Pharmaceutical Sciences, 2024, 30(1), x-x
doi:10.34172/PS.2023.24
https://ps.tbzmed.ac.ir/

Review Article

Targeting Pharmacological and Nanotechnology Based Therapeutics for Management of Hirsutism: A Comprehensive State-of-the-Art

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Article Info

Article History:
Received: 31 Jul 2023
Accepted: 30 Oct 2023
ePublished: 13 Dec 2023

Keywords:
-Androgens
-Cerosomes
-Hirsutism
-Liposomes
-Nanostructured Lipid Carriers
-Solid Lipid Nanoparticles

Abstract

Hirsutism is characterized by the excessive growth of coarse hair in women, resembling the typical pattern seen in men. It affects between 5 to 10 % of females of reproductive age. Excessive hair growth often leads to significant mental and emotional anguish. Hirsutism is the result of an overabundance of androgens being secreted by the ovaries or adrenal glands. This article offers a comprehensive review of numerous causes that might provoke hirsutism which includes polycystic ovarian syndrome, Cushing syndrome, idiopathic hirsutism, insulin resistance, congenital adrenal hyperplasia, ovarian or adrenal tumors, menopause, and the use of certain drugs. Polycystic ovary syndrome and ovarian tumors are frequent underlying factors of hyperandrogenism, which subsequently results in the development of Hirsutism. Mechanical and cosmetic hair removal methods are viable options for managing hirsutism. This study examines the pharmacological therapies that have proven essential in enhancing the quality of life for patients. These treatments include oral contraceptives, antiandrogen therapy like spironolactone, cyproterone acetate, flutamide, and finasteride, specific insulin-lowering medicines, gonadotrophin-releasing hormone agonists, and topical treatment such eflornithine hydrochloride cream (13.9% w/w cream). This review also explored significance of nanotechnology-based methods like nanostructured lipid carriers, solid lipid nanoparticles, liposomes, cerosomes, and nanogel in enhancing the effectiveness of medications used to treat hirsutism. A comprehensive update has been made to the latest information on clinical studies and patents linked to the treatment of hirsutism.

Introduction

Hirsutism is a medical disorder characterized by excessive and quick hair growth in females, particularly on the face or body, following a pattern often seen in men. Hirsutism is defined as the development of thick, dark hair that might come into sight on the face, chest, abdomen, back, upper arms, or legs. Approximately 5 to 10% of females in the wide-ranging population who are of reproductive age are thought to have hirsutism, a medical disorder associated with androgen hormones.[1-4] This syndrome is seen in several areas of the body where hair follicles are especially susceptible to the impacts of androgens. Hirsutism, a condition characterized by excessive hair growth, affects around seven percent of females in the United States and is projected to result in economic costs exceeding six hundred million dollars per year. Hirsutism in individuals causes significant emotional anguish, leading to negative impacts on their psychosocial development.[5,6]

Distinguishing it from virilization is important, as virilization is characterized by the simultaneous occurrence of hirsutism and a diverse array of symptoms including ambiguous external genitalia, enhanced muscle mass, baldness, deepening of the voice, acne, breast atrophy, irregular or absent menstrual periods, and increased sexual desire, which can vary depending on age. The clinical presentation of various symptoms and indicators may vary based on patient's age. Hypertrichosis and hirsutism are distinct conditions. Hypertrichosis is a condition characterized by abnormal hair growth that deviates from the normal patterns for an individual's age, sex, or race, and occurs in specific areas of the body.[7] The causes of hypertrichosis aren't well understood, although the genetic abnormalities are considered as major cause of hypertrichosis. Congenital hypertrichosis is believed to be transmitted by genetic inheritance and spontaneous mutagenesis. The primary form of congenital

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hypertrichosis is called as congenital hypertrichosis lanuginose. This disorder is characterized by an abnormal increase in the growth of a specific type of hair called lanugo hair. Lanugo hair is delicate, fine in texture, and lacks pigmentation.[8] Another form of this disorder, known as congenital hypertrichosis terminalis, is characterized by excessive growth of fully pigmented, long, and thick hair that covers a significant portion of the body.[9] Naevoid hypertrichosis is another manifestation of congenital hypertrichosis, which involves localized excessive growth of terminal hair in specific areas like as the eyebrows or birthmarks like congenital melanocytic nevus or mole.[10,11] Additionally, some cancer patients may develop a type of hypertrichosis called acquired hypertrichosis. Other variations of hypertrichosis may also manifest in people, such as generalized acquired hypertrichosis. This condition can arise as a consequence of factors including starvation, anorexia nervosa, hypothyroidism, cancer, certain medications (e.g., phenytoin, cyclosporine), and porphyria cutanea tarda. Repeated friction or scratching may also serve as a triggering element for the development of localized acquired hypertrichosis[12-14] The excessive hair presence is a characteristic feature of all types of hypertrichosis. Hypertrichosis is characterized by the presence of abnormally long hair, which may manifest in many types namely lanugo, vellus, or terminal hair. Hypertrichosis is a condition where hair grows in specific patterns, while generalised hypertrichosis refers to excessive hair growth all over the body.[15] Hirsutism, on the other hand, is primarily caused by polycystic ovary syndrome (PCOS), which leads to the overproduction of androgens by the ovaries. The prevalence of hirsutism is high; nevertheless, it often improves with medical intervention.[16]

Pathophysiology of Hirsutism

Hirsutism is a medical condition in which females have abnormal and uncontrolled hair development. The pathophysiology of hirsutism involves imbalance in androgen hormones, such as testosterone, which leads to the development of male-pattern hair growth in females. The human body is adorned with three distinct types of hair. Firstly, there is the lanugo, a fine hair that surrounds the fetus's skin but vanishes soon after birth. Secondly, there is vellus hair, which is a non-pigmented, soft hair with a diameter of less than 0.3 mm. Vellus hair covers greater part of body in both men and women. Lastly, there is terminal hair, which is coarser, pigmented, and longer. The expression of terminal hair differs between males and females.[17] The hair follicle, a highly intricate and dynamic structure, consists of various components and is responsible for the growth of hair. Hair growth follows periodic development cycle which consists of three main phases. The anagen phase is marked by rapid growth, followed by the telogen phase characterized by period of relative inactivity, and catagen phase characterized by regression through apoptosis.[18,19] Extended anagen stage, leading to conversion of vellus hairs into the terminal hairs which takes place due to influence of androgens, which are responsible for beginning and regulating the growth of sexual hair and also contribute to the development of hirsutism. Testosterone and dihydrotestosterone (DHT) are androgens that play a role in regulating hair follicles throughout the body.[20] The skin regions over face, lower belly, lower back, chest, and upper thighs are predominantly responsive to effects of androgens, while pubic and auxillary hair is less sensitive to these hormones. Elevated levels of androgens during puberty result in the conversion of vellus follicles in sex-specific areas into terminal follicles, consequential in increase in size as well as diameter of the hair follicle, with prolonged length of anagen phase. Thyroid and growth hormone execute crucial part in hair development, and a lack of these hormones may affect the different phases of hair growth. Women typically do not have hair growth in areas sensitive to androgens. The presence of such hair growth is a significant concern.[21] These androgens can be produced either through a synthetic pathway that begins with cholesterol, or through a shortcut pathway that starts with circulating DHEA-S. The cutaneous testosterone is derived either from release of hormones from the adrenal glands and ovaries into the bloodstream, or it can be produced locally in hair follicles. These hair follicles have all the essential enzymes for the production and breakdown of androgens.[22] The enzyme called 5α-reductase plays fundamental function in catalyzing the production of the majority of locally produced DHT. The existence of a local reservoir in the hair follicle prevents the use of circulating androgen levels in circulation to accurately measure the actual exposure of the hair follicle to androgens. Moreover, effects of androgens on the skin are influenced by the presence and function of androgen receptor in the specific area.[23-25] The diagram illustrating the underlying mechanisms causing hirsutism is shown in Figure 1.

Etiology of Hirsutism

Hirsutism is a sign of enhanced secretion of androgens like testosterone in females. PCOS and ovarian tumours are predominant aetiologies of hyperandrogenism arising in the ovary. Adrenal causes like androgen-producing tumours, Cushing's disease, and congenital adrenal hyperplasia are often caused by a deficit in 21-hydroxylase.[26-29] Hirsutism may be induced by hyperprolactinemia which stimulates adrenal glands to produce more dehydroepiandrosterone sulphate (DHEA-S) under specific situations.[30] Hirsutism is mostly caused by the use of androgenic medicines such as oral contraceptives, anabolic steroids, methyldopa, danazol, metoclopramide, and phenothiazines.[26] Idiopathic hirsutism may occur in around 20% of people, even in cases when their ovarian function and androgen amounts are within the normal range. The excessive development of facial hair in these females is believed to be a result of abnormalities in the functioning of peripheral androgens. Idiopathic hirsutism often starts after the beginning of puberty and progresses gradually. Idiopathic hirsutism

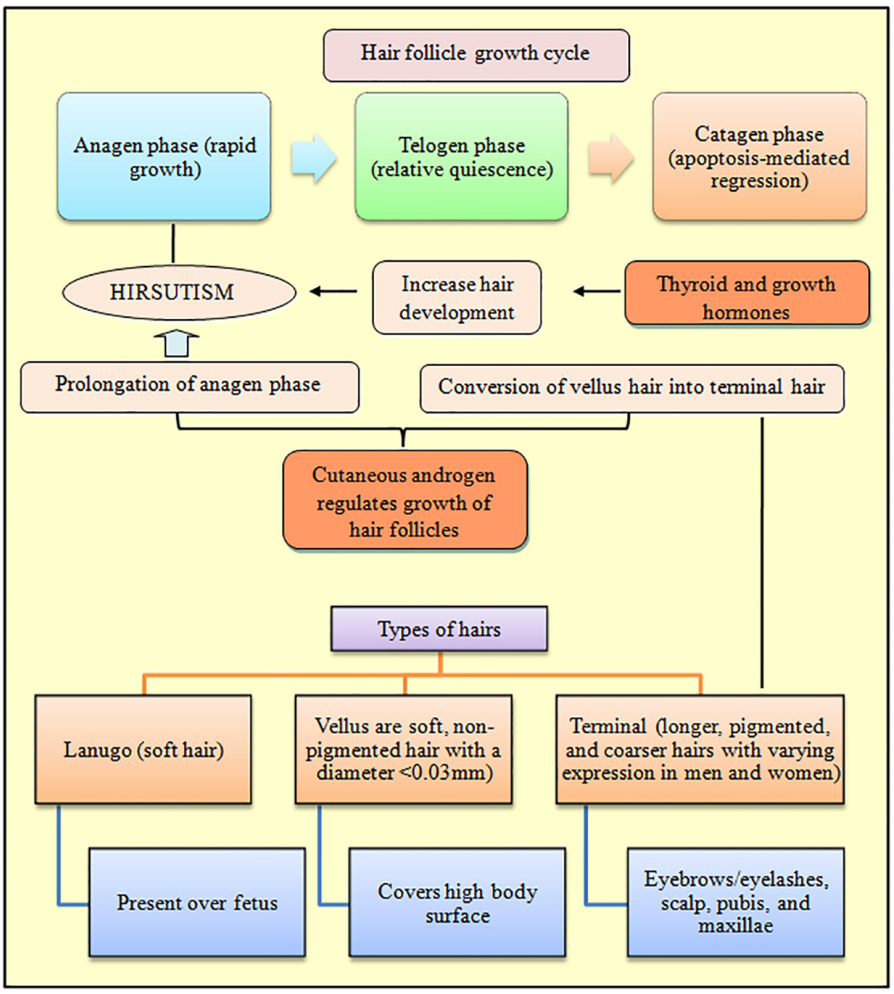

Figure 1. Pathophysiology of hirsutism.

and polycystic ovary syndrome (PCOS) account for 90% of all instances of increased hair development in females. Hirsutism, a condition characterised by increased hair growth, may occur in some females before menopause and continue for extended period after menopause. The cause of this is a reduction in the production of oestrogen by the ovary, accompanied by an increase in the synthesis of androgens. Hirsutism is characterized by the development of terminal hair on a woman's body in a typically masculine pattern. Figure 2 illustrates the several elements that may lead to the development of hirsutism.[31-33]

Polycystic ovarian syndrome

Polycystic ovarian syndrome is a complex condition of the endocrine and metabolic systems and impacts around 5 to 10 percent of the population and is the primary reason of hirsutism, responsible for 72 to 82 percent of cases of the disease. PCOS is characterized by the occurrence of minimum of two out of the following three symptoms: (i) menstrual disruption, (ii) clinical or biochemical evidence of hyperandrogenemia, and (iii) ultrasonographic evidence of polycystic ovaries.[34,35] PCOS is typically characterized by consistently elevated levels of gonadotropin-releasing hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) which causes increased androgen production and ovulatory dysfunction. The development of a number of follicles in ovaries that resemble cysts is a defining characteristic of PCOS. These nodules are actually embryonic ovarian follicles that failed to mature and ovulate normally. PCOS is marked by several symptoms, including obesity, insulin resistance, and infertility. Insulin resistance and hyperinsulinemia are two conditions that induce adrenal glands and follicles to generate more androgens.[36-38]

Cushing syndrome

This endocrine disorder is severe and uncommon which is characterized as sustained elevated cortisol production. The primary origin of endogenous cushing's syndrome is development of pituitary adenoma that produces adrenocorticotropic hormone.[39] Patients with Cushing syndrome may experience hirsutism, but this is not a defining characteristic of disorder. In female patients, Cushing syndrome is characterized by obesity, reddened and moon-shaped face, muscular frailty, diabetes, and irregular menstruation. The women receiving long-term steroid therapy have higher risk of Cushing syndrome.[40]

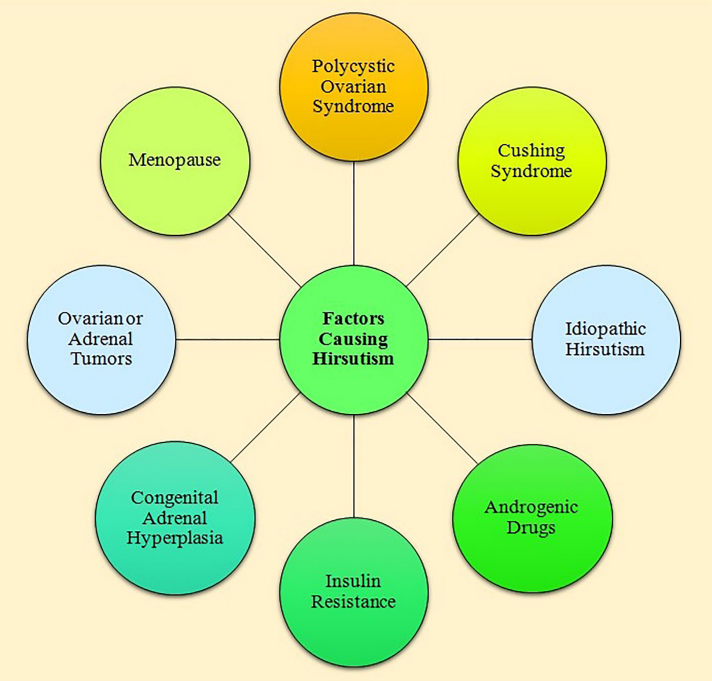

Figure 2. Triggering factors contributing to hirsutism.

Idiopathic hirsutism

Idiopathic hirsutism is well recognized as one of the prevailing forms of hirsutism. The primary causes of this condition include abnormalities in the production of adrenal steroid hormones, heightened 5α-reductase activity, and variations in androgen receptor genes that result in greater sensitivity of androgen receptor. Idiopathic hirsutism affects approximately fifty percent of all women with moderate hirsutism. Idiopathic hirsutism is characterized by normal serum androgen levels, the absence of menstrual disturbances, and the absence of any identifiable hirsutism cause in the patient.[32] Elevated levels of androgen in blood and a decreased estradiol/testosterone ratio are seen in women having idiopathic hirsutism due to the stimulation of aromatase enzyme. Idiopathic hirsutism is linked with insulin resistance, and the incidence of poor glucose tolerance is more prevalent in obese individuals.[41,42]

Insulin resistance

Insulin's indirect and direct effect on elevated levels of serum androgen in PCOS is the stimulation of steroid hormone production in theca and granulosa cells. Hyperinsulinemia in PCOS, caused by insulin resistance stimulates increased androgen secretion in the ovaries.[43] Insulin provides an additional stimulus for the secretion of androgens by activating theca cells. Insulin decreases the secretion of sex hormone-binding globulin in the liver which leads to rise in concentration of unbound active testosterone in the body. Hyperinsulinemia causes PCOS patients to have higher free testosterone levels than normal, although total testosterone levels may be modestly elevated.[44] Due to increase in androgen secretion within the ovaries, females with significant insulin resistance and hyperinsulinemia are more likely to develop hirsutism. This enhanced androgen synthesis in the ovaries may be substantially facilitated by insulin like growth factor-1 receptors which are expressed on the ovarian theca cells.[45]

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia is a collection of autosomal recessive disorders caused by the absence of one of the five enzymes required for cortisol biosynthesis in the adrenal cortex. The primary cause is lack of steroid 21-hydroxylase which accounts for nearly ninety percent of cases.[46] Cortisol deficiency can disrupts the feedback regulation mechanism which is responsible for regulating the hypophyseal levels in the hypothalamus. This defect increases the production of adrenocorticotropic hormone, resulting in adrenal hyperplasia.[47] Commonly diagnosed at birth or within the first year of life, these conditions are characterized by androgen excess, hirsutism, ambiguous genitalia, and cortisol deficit. The non-classical or late-onset form of this condition, which manifests in late infancy or early adulthood, is less severe. It is common for these women to develop hirsutism, and they may also experience primary amenorrhea or infertility. The non-classical form is typically caused by 21-hydroxylase deficiency which causes rise increase in androstenedione and 17-hydroxyprogesterone synthesis.[48,49]

Ovarian or adrenal tumors

In extremely uncommon instances, the ovaries or adrenal glands may become the site of a tumour that produces androgens. This tumour will produce extraordinarily high levels of androgen. In the majority of cases, hirsutism symptoms appear suddenly and progress rapidly. Extremely high levels of androgen can result in male-like traits such as increased muscular mass, a deeper voice, and baldness.[32,34]

Menopause

The menopause is the transition from the reproductive phase of a woman's existence to the postmenopausal phase, which occurs when the ovary ceases generating the sexual hormones estradiol and progesterone due to the depletion of all ovarian follicles.[50] When a woman reaches menopause, her ovaries cease producing oestrogen but continue producing androgens for the remainder of her life. Due to the decreased oestrogen levels, the produced androgens may cause an increment in the number of terminal hairs that are dark in color, especially on the face. A considerable percentage of postmenopausal females were distressed by the development of new facial hair, such as moustaches and sideburns, and modest receding.[51,52]

Side effects of few medications

Sometimes, the use of medicines with androgenic properties induces hirsutism. Certain bodybuilders and slender individuals use anabolic steroids, which are chemically similar to natural steroids, in order to acquire muscle mass. Other pharmaceuticals linked to increased hair growth include testosterone injections, moisturizers, patches, cyclosporine, progestins, glucocorticoids, danazol, diazoxide, phenytoin, cyclosporine, minoxidil, and diazoxide.[32] In addition to androstenedione and dehydroepiandrosterone, natural supplements such as androstenedione and dehydroepiandrosterone may also induce hirsutism.[53,54]

Management of Hirsutism

The term "hirsutism" refers to a clinical symptom as opposed to the disease itself. Therefore, the prevalence of this disease does not always necessitate treatment, particularly when it is in its mild-to-moderate forms and when a female who is affected by it is unconcerned about it. The objective of medicinal therapy for hirsutism is to limit the effects of androgens on the hair follicle itself, as well as to decrease the blood levels of unbound testosterone and total androgens. Patients should be encouraged to continue therapy for a minimum of six months, assuming the treatment is well tolerated, before declaring that any approach that has been attempted is ineffective. Because the hair development cycle takes longer periods, it is highly unlikely that any therapy will yield substantial improvements in the short term.[55,56] Hirsutism can be treated by suppressing the synthesis of androgens or diminishing androgens secretion. Additionally, mechanical hair removal is potential additional treatment option. The intensity of hirsutism score is related to many medical problems like as menstrual irregularities; systemic problems like as hypertension and diabetes mellitus. It may be difficult to treat both infertility and hirsutism at the same time.[57] Patients must be informed that the majority of hirsutism medications are contraindicated for women who are expectant or intending to become pregnant. The pregnant women have the option to undergo hair removal for cosmetic purposes. Obesity raises the levels of blood androgen and decreases the efficacy of medical therapy, so it is crucial to encourage overweight women to lose weight.[58]

Mechanical and cosmetic hair removal methods

There are numerous options for direct, impermanent hair removal. Shaving is a fast, risk-free, and effective procedure, but it must be performed on a regular basis. When hair grows back after shaving, it appears denser due to blunted, rather than tapered, tip.[59] Chemical depilation may be utilized to remove hair, however it may induce reactive dermatitis in some individuals.[60] Epilation techniques, such as plucking and waxing, may completely eradicate hairs by extracting them from the bulb. In addition to the irritation, additional adverse effects include folliculitis, scarring, and hyperpigmentation. Electrolysis, photoepilation, and laser epilation can be used to eradicate permanently the hair follicles responsible for proliferation of unwanted hair. Electrolysis, also known as electroepilation, is a method for permanently destroying hair, but it is an excruciating and tedious procedure since each hair follicle must be targeted separately.[31] In the last two decades, application of lasers for the eradication of undesired hair has become increasingly prevalent.[61] Considered to have a higher success rate than electrolysis, laser therapy also causes less discomfort and can be completed in less time. However, laser therapy is highly expensive. The primary goal of laser therapy for hair eradication is to deliberately induce thermal damage to hair follicles while avoiding harm to surrounding tissues through selective photothermolysis procedure. Photo and laser epilation are more effective on women with paler skin because lighter skin requires less energy per pulse. In general, the use of lasers as a method for the removal of undesired hair from hirsutism patients is a highly promising approach.[18,62]

Pharmacological treatments

To raise the quality of life for individuals with hirsutism, medical treatment aims to correct hormonal abnormalities. The mode of treatment depends on the underlying cause, extent and distribution of increased hair growth, the patient's inclinations, the availability and expense of currently available products. The pharmacological agents demonstrated their effects by inhibiting either the synthesis of endogenous androgens or their effects on the body.[63] Oral contraceptives that have an anti-androgenic effect are the first-line treatment for hirsutism in the majority of premenopausal females. If patient does not demonstrate clinical improvement, it is recommended that they receive oral contraceptives and antiandrogens as a combined therapy. It is recommended to maintain pharmacologic hirsutism treatment for six to nine months prior to modifying the dosage or drug class. In addition to reducing hirsutism in women with hyperandrogenism and insulin resistance, insulin sensitizers also reduce hirsutism. Except for topical application of eflornithine hydrochloride, other medications are taken orally.[64,65]

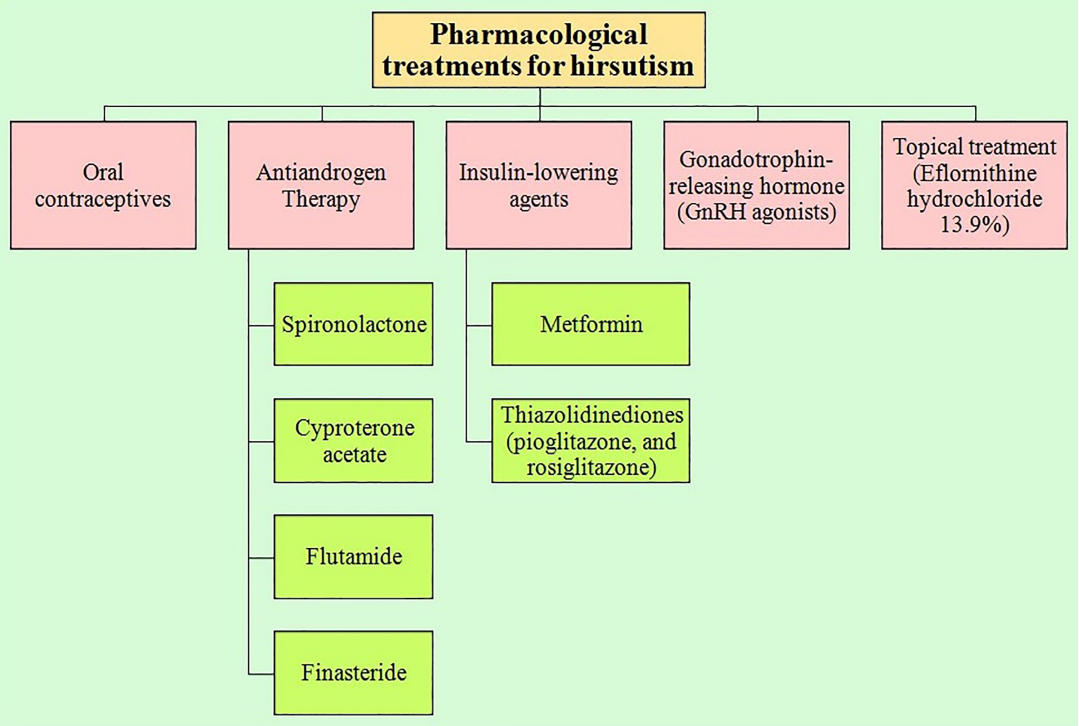

Figure 3. Medications available for hirsutism management.

Figure 3 depicts the numerous pharmacological remedies available for the treatment of hirsutism.

Oral contraceptives

Oral contraceptives are the therapy for hirsutism that is recommended to patients the most often. These medications function by decreasing the levels of LH and FSH in the body's circulation. This decreases the quantity of androgens generated by the ovaries.[63,64] The progestin in birth control medications has the potential to create an antagonistic relationship between 5α-reductase and the androgen receptor. Furthermore, the presence of estrogen in birth control pills causes increase in the sex hormone-binding globulin, which reduces the amount of free testosterone in the body. However, the progestin included in birth control pills may reduce sex hormone-binding globulin even more than the oestrogen does. The use of estrogen-containing tablets decreases the hair growth rate, regulates menstrual cycles, and prevents unintended pregnancies.[65,66]

Antiandrogen therapy

Anti-androgens are especially useful in treatment of idiopathic hirsutism or as an adjunctive therapy for androgen suppression, as they prevent androgens from exerting their effect on the target tissues. When treating moderate or severe hirsutism with combined oral contraceptive pill, the utilization of anti-androgens may increase the treatment's efficacy. In addition to this primary benefit, the combined oral contraceptive pill provides contraception for patients who are undergoing anti-androgen therapies that are effectively teratogenic.[67]

Spironolactone, cyproterone acetate, flutamide, and finasteride are the four antiandrogens that have been studied in randomized controlled trials and are frequently prescribed to hirsutism patients.[68]

Spironolactone, an aldosterone antagonist, has been demonstrated to inhibit androgen receptor competition in a dose-dependent manner. In addition, spironolactone inhibits the synthesis of ovarian androgens and has some progestational properties. It inhibits the 5α-reductase enzyme and competes with androgens to bind to sex hormone binding globulin.[69,70] Despite the severity of central hyperandrogenemia, spironolactone is a highly successful drug for reducing hirsutism. Initial dosing is 50 mg twice a day, and this dose may be enhanced to a maximum of 200 mg per day. Significant adverse effects of this drug include hyperkalemia, irregular menstruation, and teratogenicity.[71,72]

Cyproterone Acetate is widely recognized for its potent progestogenic and antiandrogenic effects. As an excellent therapy for hirsutism, it decreases the amount of LH circulating in the blood, which in turn reducesthe quantities of testosterone and androstenedione circulating in the blood.[73] It exerts its effects by inhibiting androgen receptor and 5α-reductase enzymes. The treatment of hirsutism with this medication is quite efficient. In the treatment of hirsutism, the combination of 50–100 mg of cyproterone acetate and 30–35 mg of ethinyl estradiol is as efficient as combination of 100 mg of spironolactone and oral contraceptives.[74]

Flutamide is a potent anti-androgen with a greater affinity for the androgen receptors located on hair follicle cells. It attaches to cellular receptors and hinders their capacity to

bind to naturally occurring androgens, thereby suppressing the development of hair triggered by androgens.[75] Flutamide is as effective as finasteride (5 mg/day) and spironolactone (100 mg/day) in treating of androgen-mediated hirsutism, according to a number of clinical trials. Despite the fact that these medications may be as effective as cyproterone acetate and spironolactone in treating the disease, they cannot be used to treat facial hirsutism. The therapeutic dose of flutamide for hirsutism is between 250 and 500 mg/day. It is possible to treat hirsutism effectively by initially administering a dose of 250 mg/day, followed by a maintenance dose of 125 mg/day over the long term.[67,76-78] Finasteride is a 5α-reductase inhibitor, and research indicates that it can reduce the severity of hirsutism by 30–60% while simultaneously decreasing the diameter of the hair shaft.[79] It has been demonstrated that 100 mg of spironolactone and 5 mg of finasteride are equally efficacious.[70] There is evidence that increasing the dose to 7.5 mg once daily may be more effective in treating hirsutism than the standard dose of 5 mg once daily. DHT is responsible for the growth of male external genitalia, the most significant adverse effect associated with the use of these medications is feminization of a male fetus.[80,81]

Insulin-lowering agents

Metformin and thiazolidinediones *i.e.* pioglitazone and rosiglitazone are insulin-sensitizing drugs used to treat type 2 diabetes mellitus. These drugs tends to increase insulin action by enhancing insulin sensitivity which results in the reduction of hyperinsulinemia.[82] Metformin increases insulin sensitivity while concurrently lowers the insulin levels and decreases the liver glucose production. Thiazolidinediones augment the effectiveness of insulin in adipose tissue, hepatocytes, and skeletal muscle. Thiazolidinediones and metformin have been shown to reduce hyperinsulinemia, which may reduce adrenal and androgen ovarian production, enhance sex hormone-binding globulin levels, and stimulate gonadotropin secretion. Insulin-sensitizing pharmaceuticals are able to reduce insulin levels, which in turn decreases the levels of circulating active androgens, thereby ameliorating hirsutism.[83,84]

Gonadotrophin-releasing hormone agonists (GnRH agonists)

GnRH agonists inhibit the synthesis of gonadotropins and ovarian androgens, leading to a reduction in hirsutism as well as a decline in estrogen levels.[85] Chronic administration of a GnRH agonist inhibits the production of LH and, to a lesser degree, FSH. This results in a reduction in ovarian function, which in turn decreases the quantity of androgen produced by the ovaries. They are frequently combined with low-dose oestrogen and progestin tablets to counteract estrogen deficiency's negative effects.[86-88]

Topical treatment

Eflornithine acts as an irreversible inhibitor of ornithine decarboxylase enzyme. This enzyme is responsible for catalyzing rate-limiting step in process of follicular polyamine production, which is crucial for hair growth.[89] Eflornithine hydrochloride cream in its topical formulation (13.9% w/w cream) has been granted approval for use for the management of undesirable facial hair in females in a number of different countries. Eflornithine does not eradicate hair, but rather reduces the rate of hair growth.[90-92]

Nanotherapeutic Approaches for Management of Hirsutism

Due to their progestogenic and antiandrogenic properties, hirsutism receives their treatment with a number of topical and oral medications with progestogenic and antiandrogenic properties, such as estrogen-progestin oral contraceptives, spironolactone, finasteride, and cyproterone acetate.[1,93,94] These conventional treatments may have some therapeutic efficacy, but they carry significant risks of therapeutic intolerance and dose-dependent adverse effects. Therefore, it is essential to provide patients with cutting-edge treatment strategies that can effectively mitigate associated side effects. Nanotechnology is currently at the vanguard of the swiftly evolving revolutionary diagnostic and therapeutic approaches in all medical disciplines.[95] Nanoparticles are acquiring importance in numerous fields, like as bioimaging, diagnostic technologies, and drug and gene delivery. In addition to enhancing the skin's ability to assimilate pharmaceuticals, nanoparticulate systems have potential to specifically target drugs to the skin and/or its underlying structures. The reduced particle size assures that nanocarriers come into direct contact with the stratum corneum, which may increase the bioavailability of medications that penetrate the epidermis when nanocarriers are utilized. The nanoparticles can come into intimate contact with the superficial junctions of stratum corneum which facilitate diffusion of drugs.[96-98] Figure 4 illustrates the structures of solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and cerosomes, and Table 1 describes their applications in drug delivery for the management of hirsutism.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are a form of colloidal carrier system consisting of a solid core composed of higher melting point solid lipids, which is enveloped by an aqueous surfactant coating. The solid lipid utilization as a matrix material for drug delivery is widely acknowledged, particularly in the case of lipid granules designed for oral drug delivery.[99,100] SLN's utilization of physiological lipids in the lipid matrix, resulting in a decreased risk of acute and chronic toxicity, is a significant benefit.[101,102] Utilizing solid lipid instead of liquid lipid is advantageous due to its ability to improve the modulation of the release kinetics of encapsulated substances and stability of chemically sensitive lipophilic constituents. Several physicochemical properties related to the physical condition of the lipid phase are responsible for these potential positive effects. These includes slow rate of drug diffusion within a solid

Table 1. Exploration of nanoparticles in drug delivery for management of Hirsutism.

Drug (Technique)	Excipients	Dosage Form	Outcome & Significance
Cyproterone acetate (Solvent diffusion evaporation method)	Stearic acid, Triolein, Cholesterol, Brij 35, Brij 72	Nanostructured lipid carriers (NLCs)	NLCs of intermediate size (around 300 nm) were ideal for targeting hair follicles in comparison to smaller or larger nanoparticles.[115]
Spironolactone (Ethanol injection method)	L-α phosphatidyl choline, Kolliphor RH40, Ceramide, Hyaluronic acid	Hyaluronic acid enriched cerosomes (HAECs)	*Ex-vivo* study revealed that HAECs improved the skin deposition and accumulation of Spironolactone in comparison to suspension.[116]
Finasteride (Free radical polymerization method)	Methylene bisacrylamide, Hydroxypropyl methylcellulose	Nanogel	*In-vitro* study indicated that the drug release was directly proportional to amount of HPMC present in the nanogel network. *Ex-vivo* permeation indicated that drug permeation across skin was increased with increasing HPMC content.[117]
Spironolactone (Probe ultra-sonication method)	NLCs- (Stearic acid, Oleic acid), SLNs- (Stearic acid)	NLCs and SLNs	*In-vitro* investigation has shown a significant 5.1- and 7.2-folds increase in drug release within two hours as compared to the raw drug.[118]
Cyproterone acetate	Phosphatidylcholine	Liposomes	The higher drug permeation was observed for liposomes having higher lipid content which manifested two-fold increase in drug permeation.[119]
Tamoxifen (Thin-film hydration technique)	Sorbitan monooleate, soy phosphatidylcholine	Liposomes	The animals treated with tamoxifen gel showed no hair growth even after treatment discontinuation.[120]
Cyproterone acetate (Thin film formation technique)	Cholesterol, Egg phosphatidylcholine	Liposomes	Liposomal possessed superior penetration capacity compared to conventional cyproterone acetate gel.[121]
Finasteride (Film hydration with sonication technique)	Phosphatidylcholine, Cholesterol	Liposomes	Liposomes exhibited 88.6% entrapment, higher skin permeation and 5-folds greater deposition of medication in the skin comparison to both the plain drug solution and conventional gel.[122]
Finasteride (Film hydration technique)	Egg lecithin, Cholesterol, Dimyristoyl phosphatidylcholine (DMPC), Sorbitan monopalmitate	Multilamellar vesicles (liposomes and niosomes)	*Ex-vivo* deposition study of drug vesicles showed that liquid-state vesicle prepared with DMPC or Brij 97:Brij 76 (1:1) deposited 2.1 or 2.3% of the applied dose in pilosebaceous unit which is higher than gel-state vesicles (0.35–0.51%).[123]

matrix in contrast to liquid matrix, mitigation of drug deposition over the surface of lipid particles and therefore, less chemical degradation reactions. Furthermore, it has been revealed that absorption of inadequately assimilated bioactive substances can be enhanced by their incorporation into SLNs. Multiple studies have demonstrated that replacing the liquid matrix with solid matrix can slow lipid digestion, resulting in a prolonged release of entrapped moiety.[103]

Nanostructured lipid carriers

The nanostructured lipid carriers consist of a disordered lipidic matrix containing a mixture of solid and liquid lipids, in addition to an aqueous phase containing a single or mixture of surfactants.[104] In contrast to emulsions, the solid matrix of the NLCs has the potential to effectively limit drug mobility and prevent particle coalescence. Furthermore, the movement of drug molecules that have been integrated is significantly limited in the solid state. Moreover, the presence of liquid oil particles within the solid matrix improves drug loading efficiency than SLNs. NLCs provide several benefits compared to polymeric nanoparticles, such as reduced toxicity, biodegradability, drug stability, regulated release, and avoidance of organic solvents in the manufacturing process.[105,106]

Liposomes

One or more concentric lipid bilayer encloses aqueous compartment within liposomes. The lipid membrane has the potential to entrap lipophilic agents, whereas the aqueous interior is more likely to trap hydrophilic agents. The dimension of these approximately spherical lipid vesicles can range between a few nanometers and several micrometers. The size range of liposomes used for medical purposes is typically between 50 and 450 nm.[107-109] Liposomes have advantageous biological properties such as biodegradability and biocompatibility. Due to their capability to enhance the efficiency of encapsulating agents

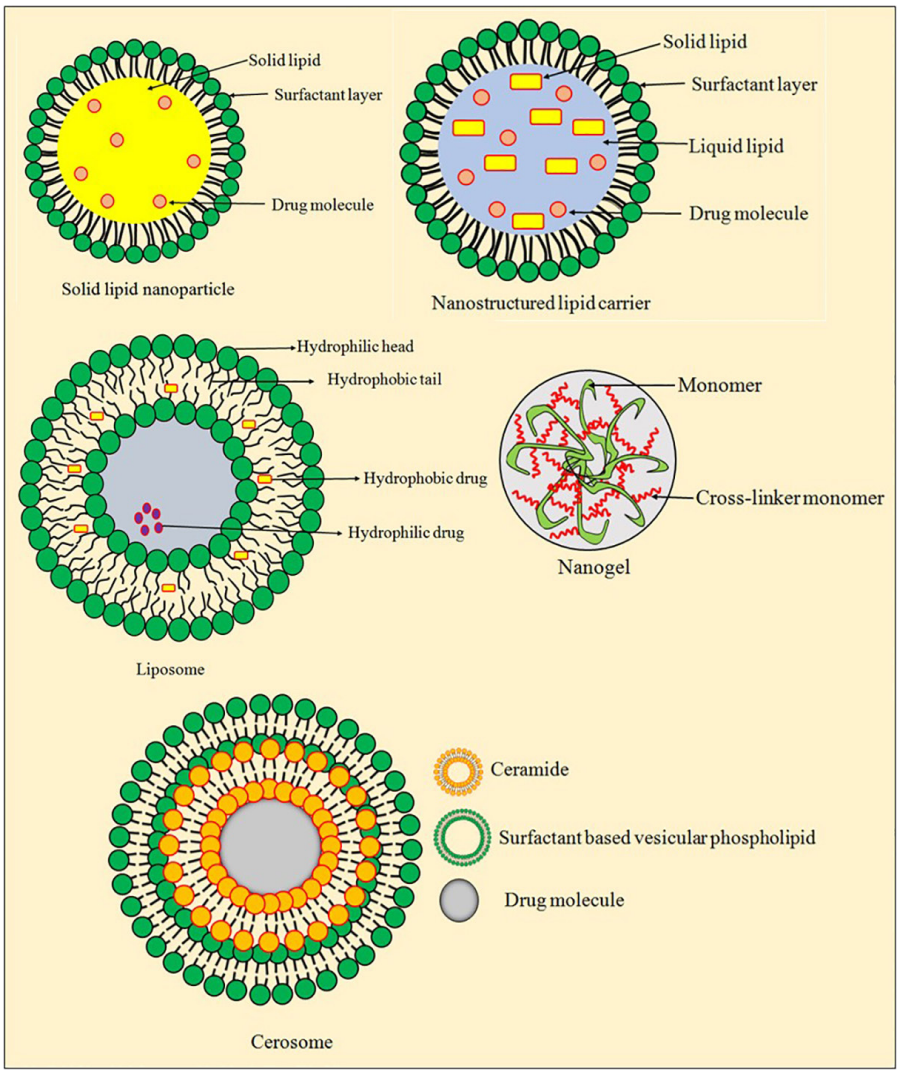

Figure 4. The outline of various types of nanocarriers used to encapsulate the drug molecules to overcome various challenges which restrict its effectiveness.

by enhancing drug stability and solubility, facilitating targeted delivery of encapsulated drugs, and assuring a continuous and controlled release of the drug, they have the potential to serve as dynamic carriers. Their sub-cellular dimensions facilitate relatively greater intracellular absorption compared to alternative particulate systems, thereby increasing the *in-vivo* bioavailability of the drug. Liposomes provide numerous advantages, including high encapsulation efficiency despite drug solubility, minimal toxicity due to phospholipid composition, and protection from degradation factors such as pH and radiation, and reduced tissue irritation.[110]

Cerosomes

Cerosomes are tubulated ceramide-enclosed vesicles generated with various surfactants and phospholipids, enabling pharmaceutical incorporation and dissolution of ceramide. They have a high level of drug bioavailability and exceptional skin tolerance and permeability when applied topically. The incorporation of surfactant into formulation facilitates the formation of extremely stable and aggregate-free double lipidic, phosphatidylcholine-ceramide mixture vesicles.[111]

Nanogel

Nanogels are a form of resilient nanoparticle composed of a hydrogel containing cross-linked hydrophilic polymer and having a particle size between 100 and 200 nm. In addition to their flexible dimension, large surface area, and high water content, nanogels are distinguished by their ability to enlarge and degrade. As a vehicle for the controlled and sustained discharge of various biologically active agents, including pharmaceuticals, nanogels have been utilized. Nanogels are distinguished by their three-dimensional structures, which allow for the entrapment of substances such as drugs, polymers, and liquid phase dispersion. Due to their distinctive chemical compositions and formulations, nanogels offer superior drug delivery mechanism in terms of efficacy and safety for hydrophilic and hydrophobic compounds.[112,113]

Patents and Clinical Trials

From 2022 to 2023, patents related to the treatment of hirsutism were explored on the official website of the World Intellectual Property Organization (WIPO) (Table 2). To address the challenges that currently exist in the field of hirsutism treatment, it is essential to conduct clinical research on novel drugs and drug combinations. Consequently, several clinical trials have been conducted in previous years. Therefore, the information in Table 3 was retrieved from the official website of clinical trials and pertains to the clinical trials which involves methods and compositions for treatment of hirsutism.[114]

Future Perspective

Approximately 19-41% of patients with hirsutism have been shown to benefit from medical treatment. Consequently, it is essential to conduct a thorough evaluation of the patient in order to determine the suitable method of treatment for both the underlying medical condition and the psychosocial characteristics of the individual. The pharmacological strategy for developing novel anti-androgenic pharmaceuticals mainly focuses on inhibiting 5α-reductase inhibitors enzyme. A wide range of such compounds have been synthesized which exhibited considerable efficiency with least side effects. 17-hydroxysteroid dehydrogenases (17-HSDs) enzyme

Table 2. Summary of patents literature related to hirsutism.

Patent number	Applicant	Publication date	Patent title and Reference
IN202111017454	Althea DRF Lifesciences Limited	24.02.2023	Composition for management of hirsutism.[124]
EP4135755	Henlez APS	22.02.2023	Compositions and methods for treating hair follicle-linked conditions.[125]
US20230021330	Varsona Therapeutics, Inc.	26.01.2023	Topical formulations of 5α-reductase inhibitors and uses thereof.[126]
IN202211005420	Chitkara Innovation Incubator Foundation	25.11.2022	A composition for hirsutism comprising solid lipid microparticles comprising 2,5-Diamino-2-(Difluoromethyl) Pentanoic acid.[127]
US20220362382	Dermaliq Therapeutics, Inc	17.11.2022	Topical composition comprising a prostaglandin analogue.[128]
CN114831901	Shaanxi Zhelian Biotechnology Co., Ltd.	02.08.2022	Application of Ursolic acid and derivatives thereof in preparation of preparation for preventing and treating dihydrotestosterone-related hair follicle diseases.[129]
WO2022125876	Olsen, Elise A.	16.06.2022	Compositions and methods for inhibiting hair growth.[130]
CA3188730	Spruce Biosciences, Inc.	17.02.2022	Methods and compositions for treating polycystic ovary syndrome.[131]

Table 3. An outline of ongoing clinical trials investigations of hirsutism.[114]

Study title	Sponsor	Study type/allocation/intervention model	NCT No.	Phase
Treatment with topical Eflornithine after laser treatment in women with facial hirsutism.	BispebjergHospital	Interventional/NA/Single Group Assignment	NCT01817894	Phase 4
Evaluation of Eflornithine on facial and forearm skin.	Allergan	Interventional/ Randomized/ Parallel Assignment	NCT00152048	Phase 4
Relative bioavailability study of bicalutamide 50 mg tablet and casodex following a 50 mg dose in healthy subjects under fed conditions.	Sandoz	Interventional/ Randomized/ Parallel Assignment	NCT00960310	Phase 1
Relative bioavailability study of bicalutamide 50 mg tablet and casodex following a 50 mg dose in healthy subjects under fasting conditions.	Sandoz	Interventional/ Randomized/ Parallel Assignment	NCT00959335	Phase 1
Investigation of FOL-005 on clinical safety and effect on hair growth.	Follicum AB	Interventional/ Randomized/ Parallel Assignment	NCT02793557	Phase 1 Phase 2
Effects of Isotretinoin on The Gonads and Hirsutism.	Kayseri Education and Research Hospital	Interventional/ Non-Randomized/ Parallel Assignment	NCT02855138	Phase 4

is a steroid which is responsible for oxidative reduction of estrogens, androgens, fatty acids, and bile acids. There have been identified fifteen isoforms of 17-HSD which may be particularly beneficial in management of disorders related to levels of estrogen and androgen. Therefore, these inhibitors present remarkable future scope for their exploration in clinical trial investigations.

Conclusion

Hirsutism has a significant detrimental influence on the psychological condition of the patient and, in rare cases, such as in androgen-secreting tumours, may be a symptom of severe malign disease. In the majority of cases, however, PCOS is the root cause for this disease. It is essential for medical professionals to have thorough understanding of the pathophysiology of this disease in addition to the proper diagnostic procedures for it in order to exclude the possibility of other diseases or tumors. When medical treatment is used to treat hirsutism, the healthcare professional is responsible for informing the patient about normal or anticipated time period of reduced hair growth. Hirsutism may be efficiently managed in many females by combining conventional hair removal treatment in conjunction with pharmacological treatments like oral contraceptives, antiandrogen therapy like spironolactone, cyproterone acetate, flutamide, and finasteride, certain insulin-lowering agents, gonadotrophin-releasing hormone agonists and topical treatment like eflornithine hydrochloride cream. In order to provide effective treatment in females with hirsutism, nanotechnology based approaches contributes in improving therapeutic efficacy of drugs in hirsutism in controlled manner as well as the targeted regions.

Acknowledgements

The authors would like to thank Department of Pharmaceutics, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana, India, 133207 for providing facilities for the completion of this review.

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Ishrat Zahoor: Conceptualization, Writing - Review & Editing. Sukhbir Singh: Conceptualization, Writing - Review & Editing. Neelam Sharma: Writing - Review & Editing. Ikmeet Kaur Grewal: Writing - Review & Editing. Shahid Nazir Wani: Visualization.

Conflict of Interest

The authors report no conflicts of interest.

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