

Clinical Perspectives on Alopecia: From Hair Follicle Biology to Advanced Therapies

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ABSTRACT

Alopecia, or hair loss, is a common medical condition that can affect anyone, regardless of age and sex. Although it is not a life-threatening condition, it can strongly affect a person's confidence, self-image and well-being. Hair loss can occur due to interruption of the natural hair growth cycle due to several factors such as genetics, hormonal changes, autoimmune responses, stress, nutritional deficiencies, medications, infections, or long-term hairstyling practices. Alopecia may be temporary or permanent based on the cause.

They can be classified into non-scarring alopecia and scarring alopecia. With proper management, non-scarring alopecia, which includes androgenetic alopecia, alopecia areata, telogen effluvium, traction alopecia, anagen effluvium, and trichotillomania, has a good chance in terms of regrowth of hair follicles. Early diagnosis of scarring alopecia, such as lichen planopilaris and frontal fibrosing alopecia is important since it involves an inflammatory stage with permanent destruction of the hair follicles. Inflammation leads to an imbalance in hair production. Diagnosis can be conducted via laboratory testing, trichoscopy, clinical examination, and sometime a scalp biopsy. The treatment methods have increased consequently over the years. The conventional treatment methods such as minoxidil and finasteride are in common usage, but other developments such as JAK inhibitors, PRP therapy, stem cell therapy, low-level laser therapy, and topical/systemic immunotherapy can provide better results. Hair transplants are considered an efficient treatment for chronic hair loss in cases of androgenetic alopecia. Apart from conventional therapies, aloe vera, amla, bhringaraj, fenugreek, onion juice, garlic, and coconut oil are used in combination for their nutrient-rich properties for hair and improving qualities of hair.

Keywords: Alopecia, hair loss, androgenetic alopecia, alopecia areata, telogen effluvium, hair growth cycle, hormonal imbalance, DHT, JAK inhibitors, PRP therapy, stem cell therapy, immunotherapy, hair transplantation, scarring alopecia, non-scarring alopecia, herbal remedies.

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INTRODUCTION

Alopecia is a condition where a person starts losing hair from the head or other parts of the body where hair usually grows. It affects individuals of all ages and backgrounds. This condition can lower self-confidence and affect patients both mentally and socially [1]. There are many types of alopecia, but the commonest are androgenetic alopecia, alopecia areata, and chemotherapy-induced alopecia [2]. Causes of the conditions are many, including stress, heredity, hormonal imbalances, nutrition, some sickness, as well as certain medications like those prescribed for cancer [3,4].

Although the FDA permits only two serendipitous drugs (finasteride and minoxidil) for the management of alopecia, there are many unapproved medications that are claimed to reverse the condition [5]. Other products that are claimed to reverse hair loss lack effective proof from controlled scientific experiments, thereby inhibiting wider use and commercialization.

Hair is an essential part of the body, derived from the ectoderm of the skin, and acts as a protective appendage. Along with sweat glands, nails, and sebaceous glands, it is considered an accessory structure of the integument. Since hair develops from the epidermis during embryonic development, it is likewise categorized as an epidermal offshoot. This essential structure is important for both safeguarding the body and improving beauty [6].

Hair falls out of the head on a daily basis, especially during bathing and brushing. Hair loss of 70-100 hairs per day is extremely typical; however, hair loss of more than 100 hairs per day for more than a few weeks is a major condition. Hairstyles get thinner when more hair falls out than grows in; if this procedure continues, baldness may result [7]. Alopecia usually starts with one or more small, circular, delicate bald patches on the scalp and progresses to complete scalp hair loss and whole-body hair loss [8].

Hair growth cycle and its mechanism

The cycle of hair growth is repetitive and is composed of the anagen, catagen, and telogen phases. In the anagen phase, a hair follicle is actively growing, whereas the catagen phase is marked by resorption of the hair follicle's lower part and eventual degeneration. When a hair follicle is in its resting state, it is called the telogen phase. From this point on, it continues to regrow. The hair cycle is shown in Figure 1 [7,9]. The most active phase of hair growth, commonly known as the anagen, lasts for a period of 2 to 7 years, and about 90% of hair in a healthy scalp is in this phase [10]. The anagen phase becomes shorter progressively after each cycle, causing the production of weaker and vellus hair. The phases that follow after the anagen are characterized by hair recession and are shorter in a healthy scalp [11].

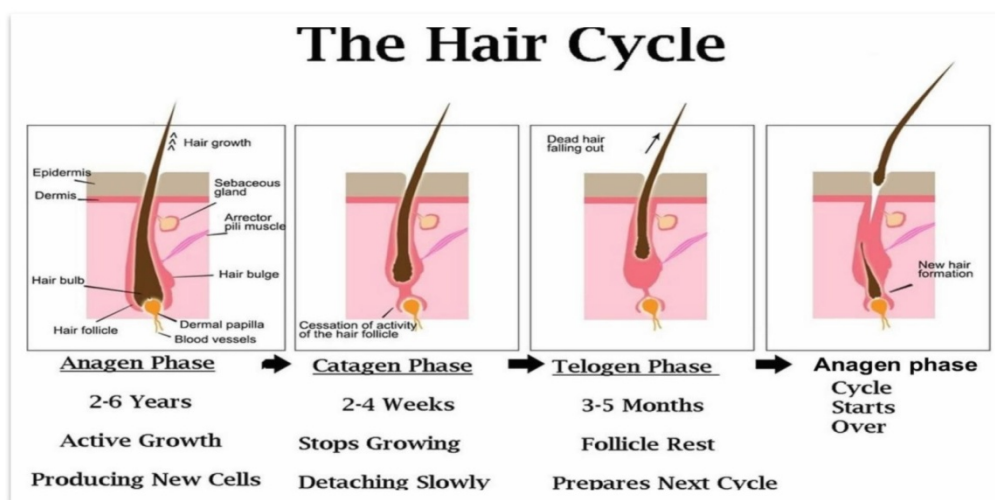


Figure 1: Hair Growth cycle [9]

- **Anagen phase** - Anagen phase can be as short as 2 years or as long as 6 years. Approximately 80% of hair is usually in the anagen phase.
- **Catagen phase** - In the catagen phase, the growth activity increases, and hair moves to the next phase. The catagen phase is between 2 and 4 weeks [12].
- **Telogen phase** - The telogen phase is a state at which the hairs move into a resting state. This phase lasts for 3-5 months. In general, 50-100 hairs at random are shed every day. An increase of more than 100 hairs per 6 constituents indicates a state of hair loss or alopecia, though it could be temporary [13].

All types of alopecia affect the natural cycle of hair growth in two ways—

1. **Shortening of the anagen phase-** Usually hair remains in the growth phase for a longer time than in the resting phase with a ratio of about 6:1. However, in situations such as androgenetic alopecia, anagen phase becomes shorter, and the telogen phase becomes longer, so more hair falls out.

2. **Shrinking of the dermal papilla-** The dermal papilla is the part of the hair follicle where the hair gets all the nutrients and signals necessary for hair production. When the blood vessels supplying it narrow, it will result in a lower supply of nutrients and oxygen to the hair follicle. Therefore, this will cause a reduction in the dermal papilla, resulting in weak, thin, and light-colored hair, which is very different from the thick dark hair [14].

TYPES OF ALOPECIA - Alopecia exists in several forms, each linked to different underlying causes. The most common types include androgenetic alopecia, alopecia areata, chemotherapy-induced alopecia (CIA), anagen effluvium, telogen effluvium, traction alopecia, and trichotillomania. This condition is generally divided into two main types: scarring alopecia, which results from inflammatory responses that damage hair follicles, and the more common non-scarring alopecia, which can be triggered by factors such as hormones, medications, nutritional deficiencies, and certain health conditions [15].

Type of alopecia	Description	Clinical features	Pathogenesis	Diagnosis methods	Treatment options	Prognosis	References
Alopecia areata	Autoimmune non-scarring patchy hair loss	Well-demarcated round patches, “exclamation mark” hairs	Autoimmune T-cellmediated follicle attack	Clinical exam, dermoscopy, biopsy	Corticosteroids, JAK inhibitors, immunotherapy	Variable, can remit or progress	[16]
Androgenetic alopecia	Genetic hormonal patterned hair loss in men and women	Men: biotemporal/vertex loss; Women: diffuse crown thinning, widened part	DHT causes follicle miniaturization and a shortened anagen phase.	Clinical patterns, trichoscopy	Minoxidil, finasteride (men), laser therapy, PRP, transplant	Chronic, progressive, but treatable	[17]
Telogen effluvium	Diffuse hair shedding	Diffuse hair thinning, increased hair fall	Premature shift of follicles into telogen Triggered by stress, illness, hormones, drugs	Clinical history, hair pull test, thyroid tests	Remove triggers, topical minoxidil, and nutritional support.	Usually reversible	[18]

Cicatricial alopecia	Scarring hair loss with follicle destruction	Smooth shiny patches; no follicular openings	Autoimmune or destructive inflammation	Scalp Biopsy	Antiinflammatory drugs, immuno suppressants	Irreversible; only progression can be slowed.	[19]
Chemotherapy induced alopecia	Hair loss is caused by cytotoxic chemotherapy agents.	Sudden diffuse hair loss (patchy or total scalp hair loss)	Chemotherapy targets rapidly dividing anagen matrix cells—abrupt anagen arrest.	History of chemotherapy, scalp exam	Scalp cooling, topical minoxidil,	Usually reversible; some drugs may cause persistent thinning.	[20]
Trichotillomania	Psychiatric disorder of compulsive hair pulling	Irregular patches of broken hair, bizarre patches	Compulsive self-pulling	Clinical exam, history, sometimes biopsy, dermoscopy	Behavioral therapy, psychotherapy, SSRIs	Chronic but manageable	[21]
Anagen effluvium	Sudden loss of anagen hairs from toxins	Rapid diffuse hair loss 1-2 weeks after exposure	Toxins damage rapidly dividing matrix cell	Clinical history	Remove cause, supportive care	Reversible in most cases	[22]
Traction alopecia	Hair loss at sites of chronic pulling/tension	Hair loss along the hairline and areas under tension	Chronic mechanical traction causing follicle damage	Clinical history, examination	Avoidance of traction styles, topical minoxidil,	Early stages are reversible; late-stage scarring is permanent.	[23]

Table 1: Types of alopecia

Androgenetic alopecia: Also known as male or female pattern baldness, androgenetic alopecia is a common form of hair loss that affects both men and women; however, it is more common in men. Women typically notice a general thinning of hair without a receding hairline, but men typically start with a receding hairline and thinning at the crown [24]. This condition happens mainly because the male hormone testosterone is metabolized into dihydrotestosterone (DHT) by the enzyme 5-alpha reductase. Approximately 10% of the

testosterone in the body is converted to DHT, which binds to hair follicle receptors more tightly and for longer than testosterone does [25, 26]. Over time, this causes the hair follicles to shrink and weaken, shortening the growth phase and lengthening the resting phase of hair growth. As a result, hair becomes thinner and eventually stops growing. Studies show that around 70% of men and 40% of women experience this condition during their lives. Prevalence across gender and race is shown in table 1 [26].



Figure 2: Androgenetic alopecia [24]

Alopecia areata: Alopecia areata is an autoimmune disorder that causes non-scarring hair loss or hair fall. It starts with a disruption in the hair follicle, making it weak, so the hair falls out [27]. Alopecia areata may incite in one or all parts of the head in patches, also called patchy baldness [28]. It also affects facial hairs and can develop anywhere on the scalp, beard, eyebrows, eyelashes, ears, etc [29]. The patches vary in size—from about 1 cm to much larger areas—and may develop in one or multiple spots [30]. Pregnant women

may experience little patches of hair loss as well [31]. While hair may regrow spontaneously, it can fall out again, and the new hair might differ in colour or texture from the original [32]. The exact cause of alopecia areata is still unclear, but researchers believe it may involve a targeted immune response by T cells against hair follicles, possibly triggered by genetic and environmental factors. The condition can come and go, and early management may help prevent it from spreading [33].



Figure 3: Alopecia areata

Types and Prevalence of AA: The types of alopecia can vary subsequently; alopecia universalis (AU) depicts the complete loss of hair on the head and body, as opposed to alopecia totalis (AT), which only affects the head. Then, there is alopecia ophiasis (AO), a rare subtype of alopecia areata that starts to occur from the back and sides of the head [34].

People with alopecia universalis or alopecia totalis usually have a lower chance of seeing major hair regrowth compared to those with alopecia areata (AA). About 7-30% of all alopecia areata are estimated to be caused by alopecia totalis and universalis [35]. About 60% of alopecia areata patients observe their first bald

patch before the age of 30, and the average lifetime risk of the condition is believed to be between 1.7 and 2.1%. Around 20% of instances involve minors [36, 37].

➤ **Traction alopecia:** It is often brought on by tight hairstyles like braids, ponytails, or buns. Traction alopecia is a form of hair loss that occurs as a result of constant pulling or stress on hair. Particularly around the hairline, this constant stress can cause harm to the hair follicles, resulting in breaking and bald patches. This condition can affect anyone, regardless of gender or cultural background, when the same styling habits are followed, but it is more common in middle-aged women who style their

hair regularly to look neat [38,39]. Some chemicals, such as those used for bleaching and colouring, can make the hair weaker, increasing the risk of hair fall. The condition usually begins with a thinning of areas under the most tension, but it can be avoided by taking regular breaks from the tight hairstyles and choosing looser hairstyles and limiting harsh treatments. If a person observes early signs of hair

loss such as area of thinning or bald spots, changing their hairstyle this way would help to prevent further damage. Encouraging good hair practices and accepting natural hairstyles would help in reducing hair-related issues, maintaining hair health, as well as promoting personal confidence [40].



➤ **Telogen effluvium:** Telogen effluvium represents a very common and temporary form of hair loss that happens when a large number of hair follicles enter the resting or telogen phase of the hair growth cycle before it normally would. This leads to an observable shedding or thinning of hair, which leads to worry about personal appearance. Hair loss occurs mostly because of physical or emotional stress, like surgery, childbirth, severe illness, or sudden weight loss.. The degree of hair loss normally varies based on how severe and long-lasting the triggering factor is, rather than what the trigger actually is, and then there are several types

of telogen effluvium. Acute telogen effluvium represents a condition lasting less than six months and usually resolves once the underlying cause is treated. Chronic telogen effluvium lasts for more than six months, and then there's chronic repetitive telogen effluvium, which affects hair with time [41]. Recovery would start as soon as the underlying reason for it is treated, and there would be a start towards hair regrowth. In some persistent or severe cases, it may be a good option to seek consultation with a dermatologist, which may be necessary to explore alternative treatments like topical preparations or dietary supplements [38].



➤ **Anagen effluvium:** Anagen effluvium is a form of hair loss that occurs when the hair in the active growth or anagen phase suddenly falls out, often due to strong medications like chemotherapy. This kind of hair loss can also be triggered by other drugs, including blood thinners, birth control pills,

diuretics, and some acne treatments. When this happens, the hair stops growing and enters a resting phase that can last as long as the treatment continues. In many cases, hair starts to grow back a few months after stopping the medication, but sometimes the loss can be permanent [42,43].



➤ **Chemotherapy-induced alopecia:** Hair loss due to chemotherapy is a very common side effect and can be one of the scariest parts of treatment for many patients [45]. Chemotherapy drugs are basically designed to target fast-growing cells within the body to kill cancer, but unfortunately they can't tell the difference between cancer cells and other fast-growing cells, like those in hair follicles. Because hair cells grow quickly when they're in the active "anagen" phase, the drugs often damage them, causing the hair to break or fall out [46]. After treatment starts, many of these hair cells stop

growing and enter a resting phase, known as "telogen," during which hair sheds more easily and doesn't grow back right away. This breaks the normal hair growth cycle, temporarily extending the resting phase. Luckily, hair normally regrows once chemotherapy is completed because the stem cells within hair follicles remain alive and can produce new hairs. Researchers are also finding methods that could protect these hair cells during treatment—by preventing them from dying or by helping them to stay in the growing phase longer [47].



➤ **Trichotillomania:** Trichotillomania, also known as hair-pulling disorder. It represents a condition where a person experience a strong urge to pull out their own hair—usually from the scalp or elsewhere on the body. This will result in visible loss of hair and sometimes damage to the skin. The behavior is often linked to stress, anxiety, boredom, or other emotional triggers, and many people may not even realize when they are doing it [49]. This condition is mostly common in children but can continue into adulthood, where it may cause emotional distress, lower self-esteem, and social embarrassment. Treatment mainly focuses on understanding and managing the triggers behind the behavior. Cognitive behavioral therapy (CBT), especially habit reversal training and mindfulness exercises, can be very effective. Children often improve as they grow older, especially when they are supported by a calm and understanding environment. Activities like crafts or using fidget toys can also help redirect the urge to pull hair. In some cases,

medication or participation in support groups may be helpful in managing the condition and improving overall well-being [50,51].

➤ **Cicatricial Alopecia:** Cicatricial alopecia, also known as scarring alopecia, refers to a group of hair loss conditions that results in permanent damage to the hair follicles and replaced with scar tissue. It arises because of the conditions such as inflammatory diseases, autoimmune responses, infections, trauma, or burns. It differs from non-scarring alopecia as it involves inflammation that irreversibly damages hair follicles, and cause permanent hair loss. Cicatricial alopecia patients will be able to identify with symptoms such as redness, itching, and pain. Over time, these symptoms will lead to mental stress and loss of confidence. Examples of scarring alopecia include disorders like follicular lichen planus, central centrifugal cicatricial alopecia, and discoid lupus erythematosus. Diagnosing a case of alopecia requires a physical, which involves clinical

examination and scalp biopsy. Although it should be noted that lost hair cannot regrow, early treatment can help control symptoms and prevent further damage. Treatment options may include anti-inflammatory medications, corticosteroids, and sometimes hair transplants [52,53].

ETIOLOGY

The causes of alopecia depend on the type. Broadly, it is classified into non-scarring (reversible) and scarring (permanent) alopecias.

- **Non-scarring alopecia:** In this the hair follicles are still alive, so hair can grow back if the cause is treated.

Examples include androgenetic alopecia, alopecia areata, telogen effluvium, traction alopecia, trichotillomania, alopecia due to syphilis, etc.

1. **Androgenetic alopecia (pattern hair loss):** Also called hereditary alopecia, male balding or female pattern hair loss. It is the most common type in men, women, and even adolescents. Progresses slowly.

Men: Hair loss on crown, temples, and mid-front scalp.

Women: Thinning mainly in the central scalp, usually keeping the front hairline intact [54].

2. **Alopecia Areata:** An autoimmune disease (the immune system attacks hair follicles). Causes sudden patchy bald spots on the scalp. Can affect children and adults of both sexes. Sometimes leads to Alopecia totalis - complete scalp hair loss.
3. **Alopecia universalis** - loss of all body hair [55].
4. **Telogen Effluvium:** A temporary condition where many hairs enter the shedding phase at once. Triggers: stress, illness, childbirth, poor nutrition, infections, hormonal problems, surgery, or medicines (e.g., antidepressants, blood thinners, contraceptives, or retinoids). Hair loss starts about 3 months after the trigger.

Usually recovers on its own within 6 months [56].

- **Scarring Alopecias (Cicatricial Alopecias):** Here, the hair follicles are destroyed permanently, so regrowth is not possible. Dividing into primary (disease directly damages follicles) and secondary (damage due to trauma, infections, or other causes).

Types of Primary Scarring Alopecia:

1. **Lymphocytic:** FFA, LLP, central centrifugal alopecia, discoid lupus erythematosus (most common type of cutaneous lupus), pseudopelade of Brocq, alopecia mucinosa, and keratosis follicularis spinulosa decalvans.

2. **Neutrophilic:** Dissecting cellulitis, folliculitis decalvans.

3. **Mixed:** Acne keloidalis nuchae, acne necrotica, and erosive pustular dermatosis[57].

The most common scarring alopecias are FFA (Frontal Fibrosing Alopecia) and LLP (Lichen Planopilaris).

1. **Frontal Fibrosing Alopecia (FFA)** - Appears as a gradually receding band of hair loss along the frontal hairline. Mostly affects postmenopausal women. Some patients (about 25%) may feel itching or pain, while others have no symptoms.
2. **Lichen planopilaris (LPP)** - mostly affects women. It starts with redness and scaling around hair follicles, then leads to patchy bald areas (usually on the crown/vertex). Sometimes affects body hair too. Symptoms can include itching, burning, or tenderness [58, 59].

Secondary scarring follicles are destroyed due to other external conditions:

- Localized scleroderma
- Pemphigoid
- Tumors (neoplasms)
- Radiation therapy
- Chemical or physical trauma
- Bacterial or fungal infections [60].

EPIDEMIOLOGY:

A 2019 multicenter retrospective study was performed to analyze “the frequency of the types of alopecia in patients consulting at specialist hair clinics and to assess for global variation.” Over 3000 diagnoses of alopecia were included, of which 73% were non-scarring and 27% were scarring.

- Nonscarring Alopecia Frequency

Androgenetic alopecia: 37.7%

Alopecia areata: 18.2%

Telogen effluvium: 11.3%

- Scarring Alopecia Frequency

Frontal fibrosing alopecia: 10.8%

Lichen planopilaris: 7.6%

Folliculitis decalvans: 2.8%

The frequency of the other alopecia types listed is less than 2% [61].

PATHOGENESIS

The hair growth cycle plays an important role in the process of hair regeneration. Follicles undergo several phases: anagen, catagen, and telogen. Disruptions in this hair growth cycle are mainly caused by genetic,

hormonal, or environmental factors and can result in premature entry into the telogen phase, leading to excessive shedding.

1. Genetic and Molecular Mechanisms: In conditions like androgenetic alopecia, genetic factors have an important role. Variations in some genes, particularly those that affect androgen receptors, can increase the risk of hair loss [62].

Studies have also discovered some of the molecular mechanisms that control the growth of hair follicle cycles. When these cycles are disrupted, hair follicles may potentially lose their capacity to develop properly, thus causing premature transition from the growth phase to the resting phase [63]. Several types of genetic variations, such as single nucleotide polymorphisms (SNPs), microsatellite repeats, and structural mutations, contribute to this susceptibility [64].

2. Hormonal mechanisms: Hormones play a major role in regulating hair growth by interacting with specialized receptors inside the dermal papilla cells (DPCs) of hair follicles. The effect of these hormones may vary from one body part to another [65,66].

- **Androgens:** Androgens are the hormones that regulate the hair growth by interacting with special receptors in the DPCs of hair follicles [67]. Hormones such as dihydrotestosterone (DHT) bind to these receptors; it changes how certain genes work, resulting in shrinking of hair follicles on the head, shortening the growth phase. With the passage of time, thicker, terminal hair is transformed into finer, less pigmented hair. Interestingly, while androgens can cause scalp hair loss, they also stimulate thicker hair growth in areas like the face, underarms, and pubic region [68]. Researchers find that without testosterone, as has been seen in eunuchs or castrated males; male pattern baldness is not observed [69].

- **Estrogens:** Estrogens help to prolong the growth phase of hair by acting on hair follicle receptors [70,71]. The causative factors and treatment approaches for conditions like hair loss and unwanted hair growth are different in postmenopausal and premenopausal women [72,73]. At the age of menopause, levels of estrogen and progesterone drop, which can result in problems such as thinning hair or female pattern hair loss. The high amount of estrogen during pregnancy causes the hair to be thicker and fuller, but when the level of estrogen decreases after childbirth, many women experience temporary hair shedding known as postpartum hair loss [74,75].

- **Prolactin:** Prolactin, the hormone mainly responsible for lactation, also affects hair growth, although its precise function is not known. Elevated prolactin secretion, as seen in hyperprolactinemia, may result in hair thinning similar to male or female pattern baldness and may also lead to acne, irregular periods, or excessive hair growth.

This might happen because androgen production increases due to elevated prolactin level, which can harm hair follicles. Notably, very low prolactin levels may also cause early hair loss, suggesting that balanced prolactin levels are important for healthy hair [76, 77].

- **Growth Hormone:** Growth hormone helps to keep the hair healthy by promoting hair follicles through several growth factors like IGF-1. It promotes the hair to shift from the resting stage to the growth stage. Low GH secretion may result in weak hair follicles, thereby causing hair thinning or hair loss [78]. Elevated GH level as seen in conditions like acromegaly, can lead to excessive hair growth, while very low GH activity, such as in Laron syndrome, is associated to hair loss and follicle issues [79,80].

- **Melatonin:** Melatonin is a hormone that is known for helping sleep-wake cycle but also plays a part in keeping hair healthy [81]. Melatonin's affect isn't limited to hair follicles—it's found in other skin parts like sweat glands and a blood vessel, showing it affects skin and hair in multiple ways. It has been proven that melatonin can help make hair colour stronger by boosting cells that produce pigment. It can also keep hairs growing longer by extending the growth phase of the hair cycle, which helps in preventing hair thinning and hair loss [82]. In addition, the activation of the antioxidant pathways by melatonin's provides protection against oxidative stress—a major contributor to hair follicle damage [83, 84].

- **Cortisol:** Stress effects hair health via a cascade of hormones that include CRH, ACTH, as well as cortisol—integral components of the body's stress response mechanism. When stress happens, CRH is released from the hypothalamus, which results in stimulate the pituitary gland to produce ACTH. ACTH signals the adrenal glands to secrete cortisol [85]. However, these stress hormones can harm hair follicles. They may cause hair to stop growing sooner than normal and slow down hair shaft development, making hair thinner or causing it to fall out [86]. In some hair loss conditions, high stress hormones can mess with the immune system around hair follicles, leading to the body attacking its own hair. Stress hormones can also destroy skin

components around hair roots, causing hair loss to worsen. So, both short-term and long-term stress can adversely affect hair health [87].

- **Thyroid hormones:** Thyroid hormones impact the anagen and telogen phases by supporting cell growth and activity in the hair follicle. During development, these hormones help the follicle to form correctly, and in adulthood they keep the anagen phase active, which is necessary for healthy hair growth [88]. When thyroid hormone levels are imbalanced, hair loss can happen in several ways. In hypothyroidism, low hormone levels slow down cell division and shorten the growth phase, leading to thinning hair and more shedding. In hyperthyroidism, high hormone levels increase the production of reactive oxygen species, which can cause stress and damage to hair follicle cells, disturbing the normal cycle. Thyroid hormones also affect hair color by stimulating melanin production, so imbalances may change hair pigmentation as well [89, 90].
- 3. **Inflammatory and immune mechanisms:** In addition to hormonal factors, the immune system also plays an important role in some types of hair loss, especially alopecia areata [87]. Abnormal T-cell activity and imbalances involving signaling molecules (cytokines) create inflammation that attacks hair follicles [91]. Research shows that certain groups of T-cells may be directly responsible for damaging follicle structures [92]. Oxidative stress—caused by too many reactive oxygen molecules and too few antioxidants—makes this inflammation and damage worse [93]. The body does try to activate its natural antioxidant defenses, but these are often not strong enough to fully protect against ongoing inflammation [94].
- 4. **Environmental and Lifestyle Factors:** External factors like pollution, poor nutrition, and long-term stress have been linked to hair loss. Pollutants in the environment can trigger inflammation that harms scalp health [95]. Not getting enough proteins, vitamins, or minerals can weaken the structure of hair fibers [96,97]. Chronic stress affects body systems that may speed up hair shedding [88]. Lifestyle habits such as smoking and irregular sleep also influence hair follicle health [98]. Smoking, in particular, has been tied to a higher risk of alopecia areata. This is because toxins in cigarette smoke create an inflammatory environment and increase free radicals, both of which damage the protective state of hair follicles [99]. In addition, certain medications—including chemotherapy drugs, biologics, and other immune-modifying treatments—can cause different types of hair loss [100].

TREATMENT

Treatment mainly focuses on the restoration of the normal hair growth cycle and the prevention of further loss by targeting the underlying cause. The principle is to inactivate or damage hair follicles, improve scalp circulation, and normalize hormonal-immune function. . Therapeutic approaches include topical or procedural methods that stimulate follicular activity and stimulate hair regrowth. Supportive measures such as adequate nutrition and stress control are also essential, as they create a favorable environment for healthy hair growth. Its aim is to achieve sustained regrowth, strengthen existing follicles, and improve overall well-being [101].

Medication for alopecia

Hair loss treatments vary depending on the cause and severity of the condition.

Common medications for hair loss include:

a) FDA-approved drugs:

Minoxidil: Minoxidil is a widely used FDA-approved topical medication for the treatment of androgenetic alopecia in both males and females. Minoxidil acts by stimulating hair growth through an increase in blood flow to the hair follicles. Increased blood flow leads to an increased supply of oxygen and nutrients to hair follicles, hence triggering the hair growth. In addition, minoxidil prolongs the anagen phase of the hair life cycle and shortens the telogen phase. Comes in 2% and 5% strengths; up to 40% of men and 20-30% of women experience regrowth [102]. It may cause side effects such as irritation of the scalp, itching, and redness. Hypertrichosis, a common side effect, can cause excessive hair growth in regions such as the face or neck [103].

Finasteride: This FDA-approved drug is used for androgenetic alopecia in males. Finasteride prevents the action of 5-alpha-reductase, an enzyme involved in the formation of dihydrotestosterone from testosterone, a potent form of male sex hormone. High levels of dihydrotestosterone have a strong correlation with miniaturized hair follicles in androgenetic alopecia. As a result, hair may become thinner and shorter over time, thus leading to a loss of hair. Finasteride prevents hair loss in men by reducing dihydrotestosterone in the scalp and thus prevents hair thinning. 80-90% of men notice less hair loss; results appear within 3-6 months. Side effects include sexual dysfunction in 1-2% of patients, and possible effects like depression and anxiety have been observed [104].

b) JAK Inhibitors: JAK inhibitors are small molecules which work by inhibiting the specific immune signals such as interferon- γ and interleukin-15 which cause balding in patients with alopecia areata [105]. JAK inhibitors have been used in both topically systemically.

- **Tofacitinib** is a selective JAK 1/3 inhibitor but used in different topical forms, but topical formulations usually work unpredictably on scalp hair because they don't get absorbed properly [106]. Tofacitinib given systemically (oral) has been used in adults and children. One retrospective analysis of 275 patients showed 54% good to complete regrowth and 26% partial regrowth. [107]
Common **side effects** include mild folliculitis, headache, and small amount of weight gain. Weight gain can be attributed to how JAK inhibitors impact leptin. Approximately 25% of patients relapse when they discontinue this medication [108]. The sublingual form of tofacitinib can provide better absorption and fewer stomach-related side effects because it avoids first-pass metabolism [109].
- **Ruxolitinib** is a selective JAK1/2 inhibitor available in a 1.5% cream formulation, but studies show the cream does not work well for alopecia areata. In a trial of 78 adults, applying the cream twice daily for 24 weeks did not give better results than placebo, and no major side effects were seen [110]. However, oral ruxolitinib works much better. In one study, taking 20 mg twice daily led to SALT 50 improvement in about 84% of patients. It may include side effects such as urinary infections (13.2%), headache (5.3%), elevated liver enzymes (7.9%), folliculitis (2.6%), and some weight gain (2.6%) [108].
- **Baricitinib**, a selective reversible inhibitor of JAK1 and 2, was recently approved by the FDA for severe alopecia areata in adults. The usual dose is 2 mg daily, which can be increased to 4 mg. For very severe cases or eyelash/eyebrow involvement, doctors often start with 4 mg, then reduce to 2 mg once good regrowth happens [111]. In a large phase-3 study, over 30% of patients achieved a SALT score ≤ 20 after 36 weeks. Around 35-37% also had major improvement in eyelashes and eyebrows with the 4 mg dose. Acne, infections, and increased levels of LDL cholesterol and CK (creatin kinase) are other common side effects [112].
- **Ritlecitinib** is an oral inhibitor of JAK3/TEC a tyrosine kinase expressed in hepatocellular carcinoma, and **Beprocitinib** an inhibitor of TYK2/JAK1 have both been tested for alopecia areata.

In a phase 2 study of adults with severe AA (SALT ≥ 50):

- 50% of people taking ritlecitinib improved (SALT ≤ 30).
- 64% improved with beprocitinib.

- Only 2% improved with placebo [112].

A large phase 2b/3 study tested different ritlecitinib doses. After 24 weeks, the highest dose gives SALT ≤ 20 in 38% of cases, but this happens in just 1% with the lowest dose treatment, showing a clear dose-response.

In a long-term phase 3 studies (ALLEGRO-LT), after 24 weeks:

- 62.5% had SALT ≤ 10 .
- 69.6% had SALT ≤ 20 [113].

Common side effects were headache, acne, and mild throat infection. Shingles occurred in 0.9%, and some patients contracted Covid, but this was very rare indeed.

- **Deuruxolitinib** (CTP-543) is a modified form of ruxolitinib. In a phase 2 study:
 - 58% of patients taking the highest dose (12mg twice daily) had SALT 50 improvement.
 - Only 21% improved on 4 mg twice daily.

Side effects included acne and headache (more common at higher doses). Some patients had increases in CK or LDL, but no bleeding or clotting events were seen [114].

c) Platelet-rich plasma (PRP) therapy: PRP is an innovative treatment approach that uses the body's own healing mechanisms to promote hair growth. It is commonly used for individuals suffering from several forms of alopecia and is considered a safe, nonsurgical option. The process begins with a simple blood draw from the patient, typically from the arm. This blood is then placed in a centrifuge, which spins the blood at high speed to separate its components. The spinning separates the blood into three layers:

- Red blood cell at the bottom**
- Platelet-rich plasma (PRP) in the middle**
- Clear plasma/serum at the top**

The PRP with middle layers is considered to be most important since it contains a higher concentration of platelets, growth factors, and healing proteins. With these components, damaged tissue can be repaired, enhancing blood circulation as well as stimulating hair follicles. After deriving PRP, it is injected into regions with thinning hair and where hair loss is clear. Growth factors are used to improve weak hair follicles, promote thick hair, and promote a healthy scalp [115].

Common side effects include soreness or a mild pain in the area of injection, which can sometimes be accompanied by redness, swelling, and bruising of the skin. Some patients may also experience headaches after being injected [116].

d) Stem cell therapy: This is innovative therapy used in managing hair loss, especially in androgenetic alopecia

and other non-scarring alopecia [117]. The therapy is performed by injecting patients with their own adipose-derived [118], mesenchymal [119], or hair follicle-derived stem cells. Stem cells are believed to modulate androgenetic alopecia by regenerating hair follicles and enhancing hair growth [117]. It is generally safe, but may have some mild side effects such as swelling, redness, tenderness, or itching at the injection site [120].

e) Immunotherapy: Immunotherapy is an emerging therapy which assists in improving the function of the immune system. In alopecia areata, an autoimmune condition, the immune system erroneously attacks hair follicles. Immunotherapy assists in lessening this attack so that hair can regrow. Topical immunotherapy using diphencyprone or DPCP is a common treatment in which these chemicals are painted onto the head to provoke an allergic reaction. The immune system gets diverted in this way, focusing less on the hair follicles. Patients respond very well to this treatment if the hair loss is not widespread [121]. Other treatment options include systemic immunosuppressants such as methotrexate or cyclosporin, which can be used in serious situations to relax

the immune system. Although they can be effective, they require intensive observation because they have potent side effects. Topical intralesional corticosteroids can also be used as immune-modulating therapies in addition to stimulating hair regrowth in affected patches [122]. Common side effects include mild redness, itching, or swelling in the affected area. Some people may suffer from allergic reactions like rashes or hives. Systemic treatments can cause fatigue, fever, or flu-like symptoms. In rare cases, they may trigger other autoimmune issues [121,122].

f) Low-level laser therapy (LLLT): Low-level laser therapy (LLLT) uses low-energy lasers with wavelengths between 600 and 1,100 nm to stimulate hair follicles and improve hair growth [123]. The lasers penetrate the scalp, enhancing cellular metabolism and blood flow to the hair follicles, which is believed to increase hair density. It is a painless, noninvasive treatment that uses gentle light to stimulate cells. It is commonly used to help treat hair loss, especially in androgenetic alopecia and alopecia areata. The light used in LLLT can enter the skin and activate the cells in the scalp. This improves blood flow, brings more oxygen and nutrients to the hair follicles, and helps “wake up” weak or inactive follicles. LLLT also boosts the activity of mitochondria, increasing ATP production, which supports healthier hair growth. Many studies show that people experience improvements in hair thickness and density after regular treatment [124]. LLLT is generally safe. Mild and temporary **side effects** include slight redness or itching of the scalp, mild

warmth during treatment, headaches or eye strain if eye protection is not used, and rare photosensitivity in people with sensitive skin. Overall, LLLT is a well-tolerated option for those who want a gentle, non-surgical approach to improve hair growth [125].

g) Corticosteroid therapy: It is a widely used treatment option for several types of alopecia, particularly alopecia areata. These are synthetic drugs that mimic the effects of hormones produced naturally by the adrenal glands, specifically cortisol. These medications work by reducing inflammation and suppressing the immune system, which is especially beneficial in conditions where the body mistakenly attacks its own hair follicles, leading to hair loss. In alopecia areata, the immune system mistakenly attacks hair follicles, causing inflammation and hair loss. Corticosteroids reduce this immune response, helping hair follicles recover and promoting regrowth.

Treatment options—topical, intralesional, or systemic—are chosen based on the severity and extent of hair loss. It can lead to several side effects, particularly with long-term use or high doses. Common local side effects include skin thinning (atrophy), skin discoloration, and stretch marks. When administered orally or via injection, systemic side effects may occur, including weight gain, mood swings, increased appetite, and sleep disturbances. Prolonged use can disrupt hormone balance, leading to adrenal suppression, and may elevate blood sugar levels [126].

h) Hair transplantation: Hair transplant is a surgical method where the hair-bearing skin is taken from one part of the scalp (usually the sides or back) and moved to the bald areas. The temporal and occipital regions of the scalp are not normally affected by the androgens and can be a source for hair-bearing tissue to be transplanted to bald portions of the scalp. It is mainly used for male pattern baldness. The two most common surgical procedures are follicular unit strip surgery (FUSS) and follicular unit extraction (FUE). Although effective; the procedure needs highly skilled doctors and careful handling. There is also no guarantee that the transplanted hair will grow long-term, as some follicles may still enter the resting phase [127, 128]. Common side effects include swelling, redness, tenderness, itching, and crusting in the donor and recipient areas, along with the feeling of tightness in the scalp [129].

i) Herbal and natural therapies: Herbal medications are alternatives for the treatment of alopecia that are safe and more efficient. Herbs slow the pace of hair loss while also boosting newer hair growth [130]. In addition to vitamins and minerals, herbs and botanicals, as well as probiotics, are the natural products that can be sold as dietary supplements all over the world without FDA

permission [131]. **Herbs used in the treatment of alopecia**

1. Aloe Barbadensis (aloe vera)

- **Chemical Constituents:** Barbaloin, Aloe-Emodin, Aloenin
- **Mechanism of action:** Aloe vera includes vitamins A, C, and E, which strengthen and repair hair strands. These vitamins encourage healthy cell development, support cell regeneration, and add shine to hair. Aloe vera gel also contains folic acid and vitamin B12, which prevent hair loss [132].

2. Phyllanthus Emblica (Amla)

- **Chemical Constituents:** Ascorbic acid (Vitamin C), Gallic acid, and Ellagic acid.
- **Mechanism of action:** It has antifungal properties that help prevent dandruff and other fungal infections and improve scalp health. Amla is a powerful 5-alpha reductase inhibitor [133].

3. Allium Cepa (Onion)

- **Chemical Constituents:** Protein (albumin), allyl propyl disulphide, diallyl sulphide, alliin, and allicin.
- **Mechanism of action:** Sulphur present in onion promotes strong, thick hair, thereby preventing hair loss and promoting hair growth. Collagen supports the production of healthy skin cells and hair growth [134,132].

4. Allium Sativum (garlic)

- **Chemical Constituents:** Allicin, amino acids, essential oil (0.06-0.1%) containing allyl propyl disulphide, diallyl disulphide
- **Mechanism of action:** Garlic has antibacterial properties, killing germs and bacteria that cause scalp damage and further hindering hair growth. Raw garlic is known to be rich in vitamin C, and promotes hair health. It also stimulates the production of collagen, which promotes hair growth [135].

5. Eclipta Alba (Bhringraj)

- **Chemical Constituents:** Wedelolactone, Daucosterol.
- **Mechanism of action:** Eclipta alba methanol extract promotes anagen in hair follicles in the telogen (resting) phase, thereby increasing hair growth [136,134].

6. Thea Sinesis (Tea):

- **Chemical Constituents:** Caffeine, Catechin, and Theaflavin.
- **Mechanism of action:** Tea contains caffeine, which stimulates hair follicles and increases blood flow to the scalp [136].

7. Trigonella Foenum-graecum (fenugreek)

- **Chemical Constituents:** Carbohydrates, proteins, lipids, alkaloids, flavonoids, fibers, saponins, steroidal saponins, vitamins and minerals, and nitrogen compounds.
- **Mechanism of action:** Several plant compounds in fenugreek can interact with a chemical in the body known as DHT (dihydrotestosterone). When DHT attaches to hair follicles, sooner or later it leads to hair loss. Fenugreek can reduce the ability of DHT to bind to hair follicles [133,132].

8. Cocos nucifera L. (Coconut):

- **Chemical Constituents:** Coconut oil is mostly made of saturated fats, especially medium-chain fatty acids like caprylic (2%), capric (50-80%), lauric (3%), and myristic acids (1%).
- **Mechanism of action:** Lauric acid sticks to hair proteins, protecting strands and roots from damage. Coconut oil goes deep into the hair shaft, guarding it from heat and pollution. Its antioxidants support healthy growth, and its natural anti-fungal and anti-bacterial properties help prevent scalp infections that can slow down hair growth [132].

9. Prunus amygdalus (Almond)

- **Chemical Constituents:** Almonds contain 40-55% fatty oils and about 20% proteins, mucilages, and emulsions. Bitter almonds contain 2.4-4.1% of colorless, crystalline cyanogenic glycoside amygdalin.
- **Mechanism of action:** Almond oil includes biotin, so massaging hair with it is a good method to give it enough of the vitamin to encourage hair growth and stop thinning [132].

10. Oscimum Sanctum (Tulsi)

- **Chemical Constituents:** Rich in eugenol (about 70%), eugenol methyl ether (20%), carvacrol, and caryophyllene. Also contains alkaloids, glycosides, saponins, tannins, major levels of vitamin C, and small amounts of organic acids like maleic, citric, and tartaric acid.
- **Mechanism of action:** Tulsi helps reduce hair loss by boosting blood circulation to the scalp, cooling it, and revitalizing hair follicles—making roots stronger and promoting hair growth [132].

CONCLUSION

Alopecia is a complex condition with many causes, such as hormones, genetics, stress, immune related problems, and environmental factors. All forms of alopecia affect the natural hair growth cycle and cause disruption in it, which leads to thinning or loss of hair. Even though common medications like minoxidil and finasteride are still widely used, newer alternatives such as JAK

inhibitors, platelet-rich plasma therapy, stem cell treatments, immunotherapy, as well as lowlevel laser therapy—are providing patients more choices and consequently better results. However, there is yet no single treatment that works for everyone. Because of this, early identification and individualized treatment plans are very necessary. Combining medical treatments with healthy lifestyle changes, good nutrition, and stress management can significantly enhance outcomes and overall well-being. To better understand the molecular and immunological mechanisms underlying alopecia and to create safer, more effective and long-lasting treatments, further research is required. Alopecia can be effectively treated with detailed and holistic approach, giving patients greater control over their condition.

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