

Alopecia—reason and possible treatments

Abstract

Alopecia (Hair loss) is a very common problem in recent scenario. Alopecia, which is associated with progressive thinning of the scalp hair, follows a defined pattern. Genetic involvement is pronounced but still poorly understood, however, advances have been achieved in understanding principle elements involve in alopecia. Alopecia can be classified in two category i.e. scarring (cicatricial) alopecia and non-scarring (non-cicatricial) alopecia. In cicatrical alopecia, hair loss accompanied with scars that destroy the hair follicle, which resulted into permanent hair loss. In case of non-cicatrical alopecia, permanent hair loss is not usually observed. The types, classification, clinical, therapeutic (herbal and synthetic drug treatment) and future therapies are discussed are reviewed in this paper giving emphasize on the diagnostic tests that are important in identifying type of alopecia in non-cicatrical (Androgen alopecia, alopecia areata, anagen effluvium and telogen effluvium) and cicatrical case (syphilitic alopecia, lupus erythematosus alopecia etc.). Recently, alopecia is considered as an autoimmune disease with genetic factors. Synthetic compounds used for treatment of alopecia are associated with the numerous side effects including dermatitis, itching, erythema, scaling, pruritus etc. Thus, considering the advantages of natural therapy, treatment options based on natural products are also discussed. Aromatherapy, Nutritional supplement, 5-dihydrotestosterone (DHT) blockers and 5- α -Reductase (enzyme) inhibitor are the proposed approaches for the treatment of alopecia. These approached offers advantages like low side effects and cost, improved patient compliance, easy availability and possibilities of multiple mode of action due to presence of phytoconstituents in natural product. We have also discussed the significance of available recent therapies in the pharmacological management of hair loss, which demands rational strategies for alopecia treatment.

Keywords: alopecia, hair loss, types of alopecia, classification of alopecia, natural therapy of alopecia, treatment of alopecia

Introduction

Alopecia is a condition where patchy, confluent or diffuse pattern hair loss occurs from different areas of the body, usually from the scalp.¹ In 1–2% of cases, the condition may spread to the entire scalp or epidermis known as either alopecia totalis or alopecia universalis, respectively. Incidence of alopecia is approximately 0.1–0.2% with a lifetime risk of men and women equally.² The etiology of alopecia is not entirely clear however many factors are reported in recent time and one of the strongest reason is associated with autoimmune disorders. High prevalence of mood change, depression and anxiety disorders are usually seen in patients with Alopecia.^{3,4} However, psychiatric morbidity can be both a cause and effect of Alopecia. In this review, we have systematically discussed the history of alopecia and research carried out aiming treatments along with pros and cons of different treatment modalities. Hair follicle growth occurs in cycles which are i) a long growing phase (anagen), ii) a short transitional phase (catagen), iii) and a short resting phase (telogen). The hair falls out (exogen) at the end of the cycle before a new hair starts growing in the follicle, beginning the cycle again.^{5–7} Each day, more than 100strands of hair reach to the end of their resting phase before they fall out. Hair loss in non-scarring alopecia is just a disorder of hair follicle growth cycle.^{8,9} Alopecia is usually triggered by autoimmune lymphocytic attack on the hair bulb. This leads in inflammation on hair bulb and causes anagen arrest which in turn shows abnormal loss of anagen hairs, which is also known as anagen effluvium.¹⁰ A related condition frequently observed in women is called ‘telogen effluvium’.

In this condition, the affected hairs undergo an abrupt conversion from anagen to telogen (anagen release) phase. Clinically, it is observed as localized shedding of hair in the telogen phase and can be identified morphologically as hair with a de-pigmented bulb.¹¹ It is well established that alopecia is an organ specific autoimmune disease with varied genetic predisposition.¹² In psychological disorders, emotional stress contributes to the condition of alopecia as suggested by different studies in which emotional trauma precedes the hair fall. However, few studies contradict these results, and suggest no link between emotional phenomena and the development of alopecia areata.¹³ A plausible explanation of the pathogenic mechanisms triggered by emotional stress could be associated with the production of neuro-mediators, which interfere the immunity. These sensory neurons release CGRP (a 37-amino acid neuropeptide), in dorsal root ganglion (DRG) and has potential vasodilatory activity leading to tissue hyperemia. Isoflavone (a phytoestrogen), and estrogen (sex hormone) increases CGRP production in sensory neurons by increasing its transcription suggesting that administration of isoflavone might increase Insulin growth factor (IGF-I) production, thereby promoting hair growth.^{14,15}

Hormonal regulation of human hair growth

Hormonal changes with season, sexual growth with age and regular development make differences in hair growth. Hormones affect many properties of dermal papilla size, growing time, and dermal papilla cell, movement of keratinocyte and melanocyte evolution.¹⁶ Growth hormone like IGF affects many things such as epithelial interaction

growing time, dermal papilla size, melanocyte and keratinocyte progression activity etc. Hair development in human body always coordinate by hormones, usually directly parallel to change in age, developmental stage and environmental changes so that upcoming new hairs is different in size and color.^{17,18}

The most obvious regulators of hair growth are androgens, nutritional food and thyroid function. During pregnancy some specific hormone (Prolectin and 17 α -oestradiol) are also released known as pregnancy hormone, which affect hair growth. These hormones maintain follicles in proliferation phase (anagen), but after child birth many hair follicles transfer into resting and regression phase (catagen), causing partial shedding.¹⁹ Hair follicle contains prolectin and 17 α -oestradiol receptors and this receptor inhibit human follicle and accelerate catagen phase, and reduce hair follicular growth and supports post-partum shedding.²⁰ Androgen instruct the hair follicle to undergo appreciate changes so that next hair cycle produce different hair with new color and size.²¹

Impact of testosterone on hair growth

The relationship between testosterone and alopecia is still complicated. Testosterone, a male androgen, exists in human body in different forms. The “free” testosterone that is not bound to proteins in body is the form of testosterone, which is mostly available to act within the body. Androgens play an important role in androgenic hair loss, even if androgen levels are within normal ranges.²²

Role of androgen on alopecia in male

Testosterone (T) is the main male androgen, which attach with androgen receptors in specific tissue. Testosterone is metabolized in to a more potent 5-dihydrotestosterone (5 α -DHT) by 5 α -reductase enzymes, which binds with androgen receptor to activate gene expression.²³ Androgenic alopecia (AGA) is caused by overproduction of 5 α -DHT, which regulating androgen sensitive genes.²⁴ 5 α -DHT have five times more binding affinity and potency than T for androgen-sensitive genes, which act as growth factors. High production of 5 α -DHT at elderly age induces down-regulation of growth factors, which causes thick-pigmented terminal hair to un-pigmented vellus hair resulting in baldness.²⁵ For adult body hair, all androgen dependent follicle require receptors for complete androgen insensitivity. Androgen and other steroid hormone pass through plasma membrane to target receptor of follicle and make androgen-receptor complex transcript. This type of conformational changes act on particular hormone response elements and thus regulate expression of specific, hormone-regulated genes, which regulate the androgen alopecia.^{26,27} In a study, reduction in testosterone metabolism using 5 α -reductase enzyme (5 α -R) showed high hair growth. 5 α -R enzyme present in two isoforms i.e., 5 α -reductase type 1 (5 α -R1) and 5 α -reductase type 2 (5 α -R2). However, 5 α -R2 present in beard and pubic hair only and therefore this enzyme do not show any effect on scalp hair.²⁸ Individuals with 5 α -R2 enzyme deficiency only produce female patterns of pubic and auxiliary hair, although their body shapes become masculinized. This means that 5 α DHT is necessary for beard, chest and upper pubic, like the prostate in male, while testosterone itself can stimulate the axilla and lower pubic triangle follicles characteristic of women. Stimulates beard growth in elderly men and castration (Gonadectomy) decrease testosterone release in human

body, which inhibits the beard and male pattern baldness. Finasteroid is a growth hormone, which is present in human body and promotes the hair follicle formation, this growth hormone leads to hair growth process by blocking the action of conversion of testosterone (T) to dihydroxytestosterone (DHT).²⁹⁻³¹

Role of androgen on alopecia in female

The recent studies have shown that around 6% of women under 50years of age are affected and this proportion increases around 40% of women at the age of 70years. Hair loss is considered as a genetic disorder and androgen dependent which occurs in a defined pattern. Terminal coarse hair in female in a male like distribution known as hisutism, affect 5–10% of the women. The reason mainly hyperandrogenism, a condition in which androgen metabolite like androstendione level is increased. Finasteroid plays an important role in treatment of histusim by inhibiting androstendione in female.³²

Types of Alopecia

Alopecia is a generic term that is generally used for hair fall. However, alopecia could be differentiate among androgen alopecia (common baldness), Alopecia areata, alopecia universalis, Syphilitic Alopecia, Telogen Effluvium, Stress induced alopecia, and chemotherapy induced alopecia. Based on occurrence, alopecia can be classified into two broad categories, i.e. Non-Cicatrical (Non-Scarring) and Cicatrical (Scarring). In cicatrical alopecia, hair loss accompanied with scars that destroy the hair follicle, which resulted into permanent hair loss. In case of non-cicatrical alopecia, hair loss is not permanent.³³

Non-cicatrical alopecia

Androgen alopecia

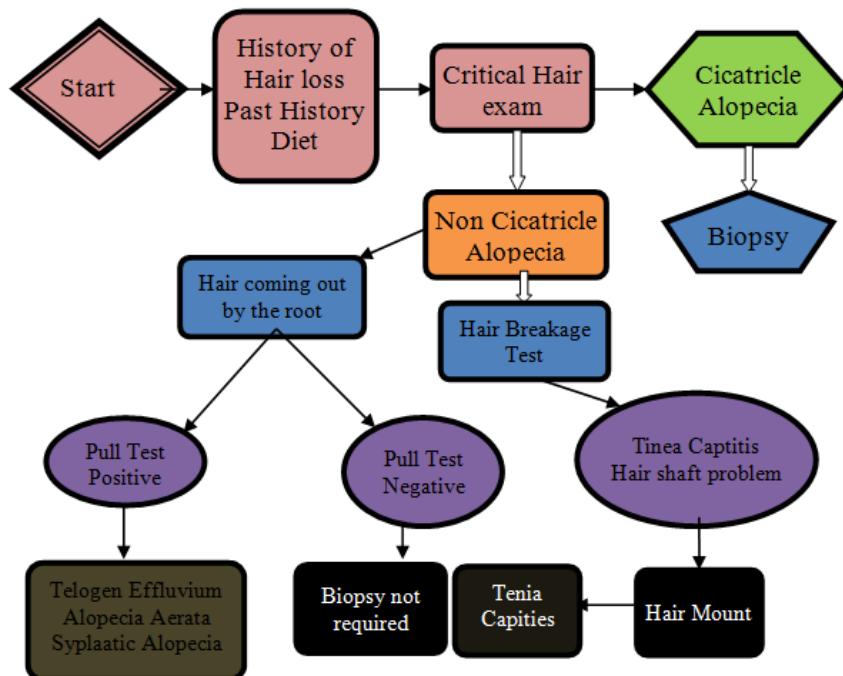
In androgen alopecia, hair follicles decreases in specific and specialized patterns over the scalp in male and female. Androgen especially testosterone is required for androgen dependent alopecia in men. In women, there is no evidence that the hair loss are truly dependent on hormone, although both male and female pattern alopecia results in decrease in hair follicle size. AGA is a common hereditary thinning of hair induced by androgens and this condition is known as common baldness in men and as female-pattern baldness in women.³⁴

Alopecia areata

Alopecia areata is characterized by patchy scalp baldness. Most common reasons of alopecia areata are pregnancy, hormone pills, thyroids disorder, and sexually transmitted disease like syphilis, gonorrhea, anemia and arthritis Figure 1.³⁵

Alopecia universalis

Alopecia universalis (AU) is a type of alopecia in which hair loss occurs from whole body. AU are usually observed in patients with thyroid and vitiligo disease. Patient do not have other symptoms, but experience a burning or itching sensation. It is associated with other conditions such as atopic dermatitis and nail changes (such as pitting).³⁶

**Figure 1** Diagnostics and test used in alopecia.

Anagen arrest/anagen effluvium

Anagen effluvium (AE) is associated with diffuse hair loss, which usually occurs after the administration of cytotoxic drugs, radiation treatment or various chemical agents and more appropriately can be characterized as hair breakage rather than hair loss. AE occurs during

the anagen phase of growth because hair bulb cell divide rapidly at this stage and are sensitive to cytotoxic agents. Cytotoxic drugs impair the mitotic and metabolic processes in actively growing hair follicles, leading to thinning of the shaft, which becomes fragile and susceptible to fracture with minimal trauma Figure 2.³⁷

**Figure 2** Natural Product used in alopecia treatment.

Telogen effluvium

Telogen effluvium characterized by sudden diffuse hair loss and resulting in general thinning of hair within months. Shedding is most common experienced observed by women after delivery and with patients undergoing chemotherapy. Other disease conditions can also cause this type of hair loss such as infection, severe chronic illness, and hyperthyroidism. These factors causes a disruption in the normal hair cycle and consequently leads in premature cessation of the Anagen (growth) phase.^{38,39}

Cicatricial alopecia

Cicatricial (scarring) alopecia is linked with inflammation, which subsequently destruct the hair follicle, resulting in permanent hair loss. Cicatricial alopecia is categorized into primary or secondary type. In primary cicatricial alopecia, hair follicles are affected by inflammation of cell by lymphocytic or it's predominant. Discoid lupus erythematosus is an example of primary cicatricial alopecia. In secondary type, inflammation due to systemic disorder such as sarcoidosis and granulomatous is involved.⁴⁰ Central centrifugal cicatricial alopecia is seen primarily in black women and has been referred to as “follicular degeneration syndrome” or “hot comb alopecia. Tinea Capitis is a type of cicatricial alopecia mostly observed in children. Tinea Capitis is a superficial fungal infection characterized by bare patches of skin on the scalp, with property of attacking hair follicle. Both acute and chronic inflammation after fungal infection damage the hair follicle leading to secondary cicatricial alopecia.⁴¹

Syphilitic alopecia

Syphilis is a disease caused by *Treponema pallidum* and usually occurs in the secondary stage and can occur in as many as 48% of population. Individuals with syphilitic alopecia suffer from a sudden onset and incomplete hair loss.⁴²

Chronic cutaneous lupus erythematosus

Chronic cutaneous lupus erythematosus is a common cause of scarring alopecia. Cutaneous lupus erythematosus, an autoimmune inflammatory disorder of the skin and can result to permanent hair loss which lead to cicatricial alopecia. It is characterized by disk-like plaques on scalp that may cause pigmentary changes and hair loss. Factors involved in chronic cutaneous lupus erythematosus are genetic predisposition, exposure to sunlight, toxins such as cigarette smoke and Hormones. It is 5times more common in females than males, and can affect males and females at any age but mostly often between the age of 20 and 40years mostly. Signs and symptoms of generalized chronic Cutaneous Lupus erythematosus includes plaques on anterior chest, upper back, backs of hands, Can affect palms and soles, can affect anogenital mucosa.⁴³

Trichotillomania

A condition of pulling of one's own hair for pleasure, gratification, or relief is known as trichotillomania. Patchy or full alopecia of the scalp, areas often have bizarre shapes, irregular borders, and contain hairs of varying lengths are usually observed in this type.^{44,45}

Alopecia: other types

Chemotherapy-induced alopecia (CIA)

Chemotherapy disrupts the proliferation of matrix keratinocytes in the anagen bulb, which produces the hair shaft during proliferation. This anagen hairs enter into catagen phase where hair shaft is compromised and hair follicle breaks causing hair fall. Hair loss is one of the most distractive and emotional side effect with chemotherapy. After chemotherapy treatment, hairs do eventually again re-grow, because the cycling follicular stem cells regenerate a new hair follicle.^{46,47}

Stress induced alopecia (SIA)

In general, stressed condition doesn't directly promote hair loss but behavioral and emotional changes leads to hair fall. Thus, balanced diet, exercise and reduction in stress level is the best treatment for SIA. Nerve growth factor (NGF) is the main and central element in perifollicular neurons. Neurogenic inflammation of neurons develops during stress and antagonize the effect of NGF, which is responsible for hair follicle development. In a study, stress is induced in animal models by fear and behavioral deficits to analyze the alteration of circulating NGF levels. It was suggested that sensory nerves and immune cells in the hair cells promote release of NGF in stress condition, which subsequently activate mast cell and cause migration of macrophages near the hair follicle. In consequence, apoptosis of hair follicles and hair follicle stem cells is increased in stressed mice, which cause hair loss.^{48,49}

Quantification of hair loss

Many resources are available for the assessment of alopecia. Quantification of alopecia categorized into scalp biopsies, semi biopsies (trichogram) and non-invasive (eg, trichoscopy, hair count and microscopic evaluation). Several test are available to determine the hair loss like hair pull test, pluck test, wash test etc.

Scalp biopsy

Biopsy is a very small process and performed under influence of local anesthesia. Dissected scalp hairs are subjected for hair count and photo-imaging by using microscopic. This test differentiate between non- scarring and scarring hair loss.⁵⁰ Scalp biopsy is a useful method for the evaluation in cicatricial alopecia and some cases of noncicatricial alopecia. In scalp biopsy 4mm punch biopsy can be used for a more definitive diagnosis, which can be vertically or horizontally oriented. On the other hand, vertical or longitudinal punch biopsy is appropriate for the assessment of alopecia's associated with lichenoid infiltrates. The ideal location for biopsy is depends on the presumed diagnosis. For example, in noncicatricial alopecia, a punch biopsy in the center of the lesion is appropriate whereas in cicatricial alopecia, the punch should be taken from areas of inflammation.⁵¹

Daily hair count: In this test, hair counting should be performed from the morning combing or during hair washing. This is the clinical hair evaluation method and hair is collected in a plastic transparent poly bag for about 10–14days. If hair counts more than 100 to 150/day, it is considered as hair fall condition.⁵²

Hair pull test

This test is performed to evaluate diffuse scalp alopecia. The number of pulled hairs is evaluated by counting under ultramicroscope.⁵³

The pluck test

In pluck test, a single hair starch out by the root sheath and the plucked hair root is examined under electron microscope to check the growth phase and to determine defect in any phase i.e. anagen, catagen and telogen. Tiny bulb is present in telogen hairs without sheaths at root. In the telogen effluvium disorder, a high percentage of hairs under microscope is seen whereas in anagen, sheath is attached to the hair root. Anagen effluvium shows decrease hairs in resting phase and increase number of damaged and broken hair.⁵⁴

Wash test

The wash test is a valuable method in which hairs shed during shampooing is collected. In this test, hairs were washed, counted and divided into groups of 3cm or shorter, (considered telogen vellus hairs), intermediate length (3–5cm), and 5cm or longer. Patients with 10% telogen vellus hairs were classified as having androgenetic alopecia.⁵⁵

Trichoscopy

This test performed with the use of video dermoscope. In this test, scalp and hair structure visualized at many fold magnification (currently magnification folds range from 10–75 folds). As an example of alopecia condition, trichoscopy magnification folds show “black dot” and “yellow dot”. Yellow dot defined microclimation of marks hairs and black dot indicate non-microclimation hair. Trichoscopic evaluation is broadly grouped into hair signs, pigment patterns, vascular patterns and interfollicular patterns. Trichoscopy evaluation detect different type of alopecia i.e. androgen alopecia, alopecia areata, tinea capitis and hair shaft disorder.^{56,57}

Etiopathogenesis of alopecia

Alopecia is multifactorial disease, which involve different factors like hormonal changes, genetic factors, immunological factors and psychological factors.

Genetic factors

In the genesis of alopecia, high frequency of family history are involved with varying from 10–42%. In the family history, 37% patient are those whom hair loss began at the age of 30 years. Hereditary is also another indication for participation of genetic factors in hair loss with atrophy. There are correlations between the presence of atrophy and the severity of alopecia areata, which is frequently present a more serious form. A study from Hospital das Clinicas (FMUSP) suggest the presence of atrophy in 42.8% of the alopecia areata patients against 26.6% of the paired controls. Numerous studies have demonstrated an important participation of genetic factors in the genesis of alopecia areata, which is possibly a polygenic disease with participation of related genes both in terms of susceptibility and disease severity.⁵⁸ It has been reported that 80% of the AGA related to genetic factor. Recent studies like genome-wide association (GWS) analyses have reported a large number of single nucleotide polymorphisms (SNPs) involved in androgenetic alopecia

progression. Chromosome X region contain two neighboring genes of ectodysplasin A2 receptor (EDA2R) and androgen receptor (AR) which is involve in androgenetic alopecia. Magdalena Marcińska et al reported that Xq12, comprising AR/EDA2R and region on 20p11 are major determinants of AGA in European populations.⁵⁹

Immunological factors

There are many immunological mechanisms are involved in the pathogenesis of alopecia. In the expression of alopecia, the autoimmune diseases, circulating antibodies and immunologically active cells are responsible for inflammatory infiltrations. Autoimmune diseases such as thyroid, pernicious anemia, lupus erythematosus, myasthenia gravis, polymyalgia rheumatic, ulcerative colitis and diabetes are reported to be the reason of alopecia. In the thyroid disease, 8–8.11% incidents of alopecia are possible and in the case of vitiligo, patient experienced four times more alopecia like symptoms as compared to patients with other diseases. In AGA patient, particularly anti-gastric parietal cell antibodies and thyroid anti-microsomal antibodies are frequently detected. These antibodies represents immunological phenomenon, which is involving in the pilar follicles. The anti-antibodies in follicular structure can be detected by western blot, immunofluorescence, IgM and by C₃ antibodies. Some authors have reported anti-follicular antibodies in 100% of the hair loss, against 44% normal control in western blot analysis. Circulating antibodies are identify in matrix, internal membrane and follicular structure by indirect immunoofluorescence.^{60,61}

Physiological trauma

Emotional stress is certainly precedes the alopecia, that generate neuromodulator changes which lead to genesis of alopecia lesions. It is associated with the restriction in blood flow in capillaries surrounding the hair follicles and dermal papilla, which lead in shortage of nutrients thus impair cell metabolism causing adverse effect on the hair growth.⁶²

Hair growth promoters (alopecia treatment)

Treatment regime of alopecia

Hair growth promoters that claims to be useful for alopecia treatment steadily growing as a multibillion-dollar market. Few research areas and many patents claiming as the anti-alopécic agents and yet, pharmaceutical alopecia management still within a clinical trial phase. There are many drugs available to increase the hair growth on head. Minoxidil topical solution (Rogaine 2%, Pharmacia & Upjohn, USA) is clinically approved and effective hair growth stimulant. Minoxidil also reduce hair loss and maintain hair growth. However, minoxidil was developed originally as an anti-hypertensive drug and hair growth was a side effect. Numerous other allopathic and herbal products are available in market for hair growth and hair care.^{63,64}

Herbal drug used in treatment of alopecia

Use of synthetic drugs are associated with many adverse drug reaction and generally not prescribed for effective and safe management of alopecia. Therefore, the natural origin drugs are emerged as an alternative to reduce the adverse drug reaction associated with synthetic drug.⁶⁵ To cope the alopecia problem, here

we have looked into the treasure of natural origin and found a number of natural product, which are effective for alopecia treatment. Lots of benefits are associated with natural products such as less side effect, improved patient compliance and polyherbal treatment gives more than one mode of action for treatment of Alopecia.⁶⁶ The natural product used in the treatment of alopecia are usually DHT blockers and 5- α -Reductase blockers, and provides nutritional requirement and improved scalp blood circulation Table 1. Iron, copper, chromium, zinc and magnesium are very important to maintain healthy hairs and natural products provide these mineral to regulate the blood circulation that increases hair growth. Vitamin like B complex (B6, B3, B5 and folic acid), biotin (biotin source are: egg yolk, whole grains, rice and milk) and vitamin A are important for hair growth, as it keeps the hair root lubricated.⁶⁷ There are some natural product that have proved potential for inhibiting 5 α -reductase and DHT like *Camellia sinensis*, Ginseng, and *Pygeum africanum*. Herbal drugs are also used in aromatherapy, which are taken orally and the essential oils present in herbal drugs directly reach to blood vessel, where they attached to receptors. These essential oils work on a cellular level to calm the nervous system, providing with a sense of well-being. Aromatherapy stimulates blood circulation at base of hair follicles and it is proved as effective and safest way to cope up with different type of hair loss (alopecia). However, exact pharmacological actions of these herbs and oils are yet not known.⁶⁸ Many natural product having potency for treating alopecia without producing side effect. Plant extracts having multiple phyto-constituents and can treat hair loss either by providing or by acting as DHT and 5- α -Reductase

blockers or nutritional supplements. They also have essential oil, which can helpful in treating alopecia by aromatherapy by improving blood circulation in scalp Table 2.⁶⁹

Table 1 Classification of alopecia

Non-cicatricial alopecia (non-scarring)	Cicatricial alopecia (scarring)
Androgenetic Alopecia	Central centrifugal cicatricial alopecia
Alopecia areata	Trichotillomania
Telogen effluvium	Tinea capitis
Anagen effluvium	Alopecia areata (Syphilis)
alopecia universalis	Chronic Cutaneous Lupus Erythematosus

Synthetic drugs in the treatment of alopecia

Various drugs, which are in use for the treatment of alopecia are originally developed for other diseases such as anti-epileptics drug (phenytoin), antihypertensive (diazoxide), topical corticosteroids.⁷⁰⁻⁷² Table 2 represents such few drugs available in market for alopecia treatment.

Current therapies in the alopecia treatment

Management of patients with alopecia areata is a challenging as a number of risk factors and mechanisms are involved in its etiology Table 3.

Table 2 List of some herbs used for hair growth & hair care

Botanical name	Common name	Chemical cons	Mechanism of action
<i>Persea americana</i>	Avocado	Isoflavonoid, Terpanoids	5- α reductase type I inhibitor and Sebum secretion inhibitor
<i>Acacia concinna</i>	Shikakai	Terpenoids	Pods extract is used as hair cleanser for control of dandruff.
<i>Arnica montana</i>	Arnica	Terpenoids	Flowers extract is used in hair tonic material.
<i>Allium cepa</i> (Onion)	Onion	Tepenoids	For hair dyeing.
<i>Betula pendula</i>	Birch	Polyphenol	Extracts of leaves used as anti- dandruff.
<i>Brassica</i> spp.	Mustard	Tannins	Seed oil is used as hair oil and useful for hair nourishment.
<i>Camellia sinensis</i>	Tea	Catechins, Epicatechins	5- α reductase inhibitor
<i>Calendula officinalis</i>	Marigold	Flavonoids	Flower extract is used in hair cream for smoothing effect.
<i>Capsicum annum</i>	Pepper	Isoflavone	Nerve stimulation and production of IGF- I
<i>Centella asiatica</i>	Mandukparni	Essential Oil	Whole plant extract is used for growth & maintenance of hair.
<i>Cocos nucifera</i>	Nariyal	Essential Oil	Aromatherapy
<i>Eclipta alba</i>	Bringraj	Glycosides	Anagen phase enlargement.
<i>Hibiscus rosa sinensis</i>	Gudhal	Alkaloids, Flavone	Follicular enlargement and prolongation of Anagen phase
<i>Humulus Lupulas</i>	Hop	Essential Oil	5- α reductase inhibitor
<i>Lawsonia inermis</i>	Henna	Terpenoids	Hair growth promoter.
<i>Nardostachys jatamansi</i>	Jatamansi	Phytoestrogen	Extracts of rhizome is used in hair tonics for their growth.
<i>Phyllanthus embelica</i>	Amla	Vitamin C	Fruit extract is used in oils for hair growth promotion.
<i>Panax ginseng</i>	Ginseng	Phytoestrogen	5- α reductase inhibitor
<i>Pygeum africanum</i>	Pygeum	Ferulic acid esters	Lower down DHT levels
<i>Saw Palmetto</i>	Serenoa	Flavonoids	5- α reductase inhibitor and lower down DHT levels

Table 3 The synthetic drug used for treatment of hair loss with disadvantage and side effect

Drug	Mechanism of action	Use	Disadvantage/side effects
Minoxidil (Rogaine, Headway)	Act by gradually enlarging and lengthening hair follicles in AA.	Treatment of Androgenetic Alopecia (AA)	1. It is expensive, 2. Tachycardia, angina pectoris, fluid retention
Finasteride	It is specific inhibitor of type 2–5 alpha reductase.	Tablet is taken once a day for treatment of AA	1. It is expensive and should be continued. Used only for men and not for women and children.
Zinc	Zinc inhibits 5a reductase enzyme.	AA, Pattern baldness, can be used with vitamin B6 azelaic acid	1. It is expensive and Used should be continued
Skinoren/Azelaic Acid	Potent inhibitor of 5 alpha reductase	In acne, skin conditions, AA	
Ketoconazole (Nizoral)	Antiandrogenic effect cause reduction in testosterone and other androgens by adrenal gland and reproductive organs	In AA, Antifungal agent, In Sebbohemic dermatitis	Skin Irritation
Cyproterone Acetate with Ethynodiol diacetate	Block peripheral action of male hormones in female body	Hormonal contraceptive, severe acne, Hirsutism, women, female pattern baldness.	Continued use is required Breast tenderness, headaches, decreased libido
Cimetidine (Tagamet)	Blocks binding of dihydro testosterone to its receptor.	Stomach and duodenal ulcers, Hirsutism, AA	Not used by men due to feminizing effects.
Cyproterone Acetate	Block binding of DHT to its receptors	Hirsutism in women	Not used by men
Spironolactone	Antiandrogenic	In treatment of high BP, AA.	Limited used in men
Prezatide copper (Lamin)	It is copper binding peptide and required for melanin production.	As a anti-inflammatory	It is available only to transplant surgeons
Copper chloride	Androgen inhibitor of 5alpha reductase	Used after transplant	Skin, Eye and Respiratory Irritation
Arginine/arginine and cysteine (Amino Acid)	Help hair follicle to make more hair	For treatment of Androgenetic alopecia	It is expensive

Glucocorticoids

Systemic corticosteroids have been used in patients with extensive alopecia. The side effects of systemic steroids include hyperglycemia, osteoporosis, cataracts, immunosuppression, mood changes, obesity, dysmenorrhea, acne, and cushing syndrome. Topical and intralesional steroids have used as a first line of therapy for the management of the alopecia. Glucocorticoids are popular due to its anti-inflammatory effects for Alopecia areata.⁷³

Intra-lesional corticosteroids

For circumscribed alopecia areata, intra-lesional corticosteroids are the first line treatment. In this treatment, triamcinolone acetonide (10mg/ml) is administered in multiple (0.1ml) injections. Additional treatments are repeated every 4–6 weeks. Corticosteroids is very good option in children due to their painless application and wide safety margin. Systemic corticosteroids are the second line treatment for alopecia due to its side effects. Treatment range from first to six months, but long treatment should be avoided due to side effects especially when children are treated.⁷⁴

Oral mini pulse steroids

Betamethasone oral mini pulse steroids therapy is a convenient and effective treatment modality for extensive alopecia areata. However, it is proposed that randomized controlled trials with standard therapies on a larger number of patients are required to give more insight into the efficacy and safety of oral mini-pulse therapy.⁷⁵

Minoxidil

Minoxidil affects hair follicles by inducing proliferation and differentiation of the dermal papilla cell at the bulb base. In recent years, a quite a lot of studies have been focused on different types of approaches such as minoxidil, vasodilator to prevent excessive hair loss, enlarge exiting hairs and promote hair growth by affecting hair growth cycle in AGA. In alopecia treatment when minoxidil is used, it causing telogen hair premature termination and increase the anagen phase which lead to hair growth. Minoxidil has shown considerable results in the management of alopecia. Combination therapy of minoxidil 5% lotion with anthralin has shown a better result. Minoxidil still in first line drug in the treatment of AGA, yet it remains the only drug and medical treatment in alopecia which proven efficacy when used topically and is the only drug (treatment) approved for hair loss in women's alopecia.⁷⁶

Anthralin

It also acts through its immunosuppressive and anti-inflammatory properties via the generation of free radical scavenging activity and it is suitable for treatment of children under 10 years of age. Adverse effects with anthralin are scaling and staining of treated skin and fabrics.⁷⁷

Topical immune-modulators

Topical immunotherapy relies on inciting an allergic contact dermatitis (ACD) by applying potent contact allergens to the affected

skin. Adverse effects of topical immunotherapy include pruritus, mild erythema, scaling, and postauricular lymphadenopathy.⁷⁸⁻⁷⁹

Phototherapy (PUVA)

Phototherapy with oral or topical psoralen plus ultraviolet-A light (PUVA) is the techniques used in management of alopecia. The use of 8-methoxysoralen with UVA radiation was found to be effective in 85% of patients in alopecia universalis. Insufficient evidence as well as the risk of cutaneous malignancies with PUVA makes it less favored treatment option.⁸⁰

Cyclosporine-A (CSA)

Cyclosporine A is a common antimetabolite drug used in post-transplantation patients, which exerts its effect via inhibition of T-cell activation. A common cutaneous side effect is hypertrichosis, which prolong the anagen phase. Other side effects are gingival hyperplasia, headaches, tremors and hyperlipidemia.⁸¹

Tacrolimus

Tacrolimus is a topical calcineurin inhibitor that inhibits transcription following T-cell activation of several cytokines including interleukin 2; interferon and tumor necrosis factor. Yamamoto et al. reported that tacrolimus has ability to stimulated hair growth in mice.⁸²

Sulfasalazine

The drug has immune-modulatory effect and inhibit inflammatory cell and chemical mediator like cytokine CD4/CD8 lymphocyte, and interleukin-10 secretion. Sulfasalazine has been shown to inhibit the release of these chemical mediator, which promote the directly hair growth proliferation and differentiation of perifollicular cell of hair bulb.⁸³

Mesotherapy

Mesotherapy is a combination treatment with ayurveda, homeopathic and allopathic and employs multiple injections of medications, plant extracts, vitamins, and other ingredients into the target tissue. However, this approach is expensive and not very effective, thus its widespread use is restricted.⁸⁴

Hormone antagonists

5AR inhibition by using anti-androgens in topical formulation has always been an attractive proposition, with minimal risk of systemic adverse effects. A strong and comparable inhibition of DHT was observed with topical finasteroid and can be considered for hair density maintenance.⁸⁵ Another drug dutasteride, is a dual 5AR inhibitor and is 3times more potent at inhibiting 5AR-Type II and 100times more potent at inhibiting iso-enzyme type-I compared to finasteroid. Combination of these drugs with oral contraceptive pills (OCPs) provide additional hair growth stimulatory effects. It has been suggested that estrogens act by prolonging the anagen phase and by increasing sex hormone binding globulin (SHBG) production, which reduces androgen levels.^{85,86}

Future potential treatments that may be effective in AGA

Low-level laser/light therapy (LLLT)

LLLT laser comb is approved by the FDA as a safe treatment for

alopecia treatment in male and female respectively. LLLT stimulate anagen re-entry in telogen hair follicles, prolong duration of anagen phase, and increase rates of proliferation in active anagen hair follicles and to prevent premature catagen development. LLLT increased adenosine tri-phosphate (ATP) production, modulation of reactive oxygen species (ROS), and transcription factors.⁸⁷

Prostaglandin-based therapies

Drugs that block prostaglandin signaling or enhance prostaglandin are under trial for evaluation of their efficacy and safety in alopecia. The prostaglandin analogue latanoprost and bimatoprost, commonly discovered to be promoters of hair growth.⁸⁸

Hair stimulating complex (HSC)

Hair stimulating complex (HSC) is a human cell derived bioengineered formulation containing epidermal growth factors, follistatin (manufactured from naturally secreted growth Factors), proteins and bio-products that are derived from culture of newborn cells grown in an oxygen-deficient embryonic environment. In phase I trial, intradermal application of HSC, resulted in significantly increased hair density, hair shaft thickness and number of total terminal hair without any significant adverse effects. Phase II trials are ongoing to gather more evidence in favour of HSC.^{89,90}

Nitric oxide and vitamin D3

Nitric oxide (NO) gel has been shown to promote hair follicle formation through stem cell development, hair regeneration, hair shaft elongation and increased growth rate in rats and mice. The vitamin D receptor (VDR) is expressed in hair follicle keratinocytes during late anagen and catagen. Additionally, vitamin D3 (VD3) has also been shown to modulate Wnt10b gene expression. Studies based on VD3 gene knock-out and VD3 supplementation in nude mice has revealed encouraging hair growth promoting effects of VD3.^{91,92}

Conclusion

There are many useful evaluative approaches available to aid diagnosis of both cicatricial and noncicatricial alopecia. Scalp biopsies, microscopic evaluation, trichoscopy, or hair counts are just to name a few. Following diagnosis a variety of treatments are available. In the recent scenario cosmetics from natural products are of greatest popularity. Herbal cosmetics have attracted and growing demand on the grounds that of their good effect and comparatively lesser side effect. In alopecia treatment market a lot of products are available which are formulated from herbal extracts as their basic ingredients. Herbal hair tonic, herbal hair oil, herbal hair lotions and herbal pills available as a product for external or topical application for hair fall treatment. The use of natural system stimulate the dermis and provide protein, nutrition, antioxidant in a natural way. Further, promising new therapies are being considered, including those that target peroxisome proliferator-activated receptor pathways and hair follicle stem cells for the treatment of alopecia. Continued advances will aid the clinician in effectively treating both cicatricial and noncicatricial alopecia in the future.⁹²

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Conflict of interest

The author declares that there is no conflict of interest.

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