NANOPARTICLE BASED HERBAL REMIDIES 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 areataand 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

EPIDERMIOLOGY

Hair fall is a dermatological disorder and was first reported more than 2000 years back and it affects 2% of the world population [. 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 bythe 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 Here are the few statistics showing hair fall in various genders • 5% 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

ANDROGENETIC ALOPECIA

There are 2 isoforms of 5 -reductases which further regulates steroid transformation. The Levels of dihydrotestosterone (DHT) and 5 - reductase and the rise in levels of 5- 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 . In women, using estrogens as contraceptive pills has beneficial effect on alopecia bystimulating the proliferative effect of dermal papilla cells whereas that using non testosterone derivative like levonorgesterol, alopecia worsens

Alopecia

a reata The increase in levels of catagen and telogen follicles, lymphocytic infiltration maybe 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

Chemotherapy-

 In cancer, chemotherapyis 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

 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.

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**

Animal models of hair loss

 he most widely used animal model for Hair loss are Dundee experimental bald rats (DEBR), C3H/HeJ mice and C57BL/6 mice . 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 . 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

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.

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 initiallystarts from ventral pelage, especiallyaround 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.

Molecular pathway involved in hair growth

Based on sub cellular localization of β-catenin, the importance of Wnt signalling pathwaycame into picture in hair growth. When Wnt signal is absent, β-catenin gets phosporylated which accounts for degradation of β-catenin byproteins like axin, glycogen synthase 3-β (GSK3-β) and adenomatous polyposis coli tumor suppressor protein (APC). When Wnt signal is present, the degradation of βcatenin 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 epidermal keratinocytes . 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. The second stage is considered by immense proliferation of keratinocytes which directs to development of hair germ in which cyclin D1 levels increased] 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 5th to 8th stage where sheet of epithelial differentiation in hair follicle morphologicallyseen. 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 . Melanin produced byhair follicle pigmentaryunit and sebocytes are produced bydistal hair follicle epithelium in stage 5 followed by accumulation of lymphocytes and langerhans cells. The accumulated lymphocytes are expressed differentlyin 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. The variation in levels of promoter and repressor activation determines size and spacing of hair follicle. The primarydermal signal is produced byβ-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.

Pathogenesis involved in h air loss-

Alopecia areata Based on microarrayresults obtained in mouse model reported that 42 known genes regulation responsible for pathogenesis of hair loss. Of 114 genes regulate immunoglobin response and cause autoantibodyproduction 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 saythat 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 resist an 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.

Nanoparticle 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 . 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. 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. Over the past two decades, continuous research is going on to deliver the drugs through various barriers like cutaneous, blood brain bar

Mechanism of penetration of nanopartic

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 towr d hair follicles during the hairs in motion. Based on the size, nanoparticles reach different extents of depth into hair follicle. 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.

Nanoparticles 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 ging phase [97]. The lipid nano carriers, squaparticles combined with anti-platelet derived growth factor (PDGF)-receptor 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 inreased 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 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 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

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

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