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Concomitant immobilization of androgen receptors and 5 α - reductase in androgenic alopecia

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Abstract

The present study report the efficacy of a herbal preparation in arresting testosterone binding on hair root in-vitro and having effect in inhibiting alpha reductase enzyme. Alpha reductase enzyme arrest the conversion of testosterone and thereby DHT lead inactivation hair root is hindered. But our finding clearly show the formulation we tested not only has DHT conversion inhibition but also has effect on direct interaction between testosterone and hair root and binding of the same over hair root. The present findings show the possible usefulness of the formulation in addressing the problem of androgenic alopecia in lieu of finasteride which has serious safety concern.

Keywords: Alopecia, hibiscus, hair growth, hair root, EGCG

Introduction

Androgenetic alopecia or male pattern baldness is known to affect the self-esteem of people of all socio-economic fabric in both rural and urban settlement ^[1]. The problem of hair loss often begin with late teenage, and as a result, many people before the age of 30 would suffer severe hair loss and baldness ^[2]. Though hair loss is not considered as a medical problem instead a normal physiology of aging still the population seeking treatment for the problem is growing day by day. Hair is always associated with sign of beauty and the loss of hair on the contrary is considered adversely.

Several treatment options are though available, but solution to the problem is still a distant dream. Many vasodilating agents are used, but the medical use of such treatment option is limited due to their narrow pharmacological action. For, example, Minoxidil is an excellent vasodilating agent but its usefulness is limited due to its narrow spectrum of activity ^[3]. The principal cause of androgenetic alopecia is due to the hormone- testosterone which is otherwise called as male hormone ^[4]. This is hormone is produced both in male and female. In female, its dominance is seen especially when estrogen level decreases with the onset of menopause. The excess amount of testosterone is metabolized by the enzyme 5 α - reductase to eliminate from the system ^[5]. The metabolized end product of testosterone by 5 α -reductase is DHT (Dihydro-testosterone). The hair root has abundant androgen receptors and the affinity of DHT over androgen receptors is very high. As a result, the DHT would gather and accumulate over the hair root, making hair root shrink, withdraw from division and die, resulting in permanent hair loss ^[6].

Finasteride is the drug of choice for inhibiting 5 α - reductase enzyme but the drug always come with severe side effects ^[7]. Several herbal preparations are although available but have limited efficacy.

Anagen grow is an aqua based hair serum composed of several herbal extracts containing phytoactives similar to EGCG. Our study on Anagen grow has proved the co-immobilizing effect of Anagen grow in inhibiting 5 α - reductase enzyme and testosterone binding on androgen receptors in hair root. The dual pharmacological effect of Anagen, we, presume may offer the much needed remedy for the problem of androgenetic alopecia and hair loss. Details are presented in the article.

Methodology

Testosterone binding assay by ELISA

The effect of Anagen grow in inhibiting the binding of testosterone on hair root was evaluated by using freshly collected hair root samples. The hair root was plucked and then washed gently with PBS. After washing, the hair root was treated in lysis buffer to open the androgen receptors^[8].

Incubation with Testosterone

The hair root lysates was incubated with testosterone in PBS buffer to allow the binding of testosterone to the androgen receptors, for 1-2 hours at 37 °C. In one group, the pre-treatment of the hair lysate was performed with anagen grow at varying concentrations prior to incubation of hair root with testosterone. The concentration of testosterone used for the study 2 µg/ml. The concentration of anagen grow used for the study was 5, 10, 15 and 20 µg/ml.

Antibody Binding (AR Antibody)

After incubation with testosterone to enable the binding of testosterone on androgen receptor, the specific antibody was added to the mixture. The antibody will bind to the androgen receptors (ARs) that are either free or bound to testosterone. Antibody binding assay was performed at room temperature for 1-2 hrs.

Enzyme-Linked Detection (ELISA)

Using an ELISA kit, the free testosterone in the reaction mixture was detected (unbound testosterone) in the reaction mixture. The amount of free testosterone in the reaction mixture is directly proportional to the bound testosterone on the androgen receptors. Reading was taken using a microplate reader at 450 nm.

Data Analysis

The rate of testosterone binding on androgen receptor in hair root treated and untreated with anagen grow was compared

to understand the specific effect of anagen grow in inhibiting testosterone binding on androgen receptors.

5-α reductase inhibition assay

In-vitro 5-α alpha reductase activity was performed using liver and prostate gland microsome fraction from male Wistar rat by following standard procedure. Finasteride was used as positive control and reading was taken using spectrophotometer^[9].

Assays of 5α-reductase activity

The liver-prostate microsome fraction would catalyse - reduce testosterone. The assay was carried out at 37 °C for 30 min in 200 µL of 40 mM phosphate buffer (pH 7.0) containing 60 µM testosterone, 800 µM NADPH and 55 - 1100 ng mL⁻¹ microsome protein. The reaction was started by adding the microsomes (20 µL) and stopped by heating at 80 °C for 5 min. After cooling to room temperature, a portion (100 µL) of the reaction mixture was transferred to a cuvette, 850 µL of the cycling reagent (0.1 M potassium phosphate buffer, pH 8.0, containing 1.76 mM thio-NAD and 0.6 mM NADH) was added and the mixture was warmed to 37 °C for 3 min.

Enzymatic cycling was initiated by adding 50 µL of 400 U mL⁻¹ 3α-HSD and ΔA1-4 min at 400 nm was measured. As a control, the liver microsome was used after heating at 80 °C for 5 min. The readings were taken spectrophotometrically at 340 nm and the activity of the test material was compared with Finasteride. The concentration of anagen grow and other herbal extract used for the assay was 5 and 10 µg/ml.

Results

Testosterone binding assay

Anagen grow pre-treatment showed significant inhibition of testosterone binding over hair root, especially the androgen receptor and the inhibition is definite and concentration dependent, Table 1

Table 1: Effect of test concentration on testosterone binding (% of control)

Con. of test (µg/ml)	% testosterone binding in treatment over control (control=100)
5	40
10	31
15	18
20	9

Among various herbs tested, Hibiscus rosa sinensis showed highest effect in inhibiting testosterone binding over hair root though such activity did not correlate well with

concentration. Other herbs tested did not show great effect in inhibiting testosterone binding over hair root, Table 2

Table 2: Effect of different plant extracts on testosterone binding (%) at various test concentrations (µg/ml)

Test details	% of testosterone binding/concentration of test samples in µg/ml			
	5	10	15	20
Murraya koenigii	80	81	78	64
Lawsonia alba	79	68	66	65
Indigofera tinctoria	82	79	78	79
Hibiscus rosa sinensis	50	42	33	29
Eclipta prostrata	69	68	63	64
Phyllanthus emblica	70	69	68	62

5-α Reductase enzyme activity

Anagen grow inhibit the activity of 5-α reductase enzyme by 85% at 10 µg/ml concentration which was superior of

EGCG. Among various herbs screened, Hibiscus rosa sinensis showed better activity against the enzyme than other herbs, Table 3.

Table 3: Effect of test samples (2 mg/ml) on 5 α -reductase activity at different concentrations

Sample details (2mg/ml)	Concentration in μ g /% reduction of 5 α reductase activity	
	5 μ g	10 μ g
Murraya koenigii	6	7.4
Lawsonia alba	3	5
Indigofera tinctoria	5	7
Hibiscus rosa sinensis	13	21
Eclipta prostrata	7	11
Phyllanthus emblica	4	5
Anagen grow	32.65	85.07
EGCG extract	14	57.4
Finasteride (at 0.02 μ g)	34	

Discussion

Treating hair fall/androgenetic alopecia due to hormonal cause, especially due to testosterone binding over hair root is almost difficult to contain, however the same can be reduced significantly. If the treatment is initiated with the onset of testosterone build up over hair root, the reduction of hair loss can be minimized greatly. In the conventional treatment line, the drug finasteride alone is available for the above purpose. But the drug is known to affect the sterility in male^[10]. The people who seek treatment for hair loss are often in the post teenage age group and hence the use of finasteride is redundant in the group due to the above side effect. Minoxidil topical preparation is also available, but androgenetic alopecia seldom responds well to topical Minoxidil.

Herbal preparations are though claimed to have effect in promoting hair growth, but scientific and clinical proof is lacking for most herbal preparations. Lack of science and dubious claims on herbal products have made the credence of herbal preparation quite weak.

The enzyme that plays the major role in the build-up of testosterone on hair root is 5 - α reductase enzyme which metabolizes the excess testosterone to excrete out as dihydrotestosterone (DHT). Hindering the enzyme has been used as a strategy to prevent the conversion of testosterone to DHT. But such strategy can only meet the half of the need and not the full. Beyond targeting the enzyme, preventing the binding of testosterone over hair root directly may offer better and an additional treatment strategy for the treatment of androgenetic alopecia besides enzyme inhibition.

The herbal formulation that we tested showed could prevent the binding of testosterone over hair root suggesting the herbal preparation may be hindering the binding of androgen receptors or modifying them or making them unfavourable for the binding of testosterone hormone. The androgen receptor in hair root allows the binding of both testosterone and DHT equally but the binding affinity of DHT is more stable than testosterone. Therefore, the findings on the inhibition of testosterone over hair root answers well for DHT as well. The possible inhibition of binding of testosterone over hair root can be explained in other words also as either poor binding of DHT or may fasten the dissociation rate of the same from the hair root. Nevertheless, any of the above possibly shall protect the hair root from shrinkage, atrophy and death.

The hair roots are once protected from testosterone and its metabolic end product, the androgenetic alopecia can be reduced if not fully treated. The formulation having effect on enzyme and also can modify or mask or emasculate the androgen receptors in the hair root (the exact mechanism of

action is yet to be established) may offer a near complete solution to the problem of androgenetic alopecia.

A quick rekey/ reconnaissance of various herbal constituents in the formulation having such activity has revealed the extract of Hibiscus rosa sinensis having effect in inhibiting the enzyme activity and also prevent testosterone binding over androgen receptors in hair root. Various ancillary benefits of other herbs such as antioxidant, vasodilatation, keratinocyte cell activation, anagen hair growth specific protein through mRNA expression have been established earlier^[12-16].

In the present context, the various study findings including the one that we have established, anagen grow hair serum may offer the much needed treatment solution to androgenetic alopecia. We believe, this may be one of the best studied herbal products for the treatment of hair loss and androgenetic alopecia. The findings clearly indicate its usefulness though more rigorous studies are needed.

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