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*Review*

# The Advancement of Herbal-Based Nanomedicine for Hair

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**Abstract:** Polymer, lipid, and natural protein-based hair care nanocarriers are in preclinical testing. Nanomedicine has enhanced therapeutic efficacy and decreased side effects. This review examines herbal nanomedicine for hair care. We also reviewed the hair cycle, its morphology, and the mechanisms of herbal-based medicine that regulate the hair cycle to treat hair loss. Nano-formulations have better solubility, permeability, therapeutic efficacy, and prolonged distribution than standard herbal medicines. This review also discussed the nanotechnology barrier and nano formulations for hair loss and growth and includes a recent herbal nanomedicine study. Researchers interested in using herbs to treat hair problems and clinically translating hair care products may find the results presented significant.

**Keywords:** herbal nanomedicine; hair cycle; hair follicle; herbal nano-formulations; hair growth



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## 1. Introduction

The hair is made up of dermal papilla cells and ends up going all the way to the top of the dermis [1]. Hair protects the body from the outside world, makes the body look elegant, and adds to the person's personality. Environmental factors, stress, hormonal imbalances, and changing lifestyles can cause hair problems like hair loss, dandruff, dry hair, gray hair, and split ends. Scientists are making herbal nano-formulations to help people with hair problems. Oils, serums, conditioners, hair color, shampoos, gels, and wax are just some of the hair products that have been made to help with hair problems. Millions of herbal medicines and phytoconstituents are used to treat hair problems all over the world [2].

Europe, North America, Asia-Pacific, and South America demand natural hair care products, according to market figures [3]. According to the compound annual growth rate (CAGR), hair market revenue is projected to reach $2875.9 million by 2022. From 2020 to 2024, the hair market will increase by $4.9 billion. The COVID-19 infection relates to baldness. Androgenic alopecia (affecting 30.7% female, 86.4% male) was the most prevalent kind of hair loss, followed by telogen effluvium (9.8% female, 9.3% male) and alopecia areata (7.0%, 40% male), according to the literature. The onset of COVID-19 symptoms may be preceded by androgenetic alopecia. Therefore, COVID-19 is commonly responsible (93.6%) for the start of new telogen effluvium; 95% of individuals with preexisting conditions are more likely to develop alopecia areata [4,5]. About half of the drug companies that treat hair problems with herbal agents obtain them from nature [6]. Herbal plants have been used to treat a wide range of hair problems, according to the Unani, Chinese, and Ayurvedic systems of medicine, among others. Using synthetic hair treatments like minoxidil, finasteride, and different herbal drugs to treat hair problems is effective [7]. The most common problem with minoxidil is that it makes the skin red and itchy. Nevertheless, the

current market shows that herbal drugs are being used more and more. Plant extracts have many different effects, such as anti-inflammatory, anti-fungal, antiseptic, and antimicrobial effects. Because herbal nanomedicine has few side effects, it is often used in cosmetics [8,9]. Herbal drugs for treating and preventing hair loss are easier to find now that we know more about how herbs work and how to control their quality.

Below we review everything you need to know about the shape of hair, the hair cycle, hair problems and disorders, and the ways to prevent and treat them. In the review, we discuss how the growth of nanotechnology has led to the development of nano-formulations of active herbal plants to make them safer and more effective. We then discuss how hair medicines affect the hair cycle and how they can change its hair cycle. This will help a new researcher understand some hair problems and come up with an effective strategy for developing nanomedicines in the future.

## 2. Hair Morphology

In our everyday lives, human hair is important. Hair is an epidermal derivative created when ectoderm-derived germinative cells undergo keratinization [8,10]. Only the fingers, soles, and palms of the human body lack hair. Among its various roles, hair controls body temperature, lessens friction between hair shafts, protects from sunlight, and defends against environmental factors [11]. Carbon is one of the chemical components of the fibrous alpha-keratin proteins that make up hair. The hair structure is explained below.

### *2.1. Hair Follicle*

A hair follicle looks like a sac or tube. The hair root is in the dermis layer of the skin, therefore it cannot be seen. It is a living part of the hair shaft and has two sheaths, one on the inside and one on the outside. The growing hair shaft is protected by the skin on its outside. The hair follicle is made up of three parts. The infundibulum is the part on the outside, from the ostium to where the sebaceous duct opens. The isthmus is the part in the middle that goes from the sebaceous duct to where the arrector pili muscle attaches. The hair bulb is the part of the hair follicle at the bottom that is relatively enlarged and is called the inferior segment. The bulb is a living, growing cell that is an important part of hair growth [1,10,12].

As depicted in Figure 1, the bulb surrounds a cone-shaped structure, known as the dermal papilla that is located near the hair follicle's base. It contains blood vessels and connective tissue that nourish the hair with nutrition and stimulate its growth [11]. The dermal papilla contains mesenchymal cells and epithelial cells [13]. Mesenchymal cells are primarily responsible for hair growth and color. In the keratin matrix, cells undergoing mitosis-type cell division generate hair. In the germinal matrix, melanocyte cells are present. Melanocyte cells generate the pigment melanin, which imparts color to hair [1,10]. The arrector pili muscle is a smooth muscle situated beneath the hair follicle. When the muscle contracts, we tend to get goosebumps [1,10]. The sebaceous gland is the skin oil gland that secretes sebum (fatty, oily substance). This gland is connected to the hair follicle and maintains its luster [1].

### *2.2. Shaft*

The hair shaft is keratinized, and the non-living part is above the skin surface. It is employed for diagnostic purposes. The hair shaft comprises three elements.

#### 2.2.1. Medulla

The medulla is the innermost central part of the hair shaft. It is a thin cylindrical layer located at the center of the hair shaft. It has a poor cysteine (>30%) and a high lipid concentration [10].

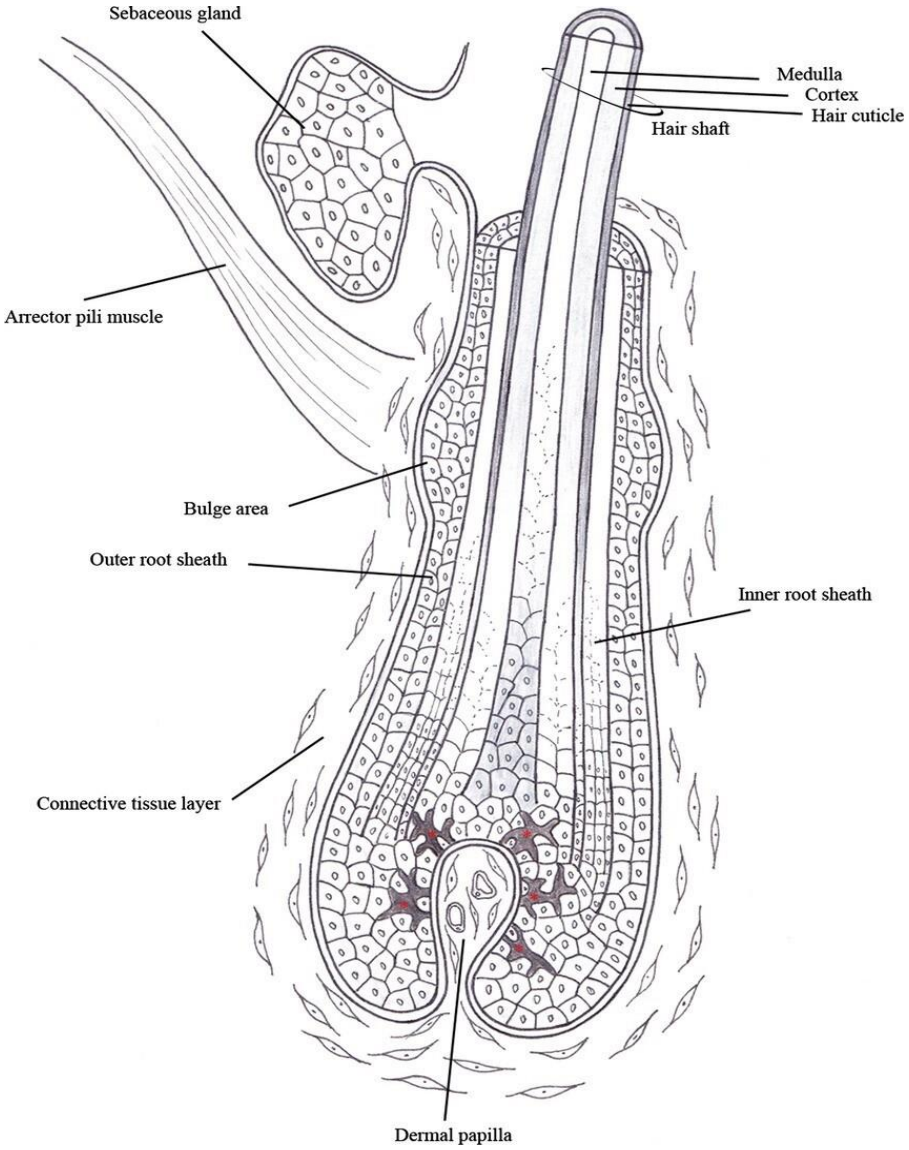


**Figure 1.** The Hair structure "Reprinted with permission from Ref. [The human hair: From anatomy to physiology. Int. J. Dermatol.] 2013, Buffoli, B.; Rinaldi, F.; Labanca, M.; Sorbellini, E.; Trink, A.; Guanziroli, E.; Rezzani, R.; Rodella, L.F. et al. [1].

#### 2.2.2. Cortex

The cortex is the part of a shaft between the cuticle and the medulla [11]. Most of the hair shaft, or 75%, is made up of the cortex. It is composed of cells that look like spindles and are 50–60 µm long and 3 µm wide. In the cortex, protofilaments, microfilaments, and microfilaments wrap around keratin filaments. The keratin filaments run in the same direction as the hair shaft's long axis [8]. A cortex has an amorphous matrix with a lot of sulfur-containing proteins. When cysteine residues from two neighboring keratin filaments come together, they form strong covalent disulfides. The covalent bond gives the hair its shape, flexibility, and texture. The color of the hair comes from several proteins in the cortex. The cortex gives hair its physical and chemical properties.

#### 2.2.3. Cuticle

The outer layer that protects each hair shaft, the cuticle, is transparent and hardy [11]. Hair gel, hair spray, conditioners, hair colors, and other cosmetic treatments leave behind deposits on the cuticle layer and have an impact on the cuticle [1]. The cuticle is distin-

guished by its sheen, smooth appearance, ability to reflect light, and capacity to reduce friction between hair shafts. Three layers make up the cuticle:

1. Layer A, which is formed of cross-linked cysteine, is a very resistant layer. This connection provides mechanical and physical resistance [8].
2. Exocuticle: This structure is also known as the B layer. Though not quite as hard as the A layer, it is physically rigid and high in cysteine concentration.
3. Epicuticle: The 8-methyleicosonic acid-containing epicuticle is a hydrophobic lipid layer that covers the exterior of the hair shaft [14]. Approximately 3% of the epicuticle is likewise made up of cystine. As a soft layer, it expands and turns brittle when exposed to water, which explains why wet hair breaks when combed [8].

### *2.3. Hair Cycle*

Hair follicles have a natural cycle that starts with the anagen phase, continues with the catagen phase (regression), and ends with the telogen phase (non-growing stage).

#### 2.3.1. Anagen Phase

The Anagen phase is the period of follicle regeneration and growth. As shown in Figure 2, this phase involves high mitotic division (proliferation) and active hair growth [14]. The follicles enlarge during this phase, as new cells are produced which support the hair growth and lengthen hair. Pigmentation occurs only during the anagen phase [10]. The anagen phase lasts from 2 to 7 years, during which hair may grow faster. The average hair growth rate is 2 cm per month [15].

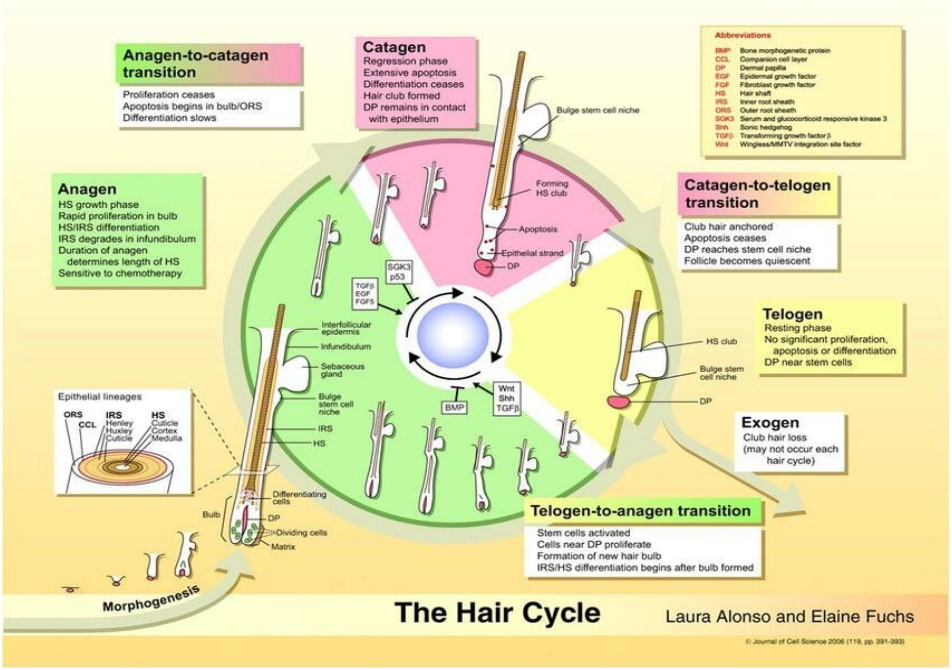


**Figure 2.** The Hair cycle "Reprinted with permission from Ref. [The hair cycle. Journal of cell science]. 2022, Alonso L, Fuchs E. et al." [16].

#### 2.3.2. Catagen Phase

The catagen phase is a regressive phase. In this phase of the cell, mitotic activity decreases, and apoptosis occurs due to the suppression of bcl-2 [15]. This lasts for approximately two weeks. Figure 2 shows the follicle rests on the dermal papilla and slows down cell production. The melanocytes contract and melanin production cease [1,15]. The inducer of the catagen is FGF-5 [10].

#### 2.3.3. Telogen Phase

There is a resting phase in the follicle called the telogen phase. It lasts for approximately four months. The follicle is in a state of quiescence between follicular regression and the beginning of the anagen phase [1,10].

#### 2.3.4. Exogen

The process of hair shedding is called exogen. It is an active phase [1,15].

## 3. Role of Stratum Corneum Barriers in the Design of Nanocarriers

### *3.1. Stratum Corneum Barriers*

For effective chemical delivery across the skin to prevent and treat hair diseases and disorders and to stop them from happening in the first place, these barriers must be overcome. Several herbal extracts and their isolated parts work well in in vitro studies, but in vivo studies show less promise because the skin acts as a barrier [17]. Phytoconstituents can be either water-loving or fat-loving. The skin is made up of two layers of lipids. The stratum corneum can greatly reduce the bioavailability, effectiveness, and pharmacokinetics of highly hydrophilic molecules. Large molecules are also ineffectual because they cannot easily pass through membranes [18]. The stratum corneum forms a barrier to herbal medicines getting into the body. The stratum corneum is the outermost layer of the epidermis and is mostly made up of proteins and fats. Bundles of keratin filaments wrap around the corneocytes to make up the protein structure. There are no nuclei or organelles in these corneocytes. Their hard outer shell is made up of several proteins [19]. Figure 3 shows that a corneocyte has an extracellular lipid matrix all around it. Cross-linked like a cornfield, the extracellular lipid matrix has a double layer of free fatty acids, ceramides, and cholesterol [20]. How porous the cell membrane is determined by how much lipid is in the cell [20]. The enriched lipid structure stops lipophilic drugs from getting in but allows hydrophilic drugs to stay there [21].

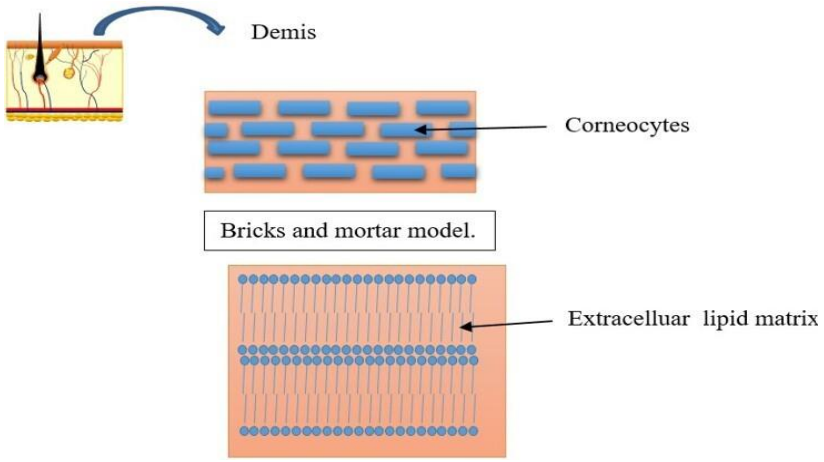


**Figure 3.** The structure of Stratum Corneum.

Extracellular lipids produce a bilayer lamellar phase. Lateral packing is essential for skin health. Orthorhombic packing density is high. Hexagonal packing density is lower. A lamellar structure is determined by the concentration of lipids, specifically ceramides. This concentration justifies SC's barrier qualities [20]. Transdermal administration provides advantages over conventional methods of administration, such as its long-acting qualities. The Transdermal Drug Delivery System (TDDS) and the trans appendageal route circumvents first-pass metabolism and patient adherence [22]. For effective administration of herbal medication in herbal treatment, biological barriers of stratum corneum must be overcome in the design of innovative nanomedicine-based formulations [23,24]. The literature contains reports on the application of a permeation enhancer to an interdigitated

lipid bilayer and the breakdown of the lipid bilayer. Overcoming the stratum corneum barrier is one of the key strategies for successful transport of herbal medications over the skin [25].

### 3.2. Design of Nanotechnology-Based Nanocarriers

Nanotechnology has had a big impact on the world of natural remedies. Nanopharmaceuticals have improved biological products for an intended purpose and solved several issues [26,27]. Depending on their phytochemical characteristics, nanoparticles can penetrate the hair follicle to different depths [28]. Because there is a bigger network of blood capillaries around hair follicles than there is in the stratum corneum, delayed release is more effective in terms of duration of action and is best suited for systemic circulation and adjacent skin layers. Once the medication has penetrated the hair follicle deeply, it remains there until it is flushed away either by sebum production or hair growth. The diffusion of particles between 300 nm and 600 nm into hair follicles is a successful tactic when compared to non-particulate medicines. The deposit time for pharmaceuticals with nanoparticles was 10 days as opposed to just 4 days for treatments without them. Herbal nano-formulations achieve high bioavailability, target benefits, protective effects, less adverse effects, and dose reduction in this way [29,30]. Different transdermal administration methods, including liposomes, micro-emulsions, super-loaded formulations, inclusion complexes, nanoparticles, coacervation effect, eutectic mixes, polymersomes, and vesicles for antiviral agents, are being studied by researchers [31,32]. It is difficult for nanosystems to transfer technology from a small lab size to the business world. Nanotoxicology is the study of these adverse effects, which nanotechnology may have [33]. The effectiveness of plant-based medications was boosted by nano-formulation [34]. Scientists have created a range of herbal compositions utilizing nanotechnology, as indicated in Table 1 [35].

### 3.3. Nano-Formulations for Herbal Hair Care

#### 3.3.1. Liposomes

The use of liposomes in hair care products has grown since the FDA gave its approval a few decades ago. Most of the time, these liposomes are used to deliver drugs in hair nanocosmetics. Its structure is made up of both water and phospholipid, which makes it easy to give drugs that are hydrophilic or lipophilic [36,37].

#### 3.3.2. Phytosome

With a patented technology called Phytosome, plant extracts or polar phytoconstituents are mixed with phospholipids to make phytosomes. These are molecular complexes that are compatible with lipids and make nutrients more bioavailable and easier to absorb [38]. In contrast to liposomes, phytosomes are made up of a molecular complex made of phosphatidylcholine that is chemically bound to plant parts [39]. The aqueous extracts of *Abrus precatorius* and *Trichosanthes curcumerina* were mixed to make polyherbal phytosomes that can be used on the skin [40,41]. These showed that they could help hair grow, and the composition was just as effective as a course of minoxidil treatment. Using nanotechnology, herbal nanomedicine is used to treat alopecia [42].

#### 3.3.3. Ethosome

Alcohol is incorporated to the lipid bilayer of ethosomes, which are another type of flexible liposome, to make the structure flexible and better at getting into cells. Ethosomes can hold medicines that are hydrophilic, lipophilic, or amphiphilic, all of which can get through the skin and into the bloodstream [43]. Ethosomes were made with the help of vitamins A, E, and C [44]. Because all the vitamins worked together and were spread to the deep layers of the skin, the formulation had a stronger antioxidant effect than the usual way that drugs are delivered.

The serum is made of nanoscale parts and rice, which strengthens the roots of hair and stops hair loss. Herbal nano-formulation was also used to take care of hair. Some of these

are the citrus mint shampoo and conditioner, which have nanoclusters that make hair shine. Another ingredient with an herbal mix that could be any of the following: chamomile mixed with citrus and mint oils, black elderberry extract, or nettle leaf extract. These herbal concoctions are used to nourish hair. These shampoos help to strengthen hair follicles, improve circulation on the scalp, reduce inflammation, stop dandruff, add volume to the hair, and make it shine. Fermented medicinal herb extract blends (4HGF) made from the mushrooms *Phellinus linteus* grown on sprouted brown rice and *Cordyceps militaris* grown on germinated soybeans, or plants *Ficus carica*, *Cacos nucifera* oil, and *Polygonum multiflorum* have been found to have significant anti-inflammatory properties related to promoting hair growth. However, up until now, their inability to effectively penetrate hair follicles has severely limited their usefulness in treating those who are experiencing hair loss.

#### 3.3.4. Cubosome

Herman et al. made a hinokitiol-loaded cubosome (the source is the wood of a plant in the Cupressaceae family) and tested it on the dorsal skin of hairless female mice in a laboratory. Based on the results, the permeability of this mixture was much higher than when hinokitiol (HKL) was dissolved in water. Because of this, the ingredient is seen as one of the most powerful carriers of a thickening agent that promises to help hair grow [45,46].

#### 3.3.5. Polymeric Nanoparticles

For herbal hair care, a different class of nanocarriers is utilized. Androgenic alopecia can be treated with quercetin. Dipalmitoylphosphatidylcholine (DPPC)-reinforced poly lactide-co-glycolides nanoparticles (DPPC-PLGA hybrid nanoparticles) are used in the preparation of nanoparticles by a double emulsification sol-vent evaporative process. trans-follicular delivery method for nanoparticles. According to FTIR research, the nanoparticles were amorphous, 339 nm in size, −32.6 mv in zeta potential, and 78.5% in entrapment efficiency describe these nanoparticles. Studies using fluorescence microscopy showed that the NPs were present in hair follicles. Hair regrowth is accelerated by nanoparticles, which also prevent apoptosis [47]. The ionic gelation process is used to create nanoparticles. Fermented herbal extract from a combination of *P. linteus*, *C. militaris*, *P. multiflorum*, *F. carica*, and *C. nucifera* oil is contained in nanoparticles that are made of poly(-glutamic acid)/chitosan hydrogel. Spherical hydrogels with a size of 400 nm are what it is. The penetration rate of nanoparticles was demonstrated by green fluorescence originating from FITC. Delivered at HF, PGA-4HGF nanoparticles encourage hair development. Further research on mice revealed that the hair bulb was enlarged [48].

Researchers created nanoparticles of deacetylated chitin and microfibers made of chitosan. The ability of nanoparticles to stimulate hair development is examined. On day 3 following the start of therapy, chitosan and surface-deacetylated chitin nanofibers (SDACNF) were demonstrated to boost human follicular dermal papilla cell proliferation, together with an increase in these cells' synthesis of fibroblast growth factor-7 (FGF-7) [49]. The HF regeneration can make advantage of nanoarchitectonics [50].

#### 3.3.6. Melatonin Nanostructured Lipid Carrier

Hatem et al. and their colleagues investigated using melatonin nanoparticles with antioxidant oils to treat androgenic alopecia. Compared to standard melatonin solution, melatonin NLC had effects that were good from a clinical point of view. Additionally, NLCs were easy to store and made the skin deposit 6.8 times more melatonin in the dermis and 4.5 times more in the stratum corneum than the melatonin solution. Melatonin NLCs showed more clinically beneficial effects than melatonin solution in people with androgenetic alopecia (AGA), as shown by better hair density and thickness and less hair loss. [51]. Extracts of florets of *Carthamus tinctorius* contain phytoconstituents that stop the enzyme 5-reductase from working and help hair grow. The loaded nanostructured lipid carriers were made with a method called "hot high-pressure homogenization". To make NLC, you need monostearin, monostearin laureth-4, sorbitan monostearate, polysorbate 60,

Pluronic® F6, and DMDM hypodimethyl ether. The particle size (100 nm), zeta potential (−40 to −49) Mv, and physical properties of this NLC have all been tested. When NLC was put on the skin of C57BL/6 mice, more hair grew than with minoxidil [52].

#### 3.3.7. Solid Lipid Nanoparticles

Researchers synthesized solid lipid nanoparticles (SLN) to allow *Pueraria mirifica* ethanolic extract to pass through the epidermal barrier. A formulation devoid of cytotoxicity and exhibiting exceptional safety. The SLN aids with hair development. [51] Particles have a size of 93.83 0.32 nm and are negatively charged. Fenugreek seeds are used to treat several types of alopecia; however they frequently cause systemic side effects. Researchers have generated loaded solid lipid nanoparticle carriers utilizing the melt emulsification method. They measured a particle size of 223 nm and a PDI of 0.3 [53]. The cyclodextrin inclusion complex is an emerging approach of integrating natural-based components in nanotechnology. The cyclodextrin complex is used to treat natural components such as linolenic acid, sitosterol, epigallocatechin gallate, and genistein. The formulation's safety is evaluated [54].

Microfibers produced from chitosan and deacetylated chi-tin nanoparticles were created by researchers. Nanoparticles were tested for their ability to promote hair development [49]. Hatem et al. and others investigated melatonin nanoparticles in combination with antioxidant oils for the treatment of androgenic alopecia. Melatonin NLC demonstrated clinically beneficial effects in comparison to melatonin solution. Nanoparticles are nanometer-sized, have a high entrapment effectiveness, and can pass through the stratum corneum [55,56]. Table 1 shows nano-formulations used in natural health care.

**Table 1.** Nano-formulation for herbal medicines.

| Biological Source | Technique | Outcomes | Reference |
|---|---|---|---|
| *Carthamus tinctorius* florets extract | Loaded nanostructured lipid carriers | Particle size around 100 nm, zeta potential −40 to −49 mv. NLC promoted hair growth in the mice better than minoxidil. Good physical properties and stabilities. | [52] |
| Quercetin | Phospholipid-polymer hybrid nanoparticle-mediated trans-follicular delivery | Particle size 339 ± 0.6. Zeta potential −32.6 ± 0.5. Entrapment efficiency 78 ± 5.5 Treatment of androgenic alopecia. | [47] |
| Mixtures of *P. linteus*, *C. militaris*, *P. multiflorum*, *F. carica*, and *C. nucifera* oil | Poly(γ-glutamic acid)/chitosan hydrogel nanoparticles | Control release. Prolong growth-promoting effect. Enlarge in hair bulbs. Induction of hair growth. Delivery phytoconstituents at hair follicles. | [48] |
| Chitosan | Surface-deacetylated chitin nanofibers | Promoted hair growth. Upregulated levels of FGF−7 and sonic hedgehog hair follicles. | [49] |
| Almond oil, g primrose oil, olive oil, and soybean oil | Nanostructured lipid carriers | Nanometer size. Negatively charged surface. High entrapment efficiency. High anti-oxidant potential. Sustained release for 6 h. Good storage stability. Increased hair density and thickness. Decreased hair loss. | [55] |
| *Pueraria mirifica* ethanolic extract | Solid lipid nanoparticles | Particle size (93.83 ± 0.32 nm). Entrapment efficiency (42.64 ± 0.47%) Good safety herbal extract.SLN containing 5% (*w*/*v*) extract can pass through the skin. | [51] |

**Table 1.** *Cont.*

| Biological Source | Technique | Outcomes | Reference |
| --- | --- | --- | --- |
| Fenugreek seed extract | Solid lipid nanoparticles-based hydrogels | The particle size of 223.36 nm. PDI of 0.33. Entrapment efficiency 74.56 ± 0.2%. Management of alopecia. Reduce the systemic side effects. | [53] |
| *Carthamus tinctorius* (safflower) florets extract | Nanostructured lipid carriers (NLC) | Particle size around 00 nm. Zeta potential (−40 to −49) mv. NLC promoted hair growth in the mice better than minoxidil. | [52] |
| A natural-based formula containing γ linolenic acid, β-sitosterol, epigallocatechin gallate, and genistein | B-cyclodextrin inclusion complex | Nine-month uncontrolled, open-label case series, 0 day -low vertex scalp hair 90 day—negative hair growth cycle altered. 80 days—hair thickening on the scalp. 270 day—hair observed with a full thickness on the scalp. | [54] |
| *Moringa oleifera* | Ethosomes | Better skin penetration and Hair growth-enhancing activity | [57] |
| Black tea | Ethosomes | Increases transdermal absorption rates and Hair dye | [58] |

### *3.4. Regulatory Aspects of Herbal Nanomedicine for Hair Care*

Nanomedicine [59] includes both biological (made from natural sources) and non-biological (made from man-made sources) medicines.

Before it can be sold, the medicine must pass several quality tests that look at how well it works, how safe it is, how similar it is to another treatment, and how similar it is to itself [60]. Before finished drugs or other items can be sold, they must pass a number of financial controls and quality checks that are specific to each country. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are the two main groups that set rules for non-clinical studies, clinical studies, and comparative quality studies [61]. To keep the particle properties, stability, and homogeneity as well as the bioavailability and cytoplasm level concentration of nanomedicine preparations, which can affect the toxicity point and kinetic parameters, the European Medicines Agency (EMA) set up guideline papers for new medication developers [62]. The interdisciplinary method of health care technology evaluation (HTA), which gives information on how well, how safe, and how cost-effective medications are, is being made so that patients can get them [63]. The US-FDA regulates nanomedicines under two acts: the FDCA act, which covers pure synthetic formulations and devices, and the Public Health Service act, which covers naturally derived medicinal goods.

The US FDA released the nanotechnology guidance documents, which talk about the risk-based framework for nanotechnology, the specific requirements for doing non-clinical trials as well as clinical trials, production, quality control studies, and different environmental assumptions for biological and pharmaceutical nanomaterial products. Currently, there are no regulations that govern the quality requirements of herbal nano-formulations for herbal nanomedicines in a specific way. Even though there are rules in place for natural remedies in places like Africa, Korea, the European Union, and the Philippines, which apply before they go on the market and after they go on the market, and for planning product quality procedures, the rules only apply to traditional herbal medicines. For example, herbal medicines that have been used for a long time in India are thought to be safe, but there are no standards for monitoring them. Therefore, there is a need for regulatory bodies and watchdogs that can keep an eye on HNMs and make sure they meet standards in different ways, such as by making clinical uses and after-clinical observations.

This is because the number of people using herbal nano-formulations has been growing recently. This is because they have benefits beyond traditional herbal preparations and follow safety rules. As of right now, there are no regulations that specifically address herbal nanomedicines [64,65] in terms of their quality requirements.

## 4. Hair Problems

### 4.1. Hair Loss

Hair loss or hair fall is a major problem [11]. Hair loss has multiple reasons such as modulation in the hair cycle, hormonal imbalance, and modulation in signaling pathways, which are described in brief below.

### 4.2. Gray Hair

Without melanin, the shade of hair seems dark or white. A few examinations showed that the interruption of melanin creation is a result of DNA harm and the development of hydrogen peroxide in the follicles [11].

### 4.3. Dandruff

Dandruff is a little white part of dead skin in hair, it is brought about by an organism, the yeast *malassezia*, commonly and *malassezia globosa*, previously called *Pityrosporum*. *malassezia* utilizes the lipid and protein of dermal cells. It causes the proinflammatory free unsaturated fats delivered by lipase movement. It creates aggravation and tissue damage to the dermal layer [8].

### 4.4. Frizzy Hair

Frizzy hair is a condition that decreases the moisture levels of hair beneath ordinary levels. Hair becomes dull looking with the use of synthetic compounds and hair treatments.

### 4.5. Dull Hair

It is caused by using hard water and extremely high-temperature water for the washing of hair.

### 4.6. Androgenic Alopecia

Hair loss or baldness is medically described as alopecia. Androgenetic alopecia is the type of alopecia in these conditions level of 5-alpha reductase enzymes activity and dihydrotestosterone (DHT) is increased. Androgen receptors are present in follicles. Dihydrotestosterone binds to a receptor and activates the gene responsible for the transformation of the normal hair follicle into the miniaturized follicle [66,67]. This results in a reduction in hair follicle size. Because of this anagen phase is diminished and increases the percentage of the hair follicle in telogen. As a result, this causes hair loss or hair fall. Androgenic alopecia can be treated by FDA-approved drugs such as minoxidil and finasteride [68]; however, it can be treated by the natural marketed preparation due to its fewer side effects and no toxic effects [67].

### 4.7. Alopecia Areta

It is an autoimmune disease. In alopecia areta the HF immune privilege is collapse or we can say as the presence of antigen in the follicle [10].

### 4.8. Telogen Effluvium

The excessive hair follicle starts to enter the resting phase (telogen) which causes the shedding of hair. Extreme stress is the reason behind telogen effluvium [6].

## 5. Mechanism of Action of Herbal Medicines on Hair

### *5.1. Modulation in the Hair Cycle by Alteration in Signaling Pathways*

As shown in the Figure 4. Several researchers have investigated the effects of different factors on hair physiology:prostaglandin synthase (PGDS), B-catenin, sonic hedgehog (SHH), hepatocytes growth factor, fibroblast growth factor 7, vascular endothelial growth factor, lymphatic enhancement factor, protein kinase, and the Wnt pathway. As shown in the Table 2. These factors are majorly involved in hair cycle physiology. Garza et al. concluded that overexpression of prostaglandin synthase (PGDS) induces premature catagen. The premature phase results in inhibition of hair growth. Heilman et al. found that genetic evidence for PGDS were lacking in genome studies, but there may be a role for WNT04 expression (Wnt pathway). Leiros et al. discovered that the canonical Wnt/β-Catenin activity is inhibited by androgen action, resulting in the miniaturization of hair follicles. Hair follicle development is controlled by gene expression by proteins and other factors [69]. B-catenin is essential for hair follicle development. This factor participates in Wnt signaling [69]. Sonic hedgehog (SHH) facilitates completing the telogen phase for follicles to enter the anagen phase [70]. The hepatocyte's growth factor promotes follicles to enter the anagen phase [71]. Fibroblast growth factor 7 facilitates the entry of hair follicles into the anagen phase and increases hair follicle numbers [71]. Vascular endothelial growth factor increases the proliferation of dermal papilla cells and blood circulation. The lymphatic enhancement factor is involved in the Wnt signaling pathway, responsible for regulating hair growth. The melanin receptor, which is responsible for changes in hair color hormone that stimulate alpha melanocytes to bind to the MCR and activate adenylate cyclase, which increases cAMP. The tyrosine enzyme is activated by cAMP through protein kinase enzyme, which results in the synthesis of melanin [72].

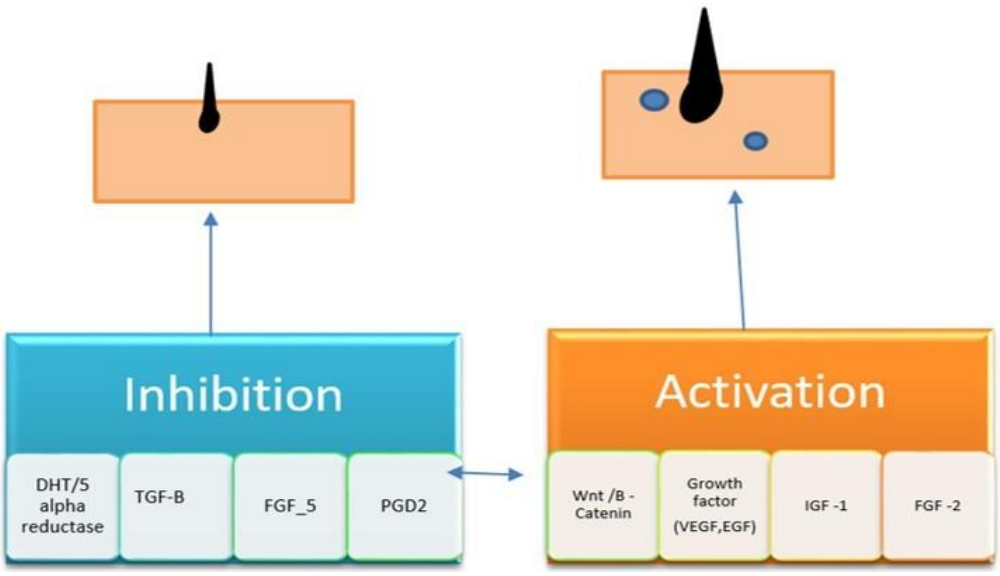


**Figure 4.** Factors affecting gene expression.

**Table 2.** The factors acting on a hair growth cycle.

| Sr. No | Factors | Effects | Stimulation/Inhibition for Growth. |
|---|---|---|---|
| 1 | Insulin-like Growth Factor (IGF) | Stimulates cellular proliferation and inhibits DHT. | Stimulation |
| 2 | Vascular endothelial growth factor (VEGF) | Supply the nutrients and increased the blood circulation on the scalp, resulting in stimulation of hair growth. | Stimulation |

**Table 2.** *Cont.*

| Sr. No | Factors | Effects | Stimulation/Inhibition for Growth. |
|---|---|---|---|
| 3 | Fibroblast growth factor-2 (FGF-2) | Stimulation to the hair follicle development. | Stimulation |
| 4 | Fibroblast growth factor-5 (FGF-5) | Inhibition of hair growth in the anagen phase. | Inhibition |
| 5 | Epidermal growth factor (EGF) | Proliferation and formation of hair follicles. | Stimulation |
| 6 | Wingless-related integration site (WNT) | Stimulates, the growth, and development of hair follicles. | Stimulation |
| 8 | Prostaglandin (PGD) | Hair growth inhibition. | Inhibition |
| 9 | Transforming growth factor beta (TGF-β) | Reduce the duration of a cycle. | Inhibition |

As shown in the Table 3. Sweet potato shochu: shochu is made from sweet potato and is a distilled alcoholic beverage. This oil increases the expression of vascular endothelial growth factors and activates the hair cycle. The oil contains ethyl α-linoleate, ethyl laurate, ethyl linoleate, ethyl caprate, ethyl myristate, and ethyl palmitate. It has a hair growth-inducing effect [73]. *Ginkgo biloba* is known as the maidenhair tree and belongs to Ginkgoaceae. The ethanolic extract increases the expression of VEGF and HGF level and decreases inflammatory factors such as TNF-α and IL-β. It has a hair growth-promoting effect and hair tonic [74]. *Prunus mira*, the smooth stone peach, belongs to the Rosaceae family. The petroleum ether extract contains β-sitosterol, linoleic acid, and α-tocopherol. The extract induce the anagen phase, by Wnt\β-catenin, protein expression. It promotes hair growth [75]. Fructus *Panax ginseng* of the araliaceae family is a species where the root is part of a perennial. It contains ginsenoside Rb which increases VEGFA and VEGF-R2 while decreasing the TGF-β expression in hair follicles. The extract promotes the hair growth and proliferation of hair matrix keratinocytes [76]. *Cinnamomum osmophloeum* known as pseudo cinnamomum belongs to the lauraceae family. The aqueous leaf extract increases HGF, VEGF, KGF, and TGF-β2 expression. which results in promoting anagen by the proliferation of dermal papilla cells [77].

**Table 3.** Herbal drugs act on stimulation and inhibition by different factors.

| Biological Source | Extract. | Mechanism of Action | Effects | Reference |
|---|---|---|---|---|
| Sweet potato shochu | - | Increases expression of vascular endothelial growth factor | The hair growth-inducing effect promotes hair growth and activates the hair growth cycle. Act as a hair restorer | [73] |
| *Ginkgo biloba* | Ethanolic | Increase VEGF and HGF levels, and decrease Inflammatory factors such as TNF-α and IL-β. | The hair-growth promoting effect, treat alopecia areata, | [74] |
| *Prunus mira* | Pet. ether | Induce anagen, by Wnt\β-catenin, protein expression. | Promoting hair growth, induction of anagen phase. | [75] |
| Ginsenoside Rb | - | Increases VEGFA and VEGF-R2, while decreasing the TGF-β expression in hair follicles and DPCs. | Promoted the growth of hair follicle cells. Induce the growth of DPCs. | [76] |

**Table 3.** *Cont.*

| Biological Source | Extract. | Mechanism of Action | Effects | Reference |
|---|---|---|---|---|
| *Cinnamomum osmophloeum* | Aqueous | Increases HGF, VEGF, KGF, TGF-β2 (↑) | Promotion of anagen, proliferation of dermal papilla cells, stimulate hair growth, prevent hair loss. | [77] |
| *Centella asiatica* | Ethanolic | Increases expression VEGF in DPCs | Hair growth stimulating effect, modulating DPCs, antioxidant activity. | [78] |
| *Sargassum muticum* | | Activates the Wnt/β-Catenin, VEGF-R2 | Hair-fiber lengths increase promotes the anagen phase and the proliferation of dermal papilla cells | [79] |

*Centella asiatica*, a perennial plant, is called Gotu kola or Kodava. It is an herbaceous plant belonging to the apiaceae family. The ethanolic extract increases the VEGF level and inhibits the STAT signaling pathway. It has a hair growth stimulating effect [78]. *Sargassum muticum* is also called Japanese wireweed of the family sargassaceae. *Sargassum muticum* contains fucoxanthinone a compound that activates the Wnt/β-Catenin, VEGF-R2. It increases the hair-fiber length and proliferates dermal papilla cells [79].

### *5.2. Hair Cycle Modulation*

#### 5.2.1. Anagen Phase

Anagen is the hair growth phase. Anagen is a part of the hair growth cycle, and it is directly proportional to the length of hair. As the anagen stage is the phase of growth, the matrix of the hair is constantly stimulated which builds hair continuously. It was found that the dermal papilla cells are mainly responsible for causing the anagen phase to occur [80]. As a result, hair length increases. If the duration of anagen reduces, the rate of hair growth decreases. Figure 5 shows that WNT proteins, sonic hedgehog, BMPs, insulin-like growth factor- (IGF-), vascular endothelial growth factor (VEGF), fibroblast growth factor-7, and hepatic growth factor (HGF) are involved in the anagen phase [10]. Some natural drugs act in this phase, thereby extending anagen's duration [81].

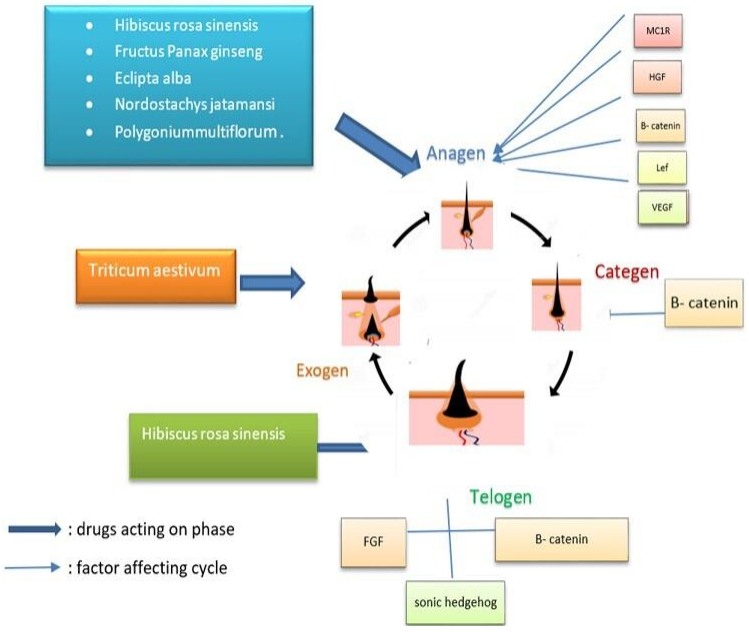


**Figure 5.** Drugs act on the hair cycle and factors affecting it.

Wnt signaling is very important for the hair follicle. Wnt/b-catenin and Shh are anagen-inducing factors. Insulin-like growth factor (IGF-), vascular endothelial growth factor (VEGF), and hepatic growth factor (HGF) are also involved in the anagen phase [82]. The FGF5 induces catagens, and deficiency of it leads to prolonged anagen phases [83]. Factors TGF-b, BDNF, BMP2/4, and interleukin-b also trigger catagen induction [82]. *Hibiscus rosa-sinensis*, fructus *Panax ginseng*, *Eclipta alba*, *Nardostachys jatamansi*, *Polygonum multiflorum* all acts on the anagen phase.

#### 5.2.2. Hair Follicle Telogen Phase

When the duration of the telogen phase is prolonged, relatively more hair follicles are shed. New hair follicles do not enter the anagen phase to form new hair fiber [81]. This results in the development of alopecia. To overcome this, natural drugs can act upon the telogen phase, e.g., from *Hibiscus rosa-sinensis*, to reduce its duration.

#### 5.2.3. Hair Follicle Exogen Event

The prolonged anagen phase does not contribute to the increase in hair density. Instead, exogen and anagen phases combined contribute to the increase in hair density. There is an increased number of hair fibers if there is no shedding in the exogen phase. Old telogen phase hair fiber and new anagen phase hair follicles exist in the same hair follicle [81].

#### 5.2.4. Dystrophic Anagen Growth Phase

A condition where the hair fiber does not form even though the follicle is active is called anagen effluvium. Herbal medicine act at this phase and overcomes anagen effluvium [81].

As shown in the Table 4. *Punica granatum* is also known as pomegranate. Alcoholic and aqueous extracts of *Punica granatum* have antidandruff activity and growth-promoting effects on hair. The extracts stimulate anagen follicles, making them larger [84]. *Hibiscus rosa-sinensis* is an evergreen shrub belonging to the family Malvaceae. The petroleum ether extract of *Hibiscus rosa-sinensis* prevents graying of hair and thickens hair. It mainly acts by transferring the telogen phase to the anagen phase [85,86]. *Nardostachys jatamansi* is a flowering plant belonging to the Caprifoliaceae family. The hexane extract causes the enlargement of follicles with a prolonged anagen phase in mice. Because of prolongation in the anagen phase, hair growth-promoting activity increases [87,88]. *Polygonum multiflorum* is flowering plant species of the family Polygonaceae. The aqueous extract increases the hair fiber length. It prolongs the anagen phase by delaying the catagen phase. The catagen phase is delayed by reducing catagen inducer protein expression [69,89]. *Crataegus pinnatifida* is called mountain hawthorn. The extract of *Crataegus pinnatifida* activates mitogen-activated protein kinases and induces the anagen phase. The extract promotes hair growth activity and increases hair density [90]. *Origanum vulgare* is a perennial plant of the family Lamiaceae. *Origanum vulgare* extract stimulates the insulin growth factor (IGF) and causes proliferation of hair dermal papilla cells [91]. Fructus Panax, or the fruit of *Panax ginseng*, of the Araliaceae family is a species where the root part of the perennial plant is used as ginseng. The ethanolic extract promotes hair regeneration, and elongation of the anagen phase, and has anti-apoptotic activation. It can be used to treat alopecia [92].

**Table 4.** Herbal medicines act by modulating the hair cycle.

| Biological Source | Extract | Mechanism of Action | Effects | Reference |
|---|---|---|---|---|
| *Punica granatum* | Alcoholic and aqueous extracts | Stimulate telogen follicle and makes larger anagen follicles size. | Anti-dandruff activity and growth-promoting effects on hair. | [84] |
| *Hibiscus rosa-sinensis* | Petroleum ether | Transformation from telogen to anagen phase. | Thicker hair and prevents graying of hair | [85] |

**Table 4.** *Cont.*

| Biological Source | Extract | Mechanism of Action | Effects | Reference |
|---|---|---|---|---|
| *Nardostachys jatamansi* | Hexane | Enlargement of follicles prolongs the anagen phase. | Hair growth-promoting activity | [87] |
| *Polygonum multiflorum* extract | Aqueous | Proliferation by MTT (↑) | Increased in hair fiber length | [89] |
| *Crataegus pinnatifida* extract | - | Activates protein kinases. | Induction of anagen phase | [90] |
| *Origanum vulgare* extract | - | Stimulation of insulin growth factor- (IGF-) | The proliferation of hair dermal papilla cells. | [91] |
| *Panax ginseng* | Ethanolic | Anti-apoptotic activation. | Elongation of the anagen phase. | [92] |
| *Aconitum ciliare* Tuber extract | Aqueous | Activates the Wnt/β-catenin signaling pathway | Induce anagen hair growth | [93] |
| *Schisandra nigra* extract | Ethanolic | Transforming growth factor-beta2 (TGF-beta2) | Promote hair growth | [79] |
| *Erica multiflora* extract | Ethanolic | Proliferation by MTT (↑) G2/M phase in the cell cycle (↑) | Telogen to anagen induction | [94] |
| Asiasari radix extract | Ethanolic | Thymidine incorporation (↑), VEGF (↑) | Telogen to anagen conversion | [95] |

*Aconitum ciliare*, also called aconite or devil's helmet, is a flowering plant of the Ranunculaceae family. The aqueous extract of its herb, Aconiti Ciliare Tuber, activates the Wnt/β-catenin signaling pathway. The extract induces anagen hair growth causing follicular morphogenesis [93]. *Schisandra nigra* is a species found in Japan. Its ethanolic extract acts on transforming growth factor-beta2 (TGF-beta2) and promotes hair growth. The extract proliferates dermal papilla cells, which were studied in the rat [79]. *Erica multiflora* is an aromatic flowering species belonging to the Ericaceae family. The ethanolic extract of *Erica multiflora* was evaluated by MTT assay (G2/M phase in the cell cycle in dermal papilla cells). The extract shows hair growth by induction of anagen to telogen [94]. The ethanolic extract of Asiasari radix was evaluated for hair growth activity. The extract transferred telogen to anagen conversion by thymidine incorporation and induced expression of VEGF when studied in mice [95,96].

### 5.3. Hormones

Testosterone is a circulatory hormone for men. This hormone is converted into the form of dihydrotestosterone (DHT) by 5α-reductase enzymes. This hormone binds with androgen receptors in the follicle. The DHT and receptor complex modulate gene expression, resulting in hair loss [81]. The complex also reduces the anagen phase and increases the apoptosis of hair, hence miniaturizing the hair follicle [97]. Figure 6 describes many herbal drugs inhibit testosterone's ability to form DHT by inhibiting 5α-reductase enzymes.

As shown in the Table 5. *Eclipta alba*, also called Bhringraj, belongs to the Asteraceae family; the whole plant has biological activity. The methanolic extract of *Eclipta alba* blocks 5-reductase and promotes hair growth activity [98]. *Cuscuta reflexa* is a parasitic plant of the family Convolvulaceae. The petroleum ether extract of *Cuscuta reflexa* acts by inhibiting 5a-reductase activity and promoting hair growth [99]. *Boehmeria nipononivea* belongs to the family Urticaceae, and its extracts contain linoleic, stearic acids, and elaidic acid. These phytoconstituents have hair growth effects. The acetone extract inhibits 5α-reductase. It is a type II Inhibitor having hair regrowth promotion activity studied on mice [100]. *Emblica officinalis* is also called myrobalan, an amla belonging to the Phyllanthaceae family. The aqueous extract stimulates the proliferation of dermal papilla cells and promotes hair growth and prolongs the anagen phase. It is a powerful inhibitor of 5α-reductase. It

has also antibacterial and anti-microbial properties and nourishes hair [101]. *Rosmarinus officinalis* is a medicinal evergreen plant also known as rosemary of the family Lamiaceae. It contains essential oils that inhibits 5-alpha-reductase and improves the vascularity of the scalp. The oil stimulates the growth of hair follicles regeneration [102]. *Scutellaria baicalensis*, also called Baikal skullcap, is a flowering plant of the family Lamiaceae. The extract contains baicalin (flavonoid) and acts by the androgen receptor antagonistic effect. It prevents androgenetic alopecia and proliferates dermal papilla cells [103].

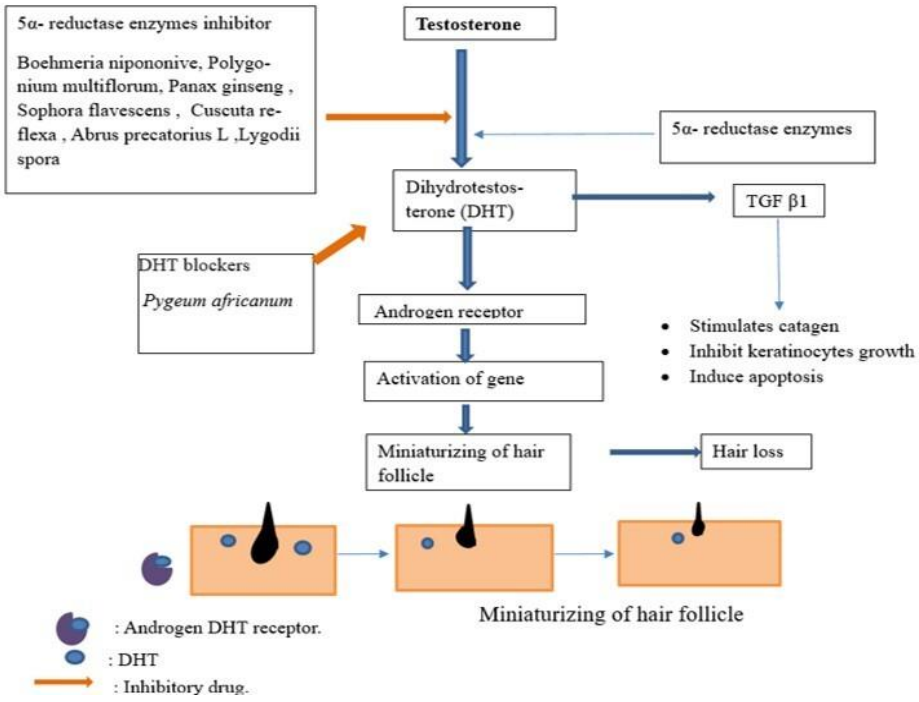


**Figure 6.** Herbal medicines acting on DHT and 5α-reductase.

**Table 5.** Herbal medicines act on DHT and 5α-reductase.

| Biological Source | Extract | Mechanism of Action | Effects | Reference |
|---|---|---|---|---|
| *Eclipta alba* | Methanolic | 5-reductase inhibition | Hair growth-promoting activity | [98] |
| *Cuscuta reflexa* | Pet. ether | Inhibition of 5a-reductase activity | Hair growth promote | [99,104] |
| *Boehmeria nipononivea* | Acetone | 5 reductase Type II Inhibitors | Hair regrowth promotion | [100] |
| *Emblica officinalis* | Aqueous | Powerful inhibitor of 5α-reductase | Antibacterial and anti-microbial properties nourish hair. | [101] |
| *Rosmarinus officinalis* | Essential oils | Inhibiting 5-alpha-reductase, improving vascularity of scalp. | Stimulate the growth of hair regeneration of follicles | [102] |
| *Scutellaria baicalensis* extract | - | Androgen receptor antagonistic effect DHT (↓) | The proliferation of hair dermal papilla cells | [79,103] |

### *5.4. Protein Kinase*

A protein kinase enzyme inhibits hair follicle growth and stops hair fiber production. Some natural drugs work by inhibiting the gene transduction process, which is mediated by the PKC enzyme and stimulates the anagen phase of hair growth [105]. The PKC enzyme inhibits follicular growth, hence anagen phase is inhibited. As shown in the Figure 7.

Herbal medicines, such as the *Bacopa monniera* extract and procyanidin B-2, inhibit PKC enzyme action and induce the anagen phase.

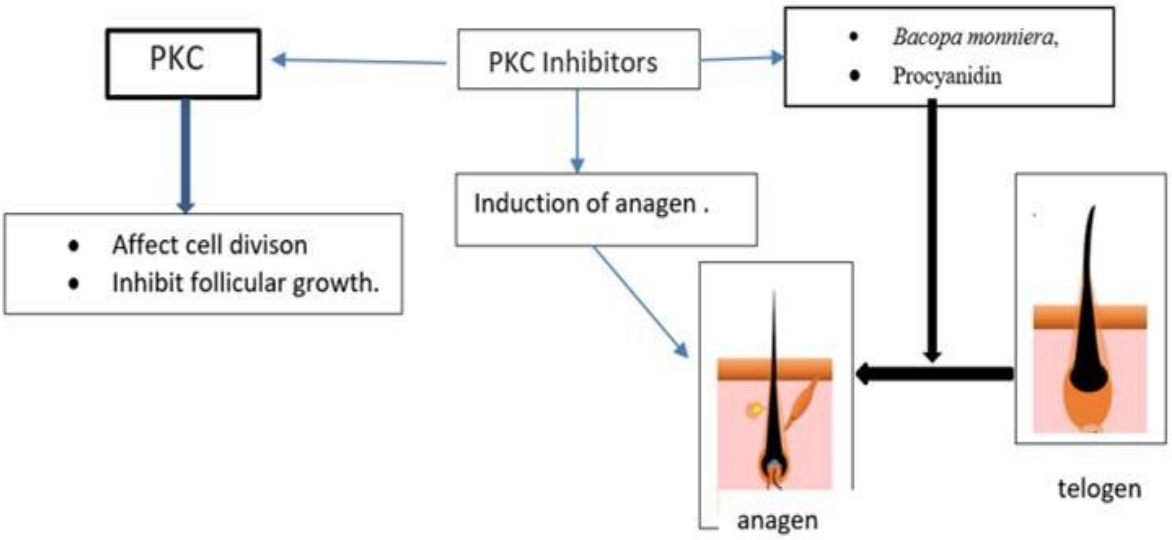


**Figure 7.** Drugs affecting PKC enzyme.

As shown in the Table 6. Procyanidin B-2 is a proanthocyanidin. Procyanidin B-2 is found in *Chinchona*, Ceylon cinnamon, apple, *Crataegus monogyna*, *Uncaria guianensis*, and *Vitis vinifera*. It is reported that Procyanidin B is in *Bacopa monniera*, a perennial plant belonging to the Plantaginaceae family. The extract of *Bacopa monniera* acts by inhibiting protein kinase C (PKC). The extract causes the enlargement of the follicle, prolongation of anagen phase duration, and prevents hair loss [106].

**Table 6.** Herbal drugs acting on PKC enzyme.

| Biological Source/Phytoconstituents | Mechanism of Action | Effects | Reference |
|---|---|---|---|
| *Cinnamomum verum* | Protein kinase C (PKC) inhibitors, | Promotion of epithelial cell growth and induce anagen phase. | [105] |
| *Bacopa monniera* | Protein kinase C (PKC) inhibitors, | enlargement of follicular size and prolongation of the anagen phase | [106] |

### *5.5. IGF*

The IGF enhances hair follicle production and prolongs the anagen phase. The IGF stimulates the proliferation of cells in the matrix of hair follicles, as well as down-regulating TGF. The TGF increases androgen receptor activation. In Figure 8, several herbal medicines, such as extracts of *Capsicum annum* and *Stephania cepharantha*, have been found to increase the production of IGF [107,108].

*Capsicum annum* is an annual plant, a shrubby perennial herb of the family Solanaceae. In Table 7, *Capsicum annum* contains capsaicin, which activates the vanilloid receptor and increases CGRP release from the sensory nerve. This CGRP starts to produce IGF-I in the dermal papilla cells leading to an increase in hair matrix number and promoting hair growth [107]. Cepharanthine is a biscoclaurine alkaloid extracted from *Stephania cepharantha* belonging to the Menispermaceae family. Cepharanthine acts on the upregulation of IGF and proliferates dermal cells. It induces hair growth when studied on the mouse. It is effective against alopecia areata [109].

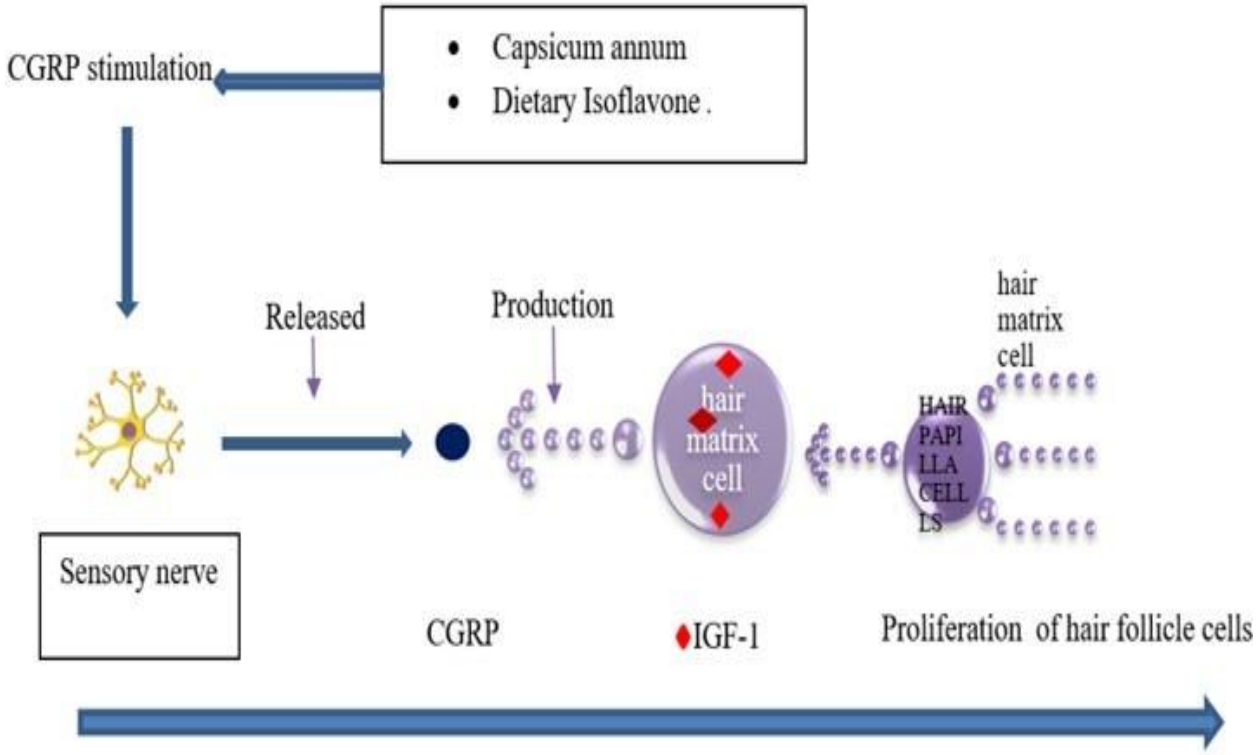


**Figure 8.** Drugs affecting the IGF factor.

**Table 7.** Herbal drugs acting on IGF.

| Biological Source/Phytoconstituents. | Mechanism of Action | Effects | Reference |
|---|---|---|---|
| *Capsicum annum* | Production of IGF-I | Promotes hair growth. | [107] |
| *Stephania cepharanthap* | Production of IGF-I | Induction of hair growth | [108,109] |

## 6. Herbal Treatment

Ayurveda is the oldest system of healing. Ayurveda plays a role in prevention of illness and encourages the maintenance of health and is more selective due to fewer side effects [7,8]. Herbal preparations attempt to balance the body with fewer side effects [110]. In herbal formulations, natural products are used as a hair tonic, hair cleaning agent, hair conditioner, growth promoter, dandruff agent, and to treat alopecia. The bio-active material from the natural system stimulates the epidermis biology and prevents hair loss and promotes hair growth [6,111,112].

## 7. Herbal Plants for Hair Care

Various herbal products are available in the market that contains herbal drugs, such as hair tonic, hair oils, hair gels, hair cleansing agents, and hair conditioners, for the treatment of various hair problems. In Indian Ayurvedic literature, various parts of plants, such as *Punica granatum*, *Hibiscus rosa-sinensis*, *Nardostachys jatamansi*, *Polygonum multiflorum*, *Crataegus pinnatifida*, and *Origanum vulgare* are used in extracts by traditional communities. A natural treatment is a low-cost treatment with very few or no side effects. These natural drugs will be handled with great respect and care. By using modern nanotechnology, various medicaments will be made that are safe for all humans.

### 7.1. Panax ginseng

Constituents: Ginsenosides, ginsenoside-Rb, and ginsenoside-Rg3, polysaccharides, saponins, steroids, choline, phenolic compounds, essential oil, vitamin- B, C, E, sesquiterpenes [92].

Mechanism: DHT is the inhibitor of the proliferation of dermal papilla cells and induced apoptosis of hair matrix cells. Ginsenoside-Rb enhances the proliferation of hair follicles by activating phosphor-ERK expression and AKT, this is studied using western blot analysis [92]. RGO(red ginseng oil) acts by upregulation of Wnt/β-catenin, Lef-, Sonic Hedgehog, Cyclin D, and Cyclin E and down-regulates TGF-β [92,113]. Red ginseng oil promotes hair regeneration. It induces the early telogen phase to the anagen phase [114].

Applications: It has an anti-apoptotic c effect. It promotes hair growth by acting on different mechanisms giving a synergistic effect. Red ginseng oil contains linoleic acid which has a hair growth effect. The topical application of red ginseng oil on mice for 2 days, promotes hair growth [114]. The metabolic extract of red ginseng inhibits the 5-alpha reductase enzyme. The RGO contributes antioxidant and anti-inflammatory properties [115]. Ginseng exhibits antiapoptotic effects in keratinocytes [115].

### 7.2. Eclipta alba

Constituents: It contains various secondary metabolites such as wedelolactone (0.6%), ecliptic, stigma sterol, sapiens, demethylwedelolactone, hentriacontanol, beta-sitosterol, beta-amyrin, heptacosanol [98,116].

Mechanism: The petroleum ether extract proliferates keratinocyte cells in the matrix. Shahnaz and others determined the level of TGF-β level by using western blot analysis in mice treated with PEE extract, which showed a decreased expression of TGF in the early anagen phase [98,116].

Applications: The PEE extract of *Eclipta alba* is used in hair oil as a hair tonic for smoother hair, thicker hair, and increased hair density, stimulating hair growth. The metabolic extract has a hair growth-promoting effect and petroleum ether extract increases the hair follicles number in extract-treated mice than in control mice [117]. The petroleum ether extract of *Eclipta alba* enhances the proliferation of keratinocytes cells in treated mice. Furthermore, it is used in the management of alopecia [98,117].

### 7.3. Camellia sinensis (Green Tea)

Constituents: Flavonoid, quercetin, myricetin, gallic acid, linolenic acids, vitamins (A, C, E, K and B), mineral elements, Catechin, (−)-epigallocatechin gallate, (-) epicatechin-3-gallate, (−)-gallocatechin (GC), (−)-epicatechin, (−)-epigallocatechin caffeine [118].

Mechanism: The catechins and caffeine present in green tea blocks the 5-alpha-reductase activity, which leads to a decrease in DHT level in hair follicles and ultimately lengthens the duration of the antigen phase [119]. Epigallocatechin-3-gallate, present in the extract, has 5-alpha-reductase inhibitory activity and in vivo study showed the proliferation of dermal papilla cells. Kwon and others concluded that EGCG acts in two ways, anti-apoptotic effects, and proliferative effects [118].

Fischer and others found that the application of caffeine on the skin caused a reduction in muscle tension near the hair follicle, as a result increasing the microcirculation of the papilla, which supply the nutrients to the matrix [120].

Applications: It is effective in androgenic alopecia, hair loss, and dandruff. These plants also show antioxidant activity [118]. Chanchanok and others evaluated green tea hair tonic for the oily scalp in 20 volunteers. They concluded that this tonic reduces sebum secretion, hair loss, and dandruff [121]. The acetone extract of *Camellia sinensis* is active against *candida* species, having antifungal activity [122]. Epigallocatechin-3-gallate proliferates and anti-apoptotic effects on DPCs lead to stimulating human hair growth [122].

### 7.4. Solanum nigrum

Constituents: Linoleic acid, steroidal glycoalkaloids, palmitic, elaidic and stearic acids, linoleic, alpha-linolenic [123].

Mechanism: *Solanum nigrum* contains linoleic acid which is blocking the 5-alpha-reductase [124]. The aqueous extract downregulates the AKT signaling pathways [80]. The acetone extract of *Boehmeria nipononivea* showed hair regrowth effects on mice by inhibiting block 5-alpha-reductase due to the presence of linoleic acid.

Applications: Hair growth promotion effects and treatment of alopecia. The extract *of Solanum nigrum* berries has a hair growth-promoting effect [80] The root part contains saponin which contributes to anti-microbial and antioxidant effects [123].

### 7.5. Hibiscus rosa-sinensis

Constituents: Beta-sitosterol, flavonoids, quercetin, taraxeryl acetate, diosgenin, luteolin, saponins, minerals (calcium, zinc, magnesium), stigmasterol, ergosterol, oxalic acids, citric acid, etc. [80].

Mechanism: Mauro LM et al. studied the effect of *Hibiscus rosa-sinensis* on the mouse for evaluation of hair growth activity. Quercetin is an inhibitor of 5-alpha-reductase. Histological studies showed that 40% of follicles were active on the 0th day and at the end of the study 7% of follicles were active in treated mice. The petroleum ether extract causes transformation of follicles cycles from the telogen to the anagen phase and causes prolongation of the anagen phase [86].

Application: Petroleum ether extract is useful in the promotion of hair growth by stimulating hair follicles [124]. Leaf extract has more potential than flower extract for hair growth, it lengthens hair and increases the anagen/telogen ratio [85].

### 7.6. Serenoa repens

Constituents: Phytosterol, palmitic acid, fatty acids, oleic acid, and beta-sitosterol [6].

Mechanism: Phytosterol, which blocks 5-alpha-reductase and reduces DHT, leads to blocking the binding of DHT to androgen receptors [6,119].

Applications: These plants are used in various formulations such as shampoo, and gel. It is effective in androgenetic alopecia [125]. Wessagowit and others studied the effect of *Serenoa repens* extract on 50 male subjects for 24 weeks to check the efficacy after topical application. The hair count from baseline to 2 and 24 weeks was increased and the authors concluded that this was effective against the male androgenetic alopecia [119].

### 7.7. Trigonella foenum-graecum

Constituents: Quercetin, diosgenin, luteolin trigonelline, carbohydrates, flavonoids, tigogenin, gitogenin, fats (6%), saponins, protein, galactomannan (44%), magnesium, zinc, iron, calcium [80].

Mechanism: *Trigonella foenum-graecum* shows positive effects on hair growth, but the exact mechanism is unknown [126].

Application: Ethanoic and petroleum ether extracts of leaves of *Trigonella foenum-graecum* contain phenolic compounds [126]. The ethanoic extract is effective against alopecia, which was studied in mice. The ethanoic extract of *Trigonella foenum-graecum* leaves has a high potential for hair growth than minoxidil drug. This plant also shows antioxidant, anti-bacterial, and anti-fungal properties [127]. The seeds have anti-dandruff and soothing effects and prevent hair fall [128]. *Trigonella foenum-graecum* contains zinc, which is useful for healthy hair [127].

### 7.8. Emblica officinalis

Constituents: Alkaloids (phyllantidine, phyllantine, phyllemblic acid, gallic acid), phosphorus, iron, calcium, vitamin C, gallotannis (5%), and ellagic acid [129].

Mechanism: The alcoholic extract of *Emblica officinalis* was evaluated for hair growth activity on albino rats, it showed enlargement of follicle and prolongation of the anagen

phase; it blocks the 5α-reductase enzyme; the extract shows proliferation of hair follicles and HaCaT keratinocytes [101,130]. Emblica is a concern with iron metabolism; iron is involved in oxygenation in red blood cells. For normal healthy hair originated blood should be provided, deficiency of originated blood leads to hair loss [80].

Application: Jae Young and others performed clinical trials for safety and efficacy, statistically show significant hair growth, and treatment of hair loss [130]. The extract prolongs the anagen phase, which means lengthening hair growth by the proliferation of dermal papilla cells. It has antioxidant, anti-bacterial, and anti-fungal properties. It is used as a hair tonic, prevents graying of hair, and nourishes hair [131].

### 7.9. *Pueraria thunbergiana*

Constituents: Puerarin, glycirin, tectoridin, biochanin A, piperine,6″-O-xyloglycitin, (-)-cubebin, (-)-3,4-dimethoxy-3,4-desmethylenedioxycubebin, genistin, spinasterol [132].

Mechanism: The leaf extract has effects on melanogenesis and 5-alpha-reductase inhibitory effects. Ethanolic extracts of the leaf show anti-androgenic activity in male mice. Hair pigmentation and graying of hair are mainly dependent on follicular melanocyte cells due to Bcl2 deficiency [133]. It contains puerarin that stimulates melanogenesis in follicular melanocyte cells via the cAMP/MITF-M signaling pathway and prevents depigmentation. It was also shown that it has scavenging activity on reactive oxygen species [133].

Application: It has antiandrogenic activity [130]. Root and flower extracts stimulate hair growth, strengthen the hair follicle, and promote hair growth. The active compound, puerarin, in the extract has significant effects on the maintenance of melanin pigmentation in hair and antioxidant effects [134]. It is used to treat graying of hair [132].

### 7.10. *Capsicum annum*

Constituents: Capsaicin, vitamins A and C, isoflavone [80].

Mechanism: The insulin-like growth factor-I (IGF-) is responsible for hair growth. Capsaicin upregulates IGF production in hair follicles and causes hair growth. Capsaicin and isoflavone activate vanilloid receptors, which releases calcitonin gene-related peptide (CGRP) from the nerve, and CGRP causes the production of IGF hair follicles and proliferates dermal cells, which induce hair growth [107].

Application: Capsaicin promotes hair growth and is used to treat alopecia and induce the anagen phase [80]. It is a powerful stimulant for blood flow towards every hair follicle that causes hair growth. *Capsicum annum* shows significant activity against diabetes, obesity, and cardiovascular diseases [80].

### 7.11. *Asiasari radix*

Constituents: The roots and rhizomes contains safrole, asarinol, methyl eugenol, asarinin, elemicin, sesamin. The methanolic extract of *asiasari radix* contains wedelolactone, which was confirmed by chromatographic analysis [80].

Mechanism: It shows regulatory effects on gene expression, increased protein synthesis in follicles, and proliferates HaCaT and human DP cells [135]. It also inhibits 5α-reductase activity and activation of hair follicles cells [80].

Application: The extract stimulates hair growth and shows activity against alopecia studied on mice. It prevents hair loss and promotes hair growth by induction of the anagen phase without any toxicity [96]. Experimental studies found that the extract promotes hair growth by induction of the anagen phase and shortens the period of transformation from telogen to anagen phase of the hair growth cycle [95].

### 7.12. *Punica granatum (Pomegranate)*

Constituents: Polyphenols, cyanidins, zinc, flavonoids, tannins, potassium, iron, vitamins E, K, and C [84].

Mechanism: Bhinge and others studied the effects of the extract on mice. They used counts of hair follicles to show a transition from the telogen to the anagen phase [84]. Pomegranate extract was associated with the expression of interleukin-6 [136].

Application: Alcoholic and aqueous extracts of *Punica granatum* show anti-dandruff and hair growth-promoting effects. Along with antimicrobial, antioxidant activity, and anti-lice activity, this provides nutrition to the hair [84]. It is effective in androgenic alopecia [84]. The most unique use of *Punica granatum* is a reduction in the alteration of hair color. Solar radiation causes fading of hair color due to the regeneration of free radicles that oxidize pigment and cause color fading [137]. The hydro-alcoholic extract contains polyphenols and tannins that have anti-oxidant effects [137].

### 7.13. *Nardostachys jatamansi*

Constituents: Nardal, jatamansic acid, bornyl acetate, nardin, 8-cineol, valeranone, menthylthymyl-ether, 8-cineol [88].

Mechanism: It is reported that ethanolic extract exerts hair growth activity by enlargement in follicular size and induction and prolongation of the anagen phase [87].

Application: The hexane extract of rhizomes has hair promotion effects and contains nardin and jatamansic acid. It is effective in alopecia [80], useful in male baldness, prevents hair loss, and makes hair stronger. It is used as an aromatic adjunct in herbal oils, for imparting blackness and hair growth. The roots of *N. jatamansi* have antifungal and antimicrobial properties [87].

### 7.14. *Cuscuta reflexa*

Constituents: Beta-sitosterol, quercetin, cuscutin, kaempferol, amarbelin, stigmasterol, coumarin, dulcitol, mycricetin [80].

Mechanism: The petroleum ether extract inhibits the 5α-reductase enzyme [104].

Application: The petroleum ether extracts promote hair growth activity and are useful in androgen alopecia [80]. The extract causes increases in changes in follicular density, follicular size, and the anagen/telogen ratio [80,104].

### 7.15. *Polygonum multiflorum*

Constituents: Beta-sitosterol, emodin, rutin, apigenin, vitexin, noreugenin, hyperoside, beta-amyrin, daucosterol [89,138].

Mechanism: The *polygonum multiflorum* extract was studied in zebrafish to evaluate melanin formation; it acts by upregulating the MCR//tyrosinase pathway and induced pigmentation [69,139]. The *polygonum multiflorum* extract up-regulates the shh and β-catenin in resting hair follicles. It transits telogen to anagen phase and studies show the number of hair follicles and their size increased in treated mice [140]. Experimental studies conclude that the *polygonum multiflorum* extract inhibits 5 alpha-reductase enzymes [80].

Application: The root extract stimulates hair growth in mice and induction of the anagen phase. It is also effective in early graying hair, hair loss, hair length increases, and the proliferation of DPCs [139–141].

### 7.16. *Acanthopanax koreanum*

Constituents: acankoreoside J, lupane-triterpene [142].

Mechanism: The leaf extract causes proliferation of DPCs studied in the rat. Acankoreoside J acts by upregulation of the β-catenin pathway and regulating the hair cycle, along with cyclin D, CDK2, cyclin E, and down-regulates p27kip [142].

Application: Promotes the hair growth, and proliferation of dermal papilla cells [142]. The topical application containing *Acanthopanax koreanum* prevents baldness and is used in the prevention and treatment of alopecia.

### 7.17. *Crataegus pinnatifida*

Constituents: Chlorogenic, caffeic, terpenoids, quercetin, steroids, epicatechin gallate (ECG), naringenin, gallic acid, proanthocyanidin [90].

Mechanism: The *Crataegus pinnatifida* extract induced the anagen phase from the telogen phase by activation protein kinases, and the proliferation of dermal papilla cells. Follicular size and number changes were observed in mice which indicate anagen induction [90,143].

Application: Increased blood circulation around the dermal papilla and provides nutrition to the hair, promoting hair growth [90].

### 7.18. Malus pumila (Apple)

Constituents: Oligomeric procyanidins, procyanidin B2, phytosterols, vitamins (A, C, and E), metal elements (i.e., potassium, magnesium, zinc, sulfur, calcium, copper, manganese, iron) phenols, protein [144].

Mechanism: Procyanidin B2, from apples, induced the anagen phase, promoted epithelial cell growth, and enhances keratin expression [145,146]. Polyphenols in apples inhibit the pentose phosphate pathway and amino acid oxidation, which causes an increase in keratin production in hair follicles [145].

Application: Increased hair growth and density. Polyphenols act as an antioxidant [144]. It stimulates hair growth and prevents hair loss; it prolongs the anagen phase, increases the protein content, and rejuvenates hair follicles [146].

### 7.19. *Allium sativum (Garlic)*

Constituents: Fiber, proteins, vitamins (mainly C and A), phytosterols, minerals (such as magnesium,), phosphorus, iron, and, potassium, sodium), and phenolic derivatives, lipids, carbohydrates (fructose) [147].

Application: Exposure to ultraviolet rays causes keratinocyte damage which can be prevented by *Allium sativum* [147]. Recently, it was concluded that *Allium sativum* can be used in the treatment of androgenic alopecia [80]. Tetrahydro-β-Carboline exhibits antioxidant activity [148].

### 7.20. *Coffea arabica (Coffee)*

Constituents: Caffeine, sterols, diterpenes, triacylglycerol, phospholipids, keratin [120,149].

Mechanism: Acts by downregulating TGF-β2 and upregulating IGF- in the hair follicle, stimulating proliferation and inhibiting apoptosis [120,149,150].

Application: Hair elongation because of prolongation of the anagen phase and proliferation of keratinocytes. The topical application of caffeine is more effective than a 5% topical solution of minoxidil for AGA [120,149]. It also imparts shine, increases elasticity, revitalizes the scalp, and stops hair loss. Caffeine promotes hair growth by stimulating hair follicles in AGA patients.

### 7.21. *Rosmarinus officinalis (Rosemary)*

Constituents: 2% volatile oil, rosmarinic acid, carnosic acid (CaA), carnosol, caffeic acid, chlorogenic acid, ursolic acid, luteolin, eugenol, camphor, carnosol, eucalptol, alpha-pinene, 8-cineole, luteolin [102,151].

Mechanism: Rosmarinic acid improved microcapillary perfusion. 2-methoxycarnosic acid inhibits 5α-reductase activity which is used to treat androgenic alopecia [102,151].

Application: The phenolic extract contains carnosic acid which has anti-microbial and antioxidant activity. The leaf extract promotes hair growth in mice [102,151]. Rosemary oil is an essential oil that reduces hair loss, stimulates the growth of hair in anagen, and is effective in the treatment of androgenic alopecia. Furthermore, it can be used to treat dandruff and preventing of hair. *Rosmarinus officinalis* exhibit various pharmacological activity such as antimicrobial (alpha-pinene), antioxidant (caffeic acid, carnosic acid),

anti-inflammatory (carnosic acid), anti-infective (chlorogenic acid), anti-fungal activity (eugenol). Aromatherapy is effective to treat alopecia areata [80].

### 7.22. *Carthamus tinctorius (Safflower) Floret*

Constituents: Oleic and linoleic acids, hydroxysafflor yellow A [152].

Mechanism: Ethanolic extract stimulates the mRNA expressions of vascular endothelial growth factors and causes the proliferation of dermal papilla cells and HaCaT. It stimulates the keratinocyte growth factor and suppresses the transforming growth factor-β [153]. The extract blocks the 5α-reductase activity [52].

Application: *Carthamus tinctorius* promotes hair growth. The *C. tinctorius* extract (CTE) causes the proliferation of dermal papilla cells and keratinocytes, and significantly stimulates hair growth [153].

### 7.23. *Thuja orientalis*

Constituents: Flavonoid (quercetin, rutin) and diterpene, b-sitosteryl B–d—glucosides, luteolin, ferulic acid, p-coumaric acid, alpha-terpinolene, alpha-pinene, limonene, caryophyllene, delta-3-carene [154].

Mechanism: The *T. orientalis* extract induces and prolongs the anagen phase from the telogen phase. The *T. orientalis* extract also induces β-catenin in hair follicles, and the Shh proteins investigated by immune histochemical analysis, flavonoid and diterpene in water extract, inhibited the 5α-reductase enzymes [155]. The *T. orientalis* leaf extract increases the mRNA of VEGF and the KGF levels, and Wnt and Lef in dermal papilla cells and human epidermal keratinocytes cultured cells [156].

Application: It is effective in baldness and prevents hair loss. The water extract of *T. orientalis* studied in mice induced the hair cycle. It is a potential hair growth-promoting agent. It was effective against androgenic alopecia [155]. The ethanol extract of *T. orientalis* suppressed the sebum level in the scalp and promoted hair growth [156].

### 7.24. *Nasturtium officinale (Watercress)*

Constituents: Mono-unsaturated fatty acids (cis-3-eicosenoic acid, cis—octadecenoic acid, cis-3-docosenoic acid, docosanol), saturated fatty acid n-Hexadecanoic acid, microelements (magnesium, phosphorus, calcium, and potassium, magnesium), and macro elements (zinc, copper, and iron) [157].

Mechanism: The mitogen-activated protein kinases (MAPKs) stimulate the anagen phase in the cycle and regenerate hair follicles cells. Molecular docking studies found that promotion in hair growth effect due to the fatty acids by activation of MAPK, MAPK3, and MAPKp38 receptors [158,159].

Application: The *Nasturtium officinale* extract promotes hair growth, strengthens hair, and prevents hair fall [157], increases hair length and density [160], and has antioxidant effects [161].

### 7.25. *Sophora angustifolia*

Constituents: L-maackiain and medicarpin, flavonoids *Sophora flavanone* G, s kushenol I, kurarinone, Pterocarpan derivatives (maackiain-3-O-glucoside, s, maackiain. Stigmasterol, isoliquiritigenin) [162,163].

Mechanism: It exerts effects by regulating growth factors. It increased the mRNA level of IGF and KGF [164]. It also inhibits the 5alpha-reductase enzyme. The extract induced the anagen phase in mice.

Application: The root extract of *Sophora flavescens* used in hair products has hair growth-promoting effects [164]. A clinical study showed that the *S. flavescens* extract is effective in the treatment of androgenetic alopecia (AGA) [162]. L-maackiain and medicarpin, are active compounds that cause the proliferation of hair keratinocytes [162].

## 8. Patents in Herbal Extract

In Table 8 we list various patents for herbal extract and nanotechnology used in formulation development. Nanotechnology provides multiple advantages over traditional technology.

**Table 8.** Patents for herbal extract-based nanomedicines.

| Patent Number | Title | Description | Reference |
|---|---|---|---|
| Us 2010/0104646a1 | Nanoparticle composition for prevention of hair loss and promotion of hair growth | This invention formulates the herbal hair care composition-based lecithin-capsuled nanoparticles. Nanoparticles activates hair follicles. It has antioxidant effects. | [165] |
| Kr1020050024694ar100675808b1 | Composition for nano particle comprising henna extract and manufacturing method for nano particle using it | This invention relates to a nano particle comprising henna extract, lecithin, ethanol, triglyceride, anionic surfactant for hair treatments. | [166] |
| Wo2017057881a1 | Composition for preventing hair loss or promoting hair growth, containing ginseng-derived exosome-like vesicles | This invention formulates ginseng-derived exosome-like vesicles for hair loss or promoting hair growth | [167] |
| Kr101536996b1 | Hair growth-promoting ingredient-loaded and skin temperature-responsive ionic polymer-immobilized lipidic nanostructures and method for preparation of the same | This invention formulates ionic polymer-immobilized lipidic nanostructures contains *Thuja orientalis*, *Polygonum multiflorum*, and espinosilla. For promoting hair growth | [168] |
| Kr101883719b1 | Composition for transdermal delivery comprising nanoemulsion and modified layered double hydroxide | This invention formulates nanoemulsion and modified layered double hydroxide for hair care | [169] |
| Kr20040033117a | Compositions for hair cosmetic containing nano-emulsion | This invention is concerned with nano-emulsion based natural source polymer for hair care | [170] |

## 9. Conclusions and Future Scope

In this review, we provide an overview of current knowledge regarding herbal medicine and nano-formulations used in hair care products, the morphology and modulation of the hair cycle. Today, the world is more interested in natural remedies to avoid the potential side effects of active therapeutic agents. In the literature, heavy metals used in cosmetics are studied effectively [144]. Herbal medicines are in great demand in both developed and developing countries due to their safety, minimum toxic effect, and lower cost. Herbal drugs are effective in treating hair problems through various mechanisms. Some herbal marketed preparations are Keshamrit Oil (Amla, Bring raj), Siddha Shampoo (Tulsi, Neem), Nutrich Capsule (Bhringgraj, Godanti), Chirayu Herbal Oil (Amla, Bhringaraj, Brahmi), Hairbac Tablets (Amla, Bhringaraj, Guduchi). These marketed formulations contain various constituents that act by different mechanisms on hair. This results in hair growth, induction of the anagen phase, effectiveness in alopecia, and various hair problems. The composition formulated by scientists is based on nanotechnology, which has more advancements, such as small particle size, allowing penetration through stratum corneum and strong effectiveness. In comparison to synthetic drugs such as minoxidil, finasteride, etc., herbal medication is free from side effects and toxicity. Herbal drug products are highly effective in treating androgenetic alopecia. Herbal medicines act by different mech-

anisms on the hair cycle and have synergistic effects. The use of nanotechnology makes herbal medicines very effective and overcomes skin barriers. Various formulation such as nanoparticles, Nanostructured lipid carriers, nanofiber, and B-cyclodextrin inclusion complex have been developed by many researchers. One more advantage is their inherent acceptability due to their regular use in daily life—for that reason herbal drugs give very few side effects. Herbal drugs act in a synergistic and long-lasting manner, that is why today's generation prefers natural medicines.

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