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REVIEW

# Application of Non-Pharmacologic Therapy in Hair Loss Treatment and Hair Regrowth

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**Purpose:** Alopecia significantly affects the appearance and psychology of patients, and pharmacological therapies and hair transplantation are the main treatments for alopecia, but both have limitations. This review aimed to summarize the non-pharmacological therapies that promote hair growth and regeneration.

**Patients and Methods:** This is a non-systematic review. Multiple databases was searched with relevant data published between 1997 and 2024. Searching and screening followed the PRISMA guidelines.

**Results:** Novel therapeutic modalities, such as gas molecules, platelet-rich plasma, laser, and microneedling, can change the microenvironment of hair follicles, activate hair follicle stem cells, and promote hair growth and regeneration.

**Conclusion:** This paper reviews research on the application of non-pharmacological therapies in alopecia treatment and hair regeneration, with a view to providing an important basis for future research on alopecia treatment and the postoperative treatment of patients after hair transplantation.

**Keywords:** alopecia, hair regrowth, non-pharmacologic, gas therapy, regenerative cellular therapy, laser therapy, microneedle therapy

## Introduction

Alopecia or baldness is a common and unpleasant problem that directly influences the self-confidence and quality of life of patients. It is generally categorized into scarring alopecia and non-scarring alopecia, which includes primary scarring alopecia caused by autoimmune diseases and secondary scarring alopecia caused by burns, trauma, and infections. Non-scarring alopecia includes androgenic alopecia (AGA), alopecia areata (AA), and telogen effluvium.

Hair is the appendage of the skin. It is a special tissue composed of keratinocytes arranged in concentric circles, hair shafts, and hair follicles (HFs). HFs are located in the dermis and subcutaneous tissues, and are necessary for hair growth.[1]

Hair follicles undergo the anagen, catagen, and telogen phases, forming a repetitive regenerative cycle of hair growth, shedding, and regrowth.[2] The most important cell type in HF is the dermal papilla (DP).[3] Dermal papilla produce signals that control the sequential cycling of the follicular epithelium. Epithelial stem cells, which reside in the bulge area of HFs, respond to signals from DP[4] (Figure 1).

Normal cyclic changes and hair regeneration depend on the regulation of signaling factors from the surrounding cellular microenvironment, including various hormones, cells, cytokines, and signaling pathways.[2] Many growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-5S, and insulin-like growth factor (IGF)-1, play significant roles in regulating HF cycling and hair regeneration. Several signaling pathways are involved in hair growth and cycle regulation, with the Wnt/β-catenin signaling pathway being the most well-studied. Others include the bone morphogenetic protein (BMP), Notch, Sonic Hedgehog (Shh), FGF, HGF, and Eda-A 1 signaling pathways.[5] In

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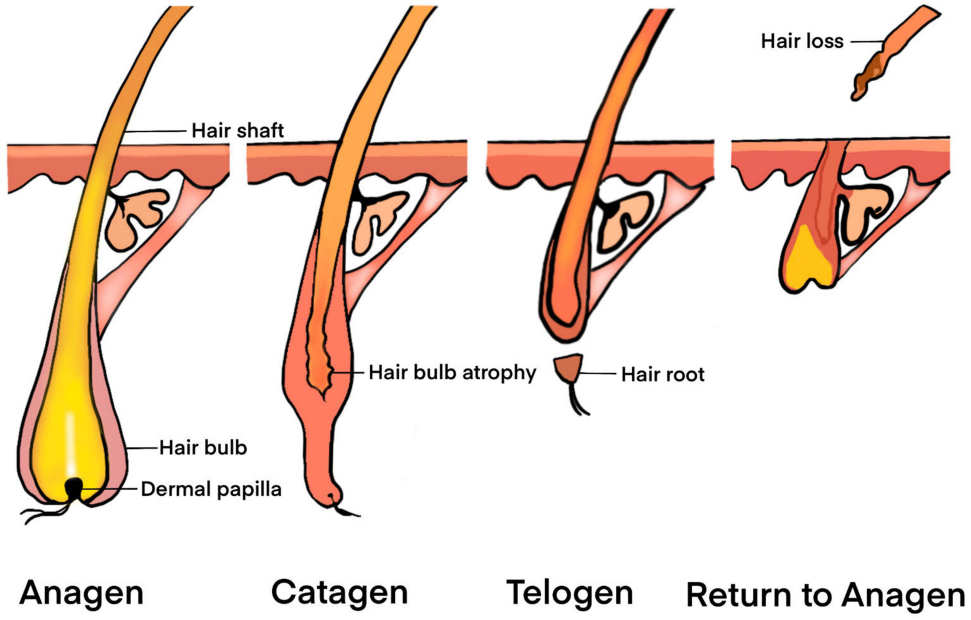


**Figure 1** Hair follicle structure and hair cycle. Quiescent HFSCs reside in the bulge region and they are transiently activated in early anagen. HFs progress through catagen (regressing phase), telogen (resting phase) and anagen (growing phase) cyclically. In catagen, the hair bulb shrinks and the lower portion of the HF regresses through a progressively shortened epithelial strand into the telogen stage. In telogen, HFSCs in the secondary hair germ and bulge remain inactivated. HFs, hair follicles. HFSCs, hair follicle stem cells.

addition, there is increasing evidence that the circadian clock and miRNAs exert a significant influence on the regulation of hair growth and hair cycle.[6]

Current guidelines and consensus on alopecia indicate that medication remains the primary treatment strategy. For AGA, the main treatments include oral finasteride, topical minoxidil, and hair transplantation;[7,8] the available treatments for AA include corticosteroids and other immunomodulators, minoxidil, Janus kinase (JAK) inhibitors, etc.[9] Drug treatments are effective but have many limitations, such as limited efficacy, high risk of adverse effects, high recurrence rates, and poor patient compliance with long-term medication. Topical minoxidil, the only FDA-approved topical drug for AGA treatment, has a limited treatment response, which is related to sulfotransferase activity in the plucked hair follicles of patients.[10] Side effects of topical minoxidil including irritant contact dermatitis among others have been reported.[11] At the same time, many patients are discouraged from hair transplantation due to their high cost, surgical trauma, and unpredictability of the progression of their hair loss. These drawbacks compelled us to explore new therapies that have minimal or no side effects.

In recent years, non-pharmacological treatment modalities, such as hydrogen, hyperbaric oxygen, platelet-rich plasma, laser therapy, and microneedling, have been found to regulate the signaling pathway of hair growth, improve the cellular microenvironment, activate hair follicle stem cells (HFSCs), and promote hair growth and regeneration.

This paper summarizes the non-pharmacological methods used in recent years to treat alopecia and promote hair regeneration, providing an important basis for future research on alopecia treatment and postoperative treatment of patients after hair transplantation.

## Non-Pharmacological Therapies

### Gas Therapy

Gas molecules have unique physicochemical properties and special signal transduction modes, such as a small molecular size, free diffusion, and non-dependence on the corresponding membrane receptors, which provide new ideas for regulating physiological activities and metabolism.

## Hydrogen

Hydrogen ($H_2$) is a colorless, tasteless, odorless gas that has long been considered physiologically inert. $H_2$ have the properties of a small size, low mass, neutral charge, non-polarity, and high rate of diffusion, enabling it to easily penetrate cellular biomembranes and rapidly diffuse into the cytosol, mitochondria, nucleus, and other organelles. In recent years, studies have shown that $H_2$ has potential protective effects against neurodegenerative diseases, metabolic diseases, inflammatory diseases, mitochondrial diseases, and tumors.[12] Scholars have found that $H_2$ protects cells from oxidative stress and inflammatory damage, and helps repair tissue trauma.[13] Researchers found that $H_2$, applied by respiration and transdermal topical application, can significantly promote wound healing in mice with total skin defects, and the accumulation of collagen in the skin can be observed within 1 day, which is about 2 days earlier than that of the control group, and the expression of Col-I, Fibronectin and Laminin in dermis layer at the edge of wounds in the $H_2$ group increased significantly. Additionally, Col-III expression in the epithelial layer at the edge of the wound was significantly increased. In addition, the expression of Col-XVII in the epidermal-dermal tight junction layer, which is an important protein for maintaining the activity of hair follicle stem cells, is significantly increased.[13] $H_2$ has been shown to maintain bone marrow stem cell activity in vitro[14] and inhibit radiation-induced damage to hematopoietic stem cell damage.[15] Ma et al found that $H_2$ promotes an increase in local hemorrhagic oxygenation and induces the growth of large numbers of autologous stem cells, such as interfollicular epidermis (IFE) and HFSCs, at an early stage of the tissue repair process.[13] The team also demonstrated that $H_2$ can ameliorate local inflammation by promoting macrophage polarization from M1 to M2,[16] thus potentially creating a favorable microenvironment for hair growth. In conclusion, it can be speculated that $H_2$ has great potential in stem cell and regenerative medicine, and may play a role in repairing and regenerating damaged hair follicle stem cells in alopecia patients.

## Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is a therapeutic approach based on exposure to pure oxygen at an increased pressure, leading to increased oxygen levels in the blood and tissue. The first documented use of HBOT dates back to 1662; currently, there are 14 approved indications for HBOT, including a wide variety of complications such as air embolism, severe anemia, certain infectious diseases, or idiopathic sensorial hearing loss.[17] It has been found that HBOT can increase the partial pressure of oxygen, increase the oxygen content of blood and tissues, enhance the effective diffusion distance and diffusion rate of oxygen, promote cerebral blood vessels contract, reduce cerebral blood flow, reduce cerebral haematomas, and improve the cerebral metabolism, and so on.[18] Besides, studies have confirmed that HBOT has antioxidant, anti-inflammatory properties, promotes capillary regeneration, and reduces ischemia-reperfusion injury, which may have an adjuvant therapeutic effect on multiple pathological states[19,20](Figure 2). Fan et al investigated the effects of hair transplantation combined with hyperbaric oxygen therapy, and showed that hyperbaric oxygen therapy effectively decreased follicular shedding, reduced follicular inflammation, and relieved itching symptoms after the surgical procedure.[21]

## Nitric Oxide

Nitric oxide (NO), a gaseous transmitter extensively present in the human body, regulates vascular relaxation, immune responses, inflammation, neurotransmission, and other crucial functions.[22] NO has been used clinically to treat angina, heart failure, pulmonary hypertension, erectile dysfunction, and recently as an anticancer therapy.[23] In particular, it can induce synergistic effects with other conventional therapies by regulating the activity of P-glycoprotein, acting as a vascular relaxant to relieve tumor hypoxia, and participating in ROS metabolism of reactive oxygen species.[24]

Ma et al treated AGA with a composite of NO and minoxidil mediated by hyaluronic acid liposomes and found that NO induces vasodilatation of scalp blood vessels, accelerates the rate of blood flow, and prolongs the retention time of minoxidil in patients with AGA. In addition, the combination of NO and minoxidil can downregulate interleukin (IL)-6 and transforming growth factor (TGF) -β1 and increase the expression of Ki67 and proliferating cell nuclear antigen (PCNA) proteins in the hair follicle, thereby promoting hair growth and regeneration, thus synergistically achieving a multifaceted therapeutic effect in patients with AGA.[25]

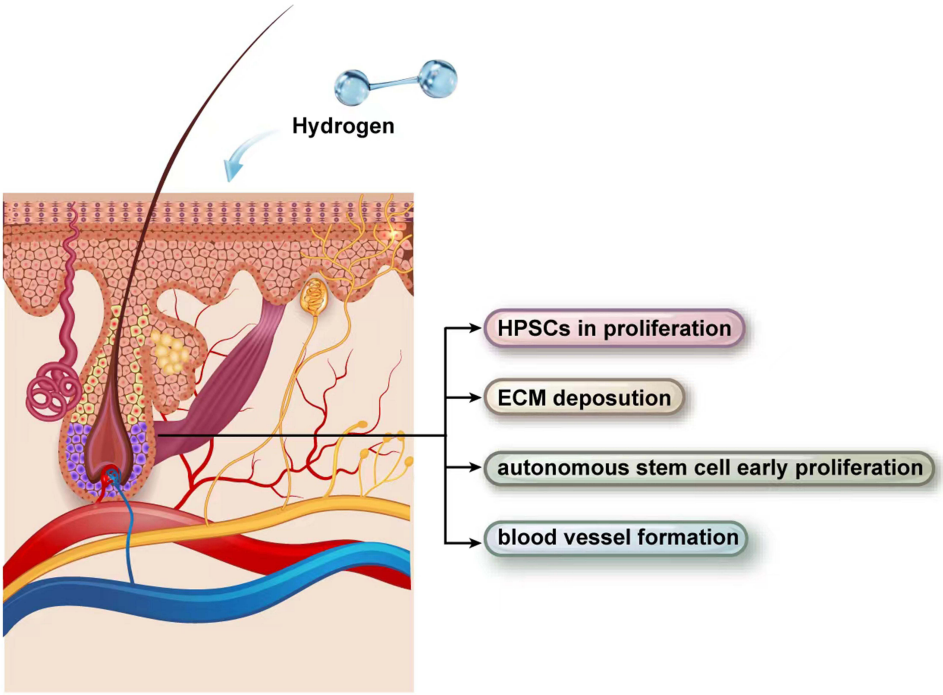


**Figure 2** Schematic representation of the hair follicle under $H_2$ treatment. Studies have shown that $H_2$ treatment might ameliorates local inflammation, induces the growth of large numbers of autologous stem cells including HFSCs, promotes ECM deposit and blood vessel formation. HFSCs, hair follicle stem cells. ECM, extracellular matrix.

Gas therapies have shown great potential in the treatment of skin diseases, but it is still in the early stage of research and requires further research.

## Regenerative Cellular Therapies

Regenerative cellular therapies, generally autologous/allogenic, are free from the adverse effects of conventional medicines and have good patient compliance. They can be classified into growth factor-rich and stem cell-rich therapies. The growth factor-rich group included platelet-rich plasma, platelet-rich fibrin, and concentrated growth factor, whereas adult stem cells and perinatal stem cells (umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), Wharton jelly derived MSCs (WJ-MSCs), amniotic fluid-derived MSCs (AF-MSCs), and placental MSCs) were grouped into the stem cell-rich group.[26]

### Growth Factor-Rich Therapies

Platelet-rich plasma (PRP) is a plasma component containing a high concentration of platelets obtained by centrifugation of autologous whole blood and contains a variety of growth factors and cytokines that promote tissue repair and regeneration. PRP has become a popular therapy in multiple fields such as sports medicine, regenerative medicine, cosmetic medicine, and skin disease treatment.[27,28]

Numerous studies have shown that PRP has a desirable therapeutic effect in alopecia.[29] Evidence has shown that PRP can induce the proliferation of dermal papilla cells, prolonging cell viability and promoting vascularization of HF. It can also promote the entry of HF into the anagen phase.[30] A randomized, placebo-controlled study showed a significant increase in the number of hair follicles after PRP injections alone compared with controls.[31] An observational study evaluating topical 5% minoxidil with PRP reported an increase in hair diameter after one year of combination treatment compared to minoxidil monotherapy.[32,33]

In addition, PRP is reported to be safe, with only mild erythema, oedema, mild pain, and temporary swelling from injections; there have been no reports of serious infections.[29]

PRP has been widely used clinically to treat alopecia. Researchers have optimized and updated platelet-rich fibrin (PRF) as a second-generation autologous platelet concentrate, which is easier to prepare, more stable, does not require any other biological additives, and has a high concentration of growth factors.[34]

Concentrated growth factor (CGF) is a third-generation autologous platelet concentrate that is enriched with softer and thinner organic fibrin lattices and is relatively stable with a high growth factor concentration.[35] One study investigated the safety and clinical efficacy of CGF sprays in patients with AGA. The results showed that the patients presented an increased amount of hair in the target area and a mean increase in total hair density compared with the baseline at the end of 3 months of treatment.[36]

Generally speaking, growth factor-rich therapies holds considerable promise in alopecia treatment, and future studies should standardize the treatment protocols for specific indications.

### Stem Cell-Rich Therapies

MSCs are the most dynamic, immature, diverse, and multipotent stromal progenitor cells, with the capacity to transdifferentiate into a range of tissues of ectoderm, endoderm, and mesodermal origin. MSCs are found in the bone marrow, placenta, umbilical cord, fat, menstrual blood, molars, and amniotic fluid. Several studies have suggested that many types of MSCs have high potential for hair regeneration.[37,38] The proposed mechanisms include the reversal of the pathophysiology of alopecia and regeneration of partially destroyed hair follicles or stem cells.[39]

One study showed when 1 mL/cm$^3$ of stromal vascular fraction (SVF) from fat tissue was injected subcutaneously into the scalp, there was a significant increase in hair density (31 hair/cm$^2$), and the combination of SVF with fat graft increased the density to 44.1 hair/cm$^3$.[40] A placebo-controlled study was conducted on 11 patients with AGA; mean hair count and hair density improvement (29%±5% vs placebo 1% increase) were observed 23 weeks after the last treatment.[39]

## Laser Therapy

### Low-Level Light Therapy

Low-level light therapy (LLLT) is associated with a range of wavelengths from red (600–700 nm) to near-infrared light (600–950 nm), which promotes tissue repair and regeneration.[41]

LLLT has a wide range of biological effects and has been used clinically to treat a variety of diseases, including hair growth, wound healing, and nerve regeneration.[42] LLLT has been reported to stimulate hair growth in androgenetic alopecia (AGA) in men and women, and was approved by the US FDA in 2007.[43]

One proposed mechanism for LLLT treatment of AGA is that low-level light absorbed by chromophores can lead to the production of nitric oxide (NO) and modulation of reactive oxygen species (ROS). These mobilized molecules subsequently activate redox-related signaling pathways in HF and perifollicular cells. Finally, these activated cells participate in HF regrowth.[44] Whole-genome analysis of LLLT-treated scalp biopsies of AGA patients showed down-regulation of scalp inflammatory biomarkers, such as AP1/FOSB messenger RNA (mRNA) and mir21, together with the disappearance of CD69 mRNA, specific to scalp-infiltrating T cells in approximately 50% of the studied volunteers prior to LLLT treatment.[45]

In a randomized controlled trial that included 45 female patients with AGA, 15 patients were randomized to receive either topical 5% minoxidil (twice daily), a helmet device with a 650–670 nm LED light source (3 times weekly), or minoxidil combined with helmet for 4 months. The results showed a significant increase in the number of regrown hair follicles in all three groups, and the efficacy of topical minoxidil was similar to that of low-energy irradiation, with the combination treatment improving the efficacy and shortening the onset time.[46] Another clinical study with 100 AGA patients consistently concluded that patients treated with 650 nm or 660 nm lasers gained significantly better hair coverage and better improvements in hair diameter and counts on the treated side than on the control side.[47] Barikbin et al conducted a randomised controlled trial in 90 patients with AGA and showed that the 655 nm laser alone or in combination with the 808 nm laser was superior to the simulated control treatment group, and that the increase in final hair counts in the treatment group was predominantly in the central region.[48]

However, the effects of LLLT on chemotherapy-induced alopecia remain unclear. A randomized controlled trial assessing the effect of a helmet, a home-use LLLT device for chemotherapy-induced alopecia, showed that LLLT improves cancer patients' quality of life and provides clinical evidence;[49] however, a previous study on breast cancer patients showed limited benefits.[50]

Low-energy lasers are also widely used in the clinical treatment of AA, mainly includes He-Ne laser, pulsed infrared diode laser, etc. A systematic review of the treatment of pediatric severe AA using LLLT revealed an average effectiveness of 52.55% and was well tolerated.[51]

## High-Intensity Laser Therapy

High-intensity laser therapy is usually divided into ablative and non-ablative lasers, with the former causing varying degrees of damage to the skin and the latter leading to a low degree of damage while maintaining the integrity of the skin surface. The potential mechanism of high-intensity laser therapy in hair regeneration might be the thermal injury healing process, in which many cytokines participate, such as fibroblast growth factor, IGF, and VEGF. In addition to their direct effect on hair growth, high-intensity lasers also enhance the penetration of topical medications, which is called laser-assisted drug delivery.[52]

A cohort study was conducted on 23 patients with AGA treated with a 1550 nm erbium glass fractional laser. The results showed a significant increase in the final hair count and hair diameter after treatment compared to baseline, and histological assessment demonstrated an increase in follicular units, anagen follicle counts, and the anagen/resting phase ratio.[53] A half-head trial that included 10 male patients with AGA showed a significant increase in mean hair count and diameter relative to baseline after treatment with 1927 nm fractional thulium laser therapy.[54]

Animal studies have shown that fractional carbon dioxide (CO2) laser treatment induces hair regrowth in a mouse model by activating the Wnt/β-catenin signaling pathway during the wound healing process.[55] In a half-head trial that included 28 male patients with AGA, patients were treated with topical hair growth factors on the entire scalp and randomly selected to receive fractional CO2 laser treatment on one side of the scalp for a total of six sessions. After four months of treatment, the mean hair density on both sides of the scalp increased significantly relative to baseline, and the increase on the laser side was significantly greater than that of drug treatment alone.[56] A comparative study between the topical application of triamcinolone acetonide after fractional CO2 laser and microneedling for the treatment of resistant AA showed no significant difference between the two treatment methods.[57]

## Ultraviolet Radiation Therapy

Ultraviolet radiation (UVR) involves the controlled administration of non-ionizing radiation to the skin in various dermatoses, which commonly involves the ultraviolet A (UVA) spectrum, ultraviolet A-1 (UVA-1) spectrum, UVA spectrum with a psoralen sensitizer (PUVA), and ultraviolet B (UVB) spectrum (280–320 nm), that is, broadband (BB)-UVB or narrow-band (NB)-UVB.[58,59] The mechanisms of UVB are unclear but include the induction of cis-urocanic acid, Langerhans cell depletion, altered antigen presentation, decreased activity of natural killer cells, and apoptosis of T lymphocytes and keratinocytes. The mechanisms of action of PUVA include cross-linking of DNA through psoralen photoadducts, inhibition of DNA replication, depletion of Langerhans cells, and immunosuppressive effects on T-lymphocyte function and migration. UVA-1 phototherapy penetrates deeper into the dermis and induces interstitial collagenase and cytokines, resulting in softening of sclerotic skin.[60–62]

This study was designed to evaluate the effectiveness and progressive dosimetry of UVA-1 for the treatment of AA. An increase in anagen hairs and a decrease in telogen/catagen hairs were observed after UVA-1 treatment, and the improvement continued for six months post-treatment.[63] Taieb et al compared the efficacy of topical calcipotriol and NB-UVB in the treatment of AA and showed that both are effective therapies in the treatment of AA and are associated with improvement in the SALT score and vitamin D3 levels.[64] A study evaluating the factors influencing the efficacy and safety of the 308 nm excimer lamp used on a monthly basis achieved a good clinical response (100% of patients achieved clinical response) with minor adverse effects.[65] Nevertheless, treatment with UVR for other types of alopecia has not yet been reported.

Laser therapy represents a non-invasive, safe, and potentially effective treatment option for patients with AGA or AA who do not respond or are not tolerant to standard treatment methods. Moreover, combining laser with medication therapy may act synergistic to enhance hair regrowth. However, the level of evidence of the studies is still low and hence more controlled large studies are needed.

## Microneedling

Microneedling is a minimally invasive treatment technique widely used to treat alopecia. Some studies suggest that micro-injuries caused by microneedling trigger platelets and neutrophils to release growth factors, such as platelet-derived growth factor (PGF), transforming growth factor (TGF) alpha, and beta. Furthermore, it was found to increase the expression of Wnt proteins Wnt3a and Wnt10b in HF, thus encouraging the differentiation of HFSCs into various parts of the HF and regulating the hair cycle. Microneedling was also found to activate revascularization of the skin, providing proper nourishment to HF.[66]

Minoxidil is often accompanied by microneedling, as microneedling is thought to establish microchannels in the epidermis which can promote absorption of medication.[67] Moreover, microneedling may increase the efficacy of minoxidil by upregulating follicular sulfotransferase enzymes.[68] Research has found that compared to single minoxidil or single microneedle treatment, the combination therapy showed superior therapeutic effects clinically, with further upregulation of FZD3, β-catenin, and LEF-1 expression levels at both the mRNA and protein levels in the treated areas.[69]

A randomized, double-blind, placebo-controlled study of microneedling combined with topical 0.01% dutasteride solution for the treatment of male AGA showed a significant improvement in hair density and cui/terminal hair ratio compared to the placebo group.[70]

## Other Therapies

Numerous studies have confirmed that extracellular matrix (ECM) plays an important role in hair growth. Extracellular collagen maintains DP growth and function Proteoglycans which are believed to mediate the transport of ECM macromolecules, can also release cell adhesion factors, transmembrane signaling molecules, and growth factors.[71]

Glycosaminoglycans (GAG) are naturally occurring acidic polysaccharides that are composed of repeating disaccharide units. They are commonly classified into four types based on their monosaccharide composition, glycosidic bonding, and sulphation patterns.[72] GAG play an important role in various physiological and pathological processes, including cell growth, differentiation, and neurodegenerative diseases, and have been found to affect scalp aging and hair loss.[73]

Stephane et al used infrared spectroscopic imaging and Western blotting to monitor the spatial location and degree of expression of heparan sulfate proteoglycans (HSPG) and Glypican-1 proteins in the ECM, suggesting that some ECM components may be involved in hair growth and cycle regulation.[74]

It has also been found that the cellular microenvironment of the aging female scalp shows significant structural and biological changes that affect hair growth. Some researchers have cultured human hair follicles in vitro in a GAG hydrogel that mimics the dermal matrix, and the structure was shown to significantly promote sustained cell survival and the maintenance of a highly proliferative phenotype in the hair bulb and suprabulbar region. In the meantime, activation of the Wnt/β-catenin signaling pathway, as well as with stem cell markers (eg CK15, CD34) and the expression of growth factors (TGF β2, FGF10, etc.) was observed, leading to the conclusion that the GAG might be an important component in the regulation of the growth cycle of the human hair follicle.[75]

# Summary

The prevalence of alopecia has recently increased, and it causes cosmetic defects and profoundly affects the psychological health of patients. Complex factors are believed to be responsible for activating HFs, including hormones, cytokines, and signaling pathways; however, the exact mechanisms are unclear. Considering the limitations of traditional pharmacological treatments and hair transplantation for alopecia, nonpharmacological therapy is an emerging research frontier that deserves further exploration. In this review, we have detailed the significant recent progress in non-pharmacological treatments for alopecia, such as hydrogen, hyperbaric oxygen, regenerative cellular therapy, laser therapy, and microneedling. However, the limitations include a lack of protocols, few randomized controlled studies,

and unclear therapeutic mechanisms. An improved understanding of the mechanisms of these strategies and more clinical practice will be key to realizing this potential.

## Disclosure

The authors report no conflicts of interest in this work.

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