrients like vitamins, minerals, proteins, and antioxidants. Both the regular hair cycle and the fast division of follicular bulb cells depend on nutrients. Copper, zinc, iron, calcium, vitamins, proteins, antioxidants, and fatty acids are important components associated with early hair greying. Skin problems, hair whitening, scant hair, and hair loss can result from deficiencies, particularly in micronutrients.[42] About 100,000 hair follicles make up the human scalp, and 90% of them are in the anagen (growth) phase. For healthy hair creation, these follicles need proteins, vitamins, and minerals. Micronutrient deficiencies can affect pigmentation and cause premature hair greying since they are necessary for melanin formation and healthy melanocyte function.[6]

15. CLINICAL FEATURES:

The majority of people have some grey hair by the age of 60, and hair greying is closely associated with aging. After puberty, it typically starts near the frontal hairline in women and the temples and sideburns in men. The pattern and rate can differ across people and different areas of the scalp and are primarily hereditary. Although early depigmentation is uncommon, greying is typically irreversible and develops over time.[6] The prevalence of premature greying is not sex-related.[43] According to studies, the average age at which premature hair greying (PHG) first appears is between 11 and 14 years old, while occurrences can occur as early as 2 to 3 years. Usually diffuse, greying first appears in the frontal or temporal regions before moving on to the vertex and occiput. Because light interacts with keratin, non-pigmented hair appears white, grows more quickly, and is thicker and coarser.[44]

16. PSYCHOLOGICAL AND SOCIAL IMPACT OF PREMATURE CANITIES:

Concerns regarding the psychological effects of premature hair greying have grown due to its rising incidence, which affects Caucasians before the age of 20 and Africans before the age of 30. A cross-sectional study among medical students was conducted to determine its frequency and impact on mental health, self-esteem, and cultural adjustment, despite the fact that studies have been conducted in nations like Turkey and India.[45] Due to their naturally dark hair, Indians are more likely to get premature canities. With its increasing incidence and early onset, more individuals are seeking medical help due to its psychological impact.[46] Sudden hair whitening has been documented in historical people such as Ludwig van Beethoven, Mary, Queen of Scots, and Thomas More. This phenomenon is frequently associated with stress or traumatic experiences. Celebrities' contemporary testimonies also point to a potential link between stress and pigmentation changes in the hair.[47]

17. ROLE OF ETHNICITY AND GENDER:

White people get premature greying before the age of 20, Asian people before the age of 25, and Black people before the age of 30. African and Asian populations experience it less frequently and with less severity, whereas lighter-haired groups experience it more intensely. Men commonly grey in the temples and sideburns, while women start at the frontal area; the occipital region is usually impacted last; however, both genders are equally affected.[48]

18.INVESTIGATION:

In order to determine the underlying causes of premature canities, laboratory research is crucial. Haemoglobin estimation, serum ferritin levels, vitamin B12 levels, folic acid levels, biotin levels, and thyroid function tests (T3, T4, and TSH) are common examinations. These tests aid in the identification of endocrine disorders, anaemia, and micronutrient deficiencies that may be linked to early hair greying. According to a number of clinical investigations, vitamin B12, ferritin, and folic acid levels are frequently lower in patients with early canities than in premature hair greying; certain studies have also assessed oxidative stress markers and trace elements. As a result, suitable laboratory tests are helpful in determining potential causes and directing treatment of the illness.

Greying is thought to have a complex aetiology that involves oxidative stressors, environmental variables, nutritional factors, and genetic components. Premature hair greying (PHG) is thought to be mostly caused by genetics, with autoimmune conditions like vitiligo, pernicious anaemia, and autoimmune thyroid disorders being additional factors. Additionally, it has been linked to syndromes, such as Werner syndrome. PHG can also result from environmental variables such UV light and temperature, smoking, medications, trace element deficits, and nutritional inadequacies. It is also believed that photodamage, a significant factor in skin aging, does not accelerate hair greying. However, the precise aetiology or cause has not yet been identified. Finding any correlation between items like serum is the goal of this investigation.[6]

18.1 Greying duration and cause:

At the time of presentation, the average length of greying was 47.8 ± 32.4 months (range: 3 months–14 years). The length of greying did not differ statistically significantly between males

and females. The majority of patients reported that greying began in the temporal regions of the scalp (n = 25; 35.2%), followed by the frontal region in 13 (18.3%), the vertex in 10 (14.1%), the occipital in 8 (11.3%), and diffuse or undefined in the remaining 15 (21.1%) cases.

Other hairy areas have the following history of premature greying: eyebrows (one lady) and beard (three men); additional areas, such as the lashes, moustache, all the cases.[49]

Early Greying of Hair

↓

Detailed History

(Age, Family history, Diet, Drugs)

↓

Clinical Examination

(Diffuse / Patchy, Skin changes)

↓

Laboratory Investigations

CBC

Vitamin B12

Ferritin

Thyroid Profile

↓

Identify Cause

(Nutritional / Endocrine / Genetic)

↓

Management

18.2 Family history:

In 64 (90.1%) of the cases, a positive family history of PHG (at least one of the biological parents or siblings) was found. Even though an effort was made to focus on the history of PHG in older generations, with the exception of one peculiar instance, the index cases pertaining to the history of PHG in grandparents and second-degree maternal and paternal aunts, uncles, and cousins were not well remembered. Of the 64 cases, 50 cases (78.1%) reported PHG in one parent (22 maternal and 28 paternal; no statistically significant difference) and 14 cases

(21.9%) reported PHG in both parents. As a result, there was no clear inherited sexual preference. Additionally, 17 of these 64 patients (26.6%) said that at least one of their siblings had PHG.[9]

18.3 Correlation with haematology and biochemical parameters:

The study group's mean serum vitamin B12 level was statistically substantially lower than that of the normal population ($t(69) = -2.785$; $P = 0.007$). When compared to the normal population, the study group's mean serum TSH levels were statistically substantially higher [10] ($t(69) = 8.169$; $P < 0.005$). The patients' haemoglobin levels were found to be lower than anticipated for their age and gender, although the difference was not statistically significant. For females, the mean serum ferritin level was 35.41 ng/ml ($t(69) = 0.613$; $P = 0.544$), and for men, it was 55.86 ng/ml ($t(69) = -0.569$; $P = 0.573$). These results were not statistically different from the normal population. Only one case was male, and nine out of the 71 patients (12.7%) exhibited a positive interparietal cell IgG antibody. The majority of these patients were female. The serum levels of vitamin B12 were low in these nine patients. Fasting hyperglycaemia was not found in any of the patients. Of note, none of the patients with Vitamin B12 deficiency or raised serum TSH had any specific symptoms of the biochemical abnormality, except for complaints of a general feeling of weakness during heavy physical activity. [2]

19.DIFFERENT DIAGNOSIS:

19.1Vitiligo:

Different dermatological, systemic, and genetic disorders that impact melanocyte function or melanin synthesis the characterization by distinct patches and macules of should be distinguished from hair found in premature canities.

Poliosis is characterised by affected areas turning white, which helps differentiate it from diffuse greying. Alopecia Areata manifests as patches of hair loss. Melanocyte malfunction frequently results in non-pigmented regenerating hair.

Poisonous Anaemia linked to a vitamin B12 shortage that causes systemic symptoms including glossitis and exhaustion in addition to early greying.

The symptoms of hypothyroidism include dry, coarse hair and pigmentation loss. Often linked to early ageing.[2]

19.2Hyperthyroidism:

Generates altered pigmentation and hair loss as a result of elevated metabolic activity. Waardenburg Syndrome: A congenital disorder characterised by sensorineural deafness, heterochromia, and white forelock.

Sclerosis tuberous has ash-leaf patches, or hypopigmented macules, and may also have hypopigmented hair. Lighter skin and hair are the result of phenylketonuria's decreased melanin production.[2]

Inadequate Nutrition

Premature greying is frequently linked to deficiencies in vitamin B12, iron (low ferritin), folic acid, and biotin. Greying caused by drugs

Melanocyte activity may be impacted by several medications (such as chemotherapeutic medicines and chloroquine).

Research has shown a high correlation with premature canities and:

Lack of vitamin B12 Low levels of ferritin in the serum

Melanocytes are harmed by increased oxidative stress and thyroid dysfunction.[15]

20.MANAGEMENT AND TREATMENT:

The primary goals of managing premature canities are to address underlying causes and stop further development. Since there is currently no known cure, treatment is mostly supportive. Nutritional Management Control Correcting deficits in micronutrients is crucial: Supplementing with vitamin B12 Supplementing with iron (for low ferritin levels) The primary goals of managing premature canities are to address underlying causes and Biotin and folic acid Melanocyte activity and melanin synthesis depend on these nutrients. Health Care Administration Therapy for thyroid conditions Handling autoimmune conditions Stopping medications that cause hair to turn gray Thus: Supplementing with vitamins C and E Formulations of catalase or pseudo catalase They shield melanocytes from oxidative injury. Canities needs to be differentiated from hypomelanotic hair disorders. The latter may present in a diffuse or localized fashion. Pigmentary dilution disorders include various types of oculocutaneous albinism including Hermansky-Pudlak and Chediak-Higashi syndromes and Tietz syndrome. Disorders with disrupted melanosomes transfer resulting in characteristic silver hair include Ghiselli, Elejalde, and Chediak-Higashi syndromes. CROSS syndrome may also present with silvery hair [6]. In Menke′s syndrome, hair are sparse and light coloured with a steel wool quality and associated with shaft abnormalities. Metabolic syndromes like phenylketonuria, histidine Mia, and homocystinuria may also present with light-coloured hair. Outhouse disease, a disorder of methionine metabolism, also presents with light hair and recurrent edema. Localized whitening of hair, known as poliosis, may be seen in vitiligo, piebald’s, Wardenburg syndrome, Woolf syndrome, Zurkowski Margolis syndrome, and tuberous sclerosis. An acquired localized area of white hair should prompt the clinician to look for depigmentation of underlying skin to rule out vitiligo. Reports of sudden overnight graying of hair (canities subito) have been attributed to vitiligo, telogen effluvium, and alopecia areata. An acute episode of alopecia areata may present with very sudden overnight graying due to preferential targeting of pigmented hair by the autoimmune pathology; this never occurs in true canities.[9]

20.1 Topical treatment:

Agents that stimulate melanin Preparations of herbal antioxidants Management of Cosmetics. Hair colouring (short-term fix) Henna and other natural dyes Changes in Lifestyle stress reduction: a well-balanced diet. Steer clear of pollution and smoking.[51]

21.PREVENTION:

Prevention of the major goals of reducing risk variables and preserve melanocyte activity. The onset and progression of hair greying can be significantly delayed by a number of changeable factors, even while hereditary predisposition cannot be changed.[52] Nutritional Measures Sufficient consumption of vital micronutrients such vitamin B12, iron (ferritin), folic acid, and biotin. Melanogenesis and the health of hair follicles depend on these substances. Early greying has been closely linked to these deficiencies.[2]

Reducing Oxidative Stress: One of the main causes of melanocyte destruction is oxidative stress. Among the preventive tactics are: Antioxidant-rich diet (fruits, veggies) Refraining from smoking and contaminating the environment.

Changes in Lifestyle: Stress reduction techniques (yoga, meditation) A healthy sleep schedule Steer clear of using too many chemicals on your hair. Early identification of thyroid problems by medical screening Checking for nutritional deficits and anaemia.[53].

22.RECENT ADVANCES & EMERGING THERAPIES:

The complicated pathophysiology of premature canities, which includes oxidative stress, genetic susceptibility, and melanocyte stem cell malfunction, has drawn more attention from researchers. In order to provide more potent therapeutic approaches, recent developments concentrate on addressing these fundamental mechanisms.[2]

One of the main causes of premature greying has been shown to be oxidative stress Overproduction of reactive oxygen species, especially hydrogen peroxide, damages melanocytes and lowers tyrosinase activity, which hinders the production of melanin. Antioxidants like vitamin C and vitamin E prevent oxidative damage and preserve melanocyte function, while therapeutic strategies like catalase and pseudo catalase formulations aid in the breakdown of hydrogen peroxide.[9]

The function of melanocyte stem cells found in the hair follicle bulge region is another important field of study. Loss of pigment production results from these cells' malfunction or depletion. In order to re-establish melanogenesis, emerging medicines concentrate on activating or rebuilding these stem cells. Stem cell-based methods show great promise for the future, even if they are still being investigated experimentally.[53]

Important genes and signalling pathways involved in pigmentation have also been discovered thanks to developments in molecular biology. Melanocyte survival and melanin production depend heavily on transcription factors like MITF and enzymes like tyrosinase. Gene-based treatments that target these molecular pathways may aid in the restoration of normal pigmentation, albeit these strategies are still in their infancy.[26]

Moreover, the potential of innovative topical treatments including as melanin-stimulating chemicals, herbal antioxidant formulations, and pseudo catalase-based creams to enhance pigmentation is being investigated. These treatments mainly work by increasing melanocyte activity in the hair follicle and lowering oxidative stress.

Advanced drug delivery systems that enable the targeted delivery of medicinal medicines directly to hair follicles have been made possible by recent advancements in This strategy

reduces systemic adverse effects and increases nanotechnology medication efficacy, making it an attractive field for further study.

In general, current developments highlight a multi-targeted strategy that includes molecular control, stem cell regeneration, and antioxidant therapy. These new treatments offer hope for better control and perhaps reversal of premature canities in the future, even if there are still few therapy choices available.[54]

CONCLUSION:

Oxidative stress and melanocyte dysfunction are key components in the development of premature canities, a complex disorder impacted by genetic, environmental, and physiological factors. There is still little effective curative treatment, despite tremendous advancements in our understanding of its etiology. Reducing oxidative damage, managing related diseases, and correcting nutritional deficiencies are the main goals of current supportive treatment techniques. However, new developments in molecular biology, stem cell research, and antioxidant therapy present encouraging avenues for further treatment. The onset and advancement of hair greying may be postponed with early risk factor identification and suitable lifestyle changes. To prevent and reverse premature canities, further research is required to create focused and efficient therapy approaches.

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