International Journal of Pharmaceutical and Clinical Research

ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 5.2
IJAN 2023; 5(2): 111-116
www.pharmaceuticaljournal.in
Received: 13-07-2023
Accepted: 19-08-2023

Tenzin Pema
Al-Ameen College of Pharmacy, Bangalore, Karnataka, India

Aisha Khanum
Al-Ameen College of Pharmacy, Bangalore, Karnataka, India

Harish PB
Al-Ameen College of Pharmacy, Bangalore, Karnataka, India

Corresponding Author:
Tenzin Pema
Al-Ameen College of Pharmacy, Bangalore, Karnataka, India

A review on follicular targeting for the treatment of hirsutism

Tenzin Pema, Aisha Khanum and Harish PB

DOI: https://doi.org/10.33545/26647591.2023.v5.i2b.69

Abstract
Hirsutism characterized by excessive hair growth in women, poses significant psychological and social challenges. Conventional treatment modalities, while effective to some extent, may not always provide satisfactory results. This review focuses on the emerging concept of follicular targeting as a novel approach to treating hirsutism. By selectively targeting the hair follicles with specific interventions, follicular targeting holds promise in achieving enhanced clinical outcomes and minimizing side effects. This review outlines rationale, techniques, and potential future and directions of follicular targeting in the management of hirsutism.

Keywords: Hirsutism, hair growth, follicular targeting

Introduction
Hirsutism refers to relatively excessive, male-pattern hair growth with excessive coarse hairs on areas including the face, chest, abdomen, and thighs which are relatively sensitive to androgen [1]. Idiopathic hirsutism (IH) is the most common cause of hirsutism. The prevalence of IH is 5%-20% approximately, varying by ethnicity, with Mediterranean heritage having a higher frequency [2, 5]. A recent systemic review of studies published from inception from July 2021 estimated the prevalence of IH by 7.74% [6]. In India the prevalence ranges from 8.2% to 22.5%, based on the diagnostic criteria used [7, 8]. It has a remarkable adverse effect on psychosocial development and is usually the underlying result of adrenal, ovarian, and endocrine abnormality namely, androgen excess. Figure 1 highlights some of the associated co-morbidities. The general cause of androgen excess is polycystic ovary syndrome (PCOS), androgen-secreting tumors, and less frequently due to androgenic drug intake [9, 10]. In women of conceptual age, hirsutism affects 5-10% of them. It could be a minor cosmetic issue that simply needs cosmetic therapy or it may also have significant psychological or medical effects.

Many therapies are available for the management of hirsutism such as non-pharmacological and pharmacological therapies. Later includes topical therapy like Eflornithine Hydrochloride cream, Hormonal combined contraceptives, anti-androgen therapy, and Glucocorticoid therapy. Nonpharmacological therapies such as behavioral and lifestyle changes and the use of hair removal creams and devices [11]. But cosmetic intervention comes with limitations such as daily shaving, skin irritation, cuts, and bristles. Systemic side effects, including gastrointestinal disturbances, weight gain, mood changes, and potential risks for cardiovascular health. Due to these negative impacts, patients may be reluctant to continue long-term medication in pharmacological intervention [12]. To eliminate the drawbacks of conventional therapies a novel follicular targeting can be placed. Drug delivery targeting hair follicles has gained a lot of attraction in the last several years as a treatment for disorders connected to hair follicles, such as androgen-associated diseases and hair loss. Follicle delivery systems are crucial because they increase the effectiveness of topical treatments for these conditions and lower systemic side effects, offering a promising approach for the treatment of aberrant hair development, diseases associated with hair follicles, and general skin issues [13].

Hair cycle

Hair follicles progress through a growth cycle (fig 2) consisting of three primary phases: 1) Anagen, during which cells rapidly multiply and ascend to form the hair shaft. 2) Catagen, signifying the conclusion of mitosis, lower follicle segment reabsorption, and cell death, and 3) Telogen, a resting phase before hair shedding occurs [14]. Recently, two additional stages of the hair cycle have been identified: 4) Exogen, which involves the release of telogen fibers from hair follicles, and 5) Kenogen, a pause between exogen and the development of new anagen fibers [15].

Typically, approximately 85-90% of scalp follicles are in the anagen phase, lasting 2-6 years, while 1-2% are in the catagen phase, which spans 2 weeks, and around 10% are in the telogen phase, extending for 2-4 months. The rate of elongation of scalp hair shafts falls between 0.3 and 0.4 mm per day, with some authors stating 0.5 mm per day. This rate is contingent upon the proliferation and subsequent differentiation of matrix keratinocytes within the hair bulb. The thickness of the hair shaft is directly related to the size of the hair bulb [16, 17].

Management of hirsutism

The management of hirsutism should be done on the severity of the condition and the level of distress it is causing the patient. Hirsutism is a clinical sign and is not a disease by itself, and it may not always demand medical intervention. Nevertheless, the understanding of having male-pattern body hair, regardless of its actual extent, can negatively effect on psychological well-being of women, even when hirsutism is mild. For mild hirsutism, cosmetic measures are often successful in managing the condition, especially when thick terminal hair is primarily concentrated in highly visible areas like the face. However, in cases of moderate to severe hirsutism, or when the excess hair covers larger androgen-sensitive areas, a pharmaceutical intervention is usually necessary. It's important to note that drugs may only offer partial relief when dealing with terminal hair. As a result, effective management of clinically significant hirsutism typically involves a two-pronged strategy: the use of pharmaceutical treatments to reduce androgen production and/or its effects, combined with the removal of existing terminal hair. Treatment is classified into two broad categories 1) Non-pharmacological and 2) Pharmacological treatment.

Non-pharmacological treatment

- **Lifestyle modification:** It is advised that lifestyle modifications, such as diet, exercise, and weight loss, be initiated as the first line of treatment for hirsute women with PCOS and should come before or alongside pharmacological treatment.
- **Mechanical hair removals:** There are numerous temporary hair removal techniques are available. Shaving is quick, secure, and efficient, but it requires repeated application. Hairs can be removed chemically by depilation, yet this procedure may result in reactive dermatitis. Epilation techniques like waxing or plucking remove hairs down to the bulb, but they can cause hyperpigmentation, folliculitis, and scarring in addition to irritation [18].
- **Permanent methods include electrolysis, laser epilation, and photoepilation:** All the options are painful and time-consuming because each hair needs to be targeted so comparatively electrolysis is less painful but it is appropriate only for treating limited sections of skin. Laser therapy is less painful, faster, and commonly thought to be more successful than electrolysis; nevertheless, it is also more expensive [19].

Pharmacological treatment

Topical therapy

Eflornithine hydrochloride cream (Vaniqa 13.9%), an ornithine decarboxylase inhibitor, has been shown to reduce facial hirsutism over a placebo after 8 weeks of use. Eflornithine, originally developed to treat trypanosomal sleeping sickness, is an irreversible inhibitor of L-ornithine decarboxylase. This enzyme is responsible for transforming ornithine into putrescine, a vital polyamine involved in governing cell growth and differentiation within the hair follicle. Continuous application of eflornithine cream to the face reversibly decreases facial hair growth in up to 70% of patients treated. However, eflornithine is not approved for the treatment of unwanted terminal hair in areas other than the face, and its cost is relatively high. The issue that precludes the use of eflornithine cream in wider skin areas is the possibility of undesirable effects in the case of significant systemic absorption [20, 21].

Anti-androgen

Antiandrogens inhibit the intracellular androgen receptors, thus avoids androgen cellular action. Cyproterone acetate (CPA), chlormadinone acetate (CMA), and dienogest are potent, orally active progestIns, which have antiandrogenic instead of partial androgenic activity. The mechanism of action is by inhibiting androgen receptors in target organs and also helps in lowering the activity of skin 5α-reductase, the enzyme needed for converting testosterone to the more potent androgen. CMA and CPA repress the secretion of gonadotropin and thus reduce ovarian and adrenal androgen production. CPA has steroidal adverse effects, that can lead to liver function abnormalities, and to frequent menstrual irregularity [22].

Dienogest is a combination of progesterone and 19-nortestosterone based progestogens. CMA and CPA show high affinity to progesterone receptor, and it is one-third higher than progesterone itself [23].

Spironolactone, a competitive inhibitor of 5-alpha reductase and androgen receptors, has been demonstrated to be effective in the treatment of hirsutism. In women of reproductive age, reliable contraception should be used before starting antiandrogen medication. Spironolactone is often used to treat hirsutism in doses ranging from 100 mg to 200 mg per day. The potential adverse effect includes polyuria, postural hypotension, irregular cycle, hyperkalemia, and liver issues, etc. Spironolactone has been proven in animal studies to be tumorigenic; however, this has not been demonstrated in humans [24].

Oral contraceptives pills (OCP)

In cases of ovarian hyperandrogenism and idiopathic hirsutism, oral contraceptives are typically the first line of defense. Oral contraceptives also improve in enhancing anti hirsutism benefits and preventing the negative effects of spironolactone and other antiandrogen-therapy-induced menstrual period irregularities. The combinations of estrogen and progestin in OCP are widely regarded as safe and cost-effective.

Insulin sensitizing agent

Insulin sensitizing agents are rosiglitazone, metformin and pioglitazone. They are widely accessible standard drugs for the treatment of noninsulin-dependent diabetic mellitus. While they lower blood sugar levels in diabetics, they do not affect nondiabetic patients. Insulin-sensitizing drugs increase insulin action by improving insulin sensitivity and lowering hyperinsulinemia. Metformin reduces hepatic glucose synthesis and insulin levels while improving insulin sensitivity, with an elimination half-life of roughly 6 hours. By reducing hyperinsulinemia, metformin reduces adrenal and ovarian androgen. Medical treatment of hirsutism biosynthesis and improve gonadotropin secretion [25, 26].

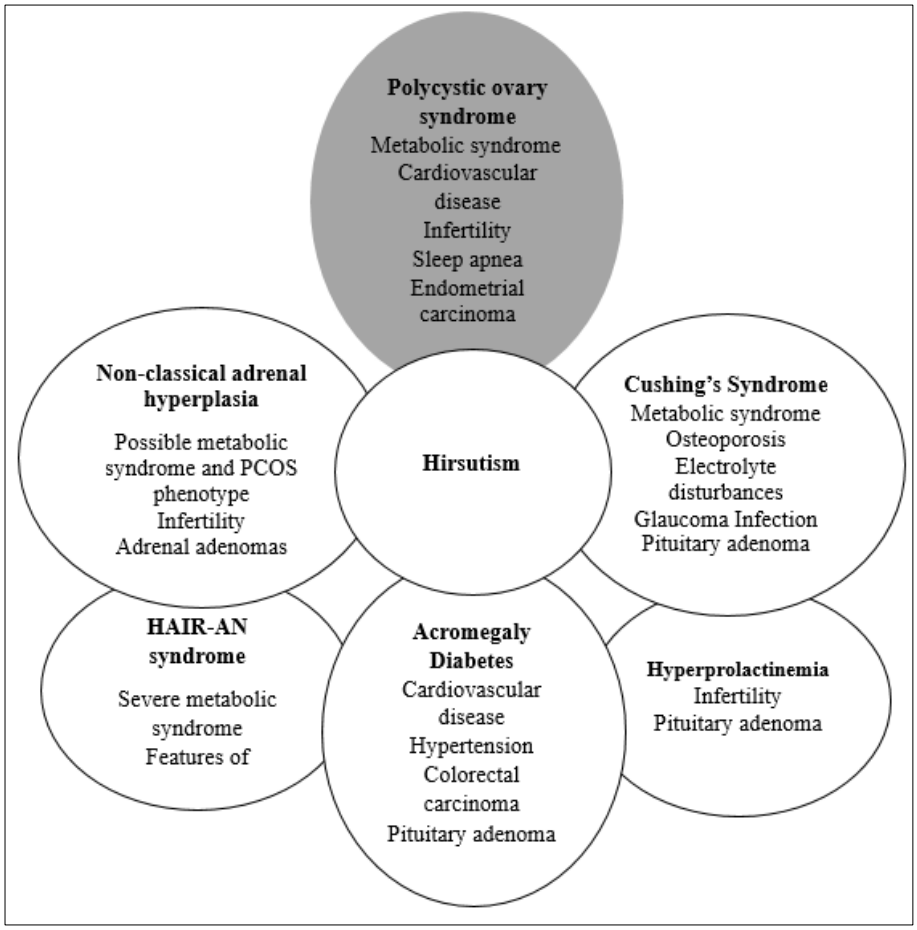

Fig 1: Co-morbidities associated with hirsutism.

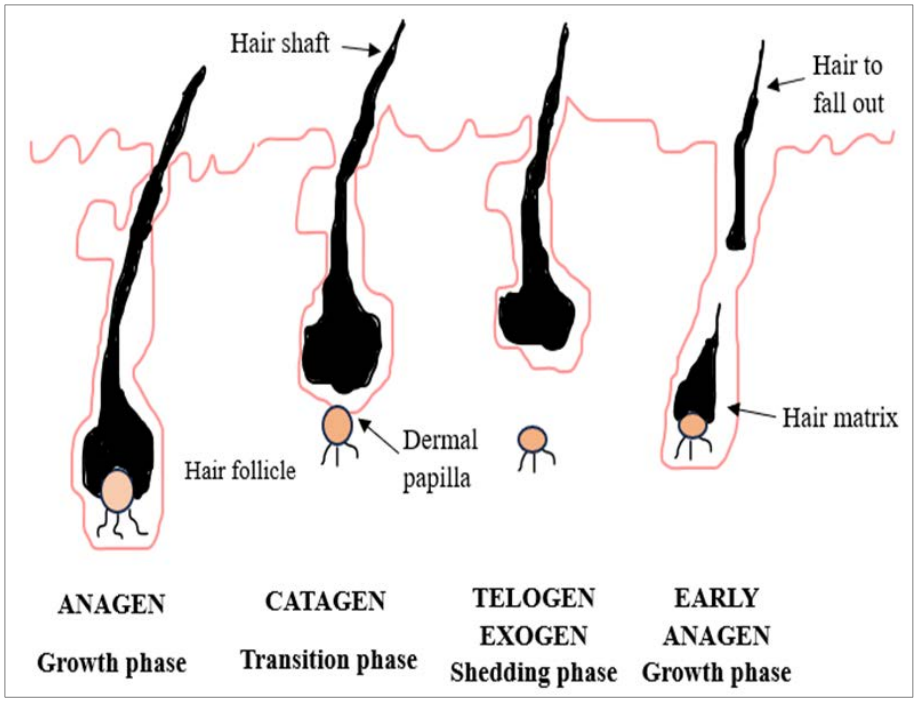

Fig 2: hair growth cycle

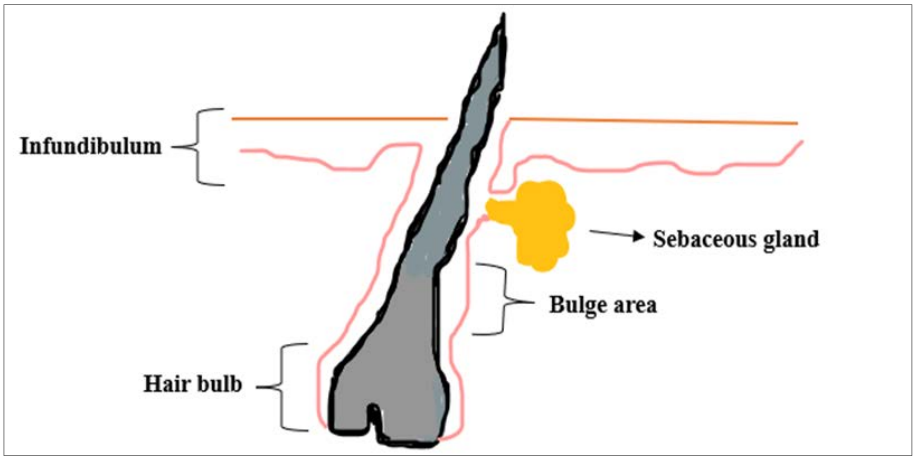

Fig 3: Follicular targeting aims to selectively bring active compounds into human follicles

Follicular targeting

The human hair follicle serves as a vital reservoir, an entrance point for topically applied substances, and a major contributor to the transportation of medication onto the skin. As evidence of this, consider that compared to hairless skin, hairy skin has significantly better corticosteroid penetration [27, 28] Several studies have shown the benefits of the trans follicular route on porcine ear skin [29, 30]. Furthermore, nanoparticles were still detectable in the hair follicles after 10 days, whereas nanoparticles in the stratum corneum reservoir were only retained for a single day. These findings suggest that hair follicles may be a useful method for long-term drug release [31]. Depending upon the structure of human hair follicles, three major follicular targeting methods are possible. Fig no 3

The follicular infundibulum: The stratum corneum, which covers the acro infundibulum of the hair follicle, remains intact and somewhat impermeable, but it is interrupted in the lower follicular infundibulum when the differentiation pattern changes from epidermal to trichilemmal. The remaining corneocytes are few to poorly differentiated, and the epidermis needs to be regarded as very permeable. The follicular epithelium's enhanced permeability makes epithelial cells and related cell populations such as mast cells, antigen-presenting cells, and others easily accessible for topically applied substances.

The sebaceous gland: The sebaceous duct, which enters the follicular duct at the lower infundibulum, connects the sebaceous gland to the human hair follicle there is evidence that substances administered topically and encapsulated in liposomes build up in the sebaceous gland as well as the hair follicle. The penetration of the antiandrogen RU 58841 in both scarred hairless skin lacking sebaceous glands and normal hairless rat skin was investigated by Bernard *et al*. According to Bernard *et al*. (1997), they discovered that the solution was primarily located in the stratum corneum, while liposome-entrapped RU 58841 was primarily found in the sebaceous glands. These results imply that follicular targeting might be a useful strategy for treating topical acne [32].

The bulge region in the outer root sheath, at the insertion level of the M. arrector pili, is a reservoir of epithelial stem cells that can regenerate both the interfollicular epidermis and the hair follicle [33]. Hair loss, hair overgrowth, and skin problems may all be treated by the therapeutic manipulation of stem cells. Treatment options for pigmentation disorders are further enhanced by the recent location of melanocyte stem cells in this lower region of the permanent hair follicle [34]. Gene therapy strategies are particularly interesting in the bulge region. Hair follicles are easily accessible, and liposomes loaded with DNA have been shown to target hair follicles *in vitro* by Li *et al*. (1993) [35]. Building on these discoveries, Domashenko *et al*. (2000) [36] used a xenograft model to successfully deliver plasmid DNA encoding for the lacZ reporter gene into human hair follicles. Genes can be inserted into follicular stem cells to create a wide range of new therapy options for skin and hair disorders [36].

The mechanism of hair follicle-targeting drug delivery

Due to the complex anatomy of hair follicles, the precise mechanism of drug transport through hair follicles is still unknown. Generally, when the medication is encapsulated in a particulate carrier, the transepidermal transport usually decreases because the particles penetrate and highly deposit in the orifice of hair follicles [37]. The hair follicle delivery is dependent on many factors involving the physicochemical characteristics of drug molecules, such as the oil-water partition coefficient, molecular weight, and size, as well as those of carriers, such as particle size, lipophilicity, and surface charge [38, 39]. The range of 300-500 nm was determined to be the ideal particle size for deeply penetrating the hair follicle. On the other hand, larger particles mostly stayed on the skin's surface, whereas smaller particles mostly reached the deeper layers of the skin [40]. More over the effect of nanoparticles surface charge on hair follicle targeting was broadly studied but remains unclear. Recent research has shown that nanoparticles with lipophilic surface characteristics and negative surface charge can accumulate in large amounts within hair follicles [41].

Drug Carrier Systems

Hair follicles are the preferred penetration channels for some drug delivery systems. Compared to passing across the stratum corneum, they enter these shunts more quickly and hence present the chance to produce substantial local concentrations of the active ingredients inside the follicular tube. With the help of nano-technology therapeutic substances can be delivered to the pre-determined target sites of the hair follicle. Furthermore, microneedles can bypass the skin barrier and can introduce therapeutic

substances straight to the areas around the hair follicle, achieving accurate and fast mapping.

Liposomes

Liposomes are phospholipid-based self-assembled supramolecular structures, prepared using phospholipid and cholesterol. Tamoxifen (TAM) loaded liposomal gel was applied on adult female Laca mice to arrest hair growth. Study results showed that the animal groups treated with saline and placebo gel started to show hair growth on the 15th day and no hair growth was seen in the animal group treated with TAM gel, even after the termination of treatment. This shows that TAM gel penetrated preferentially into the follicle. Thus, liposomal formulations have drawn increasing attention as a follicular targeting [42].

Polymeric nanoparticles

Polymeric nanoparticles are solid particles in the nanometer range. It's the most promising technology to target follicles as they display good stability and effectively mask the intrinsic properties of encapsulated drugs. These characteristics facilitate the entrance of poorly soluble substances in sebum and make them available in hair follicles [43]. Rancan *et al*. proved that the capacity of Poly (D, L-lactide) nanoparticles (228 and 365 nm) synthesized using the original nanoprecipitation method to efficiently target the hair follicles and reach a maximal depth equivalent to the entry of the sebaceous gland [44].

Lipid nanoparticles

Lipid nanoparticles, such as nano lipid structure (NLC) and solid lipid nanoparticles (SLNs), are thought to be suitable drug delivery systems because of their low toxicity, biocompatibility, and degradability. Soliman Mohammadi-Samani (2019) [45]. researched the effect of particle size on skin penetration and follicular targeting. Nano-lipid structured carrier of antiandrogenic drug cyproterone acetate prepared. *In-vivo* follicular targeting was evaluated using Rhodamine-B as a fluorescent dye and it proved that a particle size of 300nm showed higher fluorescent intensity compared to 100nm and the average size of 600 resulted in no fluorescent emission [45].

Conclusion

Recent advancements in follicular drug delivery formulations have demonstrated significant improvements in overall performance. These advancements enhance drug efficacy by facilitating more efficient delivery to the skin and hair follicles while reducing undesirable side effects when compared to traditional formulations. Due to the unique characteristics of hair follicles, these formulations allow for the sustained and controlled release of drugs trapped within the follicles. This approach not only promotes better patient compliance but also enhances treatment efficiency.

In recent years, the potential of using hair follicles as a pathway for addressing hair follicle-related conditions such as hirsutism, hair loss, and acne vulgaris has gained recognition. So far and overall, hair follicle-targeting drug delivery represents a promising concept in future.

References

1. Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. American journal of obstetrics and gynecology. 1981 Aug 1;140(7):815-30.
2. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1105-20.
3. Tehrani FR, Rashidi H, Azizi F. The prevalence of idiopathic hirsutism and polycystic ovary syndrome in the Tehran Lipid and Glucose Study. Reproductive biology and endocrinology. 2011 Dec;9:1-8.
4. Rosenfield RL. Polycystic ovary syndrome and insulin-resistant hyperinsulinemia. Journal of the American academy of Dermatology. 2001 Sep 1;45(3):95-104.
5. Jiang M, Aittomäki K, Nilsson C, Pakarinen P, Iitiä A, Torresani T, et al. The frequency of an inactivating point mutation (566C→ T) of the human follicle-stimulating hormone receptor gene in four populations using allele-specific hybridization and time-resolved fluorometry. The Journal of Clinical Endocrinology & Metabolism. 1998 Dec 1;83(12):4338-43.
6. Amiri M, Mahmoudieh L, Sheidaei A, Ramezani Tehrani F. Idiopathic hirsutism and dyslipidemia: A systematic review, meta-analysis, and meta-regressions. Journal of Cosmetic Dermatology. 2023 May;22(5):1449-62.
7. Gupta MSD, Toppo M, Priya A, Sethia S, Gupta P. A cross sectional study of polycystic ovarian syndrome among young women in Bhopal, Central India. Int. J Community Med Public Health. 2018;5:95-100.5.
8. Joshi B, Mukherjee S, Patil A, Purandare A, Chauhan S, Vaidya R. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Indian J Endocrinol Metab. 2014;18:317-24.
9. Somani N, Turvy D. Hirsutism: an evidence-based treatment update. American journal of clinical dermatology. 2014 Jul;15:247-66.
10. Azziz R. The evaluation and management of hirsutism. Obstetrics & Gynecology. 2003 May 1;101(5):995-1007.
11. Castelo-Branco C, Jesus Cancelo M. Comprehensive clinical management of hirsutism. Gynecological Endocrinology. 2010 Jul 1;26(7):484-93.
12. Oláh KS. The modern management of hirsutism. Reviews in Gynaecological practice. 2004 Dec 1;4(4):211-20.
13. Gu Y, Bian Q, Zhou Y, Huang Q, Gao J. Hair follicle-targeting drug delivery strategies for the management of hair follicle-associated disorders. Asian Journal of Pharmaceutical Sciences; c2022 May.
14. Meidan VM, Bonner MC, Michniak BB. Transfollicular drug delivery-is it a reality? International journal of pharmaceutics. 2005 Dec 8;306(1-2):1-4.
15. Hordinsky M. Advances in hair diseases. Adv Dermatol. 2008;24:245-59.
16. Krause K, Foitzik K. Biology of the hair follicle: the basics. InSeminars in cutaneous medicine and surgery 2006 Mar 1 (Vol. 25, No. 1, pp. 2-10). Philadelphia, PA: WB Saunders Co; c1996.
17. Bode D, Seehusen DA, Baird D. Hirsutism in women. American family physician. 2012 Feb 15;85(4):373-80.

18. Kini S, Ramalingam M. Hirsutism. Obstetrics, Gynaecology & Reproductive Medicine. 2018 May 1;28(5):129-35.
19. Balfour JA, McClellan K. Topical eflornithine. American journal of clinical dermatology. 2001 Jun;2:197-201.
20. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Human reproduction update. 2012 Mar 1;18(2):146-70.
21. Blume-Peytavi U, Hahn S. Medical treatment of hirsutism. Dermatologic therapy. 2008 Sep;21(5):329-39.
22. Raudrant D, Rabe T. Progestogens with antiandrogenic properties. Drugs. 2003;63:463-492.
23. Tewary S, Davies R, Prakash A. Hirsutism. Obstetrics, Gynaecology & Reproductive Medicine. 2021 Apr 1;31(4):103-8.
24. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1105-20.
25. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. The Cochrane database of systematic reviews. 2003 Jan 1(3):CD003053.
26. Cosma M, Swiglo BA, Flynn DN, Kurtz DM, La Bella ML, Mullan RJ. Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1135-42.
27. Hueber F, Besnard M, Schaefer H, Wepierre J. Percutaneous absorption of estradiol and progesterone in normal and appendage-free skin of the hairless rat: lack of importance of nutritional blood flow. Skin Pharmacology and Physiology. 1994 Mar 31;7(5):245-56.
28. Tenjarla SN, Kasina R, Puranajoti P, Omar MS, Harris WT. Synthesis and evaluation of N-acetylprolinate esters-novel skin penetration enhancers. International journal of pharmaceutics. 1999 Dec 10;192(2):147-58.
29. Klein AL, Lubda M, Skov PS, Vogt A, Keck CM. Investigation of transfollicular caffeine penetration using microdialysis on ex vivo porcine ear skin. European Journal of Pharmaceutics and Biopharmaceutics. 2020 Dec 1;157:1-8.
30. Subongkot T, Sirirak T. Development and skin penetration pathway evaluation of microemulsions for enhancing the dermal delivery of celecoxib. Colloids and Surfaces B: Biointerfaces. 2020 Sep 1;193:111103.
31. Lademann J, Richter H, Schaefer UF, Blume-Peytavi U, Teichmann A. Hair follicles-a long-term reservoir for drug delivery. Skin pharmacology and physiology. 2006 Jul 14;19(4):232-6.
32. Bernard E, Dubois JL, Wepierre J. Importance of sebaceous glands in cutaneous penetration of an antiandrogen: target effect of liposomes. Journal of pharmaceutical sciences. 1997 May;86(5):573-8.
33. Taylor G, Lehrer MS, Jensen PJ, Sun TT, Lavker RM. Involvement of follicular stem cells in forming not only the follicle but also the epidermis. Cell. 2000 Aug 18;102(4):451-61.
34. Nishimura EK, Jordan SA, Oshima H, Yoshida H, Osawa M. Dominant role of the niche in melanocyte stem-cell fate determination. Nature. 2002 Apr 25;416(6883):854-60.
35. Li L, Hoffman RM, Lishko V. Liposome targeting of high molecular weight DNA to the hair follicles of histocultured skin: a model for gene therapy of the hair growth processes. *In vitro* Cellular & Developmental Biology. Animal. 1993 Apr 1:258-60.
36. Domashenko A, Gupta S, Cotsarelis G. Efficient delivery of transgenes to human hair follicle progenitor cells using topical lipoplex. Nature biotechnology. 2000 Apr;18(4):420-3.
37. Vora LK, Donnelly RF, Larrañeta E, González-Vázquez P, Thakur RR, Vavia PR. Novel bilayer dissolving microneedle arrays with concentrated PLGA nano-microparticles for targeted intradermal delivery: Proof of concept. Journal of Controlled Release. 2017 Nov 10;265:93-101.
38. Friedman N, Dagan A, Elia J, Merims S, Benny O. Physical properties of gold nanoparticles affect skin penetration via hair follicles. Nanomedicine: Nanotechnology, Biology and Medicine. 2021 Aug 1;36:102414.
39. Al Mahrooqi JH, Khutoryanskiy VV, Williams AC. Thiolated and PEGylated silica nanoparticle delivery to hair follicles. International Journal of Pharmaceutics. 2021 Jan 25;593:120130.
40. Cuggino JC, Blanco ER, Gugliotta LM, Igarzabal CI, Calderón M. Crossing biological barriers with nanogels to improve drug delivery performance. Journal of Controlled Release. 2019 Aug 10;307:221-46.
41. Raber AS, Mittal A, Schäfer J, Bakowsky U. Quantification of nanoparticle uptake into hair follicles in pig ear and human forearm. Journal of Controlled Release. 2014 Apr 10;179:25-32.
42. Bhatia, B, Singh, B, Amarji OP, Katare, Tamoxifen-loaded liposomal topical formulation arrests hair growth in mice, British Journal of Dermatology. 2010 Aug;163(2):412-415. https://DOI.org/10.1111/j.1365-2133.2010.09772.x
43. Guterres SS, Alves MP, Pohlmann AR. Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications. Drug target insights. 2007 Jan;2:117739280700200002.
44. Rancan F, Papakostas D, Hadam S, Hackbarth S. Investigation of polylactic acid (PLA) nanoparticles as drug delivery systems for local dermatotherapy. Pharmaceutical research. 2009 Aug;26:2027-36.
45. Ghasemiyeh P, Azadi A, Daneshamouz S, Heidari R, Azarpira N, Mohammadi-Samani S. Cyproterone acetate-loaded nanostructured lipid carriers: effect of particle size on skin penetration and follicular targeting. Pharmaceutical development and technology. 2019 Aug 9;24(7):812-23.