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Review

What Can Complex Dietary Supplements Do for Hair Loss and How Can It Be Validly Measured—A Review

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Abstract: Hair plays a major role in perception within a society. It provides information about gender, age, health, and social status. It is therefore not surprising that those affected are exposed to great suffering due to the widespread occurrence of hair loss. As a result, the demand for new products to remedy this problem is not diminishing. Hair grows in cycles, and a hair follicle goes through several phases called the hair cycle. The active growth phase (anagen phase) lasts 2–6 years. In this state a hair follicle shows a growth of about 1 cm per month. In order to improve the existing hair status, hair should be kept in the active anagen phase as long as possible, or the transition to anagen should be stimulated. A number of reviews already describe the influence of individual active ingredients on hair growth. However, the following review describes existing studies of complex dietary supplements with their experimental weaknesses and strengths and their influence on hair loss. Also, for the determination of hair loss, it is important to use a valid method with high acceptance by the test persons. In this context, the TrichoScale® is a validated and non-invasive tool for quantifying hair loss/hair growth. Thus, it is an ideal measuring instrument to objectively quantify the effectiveness of a hair loss treatment.

Keywords: TrichoScale®; hair loss; dietary supplements

Hair gives us information about age, sex, and social position. Hair serves as decoration and at the same time it is a status symbol for wealth and beauty. If hair falls out, it puts a strain on the psyche of many affected people. Here, hair loss is a major psychological problem not only for women, but also for men [1]. In 2017, the market value of the worldwide market for hair loss treatment was $3 billion USD. It is therefore not surprising that the worldwide market for hair loss treatment products is expected to grow by approximately 4% by 2024. The fastest growing market is currently South America, and the largest market for hair loss treatment products is Asia [2].

1. Hair Growth Cycle

To understand the problems of hair loss, it is important to understand the hair cycle. From the beginning of the growth of a hair until it falls out, every hair goes through three phases. These are the anagen (growth phase), catagen (intermediate phase), and telogen phase (resting phase) [3]. These three phases will now be described in more detail.

The anagen phase starts with the growth of the hair. The duration of this growth phase is genetically predetermined and lasts between three and six years (in exceptional cases, even longer) [4]. With a growth of 1 cm per month, the hair can grow up to 75 cm long. This means that the maximum achievable length of the hair depends primarily on the duration of the growth phase. However, the older a person gets, the shorter the anagen phase becomes [5]. In addition to age and genetic predisposition, sex also plays a role—male hair does not tend to grow as long, but it usually grows faster than female hair [6,7].

The individual hairs are all in different phases; otherwise, we would develop a bald head from time to time, similar to the trees in autumn, shedding their leaves. However, if a hair is pulled out, the next period of hair growth is initiated.

The anagen phase is followed the so-called catagen phase. This transition from anagen to catagen phase is regulated by the growth-maintaining insulin-like growth receptor 1 (IGF-1) [5] and the catagen-promoting transforming growth factor-beta2 (TGF-ß2) [8]. This phase lasts for about two to four weeks. In this phase, the keratinocytes of the hair root degenerate, and hair growth comes to a halt. The hair root loses volume, moves slowly to the surface of the skin, and the connection to the hair papilla is severed, causing the hair to be shed.

In the telogen phase, which lasts 3–4 months, the hair falls out naturally due to external influences such as washing the hair, brushing, or the pressure of a new root forming under the scalp. This is followed by a rest phase until a new cycle begins.

Normally, over 80% of our hair is in the anagen phase. However, under certain circumstances, the proportion of hair in the telogen phase can rise to 30%, and our main hair visibly loses density quickly.

2. Hair Loss

There are various forms of hair loss. Androgenetic alopecia (AGA) is the most common form. It is highly heritable, and genetic susceptibility loci have been identified [9,10]. However, its onset is not congenital. AGA is found in about 50% of men and 40% of women around the age of 70 [11,12]. In this context, AGA is also known in women as female pattern hair loss and in men as male pattern hair loss.

In men, the typical receding hairlines and baldness at the back of the head develop, while in women, a clearing of the mid-crown is seen initially. In AGA, the anagen/telogen ratio is altered, i.e., the telogen phase is prolonged, and the anagen phase is shortened [13]. At the same time, the size of the hair bulb is also affected by the hair thickness [14]. Possible causes of AGA are different variants of the androgen receptor as well as an increased sensitivity to 5alpha-dihydrotestosterone (5a-DHT). Therefore, inhibition of 5a-DHT significantly ameliorates AGA.

Classification systems are available to determine the stage of hair loss in men and women. Here, the Hamilton Norwood system and the Ludwig system are the most commonly used [15].

The Hamilton Norwood system for male genetic hair loss was first created by James Hamilton in 1951 and modified by O'Tar Norwood in 1975. Generally, the stages of hair loss are divided into two categories—(a) scalp that is not bald (types I–III) and (b) scalp that is bald (types IV–VIII).

A similar scheme for androgenetic alopecia in women was developed by E. Ludwig in 1977 [15]. Female hair loss is classified into three grades as follows:

Type I: Perceptible thinning of the hair on the crown, limited by a line situated 1–3 cm behind the frontal hair line.

Type II: Pronounced rarefaction of the hair on the crown within the area seen in type I.

Type III: Full baldness (total denudation) within the area seen in types I and II [15].

Another type of hair loss is alopeacia areata (AA), characterized by circular hair loss. The aetiology of AA is not fully understood, but there are indications for a T-cell-dependent auto-immune disorder.

In contrast to AGA and AA, cicatricial alopecia comprises a group of hair loss disorders in which the hair follicle is irreversibly destroyed. Thus, a permanent loss of hair in the affected patches occur. Telogen effluvium is a non-scarring diffuse hair-loss resulting from the early entry of hair in the telogen phase. It is triggered among others by physiological and metabolic stress. Senescent alopecia (SA) is defined as an ageing of the follicle. This may be caused by reactive oxygen species and other endogenous and exogenous stress factors.

Hair loss is based on various biochemical mechanisms including inflammation [16–19] and oxidative stress, androgenic metabolism [20], reduction of microcirculation [21], and alteration of the cross-talk between the matrix cells and dermal papilla [22]. Thus, depending on the mechanism,

cosmetic intervention with food supplements containing anti-oxidants or which aim to improve the microcirculation like green tea [23] can help with hair loss.

3. Measurements to Determine Hair Loss

How can this hair loss be measured with objective and valid test methods?

The hair pulling test, the trichogram, and the dermatoscopy with fully automated hair analysis software are the diagnostic possibilities to objectively confirm subjective hair loss.

The hair pulling test is the fastest and simplest type of examination. To do this, a strand of about 60 hairs is wrapped around the thumb and forefinger and gently pulled upwards. If more than 10% of the hair is pulled out without effort and pain, this is considered an indication of a problem [24].

The disadvantage of this test is inaccuracy. Both the exact number of hairs and the force with which they are pulled cannot be standardized.

The trichogram is an analysis of the hair roots. Using a clamp, which is covered with a silicone tube to protect the hair, a narrow row of 50–100 hairs is extracted in the direction of growth at two different points. The hair sample is then fixed between two glass plates, and the root area is examined under the light microscope to assign them to the different growth phases. This way, the hairs in the anagen phase can be distinguished from hairs in the telogen phase. Disadvantages of this method are the somewhat painful pulling out of the hair and an incorrect removal technique resulting in the hair breaking off. Furthermore, this method requires a lot of experience to assess the hair root.

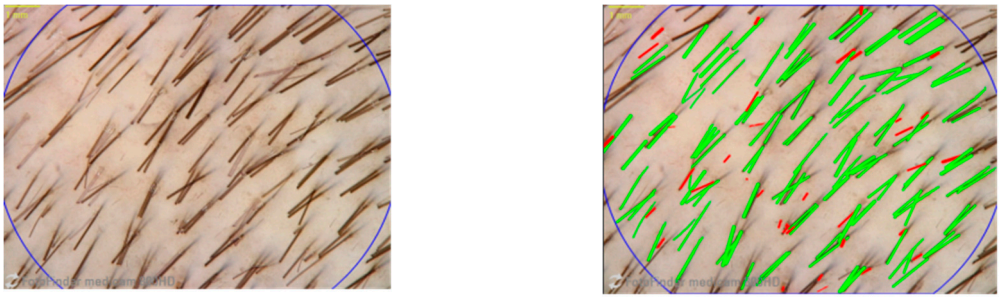
Furthermore, there are three commercially available devices that combine dermatoscopy with fully automated hair analysis software. These devices are the TrichoScan® (FotoFinder Systems GmbH, Bad Birnach, Germany), the Folliscope™ (LeedM Corportion Seoul, South Korea), and Hair Metrix® (Canfield Scientific, Parsippany, NJ, USA) with a simple and fast image processing and image editing. These devices consist of a handheld unit for reflected light microscopy, which captures the scalp under magnification, and corresponding software for hair analysis. In addition, these devices can also be used to assess the scalp for inflammation, dandruff, infection, and scarring and to detect damage to the hair shaft and hair structure as well as hair breakage.

The Canfield's HairMetrix® offers a fully automatic real-time analysis of the data recorded by the VisioMed D200evo camera. Both the Folliscope™ and the Canfield's HairMetrix® offer the following parameters: number and size of follicular units, follicular width to see increase/decrease in shaft diameter, measurement of vellus/terminal hair ratio. In principle, however, a manual evaluation of the images regarding anagen and telogen rate would also be possible here with the Folliscope as well as Canfield's HairMetrix®.

TrichoScan® is a fully automated method for the measurement of biological parameters of hair growth and hair cycle. The TrichoScan® method [25–29] is a modification of the classic trichogram. Thus, the anagen and telogen hairs are primarily determined as in the trichogram.

The TrichoScan® software (TrichoScan 3.0 Research Edition, GCP validated), however, is based on the assumption that anagen hair grows by approximately 0.3 mm a day, while telogen hair does not grow [30]. Furthermore, the software can calculate a number of other parameters such as hair density (n/cm^2), hair diameter (µm), hair growth rate (mm/day) and vellus and terminal hair density. The measuring procedure is as follows: On the first day, the test field is identified, and the hair is clipped evenly to a length of 1 mm in a measuring field of 18 mm by means of a mini hair trimmer. Images are taken at a 20-fold magnification in order to evaluate the evenness of the clipped measurement area. After three days, hair growth is monitored after hair dying for approximately 10–15 min. Three images of the same area should be recorded and then analysed by the software [31]. A further development of the computer-aided TrichoScan® hair analysis was the FotoFinder TrichoScale® system in 2012. In the newer version, the images could primarily be corrected manually, e.g., if individual hairs lie on top of each other and are not recognized by the software. Interestingly, the TrichoScale® method has recently been validated as a diagnostic tool for dogs due to its easy, noninvasive and fast measurement [32].

The biggest advantage of these methods is that it can be performed non-invasively and it is therefore completely painless and provides a whole range of parameters. However, experience in implementation is also important here. For example, the software must be corrected manually for hairs that lie on top of each other (Figure 1).



(**a**) (**b**)

Figure 1. (**a**) Test area three days after hair clipping.; (**b**) Test area three days after hair clipping and analyzed by TrichoScale software. Hairs highlighted in green are defined as anagen.

4. Complex Dietary Supplements for Hair Loss Treatment

As we have described previously, the genetic predisposition is important and determines how long the anagen phase lasts. Thus, the length of the anagen phase and therefore the hair length cannot be changed by external influences. But the hair follicle is highly sensitive to external factors such as metabolism, hormone balance or the supply of nutrients to the hair root. However, in order to have a positive effect on the hair root, topical products can only work if they penetrate into the scalp. Therefore, oral treatments are certainly considered more effective.

In this context, there is a whole series of reviews that have dealt with the effects of individual active ingredients. Here, we would like to mention two current, excellent reviews. For a more detailed overview in the role of vitamins, iron selenium, riboflavin and zinc we would like to refer to the review article of Almohann et al., who reviewed 125 publications in detail [33]. Daniels et al. give a comprehensive review on the role of phytochemicals from caffeine to ginseng to pumpkin seed oil [34]. However, the advantage of oral complex dietary supplements should be a synergistic effect. If there is a synergistic effect, it is important to distinguish this from an additive effect.

An additive effect means that the total effect is the sum of the partial effects. If two substances have an additive effect, then the bioactivity can be added. A synergistic effect, on the other hand, is achieved when the bioactivity found in each substance increases in combination. Therefore, complex foods in the right combination should offer an advantage, and thus, the aim of this review is to analyze existing studies of complex dietary supplements with their experimental weaknesses and strengths and their influence on hair loss. The search key words "complex nutritional supplementation, dietary hair loss, hair growth" were used in the PubMed database. Original papers published since 2000 were used in the data analysis. Surprisingly, however, the literature of human studies on complex food supplements is very sparse. In total, 10 publications were found, which will now be discussed in detail and are listed numerically for clarity in Table 1. However, only the objective measurement methods are discussed.

Table 1. Overview of complex dietary oral supplement studies.

Study	Placebo-Controlled	Test Subjects	Type of Hair Loss	Dietary Supplements	Duration	Methods	Results of Objective Methods	Reference	Published
1	no	30 ♀	abnormal hair loss	green tea extract, vitamin C, natural beta carotene, zinc selenium, chromium borage seed oil (morning capsule) grape extract, shark cartilage, vitamin B2, B5, B6, B8, copper, iron and fish oil (evening capsule)	56 days	Brushed out hair	significantly reduced hair loss	[35]	2007
2	yes	120 ♀(60 per group)	stage I hair loss according to Ludwig scale	fish oil, blackcurrant seed oil, vitamin E and C, Lycopene	6 months	Trichogram Trichometer Global photographs Self-assessment	significant increase in anagen hair in verum group compared to placebo group	[36]	2014
3	no (against competitor product)	120 ♀(60 per group)	telogen rate >20%	Zinc, biotin, iron, vitamins A, C, E, B, folic acid, magnesium, amino acids of keratin and collagen	6 months	TrichoScale® Expert-assessment Self-assessment	significant increase in hair density in the test product and competitor product	[37]	2018
4	yes	30 ♀(26 in verum group; 14 in placebo group)(Caucasian, Asian, Hispanic)	Self-perceived thinning hair	curcumin, ashwangandha, saw palmetto, tocotrienol-rich-tocopherol complex, piperine, capsaicin, hydrolized marine collagen, hyaluronic acid, organic kelp	6 months	Macrophotographs Global photographs Hair Mass Index Self-assessment Quality of Life Questionnaire	significant increase in terminal hairs, significant increase in vellus hairs, significant increase in total hairs compared to placebo Positive trend in HMI	[38]	2018
5	yes	96 ♀(48 per group) (Caucasian, Asian, Hispanic)	Self-perceived thinning hair	blend of shark and mollusk powder, vitamin B7, C, iron	6 months	Macrophotographs Shed hair during shampooing was counted	significantly reduced hair shedding after 3 months compared to placebo significantly thicker vellus-like hair after 6 months	[39]	2015
6	yes	60 ♂(30 per group)	AGA, Norwood scale scores of 2–3	vitamin C, zinc, AminoMar® complex horsetail stem extract, flaxseed extract	6 months	TrichoScan® Quality of Life Questionnaire Expert-assessment Self-assessment	Hair count, hair density, terminal hair density significantly increased compared to baseline	[40]	2016
7	no	27 (4 ♂and 23 ♀)	Telogen effluvium >3 months	Boswellia Serrata, Curcuma long, Vitis vinifera	3 months	TrichoScan® Self-assessment	non-significant increase in hair thickness	[41]	2019
8	yes	60 (20 per group) (active substance; active substance + other ingredients; placebo)	Telogen effluvium >3 months	spermidine was administered together with methionine, vitamin C, E, B6. calcium pantotenate, zinc, polyphenols from red grape peels, copper, folic acid, biotin	2 months	Trichogram Pulltest Wash test	Anagen hair, resistance of hair stem to traction and hair loss: active substance is superior to active substance alone and to placebo	[42]	2003
9	yes	100 (23 ♂and 76 ♀)	normal healthy subjects	spermidine-based supplement (see study 9)	3 months	Trichogram K-67 marker c-Kit marker	Late anagen phase significantly increased compared to placebo	[43]	2017
10	no	10 (6 ♂and 4 ♀)	AGA, severity mild to severe	green tea extract, omega 3 and 6 fatty acids, melatonin, cholecalciferol, beta-sitosterol, soy isoflavones	6 months	Trichometer Dermoscopy Global photography assessment	Significant increase in hair count and HMI	[44]	2017

First, the studies with women are described.

Study 1: The study was conducted from November to February over a period of 56 days on 30 women aged 35–65 years with abnormal hair. However, the inclusion criteria "abnormal hair" was not further described by the authors. In this study, a complex blend, on the one hand, with green tea extract, vitamin C, natural beta carotene, zinc selenium, chromium borage seed oil (morning capsule) and, on the other hand, with grape extract, shark cartilage, vitamin B2, B5, B6, B8, copper, iron, and fish oil (evening capsule) INVERSION® Femme (Inversion Laboratoires, Hasselt, Belgium) reduced hair loss significantly compared to a pretreatment phase (28 days prior to supplementation). The weak points of this study are that it is not placebo-controlled, the period of testing of two months is extremely short, there is a lack of precise information on the inclusion criteria for hair loss, and brushed out hair for analysis was weighed [35]. A positive aspect is that there are extra capsules for morning and evening, so that the green tea extract in the morning capsule, for example, does not lead to problems falling asleep.

Study 2: In this study, 120 female volunteers with stage I hair loss according to the Ludwig Scale between 18 and 65 years of age were included. Exclusion criteria were telogen effluvium (telogen rate >30%) or any confirmed or suspected condition or pathology that may induce hair disorder. It is a placebo-controlled, randomized study. Here, a nutritional supplement with omega 3 and 6 from fish and blackcurrant seed oils with antioxidants (lycopene, vitamin C, and vitamin E) led to a statistically significant increase of anagen hair from approximately 80% to 88% after six months of supplementation measured by Trichogram. In contrast, in the control group there was no difference in the anagen rate between before and after (81%) and thus a statistically significant difference in favor of verum over placebo is given. These data were supported by global photographs, self-assessment and trichometer for hair density. This study is well thought out and of high quality [36].

Study 3: Investigated were 120 volunteers between 18 and 60 years of age. The inclusion criteria were a telogen effluvium of more than 6 months and a telogen rate of more than 20% (determined by TrichoScale®). A period from September (protocol initiation) to September of the next year (end of study) was specified. In this study a food supplement was tested against a competing product. The product to be tested (Eximia Fortalize Kera D®), which consists of zinc, biotin, iron, vitamins A, C, E, and B complex, folic acid, magnesium, and amino acids of keratin and collagen was tested against the product Pantogar®, which consists of calcium pantothenate cystine, thiamine nitrate, medicinal yeast, keratin, and aminobenzoic acid. Hair density was significantly increased by approximately 11% after 180 days and by approximately 8% by the competitor product, measured by TrichoScale®. In addition, an expert assessment of parameters such as hair loss and hair volume and a self-assessment by the volunteers was performed [37]. However, it is questionable why no more parameters of the TrichoScale were evaluated in such a complex study.

Study 4: Included were 26 subjects in the verum group and 14 in the placebo group. The age of the women was between 21 and 65 years with Asian, Caucasian, or Hispanic ethnic background and self-perceived thinning hair. Exclusion criteria were hair loss disorders. Various phytocompounds were combined in a complex called Nutrafol® Women's Capsules. Nutrafol® contains a total of 21 ingredients, the most important of which are curcumin, ashwangandha, saw palmetto, tocotrienol-rich-tocopherol complex, piperine, capsaicin, hydrolized marine collagen, hyaluronic acid, and organic kelp. This study resulted in a statistically significant increase in the number of terminal hairs, vellus hairs and total hair count in the verum group at 90 days and 180 days compared to the placebo group. This was determined using a phototrichogram (via macro photographs). In addition, there was a positive trend in the Hair Mass Index (HMI) measured by HairCheck™, Divi International Co., compared to the placebo group. In this study, a survey by means of a self-assessment questionnaire, and a quality of life questionnaire was also conducted. The study was randomized and double-blind. There is no information available at what time of year the study was conducted, and the number of subjects was very small [38].

Study 5: This study was a double-blind, placebo-controlled study with 96 female subjects aged 21–55 years from Asian, Caucasian, and Hispanic ethnic background and self-perceived thinning hair over a period of six months. AminoMar™C marine complex composed of a proprietary blend of shark and mollusk powder with vitamin B7, vitamin C, and iron showed significantly reduced hair shedding after three but not six months compared to placebo, and vellus-like hairs were getting thicker after three and six months (being statistically significant after six months). A phototrichogram (via macro photographs) was performed to determine vellus and terminal hair, and shed hair during shampooing was collected and counted [39]. There are no differences in the total number of vellus and terminal hairs, and it is unfortunate that no group comparison was made for the other parameters.

Study 6: This was a randomized double-blind placebo-controlled study with 60 male volunteers. Inclusion criteria were androgenic alopecia and a Norwood Scale scores of 2–3, and the measurements were performed by TrichoScan®. Exclusion criteria were alopecia areata, scarring alopecia, and telogen effluvium. Analogous to the female study with AminoMar™C marine complex, a study with men was also conducted. This is the commercially available product Viviscal® Man (Lifes2good, Inc.: Galway, Ireland). Each tablet contains vitamin C, zinc, AminoMar® complex horsetail stem extract, and flaxseed extract. Average hair count was shown to increase significantly from 162 to 175 hairs, average hair density increased significantly from 160 to 172 hairs, and terminal hair density increased significantly from 122 to 130 hairs after 180 days. The vellus hair density did not change. In addition, a survey by means of a quality of life questionnaire and a self-assessment questionnaire as well as an expert assessment were conducted. It was conspicuous that no group comparison was carried out as a statistical analysis, a period in which the study was conducted is also missing [40].

Finally, we come to the studies in which both men and women have been recruited.

Study 7: Included in the study were 27 subjects—four men and 23 women aged between 19 and 76 years with telogen effluvium for at least three months. The patented product Omni-Three contains Boswellia Serrata, Curcuma longa and Vitis vinifera. Although not statistically significant, the vellus hair, terminal hair and hair density in general decreased. However, the hair thickness increased non-statistically. This study also has some weaknesses. Overall, the study only ran for three months and was not placebo controlled. For evaluation, the TrichoScan® was used, and an additional self-assessment was performed [41].

Study 8: In the following we would like to discuss two very interesting publications that build on each other. Included in the first study were 60 subjects, men and women, aged 18–60 years with telogen effluvium for at least three months. In a first step, the active substance was tested alone, in combination with other ingredients and against placebo. The active substance is spermidine. Spermidine is a biogenic polyamine and occurs in all living organisms and is closely related to cell growth. In addition, spermidine was administered together with the ingredients methionine, vitamin C, vitamin E, calcium pantotenate, zinc, polyphenols from red grape peels, vitamin B6, copper, folic acid, and biotin as a complete food supplement. The trade name is Biogenina®. The microscopy assessment (trichogram) of the follicles showed a 17% increase in anagen phase for the spermidine-supplemented group, a 20% increase for the Biogenina group, and an 8% increase in the placebo group. The pull test to assess the resistance of hair stem to traction was unchanged in the placebo group and improved by 63% in the spermidine-supplemented group and by 94% in the Biogenina group at two months. In addition, a wash test was performed. The hair loss was unchanged in the placebo group and decreased by 39% in the spermidine-supplemented group and by 67% in the Biogenina group at two months. This study was a randomized, double-blind, placebo-controlled study. Particularly positive here is that, in addition to the numerous objective test methods, blood values were also taken to rule out specific deficiencies [42].

Study 9: Based on this first study, a second double-blind, randomized, and placebo-controlled study was conducted on 100 subjects with 76 women and 23 men. Exclusion criteria were androgenetic alopecia or congenital or acquired diseases affecting the hair shaft. The verum group received the spermidine-based supplement for three months. Exclusion criteria included initial signs of androgenetic

alopecia. The number of anagen V–VI hair bulbs was examined microscopically. The anagen V–VI are so-called late anagen hair follicles. The number of anagen phase V–VI hair bulbs increased from 25 to 37 (from a total of 100 bulbs) in the verum group and decreased from 26 to 20 (from a total of 100 bulbs) in the placebo group. Thus, there was a statistically significant difference between both groups. In addition, the proliferation markers Ki-67 (marker of cellular proliferation) and c-Kit (marker of apoptosis) in the hair roots were investigated. Again, there was a significant difference between both groups in favor of the verum over the placebo group [43].

Study 10: In a pilot study men and women between 18 and 65 years with a diagnosis of mild to severe AGA were investigated. Here, four men and six women tested the nutritional supplement Forti5® over a period of 6 months from September to June. It contains green tea extract, omega 3 and 6 fatty acids, melatonin, cholecalciferol, beta-sitosterol, and soy isoflavones. There was a significant increase in hair count by approx. 6% and hair mass index (HMI) by approximately 10%. The hair count was measured by demoscopy and the HMI with a trichometer. Additionally, a global photography assessment was performed [44].

5. Discussion

5.1. Efficacy of Conventional Therapies for Hair Loss Compared to Complex Nutritional Supplementation

In the present review, only complex dietary supplements were considered with regard to hair growth. However, the conventional therapies available are minoxidil and finasteride, as well as the autologous regenerative therapies based on platelet-rich plasma and stem cells such as adipose-derived mesenchymal stem cells and human hair follicle epithelial stem cells [45]. Finasteride® is an oral drug for the treatment of androgenetic alopecia by inhibiting the formation of dihydrotestosterone as a 5-alpha reductase inhibitor. Van Neste et al. show that, in a study of 212 men with AGA taking 1 mg Finasteride® daily for 48 weeks, there was a significant improvement of 17 total hairs (8%) and 27 anagen hairs (26%) compared to the placebo group [46].

Minoxidil is available as a 5% solution or 5% foam for men and 2% solution for women and is used topically. It extends the anagen period and increases hair follicles by activating prostaglandin-endoperoxide synthase-1. For minoxidil 5% it was shown that the hair density had improved by about 19 hairs/cm^2 with topical application and by about 38 hairs/cm^2 with electrodynamics micro-needle treatment plus topical minoxidil 5% after 24 weeks compared to baseline [47].

In a systematic review by Adil et al., the superiority and effectiveness of these treatments in men with AGA as well as minoxidil in women with AGA compared to placebo was shown by five meta-analyses [48].

An alternative therapy to improve hair loss is autologous activated platelet-rich plasma (PRP). It is believed that the positive effect on hair growth is mainly an anti-apoptotic effect through activation of the Bcl-2 protein and Akt signaling. In detail, it was shown that hair density improved by 28 hairs/cm^2 compared to placebo [49].

In a systematic review by Gentile and Garcovich, 12 clinical studies regarding PRP were analyzed, with the result that 84% of the study showed a positive effect as AGA treatment. 50% of the studies even showed statistically significant effects, while 34% of the studies showed an improvement in hair density and thickness. Based on these data and no major side effects, this treatment is being considered as an alternative to the above mentioned conventional therapies [50].

As a further autologous therapy, a micrograft with human hair follicle mesenchymal stem cells showed an improvement in hair density of 23 hairs/cm^2 compared to the baseline and to the placebo group. After only six months, the patients showed hair loss again [51].

Hair re-growth was also obtained by micro-graft from scalp tissue containing "Human intra and Extra Dermal Adipose Tissue-Derived Hair Follicle Stem Cells (HD-AFCS)". These, in turn, consist of approximately 6% hair follicle mesenchymal stem cells and approximately 3% hair follicle epithelia stem cells. After three injections in an interval of 45 days, test subjects showed, after half a year and

up to one year after the last injections, an improvement in hair density of 33% and 27%, respectively. Only three treated patients showed a relapse of hair loss in the following 16 months [52].

However, the present review shows that hair growth can also be improved by nutritional supplementation even though the publications are very sparse with statements on anagen and telogen rate. For example, a 20% increase in the anagen rate could be achieved by taking the product Biogenina® [42] and the hair density was improved by 12 hairs/cm^2 using Viviscal® Man [40].

5.2. Active Ingredients and Their Mechanisms of Action

In order to positively influence the various biological mechanisms of hair loss, various active ingredients were selected in the complex dietary supplements (Table 1). Here, the results of studies 2, 6, and 8 are particularly positive, so these ingredients are looked at more closely.

Black currant seed oil contains stearidonic acid (SDA). SDA is a precursor of eicosapentaenoic acid (*EPA*) that is recognized for its anti-inflammatory efficacy [53,54]. Furthermore, fish oils, mussel extracts as well as flaxseed extract contains omega-3 and omega-6 fatty acids, which are also known for their anti-inflammatory effects, were used.

Vitamins as well as lycopene [55] or polyphenols from red grape peel have most likely been selected for their anti-oxidant activity. Also, in this context, the EFSA has recognized the following claim: "Vitamin E contributes to the protection of cell constitutes."

The lower hair follicle part is surrounded by blood vessels that supply it with important nutrients for growth. A decrease in microcirculation can therefore reduce the supply of nutrients and oxygen to the hair follicle. The shark extract is made of collagen, and collagen is involved in the structure integrity of the skin and blood vessels. Here, vitamin C also plays an important role in collagen formation and healthy blood vessels. Here, the EFSA accepts the claim that vitamin C contributes to normal collagen formulation and the normal function of blood vessels.

It is well known that zinc can lead to hair deficiency [56,57], and Neve et al. 1996 shows the positive effect of zinc after gastroplasty [58]. Thus, the European Food Safety Authority (EFSA) recognizes the claim that "Zinc contributes to the maintenance of normal hair."

Spermidine belongs to the family of polyamines and shows anti-aging properties. It reduces inflammation, induces autophagy, and regulates cell growth, proliferation, and death. These properties seem to make spermidine a potent agent in hair growth.

6. Conclusions

In summary, it is immediately apparent that many publications on complex oral supplementation are very topical and many manuscripts have been published in the period from 2014 to 2019. Overall, the quality of the studies varies greatly. A total of five studies have been conducted on women [35–39], one study in men [40], and four studies on men and women [41–44].

The duration of the studies varies between two and six months, with 6 out of 10 studies conducted over a period of six months. In general, it makes sense to carry out studies over a period of at least four months, especially in the case of dietary supplements. Based on our own experience with numerous nutritional supplement studies in both the skin and hair area, the first positive results can be expected after three months at the earliest, whereby here often only a tendency but no significance is achieved. It is noticeable in the studies that there is often a great deal of evaluation in the area of subjective assessments such as global photographs, expert- and self-assessment, and, unfortunately, the objective parameters receive less attention. In addition, the TrichoScan® or TrichoScale® procedure was used in three studies, but without exhausting all possibilities of measurement parameters, so that the parameter anagen rate is only evaluated in two or three publications and often only the total hair count or the vellus and terminal hair density is given. However, it is the anagen rate in particular that provides information about an improvement in hair loss. With regard to the results of the complex dietary supplement studies, almost all studies have shown very positive results, so that the complex dietary supplements should be given more importance on a scientific basis in the future. In future studies, however, it would

be desirable to pay more attention to purely objective measurement methods with many measurement parameters. This would certainly be desirable as a placebo-controlled study was already presented in 2008 at the 17th European Academy of Dermatology and Venerology, where both men and women showed a more balanced hair cycle with decreased hair loss (increased anagen rate) and increased hair density together with an improvement of hair quality after supplementation with antioxidants, polyunsaturated fatty acids, zinc, taurine, and plant polyphenols. Here, the objective parameters anagen rate, telogen rate, and hair density were determined exclusively by the TrichoScan method [59]. Furthermore, it would also make sense to investigate synergistic effects of active substances further.

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