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A Review on Nanoparticle Based Herbal Remedies for the Management of Alopecia

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ABSTRACT

Alopecia is the medical word for baldness or hair loss. It is a health complaint in which hair is lost from certain or all extents of the body, frequently from the scalp. Generally, hair loss can be perceived owed to hereditary and metabolic disorders like hypo and hyperthyroidism, chemical exposures, medicines, environmental triggers, nutritional deficiency, long illness or severe stress etc. Drugs concerning to these sorts are such as anticancer, immunosuppressants, hypoglycemic, oral contraceptives, and NSAIDs. Based on hair loss outline and origins, alopecia is alienated into innumerable sorts. The two notable forms i.e. Androgenetic alopecia and Alopecia areata and further negligible forms like Chemotherapy alopecia, Trichotillomania etc. Even though several synthetic therapies such as Corticosteroids, dithranol, tretinoin, minoxidil and other drugs are obtainable in the market for the Alopecia cure yet even a single or multiple drug treatments not only if adequate and everlasting aftermath to the Alopecia patients. Abundant side effects are accompanying with the deployment of these synthetic medications such as erythema, pruritis, itching, dermatitis, scaling etc. To astounded concern of Hair loss, we are aiming on the Natural remedies and nanoparticles formulation of them based on abundant outcomes, which are portentous that herbs are operative for the alopecia management. The foreseen mechanisms of exploit for these herbal medicines are Nutritional assistance, Aromatherapy, 5-α-Reductase blockers and DHT blockers. Nanoparticles possess

various advantages like enhanced penetration, improved bioavailability, specific targeting and amplified resistance. Natural drugs are having innumerable benefits while employing them, such as easy obtainability, amenability with patient, rarer side effects, less cost and acting by more than a single mechanism of action for supervision of Alopecia. So the nanoparticles of herbal remedies are beneficial for effective treatment of alopecia.

Keywords: 5-α-Reductase blockers, Alopecia, Chemotherapy, Herbal remedies, Nanoparticles

INTRODUCTION

Hair is a protein filament that grows out of the epidermis from follicles deep innermost the dermis. Each hair produced from a tiny pockmark called as hair follicle. Hair follicle maturity proceeds at the time of skin development. Hair follicle contains both epidermal and dermal portions and communication between them is important for continuous regeneration of hair. Hair found in conjunction with sweat and sebaceous glands which are responsible for secretion of sweat, temperature management and secretion of sebum (oil), for lubrication of skin and hair. Pili muscle in conjunction with follicle erects hair at the time of cold and fright conditions [1].

Hair may be subdivided into 3 parts according to length, first one is bulb emerges from dermis containing swell at base, second one is root lying underneath the skin surface, last one is the shaft found on top of skin surface. According to cross section the hair may be subdivided into 3 parts. First one is medulla, core area with loose cells and air spaces. The second one is cortex; with heavily arranged keratin and the last one is cuticle with only one layer of cells [2]. Based on texture, Hair is categorized into two subtypes viz, soft hair, found on the skin of non-human animals called as fur, and the curly hair (wool) found on the skin of sheep and goat [3]. Hair play different roles like thermal regulation, camouflage, warnings, mating, defence or protection. In humans, hairs useful for heat insulation and cooling, protection from ultraviolet radiation, sensing, protection from dirt and harmful matter [4,5].

Hair fall is one of major concern and common problem in both developed and developing countries; it may be due to various reasons like psychological disturbances, distress, depression, environmental pollution through water or air, unhealthy diets, auto-immunity and genetic factors [6-8]. Hair fall may be temporary or permanent. Diagnosis of hair fall can be done by physical examination, clinical history, biopsy of scalp etc. [9,10]. Hair fall is of 2 types; first one is non scarring hair fall which can be caused due to androgenic alopecia, alopecia areata and telogen effluvium. The later one is scarring alopecia which can be caused as a result of trauma, trichotillomania, traction alopecia, discoid lupus erythematosus, hair shaft abnormalities and infections like lichen planus, *Tinea capitis* [11,12].

LITERATURE REVEW

Epidemiology

Hair fall is a dermatological disorder and was first reported more than 2000 years back and it affects 2% of the world population [13,14]. Androgenic alopecia is the most prevalent form of hair fall found both in men and women; in the USA it affects almost half of both gender populations by the age of 40. Telogen effluvium which is also called as hair shedding is the second most commonly occurring alopecia. Patchy balding (Alopecia areata) is found in 1.7% of the US population [15,16].

Here are the few statistics showing hair fall in various genders [17]:

- 25% of men elderly 25 years obligate specific degree of clinically ostensible androgenic alopecia
- Androgenic alopecia in 42% of men
- Alopecia areata in 2% to 3% of the general population
- In trichotillomania, the ratio of women to men is 2.5:1 (https://www.clinicalkey.com/topics/dermatology/alopecia.html)

Pathophysiology of hair fall

Different phases of hair cycle: There are 3 phases in hair follicle cycle:

1. ***Anagen- Growth phase:*** The active hair growth seen in these phase on scalp for 2-7 years. In early years, the hair growth was faster. The growth rate of hair on average is 2-7 cm.
2. ***Catagen-Regression phase:*** In these phase, depletion of pigment and reduction of hair shaft associated with consequent depletion of medulla and dermal papilla cease the production of new cells resulting in cessation of dendrite and melanocytes growth. This phase lasts for 2 weeks.
3. ***Telogen-Resting phase:*** This is the dormant state of follicle and lasts for four months which stimulates the new anagen phase.
4. ***Exogen phase-Shedding phase****:* It is the phase of hair shedding seen at slightly phase of hair cycle and mostly seen in at the time of new anagen phase [18,19].

If any of these 3 stages altered, there is a chance of hair fall:

- Alopecia areata and drugs can cause anagen hair loss
- Injuries can cause early telogenization [20,21].

Normally, hair loss can be seen due to hereditary and metabolic disorders like hypo and hyperthyroidism. Drugs pertaining to the following categories: anticancer, immune-suppressant, high blood pressure (CVS), oral contraceptives, and NSAIDs can cause hair loss. Alteration in the function of pituitary gland, which controls the activity of thyroid, sex and adrenal glands results in hair loss. Nutritional deficiency due to inadequate consumptions of iron, zinc and protein supplements also results in hair loss. Fever, viral infections, tuberculosis, and syphilis are also responsible for hair loss. Psychological problems like anorexia nervosa, stress, autoimmune diseases like systemic lupus erythematosus, accident prone effects like surgical operations, haemorrhage or stroke leads to hair loss. Fungal infection of *Tinea capitis*, beauty practices like hair pulling, hair straightening, colouring, and bleaching accounts for the hair loss [22-30].

Androgenetic alopecia

There are 2 isoforms of 5α-reductases which further regulates steroid transformation. The Levels of dihydrotestosterone (DHT) and 5 α- reductase and the rise in levels of 5 α- reductase activity, which further leads to increase in the levels of dihydrotestosterone causes androgenetic alopecia. DHT binds to androgen receptor and hormone receptor complex activating the genes responsible for alopecia [31,32]. In women, using estrogens as contraceptive pills has beneficial effect on

alopecia by stimulating the proliferative effect of dermal papilla cells whereas that using non testosterone derivative like levonorgesterol, alopecia worsens [33].

Alopecia areata

The increase in levels of catagen and telogen follicles, lymphocytic infiltration may be responsible for alopecia areata. Autoimmune T-cell mediated predisposed reaction against hair follicle leads to alopecia. Viral infections, stress, thyroid disorders, gynaecological disorders, cardiac surgeries and menopause are also responsible for androgenic alopecia [34,35].

Chemotherapy-Alopecia

In cancer, chemotherapy is one of the treatments which account for alopecia in up to 65% of the patients due to their cytotoxic property and depends on chemotherapeutic drug and treatment protocol [36].

Trichotillomania

This alopecia results from the habit of hair pulling which starts at the age of preadolescent and paediatric populations. Necessary psycho education can be helpful to treat this type of alopecia [37,38].

Telogen effluvium

Various disorders and diseases like surgical trauma, fever, hypothyroidism, hyperthyroidism and dermatitis are responsible for premature termination of telogen which leads to acute telogen effluvium which lasts 2-3 months. Chronic telogen effluvium is idiopathic and lasts more than 6 months.

The food containing iron, vitamin D, zinc can prevent the telogen effluvium. Psychiatric medications, anticoagulants, retinol, interferon, anti-hyper lipidemic drugs are also responsible for alopecia. Postpartum alopecia seen up to 6 months can be recovered in patients who are having nutritional adequate food [39-46].

Animal models of hair loss

The most widely used animal model for Hair loss are Dundee experimental bald rats (DEBR), C3H/HeJ mice and C57BL/6 mice [47,48]. C3H/HeJ mouse model lacking Fas/FasL is resistant to hair fall and when Fas/FasL deficient mouse skin transplanted to alopecia areata affected mice, this intervention prevented hair loss and produced hair. Immune deficient mice injected with cloned follicular papilla cells which are grown in cell culture is best ex vivo model for studying folliculoneogenesis, skin regeneration, follicular cell lineages and to know the effect of genetic manipulation [49-51]. The explants from mice and human skin grown on gelatine sponge at liquid/air interface in culture are sustainable for 40 days and are useful to determine the various changes happening during anagen I-VI development, anagen-catagen transformation in in-vitro and the pigmentation of hair follicle. In the cell culture of hair follicle there is a lack of barriers like pilo-sebaceous glands, epidermis which does not mimic the actual physiological system as such in normal animals, so still a good model has to be developed for in vitro study of hair follicle growth [52,53].

Dundee experimental bald rats (DEBR): The onset of hair loss observed in females at the age of 5-8 moths but in males, it is observed at the age 10 months or more. First, the hair loss starts from head and then spread towards eyes and further it is

observed on flanks in the form of patches which slowly increase in size. After attaining 18 months of age, 70% of DEBR rats express a lesion which leads to thinning of pelage or expanded patches of hair loss. Complete hair loss is possible in 15% of female DEBR rats [54,55].

C3H/HeJ mouse model: A/J and C3H/HeJ are two mouse models which show frequent hair loss. At 5 months of age, onset of hair loss observed in 0.25% of females and 0.035% male's population of C3H/HeJ. Hair loss initially starts from ventral pelage, especially around forelimbs then affects the head and dorsal pelage in the form of multiple patches. Total hair loss seen in 15% of C3H/HeJ mice of either sex [55] (Table 1).

Table 1: Various animal models used for evaluation of alopecia.

Species	Type of Hair fall	Studies done so far	Significance	Reference
Dundee experimental bald rats (DEBR)	Alopecia areata	DEBR model rats are treated with OX-8 monoclonal antibody (MoAb) for 15 days	Hair re growth initiation was observed in rats within 29 days of start of treatment	K. J. Mcelwee et al. (1995) [56]
	Alopecia areata	Treated with DPCP topically for 16 weeks	In all the treated animals re growth of hair was observed	J Shapiro et al. (1999) [57]
	Alopecia areata	FK506 (tacrolimus) applied topically concentration of 0.25% and 1% for 8 weeks	Re growth of hair within 14-21 days of treatment	Freyschmidt-Paul et al. (2001) [58]
Graft - C3H/HeJ mouse model	Alopecia areata	Anti-CD44v10 injected two intervals a week for 11 weeks	The onset of AA delayed by decreasing expression of CD8+,CD4+ and MHC-I treated by Anti-CD44v10 monoclonal antibody compared to untreated	Freyschmidt-Paul et al. (2000) [59]
	Alopecia areata	0.5 mg Triamcinolone acetonide injected intra-lesional	Development of short, hair coat in alopecia regions in 11 mice	Sundberg et al. (1994) [60]
	Alopecia areata	Anti-B7.1/B7.2 (CD80/CD86 injected intra peritoneally 100µg/mouse/week/4week	Onset of AA delayed by monoclonal antibodies	Carroll J M et al. (2002) [61]
	Alopecia areata	The mice fed with 1%, 5% and 20% soya oil containing diet Genistein concentration of 1mg injected intraperitoneally 3 times a week for 10 weeks	mice fed with 1%, 5% and 20%, 86%, 39%, 18% AA developed respectively and in mice injected with genistein and control, 40% and 90% AA developedrespectively	Mc Elwee KJ et al. (2003) [62]

C3H/HeJ mouse model	Alopecia areata	Mice treated with 0.2% anthralin ointment for 5 days a week for 10 weeks	Re growth of hair was observed in 9/14 of animals	Tang L et al. (2004) [63]
	Alopecia areata	Treated with DPCP topically for 16 weeks	9/14 of animals shows re growth of hair	J Shapiro et al. (1999) [64]
	Alopecia areata	Two treatment regimens 1.0.1%, 0.5%, 1% SADBE treated rats for 7-21 weeks 2.0.1% to 1% SADBE weekly treated rats for 22 weeks	75% success of treatment 82% success of treatment	Pia Freyschmidt-Paul et al. (1999) [65] S. Gardner et al. (2000) [66]
	Alopecia areata	FK506 (tacrolimus) applied topically 5 days a week for 8 weeks	66.7% successful treatment	McElwee et al. 1997 [67]
	Alopecia areata	Cyclosporine A Two treatment Regimens 1. 0.5% applied topically two intervals a day for 6 weeks 2. 10 mg/kg 5 days a week for 7 weeks	Initiation of regrowth of hair after 2 weeks and dense hair growth at 6th week After 10 day regrowth of hair started and by 5th week significant hair growth observed	D.D. Verma et al. (2004) [68] R. F. Oliver and J. G. Lowe et al. (1995) [69]
	Alopecia areata	0.02% Mechlorethamine applied topically 5 days a week for 10 weeks	Re growth of hair observed in all of the 24 animals	Tang L et al. (2003) [70]
	Alopecia areata	10 mice are injected with IL4 and Ifng, 10- ll4, 10-saline, 6- anti-Ifng, 6-rat IgG, 6-antisense Tbx21 oligonucleotide, 6 -non-sense oligonucleotide, 8 - cationized gelatine conjugated Tbx21 siRNA, 8–naked Tbx21 siRNA, 8 cationized gelatine conjugated non-sense siRNA	Tbx21oligonucleotide more effective than non-sense oligo-nucleotide, cationized gelatine conjugated Tbx21 siRNA further effective than naked Tbx21 siRNA and non-sense siRNA, with IL4 a significant response compared to control with IgG better response compared to negative control	Nakamura M et al. (2008) [71]

Molecular pathway involved in hair growth

Based on sub cellular localization of β-catenin, the importance of Wnt signalling pathway came into picture in hair growth. When Wnt signal is absent, β-catenin gets phosporylated which accounts for degradation of β-catenin by proteins like axin, glycogen synthase 3-β (GSK3-β) and adenomatous polyposis coli tumor suppressor protein (APC). When Wnt signal is present, the degradation of β-catenin is inhibited which indications to translocation of β-catenin into nucleus further makes to bind with lymphoid enhancer binding factor/T cell factor (LEF/TCF) family which triggers transcription of target genes. The hair follicle development is classified into 8 stages. Hair placodes is initiation stage which is group of large and elongated epi dermal keratinocytes [72,73]. Placode formation causes interaction with mesenchymal cells by condensed fibroblasts. The interaction between mesenchymal cells and specialized fibrolasts of placode causes growth in size of both cells, which forms follicular dermal papilla in mesoderm and initiating downward growth of ectodermal placode [74]. The second stage is considered by immense proliferation of keratinocytes which directs to development of hair germ in which cyclin D1 levels increased [75]. In third and fourth stage of growth which is called as peg stage, more inward growth is seen, there by enwrap of dermal papilla by proximal keratinocytes leads to bulbous peg stage which imply 5^{th} to 8^{th} stage where sheet of epithelial differentiation in hair follicle morphologically seen. Hair follicle keratinocytes tends to form inner root sheath. Cells of inner root sheath are the primary epithelial cells and differentiated to form rigid tube. In midway of tube, organized and compact hair shaft is formed due to terminal trichocytes differentiation. The essential step in hair follicle morphogenesis is inner root sheath formation [72,73]. Melanin produced by hair follicle pigmentary unit and sebocytes are produced by distal hair follicle epithelium in stage 5 followed by accumulation of lymphocytes and langerhans cells. The accumulated lymphocytes are expressed differently in mouse and humans. Gamma/delta TCR+ cells are observed in mouse whole CD4+ or CD8+ alpha/beta TCR+ cells are observed in humans. The mast cells and macrophages are increased in hair follicle and in surrounding perifollicular mesenchymal cells. IL-1, TNF-α, IFNγ and adhesion molecules is also secreted by follicular keratinocytes [76]. The variation in levels of promoter and repressor activation determines size and spacing of hair follicle. The primary dermal signal is produced by β-catenin due to activation of epithelial ectodysplasin (EDA) / ectodysplasin receptor (EDAR) and epithelial Wnt signalling which promotes placode formation followed by bone morphogenic protein (BMP) activation that represses the placode formation in adjacent skin. Sonic hedgehog (SHH) signal is not prerequisite for initiation of primary epithelial signal but is essential for proliferation of follicular epithelium and formation of dermal papilla [77-79]. Based on above statements we can say that for initiation phase i.e., anagen phase wnt and β-catenin signalling is necessary, Sonic hedgehog (SHH) signal essential in lateral development and growth phase of hair follicle.

Pathogenesis involved in hair loss-Alopecia areata

Based on microarray results obtained in mouse model reported that 42 known genes regulation responsible for pathogenesis of hair loss. Of 114 genes regulate immunoglobin response and cause autoantibody production as secondary response to early disease induction. Overall stimulation of inflammation and vasodilatation leads to macrophage/antigen presenting cell action further stimulates activation of T-cells and accumulation of antibody. Hair loss studies on mouse model reported that increased levels of TNF-α, IL-6, Th1 cytokines IL-12, IFNγ, Th2 cytokines IL-4 and IL-10. Thus it can say that both Th1 and Th2 are active in hair loss mechanism.

Functional suggests that reported that both CD4+ and CD8+ are actively tangled in hair loss. Both mouse and rat model that are deficient in CD4+ and CD8+ resulting in hair re growth, while the mouse model deficient in Fas/FasL system is resistant to hair loss.

In anagen stage, dendritic cells and macrophages are stimulated around hair follicles. So these antigen presenting cells capture antigens released from hair follicles and activates expression of MHC class II and APCs move to T-cell foci, mainly to lymph nodes of the skin. Then stimulation of IL-6 and IL-12 leads to auto reactive CD4+ Th cells activation and proliferation which is pathogenic. The activated Th cells further secrete IL-2 which stimulates CD8+ Tc cells. The adhesion molecules aids in transport of Th and Tc cells to the skin around anagen stage of hair follicle where a chemical stimulus is present. Th, Tc, B, macrophage and dendritic cells together results in production of IL-2, IL-4, IL-6, IL-10, IL-12, IFNγ, and TNFα repeatedly initiates local inflammation. Peri-follicular inflammation causes disruption of keratinocyte cells through TNFα, IFNγ, secretory Fas ligand (sFasL) by acting on hair follicles. IFNγ further initiates expression of MHC class I and class II. Auto reactive Tc cells are hair follicle specific modifies to intrafollicular sites and elevation of hair follicle keratinocyte expression leads to damage the hair follicle. Tc cells and cell-cell direct interactions causes distraction of target cells through granzyme B and Fas/FasL mediated keratinocyte apoptosis. Fas, FasL and sFasL expression by hair follicle keratinocytes may stimulate autocrine and paracrine induced apoptosis. Repeated stimulation of these inflammatory cytokines leads to continuous pathogenic cell supply and leads to auto immune disease cycle [80,81].

To overcome the Hair loss problem, here we have focused into the Nature's paragon and institute a numerous herbs with established histories for the therapy of alopecia. Possessing natural property as drugs, have numerous beneficiaries of utilizing them such as compliance with patient, fewer side-effects and further than single mechanism of action for therapy of Alopecia.

Nanoparticles

Particles which are having the size between 1 and 100 mm, which is an insignificant entity and performs as a unabridged element relating to its transport and properties (size, shape, physical, chemical and biological properties) are called as nanoparticles [81,82]. Nano particles have the capability of quick identification and management of sundry diseases, for instance targeted delivery of drug to a precise set of cells [83]. Through nanotechnology, scientists are tirelessly working to reduce toxicity and side effect of drugs in applications like drug delivery, diagnostics, and neutraceuticals along with to improve biocompatibility [84,85]. Over the past two decades, continuous research is going on to deliver the drugs through various barriers like cutaneous, blood brain barrier etc. [86,87].

Mechanism of penetration of nanoparticles

Stratum corneum is foremost obstacle for drug delivery over the skin. The passage of drug through skin is possible through three mechanisms, the primary target over lipid matrix of intercellular gaps of keratinocytes, secondary over lipid matrix of transcellular gaps of keratinocytes and last one is transappendegeal which is through hair follicles, sebaceous glands and sweat glands [88-90]. The later pathway look to be best pathway due to formation of channel like architecture contributes to greater diffusivity. The appendages are present in very small number but they are responsible for straight delivery of drug to the extent of depth they reach, principally the hair follicles and sweat glands are excellent targets of nano particle drug delivery. Human hair size of 530 nm and porcine hair size of 320 nm may serve as inflating system which drives particulate constituents reflexively toward hair follicles during the hairs in motion. Based on the size, nanoparticles reach different extents of depth into hair follicle [91-95]. Once the drug reaches deep into hair follicle, it is not cleared until it washed by sebum production or by hair growth, so the duration of action is more as a result of slow release which is best suitable for systemic circulation and adjacent skin layers due to thickest web of blood capillaries surrounding hair follicles compared to stratum corneum. Particle size between 300 nm

and 600nm diffusion into hair follicles efficient compared to non-particulate drug. The depot time was 10 days in particulate drugs, where as in no-particulate drugs it is only up to 4 days.

Nano particles and hair growth

Silver nanoparticles implants promoted secondary hair follicle growth in rabbits. 6 week old mouse of C57BL/6 strain applied as shampoo and hair tonic by Poly (epsilon-caprolactone) (PCL) nano capsules showed hair promoting activity comparable to monoxidil (3%) solution [96]. Poly (lactic-co-glycolic acid) nanospheres containing hair growing ingredients, improved delivery of ingredients to hair follicles was observed and promoted new hair follicle growth in C3H mice by transformation resting phase to growing phase [97]. The lipid nano carriers, squaparticles combined with anti-platelet derived growth factor (PDGF)-receptor β antibody containing minoxidil improved VEGF expression and promoted hair growth in female nude mice [98]. Squa particles containing minoxidil and diphencyprone (DPCP), accelerates follicular uptake is 2 to 7 fold more compared to control due to increased vascular endothelial growth factor in dermal papilla cells, which in turn increase hair growth rapidly compared to control in female nude mice [99]. The outcome of study conducted on invitro skin advocates that the new formulation presents numerous good characteristics indicative of its aptness for dermal deliverance of FNS for alopecia management [100,101] (Table 2).

Table 2: Different synthetic compounds nanoparticles evaluated in different animal models for alopecia.

Drug	**Nanoparticle class**	**Animal model**	**Dose**	**Out come**	**References**
Fullerene	Nanoparticles	Mice (C57/B6) and SKH-1 hairless nude mice	3 µg of fullerenes in 300 µL PBS intra-dermal	Fullerene nanoparticles applied topically / subdermally promoted significant hair growth activity compared to vehicle treated	Z. Zhau et al. (2007) [100]
Silver	Gelatine Nanofiber Implants	Rabbits	Subcutaneous implants of silver nanoparticles	Promotion of growth of secondary hair follicles surrounding regions of implants	Tura. V et al. (2010) [101]
Hinokitol	Poly (epsilon-caprolactone) (PCL) nano capsules	Five-week old male mice (type C57BL/6)	Hair tonics and shampoos of hinokitol applied on shaved skin	Hinokitol showed remarkable hair promoting activity comparable to	Hwang S.L., Kim J.C. (2008) [102]

				monoxidil (3%) solution	
Hinokitol, Glycyrrhetinic acid, 6-Benzylaminopurine	Poly (lactic-co-glycolic acid) nanospheres	C3H mice	3 test preparations applied on shaved skin	Improved delivery of ingredients to hair follicles and promoted new hair follicle growth in C3H mice	H. Tsujimoto et al. (2007) [97]
Minoxidil	PDGF-Squarticles	Female nude mice	Minoxidil- PDGF-Squarticles applied on skin	Minoxidil improved VEGF expression and promoted hair growth in female nude mice	I.A. Aljuffali et al. (2015) [98]
Minoxidil and diphencyprone	Squarticles	Female nude mice	Minoxidil and diphencyprone squarticles applied on skin	Follicular uptake is about 2 to 7 folds and promoted hair growth in female nude mice	Al-Juffali et al. (2013) [99]
Finasteride	Polymeric nanoparticles	*In vitro* skin permeation assay	PLGA Finasteride-Loaded Nanoparticles in form of shampoo, lotion and solution	PLGA nanoparticles were revealed to be an capable encapsulation system for FNS with strong curiosity for pharmaceutical trade	Luís V. Roque et al. (2017) [103]

On Thai plants like *Catharanthus tictorius*, *Phyllanthus emblica*, *Cymbopogon citratus*, *Alpinia galanga*, *Zingiber officinale*, *Clitorea ternatea*, *Cytrus hystrix*, *Tricosanthes cucumerina*, *Tinospora rumphii*, *Ipomea aquatica*, *Averrhoa carambola*, *Andrographis paniculata*, *Cassia siamea*, *Acacia concinna*, *Sapindus rarak*, *Lawsonia inermis*, *Rhinacanthus nasutus* hair growth promoting activity evaluated by inhibition of 5α reductase. *Catharantus tinctorius, Clitorea ternatea and Emblica officinalis* showed significant 5α reductase activity which on further testing in C57BL/6 mice exhibited consistent results [104].

Korean medicinal prescription (SSY) including *Rehmanniae Radix Preparata* ethanol extract encourages hair growth in an animal model of alopecia [105].

Safflower extract loaded 0.05% nano lipid carriers had shown significant hair growth stimulating activity than minoxidil in C57Bl/6 mice [104]. In shaved and SKH-1 hairless mice fullerene nanoparticles applied topically and subdermally showed significant hair promoting activity compared to vehicle treated mice [100].

Phospholipid polymer hybrid Nanoparticles showed the effective trans-follicular deliverance system for Quercetin in the management of androgenic alopecia.

PVP covered silver nanoparticles of *Polygonum Multi florum* Thunb has a synergistic effect in encouraging hair growth in human subjects had patented [105] (Table 3).

Table 3: Numerous herbal remedies nanoparticles screened in different models.

Drug	Nanoparticle class	Animal model	Dose	Out come	References
Carthamus tinctorius (safflower)	Lipid nanoparticles	Seven-week-old male C56BL/6Mlac mice	NLC with entrapped safflower of 0.05%,0.1% by weight of safflower extract in DI water and 2% minoxidil in DIwater applied on shaved skin	NLC loaded with Safflower showed significant activity compared to minoxidil	Chaiyasut et al. (2015) [106]
Quercetin	Phospholipid polymer hybrid Nanoparticles	Testosterone-induced alopecia	Phospholipid polymer hybrid Nanoparticles of Quercetin	Hair follicular density significantly improved and histological skin tissue sections showed that hair follicle restore to normal architecture	Das L et al. (2019) [107]
Polygonum multiforum	Silver Nanoparticles	Human	*Polygonum multiforum* root ethanol, water, acetonitrile etc silver Nanoparticles	PVP covered silver nanoparticles of *Polygonum Multiflorum* Thunb has a synergistic effect in encouraging hair growth.	Tsai M (2016) [108]

CONCLUSION

Alopecia is a most commonly occurring problem these days due to stress, pollution, hereditary, and unhealthy diets etc. Nanoparticles formulations of the currently available synthetic medications even though effective in some respect by delivering medication directly to hair follicles but are associated with their respective side effects. The medicinal plants are abundant and natural sources for treatment of various ailments including alopecia. Even though few investigations are carried out on nanoparticles of herbal remedies but they showed promising actions for treatment of alopecia. So the acceleration should be made towards investigations on more natural herbs remedies nanoparticles for effective and safe utilization of them for management of alopecia.

REFERENCES

[1]. Al-Reza, S.M., Bajpai, V.K., Kang, S.C., Antioxidant and antilisterial effect of seed essential oil and organic extracts from Zizyphus jujuba. *Food Chem Toxicol*, **2009**. 47 (9): 2374-2380.

[2]. Bandaranayake, I., Mirmirani, P., Hair loss remedies-separating fact from fiction. *CUTIS-NEW YORK*. **2004**. 73 (2):107-114.

[3]. Al-Reza, S.M, Bajpai, V.K., Kang, S.C., Antioxidant and antilisterial effect of seed essential oil and organic extracts from Zizyphus jujuba. *Food Chem Toxicol*. **2009**. 47 (9):2374-2380.

[4]. Bubenik, G.A., Why do humans get" goosebumps" when they are cold, or under other circumstances. *Scientific American*, **2003**.

[5]. Dean, I., Siva-Jothy, M.T., Human fine body hair enhances ectoparasite detection. *Biology letters*, **2011**. 8 (3):358-361.

[6]. Schmitt, J.V., et al., Hair loss perception and symptoms of depression in female outpatients attending a general dermatology clinic. *An Bras Dermat*, **2012**. 87 (3):412-417.

[7]. Shrivastava, S.B., Diffuse hair loss in an adult female: approach to diagnosis and management. *Indian J Dermatol Ve*, **2009**.75 (1):20.

[8]. Chartier, M.B., Hoss, D.M., Grant-Kels, J.M., Approach to the adult female patient with diffuse nonscarring alopecia. *J Am Acad Dermatol*, **2002**. 47 (6):809-818.

[9].França, K., et al., Comprehensive overview and treatment update on hair loss. *J Cosm Dermatol Sci App*, **2013**. 3 (3):720-726.

[10]. Hawryluk, E.B., English III JC. Female adolescent hair disorders. *J Pediatr Adol Gynec*, **2009**. 22 (4):271-81.

[11]. Shapiro, J., Wiseman, M., Lui, H., Practical management of hair loss. *Can Fam Physician*, **2000**. 46 (7):1469-1477.

[12]. Kress, V.E., Kelly, B.L., McCormick, L.J., Trichotillomania: Assessment, diagnosis, and treatment. *J Coun Develop*, **2004**. 82 (2):185-190.

[13]. Hattori, M., Ogawa, H., Biochemical analysis of hair growth from the aspects of aging and enzyme activities. *J Dermatol*, **1983**. 10 (1):45-54.

[14]. Jahoda, C.A., Induction of follicle formation and hair growth by vibrissa dermal papillae implanted into rat ear wounds: vibrissa-type fibres are specified. *Development*, **1992**. 115 (4):1103-1109.

[15]. Sinclair, R., et al., The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. *J Am Acad Dermatol*, **2004**. 51 (2):189-99.

[16]. Trüeb RM. Molecular mechanisms of androgenetic alopecia. *Experimental gerontology*, **2002**. 37: 981-990.

[17]. https://www.clinicalkey.com/topics/dermatology/alopecia.html

[18]. Bhaumik, S., Jyothi, M.D., Khar, A., Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS letters*, **2000**. 483 (1):78-82.

[19]. Cash, T.F., The psychology of hair loss and its implications for patient care. *Clin Dermatol*, **2001**.19 (2):161-166.

[20]. Courtois, M., et al., Hair cycle and alopecia. *Skin Pharmacol Phys*, **1994**. 7 (1-2):84-89.

[21]. Grover, C., Khurana, A., Telogen effluvium. *Indian J Dermatol Ve*, **2013**. 79 (5):591.

[22].Patni, P., et al., Formulation and evaluation of herbal hair oil for alopecia management. *Planta indica*, **2006**. 2 (3):27-30.

[23]. Kim, H.S., Effects of the Zizyphus jujuba seed extract on the lipid components in hyperlipidemic rats. *Prev Nutr Food Sci*, **2002**. 7 (1):72-77.

[24]. Liang, T., Liao, S., Growth suppression of hamster flank organs by topical application of γ-linolenic and other fatty acid inhibitors of 5α-reductase. *J Investi Dermatol*, **1997**. 109 (2):152-157.

[25]. Oliver, R.F., The induction of hair follicle formation in the adult hooded rat by vibrissa dermal papillae. *Development,* **1970**. 23 (1):219-236.

[26]. Paus, R., Therapeutic strategies for treating hair loss. *Drug Discovery Today: Therapeutic Strategies*, **2006**. 3 (1):101-110.

[27]. Paus, R., Cotsarelis, G., The biology of hair follicles. *N Engl J Med*. **1999**. 341 (7):491-497.

[28]. Rathi, V., et al., Plants used for hair growth promotion: A review. *Pharmacognosy Reviews*, **2008**. 2 (3):185.

[29]. Roh, S.S., et al., The hair growth promoting effect of Sophora flavescens extract and its molecular regulation. *J Dermatol sci*, **2002**. 30 (1):43-9.

[30]. Souleles, C., Shammas, G., Flavonoids from the leaves of Zizyphus jujuba. *Fitoterapia,* **1998**. 59:154-156.

[31]. Price, V.H., Androgenetic alopecia in women. *J Investig Dermatol Symp Proc*, **2003**. 8 (1): 24-27.

[32]. Soni, V.K., Androgenic alopecia: A counterproductive outcome of the anabolic effect of androgens. *Medi Hypotheses*, **2009**. 73 (3):420-426.

[33]. Jamin, C., Androgenetic alopecia. I *An de Dermatol Vene*, **2002**. 129 (5): 801-803.

[34]. França, K., et al., Comprehensive overview and treatment update on hair loss. Journal of Cosmetics, *Dermatol Sci Appl*, **2013**. 3 (3):720-6.

[35]. Ruiz, D.S., Carrizosa, A., García, H.M.J., Alopecia areata: psychiatric comorbidity and adjustment to illness. *Int J Dermatol*, **2003**. 42 (6):434-437.

[36]. Gude, D., Tackling chemotherapy-induced alopecia. *In J Trichology*, **2012**. 4 (1):47.

[37]. Hanna, G.L., Trichotillomania and related disorders in children and adolescents. *Chil psy hum Developt*, **1997**. 27 (4):255-268.

[38]. Labouliere, C.D., Storch, E.A., Pediatric trichotillomania: Clinical presentation, treatment, and implications for nursing professionals. *J Pediat Nursin*, **2012**. 27 (3):225-232.

[39]. Kligman, A.M., Pathologic dynamics of human hair loss: I. Telogen effluvium. *Archi Dermatol*, **1961**. 83 (2):175-198.

[40]. Tosti, A., Piraccini, B.M., Van Neste, D.J., Telogen effluvium after allergic contact dermatitis of the scalp. *Archi Dermatol*, **2001**; 137 (2):187-190.

[41]. Olsen, E.A., et al., Iron deficiency in female pattern hair loss, chronic telogen effluvium, and control groups. *J Am Acad Dermatol*, **2010**. 63 (6):991-999.

[42]. Paus, R., et al., The skin POMC system (SPS): leads and lessons from the hair follicle. *Ann NY Acad Sci*, **1999**. 885 (1):350-63.

[43]. Arck, P.C., et al., Indications for a 'brain–hair follicle axis (BHA)': inhibition of keratinocyte proliferation and up-regulation of keratinocyte apoptosis in telogen hair follicles by stress and substance P. *FASEB J*, **2001**. 15 (13):2536-2538.

[44]. Gautam, M., Alopecia due to psychotropic medications. *Annals of Pharmacotherapy*, **1999**. 33 (5):631-637.

[45]. Eastham, J.H., Postpartum alopecia. *Annals of Pharmacotherapy*, **2001**. 35 (2):255-258.

[46] Millikan, L., Hirsutism, postpartum telogen effluvium, and male pattern alopecia. *J Cosmet dermatol*, **2006**. 5 (1):81-86.

[47]. Michie, H.J., et al., The DEBR rat: an animal model of human alopecia areata. *Br J Dermatol*, **1991**. 125 (2):94-100.

[48]. Sundberg, J.P., Cordy, W.R,, King-Jr, L.E., Alopecia areata in aging C3H/HeJ mice. J Investi Dermatol, **1994**. 102 (6):847-56.

[49]. Kamimura, J., et al., Primary mouse keratinocyte cultures contain hair follicle progenitor cells with multiple differentiation potential. *J Investi Dermatol*, **1997**. 109 (4):534-40.

[50]. Kanzler, B., et al., Differential expression of two different homeobox gene families during mouse tegument morphogenesis. *Int J Dev Biol*, **2004**. 38 (4):633-640.

[51]. Prouty, S.M., Lawrence, L., Stenn, K.S., Fibroblast-dependent induction of a murine skin lesion with similarity to human common blue nevus. *Am J Pathol*, **1996**. 148 (6):1871.

[52]. Botchkarev, V.A., et al., Neurotrophin-3 involvement in the regulation of hair follicle morphogenesis. *J Inv Dermatol*, **1998**. 111 (2):279-285.

[53]. Slominski, A.T., et al., Cutaneous Expression of CRH and CRH-R: Is There a" Skin Stress Response System?". *Anna NY Acad Sci*, **1999**. 885:287-311.

[54]. Michie, H.J., et al., The DEBR rat: an animal model of human alopecia areata. *Br J Dermatol*, **1991**. 125 (2):94-100.

[55]. Sundberg, J.P., King-Jr, L.E., Mouse mutations as animal models and biomedical tools for dermatological research. *J Invest Dermato*, **1996**. 106 (2):368-76.

[56]. McElwee, K.J., Pickett, P., Oliver, R.F., Hair follicle autoantibodies in DEBR rat sera. *J Invest Dermato*, **1995**. 995 (104):34S-35S.

[57]. Sundberg, J.P., et al., Alopecia areata-like hair loss in C3H/HeJ mice and DEBR rats can be reversed using topical diphencyprone. *In J Invest Dermatol Symp Proc*, **1999**. 4 (3): 239-243.

[58]. Freyschmidt, P.P., et al., Treatment of alopecia areata in C3H/HeJ mice with the topical immunosuppressant FK506 (Tacrolimus). *E J Dermatol*, **2001**. 11 (5):405-409.

[59]. Freyschmidt, P.P., et al., Treatment with an anti-CD44v10-specific antibody inhibits the onset of alopecia areata in C3H/HeJ mice. *J Invest Dermatol*, **2000**. 115 (4):653-657.

[60]. Sundberg, J.P., Cordy, W.R., King-Jr, L.E., Alopecia areata in aging C3H/HeJ mice. *J Invest Dermatol*, **1994**. 102 (6):847-856.

[61]. Carroll, J.M., et al., Gene array profiling and immunomodulation studies define a cell-mediated immune response underlying the pathogenesis of alopecia areata in a mouse model and humans. *J Invest Dermatol*, **2002**. 119 (2):392-402.

[62]. McElwee, K.J., et al., Dietary soy oil content and soy-derived phytoestrogen genistein increase resistance to alopecia areata onset in C3H/HeJ mice. *Exp Dermatol*, **2003**. 12 (1):30-36.

[63]. Tang, L., et al., Restoration of hair growth in mice with an alopecia areata-like disease using topical anthralin. *Exp Dermat*, **2004**. 13 (1):5-10.

[64]. Sundberg, J.P., et al., Alopecia areata-like hair loss in C3H/HeJ mice and DEBR rats can be reversed using topical diphencyprone. *J Invest Dermat Sym Proc*, **1999**. 4 (3): 239-245.

[65]. Freyschmidt, P.P., Successful treatment of alopecia areata-like hair loss with the contact sensitizer squaric acid dibutylester (SADBE) in C3H/HeJ mice. *J Invest Dermatol*, **1999**. 113 (1): 61-68.

[66]. Gardner, S., et al., Normalisation of hair follicle morphology in C3H/HeJ alopecia areata mice after treatment with squaric acid dibutylester. *E J Dermatol*, **2000**. 10 (6): 443-450.

[67]. McElwee, K.J., et al., Topical FK506: a potent immunotherapy for alopecia areata? Studies using the Dundee experimental bald rat model. *Br J Dermatol*, **1997**. 137 (4): 491-497.

[68]. Verma, D.D., et al., Treatment of alopecia areata in the DEBR model using Cyclosporin A lipid vesicles. *E J Dermatol*, **2004**.14 (5): 332-338.

[69]. Oliver, R.F., Lowe, J.G., Oral cyclosporin A restores hair growth in the DEBR rat model for alopecia areata. *Clin Exp Dermatol*, **1995**. 20 (2):127-131.

[70]. Tang, L., et al., Old wine in new bottles: reviving old therapies for alopecia areata using rodent models. *J Invest Dermat Sy Proc*, **2003**. 8 (2): 212-216.

[71]. Nakamura, M., et al., Controlled delivery of T-box21 small interfering RNA ameliorates autoimmune alopecia (Alopecia Areata) in a C3H/HeJ mouse model. *Am J Path*, **2008**. 172 (3): 650-658.

[72]. Philpott, M., Hair follicle morphogenesis. Molecular Basis of Epithelial Appendages Morphogenesis. **1998**.

[73]. Paus, R., et al., A comprehensive guide for the recognition and classification of distinct stages of hair follicle morphogenesis. *J Invest Dermatol*, **1999**. 113: 523-532.

[74]. Magerl, M., et al., Patterns of proliferation and apoptosis during murine hair follicle morphogenesis. *J Invest Dermatol*, **2001**. 116 (6): 947-955.

[75]. Mill, P., et al., Sonic hedgehog-dependent activation of Gli2 is essential for embryonic hair follicle development. *Genes & Development*, **2003**. 17 (2): 282-294.

[76]. Paus, R., et al., Generation and cyclic remodeling of the hair follicle immune system in mice. *J Invest Dermatol*, **1998**. 111 (1): 7-18.

[77]. St-Jacques, B., et al., Sonic hedgehog signaling is essential for hair development. *Cur Biol*, **1998**. 8 (19): 1058-1069.

[78]. Karlsson, L., et al., Roles for PDGF-A and sonic hedgehog in development of mesenchymal components of the hair follicle. *Development*, **1999**. 126 (12): 2611-2621.

[79]. Chiang, C., et al., Essential Role for Sonic hedgehog during Hair Follicle Morphogenesis. *Dev Boil*, **1999**. 205 (1): 1-9.

[80]. Carroll, J.M., et al., Gene array profiling and immunomodulation studies define a cell-mediated immune response underlying the pathogenesis of alopecia areata in a mouse model and humans. *J Invest Dermatol*, **2002**. 119 (2): 392-402.

[81]. www.epa.gov

[82]. Leary, S.P., Liu, C.Y., Apuzzo, M.L., Toward the emergence of nanoneurosurgery: part III--nanomedicine: targeted nanotherapy, nanosurgery, and progress toward the realization of nanoneurosurgery. *Neurosurgery*, **2006**. 58 (6): 1009-1026.

[83]. Petros, R.A., DeSimone, J.M., Strategies in the design of nanoparticles for therapeutic applications. *Nat Rev Drug Discov*, **2010**. 9 (8): 6-15.

[84]. Duncan, R., The dawning era of polymer therapeutics. *Nat Rev Drug Discov*, **2003**. 2 (5): 34-37.

[85]. Ferrari, M., Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer*, **2005**. 5 (3): 16-21.

[86]. Lademann, J., et al., Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. *Skin Pharmacol Phys*, **1999**. 12 (5): 247-256.

[87]. Cheng, Y., et al., Blood-brain barrier permeable gold nanoparticles: an efficient delivery platform for enhanced malignant glioma therapy and imaging. *Small*, **2014**. 10 (24): 5137-5150.

[88]. Naik, A., et al., Enhancement of topical delivery from biodegradable nanoparticles. *Pharm Res*. **2004**. 21 (10): 1818-1825.

[89]. Toll, R., et al., Penetration profile of microspheres in follicular targeting of terminal hair follicles. *J Invest Dermatol*, **2004**. 123 (1): 168-176.

[90]. Hadgraft, J., Modulation of the barrier functions of the skin. *Skin Pharmacol Phys*, **2001**. 14 (1): 72-81.

[91]. Lademann, J., et al., Hair follicles–an efficient storage and penetration pathway for topically applied substances. *Skin pharmacol Phys*, **2008**. 21 (3): 150-155.

[92]. Lademann, J., et al., How safe are nanoparticles? Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete, **2009**. 60 (4): 305-309.

[93]. Lademann, J., et al., Hair follicles–a long-term reservoir for drug delivery. *Skin pharmacol Phys*, **2006**. 19 (4): 232-236.

[94]. Lademann, J., et al., Nanoparticles–an efficient carrier for drug delivery into the hair follicles. *E J Pharm Biophar*, **2007**. 66 (2): 159-164.

[95]. Nohynek, G.J,, Dufour, E.K., Roberts, M.S., Nanotechnology, cosmetics and the skin: Is there a health risk?. *Skin Pharmacol Phys*, **2008**. 21 (3): 136-149.

[96]. Hwang, S.L., Kim, J.C., *In vivo* hair growth promotion effects of cosmetic preparations containing hinokitiol-loaded poly (ε-caprolacton) nanocapsules. *J Microencapsul*, **2008**. 25 (5): 351-356.

[97]. Tsujimoto, H., et al., Evaluation of the permeability of hair growing ingredient encapsulated PLGA nanospheres to hair follicles and their hair growing effects. *Bioorg Med Chem Lett*, **2007**. 17 (17): 4771-4777.

[98]. Aljuffali, I.A., et al., Squarticles as a lipid nanocarrier for delivering diphencyprone and minoxidil to hair follicles and human dermal papilla cells. *AAPS J*, **2014**. 16 (1): 140-150.

[99]. Aljuffali, I.A., et al., Anti-PDGF receptor β antibody-conjugated squarticles loaded with minoxidil for alopecia treatment by targeting hair follicles and dermal papilla cells. *Nanomedicine: Nanotechnology, Biology and Medicine*, **2015**. 11 (6):1321-1330.

[100]. Zhou, Z., et al., Fullerene nanomaterials potentiate hair growth. *Nanomedicine: Nanotechnology, Biology and Medicine*, **2009**. 5 (2): 202-207.

[101]. Tura, V., Hagiu, B.A., Mangalagiu, I.I., Hair follicles stimulation effects of gelatin nanofibers containing silver nanoparticles. *J Biomed nanotechnol*, **2010**.6 (2):192-197.

[102]. Hwang, S.L., Kim, J,C., *In vivo* hair growth promotion effects of cosmetic preparations containing hinokitiol-loaded poly (ε-caprolacton) nanocapsules. *J microencapsul*, **2008**. 25 (5): 351-356.

[103]. Roque, L.V., et al., Design of finasteride-loaded nanoparticles for potential treatment of alopecia. *Skin Pharmacol Phys*, **2017**. 30 (4):197-204.

[104]. Kumar, N., et al, 5α-reductase inhibition and hair growth promotion of some Thai plants traditionally used for hair treatment. *J Ethnopharmacol*. **2012**. 139 (3): 765-7671.

[105]. Yoon, K.J., Jin, P.H., Ryeo, K.M., Ethanol extract of a Korean medicinal prescription (SSY) including Rehmanniae Radix Preparata promote hair growth in an alopecia animal model. *Korea J Herbol*, **2015**. 274-281.

[106]. Kumar, N., Chaiyasut, C., Hair growth promoting activity of Carthamus tinctorius florets extract-loaded nanostructured lipid carriers. *Int J Pharm Pharm Sci*, **2015**. 2 (4): 27-36.

[107]. Das, L., Kaurav, M., Pandey, R.S., Phospholipid–polymer hybrid nanoparticle-mediated transfollicular delivery of quercetin: prospective implement for the treatment of androgenic alopecia. *Drug Dev Ind Pharma*, **2019**. 45 (10): 1654-1663.

[108]. Tsai, M., Inventor: Skylight Technology Limited, assignee. Composition comprising silver nanoparticles and extracts of Polygonum Multiforum Thunb and the use thereof. United States patent US 9,295,694. **2016**.