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## Baldness: Comprehensive aspects and its reassuring remedies

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**Abstract:** The medical term for baldness is alopecia. It refers to the condition where hair is lost from one or more areas of the body, commonly from the scalp. Balding can result from various factors, including genetic predisposition, environmental triggers, exposure to chemicals, medications, nutritional deficiencies, excessive stress, or prolonged illness. Depending on the pattern of hair loss and its underlying cause, alopecia is categorized into several types. Among these, androgenetic alopecia and alopecia areata are of primary concern. Presently, there are numerous synthetic treatments available for managing alopecia (both areata and androgenetic alopecia), including minoxidil, corticosteroids, zinc, dithranol, systemic cortisone, tretinoin, irritants, immunosuppressants, azelaic acid, and finasteride. However, these treatments often fail to provide satisfactory and long-lasting results for individuals with alopecia. Moreover, these synthetic products are associated with adverse effects, such as itching, redness, dermatitis, flaking, and irritation. Natural remedies have been explored to address the challenge of hair loss. A variety of herbs have demonstrated efficacy in managing alopecia. These natural remedies operate through mechanisms such as nutritional support, 5- $\alpha$ -reductase and DHT (dihydrotestosterone) inhibition, aromatherapy, and improved scalp blood circulation. Utilizing these natural treatments offers several advantages, including patient adherence, minimal side effects, easy accessibility, affordability, and diverse modes of therapeutic action for hair loss management. In this review, we highlighted the causes of alopecia and its promising, cost-effective treatments, which might significantly alter the lives of those impacted by baldness by providing them with a road to greater self-assurance, well-being, and quality of life.

## Introduction

“Eunuchs are not vulnerable to gout nor do they get bald,” said “Hippocrates,” an ancient Greek physician, around the year 400 BC (Chadwick and Mann, 1950) from an observation, and it remained in the *Hippocratic Corpus* – the book of medical records written by Hippocrates, as a brief medical fact or proverb. Aristotle was fascinated by the fact that eunuchs did not go bald and even had no hair

on their chests despite being bald himself (Montagna and Ellis, 2014). This surveillance was either overlooked or forgotten for the upcoming twenty-five centuries. The medical field remained confused by male pattern alopecia till an anatomist named James B. Hamilton, in 1949, further made the same examination over eunuchs and from there he figured out that androgens are responsible and essential for male pattern baldness as eunuchs are the men those who have

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gone through castration and his later classification of grades and pattern of baldness becomes the leading light for the study of alopecia (Hamilton et al., 1942; Hamilton et al., 1951). Several scrutinizes on hair fall have established the androgenic significance, and his classifications remain the only acceptable. He also proved decisively that androgens, genetic predisposition, and age all have a role in the extent and progression of male pattern baldness (Ellis et al., 1958). In Androgenic Alopecia (AGA) thick hair gradually converts into vellus hair through an androgen-mediated process called miniaturization (Dhurat et al., 2020). In AGA, the key enzyme is 5- $\alpha$  reductase, which converts Testosterone into Dihydrotestosterone (DHT). This DHT is a pathogenic androgen (Brotzu et al., 2019). Androgenic Alopecia poses a significant challenge, primarily due to its association with social discrimination and its potential to negatively impact self-confidence. Two distinct approaches exist for mitigating Androgenic Alopecia (ADA): a temporary approach involving cosmetic strategies and a more lasting solution centred around pharmaceutical interventions and herbal remedies. This review article focuses on identifying effective drug treatments and exploring the ethnomedicinal contributions that facilitate hair regrowth and stimulate growth. This review also highlights types of androgenic alopecia, genetic markers and endocrinological effects on AGA.

## Different forms of alopecia apart from androgenic alopecia

### Telogen effluvium

It is the most common form among all alopecia; in this case, most of the follicles rapidly undergo an exogen phase from the telogen phase, ultimately forming club hair pattern shedding. This alopecia occurs due to daily sunlight exposure or taking minoxidil daily (Headington et al., 1993).

### Alopecia induced by chemotherapy

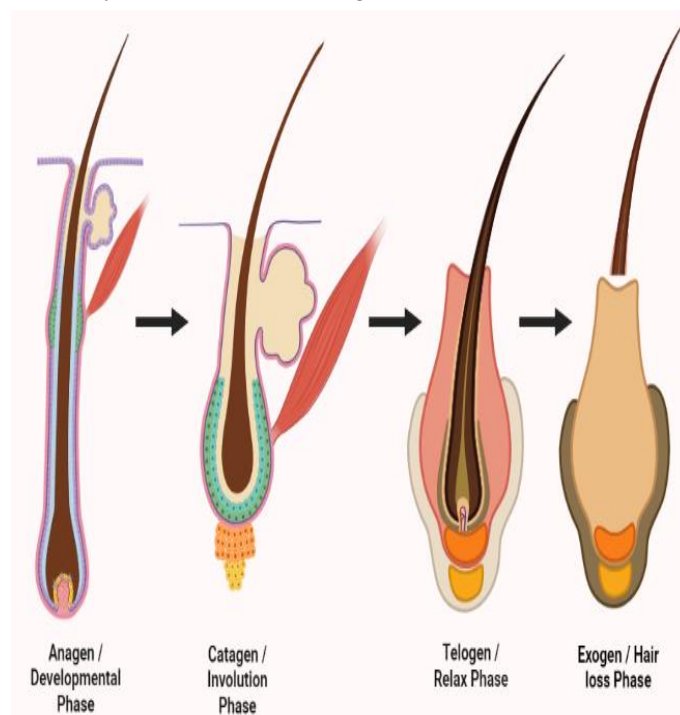
Hair shafts are produced by a particular cell type, keratinocyte, produced from the anagen bulb. This proliferation of keratinocytes may be inhibited by some drugs used in chemotherapy; the hair shaft reduces its rigidity due to the loss of keratinocytes, ultimately leading to alopecia. Chemotherapy-mediated alopecia induced by the p53 gene, an experiment that occurred on p53-inhibited mice treated with chemotherapeutic drugs exhibited no hair follicular disruption (Botchkarev et al., 2000). A novel technique was introduced to reduce chemotherapy-mediated alopecia by inhibition of CDK 2 (Cyclin dependent kinase 2) protein (Davis et al., 2009).

## Alopecia areata

It is a type of autoimmune disorder in which lymphocytes kill hair bulb cells of the anagen phase. In these cases, alopecia occurs by either scalp hair loss, called alopecia totalis or scalp or body hair loss, known as alopecia universalis (Cotsarelis and Millar, 2001). This type of alopecia is created by T-cells, which can situated mainly at the bulb region of the hair follicle and lead to a reversible pattern of hair loss (Gilhar et al., 1998).

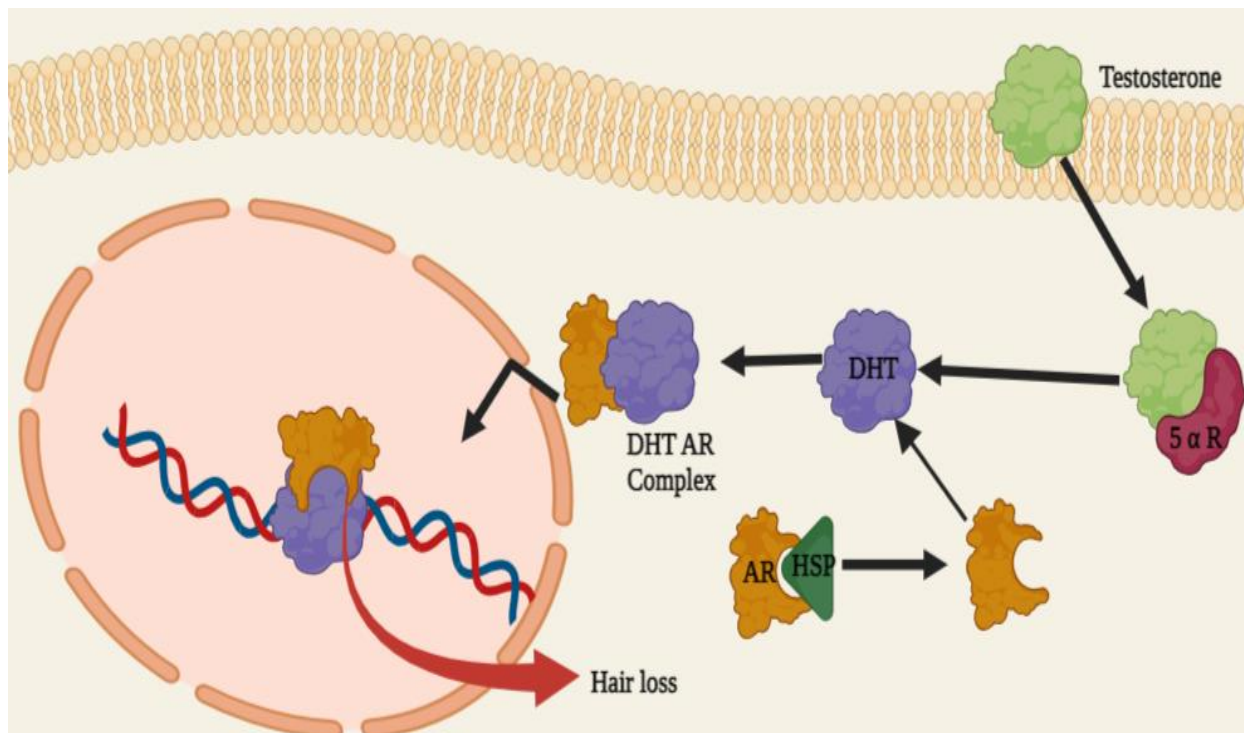
### Pathophysiology

Four phases are involved in the hair growth cycle: a developmental phase, anagen, an involitional phase, catagen, a relaxed phase telogen and the expansion phase exogen. The duration of the anagen phase is about 2-6 years, and it plays a significant role in forming nearly 8-9% of hair and determining the length of hair. Around 5% of hair formation is in catagen, and the rest is in telogen. Hair loss occurs at the exogen phase near about 100 hairs/day is common (Whiting et al., 1998).



**Figure 1. Different phases of hair development**

The 5- $\alpha$ -reductase molecule exists in two distinct isoforms: type 1 and type 2. The conversion of testosterone to DHT (dihydrotestosterone) occurs by 5- $\alpha$ -reductase and DHT binds with androgen receptor. Sebaceous organs, sweat glands, and keratinocytes contain type 1- 5- $\alpha$ -reductase chemicals. The exterior root sheath of the hair spore, seminal vesicles, vas deferens, epididymis, and prostate all contain type 2- 5- $\alpha$ -reductase chemicals. The mechanism of DHT receptor antagonists and 5- $\alpha$ -reductase blockers is depicted in Figure 2.



In general, the androgenic receptor (AR) is inhibited by Heat Shock Protein (HSP). However, in androgenic alopecia, HSP removed from AR and DHT bind with active AR, producing DHT AR complex which stimulates the production of TGF- $\beta$  protein. This protein induces hair follicular cell apoptosis, leading to androgenic alopecia.

Androgenetic baldness patients exhibit excessive dihydro-testosterone production, elevated levels of androgens, and heightened 5 $\alpha$ -reductase reception within the bald scalp. The activation of the androgenic receptor subsequently diminishes the anagen, or growth phase, in the typical hair development cycle. Within androgenetic baldness, this excessive activation leads to the progressive reduction of follicular size during a progressively shorter anagen stage. Consequently, this process culminates in the

dominant gene, a single pair of sex-linked components, and a dominant gene with extended or variable penetrance.

One or both sides of the family may have a history of androgenetic baldness (Stough et al., 2005; Kaufman et al., 2002).

#### Genetic markers

Androgenetic alopecia is thought to be the outcome of the unusual susceptibility of follicles (hair follicles) in the hairline to coursing androgenic hormones (Kaufman et al., 2002), attributable in relation to increment within the number of receptors for androgens (Sinclair et al., 1998). Type 1 and 2 5- $\alpha$  reductase catalyzed the transformation of testosterone where 5- $\alpha$  dihydrotestosterone is produced. It is accepted that both the isoforms assume one part within

**Figure 2. Mechanism of androgenic alopecia: Testosterone converts into Dihydrotestosterone (DHT) through an enzyme 5 $\alpha$ -Reductase**

production of finer and narrower follicular hair that might struggle to penetrate the skin's epidermal layer.

In pathological instances, a reduced 5:0 ratio of anagen to telogen hair is observed, diverging from the established 12:1 norm (Bienenfeld et al., 2019; Sadick et al., 2017). Despite the necessity of androgen presence and hereditary predisposition in male androgenetic baldness, the underlying pathophysiology of this condition remains elusive. While androgenetic baldness in men appears to possess an inherited component, the precise mode of inheritance remains to be deciphered. In men with polygenic inheritance, theories include a single autosomal

the digestion as well as activity of androgenic hormones, as well as their appearance shifts relying upon the body's location. Liu and Yamauchi (Liu and Yamauchi, 2008) observed a greater articulation of type 1 5- $\alpha$  reductase within the hair follicles, proposing that they assume a vital part in hair development influenced by androgens. The hair follicles contain a large amount of stem cells, which are located in the lump where they intermittently switch back and forth between enacted and quiet stages to keep up with the undifferentiated cell populace and produce new hair follicles. It is noticed that when immature microorganisms are on murine hair follicles at dynamic

conditions, the quality of FOXC1 is profoundly communicated, keeping up with undeveloped cell attachment and elevating progress to the peaceful condition. FOXC1 is a record factor engaged with the guideline of undeveloped turn of events as well as the eye. This likewise initiates the flagging of two proteins (Nfatc1 and bone morphogenetic protein), assuming one part into the support as well as improvement of follicles (hair follicles) (Wang et al., 2016).

Androgen and heredity are the significant media of albeit androgenetic alopecia. The hereditary qualities of androgenetic baldness are mind-boggling. 5- $\alpha$  reductase and androgenic receptor (AR) qualities are appealing possibilities for androgenetic baldness.

Ongoing genome-wide affiliation AGA research has recognized solid affiliation in the X chromosome's signals. The AR quality as well as the ectodysplasin A2 receptor (AR/EDA2R locus in Xq11-q12) displayed solid AGA signals (Heilmann et al., 2013). According to Prodi et al. (2008), AGA connects AR and EDA2R genes on a chromosome. SNP rs1385699, situated within EDA2R, showed the most effective affiliation signal, whereas the variation within AR rs6152 displayed minor importance. Although the job of EDA2R in androgenetic baldness is not distinct, measurable examinations exhibit that the relationship of markers between EDA2R and AR gives off an impression of being the aftereffect of linkage imbalance (Prodi et al., 2008). Maternal heredity plays a significant role in androgenetic alopecia, which is determined by the AR region located on X chromosome associated with EDA2R (Hillmer et al., 2005). Those discoveries accentuate the significance of the adrenoceptor quality answerable because of the greater risk of androgenic baldness in men, which has been proved in several independent studies. However, a genetic code impact has not happened in ladies (Martinez et al., 2018).

### Genome-Wide Association Investigation and Risk Loci for Androgenetic Alopecia

According to Heilmann et al. (2013), androgenetic baldness occurs by a multigenic factor that plays a significant role in the complicated pathway involved in androgenic baldness (Heilmann et al., 2013). Those researchers distinguished 4 dangerous androgenetic alopecia loci in 12p12.1, 5q33.3, 2q35, 3q25.1. The 2q35 shows the most grounded affiliation indication. The WNT10A quality contained in this location is communicated within the lump throughout the anagen period of the hair development hoop.

It has also been displayed to genotypically affect hair follicle articulation (Heilmann et al., 2013).

A meta-evaluation by Liang et al. (2013) recognized six recent dangerous androgenetic alopecia loci in 18q21.1, 17q21.31, 7q11.22, 7p21.1, 2q37, 1p36.22 as well as a solid relationship for androgenetic baldness in 20p11 with the AR quality (Redler et al., 2013). In the Chinese community, 20p11, the dangerous locus of androgenic baldness was observed by Liang et al. (2013). There is a danger zone at 3q26, which was distinguished within a German population (Hillmer et al., 2008) and a diversity within the APCDD1 quality situated within 18p11.2 has additionally been related to androgenetic baldness (rs3185480). That last diversity is intriguing because APCDD1 is a Wnt flagging inhibitor (Shimomura et al., 2010). The recognizable proof of another defenselessness autosomal quality within those autosomal locations proposes that non-androgen-dependent routes are additionally associated with the pathogenesis of androgenetic baldness (alopecia) (Rathnayake and Sinclair, 2010).

### Traditional treatments

AGA can be treated clinically, which is usually partitioned into androgen-dependent and androgen-independent. Agonists that are androgen-dependent work against androgen, e.g., diminish testosterone amounts, fill in as androgen receptor antagonists, or 5- $\alpha$ -reductase inhibitors (5-ARIs). Androgen-independent medications act through various mechanisms apart from hormones (Varothai and Bergfeld, 2014).

### Inhibitory Agents of 5 $\alpha$ reductase

In Androgenetic Alopecia (AGA), more testosterone is converted into dihydrotestosterone (DHT) due to the activity of 5 $\alpha$  reductase. However, a current strategy for managing AGA involves blocking this conversion of testosterone to DHT at the tissue level. In this strategy, a particular drug targets both isoforms of 5 $\alpha$  reductase (type 1 and type 2) to inhibit the conversion process. Dutasteride and finasteride are potent drugs inhibiting both type 1 and type 2 5 $\alpha$  reductase, as shown by (Hirshburg et al., 2016). Another drug used in AGA is minoxidil. It stimulates hair growth through various mechanisms. For instance, it increases the permeability of calcium into epidermal cells, which ultimately induces hair growth. Additionally, it stimulates the mitotic division of keratinocytes (Jones et al., 2018). Some inhibitors of 5  $\alpha$  reductase are given below (Table 1).

**Table 1. Dosing, Adverse effects and counselling points of 5-AR inhibitors (Hirshburg et al., 2016; Jones et al., 2018).**

Drug	Dosage	Side Effects	Counselling Points
Finasteride oral tablets (Rx only)	1 mg day by day	Orthostatic hypotension (9%), dizziness (7%), erectile dysfunction (5%-19%), ejaculatory dysfunction (1%-7%), decreased libido (2%-10%).	It may take 3 months or longer to notice the benefit. Should proceed with the item to keep up with results. Secondary effects might diminish over the long run; pregnant females or those of childbearing age ought to stay away from direct contact with squashed or broken tablets.
Dutasteride oral tablets (Rx only)	0.5 mg daily	Reduced libido (3%), gynecomastia (<1%), impotence (<5%).	It may take 3 months or longer to notice the benefit. Should proceed with the item to keep up with results. Secondary effects might diminish over the long run; pregnant females or those of childbearing age ought to stay away from direct contact with squashed or broken tablets.
Minoxidil topical foam/aerosol 5% (OTC)	One-half capful twice daily	Local erythema (6%), pruritus (6%), hair tone or surface might change	Hair tone or surface might change. Should proceed with the item to keep up with results. Foam might liquefy on warm fingers, so should run cold water over fingers and dry hands before use.
Minoxidil topical 2% or 5% solution (OTC)	1 ml twice daily	Local erythema (6%), pruritus (6%). hair colour or texture may change	Hair colour or texture may change. Must continue the product to maintain results.

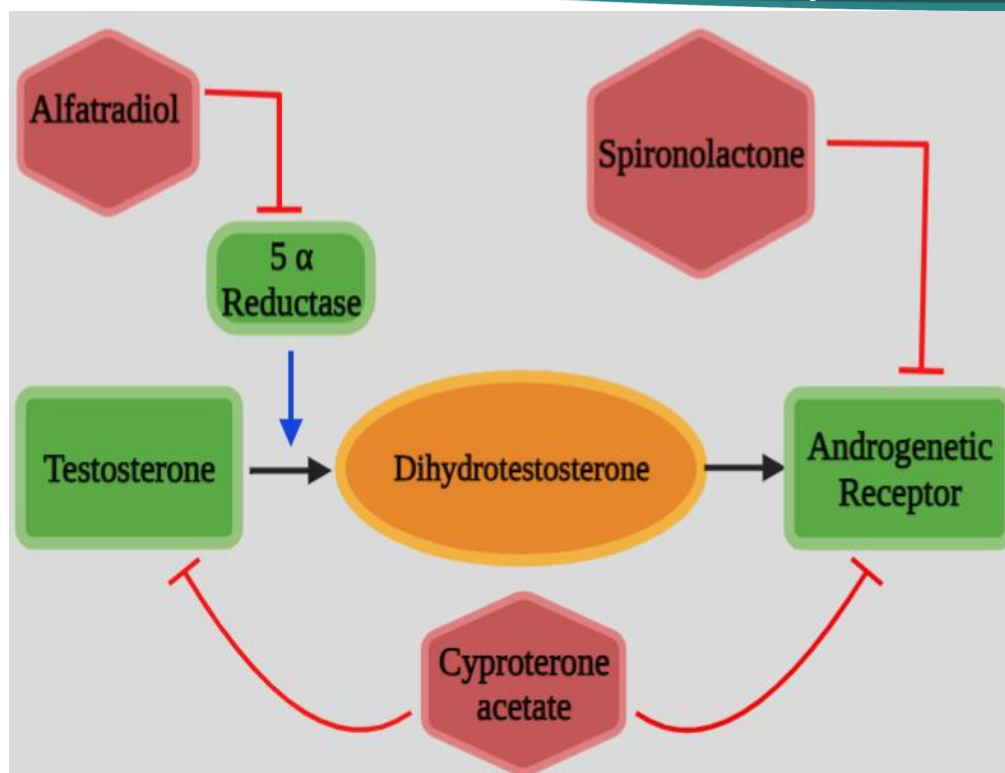
### Treatments through Estrogen and other anti-androgen

**Spironolactone:** It diminishes the androgen receptor synthesis and competitively hinders it in the objective tissue (Van et al., 2012). Uptake of spironolactone 50-200 mg/ day at least half a year can give fruitful results on Female androgenetic alopecia (FAGA). Aftereffects incorporate postural hypotension and electrolyte awkwardness (Mesinkovska and Bergfeld, 2013).

**Cyproterone acetate:** It straightforwardly obstructs the androgenetic receptor and diminishes the levels of

testosterone by stifling luteinizing hormone (LH) as well as follicle stimulating (invigorating) hormone (FSH) discharge. Treatment with acetic acid derivation of cyproterone, singly or in blend with ethinylestradiol, may further develop hair(scalp) development within FAGA (Peereboom et al., 1989).

**Alfatradiol (17 $\alpha$ -estradiol):** It is a topical anti-androgen which acts by hindering the enzyme 5-ARI. The suggested utility is 0.025 % alfatradiol moisturizer two times day by day (Blume et al., 2007).



**Figure 3. Inhibitors and their mode of action involve in Female Androgenetic Alopecia (FAGA)**

### Androgen-Independent Agents

#### Minoxidil

The proper mechanism of action (MOA) of minoxidil on hair development is still not well-defined but is most likely mediated via opening of the potassium channel, which leads to raised cutaneous blood circulation, stimulation of vascular endothelial growth factor as well as hair development enhancers in dermal papilla (Carmina and Lobo, 2003).

#### Prostaglandin Analogs

Ongoing examinations expose that an expanded prostaglandin D2 (PGD2) level is related to scaling down of hair follicles as well as additionally, effective utilization of PGD2 likewise restrained hair development (Garza et al., 2012). Interestingly, PGF2 and PGE2 are synergistic, the consequence of which actuates hair development as well as drags out anagen (Valente and Tosti, 2013).

#### Group of Ketoconazole

A type of imidazole antifungal that act as a cleanser and brings new hair in FAGA. The component of activity is muddled. Ketoconazole helps 2 % of cleansers occur at nearby interruptions of the DHT route (Perez et al., 2004; Inui and Itami, 2007).

#### Ethnopharmacological aspects

Various manufactured fixes, such as minoxidil, corticosteroids, zinc, dithranol, deliberate cortisone,

retinoin, aggravations, immunosuppressants, azelaic corrosive, and finasteride, are currently available for the treatment of baldness, but no single or diverse drug treatment is giving acceptable and long-lasting results to thinning hair patients. Likewise, pruritis, erythema, dermatitis, scaling, tingling, and other unintended consequences have been linked to the use of these produced mixes. So, in terms to address the problem of hair fall, we looked into nature's fortune and discovered a variety of tastes that have demonstrated efficacy in the treatment of alopecia. The advocated instruments of movement for these regular fixes include nutritional effect, DHT blockers and 5-reductase blockers, Aromatherapy, and further generated scalp blood dispersing. There are numerous advantages to taking regular medications. Nutritional effect, 5- $\alpha$  Reductase blockers and DHT blockers, aromatherapy and further created scalp blood scattering are the proposed instruments of movement for these regular fixes. Because they are common medications, they have a number of advantages, including patient consistency, fewer long-term effects, basic openness, low cost, and the ability to treat alopecia with more than one movement approach. Several herbal remedies as well as their mode of action have been depicted in the Table 2 and Table 3 respectively.

**Table 2. Herbs help with nutrition in the treatment of baldness**

Biological Source	Family	Common Name	Active Part used	Chemical Constituents	Action
<i>Prunus amygdalus</i>	Rosaceae	Badam	Seed oil	Minerals, fats, Vitamin B1, B2, B3, Vitamin E	CNS & Neural tonic (Jain and Das, 2016)
<i>Avena sativa</i>	Poaceae	Wild Oats	Seeds	Fibers, carbohydrate, Zn, Fe, Mn	Nourishment (Mulder and Meinardi, 2003)
<i>Daucus carota L.</i>	Apiaceae	Carrot	Roots	Minerals, B-carotene, antioxidants	Nourishment (Singh et al., 2016)
<i>Bacopa monnieri</i>	Scrophulariaceae	Brahmi	Whole plant	saponins, bacosides, triterpenoids	Nourishment and neural stimulant (Fortes et al., 2018)
<i>Juglans regia</i>	Juglandaceae	Akhrot	Fruit	Mn, Fe, K, Zn, Cu, proteins, fats	Nourishment (Gc et al., 2021)
<i>Phyllanthus emblica</i>	Euphorbiaceae	Amla	Fruit	Vitamin C, gallic acid and quercetin	Nourishment (Peiffer et al., 2013)
<i>Lactuca sativa</i>	Asteraceae	Lettuce	Leaves	Folic acid and vitamin A	Nourishment (Hajimehdipoor et al., 2019)
<i>Aloe barbadensis</i>	Liliaceae	Aloevera	Leaves	Mineral	Nourishment (Jain and Das, 2016)

**Table 3. Herbs that treat baldness and their mechanisms of action**

Biological Source	Family	Common Name	Active Parts Used	Chemical Constituents	Action
<i>Allium cepa L.</i>	Alliaceae	Onion	Cloves	Minerals, allicin, vitamin C containing compounds	Restoring hair reformation (Greenish et al., 1920)
<i>Ocimum sanctum</i>	Lamiaceae	Tulsi	Whole plant	Terpenoid	Aromatherapy (Sharquie and Al-Obaidi, 2002)
<i>Capsicum annuum</i>	Solanaceae	Pepper	Fruits	Isoflavones, capsiacin	Nerve activation and IGF-I production (Hajheydari et al., 2007)

<i>Camellia sinensis</i>	Theaceae	Tea	Leaves	Caffeine, Catechin, epicatechin and other tannins	5-alpha-reductase inhibitor (Liao and Hiipakka, 1995; Prager et al., 2002; Esfandiari and Kelly, 2005)
<i>Allium sativum</i>	Amaryllidaceae	Garlic	Cloves	Minerals, Allicin, Vitamin C containing compounds	Nerve activation & Anti-microbial activity (Harada et al., 2007)
<i>Nardostachys jatamansi</i>	Valerianaceae	Jatamansi	Rhizome	Menthylthymyl-ether and 1,8-cineol Bornyl acetate, valeranone, jonon	Expansion and extension of follicles in anagen stage (Thorat et al., 2009)
<i>Urtica dioica</i>	Urticaceae	Stinging nettle	Roots	Minerals and Vit. A, C & K	Blocking of DHT (Roy et al., 2008; Zhang et al., 2000)
<i>Eclipta alba</i> (L.) Hassk	Asteraceae	Bhringraj	Leaves	Daucosterol, Ecliptasaponin C, stigmasterol-3-Oglucoside	Expansion and extension of follicles in Anagen stage (Thorat et al., 2009; Roy et al., 2008)
<i>Pygeum africanum</i>	Rosaceae	Pygeum	Dried bark	Esters of ferulic acid (tetracosanol and n-docosanol)	Reduces levels of DHT (Zhang et al., 2000; Liu et al., 2000)
<i>Panax ginseng</i>	Araliaceae	Ginseng	Roots	Ginsenoside, phytoestrogens and minerals	5-alpha-reductase inhibitor (Prager et al., 2002; Liu et al., 2000)
<i>Serenoa repens</i>	Arecaceae	Saw Palmetto	Berries	Phytosterols, Steroidal saponins, fatty acids, resins, tannins and volatile oils	blocking of DHT (Marks et al., 2001; Chizick and Delorscio, 1999)
<i>Ginkgo biloba</i>	Ginkgoaceae	Ginkgo	Leaves	Flavonoids glycosides, terpenoids	Improves cerebral microcirculation (Marks et al., 2001; Chizick and Delorscio, 1999)



### Future aspects

Mechanical headway in delivery systems of drugs along with the possibility of finding new alopecia treatments guarantee superior medicine for going bald in near future. It will be cultivated by the popularity of hair/scalp development items as well as remunerating financial worth presented for alopecia treatment (Wipf et al., 2019). Accessibility of state-of-the-art investigation hardware and the current information foundation on the subject of hair development is relied upon to provide substantial preparation for hostile alopecia solutions (Strazzulla et al., 2018). Among the plight possibilities for oncoming alopecia treatments occurs by hypertrichotic phytochemicals, mixed medicines, improvers of dermal penetration, gene therapy, stem cell therapy as well as Platelet-rich plasma an effective adjuvant treatment methodology for AGA (Rambwawasvika et al., 2021; Girijala et al., 2018).

### Conclusion

Notwithstanding the likely market for powerful designated medicines for baldness, pharmacological ways to deal with the counteraction of balding and to hair reformation occur in the initial stages. It is backed up by a lack of knowledge of the basic mechanisms that contribute to hair loss etiology. It is now recognized that, in the presence of sufficient androgen, baldness is predominantly caused by inherited tendencies. Nonetheless, until recently, quality hunting research has only shown one hereditary link that can be replicated: the androgen receptor. The application of this finding in treatment development is hampered by a lack of understanding of the relevant arrangement variety in this quality that causes androgen receptor's upregulation in balding follicles, as well as the lack of techniques to specifically guide androgen-blockers to follicular objective tissues to avoid foundational effects. The as-of-now endorsed baldness medicines, finasteride and minoxidil are dynamically viable, and hair reformation is accomplished in just a small group of sufferers. Some creating therapeutic choices including latanoprost and dutasteride which holds expanded guarantee, however, are as yet not in view of a full comprehension of sickness etiology and there are many natural medications that are effective in treating alopecia with no adverse effects. These natural concentrates, which contain a variety of phytochemicals, can help with alopecia by providing dietary supplements or acting as 5-alpha-reductase and DHT blockers. There are also a few common chances with unstable oil dynamic ingredients that can be used as a fragrant healing for treating alopecia by improving blood circulation of the

scalp. An expanded understanding of the concealed baldness hereditary design, which might be gained via comprehensive competitor quality and genome-width affiliation research, will pave the way for the development of further effective, personalized future pharmaceutical treatment options.

### Conflict of interest

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