

Thymuskin: Clinical Efficacy, Biological Effects, Modes of Action

Growth Cycle of Hair

Hair shedding in healthy humans amounts up to 100 hairs a day; the same number of hairs grow anew. The hairs are formed in the hair roots (follicles) by keratinocytes. Each hair has a growing (anagen) phase of 2-6 years followed by a resting (catagen) phase of about 2 months and a (telogen) end-phase, during which the hair falls out. Does the loss of hair exceed the re-growth rate the hair becomes thin (alopecia) and finally baldness occurs.

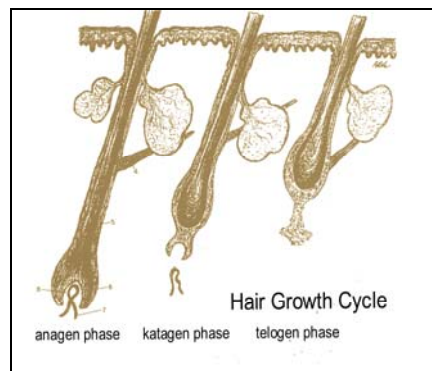


Figure 1: Hair Cycle

The Efficacy of Thymuskin in Clinical Trials

In the three most frequent forms of hair loss Thymuskin has been shown to be effective in clinical trials. These forms of hair loss which differ in their appearance, course and causes are described below:

Congenital Hormonal Hair Loss or alopecia androgenetica

In men hair loss most commonly starts in the third decade at the front and temples progresses to the vertex of the head forming a tonsure so that finally a wreath of hair remains. In this type of hair loss Thymuskin proved to be effective in 73% of the afflicted men in form of a new growth of hair or of a hold of hair loss (1).

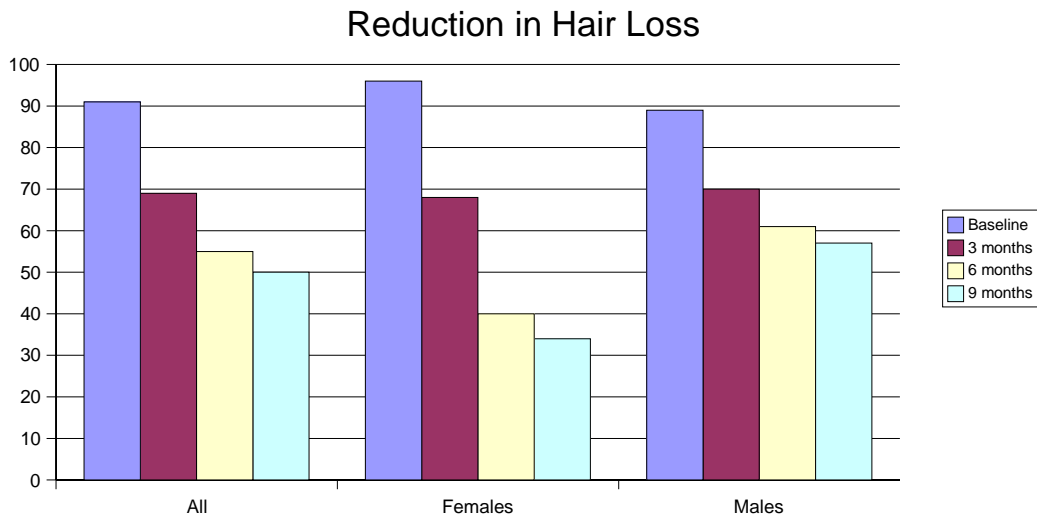
In women the congenital form of hair loss occurs less frequently, in later age and in different pattern namely more on the crown of the head. All women treated with Thymuskin stated an improvement (1).

In both genders the cause of the congenital hair loss is an increased sensitivity of the hair follicles against the sex hormone testosterone and its metabolite dihydrotestosterone, respectively.

In an exploratory study with Thymuskin GKL 02 (2) a statistical significant reduction in daily hair loss by 45 % ($p=0.01$) occurred in the 18 patients treated for 9 months; by 65% in females and 36% in males, respectively, as shown in figure 2. The ratio of anagen/telogen phases of hair as determined in the trichogram increased in 19 patients with complete data for 6 months from 5.88 to 10.46 ($p=0.10$) as shown in figure 3.

Figure 2: Reduction in Daily Hair Loss under Thymuskin GKL 02

Number	Subgroups	Baseline	3 months	6 months	9 months	T-test,2-sided	Reduction
18	All	91	69	55	50	P=0.01	45.05%
5	Females	96	68	40	34	P=0.03	65.58%
13	Males	89	70	61	57	P=0.10	35.96%



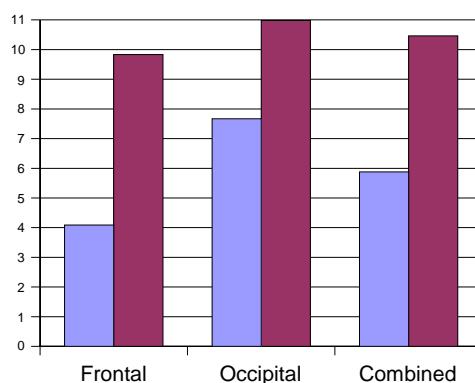
Diffuse Hair Loss or alopecia diffusa

In this form the hairs are thinning out rather uniformly on the entire scalp. Metabolic or hormonal disturbances, infections, stress and medications (especially anti-cancer drugs) may be the cause. In patients with breast and colon cancer under treatment with medium strong cancer drugs concomitant application of Thymuskin prevented in 41-81% largely or completely the expected hair loss (3). In cases with diffuse hair loss of other causes Thymuskin was effective in 73% (4).

Figure 3

Increase in anagen/telogen ratios in the trichograms
19 patients with complete data at 6 months

Scalp	Baseline	6 months	T-test 2sided
Frontal	4,09	9,83	P=0,22
Occipital	7,67	10,98	P=0,26
Combined	5,88	10,46	P=0,10



Circumscribed Hair Loss or alopecia areata

Immunological disturbances are suspected as the cause since T-lymphocytes which play a role in the defense system of the body are attacking the hair follicles. An inflammation occurs which impairs hair growth and finally leads to the loss of hair. In this severe form of alopecia 65% of the patients treated with Thymuskin experienced new hair growth at the scalp and/or body whereby in 40% of the cases a complete remission occurred (5).

Action of Thymuskin in Experimental Models and Probable Modes of Action

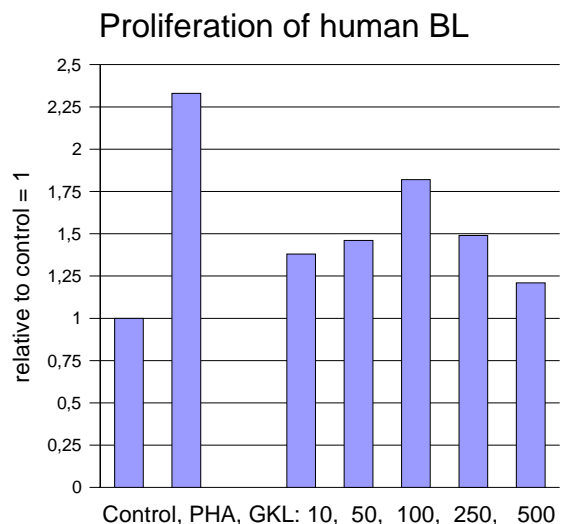
Biological activity

Thymuskin (development code GKL 02) is a synthetic peptide library identical to the former hydrolyzed extract of bovine thymus. Since Thymuskin GKL 02 consists of several components (various tetra peptides) it is difficult to clarify the mode of action and to attribute it to single components. Most likely several components contribute to the action. Though the clarification of the mode of action is desirable from a scientific point of view it is secondary for the successful treatment of hair loss. However it has been shown that Thymuskin exerts biological effects in various human cells, cultures and on biological substrates such as enzymes. These effects could explain the clinical efficacy of Thymuskin in the various forms of alopecia.

Figure 4:

Effect of Thymuskin GKL 02 on the proliferation of human blood lymphocytes (PBL)

Substance	Dose	Effect	Diff. vs contr.
Control	0	1	
PHA	0,4	2,33	P<0.01
GKL 02	10	1,38	
GKL 02	50	1,46	
GKL 02	100	1,82	P= 0,03
GKL 02	200	1,49	
GKL 02	500	1,21	



Stimulation of Proliferation

Investigations in human blood cells show that Thymuskin stimulates the proliferation of lymphocytes (6). The effect is dose dependent up to 100 µg/ml and reaches statistical significance (p=0.03) versus controls (figure4). The mechanism of proliferation stimulation is independent of interleukin, as was shown in these investigations. A stimulatory effect also on the cells of the hair follicle could explain the positive effect of Thymuskin on hair growth.

Enhancement of Cell Vitality

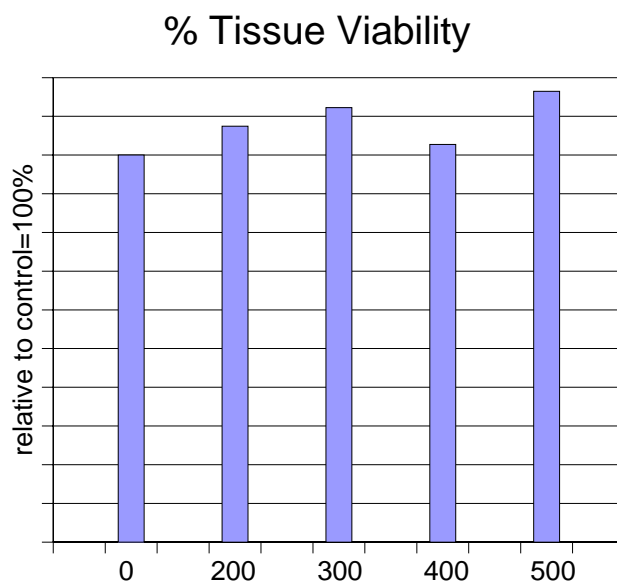
Thymuskin was tested in the EpiDerm®-model (7). The test tissue in this model consists of a multilayer culture of human keratinocytes and mimics structure and function of human skin extremely well. In this model a 10% solution of Thymuskin tended to increase the vitality of the test tissue. The viability or vitality increases dependent on the concentration and on the duration of action of Thymuskin as shown in figure 5.

Keratinocytes are skin cells which form keratin, the ground-substance of hair. It may be expected that Thymuskin exerts corresponding effects on the viability and vitality of keratinocytes in hair follicles. Thus these findings point to an important basic action which may be fundamental for the clinical efficacy. This fundamental biological effect could explain why Thymuskin is effective in hair loss of various etiologies.

Figure 5:

Increase of Tissue Vitality In the EpiDerm® Model after exposition to Thymuskin GKL 02

GKL 02 µL	Exposition	% Viability
0	5 h	100
200	2 h	107,45
300	3 h	112,27
400	4 h	102,74
500	5 h	116,47

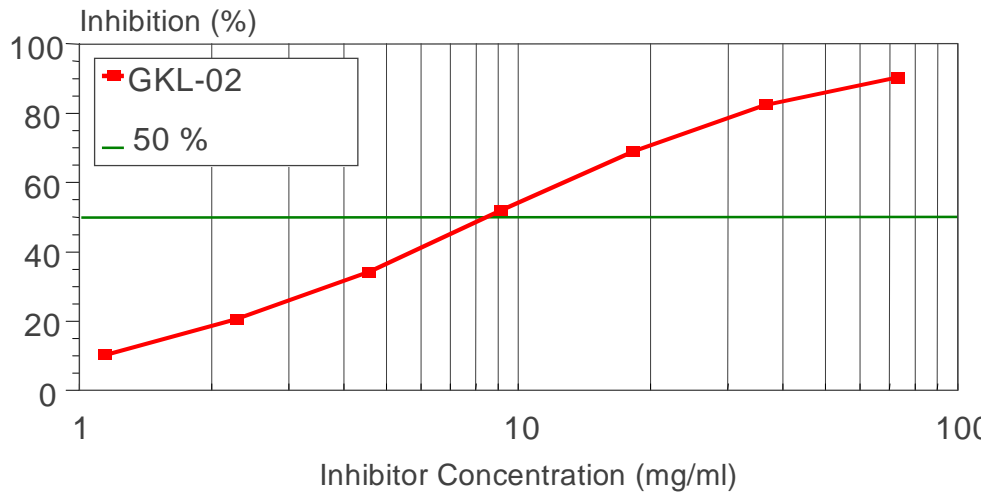


Inhibition of Mast Cells Effects on Hair Follicles

In a mouse model of alopecia it was observed under the microscope that during the catagen phase which precedes the telogen end phase of the growth cycle, the number of mast cells and their degranulation increases greatly (8). After the hairs have fallen out, the number of mast cells normalizes again. The authors conclude that mast cells play an essential role in hair loss. Mast cells of course contain the serine proteases tryptase and trypsin. The keratinocytes of human skin dispose of receptors (PAR) which are activated by serine proteases. Activation of these receptors lead to changes in cell function with not yet fully recognized consequences. It has been shown (9) that Thymuskin inhibits tryptase and trypsin (figure 6). By the way, this inhibitory action of Thymuskin on those enzymes is also utilized in an assay in quality control. From the role of mast cells in hair loss and the inhibition of the

serine proteases from mast cells it can be postulated that Thymuskin would be capable to reduce or even prevent the death of hair forming follicle cells.

Figure 6: Inhibitory Activity of Thymuskin GKL-02 on Tryptase



Good Skin Penetration

The biological effects reported above only become relevant if Thymuskin reaches the hair root in a sufficient concentration. Investigations on the penetration in vitro through human scalp and abdominal skin have documented that about 45% of a 1% solution of Thymuskin penetrates deeply enough into the skin (10). Thus it is proven that considerable amounts of topically applied Thymuskin reaches the relevant depth of the skin to exert its efficacy on the hair roots.

Executive Summary

Thymuskin has shown clinical efficacy in the three most frequent forms of hair loss in men and equally well or even better in women. In several experimental models Thymuskin has exhibited biological activity. Thymuskin stimulates the proliferation of human blood lymphocytes and might also stimulate as well the cells in the hair follicle. Thymuskin increases the viability and vitality of human keratinocytes which are greatly involved in producing the ground substance of hair. Thymuskin impairs the main enzymes of human mast cells which have been shown to play a major role in the transition of the anagen to the katagen and telogen phases of the hair growth cycle. These three actions can easily explain why Thymuskin is effective in different types of hair loss.

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