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Review Article

Impact of conventional and advanced therapies in functional hair follicular regeneration in pesticide-induced hair loss: a Pharmacological perspective of review

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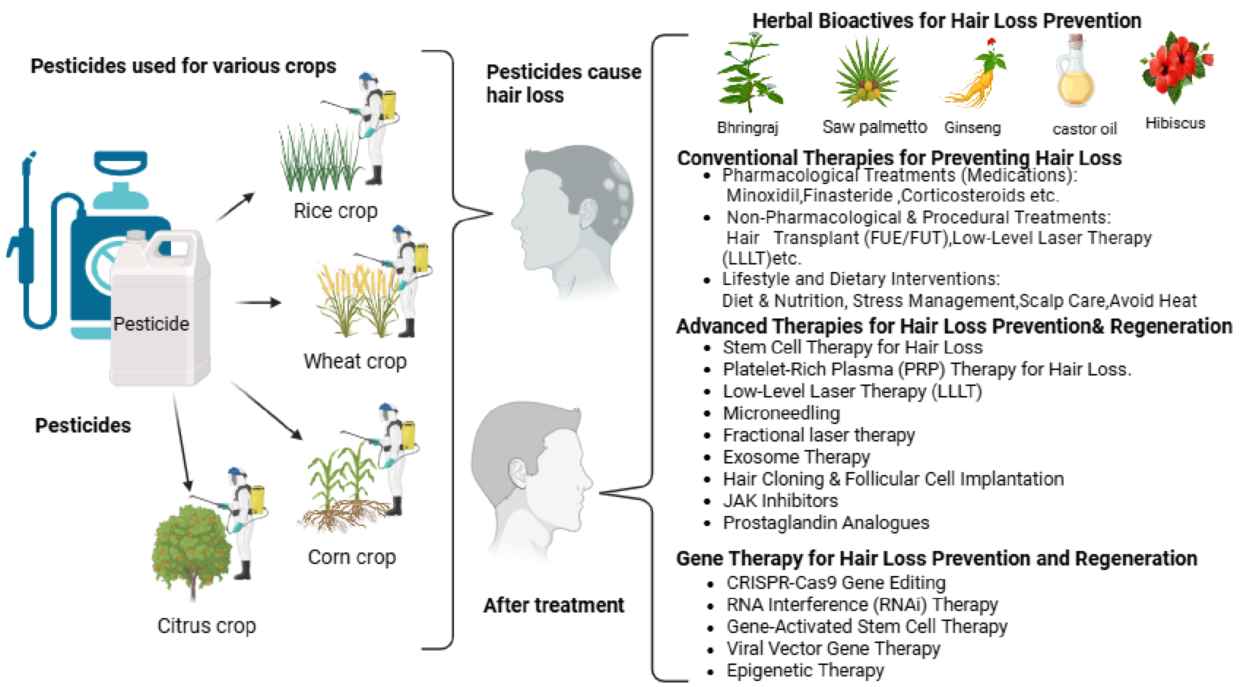
Abstract

This review highlights the impact of conventional, advanced, and gene therapy in hair follicular regeneration in pesticide-induced hair loss. Most states in India and abroad have agricultural land, where people of different age groups work and are exposed to various pesticides that affect their health and cause hair loss. Alopecia, thinning, and shedding arise from particular chemicals in pesticides that disrupt normal hair follicle function, leading to increasing concerns about hair loss due to pesticide exposure. Hormonal disruptions, oxidative damage, and inflammatory responses are a few of the mechanisms by which pesticides harm the scalp and hair roots. In this review, the authors have tried to explore the underlying mechanism of how the pesticides affect hair growth cycles and follicular health by analysing their toxicological impact, shedding light on the mechanisms that cause hair loss as well as the therapeutic effectiveness of various therapies including herbals like ginseng, green tea, hibiscus, and castor oil etc. those are able to counteract the negative impacts of pesticides with their molecular mechanism of action that will be helpful and will pave the way for further research in the field of hair growth and regeneration.

Keywords: pesticides, follicular damage, herbal bioactive, hair regeneration, advanced therapy, gene therapy

Graphical abstract



Highlights

- The widespread application of pesticides has raised concerns relating to their long-term impact on human health.
- Numerous countries are now implementing stricter regulations, promoting organic farming techniques, and delving deeper into the long-term effects of pesticide exposure on human health.
- Hair loss is a growing concern worldwide, affecting individuals of all genders and age groups.
- The presence of heavy metals and other deleterious substances in specific pesticides poses a significant threat to the integrity of hair follicle cells, resulting in premature hair thinning and subsequent loss.
- This review highlights the impact of conventional, advanced, and gene therapy in hair follicular regeneration in pesticide-induced hair loss.

List of abbreviations

AAD-American Academy of Dermatology	IPSCs -Induced pluripotent stem cells
AAVs -Adeno-associated viruses	JAK inhibitors - Janus kinase inhibitors
AChE-Acetylcholinesterase	JNK -Jun N-terminal kinase
ADSCs -Adipose-derived stem cells	LLLT -Low-Level Laser Therapy
ASK1- Apoptosis Signal-regulating Kinase	IGF-1- Insulin-like Growth Factor 1
ATP-Adenosine triphosphate	IL-1β -Interleukin-1 beta
Casp3 -Caspase 3	IL-6- Interleukin-6.
Casp-9- Caspase-9	IPSCs -Induced pluripotent stem cells
CO_2 - Carbon dioxide	IPSCs -Induced pluripotent stem cells
CRISPR-Cas9-clustered regularly interspaced short palindromic repeats - Caspase-9	JAK inhibitors - Janus kinase inhibitors
DHT -Dihydrotestosterone	JNK -Jun N-terminal kinase
DHT-Dihydrotestosterone	LLLT -Low-Level Laser Therapy
DNA- Deoxyribonucleic acid	miRNA -microRNA
DPCs -Dermal papilla cells	MSCs -Employs mesenchymal stem cells
EDCs-Endocrine-disrupting chemicals	MSCs -Mesenchymal stem cells
Er:YAG laser- Erbium-doped Yttrium Aluminum Garnet laser	NOXs -NADPH oxidases
FAO -Food and Agriculture Organization	O2 •−-Superoxide
FDA-Food and Drug Administration	PDGF -Platelet-derived growth factor
FGF -Fibroblast growth factor	PRP -Platelet-rich plasma therapy
FUE -Follicular Unit Extraction	RNAi -RNA interference therapy
FUT -Follicular Unit Transplantation	RNAi -RNA interference therapy
IGF-1- Insulin-like Growth Factor 1	RNA-Ribonucleic acid
IL-1β -Interleukin-1 beta	ROS -Reactive oxygen species
IL-6- Interleukin-6.	siRNA -small interfering RNA
IPSCs -Induced pluripotent stem cells	TGF-β -Transforming Growth Factor-beta
	TNF-α, -Tumor Necrosis Factor-alpha
	VEGF -Vascular endothelial growth factor

1. Introduction

Pesticides are extensively utilized in agriculture, public health, and household settings to control pests, boost crop production, and curb the transmission of diseases by vectors. According to the Food and Agriculture Organization (FAO), approximately 4.2 million metric tons of pesticides were used globally in 2020, with Brazil, the United States, and China being the largest users.[1] The widespread application of pesticides has sparked concerns regarding their long-term impact on both the environment and human health. Humans can be exposed to pesticides through direct skin contact, inhaling airborne pesticide particles, and consuming contaminated food and beverages.[2] Short-term exposure may lead to symptoms such as headaches, skin irritation, nausea, dizziness, and respiratory issues. The potential long-term health effects are even more alarming, as they have been linked to immune system suppression, neurological disorders, endocrine disruption, reproductive problems, and a heightened risk of cancer.[3] Some pesticides, like glyphosate and neonicotinoids, disrupt hormonal balance, while others, such as organophosphates, affect the nervous system. Numerous countries are now implementing stricter regulations, promoting organic farming techniques, and delving deeper into the long-term effects of pesticide exposure on human health. Hair loss, known as alopecia, is a growing issue worldwide, affecting individuals of all genders and ages.[4] By the age of 50, approximately 50% of men and 25% of women globally experience significant hair loss, and the American Academy of Dermatology (AAD) reports that 80 million Americans are affected by hereditary hair loss. Environmental pollutants, such as pesticides, are increasingly recognized as potential contributors. Studies indicate that pesticide exposure can lead to hair loss through mechanisms like oxidative stress, inflammation, endocrine disruption, direct damage to hair follicles, and depletion of essential nutrients.[5]The presence of heavy metals and other deleterious substances in specific pesticides poses a significant threat to the integrity of hair follicle cells, resulting in premature hair thinning and subsequent loss. Endocrine-disrupting chemicals (EDCs)found within pesticides, including organochlorines and organophosphates, interfere with hormonal regulation, compromise hair follicle strength, and contribute to scalp conditions such as dermatitis, which further aggravates hair loss. It is imperative to mitigate pesticide exposure through the implementation of protective strategies, including the utilization of protective garments, the avoidance of direct pesticide contact, the selection of organic food options, and the employment of natural hair growth treatments such as castor oil and hibiscus flower extract. Nevertheless, further empirical investigations are requisite to ascertain a definitive causal relationship between pesticide exposure and alopecia.[6] Hair concentration levels have been demonstrated to serve as a dependable biomarker of pesticide exposure across numerous bio-monitoring studies. It is plausible that pesticides have significantly accumulated within the hair matrix, as indicated by the ability to detect pesticide residues within hair shafts. Nonetheless, there exists a paucity of knowledge regarding the impact of pesticides on follicular health.[7] In a systematic review, boric acid, categorized as an insecticide, was associated with the loss of eyelashes, alopecia totalis, and anagen effluvium. These particulates may permeate the hair through transcutaneous absorption, inhalation, or ingestion, thereby influencing hair physiology via diverse mechanisms.[8]

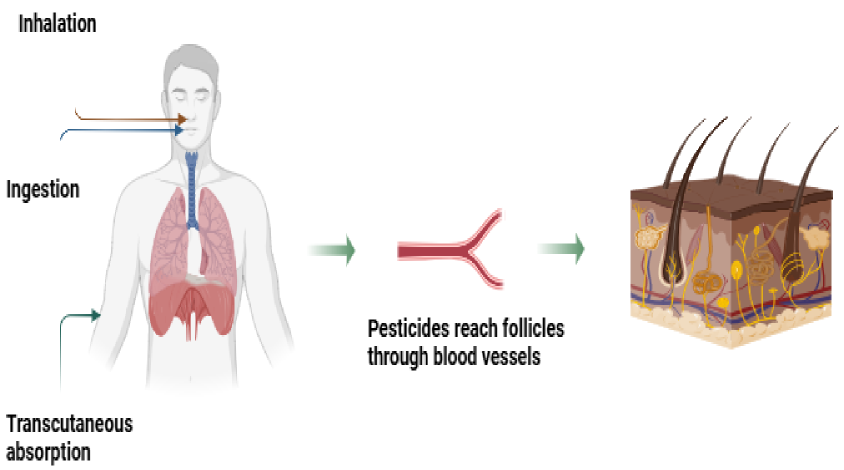


Figure 1: Major modes of Pesticides exposure. Pesticides can enter circulation via ingestion, inhalation, or transcutaneous absorption

2. Overview of Pesticides and Their Chemical Composition

Pesticides are substances, either chemical or biological, employed to hinder, eliminate, deter, or lessen pests that pose a risk to crops, livestock, human health, or property. Pests may consist of insects, weeds, fungi, rodents, nematodes, and microbes. Pesticides are essential in contemporary farming as they boost crop production, minimize losses after harvest, and manage diseases transmitted by vectors.[9]

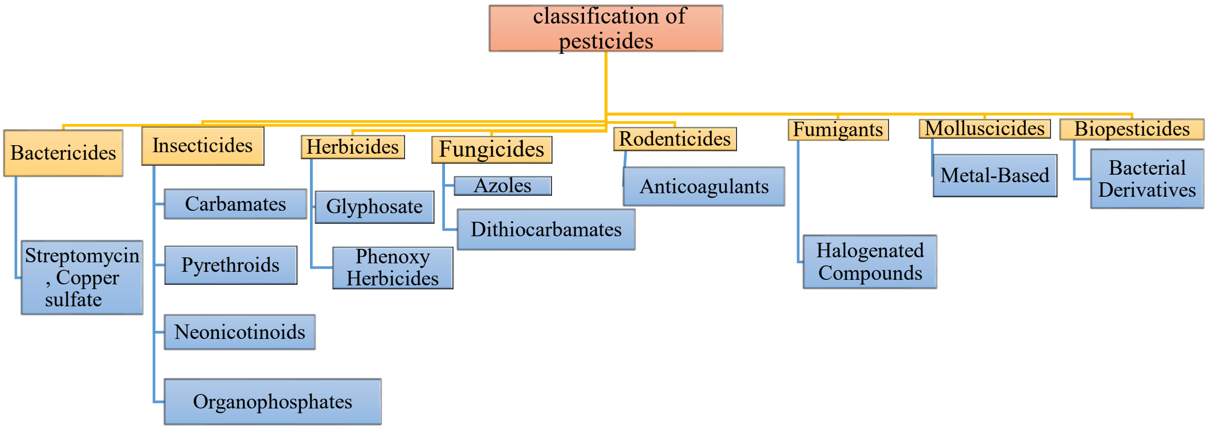


Figure 2: Diagrammatic representation of the classification of pesticides

2.1. Chemical Composition of Pesticides

The chemical composition of pesticides pertains to the particular chemical elements or combinations utilized to achieve the intended harmful effects on targeted pests. Pesticides consist of a mix of active ingredients that target the pest and inert ingredients that function as carriers, solvents, or stabilizers to improve the product's efficacy, safety, or application characteristics.[10] The active components in pesticides differ based on their chemical classification. One of the initial and most enduring varieties are the organochlorines, like DDT and lindane, made up of carbon, hydrogen, and chlorine atoms. These substances are recognized for their lasting presence in the environment and their capacity to accumulate in living organisms. Organophosphates, such as malathion and parathion, are organic substances that contain phosphorus, and they function by blocking acetylcholinesterase, an enzyme crucial for nerve activity. Carbamates such as carbaryl and aldicarb, impact the nervous system and are chemically akin to carbamic acid.[11]Pyrethroids, including permethrin and cypermethrin, are synthetic versions of pyrethrins (natural insecticides obtained from chrysanthemum blossoms) and consist of intricate esters that contain chrysanthemic acid. Another significant category, neonicotinoids like imidacloprid and thiamethoxam, is derived from a chemical structure akin to nicotine and generally includes nitro or cyano functional groups that engage with insect nervous systems.[12]Herbicides such as glyphosate consist of organophosphate compounds that interfere with particular plant enzymes, whereas triazine herbicides, like atrazine, contain nitrogen-rich ring structures that inhibit photosynthesis in vulnerable plants. Fungicides can include dithiocarbamates (such as mancozeb), azoles (like tebuconazole), or additional substances that interfere with fungal cell membranes or enzymatic processes. Along with synthetic chemicals, inorganic substances such as sulphur, copper sulphate, and boric acid are utilized in pest management. These do not possess carbon-based structures and function by physically or chemically harming the pest. Biopesticides, obtained from natural sources like plants (e.g., neem oil) or microorganisms (e.g., Bacillus thuringiensis).[13]

2.3. Mechanisms of Pesticide-Induced Hair Loss

2.3.1. Insecticides

Insecticides, especially organophosphates, carbamates, and pyrethroids, can lead to hair loss via several biological processes, such as neurotoxicity, oxidative stress, immune response activation, endocrine disruption, and blood vessel damage. Organophosphates and carbamates, including Malathion and Parathion, block acetylcholinesterase (AChE), an enzyme that decomposes acetylcholine, resulting in overstimulation of nerves.[14] This excessive stimulation may interrupt the hair growth cycle by triggering stress responses in hair follicles and decreasing blood circulation to the scalp, hindering nutrient supply and weakening hair strands. Furthermore, exposure to pesticides produces reactive oxygen species (ROS), leading to oxidative stress that harms keratinocytes and hair follicle stem cells.[15]The inflammation and cell apoptosis that occur result in the early transition of hair follicles into the catagen (regression) and telogen (shedding) stages, leading to issues like telogen effluvium and alopecia areata. Additionally, extended exposure to pesticides can stimulate the immune system, leading to an overproduction of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These inflammatory substances can harm hair follicle cells, leading to follicular injury and, in extreme cases, immune responses like alopecia areata. Persistent inflammation can lead to fibrosis (scarring) of the scalp, diminishing hair follicles' capacity to regenerate. Numerous insecticides, such as neonicotinoids and organochlorines, function as endocrine disruptors, altering hormone levels that control hair growth.[16]These substances can imitate or inhibit the actions of androgens, estrogens, and thyroid hormones, interrupting regular follicular function. Changed levels of dihydrotestosterone (DHT), a hormone associated with androgenetic alopecia, might speed up hair loss, while irregularities in thyroid hormone levels can hinder hair growth and lead to increased shedding. Moreover, vascular dysfunction caused by pesticides can result in compromised scalp circulation, denying hair follicles vital oxygen and nutrients.[17]Endothelial injury from oxidative stress and inflammation narrows blood vessels in the scalp, thereby weakening hair roots and encouraging excessive loss. The interplay of neurotoxicity, oxidative stress, immune system dysfunction, hormonal irregularity, and vascular issues leads to inflammation of the scalp, aging of follicles, and interruptions in hair growth cycles. Ultimately, these processes can result in hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia. Grasping these processes is crucial for creating preventive strategies and specific therapies to reduce pesticide-related hair loss.[18]

2.3.2. Herbicides

Herbicides, commonly utilized for managing weeds in farming and landscaping, have been linked to hair loss via several biological mechanisms, such as oxidative stress, hormonal disruption, immune system activation, and vascular dysfunction. Numerous herbicides, including glyphosate, atrazine, and paraquat, disrupt essential physiological functions in plants, yet their unexpected harmful impacts on human health, especially regarding hair follicle activity, have sparked worries. A primary way in which herbicides lead to hair loss is through oxidative stress.[19]Herbicides such as paraquat produce reactive oxygen species (ROS), causing cellular harm in keratinocytes and hair follicle stem cells. Elevated levels of ROS lead to lipid peroxidation, mitochondrial dysfunction, and DNA injury, which hasten the shift of hair follicles from the anagen (growth) stage to the catagen (regression) and telogen (shedding) stages. This oxidative harm undermines hair follicles, resulting in greater hair loss and issues like telogen effluvium.[20]Another important aspect is endocrine disruption, since numerous herbicides affect hormone regulation, essential for hair growth. Atrazine, a commonly utilized herbicide, has been demonstrated to interfere with androgen and estrogen pathways, resulting in hormonal disruptions that may adversely impact hair follicle cycling. Alterations in testosterone and dihydrotestosterone (DHT) levels might play a role in androgenetic alopecia (pattern baldness), whereas fluctuations in estrogen and thyroid hormones can result in diffuse hair loss.[21]Herbicides may activate the immune system and provoke inflammatory reactions, leading to miniaturization and loss of hair follicles. Glyphosate, for example, has been associated with heightened levels of pro-inflammatory cytokines like TNF-α and IL-6, which harm hair follicle cells and contribute to autoimmune hair loss disorders, such as alopecia areata. Persistent inflammation of the scalp can lead to fibrosis (scarring), hindering follicular regeneration and resulting in prolonged hair loss. Moreover, vascular damage from herbicides might limit blood circulation to the scalp, depriving hair follicles of vital oxygen and nutrients.[22]Certain herbicides have been linked to endothelial dysfunction, leading to narrowed blood vessels and decreased circulation, which weakens hair roots and increases their vulnerability to damage and loss. The interplay of oxidative stress, immune response, hormonal imbalance, and vascular injury elevates the risk of hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia in those exposed to herbicides. Grasping these mechanisms is essential for creating strategies to alleviate the harmful impacts of herbicides on hair health and recognizing preventive actions for those highly exposed.[23]

2.3.3. Fungicides

Fungicides, commonly utilized to inhibit fungal development in farming and different sectors, have been associated with hair loss via processes like oxidative stress, hormonal imbalance, immune response activation, and mitochondrial impairment. Typical fungicides like mancozeb, azoxystrobin, chlorothalonil, and benomyl can disrupt cellular functions crucial for sustaining hair follicle health, resulting in early hair loss and thinning.[24] A key way fungicides lead to hair loss is by inducing oxidative stress, as numerous fungicides produce reactive oxygen species (ROS) that result in DNA damage, lipid peroxidation, and dysfunction of mitochondria in hair follicle cells. This oxidative harm speeds up the shift of hair follicles from the anagen (growth) stage to the catagen (regression) and telogen (shedding) stages, weakening hair strands and causing significant hair loss. Furthermore, oxidative stress caused by fungicides can hinder keratinocyte activity, compromising the structure and integrity of the hair shaft.[25]Fungicides have been proven to interfere with endocrine function, impacting hormone levels that control hair growth. Certain fungicides, including mancozeb and benomyl, have endocrine-disrupting compounds that disrupt the thyroid, androgen, and estrogens pathways, causing imbalances that may adversely affect the hair growth cycle. Disruption of thyroid hormones, specifically, is linked to widespread hair thinning and delayed hair regrowth, while fluctuations in androgen and estrogen levels may lead to androgenetic alopecia or hormonal hair loss. In addition, fungicides may activate the immune system, resulting in an inflammatory reaction that harms hair follicle cells. Exposure to specific fungicides has been associated with elevated levels of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, which damage hair follicles and lead to disorders such as alopecia areata and chronic telogen effluvium.[26]Chronic inflammation in the scalp can lead to fibrosis (scarring), which further hinders the follicle's capacity to produce hair. Moreover, certain fungicides like chlorothalonil have been linked to mitochondrial toxicity, impacting the energy necessary for the proper functioning of hair follicle cells. Mitochondrial dysfunction results in decreased ATP generation, disrupting hair follicle metabolism and resulting in weakened hair growth and heightened hair loss. The synergistic impacts of oxidative stress, hormonal imbalance, immune response, and mitochondrial malfunction lead to hair follicle miniaturization, inflammation, and early hair loss. These processes elevate the likelihood of hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia in people exposed to fungicides. Grasping these pathways is crucial for formulating approaches to reduce the negative impacts of fungicides on hair wellness and recognizing protective actions for individuals vulnerable to extended exposure.[27]

2.3.4. Rodenticides

Rodenticides, frequently employed for managing rodent populations, have been associated with hair loss via mechanisms including oxidative stress, anticoagulant properties, endocrine disruption, immune system activation, and mitochondrial toxicity. Numerous rodenticides, such as warfarin, bromadiolone, brodifacoum, strychnine, and zinc phosphide, have harmful substances that disrupt essential physiological functions, resulting in hair follicle issues and increased hair loss.[28]A key factor in hair loss caused by rodenticides is oxidative stress, as these agents can produce reactive oxygen species (ROS) that harm keratinocytes and stem cells in hair follicles. The resultant follicular tension can compromise the hair structure, resulting in heightened loss and issues like telogen effluvium. A notable mechanism is the anticoagulant action of several rodenticides, especially warfarin, brodifacoum, and bromadiolone, which function by blocking vitamin K-dependent clotting factors.[29]This may lead to micro vascular harm and reduced blood flow to the scalp, denying hair follicles vital oxygen and nutrients. Inadequate blood circulation weakens hair follicles, increasing their vulnerability to shedding and leading to gradual diffuse hair thinning. Rodenticides may also function as endocrine disruptors, influencing hormone levels that control hair growth. Certain rodenticides have been found to affect androgen, estrogen, and thyroid hormone pathways, resulting in imbalances that disturb the regular hair follicle cycle.[30]Alterations in dihydrotestosterone (DHT) levels might play a role in androgenetic alopecia, whereas imbalances in thyroid function can result in diffuse hair thinning and delayed hair regrowth. Moreover, rodenticides may provoke immune system activation, resulting in chronic inflammation of the scalp. Extended exposure may lead to a rise in pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, which can harm hair follicle cells, resulting in autoimmune responses and hair loss disorders such as alopecia areata.[31]In extreme instances, extended inflammation can lead to fibrosis (scarring) of the scalp, which permanently harms hair follicles and diminishes their capacity to produce new hair. Certain rodenticides, like zinc phosphide, have also been associated with mitochondrial toxicity, interfering with ATP production and compromising the energy metabolism necessary for optimal hair follicle function. Mitochondrial issues can hinder cell renewal, resulting in fragile, weak hair and increased hair loss. The interplay of oxidative stress, vascular dysfunction, hormonal imbalance, immune system activation, and mitochondrial damage greatly elevates the likelihood of hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia in those who have been exposed to rodenticides.[32]

2.3.5. Fumigants

Fumigants, a category of pesticides aimed at eradicating pests in stored grains, soil, and structures, may lead to hair loss via processes like oxidative stress, neurotoxicity, disruption of endocrine function, activation of the immune system, and blood vessel damage. Typical fumigants such as methyl bromide, phosphine gas, sulfuryl fluoride, and chloropicrin emit harmful vapours that can disrupt vital biological functions supporting hair follicle operation when inhaled or absorbed through the skin.[33]A key process behind hair loss caused by fumigants is oxidative stress, as numerous fumigants produce reactive oxygen species (ROS), resulting in lipid peroxidation, mitochondrial impairment, and DNA damage in stem cells of hair follicles. Excessive oxidative stress compromises hair follicles, hastening their shift from the anagen (growth) phase to the catagen (regression) and telogen (shedding) phases, which can result in issues like telogen effluvium and general hair thinning. Fumigants have neurotoxic effects as well, especially those that disrupt acetylcholine signalling within the nervous system.[34]Neurotoxic fumigants like methyl bromide and phosphine gas interfere with nerve function, causing dysregulated stress responses that affect hair follicle cycling. Ongoing stress responses can trigger hair follicles to enter early shedding stages, leading to hair loss caused by stress. Furthermore, fumigants may function as endocrine disruptors, influencing levels of androgen, estrogen, and thyroid hormones, all of which are crucial for proper hair follicle activity. Alterations in dihydrotestosterone (DHT) concentrations may speed up androgenetic alopecia, whereas thyroid issues can cause widespread hair thinning, reduced hair regrowth, and fragile hair strands.[35]Another important route involves immune system activation, since extended exposure to fumigants may lead to chronic inflammation and autoimmune reactions that affect hair follicle cells. Certain fumigants, like chloropicrin, are recognized for inducing high levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), which play a role in alopecia areata and scalp inflammation. In severe instances, fibrosis (scarring) may develop, resulting in lasting follicular harm and hair loss. In addition, vascular damage from fumigants may hinder blood flow to the scalp, depriving hair follicles of oxygen and vital nutrients.[36]Fumigants like sulfuryl fluoride, which harm the endothelial layer of blood vessels, can reduce blood circulation to the scalp, weakening hair roots and increasing their susceptibility to falling out. The interplay of oxidative stress, neurotoxicity, endocrine disruption, immune activation, and vascular harm heightens the likelihood of experiencing hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia in those subjected to fumigants. Grasping these mechanisms is essential for creating protective strategies and mitigating the adverse impacts of fumigants on hair well-being.[37]

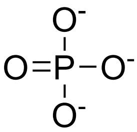
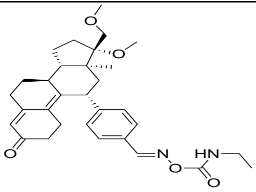
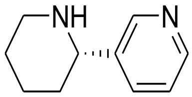
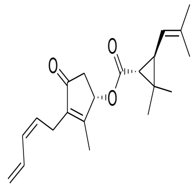
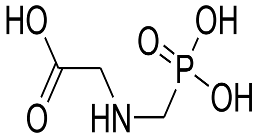
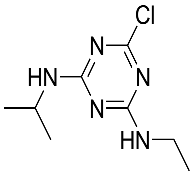
2.3.6. Biopesticides

Biopesticides, originating from natural organisms like bacteria, fungi, viruses, and plant-derived substances, are frequently viewed as safer options compared to synthetic pesticides. Nonetheless, some biopesticides may still lead to hair loss via mechanisms like oxidative stress, immune system activation, hormonal disruption, and microbiome imbalance. Frequently utilized biopesticides comprise Bacillus thuringiensis (Bt toxins), neem oil (azadirachtin), spinosad, and fungal-derived pesticides like Beauveria bassiana and Metarhizium anisopliae.[38]A key process behind biopesticide-related hair loss is oxidative stress, especially in products that generate reactive oxygen species (ROS) or include plant-based compounds that have pro-oxidant properties. High levels of ROS can result in lipid peroxidation, mitochondrial impairment, and DNA harm in hair follicle cells, diminishing their capacity to support hair growth. This oxidative harm may push hair follicles into the catagen (regression) and telogen (shedding) stages, resulting in diffuse hair thinning and telogen effluvium. Another important aspect is the activation of the immune system, since contact with microbial-derived biopesticides, like Bacillus thuringiensis (Bt) toxins or fungal pesticides, may initiate inflammatory reactions within the body.[39]Research indicates that proteins sourced from microbes might trigger an excessive immune response, leading to elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), which could harm hair follicle cells. This immune response might play a role in autoimmune hair loss disorders such as alopecia areata, where the body incorrectly attacks hair follicles, resulting in patchy hair loss. Certain biopesticides, especially neem oil (azadirachtin), possess endocrine-disrupting qualities and have been shown to affect androgen and estrogen pathways.[40] Hormonal imbalances may adversely impact the cycling of hair follicles, possibly speeding up androgenetic alopecia (pattern hair loss) or leading to hormone-related hair thinning. Furthermore, specific microbial-based biopesticides have been noted to influence thyroid function, essential for sustaining healthy hair growth. Biopesticides can also influence the microbiome equilibrium of the skin and scalp, since certain microbial and fungal-derived pesticides might change the natural makeup of helpful bacteria that aid scalp health. An imbalanced microbiome may cause scalp inflammation, seborrheic dermatitis, and greater hair loss. Although biopesticides are usually seen as less harmful than synthetic pesticides, their ability to trigger oxidative stress, immune reactions, hormonal changes, and microbiome disturbances implies they could still lead to hair loss in those with extended or significant exposure. Comprehending these processes is crucial for recognizing approaches to reduce hair damage linked to biopesticides and ensure healthy hair growth.[41]

2.3.7. Molluscicides

Molluscicides, chemicals utilized to manage slugs and snails in agriculture and gardens, may lead to hair loss via processes like oxidative stress, neurotoxicity, endocrine disruption, immune system activation, and mitochondrial dysfunction. Common molluscicides such as metaldehyde, methiocarb, iron phosphate, and nicodamid can disrupt essential biological functions needed for healthy hair growth. [42]A key mechanism behind hair loss caused by molluscicides is oxidative stress, as contact with substances such as metaldehyde and methiocarb results in excessive generation of reactive oxygen species (ROS). This oxidative harm can lead to lipid peroxidation, mitochondrial impairment, and DNA breakdown in the stem cells of hair follicles. Consequently, hair follicles might prematurely transition from the anagen (growth) stage to the catagen (regression) and telogen (shedding) stages, resulting in diffuse hair thinning and telogen effluvium.[43] Molluscicides, especially methiocarb, show neurotoxic effects by blocking acetylcholinesterase (AChE), an enzyme that controls neurotransmitter signalling. Excessive stimulation of the nervous system can interfere with the stress response and change hair follicle cycles, causing hair to enter an early shedding phase and leading to stress-related hair loss. Moreover, molluscicides like metaldehyde and methiocarb can function as endocrine disruptors, impacting levels of androgen, estrogen, and thyroid hormones. Hormonal discrepancies may adversely affect hair follicle cycles, heightening the chance of androgenetic alopecia (pattern baldness) or hormone-associated diffuse thinning. Thyroid function disturbances, especially hypothyroidism, can impede hair regrowth and lead to fragile, easily lost hair.[44]Another important aspect is the activation of the immune system, since contact with molluscicides can initiate chronic inflammation and autoimmune reactions that harm hair follicles. Some molluscicides are associated with heightened levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), which may harm hair follicle cells and lead to issues like alopecia areata. In extreme instances, persistent scalp inflammation can result in fibrosis (scarring), permanently impairing the hair follicle's capacity to regenerate. Ultimately, certain molluscicides like nicodamid have been linked to mitochondrial toxicity, hindering ATP production and affecting energy metabolism in hair follicle cells.[45]This decrease in cellular energy weakens the follicles, hindering hair growth and increasing the likelihood of breakage and shedding. The synergistic impacts of oxidative stress, neurotoxicity, endocrine disruption, immune system activation, and mitochondrial dysfunction notably heighten the likelihood of hair loss conditions like telogen effluvium, alopecia areata, and androgenetic alopecia in those exposed to molluscicides. Grasping these mechanisms is crucial for creating protective strategies and reducing the negative impacts of molluscicides on hair health.[46]

Table 1: Chemical structures of different pesticides.

Insecticides and Herbicides			
 Orthophosphate	 Carbamate J-956	 Neonicotine	 Pyrethrin I
 Glyphosate	 Atrazine	Paraquat	
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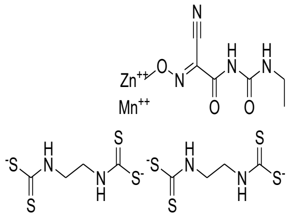
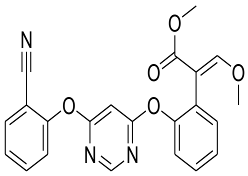
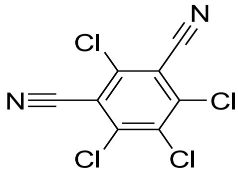
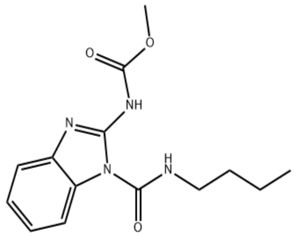
 Mancozeb	 Azoxystrobin	 Chlorothalonil	 Benomy
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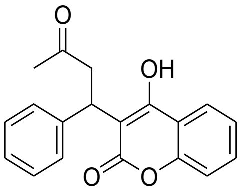
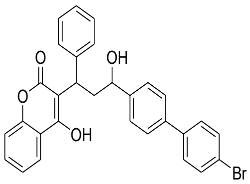
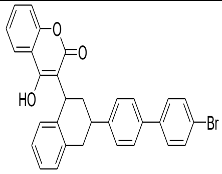
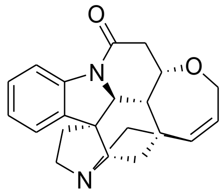
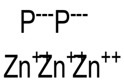
 Warfarin	 Bromadiolone	 Brodifacoum	 Strychnine
 Zinc phosphide (Zn_3P_2)			
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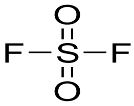
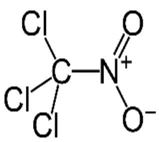
 Methyl bromide	 Sulfuryl fluoride	 Chloropicrin	

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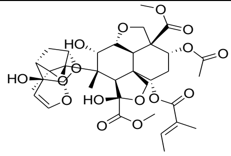
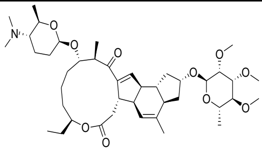
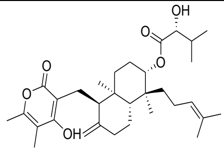
 Azadirachtin	 Spinosad factor D	 Metarhizin B	
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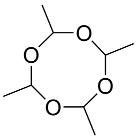
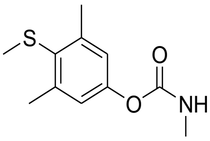
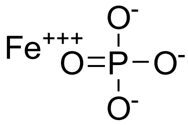
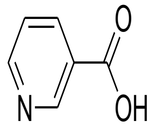
 Metaldehyde	 Methiocarb	 Iron phosphate	 Niconacid

Table 2: Studies on Pesticide Exposure and Hair Health

Study	Pesticide Type	Findings	Mechanism of Hair Loss	Ref.
Gupta et al. (2020)	Organophosphates (Malathion, Chlorpyrifos)	Elevated hair loss, inflammation of the scalp, and oxidative damage in farm workers	Oxidative strain, immune stimulation, neurotoxic effects	47
Park et al. (2019)	Herbicides (Glyphosate)	Impaired keratinocyte growth, hormonal discord, and oxidative injury in hair follicle cells	Hormonal interference, oxidative damage, follicular impairment	48
Rodriguez et al. (2021)	Fungicides (Mancozeb, Azoxystrobin)	Irritation of the scalp, fragility of hair, and damage to mitochondria in vineyard employees	Mitochondrial impairment, oxidative pressure, scalp irritation	49
France Epidemiological Study (2022)	Fumigants, Rodenticides	Higher occurrence of alopecia areata in farmworkers with long-term exposure	Hyperactivation of the immune system, inflammation	50
Case-Control Study in India (2018)	Pesticide-Contaminated Water	Increased instances of widespread hair thinning, fragile hair, and hormonal imbalances	Endocrine interference, oxidative strain, scalp discomfort	51

Table No. 3Case Studies and Epidemiological Evidence on Pesticide-Induced Hair Loss

Study/Case	Pesticide Type	Subjects	Findings	Mechanism of Hair Loss	Ref
Sharma et al. (2020) – Case Study	Organophosphates	36-year-old farmer	Intense hair loss, inflamed scalp, elevated oxidative stress indicators. Recovery following the cessation of pesticide application	Oxidative tension, inflammatory response	52

			and antioxidant treatment		
Lee et al. (2019)-Case Study	Fumigants (Methyl bromide)	Factory worker	Localized hair loss (alopecia areata), immune reaction characterized by increased TNF-α and IL-6	Activation of the immune system, inflammatory response	53
Brazil Epidemiological Study (2021)	Herbicides, Fungicides	500 agricultural workers	Increased occurrence of widespread hair thinning and scalp issues, associated with oxidative stress and hormonal imbalance.	Oxidative strain, hormonal interference	54
China Cohort Study (2020)	Organophosphates, Rodenticides	2,000 pesticide factory workers	Heightened occurrence of early baldness and hair weakness, intensifying with prolonged exposure time	Hormonal interference, follicle injury	55
India Community Study (2018)	Pesticide-Contaminated Water	Rural population	40% increased occurrence of excessive hair loss, hormonal disruptions, oxidative harm in blood tests	Oxidative strain, hormonal interference, scalp discomfort	56

3. Pathophysiology of Hair Loss Induced by Pesticides

Hair loss caused by pesticide exposure stems from an intricate interaction of oxidative stress, inflammation, hormonal disruption, and genetic changes that compromise hair follicle performance and scalp well-being. Pesticides, especially organophosphates, herbicides, fungicides, and fumigants, harm hair follicles by interfering with the anagen (growth) phase, leading to early follicular miniaturization and reduced hair strength. Scalp health is also affected since pesticide-induced inflammation causes irritation, dermatitis, and degradation of hair follicles, resulting in an environment that is not conducive to healthy hair growth.[57]A major factor contributing to pesticide-related hair loss is oxidative stress, which occurs when reactive oxygen species (ROS) build up and harm cellular components in the hair follicle. High levels of ROS cause lipid peroxidation, mitochondrial dysfunction, and DNA harm, resulting in cell death and hindered follicular regeneration. Moreover, oxidative stress stimulates the immune system, leading to a rise in pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, which play a role in chronic inflammation, follicular reduction, and hair loss. This inflammatory reaction is especially associated with disorders such as alopecia areata and telogen effluvium, wherein an overactive immune response affects the hair follicles, leading to extensive hair thinning or irregular patches of hair loss.[58] Pesticides act as endocrine disruptors, which disrupt the hormonal equilibrium of the body. Substances like glyphosate, DDT, and dithiocarbamates modify androgen, estrogen, and thyroid hormone levels, which are crucial for sustaining the hair growth cycle. Elevated androgen levels can hasten androgenetic alopecia (pattern hair loss), whereas thyroid dysfunctions result in diffuse hair thinning, weak hair, and slow regrowth. Moreover, variations in estrogen and progesterone impact hair thickness and follicle strength, which further lead to hair loss. Apart from hormonal and inflammatory pathways, exposure to pesticides has been associated with genetic and epigenetic changes that affect hair follicle activity. Research indicates that pesticides may modify the expression of genes in hair follicle stem cells, hindering hair regrowth and follicular stability. [59]Additionally, epigenetic alterations like DNA methylation and histone changes can deactivate vital growth-related genes, increasing the risk of hair loss disorders in individuals. These genetic changes, along with various toxic effects, might clarify why certain people suffer from intense or extended hair loss after being exposed to pesticides. To sum up, hair loss caused by pesticides happens through various interconnected processes, such as oxidative damage, activation of the immune system, hormonal irregularities, and genetic disturbances. These elements together disrupt hair follicle cycling, diminish scalp health, and hasten follicular deterioration, resulting in different types of hair loss. Grasping these fundamental mechanisms is essential for creating preventive measures, therapeutic approaches, and regulatory policies to reduce the adverse impacts of pesticides on hair and general health.[60]

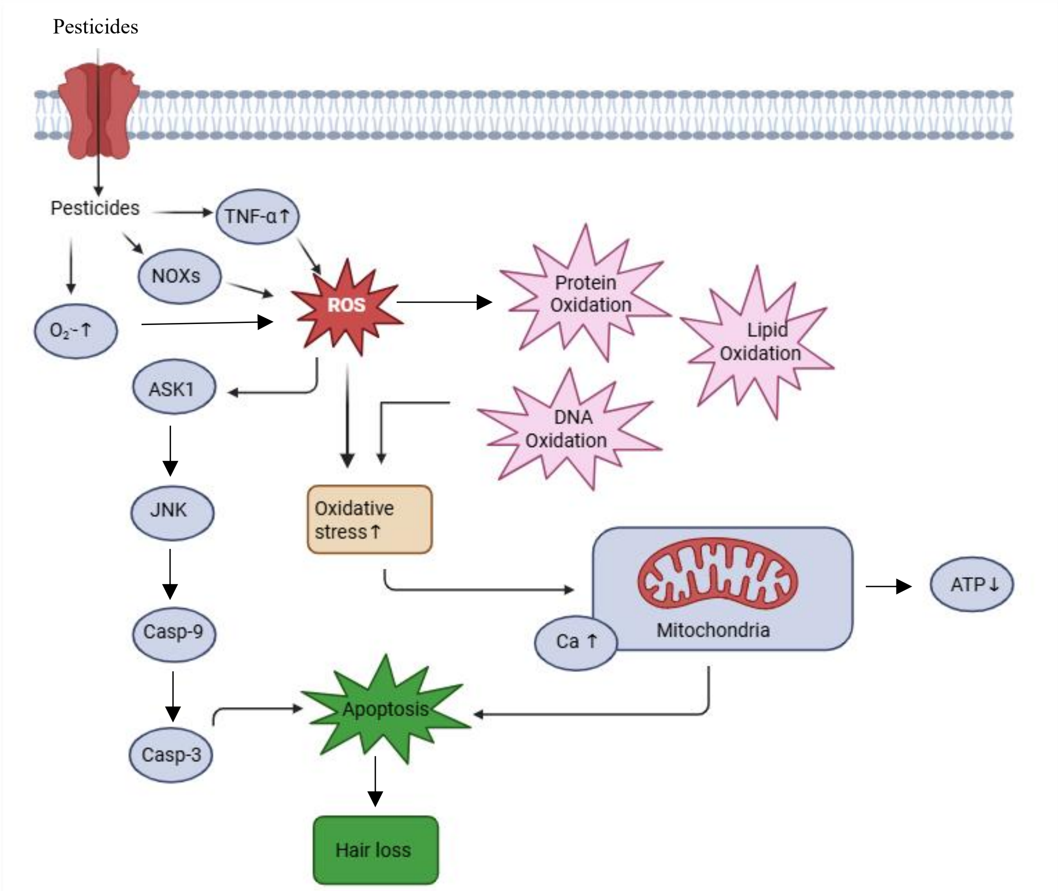


Figure 3: Schematic illustration of signalling pathways associated with pesticide-induced reactive oxygen species (ROS) and oxidative stress. Pesticides elevate levels of NADPH oxidases (NOXs), superoxide (O2−), and TNF-α, resulting in heightened ROS signalling within the cell. Elevated ROS can cause oxidation of lipids, proteins, and DNA, resulting in different toxic effects. Oxidative stress caused by pesticides results in mitochondrial impairment and cell death, which ultimately leads to damage and loss of hair follicles

4. Herbal bioactives in hair loss prevention and treatment

Hair loss is a condition affected by various factors, including genetic, hormonal, environmental, and lifestyle influences. In recent times, herbal bioactives have attracted considerable interest as potential therapeutic options for preventing and treating hair loss. These compounds from plants provide natural options with reduced side effects in comparison to traditional treatments such as minoxidil and finasteride.[61] Various bioactive compounds from plants have shown effectiveness in enhancing hair growth and decreasing hair loss. These bioactives frequently contain an abundance of phytochemicals, including flavonoids, polyphenols, saponins, and essential oils. Several well-researched herbal bioactives include Hibiscus (Hibiscus rosa-sinensis), recognized for its capacity to promote hair follicle growth and enhance hair thickness; Castor Oil (Ricinus communis), which contains Ricinoleic acid, known for its anti-inflammatory and antimicrobial properties that support scalp health and encourage hair growth; Saw Palmetto (Serenoa repens), which blocks 5-alpha reductase, lowering dihydrotestosterone (DHT) levels, a significant contributor to androgenetic alopecia; Ginseng (Panax ginseng), which boosts dermal papilla cell growth and enlarges hair follicle size; Aloe Vera (Aloe barbadensis miller), which has calming and anti-inflammatory effects that improve scalp health and nourish hair follicles; and Bhringraj (Eclipta alba), traditionally utilized in Ayurveda and known to extend the anagen (growth) phase of hair.[62]Herbal bioactives influence hair growth by employing a range of biological mechanisms. Certain compounds, like hibiscus and ginseng, can stimulate hair follicles by activating dermal papilla cells and promoting follicular proliferation. Some substances, such as saw palmetto and green tea polyphenols, reduce DHT production, a key factor in androgenetic alopecia. Moreover, numerous herbal substances, such as castor oil and aloe vera, demonstrate anti-inflammatory and antioxidant properties, alleviating oxidative stress and inflammation on the scalp, which enhances follicle lifespan. Specific ingredients like ginseng and rosemary oil enhance blood circulation, promoting improved nutrient and oxygen supply to hair follicles. In addition, various herbs influence growth factors like vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1), which are essential for hair restoration.[63] Merging various herbal bioactives can improve hair growth results because of their synergistic mechanisms of action. Synergistic effects occur when multiple bioactives collaborate to deliver a stronger therapeutic impact than when applied separately. For example, hibiscus and castor oil form a powerful pair, with hibiscus promoting follicle activity and castor oil offering nourishment and antimicrobial advantages. In a similar way, saw palmetto and ginseng provide a combined strategy for preventing hair loss, as saw palmetto blocks DHT while ginseng activates follicles. Aloe vera and bhringraj create a strong synergy, since aloe vera calms the scalp and alleviates inflammation, whereas bhringraj promotes the regeneration of hair follicles. Utilizing herbal bioactives for treating hair loss offers a hopeful natural method for addressing alopecia. Additional clinical research is required to determine the best formulations, dosages, and long-term effectiveness of these compounds.[64]

4.1. Herbal Bioactives for Hair Loss Prevention

In trichology and dermatology, herbal bioactives have gained increased attention for their potential to prevent or address hair loss caused by various factors, ssuch as pesticide exposure. Pesticides may harm hair follicles by inducing oxidative stress, inflammation, and potentially leading to follicular dormancy, which can result in hair thinning or loss. Various mechanisms are offered by the herbal bioactives outlined below to mitigate these effects and either promote hair growth or reduce hair loss.[65]

4.1.1. Bhringraj

Bhringraj, referred to scientifically as Eclipta alba (syn. Eclipta prostrata) is an herb used in medicine, well-known in Ayurveda, Siddha, and Traditional Chinese Medicine for its strong therapeutic benefits, especially regarding hair treatment and liver wellness. It belongs to the Asteraceae family. This herb has been utilized for centuries to encourage hair growth, reduce hair loss, and enhance scalp health. Due to its rich phytochemical composition, which consists of alkaloids, flavonoids, ecliptine, and wedelolactone. Bhringraj (Eclipta alba) promotes hair growth by activating follicles, balancing hormones, and providing nutrients to the scalp. By activating the Wnt/β-catenin signalling pathway, crucial for follicular growth and renewal, it extends the anagen (growth) phase of hair follicles.[66] In addition, it stimulates the function of dermal papilla cells (DPCs), essential for hair follicle development, leading to increased follicle density and hair regrowth. One of its primary mechanisms is the inhibition of 5-alpha reductase, an enzyme that converts testosterone into dihydrotestosterone (DHT), a hormone linked to shrinking hair follicles and androgenetic alopecia. Bhringraj supports the upkeep of healthy hair follicles and aids in preventing hair thinning by reducing DHT levels. [67]

4.1.2. Saw palmetto

Small palm trees such as saw palmetto (Serenoa repens) are native to the southeastern United States, which encompasses Florida, Georgia, and South Carolina. For centuries, it has been used in traditional medicine due to its dark purple berries and fan-like leaves. The health benefits of saw palmetto are linked to the high presence of bioactive compounds in its berries, including fatty acids, sterols, and flavonoids. Saw palmetto (Serenoa repens) blocks 5-alpha reductase (5-alpha reductase.), the enzyme responsible for converting testosterone into dihydrotestosterone (DHT), aiding in the treatment of hair loss, particularly androgenetic alopecia.[68]Excessive DHT leads to the miniaturization of hair follicles, reduces the duration of the anagen (growth) phase, and ultimately causes hair thinning and loss by binding to androgen receptors in the follicles. Fatty acids and phytosterols, two active compounds in Saw Palmetto, work by blocking 5-alpha reductase activity, reducing DHT production, and preventing DHT from binding to the receptors in hair follicles. Saw palmetto possesses antioxidant and anti-inflammatory properties that help enhance the overall health of hair follicles and reduce scalp inflammation. Moreover, it can enhance blood circulation to the scalp, guaranteeing an adequate delivery of nutrients essential for hair growth.[69]

4.1.3. Ginseng

Ginseng is a perennial herb belonging to the *Araliaceae* family, particularly within the genus Panax. In conventional medicine, it is among the most frequently used herbs, particularly in North American and Asian societies. The health benefits of ginseng (Panax species) have been recognized for a long time, and they might assist in preventing hair loss and promoting hair growth. Ginsenosides are the primary bioactive compounds in ginseng that give it its benefits for hair. Its role in hair regeneration is also backed by modern scientific research, primarily due to its bioactive elements.[70] Ginsenosides, the active components of the plant, are primarily responsible for the various ways ginseng encourages hair growth. These bioactive compounds stimulate dermal papilla cells, which play a crucial role in the development of hair follicles and the hair growth cycle. Ginsenosides enhance the density and thickness of hair by encouraging the growth of these cells and prolonging the anagen (growth) stage of the hair cycle.[71]Additionally, ginseng enhances blood circulation to the scalp, ensuring that hair follicles acquire increased oxygen and nutrients, thereby supporting hair growth and reducing hair loss. Another key mechanism is its ability to slow hair loss by inhibiting dihydrotestosterone (DHT), a hormone responsible for androgenetic alopecia. The potent anti-inflammatory and antioxidant properties of ginseng also protect hair follicles from ongoing inflammation and oxidative stress, both of which are key contributors to hair loss. By modifying these pathways, ginseng enhances current hair and promotes hair regrowth, thereby serving as an effective natural solution for hair loss.[72]

4.1.4. Castor oil

Castor oil is a naturally occurring vegetable oil derived from the seeds of the tropical plant Ricinus communis. Its rich content of essential fatty acids, especially Ricinoleic acid, has rendered it a favoured option for centuries in traditional medicine, skincare, and hair care. Often utilized to fortify hair strands, enhance scalp health, and promote hair growth, castor oil is recognized for its dense consistency and hydrating properties. The primary reason castor oil can treat hair loss is its elevated levels of Ricinoleic acid, known for its vasodilatory and anti-inflammatory properties.[73] Castor oil enhances blood circulation to hair follicles, supplying essential oxygen and nutrients for follicular regeneration and hair growth. It also possesses antibacterial properties that contribute to maintaining a healthy scalp and preventing infections that could lead to hair loss. Along with reinforcing the hair shaft and reducing breakage, its abundant vital fatty acids also enhance overall hair thickness. Moreover, the occlusive characteristics of castor oil assist in preserving moisture, preventing dryness and improving scalp hydration—both crucial elements for a healthy hair growth process.[74]

4.1.5. Hibiscus

Hibiscus includes over 200 species in the genus Hibiscus, belonging to the Malvaceae family of flowering plants. Globally, these plants are widely distributed in tropical and subtropical regions. The hibiscus plant's flower (Hibiscus rosa-sinensis) encourages hair follicles, blocks DHT, enhances scalp blood flow, and guards against free radical harm. Rich in flavonoids, amino acids, and vitamin C, hibiscus helps minimise premature hair loss by encouraging hair follicle growth and prolonging the anagen (growth) phase. Furthermore, it acts as a natural DHT (dihydrotestosterone) inhibitor by blocking 5-alpha reductase, an enzyme that converts testosterone into DHT and significantly contributes to androgenic alopecia.[75] The hibiscus contains anthocyanins and flavonoids that enhance blood circulation to the scalp, ensuring that hair follicles get sufficient oxygen and nutrients for denser hair strands. The strong antioxidant and anti-inflammatory properties protect hair follicles from oxidative stress and scalp irritation, helping to reduce excessive hair loss. Moreover, the natural mucilage in hibiscus deeply nourishes the scalp, preventing dandruff, dryness, and brittleness all of which can harm hair. Hibiscus flower extract effectively combats hair loss, encourages healthy hair growth, and enhances the overall condition of the scalp and hair by merging these benefits.[76]

5. Conventional therapies for preventing of hair loss

Traditional treatment for alopecia aims to decrease hair follicle shrinkage, encourage hair regrowth, and prevent further hair loss. Depending on the cause and severity of hair loss, traditional hair loss therapies offer various options. These therapies can be classified into three groups: drugs, interventions, and lifestyle modifications. These treatments can be classified into drugs, procedural therapies and lifestyle changes [77]

Table 4: Pharmacological Treatments (Medications)for preventing of hair loss

Treatment	Mechanism of Action	Indications	Form	Ref.
Minoxidil (Rogaine)	Extends the anagen phase (growth stage), boosts circulation to hair follicles, and activates inactive follicles to produce new hair	Androgenetic alopecia (baldness patterns in males and females)	Topical (2% & 5%): Outcomes appear in three to six months	78
Finasteride (Propecia)	Lowers DHT (dihydrotestosterone) levels by blocking the 5-alpha reductase enzyme. -Prevents follicle shrinkage, thus avoiding androgenic alopecia.	Androgenetic alopecia	Orally (1 mg daily): Outcomes typically appear within 6–12 months	79
Dutasteride (Avodart)	Inhibiting both Type I and Type II 5-alpha reductase enzymes, it proves to be more effective than finasteride	Significant male pattern hair loss	Oral (0.5 mg daily)	80
Corticosteroids	Reduces immune system activity and inflammation to prevent the death of hair follicles	Alopecia areata	Injections that are local, systemic, or within lesions	81
Ketoconazole (Nizoral shampoo)	Anti-inflammatory and antifungal; might reduce scalp DHT	Androgenetic alopecia, seborrheic dermatitis	Topical (shampoo at a concentration of 2%)	82
Spironolactone	Minimizes hair loss by inhibiting androgen receptors	The trend of hair loss among women	By mouth (25–100 mg daily)	83
Platelet-Rich Plasma (PRP) Therapy	Follicle stimulation through the injection of plasma rich in growth factors	Androgenetic alopecia, hair loss	Applied to the scalp	84
Biotin Supplements	Improves hair resilience and boosts keratin synthesis	Nutrient deficiencies leading to hair loss	Oral medications	85

Table 5: Non-Pharmacological & Procedural Treatments for Preventing Hair Loss

Treatment	Mechanism of Action	Indications	Procedure Type	Ref.
Hair Transplant (FUE/FUT)	Follicular Unit Transplantation (FUT) consists of taking a strip of scalp, harvesting follicles, and placing them in areas of the scalp that are hairless. Single follicles are extracted and transplanted through a method called Follicular Unit Extraction (FUE).	Androgenic alopecia	Surgical	86
Low-Level Laser Therapy (LLLT)	Activates ATP production by energizing the mitochondria within hair follicles	Androgenic alopecia	on-invasive (helmets, laser caps) Three to four times a week, for 15 to 30 minutes per session.	87
Microneedling (Dermaroller)	Creates small injuries to stimulate collagen production and improve the absorption of topical treatments	Androgenic alopecia, alopecia areata	Weekly, 0.5-1.5 mm needles are utilized. Invasive but minimal	88
Scalp Mesotherapy	Vitamin, DHT inhibitor, and peptide shots into the scalp	Hair thinning, alopecia	Injectable	89

Table 6: Lifestyle and Dietary Interventions for preventing of hair loss

Factors	Recommendation	Impact on Hair Health	Ref.
Diet and Nutrition	Increase your intake of omega-3 fatty acids, iron, zinc, biotin, and protein	Encourages the growth of follicles	90
Stress Management	Mindfulness practices, such as yoga, and reduced cortisol levels	Stops hair loss caused by stress	91
Scalp Care	Regularly cleaning and steering clear of harsh chemicals	Prevents inflammation and obstruction of the follicles	92
Avoid Heat and Chemicals	Reduce the utilization of chemical treatments, heat styling tools, and hair dyes	Prevents harm to the hair shaft	93

5.1. Combination treatments for optimal outcomes[94]

Combining various therapies for increased efficacy helps many patients:

- The combination of finasteride and minoxidil is the most effective remedy for male pattern hair loss.
- Microneedling combined with PRP boosts follicular stimulation.
- LLLT + Hair Transplant => Enhances the survival rate of transplanted hair.
- Finasteride + Ketoconazole Shampoo ⇒ Decreases inflammation and DHT on the scalp.

6. Advanced Therapies for Hair Loss Prevention & Regeneration

Technological and medical research advancements have produced novel treatments for hair loss prevention and regeneration, providing focused and efficient treatments for a range of hair loss conditions, including those brought on by genetics, oxidative stress, pesticide exposure, and hormonal imbalances. The goal of these innovative treatments is to restore the hair growth cycle, improve scalp health, and promote hair follicle regeneration by combining cell-based therapies, biomaterials, and innovative pharmacological techniques.[95]

6.1. Stem cell therapy for hair loss

Stem cell therapy has surfaced as an encouraging regenerative approach for hair loss by tapping into the body's innate capability to mend and rejuvenate harmed hair follicles. This treatment mainly employs mesenchymal stem cells (MSCs) and dermal papilla cells, which are vital for stimulating inactive follicles, prolonging the anagen (growth) phase, and inhibiting follicular miniaturization. Stem cells release growth factors, cytokines, and extracellular vesicles that boost follicular stem cell proliferation, enhance scalp microcirculation, and decrease inflammation—factors that are crucial for sustaining healthy hair growth. Moreover, adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (IPSCs) have been investigated for their capability to enhance hair density and thickness in those suffering from hair loss or baldness caused by conditions such as androgenetic alopecia, alopecia areata, and toxin-related hair loss.[96]A major benefit of stem cell therapy is its minimally invasive nature. It is generally given via injections or by applying stem cell-derived exosomes topically, which transport bioactive molecules straight to the scalp, promoting follicular regeneration without requiring surgery. Additionally, scientists are exploring hair follicle bioengineering and 3D bioprinting, in which lab-cultured follicles sourced from stem cells may be implanted into the scalp to permanently rejuvenate hair growth. Although clinical trials are ongoing to assess the long-term effectiveness and safety of stem cell hair restoration, initial research has indicated encouraging outcomes in enhancing hair density, minimizing hair loss, and repairing follicular damage.[97]

6.2. Platelet-rich plasma (PRP) therapy for hair loss

Platelet-rich plasma (PRP) therapy is a restorative treatment that harnesses the healing characteristics of platelets and growth factors to encourage hair follicle function and foster hair regrowth. This non-invasive technique entails drawing a small quantity of the patient's blood, which is subsequently centrifuged to isolate platelet-rich plasma from other blood elements. The PRP, abundant in bioactive proteins, cytokines, and growth factors like VEGF, PDGF, and TGF-β, is administered into the scalp to boost follicular regeneration, enhance blood flow, and extend the anagen (growth) phase of the hair cycle.[98] PRP therapy is especially advantageous for those experiencing androgenetic alopecia, alopecia areata, and hair loss caused by stress or environmental influences. It operates by decreasing inflammation, stopping follicular miniaturization, and stimulating inactive hair follicles, resulting in enhanced hair density, thickness, and better scalp health. The process is secure, only slightly invasive, and generally accepted, as it utilizes the patient's own blood, reducing the chances of allergic responses or infections.[99]Several PRP sessions, usually conducted every four to six weeks, are frequently suggested for the best outcomes, while maintenance therapies improve prolonged effectiveness. When used alongside other hair restoration methods, including microneedling, low-level laser therapy (LLLT), or topical solutions like minoxidil, PRP therapy demonstrates increased effectiveness. Although outcomes differ according to personal factors like genetics and the root cause of hair loss, PRP therapy continues to be a hopeful, natural, and non-invasive choice for individuals looking to restore their hair. As studies advance to improve treatment methods, PRP is gaining popularity as a remedy for hair restoration and scalp revitalization.[100]

6.3. Low-level laser therapy (LLLT)

Low-Level Laser Therapy (LLLT) is a non-invasive procedure that has become popular for encouraging hair growth in those facing hair thinning and loss. LLLT functions by providing red or near-infrared light (usually within the 650–900 nm wavelength range) to the scalp, activating hair follicles on a cellular basis. The treatment improves blood flow, boosts ATP (cellular energy) production, and decreases inflammation, fostering an ideal setting for hair regrowth. LLLT is thought to prolong the anagen (growth) stage of the hair cycle, while postponing the catagen (transitional) and telogen (resting) stages, effectively resulting in thicker and healthier hair.[101] Research indicates that LLLT can enhance hair density and thickness, especially in cases of androgenetic alopecia (male and female pattern hair loss). It is frequently utilized alongside other therapies like minoxidil, platelet-rich plasma (PRP), or microneedling to achieve improved outcomes. LLLT devices consist of laser caps, helmets, combs, and brushes that are FDA-approved for treating hair loss. Though outcomes can differ, numerous users claim to see noticeable enhancements following 3–6 months of consistent use.[102]Nonetheless, LLLT necessitates ongoing and extended use, and its results are typically more noticeable in the initial stages of hair loss compared to advanced baldness. In general, LLLT is a safe and painless therapy with few side effects, making it an appealing choice for individuals looking for a non-drug and non-invasive method for hair regrowth.[103]

6.4. Microneedling (Dermaroller, Dermapen)

Microneedling is a cutting-edge and minimally invasive method aimed at stimulating hair regrowth by inducing controlled micro-injuries to the scalp. This technique is carried out with tools like the Dermaroller, a manual roller equipped with microneedles, or the Dermapen, a pen-shaped automated instrument that provides greater precision and customizable needle depth. Microneedling boosts the skin's natural repair mechanism, promotes collagen synthesis, improves blood flow, and stimulates growth factors like platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which aid in hair follicle regeneration. Furthermore, it greatly enhances the absorption of topical hair loss solutions such as minoxidil, platelet-rich plasma (PRP), and growth serums, thus increasing their efficacy.[104] Research indicates that the combination of microneedling and minoxidil results in enhanced hair regrowth compared to using minoxidil by itself, with patients observing significant gains in hair density and thickness. The Dermapen is commonly favoured over the Dermaroller because of its accurate penetration and lesser discomfort, enhancing the effectiveness of professional treatments compared to home versions. Although microneedling is typically safe, it can result in temporary redness, irritation, or sensitivity, and proper sterilization is crucial to avoid infections. When used regularly, results usually become apparent within 8 to 12 weeks, establishing microneedling as a hopeful, affordable, and non-invasive option for those facing androgenetic alopecia and early hair thinning.[105]

6.5. Fractional laser therapy

Fractional laser therapy, especially with CO2 and Er: YAG lasers, is a sophisticated dermatological procedure that has demonstrated encouraging outcomes for preventing hair loss and revitalizing the scalp. These lasers function by generating regulated microthermal areas in the scalp, initiating a wound healing response that promotes collagen synthesis, enhances blood flow, and stimulates hair follicle stem cells. The CO_2 laser is an ablative type of laser that delves deeper into the skin, successfully encouraging tissue remodelling and follicular regeneration.[106]Conversely, the Er: YAG laser offers a more accurate and less invasive technique, making it well-suited for gentle resurfacing and promoting scalp well-being with minimal downtime. By creating micro-injuries, fractional laser treatment aids in decreasing scalp fibrosis, eliminating dead skin accumulation, and fostering a better setting for hair regrowth. Research indicates that when used alongside Platelet-Rich Plasma (PRP) therapy or topical solutions like minoxidil, fractional lasers greatly improve hair density and thickness. Patients usually have several sessions, with results becoming noticeable after 3 to 6 months. Although fractional laser therapy is typically safe, temporary redness, swelling, or sensitivity might arise after the procedure.[107]

6.6. Exosome therapy (Stem Cell-Derived Vesicles)

Exosome therapy is a cutting-edge regenerative approach for hair loss that utilizes vesicles derived from stem cells to encourage hair follicle healing and foster hair regrowth. Exosomes are small extracellular vesicles holding growth factors, proteins, RNA, and signalling molecules vital for cell communication, tissue repair, and anti-inflammatory mechanisms. In contrast to conventional stem cell therapy, exosome therapy provides the regenerative advantages of stem cells without the introduction of live cells, rendering it a safer and more effective option.[108]When administered to the scalp, exosomes activate inactive hair follicles, improve blood flow, decrease oxidative stress, and extend the anagen (growth) phase of the hair cycle, rendering them especially beneficial for androgenetic alopecia (pattern baldness) and various types of hair loss. Research indicates that exosome therapy exhibits a stronger and more enduring effect compared to Platelet-Rich Plasma (PRP) therapy, due to its elevated levels of growth factors essential for follicular regeneration. Clinical findings show that patients observe enhanced hair density and thickness after 3 to 6 months, and some see improvements following only a single session.[109] Nevertheless, since exosome therapy remains in the experimental phase, continued research is essential to develop standardized procedures and obtain FDA approval. Although it is expensive and not widely accessible, exosome therapy stands out as a minimally invasive and innovative method for hair restoration, providing hopeful outcomes for those looking for advanced treatments for hair loss.[110]

6.7. Hair cloning & follicular cell implantation

Hair cloning and follicular cell implantation are among the most cutting-edge and experimental methods for hair restoration, seeking to deliver a lasting remedy for hair loss. In contrast to conventional hair transplants that transfer hair follicles from one area of the scalp to another, hair cloning aims to replicate an individual's hair follicle cells in a lab and then reintegrate them into the scalp to produce new hair follicles. This method mainly emphasizes dermal papilla cells, which play a key role in hair follicle development and renewal.[111] The procedure starts by obtaining a limited quantity of hair follicle cells from the patient, usually taken from the rear of the scalp, where hair tends to be more resilient to thinning. The cells are subsequently cultured and increased in a laboratory, and later they are reintegrated into the thinning regions. After being introduced into the scalp, the newly implanted cells are anticipated to activate dormant follicles or create entirely new ones, leading to natural and lasting hair regrowth.[112] Although preclinical and initial human trials have yielded encouraging outcomes, hair cloning is still in the experimental stage, facing obstacles concerning cell viability, uniformity in hair regrowth, and obtaining regulatory approval. Firms and research organizations around the globe are working diligently on approaches to enhance and market this technology. If it succeeds, hair cloning could transform hair restoration by removing restrictions on donor areas and enabling limitless hair regrowth. At this time, the procedure is not broadly accessible, and additional studies are required before it can become a common solution for hair loss. [113]

6.8. JAK inhibitors (Tofacitinib, Ruxolitinib, Baricitinib)

JAK inhibitors, such as Tofacitinib, Ruxolitinib, and Baricitinib, belong to a category of medications initially created for the treatment of autoimmune conditions like rheumatoid arthritis and psoriasis. Nonetheless, they have demonstrated significant promise in addressing alopecia areata, an autoimmune type of hair loss, by focusing on the Janus kinase (JAK) pathway, which is essential in immune system signalling and inflammation.[114] In alopecia areata, the immune system erroneously targets hair follicles, resulting in uneven hair loss or total baldness. JAK inhibitors function by obstructing the inflammatory signals that initiate immune assaults on hair follicles, enabling them to heal and restart hair growth. Clinical research has shown that Tofacitinib (both oral and topical), Ruxolitinib, and Baricitinib can result in notable hair regrowth in individuals with moderate-to-severe alopecia areata, occasionally achieving complete scalp coverage within 3 to 6 months of therapy. Although they are effective, JAK inhibitors have not yet received FDA approval specifically for treating androgenetic alopecia (male and female pattern baldness), since this hair loss is caused by hormonal factors rather than immune responses. Moreover, JAK inhibitors may cause possible side effects such as a greater risk of infections, elevated liver enzymes, and lipid irregularities, necessitating close medical monitoring. Due to ongoing clinical studies and increasing research, JAK inhibitors stand out as a significant pharmaceutical advancement for autoimmune hair loss, providing optimism to those with alopecia areata and potentially other types of hair loss in the future. [115]

6.9. Prostaglandin analogues (Latanoprost, Bimatoprost)

Prostaglandin analogues, including Latanoprost and Bimatoprost, are mainly used for glaucoma treatment by lowering intraocular pressure. Nonetheless, they have attracted interest for their capacity to promote hair growth, especially in situations such as eyelash and eyebrow hypotrichosis (diminished or lost eyelashes and eyebrows).[116]These substances function by extending the anagen (growth) stage of the hair cycle, enhancing hair thickness, length, and density. Research has demonstrated that the topical use of Latanoprost and Bimatoprost can stimulate hair growth in the hair follicles of the scalp, especially in instances of androgenetic alopecia (male and female pattern hair loss). Bimatoprost, the key component in Latisse, is FDA-approved for promoting eyelash growth and has been studied for its possible effectiveness in stimulating scalp hair regrowth.[117]In contrast, Latanoprost has shown enhanced hair density in minor clinical trials, positioning it as a hopeful option for topical treatments for hair loss.

Although prostaglandin analogues seem to effectively promote hair growth, their application for restoring scalp hair is still being studied, and they have not yet received FDA approval for hair loss treatment. Possible side effects may consist of irritation of the scalp, darkening of the skin, and changes in pigmentation around the eyes if used in that area. Nonetheless, with additional research, these substances could evolve into a practical non-invasive option compared to conventional hair loss therapies such as minoxidil and finasteride. [118]

Table 7: The Greatest Combination Methods for the Most Hair Regeneration

Condition	Suggested Advanced Treatments	Ref
Early-Stage Hair Loss	LLLT + Microneedling + Minoxidil	119
Moderate Androgenic Alopecia	PRP + Microneedling + Finasteride	120
Severe Baldness	Stem Cell Therapy + Hair Transplant	121
Alopecia Areata (Autoimmune)	JAK Inhibitors + PRP	122
Post-Hair Transplant Maintenance	LLLT + PRP	123

7. Gene Therapy for Hair Loss Prevention and Regeneration

A new and innovative method of treating hair loss is gene therapy, which involves altering the genetic and molecular mechanisms responsible for of the growth, cycling, and regeneration of hair follicles. As a potential long-term or even permanent cure, gene therapy seeks to address the underlying genetic reasons of hair loss, in contrast to traditional therapies that concentrate on activating already-existing hair follicles. Gene therapy entails delivering, altering, or muting certain genes to either:

Encourage hair follicle development Stop the shrinkage of follicles, which is a symptom of androgenetic alopecia. Repair or regenerate damaged or absent hair follicles.[124]

7.1. CRISPR-Cas9 gene editing

CRISPR-Cas9 gene editing is a cutting-edge genetic engineering method that could transform hair loss therapy by directly altering genes linked to hair growth and follicle activity. In contrast to traditional remedies like minoxidil, finasteride, or hair transplant procedures that address hair loss symptoms, CRISPR-Cas9 seeks to provide a lasting solution by focusing on the underlying genetic factors responsible for hair thinning and baldness. A key use of this technology is in androgenetic alopecia (baldness in males and females), where hair follicles diminish because of their responsiveness to dihydrotestosterone (DHT).[125] By modifying androgen receptor (AR) genes, CRISPR-Cas9 might decrease follicular responsiveness to DHT, thereby stopping hair thinning and loss. Moreover, CRISPR can activate the Wnt/β-catenin signalling pathway, an essential process for promoting hair follicle regeneration and prolonging the anagen (growth) phase of the hair cycle. In addition to pattern baldness, CRISPR shows potential for addressing genetic hair conditions like hypotrichosis and alopecia universalis by rectifying faulty genes that cause hair follicle issues. [126] One more creative method includes modifying hair follicle stem cells to improve their capacity to produce new, healthy hair follicles, potentially aiding hair cloning and regenerative therapies. Although this technology is currently in the experimental phase, initial research and studies involving animals indicate encouraging outcomes. Nevertheless, issues like accurate gene delivery, possible off-target effects, and long-term safety risks need to be resolved before CRISPR-based hair loss therapies can be a standard clinical option. If it succeeds, CRISPR-Cas9 may provide a lasting and highly individualized hair restoration solution, removing the necessity for ongoing treatments or surgical interventions.[127]

7.2. RNA interference (RNAi) therapy

RNA interference (RNAi) therapy is a cutting-edge gene-silencing method that could transform hair loss treatment by focusing on and inhibiting certain genes linked to hair follicle miniaturization and hair loss. In contrast to conventional therapies that aim to promote hair growth, RNAi therapy operates by preventing the production of proteins linked to hair follicle shrinkage and impairment, providing a more targeted and lasting solution for hair restoration. A key use of RNAi therapy in addressing hair loss is silencing the androgen receptor gene, which is pivotal in androgenetic alopecia (pattern baldness).[128]Hair follicles in people with this condition are reactive to dihydrotestosterone (DHT), a hormone that attaches to androgen receptors and leads to follicle miniaturization. Through the use of small interfering RNA (siRNA) or microRNA (miRNA) to inhibit androgen receptor gene expression, RNAi therapy can significantly diminish the effects of DHT, halting additional hair loss and aiding hair regrowth.[129] Furthermore, RNAi therapy can also focus on other pathways associated with hair loss, including inflammatory cytokines (TNF-α, IL-6) and genes that play a role in oxidative stress, both of which lead to hair follicle damage. It may additionally be utilized to boost Wnt/β-catenin signalling, a critical pathway for the regeneration of hair follicles and the activation of stem cells. Although RNAi therapy shows significant potential, it remains in the experimental stage, facing obstacles concerning delivery methods, stability, and unintended.[130]

7.3. Gene-activated stem cell therapy

Gene-activated stem cell therapy represents a novel and advanced method for treating hair loss, merging the regenerative capabilities of stem cells with gene therapy to promote hair follicle renewal and enhance hair growth. In contrast to conventional treatments that aim to slow down hair loss or relocate existing follicles, this innovative method alters stem cells at the genetic level to boost their capacity to regenerate hair follicles, presenting a lasting and possibly permanent solution. This therapy mainly entails the genetic alteration of mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs) to enhance the production of crucial growth factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), and Wnt/β-catenin pathway stimulators. These elements activate inactive hair follicles, extend the anagen (growth) stage, and improve blood circulation to the scalp, encouraging thicker and healthier hair development. Furthermore, gene-activated stem cells can be modified to inhibit androgen receptor gene expression, decreasing follicular sensitivity to dihydrotestosterone (DHT), a primary factor in androgenetic alopecia (pattern baldness). Another promising use is employing CRISPR-Cas9 gene editing to fix genetic flaws in hair follicle stem cells, enabling the treatment of genetic hair conditions such as hypotrichosis or alopecia universal.[131]

7.4. Viral vector gene therapy

Viral vector gene therapy represents a hopeful next-generation method for treating hair loss, employing genetically modified viruses to directly transfer therapeutic genes into hair follicle cells. In contrast to conventional therapies such as minoxidil, finasteride, or hair transplant procedures, this method seeks to offer a lasting or potentially permanent remedy by altering the genetic pathways responsible for hair growth and follicle regeneration. This treatment commonly employs adeno-associated viruses (AAVs), lentiviruses, or retroviruses as vectors to deliver genes that activate hair follicle stem cells, trigger growth pathways, and inhibit follicle miniaturization. [132] A primary focus is the Wnt/β-catenin signalling pathway, which is essential for hair follicle development and regeneration. Viral vector therapy can boost Wnt signalling by introducing genes that activate dormant follicles, extend the anagen (growth) phase, and encourage the development of new hair follicles. Additionally, a crucial application involves suppressing androgen receptor (AZ gene expression, lowering follicular responsiveness to dihydrotestosterone (DHT)—the main trigger of androgenetic alopecia (pattern baldness). [133] Moreover, viral vectors are capable of introducing genes that enhance the synthesis of growth factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and insulin-like growth factor-1 (IGF-1), which collectively enhance scalp circulation, hair density, and follicular well-being. Although viral vector gene therapy presents considerable promise, issues related to immune reactions, possible off-target effects, long-term safety, and regulatory approvals still need to be tackled. Preclinical research and initial clinical trials are in progress to enhance the technology and boost its effectiveness and safety. [134]

7.5. Epigenetic therapy (Gene activation/Silencing)

Epigenetic treatment for hair loss is a state-of-the-art method that focuses on the modulation of gene expression instead of altering DNA sequences directly. In contrast to conventional treatments that concentrate on stimulating hair follicles or inhibiting hormones such as dihydrotestosterone (DHT), epigenetic therapy seeks to activate helpful genes and silence those that are harmful, thereby reprogramming hair follicle functions for lasting hair restoration. A crucial mechanism of epigenetic therapy includes DNA methylation and histone modification, which determine if certain genes are activated or deactivated.[135] In androgenetic alopecia (pattern baldness), genes linked to hair follicle miniaturization and sensitivity to DHT become overly active, while those involved in hair growth and follicle regeneration are inhibited. Through the application of epigenetic modulators, researchers can revert these alterations, reawaken inactive follicles and encourage new hair growth. Another encouraging use involves small molecules or RNA-based treatments to boost the Wnt/β-catenin signalling pathway, essential for activating hair follicle stem cells. Simultaneously, epigenetic silencing may decrease the activity of inflammatory cytokines (e.g., TNF-α, IL-6), frequently linked to persistent follicular inflammation and hair loss. [136]

8. Drugs for hair growth and regeneration under clinical trial:

Starting in January 2025, several drugs aimed at promoting hair growth and regeneration are undergoing clinical research. The subsequent table offers a summary of several of these drugs, their mechanisms of action, and their current status:

Table 8: Clinical Trial Status of some important drugs for hair growth and regeneration.

Drug Name	Mechanism of Action	Clinical Trial Status	Ref.
Ruxolitinib	A Janus kinase (JAK) inhibitor reduces follicular inflammation by altering the immune response.	In initial-stage research, people with alopecia areata demonstrated a significant rise in hair growth.	137
Tofacitinib	JAK inhibitor: focuses on immune pathways associated with assaults on hair follicles.	Initial studies indicated potential in promoting hair regrowth in people with alopecia areata.	138
Breezula (Clascoterone)	Androgen receptor blocker: stops DHT from binding to hair follicle receptors.	performing Phase III trials for male androgenetic alopecia.	199
Setipiprant	Antagonist of the Prostaglandin D2 receptor: designed to counteract inhibition of hair growth.	Phase II trials for androgenetic alopecia have been finished; additional research is still pending	140
WAY-316606	Sclerostin blockers boost Wntsignaling pathways, subsequently promoting hair growth.	Preclinical studies have demonstrated potential; clinical trials are yet to commence.	141

9. Clinical studies on herbal treatments for pesticide-induced hair loss

Several clinical studies have investigated the efficacy of herbal remedies in promoting hair growth and addressing hair loss from various origins, yet there is limited direct clinical research specifically focused on herbal treatments for hair loss caused by pesticides. This study provides useful insights into potential treatments for hair loss caused by pesticide exposure.

Table 9: Clinical studies on herbal treatments for pesticide-induced hair loss

S.No	Study	Herbal Treatment	Participants	Duration	Findings	Ref.
1	Efficacy of DA-5512 on Pattern Hair Loss	blend of botanical extracts (DA-5512)	Individuals exp eriencing patte rned hair loss	16 weeks	The density and diameter of hair considerably rose compared to a placebo, suggesting that DA-5512 enhances hair growth and promotes hair health.	142
2	Aromatherapy in Alopecia Areata Treatment	Essential oils: thyme, rosemary, lavender, cedarwood	Patients with alopecia areata	7 months	In patients with alopecia areata, notable hair regrowth occurred in 44% of the treatment group, while only 15% of the control group experienced this, highlighting the safety and effectiveness of aromatherapy.	143
3	Herbal Extract Combination vs. Minoxidil	Biochanin A, acetyl tetrapeptide-3, ginseng extracts	Patients with androgenetic alopecia	24 weeks	Mixing herbal extracts proved to be equally effective in promoting hair growth as a 3% minoxidil solution.	144

10. Conclusion and future perspectives

Studies on hair loss caused by pesticides and the potential of herbal bioactives to prevent it have promising prospects, although a multidisciplinary approach will be essential. Given that the widespread usage of pesticides continues to present health risks, additional studies are necessary to identify the specific chemical substances that damage hair follicles and to understand the molecular processes underlying these impacts. Future research should primarily concentrate on the role of oxidative stress, hormonal imbalance, and inflammatory pathways in alopecia caused by pesticides. Moreover, the possibility of hair re-growth should be explored in developing herbal bioactive therapies, including polyphenols, flavonoids, and essential oils. The effectiveness and bioavailability of these natural compounds can be enhanced through advancements in drug delivery technologies, including transdermal methods and nanoparticles. Moreover, to guarantee the standardization and regulatory endorsement of herbal treatments, clinical trials are required to confirm their safety and efficacy. Integrating nutrigenomics with personalized medicine could enable customized therapies based on genetic vulnerability to hair loss triggered by pesticides. In general, promoting eco-friendly agricultural practices such as organic farming and biopesticides could reduce pesticide exposure. Decreasing hair loss caused by chemical exposure necessitates more stringent regulations and increased public awareness regarding the risks of pesticides and the benefits of herbal alternatives.

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