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A Precis of the alopecia (Hair loss) associated with therapies based on nanotechnology and its impact on quality of Life (QoL)

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Abstract
Human hair exhibits additional capabilities since it is associated with aesthetic, cultural, sexual, and attractiveness characteristics in addition to its protective role. Although not a critical organ, hair has a significant impact on appearance and is a sign of health, youth, and strength. Alopecia patients have hair loss on their heads as well as occasionally other parts of their bodies. The chronically inflammatory disorder harms the hair follicles. Although it can result in skin irritation and physical problems owing to the loss of eyelashes and eyebrows, it is neither painful nor life-threatening. The actual cause and subsequent course of the development of alopecia, an autoimmune disease brought on by a synthesis of inherited and environmental variables, are unknown. In India, over 150 million people under the age of 20 suffer from hair loss, which translates to 9 out of 10 Indians experiencing hereditary hair loss at some point in their life. Every day, between 100 and 150 hair strands fall out, which is entirely natural and of no consequence. A number of causes, including ageing, pollution, and extreme stress, can hasten hair loss and, in some circumstances, result in severe hair loss. Temporary hair loss can also be a side effect of menopause or pregnancy. In Indians, men were more likely than women to develop alopecia areata, and 88% of those under the age of 40 were affected. While men or boys with earlier onset of severe alopecia were more likely to have it, women or girls with childhood onset were more likely to have it. In this review paper, we discuss alopecia, its pathophysiology, nanotechnology-based drug delivery systems, and quality of life issues related to alopecia.

Keywords: Alopecia (Hair loss), cause, epidemiology, pathophysiology, nanotechnology, quality of life (QoL)

Introduction
People with alopecia lose some or all of their hair on their heads and, occasionally, on other parts of their bodies. The condition, which damages the hair follicles, is chronically inflammatory. It is neither unpleasant nor life-threatening, although it can cause skin irritation and physical issues due to the loss of eyelashes and eyebrows. Alopecia is an autoimmune illness that results from a confluence of hereditary and environmental factors, but the exact cause and subsequent course of its development are unknown [1]. The word "alopecia", which has been used by doctors since Hippocrates, comes from the Greek word for "fox", "alopex," and was given that name because of the fur loss associated with fox mange. The name "Areata" comes from the Latin word "area", which refers to an open area or patch [2]. Alopecia, or hair loss, is a reasonably common condition seen in general medicine. When a thorough evaluation is conducted, the problem's root is frequently promptly revealed, allowing for an explanation and the most suitable treatment. But hair loss can occasionally be a sign of a serious underlying illness, be present in conjunction with other conditions, or be a side effect of treatment [3]. In a region where it is expected to have hair, alopecia refers to the lack or loss of that hair. This illness can affect both sexes and all age groups, be localized or diffuse, temporary or permanent. Alopecia is a symptom or sign that can have a variety of etiologies. It is often divided into two types: The scarring (Cicatricial) kind and the non-scarring variety. Patients may exhibit severe distress, which lowers their quality of life.

To identify the underlying reason, a thorough history, physical examination, and focused evaluation are required. This information will aid in making the best management decisions [4]. However, some patients in today's modern society are so disturbed by hair loss that, given the choice, they could sell their intelligence for more hair. Given how important hair is to most people's sense of identity, society desperately encourages research into alopecia. Therefore, progress in our knowledge of the pathophysiology and prospective therapies for alopecia will be welcome [5]. Hair loss disorders should be recognized since they might indicate serious underlying diseases and can lead to significant quality of life impairment and obvious psychological morbidity. This psychological impact was emphasized in a review of quantitative and qualitative studies on alopecia, which came to the conclusion that hair loss can result in significant mental pain and may ultimately cause issues with one's personal, social, and professional life. For instance, 63% of women have difficulty with their careers and 40% of women had marital issues as a result of their hair loss [6]. Alopecia-related psychological issues have not always been thoroughly and systematically studied. Such research frequently takes a back seat to another goal of the study (such the outcomes of a treatment, for example). The research that is available supports the idea that having alopecia is mentally harmful, results in severe emotional pain, and creates issues in one's personal life, social life, and professional life. Hair and identity have a significant relationship, especially for women. Roughly 40% of women with alopecia claim to have experienced marital issues as a result, and roughly 63% say they experienced issues with their careers [7-9]. Alopecia areata incidence and the related DALYs increased internationally from 1990 to 2019 by 49.14% and 49.51%, respectively [10]. As there are several origins of the disorder, there are numerous varieties of alopecia. There are several common kinds of alopecia, including trichotillomania, androgenic alopecia, alopecia areata, chemotherapy-induced alopecia (CIA), anagen effluvium, and telogen effluvium. Scarring alopecia (Produced by inflammatory reactions to follicle damage) and the more prevalent non-scarring form of the condition can be divided into two types. These influences include hormones, medications, nutrition, and certain illnesses [11]. The development of nanotechnology-assisted techniques for hair formulation enhancement has received more attention recently in research focusing on formulations for either hair cosmetics or hair medical treatments. Examples include nano-based treatments for ailments including alopecia and lice infestations, as well as cosmetic applications (Such as enhancing hair luster, silkiness, and general health) [12]. There are several different types of nanomaterial-based preparations for hair care and treatment that have been described, including lipid-based preparations (using vesicular nano-systems like liposomes; lipid nanoparticles (NPs), as solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs); polymer-based preparations (using natural polymers, like chitosan, dextran, and cyclodextrins [12-13]. Alopecia patients need counselling, just like those with any other social or psychological disorder, to help them cope with their illnesses. As the affected individuals struggle to accept their condition, low self-esteem might even result in deadly suicide situations.63 Counselling is essential, especially for young adults and girls who believe that their disease may have an adverse effect on their sexuality and ability to find a partner [14-15].

Common types of alopecia

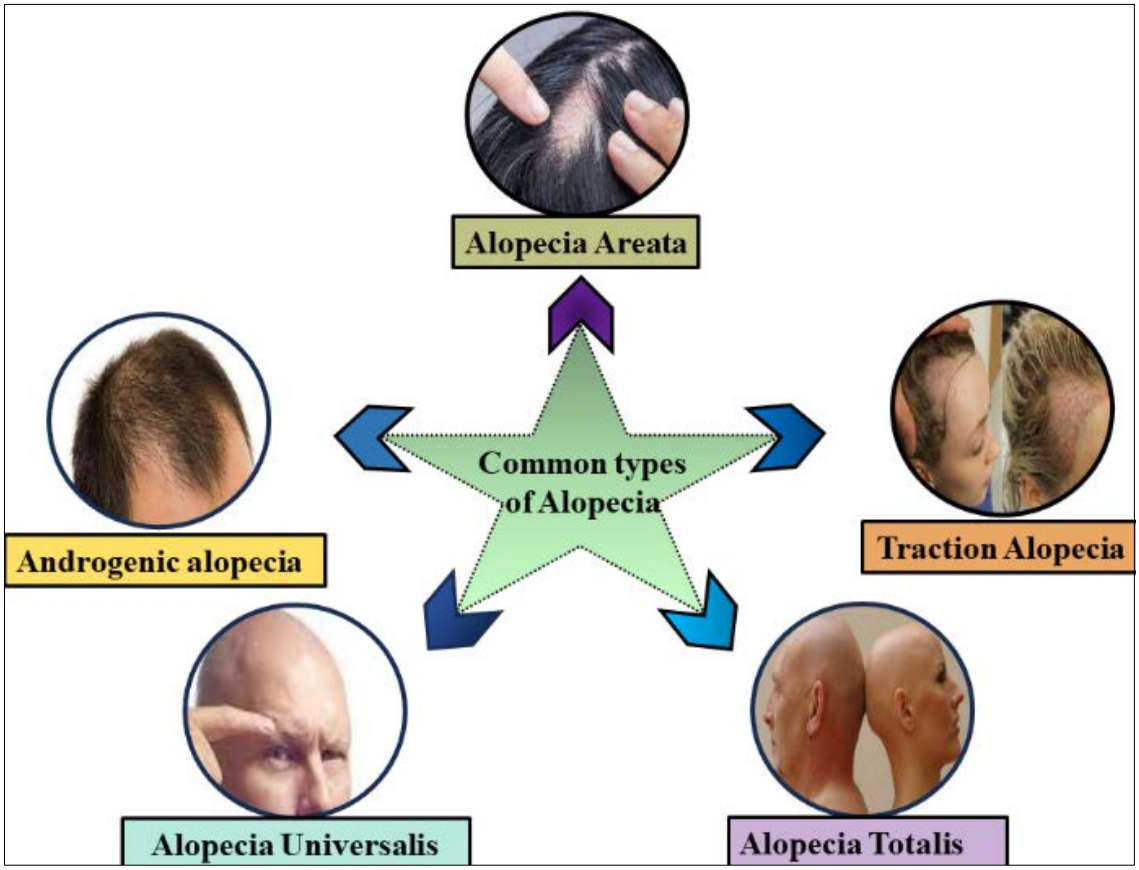

Fig 1: Alopecia common types.

Alopecia Areata
A condition where your immune system mistakenly attacks your hair follicles is known as an auto-immune illness [16].

Androgenic Alopecia
AKA Male Pattern Baldness, which occurs when our hair follicles are damaged! dlhydrotestosterone (DHT) sensitivity that runs in the family [17].

Alopecia Universalis
Causes your eyebrows and eyelashes to fall out along with all of the hair on your body [18].

Alopecia Totalis
Causes your scalp's entire hair to come out [19].

Traction Alopecia
Keeping your hair in tight hairstyles for too long might lead to permanent hair damage [20].

Reasons for alopecia
Alopecia areata is a non-scarring autoimmune disorder that causes hair loss on the scalp or in any other part of the body. The condition's cause is still unknown, however some theories suggest that a T lymphocyte-coordinated organ-explicit immune system infection may be at blame. According to other accounts, the illness may be caused by an inherited susceptibility and natural factors. The occurrence of sporadic bald patches surrounding the affected location, typically the scalp, is the condition's defining feature. If the problem is not treated, the scalp patches may get larger. Both males and females were equally affected, however newborns were most commonly impacted [21-24]. Alopecia totalis, where a patient's scalp is completely bald, is a worsening condition for alopecia areata. Alopecia universalis, a condition caused by alopecia areata, is characterized by the loss of hair throughout the entire body. When the right bodily signals are assumed, alopecia areata may not typically result in the death of hair follicle cells because hair frequently recovers following recovery. Numerous products that claimed to reverse alopecia areata have failed over time due to inefficiency and unwanted effects. Alopecia areata has been treated with a variety of drugs, with varying degrees of efficacy, including zinc, corticosteroids, dithranol, tretinoin, azelaic acid, systematic cortisone, minoxidil, and immunosuppressive medications. A good treatment for alopecia areata is still needed [16].

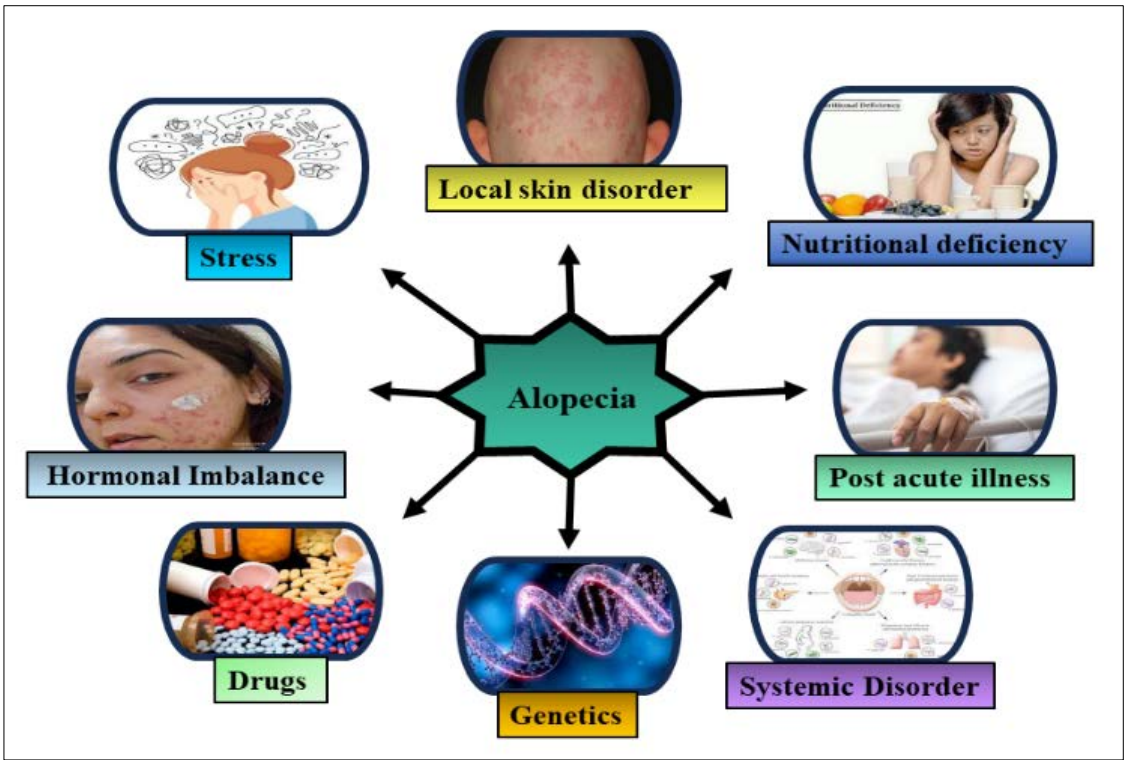

Fig 2: Several fundamental causes of alopecia [25].

Epidemiology of alopecia
Depending on the type of alopecia, a person's age, race, sex, cleanliness, hair-care habits, and state of health will determine their alopecia epidemiology. For example, Androgenetic alopecia, the most prevalent kind of alopecia with roughly 50,000 occurrences per 100,000 men and 15,000 cases per 100,000 women worldwide, is affected by age and sex. Men are more impacted than women, and the majority of affected females are post-menopausal women. Fair-skinned races are more frequently affected than dark-skinned ones, and the incidence ranges from 100 to 200 per 100,000 persons, despite the fact that sex has minimal influence on alopecia areata [26-27]. Over 150 million Indians in their early 20s experience hair loss in India, which equates to 9 out of 10 Indians experiencing genetic hair loss at least once in their lives.100–150 hair strands each day are lost, which is completely normal and not cause for concern. Age, pollution, and excessive stress are all factors that can speed up hair loss and, in some cases, cause significant hair loss. Pregnancy or menopause can also result in temporary hair loss [28]. Men were more likely to have alopecia areata than women in North Indians (M: F = 2:1), and 88% of those who had the condition were under 40. While severe alopecia was more common in boys or men with earlier

beginning, it was more common in girls or women with childhood onset [29].

Pathophysiology

According to a recent study's findings, T lymphocytes that recognise a follicular auto antigen induce alopecia areata. Mice with severe combined immunodeficiency (SCID) received transplants of scalp explants from alopecia areata patients. Then, autologous T cells that had been extracted from the affected scalp were infused into these grafts. The researchers discovered that the T lymphocytes that had been cultured with hair follicle homogenate and antigen-presenting cells were capable of inducing the changes of alopecia areata, including hair loss and T cell infiltrates around hair follicles as well as expression of the HLA-DR and ICAM-l histocompatibility loci. Grafts injected with scalp-derived T cells that had not been grown with follicular homogenate did not exhibit comparable alterations [30]. Recent research has demonstrated the critical function of prostaglandins (PGs) in controlling the hair cycle. Prostaglandins are lipidic mediators produced by specific enzymes using the Arachidonic acid route. PGD2, PGE2, and PGF2a have demonstrated activities linked to controlling the hair cycle among the examined PGs. PGD2 has been shown in tests to hinder hair development, whilst PGE2 and PGF2a have been shown to stimulate hair growth. In male scalps affected by AGA, higher levels of PGD2 and lower levels of PGE2 have been seen. The PGD2 receptors GPR44 and PTGDR both express primarily in hair follicles, where the former may cause follicle miniaturization by impeding stem cell maturation and preventing the production of terminal hair from vellus hair [3-33]. Androgenetic alopecia is a multifaceted physiological phenomenon that significantly alters patients' entire look and has significant psychological and social repercussions, particularly in younger males. Even though it is widely acknowledged that a number of pathogenic pathways contribute to the beginning of AGA, there are now only two pharmaceutical treatments available. Depending on the degree of AGA, each patient's reaction to treatment, the cost and dangers, a topical solution and an oral medication with systemic exposure are both available for usage [34-35].

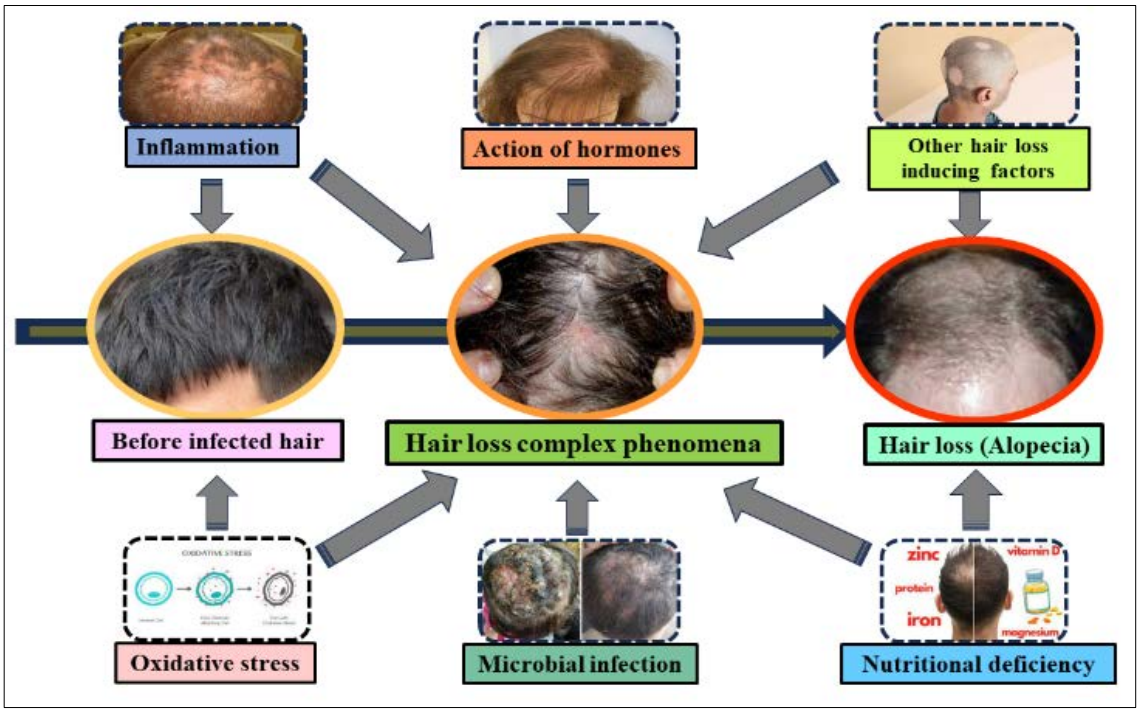

Fig 3: Alopecia's pathophysiology-related factors [36].

Drug delivery methods using nanotechnology to treat alopecia

Human skin affords a unique channel for the transport of diverse molecules while also impeding the penetration of certain formulations. These compounds penetrate through intracellular, intercellular, and trans appendageal routes, enabling the topical or transdermal administration of drugs [37]. Drug delivery pathways to the desired targeted place have already improved as a result of both active and passive penetration of skin. Acne, psoriasis, alopecia, and many other skin and scalp illnesses can be treated or managed with a variety of therapies, which is proving to be a potential platform for the administration of those active chemicals. Due to their increased effectiveness and efficiency, nano-formulations are quite popular for topical distribution. Due to the particles' nano-scale size, there are a number of benefits, including increased penetration potential, bioavailability, site-specific administration, low systemic toxicity, lower dose, etc. There is an urgent need for the deployment of a novel delivery system that might successfully enhance the therapeutic situation in alopecia because of a number of problems and a shortage of medications for the management of alopecia [38-39].

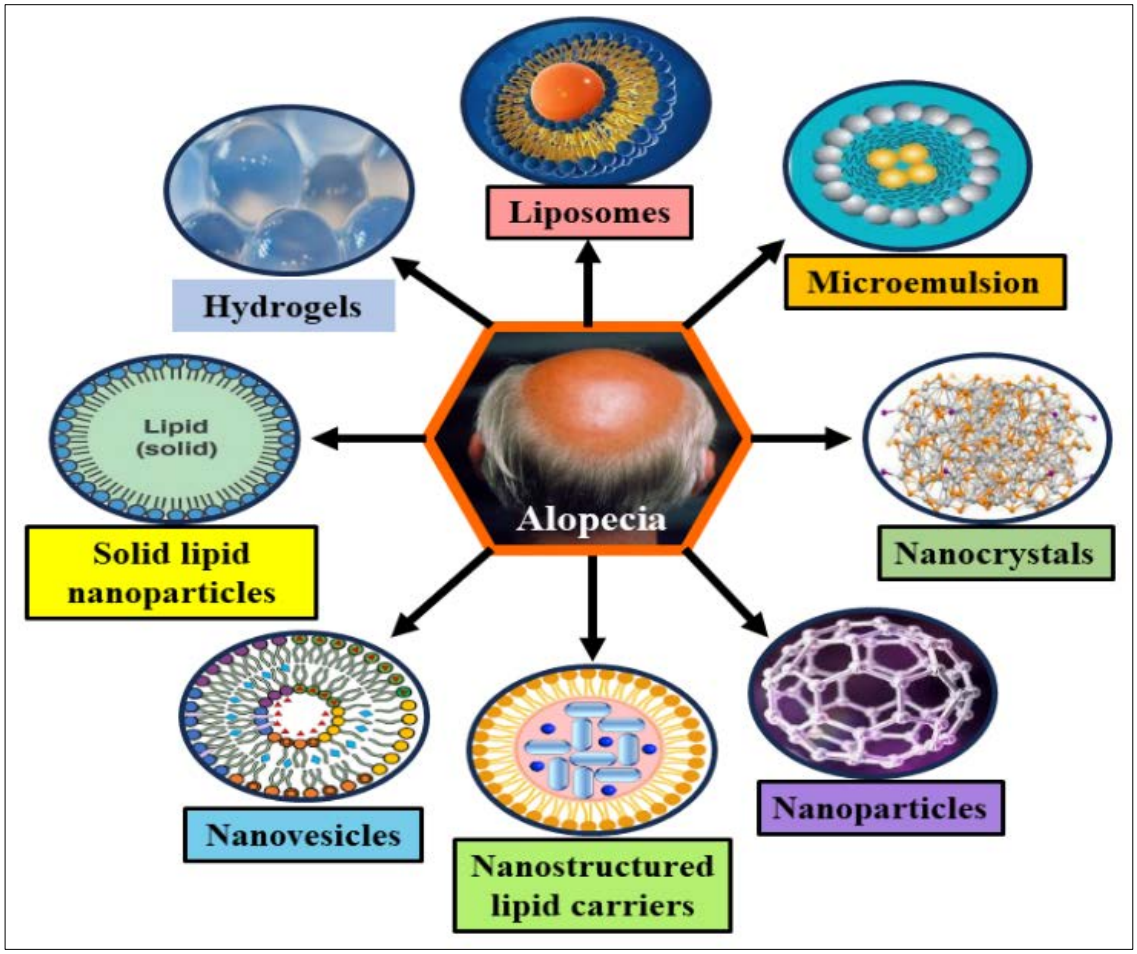

Fig 4: Alopecia can be treated using a variety of Nano-formulations [40].

Liposomes

Due to their amphiphilic nature, liposomes have the ability to transport both hydrophilic and hydrophobic drugs. The ability of the liposomes to better encapsulate drugs and have increased biocompatibility, biodegradability, and lower toxicity leads to a rise in their commercial use [41-42]. In a study on alopecia caused by anthracyclines, Balsari *et al.* showed the value of liposome-encapsulated monoclonal antibodies (MABs) for the efficient delivery of MABs. The study boosted liposome permeability into the stratum corneum layer and shown that it was highly effective in preventing alopecia caused by any anti-cancer medicines. Entrapping the calcein in the liposome allows for the delivery of calcein. The created nanostructure improved skin penetration and demonstrated itself to be a reliable platform for the safe delivery of numerous medicines and genes [43]. Li and Hoffman *et al.* conducted a comparison research between minoxidil loaded liposomes and niosomes and found that minoxidil loaded liposomes had superior augmentation in skin penetration for the hair follicles than its counterpart niosomes. In order to improve hair growth, Jain *et al.* created minoxidil-loaded liposomes that demonstrated efficient minoxidil delivery to the pilosebaceous unit. The regulated release of minoxidil from both liposomes promotes follicular development and increases dermal retention of the medication. Similar to this, a study by Tabbakhian *et al.* for a comparison of liposomes and niosomes encapsulating finasteride with finasteride hydroalcoholic solutions reported enhanced successful delivery of finasteride niosomal and liposomal formulation to pilosebaceous unit displaying effective retention of drug within the hair follicles [44-46].

Microemulsion

Microemulsions are systems made of oil, water, and surfactant that are transparent, thermodynamically stable, and optically isotropic. The microemulsion-based technology has the advantages of spontaneous preparations, promising stability, and great penetration into deeper skin layers. Scientists are becoming increasingly interested in microemulsions due to their potential for industrial use [47, 48]. Sakr and colleagues created a minoxidil and diclofenac sodium microemulsion and compared it, using tea tree oil and lauryl alcohol as the oily phase and solvents like labrasol, propylene glycol, and ethanol as the surfactant and cosurfactant in the minoxidil topical solution. This improved the delivery of the microemulsion to the hair follicular region while also overcoming the drawbacks of the traditional formulation. In order to treat psoriasis, Langasco *et al.* created a microemulsion of clobetasol propionate, which enhanced skin permeability and improved drug retention in the top layer of skin, ultimately assisting in the management of scarring alopecia [49-50]. Green and white tea ethanolic extracts were combined to create a microemulsion by Sinensis and colleagues, which produced a stable formulation. Green tea-based microemulsion, however, was more effective than white tea and promoted better follicular hair regrowth. In order to treat acne and regulate alopecia, Soleymani *et al.* developed a finasteride microemulsion to improve the drug's solubility, increase skin permeability, and improve retention in hair follicles [51, 52].

Nanocrystals

A universal formulation strategy for better drug delivery of insufficiently water-soluble medicinal compounds uses nanocrystals. Because of the higher kinetic solubility of the nanocrystals and the resulting larger concentration gradient, topical treatment of the nanocrystals is possible in addition to oral application. This promotes passive, cutaneous diffusion. Targeting pharmacological molecules into the hair follicle with nanocrystals is another intriguing application. The nanocrystals may create a depot once they have entered the hair follicle, from which the active is discharged into the hair follicle. Resulting in a very effective and long-lasting cutaneous medication administration. It has not yet been determined how well nanocrystals penetrate hair follicles or how the medium in which they are suspended affects this process [53]. Therefore, in this study, 300 nm-sized curcumin nanocrystals were created and added to gels with various characteristics. On the ex-vivo pig ear model, the effectiveness to reach the hair follicles as well as the passive, cutaneous penetration, was evaluated. The bottom region of the infundibulum was successfully penetrated by nanocrystals that were efficiently absorbed by the hair follicles. Because the barrier of the lower infundibulum is not fully established and more permeable in this area, the passive diffusion of pharmacological compounds is less hampered. This makes this area ideal for effective drug delivery [53]. The three kinds of carriers, which were either oleogels or hydrogels that varied in viscosity as well as in the kind and concentration of the gelling ingredient, had no effect on how well the nanocrystals penetrated the hair follicles. All gels exhibited shear-thinning flow behaviour, and it is hypothesised that during skin massage, all gels fluidized, resulting in viscosities that were comparable to those of the aqueous nanosuspension and equivalent penetration outcomes. Curcumin's passive, dermal penetration varied depending on the type of gel utilized, and the vehicle's superior skin-hydrating qualities were the primary factor in good passive dispersion. Hydrogels that contained a humectant had the best passive penetration. However, the humectant's inclusion diminished the ability of the nanocrystals to enter the hair follicle [53].

Nanoparticles

The use of controlled drug delivery nanoparticles to assist or improve drug delivery for the treatment of dermatological illnesses utilizing cosmetic formulations is becoming more and more popular. To increase their effectiveness and replace current dermatological formulations like ointments, lotions, and gels with them, researchers must first fully understand and optimize the drug release mechanisms and modulation from these diverse nanoparticle systems [54]. It is clear that the design of nanomedicine in cosmetics can produce a safe and effective treatment regimen. With an emphasis on local drug disposition within epidermal layers, the use of lipophilic and colloidal carrier systems has played a dual function in attaining a lower dosing regimen frequency and controlled release of drug payload [55]. Even though there are effective pharmaceutical and cosmetic treatments for hair loss, research on CRNMs for alopecia offers a substantial advantage. Research in this area points to nanosystems' superior capacity for locally and effectively delivering medication payload to skin layers and hair follicles, decreasing systemic side effects and boosting bioavailability [56].

Nanostructured lipid carrier (NLC)

The transport of drugs to skin that is wounded or inflamed can benefit greatly from the characteristics and properties of nanostructured lipid carriers (NLC). Because NLCs were created using non-toxic lipids, they are non-irritating in nature. In order to achieve the desired effect after the formation of a thin film on the skin's surface, the nano-sized particles entrapped in NLCs make sure they are close to the stratum corneum layer, which not only keeps the skin from drying out but also improves the formulation's permeation capability [57, 58]. NLCs of 2% minoxidil were successfully created by Wang *et al.*, who observed significant retention of minoxidil in hair follicles with no erythematous skin reactions. The formulation was discovered to be stable at 4 °C and room temperature for a longer period of time, proving the value of NLC as a minoxidil carrier system. A high drug loading potential and prolonged drug release from the NLCs loaded gel system were also achieved by modifying the solid lipid and liquid lipid contents in the formulation of the NLCs loaded gel of minoxidil [59, 60]. NLCs of the melatonin hormone were created by Hatem *et al.* using antioxidant oils, and they demonstrated fewer adverse effects, enhanced follicular retention, and were significantly more effective than traditional medications in the treatment of androgenetic alopecia. Integrado *et al.* investigated the anti-alopecia drug combination of finasteride and minoxidil incorporated in NLCs and demonstrated that it was a promising treatment for managing the condition due to increased drug loading capacity, controlled release pattern, enhanced aggregation of the drug in the hair follicles, and overall improved management of the hair loss [61, 62].

Nanovesicles

Nanovesicles are tiny vesicles that help skin penetration while delivering drugs to the needed place. They are made using lipids and cutting-edge activators. In a study on the synthesis and characterization of antioxidant melatonin-loaded vitamin C-based nanovesicles for the treatment of androgenetic alopecia, Hatem *et al. In vivo* research has shown that using nanovesicles and their antioxidant properties is advantageous for treating androgenetic alopecia and other dermatological conditions [63-65]. For the purpose of managing hair loss, Kumar and colleagues created oleic acid nanovesicles containing minoxidil to investigate its potential for medication transport to the follicular shaft. The study's findings showed that oleic acid can self-assemble to form nano-sized vesicles that can hold minoxidil, and they also showed that these vesicles have better drug entrapment efficiency, globular morphology, and the right vesicular size, making them a promising method for effective delivery with improved patient compliance [66]. To target the dermal papillae cells and ascertain the impact of extracellular vesicles on them, created mesenchymal stem cell extracellular vesicle was used. The study's findings showed that mesenchymal stem cell extracellular vesicles have the ability to stimulate dermal papillae cells, which increases survival, encourages growth factor activation, and also produces new hair growth [67].

Solid lipid nanoparticles

When compared to alternative delivery systems, solid lipid nanoparticles (SLNs) have lesser toxicity problems, probably as a result of not using organic solvents while they

were being developed. Additionally, they are the perfect medication delivery mechanism due to their biodegradability, continuous release, and ibility to safeguard the drug. The stratum corneum, or top layer of skin, is the main barrier to the entry of medicinal medicines applied topically and transdermally [68, 69]. In order to examine the effects of various particle sizes on the effectiveness of the nanoparticles and their penetration in the deeper dermal layer as well as their reduction in systemic assimilation, Zahra *et al.* produced an SLN formulation with a similar composition but distinct particle size. Rhodamine B, a fluorescent dye, and Precirol, a solid lipid, were both used in the hot melt homogenization method for the SLN production. According to the data, particles smaller than 100 nm are more effective for follicular delivery because they may reach deeper dermal regions and perform more effectively. The outcome indicates that they may have a lot of potential for treating alopecia [70]. The most appropriate route of delivery for lipid and colloid nano carriers is dermal. Both of these carriers have a quick time to market and provide good prospects for use in cosmetics. Benefits of using Nano formulations for cutaneous distribution include modulating the release profile, adhesion to the skin with an occlusive effect, and protection against degradation of chemically labile medicines. Patenting these nano-formulations is simple. "Codelivery of metal nanoparticles and SLN/SLM in dermal formulations" is how minoxidil SLNs were patented. The phrase "Dermal composition for minoxidil delivery" appears in another patent on minoxidil-loaded SLNs. Another patent for "Roxithromycin topical delivery to stop hair loss or for acne treatment" refers to SLNs [71].

Hydrogels and Emulgel

Hydrogels are cross-linked hydrophilic polymer matrices that hold a lot of water and shield the skin from drying out in three dimensions. Hydrogels evaporate quickly, unlike conventional formulations, and leave no trace on the skin. Due to the hydrogel formulation, the drug is more evenly distributed throughout the skin, resulting in a larger concentration of the drug at the intended spot. Topical alginate hydrogel containing minoxidil and hydroxypropyl--cyclodextrin inclusion complex was created and characterized by Lopedota *et al.* The outcomes showed successful delivery of the formulation to the hair follicles with increased hair retention as well as high penetration of the formulation through the skin without harming the epidermal region [72-74]. It is necessary to design novel hydrogel formulations without the inclusion of ethanol and propylene glycol due to the drying and itchy effects of these substances on hair. Methyl-β-cyclodextrin was used in the formulation of the minoxidil hydrogel to increase the drug's water solubility. This specially formulated hydrogel reduced and controlled hair loss while exhibiting no evidence of irritation on the hairs. To examine the impact of a hydrogel structure that resembled hair for transplantation, Jing *et al.* created hydrogel micro wells. This led to the creation of a new platform for the formation of new hair follicle structure [75, 76].

Metallic nanoparticles

Metal- or metal-oxide-based rigid nanoparticles, such as those found in iron oxide, titanium dioxide, and zinc oxide, are known as metallic nanoparticles. Drugs are either adsorbed on the surface of or encapsulated inside the core of metallic nanoparticles to facilitate targeted delivery. The transport of metallic nanoparticles to human skin and hair follicles has been the subject of numerous reports in the literature over the last few decades. Using transmission microscopy, Baroli and colleagues demonstrated that ferrous sulphate nanoparticles effectively penetrated the living epidermis and were retained in the furrows of human skin (used as a permeation barrier in *in vitro* investigations) [77]. Similar to this, Lekki and colleagues discovered that titanium dioxide nanoparticles penetrated deeper layers of human and porcine skin, but not sebaceous glands. The penetration of zinc oxide nanoparticles in *in vivo* tests carried out on human participants is reported by Zvyagin and colleagues. Daily applications of 0.3 g of metallic nano-dispersions to human participants revealed that zinc oxide was concentrated in the subcutaneous area and was discovered to reside in the skin's furrows and hair follicles [78, 79]. For the treatment of alopecia, iron oxide nanocarriers are loaded with finasteride or dutasteride. In this work, iron oxide nanoparticles were used as the maghemite core, and lauric acid was used to coat them before Finasteride or dutasteride was added. *In vitro* permeability experiments revealed that both medicines were extremely permeable when put in metallic cores [80].

Alternative methods of alopecia treatment

Surgical hair transplant

A hair transplant involves the surgical removal of scalp tissue that contains hair from a donor or from other areas of the same scalp and applying it to an area of the body that lacks hair. When compared to other types of alopecia, the procedure is more frequently used to treat male pattern baldness [81]. The scalp's temporal and occipital regions, which are often unaffected by androgens, can serve as a source for tissue that will grow hair when transplanted to bald areas of the same scalp. Follicular unit strip surgery (FUSS) and follicular unit extraction (FUE) are the two most used surgical techniques. The painstaking care required for an operation, which necessitates competent medical professionals who are sometimes hard to find, is another challenge of surgical hair transplant. Furthermore, there is no guarantee that the transplanted follicles will remain in the treated person's scalp for a longer period of time before entering the telogen stage [82-84].

Psychological and behavioral therapy

In order to manage their situation, people with alopecia need counselling, much like those with other social and psychological diseases. A person with low self-esteem may even make an attempt at suicide if they are unable to accept their circumstances. Counselling is crucial, especially for teenagers and young women who fear that their condition may negatively affect their sexuality and capacity to find romantic partners. In a study by Lemieux *et al.* to investigate the psychological impact of hair loss in cancer patients receiving chemotherapy of alopecia, patients who had hair loss reported higher levels of stress, lower self-esteem, and a negative body image compared to those who did not [6, 15]. In a different study on chemotherapy patients, Rivitti found that individuals with alopecia had higher rates of psychiatric disorder cases than those in a group without alopecia. Therefore, providing mental support is essential in the battle against alopecia. Behavioural treatments including

donning hats, wigs, or tattoos might also be recommended to patients during counselling [26, 85].

Phototherapy

There aren't many randomized controlled studies of psoralen oral or topical combined with ultraviolet a radiation (PUVA). The response rate is no better than the spontaneous remission rate, according to two sizable retrospective investigations. The lack of relevant data and the possibility of cutaneous cancers make PUVA a less preferred therapy choice. In a retrospective review of 25 AA patients, narrow-band ultraviolet B was ineffective [86]. Patchy AA has been successfully treated with the 308-nm excimer laser in a few case studies. The initial fluences were 50 mJ^{-2} cm below the erythema dosage minimum. Fluences were then raised every two sessions by 50 mJ^{-2} cm. Every patch received treatment twice weekly for a total of 24 sessions. In 41.5% of areas, hair regrowth has been observed [87].

Combination therapy

Although there is a dearth of research on combination medicines and none have received FDA approval, some patients may benefit significantly from using more than one drug, taking into account the expense and hazards involved. One of the most popular regimens for treating Androgenetic alopecia (AGA) is the combination of topical minoxidil and oral finasteride. Topical minoxidil has shown to perform less well than oral finasteride. But when combined with oral finasteride, a better clinical response has been seen to occur than with monotherapy [3]. Topical minoxidil is more effective than oral finasteride, according to a recent meta-analysis of studies involving 809 patients by Zhou *et al.* (2020). Another study found that using topical minoxidil and finasteride together for 1–12 months after stopping oral finasterid resulted in an 84.44% success rate in maintaining healthy hair density. While there was no difference in hair count, one study looked at a combination of 0.1% finasteride and 3% minoxidil solution that produced greater outcomes in overall photographic assessments than 3% minoxidil solution used alone. In a patient who had previously failed treatment, a topical retinoid, minoxidil, and oral finasteride combination was also said to be successful. Retinoid acid is thought to stimulate the follicular sulfotransferase enzymes. In other research, oral drugs have been combined for increased benefit. In a research involving 100 women, low-dose oral minoxidil (0.25 mg) and spironolactone (25 mg) were found to lessen the severity of hair loss and shedding. 5% topical minoxidil solution twice daily, 1 mg oral finasteride daily, 2.5 mg oral minoxidil daily, and 4 mL injections (lidocaine, minoxidil, caffeine, and other components) once a month on Japanese male patients showed promising clinical outcomes (3).

Alopecia's impact on quality of life (QoL)

Although alopecia areata (AA) is a biologically benign condition, it significantly lowers quality of life (QoL) by affecting social interactions, self-perception, and self-esteem. The degree to which a skin condition, like AA, affects a patient varies greatly and is poorly associated with its clinical severity [88]. Additionally, there is a discrepancy between how patients and doctors view AA. As a result, the usual metrics used to gauge the severity of the illness, like the percentage of skin afflicted, fall short of accurately capturing the psychological discomfort experienced by affected patients. Relationship difficulties as well as subjective and objective symptoms like anxiety, dissatisfaction, or itching should be taken into account. Over the past ten years, the importance of QoL outcomes has grown in dermatology. Dermatological conditions do, in fact, damage social and professional lives by bringing unpleasant feelings and bothersome symptoms [89]. Potential trigger variables that cause individuals with AA to experience a high rate of anxiety and worsening clinical results include emotions like sadness or dread. It is crucial to provide timely psychological assistance in order to promote improved self-esteem and disease adaptability. Patients with AA can benefit from counselling, support groups, and education regarding the disorder's nature. Hairpieces (such as wigs, demi wigs, toupees, fall, cascade, and winglets), hats, caps, bandanas for the scalp, artificial eyelashes, fake eyebrows, and temporary or permanent eyelash and eyebrow tattoos are other beneficial hair loss concealing treatments. Shown that inadequate coping mechanisms, such as a lack of medical advice and information, may lead to more Unfavourable evaluations of hair loss and self-image. On the other hand, patient-rated hair loss severity and QoL may improve if doctors can help patients come up with coping mechanisms. Neuro-endocrine research also support these clinical findings. Substance P and nerve growth factor are important mediators of stress-induced suppression of hair development in mice, according to recent research on AA. Additionally, individuals with AA may have elevated activity of the stress-related hypothalamic-pituitary-adrenal axis, which makes it difficult for them to cope with stressors [90-93].

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Table 1: Current status of clinical trials on Alopecia.

Drug	Mode of Administration	Disease	Enrolments	Allocation/Intervention model/ Masking	Official Title of the study	Status	Clinical trial	Year
Tofacitinib	Interventional	Alopecia	40	N/A/Single Group Assignment/None (Open Label)	Tofacitinib for the treatment of alopecia areata and its variants	NA	NCT02312882	2017
ATI-50002	Interventional	Alopecia	1	N/A/Single Group Assignment/None (Open Label)	An Open-Label Pilot Study of the Safety, Tolerability and Efficacy of ATI-50002 topical solution administered twice-daily in adult subjects with eyebrow loss due to alopecia areata, alopecia Universalis or Alopecia Totalis	Phase-2	NCT03551821	2019
Tofacitinib	Interventional	Alopecia	19	N/A/Single Group Assignment/None (Open Label)	Effectiveness and Safety of Tofacitinib in Patients With Extensive and Recalcitrant Alopecia Areata	Phase-4	NCT03800979	2022
Calcipotriol/Nar	Interventional	Alopecia	60	Randomized/Parallel	Topical Calcipotriol Versus Narrowband	NA	NCT03847441	2019

row Band UVB /Vitamin D3 Level				Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	Ultraviolet B in Treatment of Alopecia Areata: A Randomized Controlled Trial			
Etrasimod/Etrasimod/ Placebo	Interventional	Alopecia	80	Randomized/Parallel Assignment/ Double-Blind, Placebo-Controlled	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 24-week study, with a 28-week open-label extension, to assess the safety and efficacy of Etrasimod in subjects with moderate-to severe alopecia areata	Phase-2	NCT04556734	2023
Group A applied topical Clobetasol Propionate/Group B applied topical Tacrolimus	Interventional	Alopecia	70	Randomized/Parallel Assignment/None (Open Label)	Comparative Efficacy of Tacrolimus 0.1% and Clobetasol Propionate 0.05% in the Treatment of Alopecia Areata	Phase-1	NCT05885269	2023
Hydroxychloroquine	Interventional	Alopecia	16	Non-Randomized/Single Group Assignment/None (Open Label)	Open Label Study of Hydroxychloroquine for Alopecia Areata, Alopecia Totalis	Phase-4	NCT00176982	2009
CTP-543 matching placebo/CTP-543	Interventional	Alopecia	517	Randomized/Parallel Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Phase-3	NCT04797650	2023
the optimized sodium valproate-loaded nanospanlastic dispersion/mometasone furoate lotion	Interventional	Alopecia	67	Randomized/Parallel Assignment/Double (Participant Outcomes Assessor)	Assessment of Efficacy and Safety of Sodium Valproate -Loaded Nanospanlastics in Patients with Patchy Alopecia Areata in Comparison to Conventional Therapy with Topical Steroids: A Randomized Controlled Study, With Clinical, Dermoscopic and Molecular Asessements	Early Phase-1	NCT05017454	2023
Apremilast 30mg	Interventional	Alopecia	30	N/A/Single Group Assignment/None (Open Label)	Efficacy of Oral Apremilast in the Treatment of Alopecia Areata at the Tertiary Care Hospital, Karachi.	Phase-4	NCT05926882	2023
ATI-501 400 mg BID (Low dose) /ATI-501 600 mg BID (Middose)/ ATI -501 800 mg BID (High dose) / Placebo	Interventional	Alopecia	87	Randomized/Parallel Assignment/Triple (Participant Care Provider Investigator)	A Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of ATI-501 Oral Suspension Compared to Placebo in Adult Subjects With Alopecia Areata, Alopecia Universal is or Alopecia Totalis	Phase-2	NCT03594227	2020
CTP-543 matching placebo/CTP-543/CTP-543	Interventional	Alopecia	706	Randomized/Parallel Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata (THRIVE-AA1)	Phase-3	NCT04518995	2023
NA	Observational	Alopecia	10	NA	A Pilot Study of Vitamin D in Subjects with Alopecia Areata	NA	NCT01328678	2011
Vytorin	Interventional	Alopecia	29	N/A/Single Group Assignment/None (Open Label)	A Pilot Study To Evaluate the Efficacy of Vytorin (Simvastatin +Ezetimibe) In the Treatment of Alopecia Areata	Phase-1	NCT01520077	2015
Ruxolitinib	Interventional	Alopecia	12	N/A/Single Group Assignment/None (Open Label)	An Open-Label Pilot Study to Evaluate the Efficacy of Ruxolitinib in Moderate to Severe Alopecia Areata	Phase-2	NCT01950780	2019
Fractional Carbon Dioxide Laser/ Microneedling using dermapen/ Triamcinolone Acetonide/ Platelet-rich plasma	Interventional	Alopecia	60	Randomized/Parallel Assignment/None (Open Label)	Transepidermal Delivery of Triamcinolone Acetonide or Platelet Rich Plasma Using Either Fractional Carbon Dioxide Laser or Microneedling in Treatment of Alopecia Areata	NA	NCT04147845	2020
Tofacitinib	Interventional	Alopecia	12	N/A/Single Group Assignment/ None (Open Label	An Open-Label Pilot Study to Evaluate The Efficacy Of Tofacitinib In Moderate To Severe Alopecia Areata, Totalis And Universalis	Phase-2	NCT02299297	2019
Triamcinolone Acetonide/Minoxidil 5% Topical Spray /clobetasol propionate	Interventional	Alopecia	40	Randomized/Parallel Assignment/Single (Outcomes Assessor)	Combined Topical 5% Minoxidil and Potent Topical Corticosteroid Versus Intralesional Corticosteroid in the Treatment of Alopecia Areata A Randomized Controlled Trial	Phase-4	NCT03535233	2018
Dupilumab/Placebo	Interventional	Alopecia	60	Randomized/Parallel Assignment/Triple (Participant Investigator	Defining Reversal of Alopecia Areata (AA) Phenotype with Dupilumab in Patients With and Without	Phase-2	NCT03359356	2022

				Outcomes Assessor)	Associated Atopic Dermatitis (AD)			
methylprednisolone sodium succinate/methylprednisolone sodium succinate/methylprednisolone sodium succinate	Interventional	Alopecia	42	Randomized/ Parallel Assignment/Single (Outcomes Assessor)	Safety and Efficacy of Oral Mega Pulse Methylprednisolone in Severe Therapy Resistant Alopecia Areata	Phase-4	NCT01167946	2010
Tattoo machine (SOL Nova Device)	Interventional	Alopecia	5	N/A/ Single Group Assignment/ None (Open Label)	Follicular Revival in Treatment-resistant Alopecia Areata: Evaluating Use of Micro-needling	NA	NCT04338295	2022
Topical Latanoprost 0.005%/ Topical betamethasone 0.05%	Interventional	Alopecia	50	Randomized/ Parallel Assignment/ None (Open Label)	A Randomized Comparative Study of Efficacy and Safety of Topical Latanoprost Versus Topical Corticosteroid in the Treatment of Localized Alopecia Areata	Phase-4	NCT02350023	2015
Probiotic mixture/ Placebo	Interventional	Alopecia	26	Randomized/ Parallel Assignment/Double (Participant Investigator)	Randomized, Double-blind and Placebo-controlled Clinical Study to Evaluate the Effectiveness of a Probiotic Preparation Administered to Patients with Alopecia Areata	NA	NCT05599607	2022
Platelet Rich Plasma/ Normal saline	Interventional	Alopecia	30	Randomized/ Parallel Assignment/ Double (Participant Outcomes Assessor)	The Effect of Platelet Rich Plasma on Non-scarring Alopecia	NA	NCT03689452	2020
Tralokinumab/ Placebo	Interventional	Alopecia	22	Randomized/ Parallel Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Randomized Placebo-controlled Single Center Pilot Study of the Safety and Efficacy of Tralokinumab in Subjects with Moderate to Severe Alopecia Areata	Phase-2	NCT02684097	2020
SHR0302	Interventional	Alopecia	94	Randomized/ Parallel Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Randomized, Double Blind and Placebo-Controlled Phase II Study to Evaluate the Efficacy and Safety of SHR0302 Tablets in Adult Patients with Alopecia Areata	Phase-2	NCT04346316	2021
Abatacept	Interventional	Alopecia	15	N/A/ Single Group Assignment/ None (Open Label)	An Open-Label Single-Arm Clinical Trial to Evaluate the Efficacy of Abatacept in Moderate to Severe Patch Type Alopecia Areata	Phase-2	NCT02018042	2019
Hydrocortisone 1%/ Clobetasol Propionate 0.05%	Interventional	Alopecia	41	Randomized/Parallel Assignment/Triple (Participant Care Provider Investigator)	A Randomized Controlled Trial of Clobetasol Propionate 0.05% Cream Versus Hydrocortisone 1% Cream in Children with Alopecia Areata	Phase-3	NCT01453686	2013
CTP-543/ Placebo	Interventional	Alopecia	317	Randomized/ Parallel Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Study to Evaluate Maintenance of Hair Regrowth Following Dose Reduction of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	Phase-2	NCT04784533	2023
Alline pro Men/ Placebo	Interventional	Alopecia	100	Randomized/ Parallel Assignment/Double (Participant Investigator)	Double Blind, Randomized, Placebo-controlled Assessment of the Efficacy of a Food Supplement in Reducing Hair Loss in Male Subjects	NA	NCT04884347	2021
Bimatoprost 0.03% solution/ CO2 fractional laser	Interventional	Alopecia	30	Randomized/ Parallel Assignment/ None (Open Label)	Efficacy of Combined CO2 Fractional Laser with Bimatoprost 0.03% in Treatment of Alopecia Areata	Phase-1 & 2	NCT05600673	2022
DMEP kit/ Dermapen	Interventional	Alopecia	100	Randomized/ Parallel Assignment/None (Open Label)	Comparative Study Between the Effect of Superficial Cryotherapy Using Dimethyl Ether and Propane Mixture and Microneedling in Treatment of Alopecia Areata	NA	NCT04680234	2020
Alefacept	Interventional	Alopecia	45	Randomized/ Parallel Assignment/Triple (Participant Care Provider Investigator)	A Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Evaluate The Safety and Therapeutic Efficacy of Intramuscular Administration of Alefacept in Patients With Chronic, Severe Scalp Alopecia Areata	NA	NCT00167102	2019
Tofacitinib ointment	Interventional	Alopecia	10	N/A/ Single Group Assignment/ None (Open Label)	Topical Tofacitinib for the Treatment of Alopecia Areata and Its Variants	Phase 2	NCT02812342	2019
Viviscal Oral Supplement Tablets	Interventional	Alopecia	96	Randomized/Parallel Assignment/Double (Participant Investigator)	A Multi-site, Double-blind, Placebo-controlled Clinical Study to Evaluate the Effects of Viviscal Oral Supplements When Used by Females with Self-perceived Thinning Hair	NA	NCT02288858	2014
PF-06651600	Interventional	Alopecia	718	Randomized/ Parallel	A phase 2b/3 randomized, double-blind,	Phase-2	NCT03732807	2022

Induction Dose/ PF-06651600 Maintenance Dose #1/ PF-06651600 Maintenance Dose #2				Assignment/Quadruple (Participant Care Provider Investigator Outcomes Assessor)	placebo-controlled, dose-ranging study to investigate the efficacy and safety of pf-06651600 in adult and adolescent alopecia areata (aa) subjects with 50% or greater scalp hair loss	& 3		
Trichloroacetic acid	Interventional	Alopecia	40	N/A/ Single Group Assignment/ None (Open Label)	Efficacy of Trichloroacetic Acid in Patients of Alopecia Areata: Clinico-histopathological Study	NA	NCT05594316	2022

Conclusion and future direction

Our review articles begin with an introduction to alopecia (hair loss), its various kinds, causes, epidemiology, pathophysiology, advanced nanotechnology, alternative treatments, and quality of life (QoL). According to our analysis, while non-pharmacological and natural supplements provide a decent result but require time and have no negative side effects, medicine does cure but not fully. There is a need for further randomized controlled trials on the topic of treating alopecia. In the future, we want to conduct preliminary study on alopecia. With the help of our colleagues, future counseling-based research will be carried out in our country or state to assess patients' physical and mental health and produce more accurate data on alopecia and its management.

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