Draft Report No 3
Mool Hair Grow - Efficacy and Safety

1. Executive Summary

A comprehensive review has been made of the efficacy and safety of the product Mool Hair Grow that is marketed as an aid to help reduce hair loss. This review covers this product and makes reference to three closely related products and the individual bioactive constituents present in Mool Hair Grow. The evidence is strong for the beneficial effects of Mool Hair Grow in treating male pattern baldness (androgenetic alopecia), the commonest form of hair loss in both sexes. In a detailed evaluation of the safety aspects of the use of Mool Hair Grow no evidence of any meaningful adverse effects of the constituents or the final form has been found.

Although no evidence of any allergic response to Mool Hair Grow has been uncovered customers who are allergic to fish or crustacean products should be advised to avoid taking Mool Hair Grow. It should be taken during pregnancy only after taking a medical opinion. It is of no benefit in alopecia areata.

The conclusion from the available evidence is that Mool Hair Grow is a safe and effective treatment of male pattern hair loss in both sexes when used as directed.

2 Objective

The objective of this work is to provide the necessary data and documentation for Mool Hair Grow to allow it to be presented to interested parties. The document will include available data on efficacy and safety.

3. Background

Mool Hair Grow is a proprietary product. It contains a combination of nutritionals proven to be of benefit in the management of hair loss in both sexes. It is intended for use as an aid to improving the nutritional status of the consumer and as a consequence improves the function of the hair follicles, help hair regrowth and reduce hair loss. Evidence from animal and clinical studies attests to its efficacy for this indication. The product is marketed in a number of countries where it regarded as a nutritional supplement. A clinical trial attesting to the efficacy and safety of Mool Hair Grow has been published (Appendix 1)

The major active principle of Mool Hair Grow is a proteoglycan derived from marine sources this is supplemented by additional nutrients that are known to be beneficial to a good general health status that are essential for optimal hair growth in both sexes.

4. Supporting Evidence

Two direct competitors, trade names Nourkrin and ViviScal are being marketed within the EC area. In both products the major active principle is a fish protein-carbohydrate complex made up of protein and a glycosoamino-glycan, termed a proteoglycan (PG). This is similar and maybe identical to the PG in Mool Hair Grow.

Both competitors contain additional nutrients that differ from those in Mool Hair Grow and thus the three products may show different efficacies. Human trials have been reported for all three products.

A third major UK competitor is Vitabiotics, it markets two products under the Tricologic name. Tricologic for Women contains a hydrolysed marine collagen together with 24 other nutrients including grape seed extract. The identity of this substance is not defined but it might have similar properties to the PGs used in Mool Hair Grow and the two directly competitive products. Interestingly Tricologic for Men is devoid of the hydrolysed collagen but contains a lignin. A further product, Imedeen, contains a similar PG and is promoted for dermatological indications. As there are numerous similarities between skin and hair growth, the results from human studies on Imedeen may be used as support for claims relating to the mechanism of action of Hår Mool Hair Grow.

5. Composition and Manufacturing Process

The formulation for Mool Hair Grow is shown in Table 1. The major constituents by weight in Mool Hair Grow are a marine-derived cartilage containing high levels of proteoglycans (PG). The major one is chondroitin sulfate and this is believed to be the major contributor to the efficacy of the product. However as the marine -sourced cartilage in the product is a natural material it can vary in composition it is likely that it contains more than one PG and that several of these might be expected to have some bio-activity that may contribute to its action.

A minor botanical constituent is grape seed extract, obtained from a grape variety, Vitis vinifera, the active principles are polyphenols and proanthocyanadins of which the most well characterised pharmacologically are the polyphenol, resveratrol (3,5,4'-trihydroxy-trans-stilbene) that is believed to be responsible for the demonstrated benefits of consuming red wine and a mixture of proanthocyanadins that are powerful antioxidants. The additional active constituents are well specified vitamins, minerals and amino acids are all established essential nutrients. All the active constituents of Mool Hair Grow are considered to contribute to the overall efficacy of the product. The manufacturing process and analytical procedures are detailed in the product Master File Appendix 2.

6. Bioavailability

No studies on the bioavailability of Mool Hair Grow have been reported although evidence from animal and human studies implies that all constituents are bio-available to some degree. Cumulation of the active principles may occur with time and levels may vary.

Studies in Animals.

Proteoglycans.

A study in beagle dogs found that that the extent of absorption of chondroitin sulfate as indicated by the mean C(max) (21.5 microg/ml) and mean AUC (187 microg/ml h) of total disaccharides after dosing (1600 mg) provides evidence that chondroitin sulfate is absorbed orally. The bioavailability of CS ranged from 4.8 to 5.0% after single dosing and 200-278% upon multiple dosing. (Adebowale et al 2002)

Grape Seed Extract

Resveratrol is considered to be the major bioactive principle in grape seed extract. When give alone as an oral preparation it can be absorbed both from the buccal cavity and lower down the gastrointestinal tract with over 70% being absorbed. It is readily metabolised in the liver to glucuronide and sulphonate derivatives. This results in low levels of circulating resveratrol. (Marier et al 2002)

Studies in Humans

Proteoglycans.

Chondroitin sulfate is absorbed after oral administration in human healthy volunteers. In one study the absolute bioavailability was found to be 13% and the authors concluded that the bioavailability was similar in man and experimental animals More than 50% of a single dose dose of chondroitin sulfate was found to be excreted in urine during the first 24hr as both high and low molecular weight derivatives. (Conte et al. 1991). Chondroitin sulfate from a fish source reached a peak concentration after 8.7hr after oral administration to male volunteers and was found to be present as free and sulfated disaccharides. (Volpi 2003)

Grape Seed Extract.

As with rats resveratrol is readily absorbed but rapidly metabolised (Walle et al 2004). Goldberg et al (2003) have suggested that the bioactivity of resveratrol is due to its metabolites. Proanthocyanidin B1 levels in the blood of volunteers given grape seed extract reached 10.6nmol/l after 2hrs. (Sano et al 2003)

Cysteine.

Cysteine has been shown to be essential for the proliferative capacity of keratinocytes and as follicular activity is similar to that of keratinocytes it is considered that cysteine may be equally essential for hair growth (Hoeller et al 2006).

Other constituents.

As all the remaining constituents are well established nutrients and may be assumed to be readily bio-available no bioavailability studies have been reviewed.

7. Efficacy

Studies in Animals.

No animal studies have been undertaken on the Mool Hair Grow formulation but studies on the individual constituents are found in the published scientific literature.

7.1.1. Proteoglycans.

Glycosoaminoglycans that are believed to be the active component of PGs have been shown to be able to influence hair growth in mice and increase the levels of arginine-rich proteins that are known to be involved in the hair growth cycle in rats (Paus 1991) and dogs (Butler 1975). However the relevance to human hair growth is questionable.

Grape Seed Extract.

This is a complex mixture of bioactive nutrients. Of these the most widely studied is resveratrol that has been found in animal experiments to possess a range of biological activities. These range through anti-oxidative, anti-tumour, cardio-protective, anti-diabetic and anti-inflammatory properties. (Gentilli et al 2001). As resveratrol has been shown to have an effect on estrogen receptors this may contribute to its effect on hair growth. (Gehm et al 1997). Proanthocyanadin present in grape seed extract exerts antioxidant activity in rats (Yanarates 2008, Nakagawa 2005) and can ameliorate the effects of NF-KappaB (Lu et al 2010). Proanthocyanadin inhibited laser-induced thrombosis in mice by inhibiting platelet aggregation. (Sano et al 2005) This plays a significant role in skin blood flow and follicular nutrition. All these effects may prove to be beneficial to hair growth.

Cysteine

This sulphur containing, non-essential amino acid and its oxidised form cystine are constituents of normal hair. Studies in sheep have shown that a deficiency of cysteine can inhibit wool growth and that supplementation with it can improve wool growth. (Powell et al 2007). Induced alopecia in mice can be prevented by supplementation with cystine and vitamin B6. (D'Agostini et al. 2007). Zinc is essential for hair growth and a deficiency in this essential mineral can induce hair loss, cysteine has been shown to reduce zinc loss in rats exposed to ethanol. (Hsu & Smith 1983)

L- methionine

As with cysteine this is sulphur-containing amino acid is it is a good source of sulphur that can be incorporated into glutathione that is an

essential component of glutathione peroxidise an important antioxidant. It can also act as a precursor to taurine an amino acid essential for hair growth. It is a methyl donor involved in DNA methylation. A deficiency of dietary methionine in rats can lead to an over-expression over inflammatory genes and a depletion of glutathione both effects may have an adverse effect on hair growth. (Helieh et al 2008). Both cysteine and methionine can undergo biotransformation to taurine. In the adult mouse a very high density of taurine was found over the epidermis and external root sheaths near the opening of the hair follicles. The external root sheath just below the insertion of the sebaceous glands and the peripheral part of the sebaceous glands showed a high taurine distribution. (Watanabe et al. 1995). It can be concluded that both cysteine and methionine can contribute to ensuring adequate levels of taurine needed for hair growth.

Zinc Gluconate

Zinc has been shown to be essential for normal hair growth in both domestic and laboratory animals. These include mice (Plonka et al 2005), sheep (White et al 1994)

Additional Vitamins and Minerals

The additional vitamins and minerals present in hair gain can be considered to be necessary for the normal health and thus make a contribution to the maintenance of a good health status. No specific animal studies attesting to the role of these nutrients on hair growth have been identified.

Studies in Humans

Proteoglycans.

PGs have been shown to have an active role in human hair growth. They have been found to be present in the epithelial and stromal compartments of hair follicles and the transmembrane PG, syndecan is considered to play an important part in follicle morphogenesis (Couchman 1993, Westgate et al 1991). The evidence of Taylor and others suggest that PGs are involved in regulating hair growth. (Taylor et al 1992, Silbert 1982,)

Specifically, it has been demonstrated that proteoglycans can interact with growth factors as well as fibronectin and interstitial collagens and can associate in a trans-membrane relationship with the cellular cytoskeleton. In particular, chondroitin 6-sulfate appears to be concentrated in the follicle during the anagen phase of the hair growth cycle. (Couchman1993) and appear to play a role in hair protection. (Malgourlis 2007). Proteoglycans, play an important part in regulating the epithelial-mesenchymal signalling exchange that regulates the hair

follicle activity, and therefore are necessary to maintain normal hair growth (Botchkarev, Kishimoto, 2003).

7.2.1 Grape Seed Extract.

Resveratrol has been shown to activate the sirtuin gene SIRT1, known to be involved in the control of metabolism and of benefit to individuals with type 2 diabetes. However, there is no published evidence anywhere in the scientific literature of any clinical trial for efficacy in humans. Proanthocyanadins have been shown to have multiple effects in humans, these include prevention of oxidative stress damage of plasma lipids (Natella et al 2002), and a reduction of adhesion molecules (Kalin et al 2002), Both these effects may contribute to optimal follicular activity.

7.2.3 Zinc gluconate.

There is evidence that dietary zinc deficiency can lead to hair loss (Alhaj et al2007) and that oral zinc therapy can restore hair growth. (Slonim et al 1992).

Cysteine.

Cysteine has been shown to be essential for the proliferative capacity of keratinocytes and as follicular activity is similar to that of keratinocytes it is considered that cysteine may be equally essential for hair growth (Hoeller et al 2006).

Other constituents.

As all the remaining constituents are well established nutrients essential for good health and clinical efficacy and no specific studies on hair growth have been identified.

Marine Cartilage Based Products.

Four proteoglycan-based hair treatment products identified as available on European markets viz: Mool Hair Grow, Visical™ Nourkrin™, and Tricologic®for Women. All these products have a base of marine-sourced cartilage, although not necessarily from the same source, with additional nutrients that can differ between products.

The results of human trials with positive results have been published for Mool Hair Grow, Visical™ and Nourkrin™, but not for Tricologic® or Women. A further product, Imedeen® also based on marine cartilage is promoted for the improvement of skin condition, skin physiology has much in common with hair growth, and both require proteoglycans for optimal functioning.

Mool Hair Grow In a published clinical trial Thom (2001) studied the efficacy and tolerability of Mool Hair Grow in a randomised, double blind, placebo controlled clinical trial in 60 subjects of both sexes over a 6 month period. 56 subjects presented with androgenic alopecia and 4 with alopecia totalis. After 6 months both the active and control group were given Mool Hair Grow to take for a further 6 month period. Both objective (photographic) and subjective criteria were used as end points.

Regular assessments were made over the study period. A statistically significant ($p < 0.001$) improvement was found after 6 months during the controlled part of the study and also for all participants after 12 months. Tolerability was good and no adverse effects were reported. See Appendix 1.

ViviScal® and Nourkrin®

Both these products have been evaluated in a similar manner to that for Mool Hair Grow both provide with similar statistically significant positive results on hair growth. The study by Lassus and Eskelinen (1992) was confined to young males with hereditary androgenic alopecia.

A study was done in Brazil with ViviScal in human subjects. Two 300 mg tablets of the product were given twice daily for 180 days to 178 subjects with androgenic alopecia. A significant reduction in hair loss was observed in 75.3% of subjects and 14.6% showed significant re-growth. No adverse effects attributable to the treatment were noted.

Statistical Treatment

All the published data on Mool Hair Grow and competitive products containing some form of marine were examined by an independent statistics expert and subjected to a meta-analysis. Although a number of shortcomings in design and execution were identified a meta-analysis of the combined data from two of the studies was performed. The mean difference in favour of the active treatments was 9.12 (5% confidence interval of 7.71-10.53) this was considered highly significant ($p<0000.1$). This provided additional support for the claims of efficacy for HairGain^{TM} . (Appendix 2)

8. Safety

All the constituents of Mool Hair Grow and the other named products are commonly present in foods of various types. Proteoglycans are common constituents of animal connective tissues and are widely consumed worldwide on a daily basis. Grapes and grape extracts in wine have no history of adverse effects and the amino acids, vitamins and minerals that are present in Hår Vokse^{TM} can also be considered safe at the levels present in the product.

Shark Cartilage and Proteoglycans

No experimental evidence of human or animal toxicity has been found for proteoglycans and chondroitin. Adverse effects following the ingestion of high doses of powdered shark cartilage in an anti-cancer trial have been reported these include gastro-intestinal disturbances and tiredness and dizziness. (Miller et al 1998). Allergic reactions to shark cartilage are recorded on websites including cases of allergic liver damage but no published evidence has been found. (Medicine-Net.com.). No evidence of the effects on foetal development has been found for shark cartilage, proteoglycans or chondroitin.

Grape Seed Extract.

High dose levels of resveratrol (100mg/kg) given to pre-pubertal mice increased the incidence of mammary tumours but as the dose was 5000 times the level in Mool Hair Grow this effect is not considered to present a meaningful risk to humans. (Athar et al 2007) As resveratrol can bind to estrogen receptors it is possible that it may interfere with the effects of oral contraceptives but there is no published evidence to support this effect in women. A small study in healthy volunteers of up to 5g/day of trans-reservatrol caused no meaningful adverse effects. (Boocock et al 2007). Resveratrol is GRAS registered. Grape seed extract was tested for mutagenic activity with negative results. (Erexson 2003)

No experimental or human evidence of the toxicity of proantho-cyanadins was identified.

Other Constituents.

As all the remaining constituents are well established nutrients with established use and safety profiles. Most of these ingredients are GRAS approved by the FDA. The exception is folic acid and copper chlorphylin although the latter is regarded as safe by FDA it does not yet have a GRAS number. Folic acid is recognised as an essential nutrient and is one of the few nutritional supplements recognised by medical authorities in the EU and is recommended to be taken at a dose of 400µg/day during pregnancy for the prevention of foetal abnormalities. This is close to the dose in Mool Hair Grow.

9. Expert Opinion

The foregoing review has been based on published work from peer reviewed journals referenced via PubMed and Toxnet the databases available from the US National Library of Medicine; this has been supplemented by reference to published texts and personal knowledge. Details of the product were supplied by Med-Eq AS, 3101Tonsberg, Norway.

No experimental studies on the bio-availability of the individual constituents

from the Mool Hair Grow tablets have been undertaken and the appropriate values

for them have been gathered from published reports. The bioavailability of each bioactive constituent will be affected by the dissolution properties of the tablets and the presence of other active and inactive constituents. From the body of published evidence available it is believed likely that all the bio-active components of Mool Hair Grow will be readily absorbed from the gastrointestinal tract following ingestion of the tablets.

The evidence to support claims for the efficacy of Mool Hair Grow comes from the totality of the published evidence on hair growth; this consists of theoretical views from academic researchers, published studies on the role of the individual bioactive constituents considered essential for hair growth and the prevention of hair loss and the trials published in peer reviewed journals of Mool Hair Grow and the closely related products VivisCal™ and Nourkrin™. Although there are some methodological deficiencies in all three studies there is strong evidence for the efficacy of marine cartilage-derived in treating male pattern baldness (androgenetic alopecia). In two of the published studies (Lassus, Eskelinen1992, Pereira 1997) the subjects were all male diagnosed with androgenetic alopecia. In Thom's two published studies (Thom 2001, 2006) adults of both sexes were treated, 56/60 had androgenetic alopecia while 4/60 presented with alopecia totalis. No differentiation between the sexes or the two conditions was made by the author and thus the evidence for benefit in alopecia totalis is lacking. A further hair loss condition common in women during pregnancy is telogen effluvium, this is considered to be due to nutritional deficiencies and could possibly benefit from Mool Hair Grow. It is important to note that there are a number of forms of alopecia and that not all are treatable with Mool Hair Grow. Alopecia areata is a common condition considered to be an immune condition and subjects with his condition are unlikely to benefit from using Mool Hair Grow.

The use of Mool Hair Grow is considered not to present any meaningful safety concerns. Although the evidence for any allergic potential of Mool Hair Grow is lacking it is feasible that consumers who are sensitive to fish or fish products might show a cross reaction to the marine cartilage component of Mool Hair Grow. It is recommended that a warning that consumers who are allergic to fish or fish and crustacean products should not take Mool Hair Grow. There is no evidence that the use of Mool Hair Grow or its constituents can present a risk to the foetus during pregnancy however it would be prudent to add a warning to the label advising pregnant women to seek medical advice before taking Mool Hair Grow.

The conclusion from the available evidence is that Mool Hair Grow is a safe and effective the treatment of male pattern hair loss in both sexes when used as directed.

Table 1

Ingredients	E Number	Input (mg/Tab.)	A=active I=inactive	
Marine protein complex		350	A	
Ascorbic acid preparation granule, 97%		90	A	GRAS
Zinc gluconate		85.8	A	GRAS
L- cysteine		100	A	GRAS
Folic Acid		0.12	A	
D- Biotin		0.132	A	GRAS
Grape seed extract		30	A	GRAS
D- Alpha Tocopheryl Hydrogen Succinate		18	A	GRAS
Nicotinamide		17.6	A	GRAS
Calcium Pantothenate		8.25	A	GRAS
Cyanocobalamin (0.1%)		4.95	A	GRAS
Pyridoxine Hydrochloride		2.31	A	GRAS
Riboflavin		1.68	A	GRAS
Thiamine hydrochloride		1.31	A	GRAS
L- methionine		50	A	GRAS
Copper Chlorophyll	E141	40	I	*
Calcium phosphate	E341	35.848	I	GRAS
Silicon dioxide	E551	50	I	GRAS
Microcrystalline cellulose	E460	79	I	GRAS
Magnesium Stearate	E470B	10	I	GRAS
Weight of Tablet Core, mg		975		
Brown coating materials (contains: Titanium Dioxide; Hydroxy propyl methyl cellulose; & iron oxides)	E171, E464 and E172	25	I	
Total Tablet Weight, mg		1000		

Key: GRAS – Generally Recognised As Safe by F.D.A. of the USA

*Copper Chlorophylin is regarded by FDA as a safe colorant but not yet GRAS

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Appendices

Appendix 1 Thom E. Efficacy and tolerability of Mool Hair Grow in individuals with hair loss: a placebo controlled,double blind study. J Int Med Res. 2001; 29,2-6.

Appendix 2 Master File and Signed Composition Table

Appendix 3 Meta Analysis – Marine Protein Extract for Androgenic Alopecia – Dr. D. Syndercombe-Court