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Physiological perspective of Hirsutism in Unani Medicine: An Overview and Update

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ABSTRACT

Unani Medicine (Greeko Arabian Medicine) is bestowed with a vast literature of gynaecologicaland endocrine afflictions like hirsutism. Hirsutism is characterized by excessive terminal hair growth in female like male. Despite various treatment modalities available such as mechanical, cosmetic and pharmacological, not a single remedy is effective competently to ameliorate it. Although many studies have been conducted on hirsutism, majority of the published work concerning management with herbs shows considerable shortcomings.Therefore the aim of this article is to review the ancient physiological concept of hirsutism present in Unani system of Medicine in the light of available new information and to appraise the effects of herbs on hirsutism with an objective to update the current knowledge. Rigorous literature search was done to understand the physiology and management of hirsutism described in ancient Unani literature. Literature was also searched on PubMed/Google Scholar in order to achieve high quality evidences.Herbs like *Pudina*, *Daarchini*, *Neem*, *Kalonji*, *Saunf*, Soy, Nut grass andSaw Palmettomay modulate the underlying endocrine and metabolic disturbances responsible for hirsutism directly or indirectly by anti-androgenic, estrogenic, hypolipidaemic, hypoglycemic and insulin sensitizing properties, but the evidences are weak.

Keywords: Unani Medicine; Hirsutism;Herbs; Pudina; Daarchini; Neem.

1. Introduction

Hirsutism is defined as presence of excessive terminal hair on androgen dependent areas of female's body. It affects 5-10% of females in reproductive age [1]. Hirsutism is an intricate problem having variable presentations with different severity, irregularity of menstrual cycle, body mass index (BMI) within normal range, overweight or obeseandpresence of family history [2]. Its presence is commonly associated with excess androgen production (hyperandrogenism) and warrants further evaluation [3]. Regardless of etiology, presence of hirsutism is distressing to the women and causes significant psychological trauma and low self-esteem. Even in its mildest form, hirsutism may be considered as presumptive loss of femininity and exemplify itself as a challenging dilemma for management [4]. Consequently, a natural holistic pharmacological approach is often required in subjects with mild to moderate hirsutism to suppress the androgen production or its action at hair follicles and simultaneously rectifying the underlying cause.

Traditional medicines have sustained history of practice and are considered as inspiration for current perspective of medicine. It is also a known fact that strength of any medicine depends on continuous scrutiny of past theories, beliefs and practices, with zeal to develop a new attitude. This revision is necessary to promote the development of evidence based medicine with surety of safety and efficacy. There are many advantages of employing the knowledge developed from traditional medicine as several conventional drugs are derived from medicinal plants for example; aspirin is derived from willow bark, digoxin came from foxglove flowers and metformin from French lilies [5].

Thoughpresently the phenomenon of female hirsutism is the focus of medical research; little is known about the ancient concept. Ancient literature of Unani Medicine is blessed with adequate medical description of hirsutism including management [6]. Moreover several clinical trials have been conducted on hirsutism to evaluate the efficacy and safety of herbs for oral and topical use and revealed significant effects, but the mode of action and efficacy of these herbs are still controversial [4, 5, 7, 8, 9, 10, 11]. Almost all studies were not well designed and controlled. These limitations make it presently impossible to establish a conclusion regarding safe and efficacious use of herbal drugs for hirsutism. Therefore the aim of this article is to review the ancient physiological concept of hirsutism present in Unani System of Medicine in the light of available new information and to appraise the effects of herbs with an objective to update the current knowledge regarding the use of herbs for management of hirsutism.

2. Methods:

For ancient concept of hirsutism, all available old text of Unani Medicine was searched. Literature was also searched on PubMed/Google scholar with the keywords; Herbs for hirsutism, Anti-androgenic herbs, Phytoestrogens, Hirsutism,Polycystic ovarian syndrome. For data generation and analysis, clinical trials, experimental studies, reviews and meta-analysis were taken into consideration.

2.1 An Overview of Hair Growth Physiology and Differentiation:

Hair is a filament, made up of keratin arranged in layers; it grows in length by new cells passing upward from the papilla into the root. The shaft consists of three parts: The interior part is medulla, usually absent in fine hair but present in scalp hair. The middle part is cortex. Its cells are elongated and united to form fibers which contain pigment granules (melanin) in dark hair and air in white hair. The cuticle is exterior part; it consists of a single layer of flat scales which overlap on each other [12].

There are two physiologic types of hair: Vellus hair and Terminal hair.

2.2 Vellus Hair: Vellus hair are short, fine, non-pigmented, soft, do not contain a core of compacted keratinocytes and the follicles are not associated with an arrector pili muscle. These hair cover the vast area of the body, primarily those which seems to be clinically 'hairless'. Growth of vellus hair is primarily stimulated by growth hormone and thyroid hormone [13, 14].

2.3 Terminal Hair: These are longer, more rigid hair, with shorter blunter tips, penetrating further into the dermis and more pigmented than vellus hair; they contain a central core of compacted keratinocytes and associated with an arrector pili muscle. Development and growth of terminal hair is primarily depends on body regionand are stimulated by growth hormone, thyroid hormone and androgens [13, 14].

2.4 Hair growth Cycle:

There are three phases of hair growth. The active growing phase (anagen) followed by an involutional phase (catagen) in which the hair stops growing and the hair bud shrinks; finallyresting phase (telogen), then the hair shed and new hair replaces it. In human, hair hasthe appearance of growing continuouslywhile some hairare in the active phaseof growth, others are in the resting phaseand vice-versa, giving the impression of continuous growth [15].

4. Factors Controlling Hair Growth:

Several factorscanact directly or indirectly on the dermal papilla to regulatehair growth.

4.1 Local and systemic factors:

Various growth factors and cytokines have been observed to affect hair growth; these factors operate by increasing the synthesis of stromolysin, a matrix metalloproteinase that acts on the dermal papilla to accelerate growth [16].

Growth hormone (GH) directly stimulates body hair growth independent of an increase in circulating androgens and also potentiates the effect of androgen on sexual hair growth through increased production of insulin-like growth factor I (IGF-I) [17].

Thyroid hormone appears to regulate the frequency of hair growth. Hypothyroidism leads to decreased frequency of anagen, whereas hyperthyroidism leads to thin hair [15]. Parathyroid hormone through its receptor system promotes catagen [17].

Prolactin administration induces premature catagen, but clinically prolactin excess is associated with hirsutism, probably because of stimulation of hyperandrogenism [17].

Although glucocorticoids promote catagen, paradoxically glucocorticoid excess causes hypertrichosis [15].

At ovarian level, insulin acts by interactingwith its own receptor and by the insulin like growth factor (IGF) receptor type I andenhances ovarian steroidogenesis both ingranulosa and theca cells promoting hair growth [18]. Moreover, insulin is able to inhibit hepatic sexhormone binding globulin (SHBG) synthesis, bothhepatic and ovarian IGF binding protein-1 (IGFBP-1) synthesis, which bind sex steroids and IGFs, resulting in increased bioavailable (free) testosterone [18, 19].

4.2 Sex Hormones:

In sex steroids, androgens are the most important in determining the type and distribution of hair over the human body [15]. Theystimulates tiny vellus follicles producing fine, virtually colourless, almost invisible hair to transform into larger, deeper follicles forming longer, thicker, more pigmented hair by binding to specific intracellular receptors. This process is defined as terminalization [13].

In addition to stimulating the production of terminal hair in some skin areas, androgens prolong the anagen phase of body hair, while shortening the anagen phase of scalp hair [14].

The effect of androgens on hair growth and differentiation also varies by body area and presumably the local content of androgen receptors, L-ornithine decarboxylase (L-ODC), enzymes 3α-hydroxysteroid dehydrogenase and 17α-hydroxysteroid dehydrogenase [13].

Most evidences indicate that estrogen promotes catagen; may be responsible for the arrest of hair growth late in pregnancy [17].

4.3 5α-Reductase activity (5α-RA):

It is an enzyme that catalyzes the conversion of testosterone to 5α-dihydrotestosterone (DHT). 5α-RAactivity determines the production of DHT and consequently the effect of androgens on hair follicles [16].

Other factors may also control the distribution and activity of 5α-RA, like local growth factors (e.g. transforming growth factor-β and epidermal growth factor) and circulating growth factors (e.g., insulin-like factor-I, activin A, and inhibin A) [15].

4.4 Aging:
Tendency of hirsutism varies with age. Menopause decreases hair in the pubic region, axillae and extremities but increases hair growth on the face.[20]It is reported that 30% of women after menopausehave hair above the upper lip.[21]

4.5 Etiology of hirsutism: Causes of hirsutism can be divided as androgenic, non-androgenic, systemic, idiopathic and general (**Table 1**).

Table 1: Etiology of Hirsutism

a. Androgenic causes: **Ovarian:** Polycystic ovarian syndrome (PCOS) [22], Ovarian stromal hyperthecosis [23], Androgen secreting ovarian neoplasia [24, 25] Luteoma of pregnancy [25]. **Adrenal:** Cushing Syndrome,Congenital adrenal hyperplasia (classic or late onset CAH), Androgen secreting adrenal tumor [26]. **Ectopic hormones:** These lead to development of central or lateral hirsutism depending on the hormone produced by the tumour. Carcinoid tumour and metastatic lung carcinoma causes an increase in cortisol. Choriocarcinomacauses secondary hyperthyroidism [27].
b. Non androgenic causes: **Drugs:**Danazol, diazoxide, cyclosporin, phenytoin, triamterene-hydrochlorothiazide, minoxidil, hexacholorobenzene, penicillamine, psoralens, hydrocortisone, oral contraceptives of nonsteroidal progestogen type, gluco-corticosteroids and streptomycin have been reported to cause hirsutism. Once the drug is discontinued, hirsutism tends to disappear [25, 27].
c. Systemic causes: Hypothyroidism [25], Pituitary adenomas producing excess corticotropin or prolactin [25], Acromegaly [25], Insulin resistance [23].
d. Idiopathic: Idiopathic hirsutism (IH) is considered to be one of the most common forms of hirsutism [28]. It appears due to increased sensitivity of hair follicles to normal levels of circulating androgens because of increased 5α-reductase activity [29].
e. General causes: Obesity [21, 23]. smoking[23], and menopause [29].

4.6 Overview of hair growth physiology and hirsutism in Unani Medicine:
Hirsutism is mentioned in the classical Unani literature as a complication of prolonged amenorrhoea associated with other masculine features, like hoarseness of voice, male body contour, acne and clitoromegaly [6]. Hippocrates (Buqrat460-370 BC) first documented the affiliation of excess facial and body hair (hirsutism) in females with prolongedamenorrhoea, obesity and infertility [30]. Similar observations were reported by Galen (Jalinoos130-200 AD) [30].
Rabbantabri (838-870 AD), who was a renowned medieval physician, written in his legendary book Firdous al-Hikmah ("Paradise of Wisdom") that testes are responsible for the appearance of beard in a male and removal of testecles before puberty leads to non-significant growth of facial and body hair.[31]He also postulated that a specific material is being secreted from testes that cause growth of facial hair in males [31].
Rhazes(Muhammad IbnZakariyaRazi865-925 AD) recorded combination of signs conjoined with menstrual irregularities (oligomenorrhoea, amenorrhoea and menorrhagia) including hirsutism, obesity, acne, hoarseness of voice and infertility, which are suggestive of polycystic ovarian disease and hyperandrogenism [30]. Rhazes recommended regular induction of menstruation as one of treatment modality applied for hirsutism[32]. He has also given a line of management for hirsutism based on correction of temperament and menstrual irregularity by use of emmenagogue single herbs or compound formulations and local application of herbs to reduce severity of hair growth [32].
The pathophysiology of hirsutism was explained by Avicenna (IbnSina980-1037AD) and Zayn al-Din Gorgani (Ismail Jurjani1041-1136 AD). Alteration of normal temperament of female was considered as central dogma for hirsutism. It was said that persistence of amenorrhoea for a longduration causes alterations in internal environment of female body and status of equilibrium is disturbed, leading to formation of some unwanted material which is being excreted through skin pores and participate in the formation of thick hair over the body [6, 33]. It was observed by these physicians that development of masculine features are more common in obese females with robust body and broad prominent blood vessels, because obese women have almost similar temperament as males [6, 30, 32, 33, 34, 35].
Haly Abbas popularly known as Ali ibn al-Abbas al-Majusi (died 994 AD) was the first person who has explained the physiology of hair growth and differentiation. He stated that hair arises from *Bukharatedukhaniya*, a compound made up of 4 components. Its production rises at the time of puberty, especially in males due to increased secretions from testes, hot temperament and high basal metabolic rate [36].
Burhan-ud-din Kermani (died 1449AD) explained that *Bukharatedukhaniya*includes airy, watery, fiery and earthy part. Hair growth occurs from these 4 parts in such a way that *Bukharatedukhaniya* while circulating in the blood gets separated as it passes near the pores of skin and attached to specific sites. At a particulartemperament with utilization of fiery part (energy), the earthy part (keratin and melanin) participates in the formation of hairin the presence of airand watery part (androgens, growth factors and enzymes). This process occurs repeatedly and further deposition of *Bukharatedukhaniya* takes place, maintaining continuous hair growth [36, 37].
These interpretationsmade over a period of centuries describesancient physiology of hirsutism, which are suggestive of kinship between old and current perceptions involved in hair growth.

4.7 Recommended Herbs for Hirsutism in Ancient Literature:
Several single drugs and compound formulations for hirsutism were reported by ancientunani physicians for oral as well as topical use. These include oral use of *Pudina* (*Menthaspicata*Labiatae), *Daarchini* (*Cinnamomumzeylanicum*), *Manjeeth* (*Rubiacordifolia* Linn.), *Neem* (*Azadirachta indica*), *Kalonji* (*Nigella sativa* Linn.), *Afsanteen* (*Artemisia absinthium* Linn.), *Saunf* (*Foeniculumvulgare*), *Tukhmgazar* (seeds of *Daucuscarota* Linn.), *Anisoon* (*Pimpinellaanisum* Linn.), *Suddab* (*Rutagraveolens* Linn), *Zarawand* (*Aristolochia Rotunda*), *Irsaa* (*Iris ensata*), *Izkhar* (*Cymbopogonjwarancusa*), *Mur* (*Commiphoramyrrha*), *Baalchhar* (*Nardostachysjatamansi*) and for local application *Soyaa* (*Anethumsowa*), *Honey, Bargbhang* (leaves of *Cannabis sativa* Linn.), *Tukhmutangan* (seeds of *Blepharisedulis*), *Shookaran* (*Conium maculatum* Linn.) etc [30, 32, 33, 34, 35]. Despite of many herbs named, experimental studies have been conducted on few to explore pharmacological activities of these herbs and are associated with diverse limitations.

4.8 *Pudina* (Spearmint: *Menthaspicata* Labiatae):
Clinical studies conducted by M Akdogen*et al*. and Paul Grant concluded that Spearmint could be a natural alternative for women having mild hirsutism due to its anti-androgenic property [5, 7]. It was proposed that induction of CYP3A4 activity or a direct effect of spearmint on the synthesis of androgenic hormones causes significant decrease of free testosterone. Hepatic microsomal enzyme cytochrome P450 (CYP) 3A4is associated with metabolism and synthesis of drugs, cholesterol, lipids, steroids and its activation leads to altered plasma concentration of various steroid sex hormones [7].

4.9 *Daarchini* (*Cinnamomumzeylanicum*):
Clinical as well as animal studies conducted on *Daarchini* have been reported that it is able to improve the glycemic status indicators as well as obesity [38, 39, 40, 41]. It was postulated that in previous studied that polyphenols present in cinnamon expresses hypoglycemic effects by potentiating insulin activity at pre and post receptor levels (enhancing the insulin signaling) ultimately leading to markedly increased insulin dependent glucose metabolism.[10]Khan et al in 1990 reported that an unidentified factor present in cinnamon is responsible for enhancing the insulin activity in carbohydrate metabolism and this factor was termed as insulin potentiating factor (IPF) [42].
A pilot study was conducted by Wang et al (2007) to evaluate the efficacy of cinnamon extract on insulin resistance parameters in polycystic ovarian syndrome. They concluded that cinnamon improved insulin sensitivity in non-diabetic women with PCOS. They propounded that polyphenol type-A polymers, procyanidin, in cinnamon extracts exert hypoglycemic effects by potentiating insulin signaling at the postreceptor level, leading to increased PI-3 kinase activity. When this pathway activated it leads to the translocation of GLUT-4 receptors and the attenuation of the tonic inhibition on glycogen synthase, accelerating improved glucose utilization by facilitation of intracellular glucose transport and increasing glycogen synthesis, consequently. Although this is only preliminary data and no reduction was found in total testosterone level also, small sample size might be responsible for this as suggested by authors [10].

4.10 *Neem* (*Azadirachta indica*):
Several in vivo studies have been reported the anti-androgenic effect of *neem* bark, leaves and oil [43, 44]. *Neem* exhibits its anti-androgenic effect by active constituent azadirachtin-A which probably affects the androgen synthesis [47]. *Neem* acts as pancreatic glucosidase inhibitor, it also increases the peripheral utilization of glucose; thus maintain the blood sugar as well as insulin level.[46]A steroid Beta-sitosterol present in neem is likely to be responsible for its hypoglycemic property [47].

4.11 *Kalonji* (*Nigella sativa* Linn.):
Nigella sativa oil was found to be effective as add-on therapy in patients of insulin resistance syndrome and proved effective in alleviating the obesity reported by Haque et al in a randomized clinical trial [48]. Najmi et al. reported that the beneficial effect of Nigella sativa in metabolic syndrome is mainly due to its insulin sensitizing action. They have also suggested that various components of Nigella sativa may be responsible for its beneficial effects in insulin resistance syndrome like thymoquinone, thymol, various unsaturated fatty acids, lipase and tannins.[49]Parhizkar et al. in their in vivo study on 40ovariectomized Sprague Dawley ratssuggested that N. sativa possess estrogenic action in ovariectomized rat model and may be helpful in managing menopausal symptoms as an alternative for hormone replacement therapy [50].

4.12 Clinical studies on hirsutism:
Clinical efficacy of herbs for hirsutism have been evaluated in several clinical studies conducted on hirsutism and PCOS (**Table 2**), although all have shown significant results for test drugs, there are several sources of potential bias. Small sample size, short study duration, lack of control group, inefficient reporting of methodology, inappropriate assessment tools and no follow ups after treatmentto know the relapses are major drawbacks which might influence the outcome of the studies.Though some studies were randomized,only few used reliable objective measures of hair growth.

Table 2: List of retrieved clinical trials on hirsutism and PCOS

Studies retrieved on hirsutism and PCOS	Herb	Type of study	Number of patients included	Study duration	Assessment tool	Main result of studies
K. Javidnia et al. (2003), Antihirsutism activity of Fennel (fruits of *Foeniculumvulgare*) extract.	Fennel	Double-blind placebo controlled.	45 (Idiopathic hirsutism)	12 weeks.	Modified Ferriman-Gallwey score, Measurement of hair Diameter.	Efficacy was achieved with the cream containing 2% Fennel extract.
Wang et al. (2007) The effect of cinnamon extract on insulin resistance Parameters in polycystic ovary syndrome.	Cinnamon	Randomized placebo controlled pilot study.	15 (PCOS)	8 weeks.	Plasma levels of TT, FSH, E_2, HOMA-IR, QUICKI, Matsuda insulin resistance index	TT, E_2 remained unchanged, QUICKI increased significantly, HOMA-IR decreased, and Matsuda insulin resistance index increased.
M. Akdogan et al. (2007), Spearmint (*Menthaspicata*Labiatae) on androgen level in women with hirsutism.	Spearmint	Single arm with pretreatment to post treatment comparison	21 (12 PCOS and 9 Idiopathic hirsutism)	5 days.	Plasma levels of TT, FT, FSH, LH, DHEAS, E_2.	Significant decrease in FT level. No significant reduction in TT, DHEAS levels. Significant increase in FSH, LH, E_2 levels.
B Barikbin et al. (2009), Effectiveness of the Extract of *Serenoa Repens* (Saw Palmetto) in Idiopathic Facial Hirsutism.	Saw Palmetto	Single arm with pretreatment to post treatment comparison	31 (Idiopathic hirsutism)	2 months.	Hair count.	16% decrease after one month and 29% decline after 2 months of treatment.
BehnazKhani et al (2010), Effect of soy phytoestrogen on metabolic and hormonal disturbance of women with polycystic ovary syndrome.	Soy	Quasi-randomized, double-blinded, placebo controlled.	146 (PCOS)	3 months.	Plasma levels of Testosterone, DHEAS, FSH, LH.	Testosterone, LH, and DHEAS decreased significantly after treatment but FSH was not significantly different.
Paul Grant (2010), Spearmint (*Menthaspicata* Labiatae) Herbal Tea has Significant Anti-androgen Effects in Polycystic Ovarian Syndrome.	Spearmint	Randomized Double blinded Controlled.	42 (PCOS)	30 days.	Modified DQLI, Ferriman-Gallwey score, Plasma levels of TT, FT, FSH, LH.	Modified DQLI, TT, FT were significantly reduced, LH and FSH increased, no significant reduction in Ferriman-Gallwey score.
G F A El-kareem Mohammed (2012), Role of *Cyperusrotundus* oil in decreasing hair growth.	Nut grass	Randomized Single blinded controlled.	91 (Idiopathic hirsutism)	6 months.	Ferriman-Gallwey score, Hair count, assessment of global photo-graphs and self assessment by patient.	Topical *Cyperusrotundus* oil was significantly more effective ($p<0.05$) than the Placebo.

TT: Total testosterone, FSH: follicle stimulating hormone, E_2: Estradiol, HOMA-IR: Homeostasis model assessment for insulin resistance, QUICKI: Quantitative insulin-sensitivity check index, FT: Free testosterone, LH: Luteinizing hormone, DHEAS: Dehydroepiandrosterone sulfate, DQLI: Daily quality of life index.

5. Conclusion:

Many single herbs have been reported for management of hirsutism in Unani medicine, besides only some of them have been scientifically evaluated. Although the evidences are weak and insignificant to draw a conclusion, the herbs named *Pudina*, *Daarchini*, *Soy*, *Neem* and *Kalonji* may be beneficial in hirsutism due to polycystic ovarian syndrome. Saw palmetto can be implicated in hirsutism due to adrenal or ovarian origin, while Fennel and Nut grass may be indicated for idiopathic hirsutism. In order to prove significant safety and efficacy of herbs, further extensive studies on the promising herbs are required to establish a preliminary data, on which well-designed and well-controlled randomized clinical trial with double blinding, on large sample size should be conducted.

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7. Conflicts of interest:

Authors have no conflicts of interest.

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