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An Uncontrolled Case Series Using a Botanically Derived, β-Cyclodextrin Inclusion Complex in Two Androgenetic Alopecia-Affected Male Subjects †

Geno Marcovici [1,*] and Alan Bauman [2]

[1] ART Inc., 101 Raintree Ln, Mahwah, NJ 07430, USA
[2] Bauman Medical Center, 1450 S. Dixie Hwy, Boca Raton, FL 33432, USA; doctorb@baumanmedical.com
* Correspondence: dr.marcovici@hairgenesis.com; Tel./Fax.: +1-201-785-4061
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Abstract: Drug-based monotherapy provides limited clinical benefits in polygenic disorders, such as androgenetic alopecia. Possible benefits must be measured against non-trivial risks of negative side effects. Several well-controlled, peer-reviewed, basic science studies have demonstrated novel mechanisms of action and potential utility for natural-based phytochemicals in the treatment of androgen-mediated disorders, including androgenetic alopecia. Yet, due to phytochemical instability, volatility, and incompatibility, the bridge from in vitro potential to clinical efficacy remains largely unmet. Recent advances in nanomaterial manipulation provide enhanced platforms, such as cyclodextrins, in which these phytochemicals may be enveloped and delivered without triggering the loss of intended function. Unexpected, positive results of an uncontrolled case series for a cyclodextrin-enabled, natural-based formula containing γ linolenic acid, β-Sitosterol, epigallocatechin gallate, and genistein, administered concomitantly via oral and topical form in two androgenetic alopecia-affected, male subjects over the course of 270 days were found. At baseline, significant baldness in the vertex scalp of both subjects was observed. Subsequent 90-day time points demonstrated marked hair thickening. On treatment day 270 (conclusion), scalp hair loss was no longer evident in either patient. Particularly in the setting of a disorders, such as androgenetic alopecia, nano-complexed, botanically-based compositions may offer beneficial adjunctives or alternatives to traditional drug-based/surgical medical treatments.

Keywords: hair loss; advanced drug delivery; nanoparticles; natural hair loss treatment; phytochemicals; β-cyclodextrin

1. Introduction

Several hair loss phenotypes occur in humans, with androgenetic alopecia (AGA) or common pattern hair loss constituting the most prevalent form by far [1]. The connection between AGA and age-related disease remains inconclusive; however, tantalizing clues suggest a linkage between these two conditions. To cite one example, individuals with vertex baldness are at a statistically significant increased risk of developing prostate cancer [2].

Both men and women may be affected by AGA as a result of similar genetic and hormonal triggers. However, the expression pattern differs according to epigenetic and gender-specific variables. Males may begin losing hair in their late teens to early 20s, whereas it is unusual for a woman to experience AGA prior to her mid to late 30s [3].

Three principal factors drive pattern hair loss: (1) Age. Prepubescent children do not suffer from AGA, (2) Genetics, and (3) Biochemistry. Recent genome-wide association studies (GWAS) have

identified 71 susceptibility loci [4]. This link is demonstrated by androgen insensitivity syndrome wherein affected patients who do not develop AGA despite circulating androgens and a genetic predisposition [5]. However, in AGA-susceptible individuals, the onset of the disorder is triggered when 5-alpha dihydrotestosterone (DHT) is metabolized from testosterone (T) via the enzyme 5 alpha-reductase (5AR) [6]. The modified human androgen receptor (hAR) transcription factor translocates to the cell nucleus in which it dimerizes and binds to androgen receptor elements within classical target genes to modulate gene transcription. The clinical phenotype manifests in a pattern of reduced anagen and increasingly frequent telogen (Figure 1). This process may be described as a negative growth cycle thereby progressively transforming full thickness, pigmented terminal scalp hairs into moderate caliber, low caliber, and ultimately, hypo-pigmented vellus hairs [7]. As with several androgen-mediated disorders, including those linked to aging, key inflammatory markers have been identified that appear to hasten the progression of AGA. These include dikkopf-1 (DKK-1), fibroblast growth factor (FGF)-1 and 17 beta-hydroxysteroid dehydrogenase Type-3 (17-HSD-3) [8].

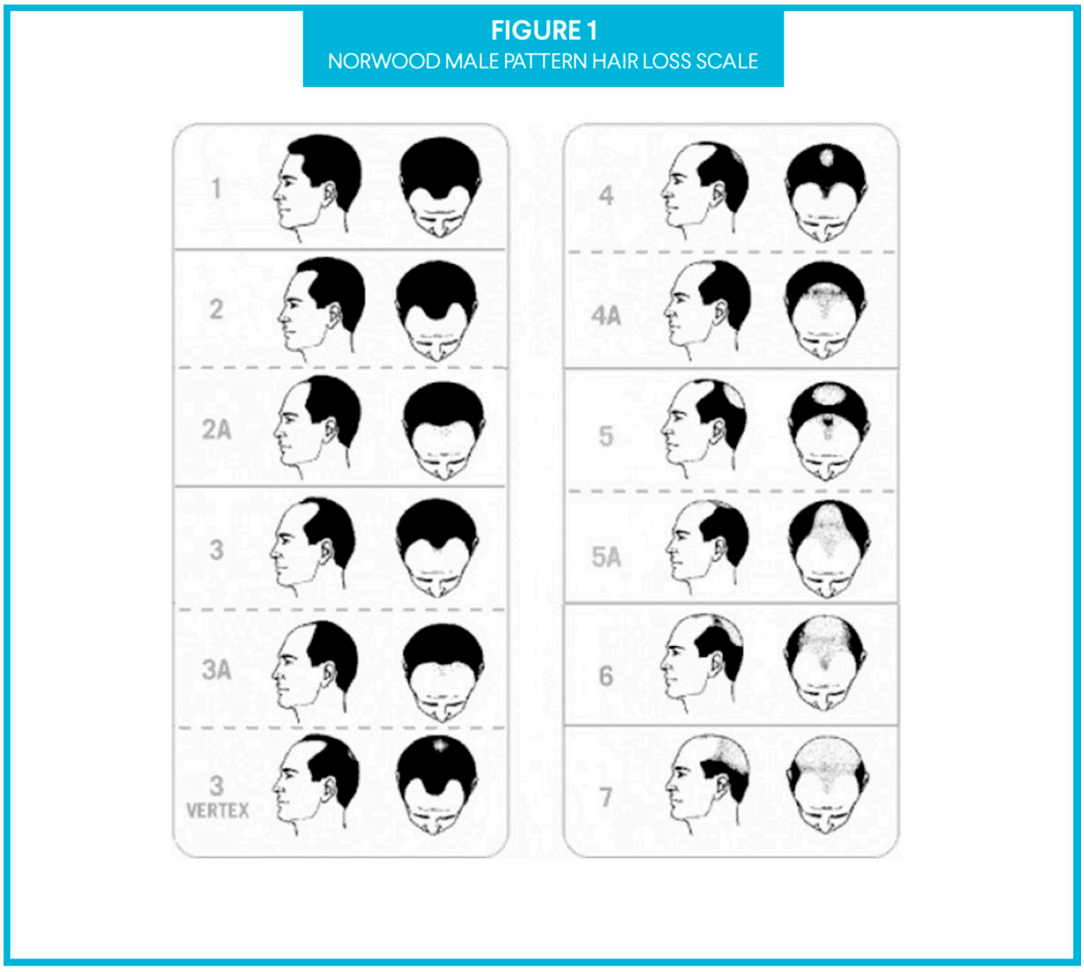

Figure 1. Male androgenetic alopecia (aga).

1.1. Drug-Based Treatment Choices

1.1.1. Minoxidil

For both patients and healthcare practitioners, each treatment choice predicates limitations and caveats that must be weighed against desired benefits. Until recently, there have been essentially two pharmaceutical options for treating AGA (Table 1). The first is minoxidil, a putative modulator of sarcolemmal potassium (K_{ATP}) channels [9]. Initially developed as an oral antihypertensive, anecdotal

reports of hair growth spurred research into repurposing the drug as a topical baldness treatment. The Food and Drug Administration (FDA) approval was granted in 1984, rendering minoxidil as the first drug ever approved by the FDA to treat pattern hair loss. To this day, minoxidil remains the only FDA-approved topical drug for the treatment of both female and male pattern hair loss [10]. Initially available in 2% concentration, extra strength 5% minoxidil was ultimately approved for men in 1997, and the higher potency version was recently approved for women. Yet, despite more than three decades of investigation and clinical application, minoxidil's precise mechanism of action in the hair follicle remains unclear [11]. Serious side effects, such as polymyalgia syndrome while rare, have been reported [12]. Less serious, but more commonly observed, cutaneous side effects include contact dermatitis, erythema, and papulovesicles of the scalp. Such negative symptoms generally self-resolve after discontinuation of minoxidil therapy [13].

Table 1. Drug-based therapy, benefits vs. risks.

Minoxidil		**Finasteride**	
Positives	**Negatives**	**Positives**	**Negatives**
• Only topical AGA Drug Approved by FDA • Successfully tested under IRB clinical trials • Now available for ♂and ♀in 5% maximum strength version • May slow or arrest progression of AGA	• Contact dermatitis common side effect • Uncommon but serious side effects reported • Monotherapy not optimal against polygenic disorder	• Most commonly prescribed oral AGA drug • Successfully tested under IRB clinical trials • May slow or arrest progression of AGA • Proven mechanism of action. Targets isoenzyme linked to AGA	• Risk of teratogenic effect • Not indicated for use by women (females cautioned against even handling powder) • Serial, potentially serious negative side effects reported • Negative side effects may persist despite discontinuation • Monotherapy not optimal against polygenic disorder

1.1.2. Finasteride

Originally developed to treat benign prostatic hyperplasia (BPH), oral finasteride is a preferential inhibitor of type two 5-alpha-reductase and constitutes the second most commonly used hair loss treatment drug [14]. The hair growth potential of finasteride was observed primarily thru evidence in BPH patients treated with the 5mg version, Proscar™. Repurposed for treatment against pattern hair loss, finasteride in 1 mg dosage received FDA approval as the first oral hair loss drug in 1997. Due in part to its teratogenic potential, Propecia™ has only ever been indicated for use by men [15]. Although clinically effective against pattern hair loss in statistically significant cohort trials, the published literature also reports serious negative side effects that appear to persist even after discontinuation of the drug. These side effects include loss of libido, ejaculatory dysfunction, disorders of the penis and testes, gynecomastia, and cognitive symptoms including suicidal ideation [16].

1.1.3. Combined Drug Therapy

Inasmuch as hair follicles are ectodermal appendages of the integument, they are susceptible to both local and systemic therapy. Thus, the concomitant use of oral finasteride and topical minoxidil constitutes a rational hypothesis that has been attempted with some success [17]. However, the caveat of amplified negative side effects may discourage clinicians and patients from considering the approach.

1.2. Botanicals, Unique Potential, Formidable Challenges

It is now well-understood that the multi-factorial phenotype, androgenetic alopecia (AGA) involves complex interactions, many of which appear to transcend simple, pleiotropic, genetic susceptibility. Here, several key paradigms converge in favor of a botanical-based treatment approach. First, as with all ectodermal appendages, scalp hair follicles are susceptible to concomitant therapy via oral and local therapeutic delivery [18]. Second, natural-based compounds may trigger fewer negative side effects. Third, botanically derived chemicals may be combined to concurrently offer multiple therapeutic actions [19]. Decades of published, well-designed, basic science studies report intriguing activity of botanically-based, candidate hair growth compounds. Yet bridging the gap between in vitro potential and clinical utility has remained an elusive goal. In recent years, several key factors contributing to the challenge have surfaced. Phytochemicals are intrinsically limited by poor aqueous solubility, weak permeation, low systemic availability, structural instability and deactivation during first pass metabolism [20]. Furthermore, promising candidate compounds tested in vitro have proven highly susceptible to volatile interaction with solubilizers, excipients, buffers, co-actives, and other components necessary to the development of stable, efficacious, clinically appropriate medicinal agents [21]. In summary, multiple lines of evidence suggest that without protective mechanisms, hair growth formulas built upon a foundation of natural phytochemicals tend to be denatured, converted, inactivated, poorly absorbed, and/or simply excreted [22]. Therefore, it is reasonable to surmise that candidate phytochemically-based formulations must be sequestered in some fashion to maintain their therapeutic potential in vivo.

Previously, we demonstrated safety and efficacy in the setting of AGA, using botanical-based compositions incorporating γ linolenic acid, β-Sitosterol, epigallocatechin gallate and genistein in an institutional review board (IRB)-monitored trial. Here, we report an unexpectedly positive outcome from a two-subject case series testing a cyclodextrin stabilized, botanically-based, oral and topical concomitant formulation.

1.3. Active Compounds

1.3.1. γ linolenic acid

The anti-inflammatory omega-6 fatty acid γ-linolenic acid (GLA) with three double bonds in the carbon chain, also known as all-cis 6,9,12-octadecatrienoic acid, belongs to the n-6 family of fatty acids. GLA has biologically important functions in the human body, such as acting as a substrate for eicosanoid synthesis, cholesterol transport and oxidation, and as an intracellular lipid membrane component. Inadequate dietary GLA intake or impaired metabolism has been linked to numerous inflammatory and degenerative diseases [23].

1.3.2. β-Sitosterol

β-Sitosterol, found in several botanical substrates, including sea buckthorn and a sub-constituent of LSESr is a highly lipophilic, naturally derived phytosterol possessing a chemical structure similar to that of cholesterol. Soluble in alcohols, sitosterols are typically white, waxy powders with a characteristic odor. Although the exact mechanism of action remains unclear, β-Sitosterol has been shown to inhibit 5-alpha-reductase [24].

1.3.3. Epigallocatechin Gallate

Epigallocatechin gallate (EGCG), a major component of green tea and one of the most active antioxidant compounds known, has been investigated as a tool against AGA. However, the compound is limited by its low chemical stability and inability to efficiently permeate either the gastric mucosa or human epidermis [25]. Recently, a basic science study was undertaken to investigate its effect on human hair follicle-derived dermal papilla cells (DPCs). Results from this study showed that epigallocatechin gallate (EGCG) protects DHT-induced cell death by regulating the cellular miRNA expression profile,

thereby attenuating DHT-mediated cell death and growth arrest. The data also showed that EGCG caused a decrease in intracellular reactive oxygen species (ROS) levels and senescence [26].

1.3.4. Genistein

Phytoestrogens are naturally occurring nonsteroidal phenolic plant compounds that due to their molecular structure and size, resemble vertebrate steroid estrogens. The main dietary sources of isoflavones for humans are soybean and soybean products, which contain high levels of genistein. Although the genetic architecture governing AGA remains incomplete, both androgens and downstream markers of inflammation have been implicated in this architecture [27]. Inferential data show that the pleiotropic isoflavone genistein may inhibit the nuclear factor kappa B (NF-kB) signaling pathway, a putative modulatory factor in hair cycling and hair loss phenotypes, including AGA [28]. In another basic science study, genistein was shown to preferentially inhibit type 2,5-alpha-reductase, the isoenzyme most strongly linked to AGA [29].

1.4. The Delivery Vector

Although synthetic nano-delivery systems include precious metals, carbon nanotubes, and other materials, several naturally-based nanoscale delivery vehicles are now available to protect, sequester, stabilize, and deliver therapeutic phytochemical compounds to the target tissue (Figure 2). These include chitosans, liposomes, and cyclodextrins. With a hydrophobic interior and hydrophilic exterior, cyclodextrins form stable, amphiphilic complexes with hydrophobic compounds. α-, β-, and γ-cyclodextrin are all generally recognized as safe by the FDA. Of note, β-cyclodextrin has emerged as the most versatile excipient among the cyclic oligosaccharides with proven utility in oral, rectal, dermal, ocular, and parenteral formulations (Figure 3). Multiple published reports have demonstrated safety and efficacy for β-cyclodextrin in the use of poorly soluble phytochemicals [30].

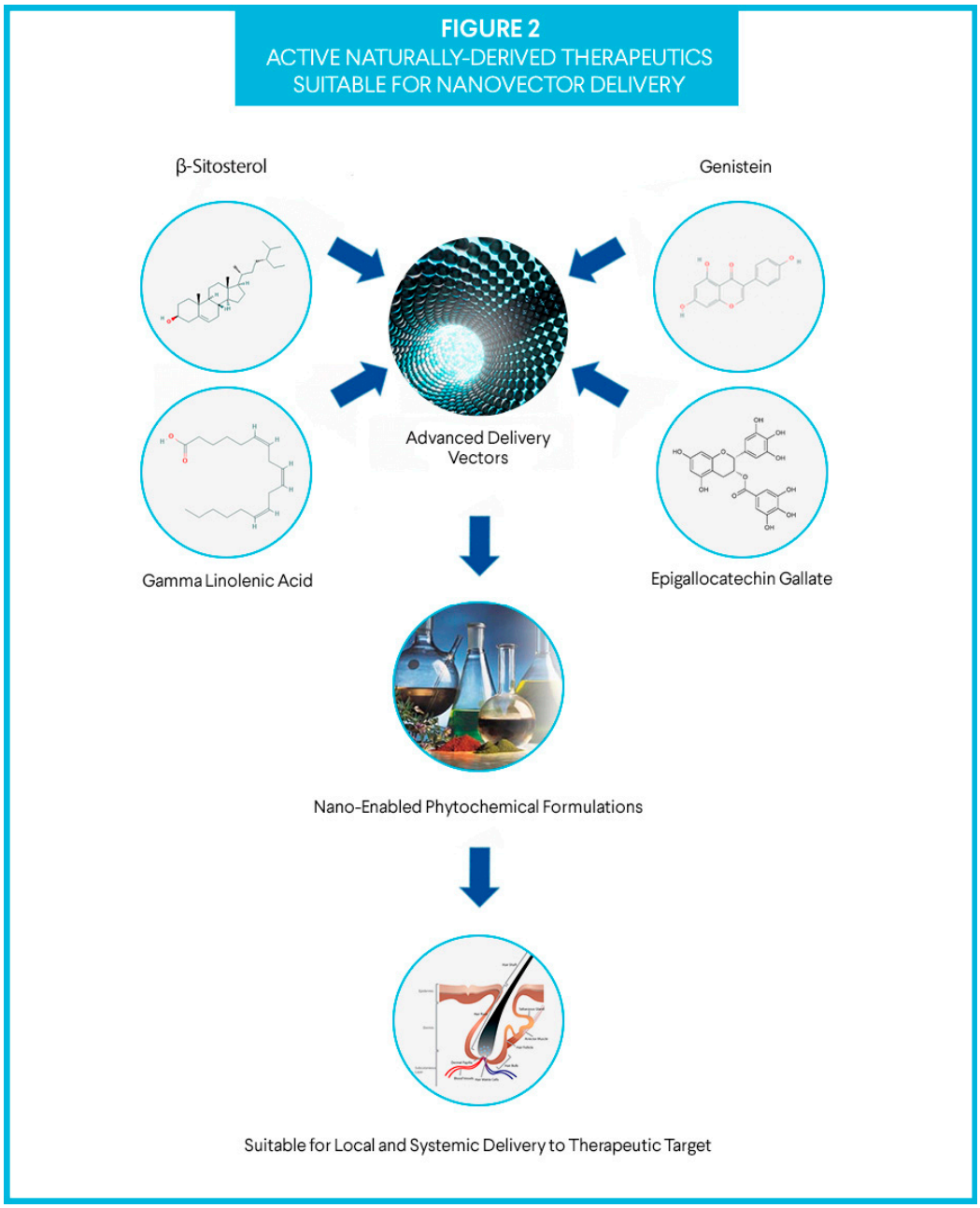

Figure 2. Active, naturally derived therapeutics suitable for nanovector delivery.

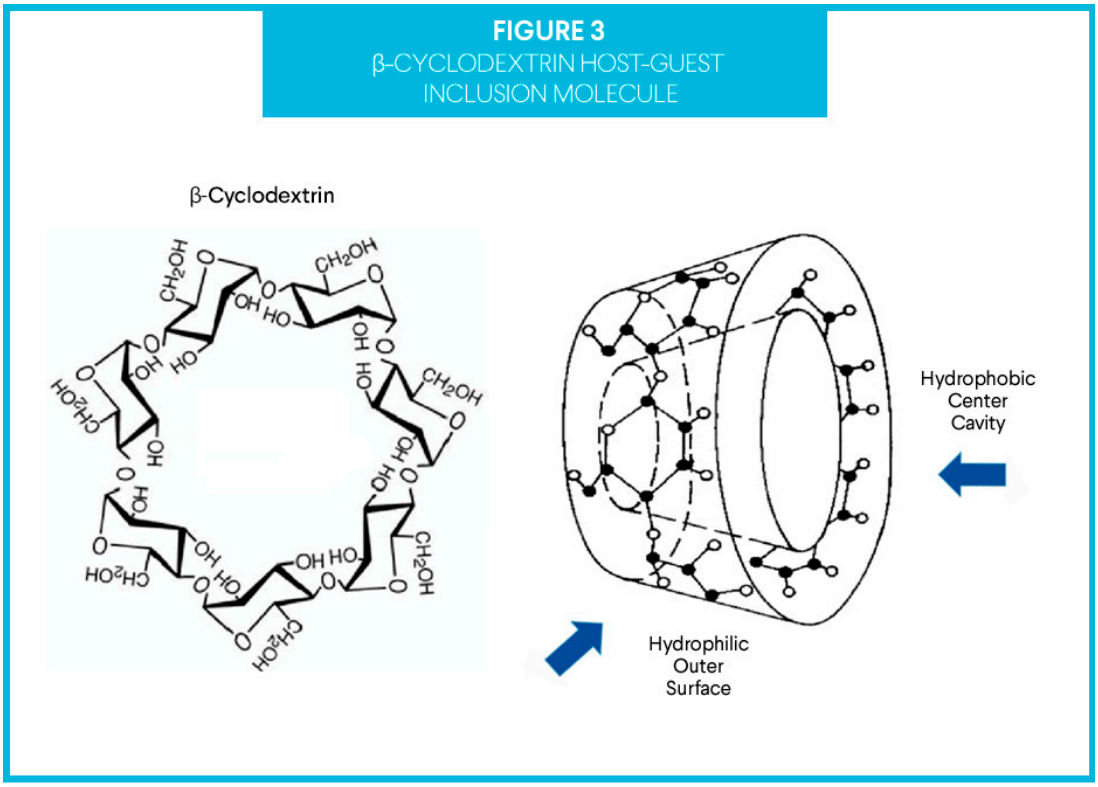

Figure 3. β-cyclodextrin molecule.

2. Methods

2.1. Preparation of Treatment Materials

For this case series, standardized, quantified materials were obtained from Sigma-Aldrich (St. Louis, MO, USA). Quantitative values were determined via liquid chromatography (LC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), and gas chromatography (GC) [31]. In LC as the liquid mobile phase passes through the column, components in the mobile phase interact to varying degrees with the solid stationary phase [also known as the chromatography media or resin]. Molecules of interest in the mobile phase are separated based on their differing physiochemical interactions with the stationary and mobile phase(s). HPLC uses pumps to pass a pressurized liquid solvent containing the analyte mixture through a column filled with a solid adsorbent material. Each substance in the sample discretely interacts with the adsorbent material, causing unique flow rates for each component, leading to their separation as they flow from the column. In MS, a sample [either solid, liquid or gaseous] is ionized by electron bombardment. The resulting ions are thereby separated according to their mass-to-charge ratio. In GC the analyte solution is injected into a gas stream which transports the sample into a column separation tube. GC operates on similar principles to column permeation chromatography (CPC), wherein a sample is dissolved in a mobile phase and passed through a porous stationary structure thereby yielding a quantitative result.

The test formula consisted of analytical standard grade betasitosterol (≥95% purity/GC; CAS Number: 83-46-5), γ linolenic acid (≥98.5% purity/GC; CAS Number: 506-26-3), epigallocatechin gallate (≥95.0% purity/HPLC; CAS Number: 989-51-5), and genistein (≥97.0% purity/HPLC; CAS Number: 446-72-0). Analytical grade β-cyclodextrin (CAS Number: 7585-39-9; ≥97% purity/MS) was likewise obtained from Sigma-Aldrich (St. Louis, MO, USA). Each active compound was incorporated into β-cyclodextrin by classic co-dissolution procedures. Chromatographic characterization of the β-cyclodextrin inclusion complex demonstrated a 1:1 host-to-guest stoichiometry. At this stage, the host–guest inclusion complex of β-cyclodextrin vehicle and each bioactive test substance was

reduced to a fine granular powder via coprecipitation, kneading, grinding, air drying and freeze drying [32]. Once again, the resulting solid-state admixture was characterized by differential scanning [HPLC] and the formation of a 1:1 water soluble inclusion complex. To prepare for oral delivery the resulting powder was combined with dicalcium phosphate, vegetable stearic acid, cellulose, sodium croscarmellose, calcium carbonate, vegetable magnesium stearate, silicon dioxide, and titanium dioxide. The excipient-loaded admixture was subsequently compressed into hard 3 mm × 8 mm oval tablets.

To optimize the botanical formula for topical application, the host–guest inclusion admixture was solubilized via sonication into a deionized aqueous solution preloaded with 1% disodium laureth sulfosuccinate and 1% isopropyl. Sorbic acid (0.010%) and citric acid (0.015%) were subsequently incorporated as preservative and antifungal and antimicrobial agents. The resulting formula with an assay pH of 4.75 was dispensed as a light foam to the scalp via a calibrated foaming pump type applicator. The foam dispersion method is advantageous due to the greater potential for ease of distribution across the scalp. Each application of the pump dispensed ~10 mL aerosolized foam equal to ~2 mL liquid.

2.2. Uncontrolled, Two Patient Case Series

The published literature reflects multiple examples of uncontrolled, proof of concept, case series, reporting outcomes for one, two or as many as eight participants [33]. In this study, over the course of nine-months, two male subjects participated in an uncontrolled case series (Table 2). Subject A was a 37-year-old adult male in good health, presenting with Norwood Class 3v AGA. Subject B was a healthy 43-year-old adult male presenting with Norwood Class 5 AGA. After reviewing and signing the informed consent, the study participants were provided with test materials sufficient for 270 days of oral and topical therapy. Each subject was advised to follow the treatment protocol but to discontinue treatment and immediately report the onset of any negative side effects. For ease of measurement a 1 cm circular zone was demarcated in the approximate center of each subject's thinning scalp, and a small permanent ink dot was affixed to act as a center point for geographic continuity throughout the case series. Within this zone, individual hairs were counted and measured for strand number and density. Evaluations occurred at treatment day zero (baseline) with follow-up at 90-day intervals. The case series concluded on treatment day 270. Results were assessed for strand density variations over time, patient reporting, and investigator observation.

Table 2. Case series design and eligibility criteria.

Study Type	**Study Start Date**
Interventional (Clinical Case Series)	3 March 2019
Enrollment 2 Participants	Study Completion Date 27 November 2019
Intervention Model Description Uncontrolled, open label trial	Primary Outcome Measure Incidence of Adverse Events
Primary Purpose Test of concept	Secondary Outcome Measure Assessment of therapeutic results
Inclusion criteria	Exclusion criteria
• Male, 30-55 years of age • Healthy scape with not cutaneous disorder • General good health • Must fall within Norwood 3 to 6 classification • Willing and able to comply with treatment regimen • Must be willing to refrain from using any hair treatment other than the provided study materials for duration of study.	• Known sensitivity to any of the test materials • History of skin diseases (e.g. eczema, seborrheic dermatitis, psoriasis) • History of hair transplant surgery

3. Results

Over the course of a nine-month uncontrolled, open label case series, two AGA-affected male subjects were treated with a cyclodextrin-complexed, phytochemically-based formula administered via concomitant oral and topical delivery. During the series, neither subject reported negative side effects. Hair counts and investigator gross evaluation on treatment day zero reflected a predominance of low caliber hairs in the vertex scalp of both participants, a finding consistent with a diagnosis of AGA. By treatment day 90, the negative growth cycle appeared to have been halted and reversed (Figure 4). As the study progressed fewer low caliber strands were evident with continued hair thickening in each patient noted on treatment day 180. Upon the final evaluation on treatment day 270, most hairs observed in both subjects were characterized as full thickness/terminal (Figure 5).

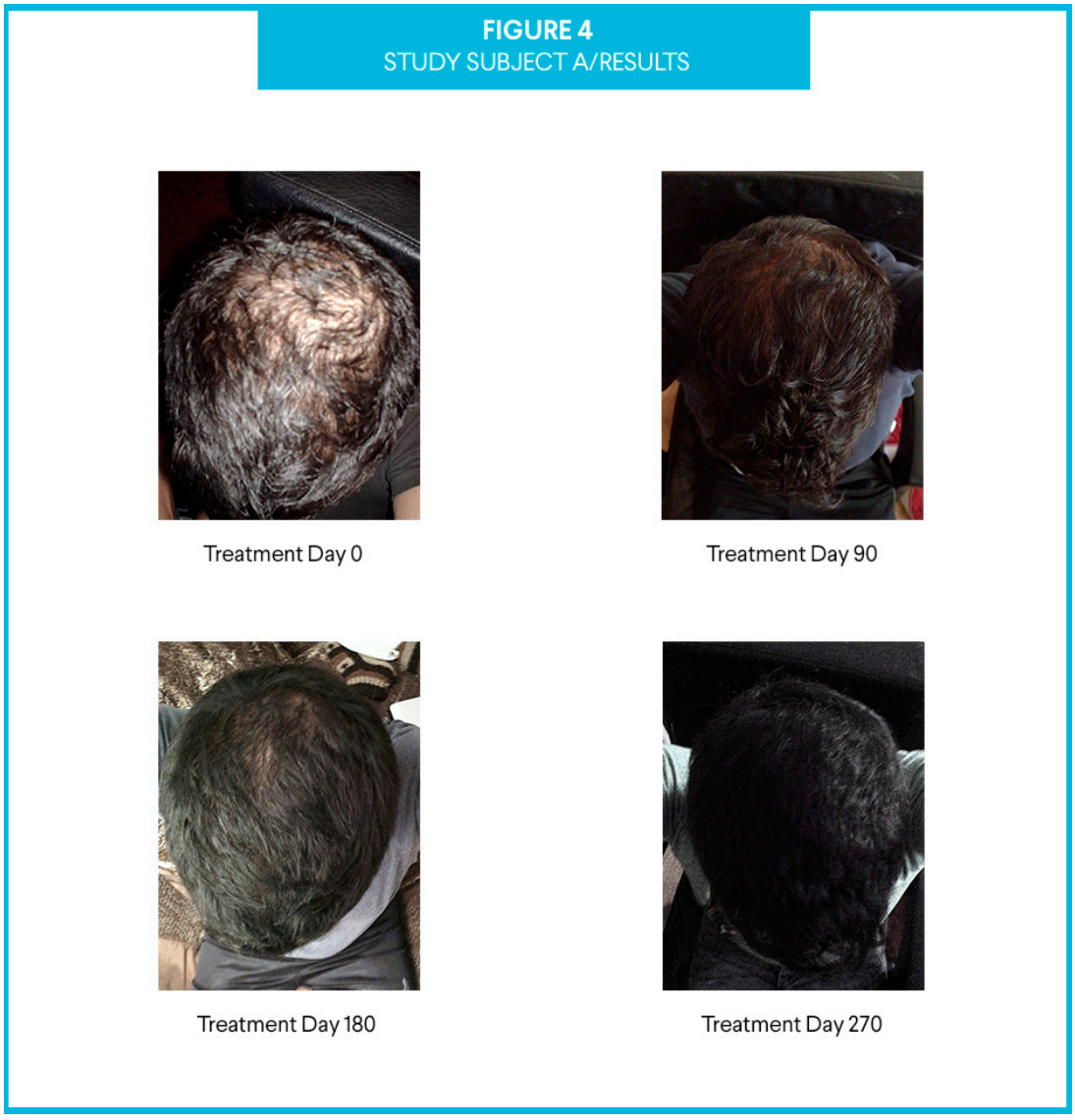

Figure 4. Subject A/hair caliber/90-day time intervals.

Figure 5. Subject B/hair caliber/90-day time intervals.

4. Discussion

The utility of oral and topical drug-based hair loss treatment products has been demonstrably proven in well-controlled, peer-reviewed research studies. An ectodermal appendage, the AGA-affected scalp hair follicle represents a particularly intriguing therapeutic target for concomitant local and systemic therapy. Although some have exploited this opportunity via combined topical minoxidil and oral finasteride, the literature-reported negative side effects of each drug has limited the widespread use of the drug-based approach.

In basic science trials, several gene markers linked to steroid-hormone driven diseases, including AGA have shown susceptibility to natural-based compounds. In particular, genistein may inhibit the nuclear factor kappa B (NF-kB) signaling pathway, a putative modulatory factor in hair cycling and hair loss phenotypes, including AGA. Likewise, epigallocatechin 3 gallate has been linked to a decrease in intracellular ROS levels and senescence, each of them factors thought to influence the progression of AGA. Moreover, a recent study showed that a γ linolenic acid containing formulation increased hair counts in AGA-affected subjects [34]. Although the exact mechanism of action remains unclear, β-Sitosterol has been shown to inhibit 5-alpha-reductase, a key precipitating isoenzyme linked to AGA. In light of their pleiotropic mechanisms, enhanced safety profile and potential utility across a spectrum

of disorders, nano-stabilized, naturally derived chemicals may represent an abundant reservoir for the interrogation and development of safe and efficacious adjunctives or alternatives to drug-based monotherapy. The nine-month, two-subject, uncontrolled, open label case series reported in this study appears to support the hypothesis.

Notwithstanding, the authors acknowledge that numerous nano-enabled phytochemical compositions are possible, and it is entirely conceivable that alternative iterations may ultimately prove equal or superior to the clinical outcomes observed. Likewise, any putative conclusions drawn from the observed results must be tempered by the uncontrolled nature of the case series. Thus, the reported outcomes merely invite follow-up larger scale, IRB-monitored trials. Such future efforts may further elucidate the therapeutic spectrum and potential role for nano-enabled phytochemicals in the setting of AGA.

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References

1. Tai, T.; Kochhar, A. Physiology and Medical Treatments for Alopecia. *Facial Plast. Surg. Clin. N. Am.* **2020**, *28*, 149–159. [CrossRef]
2. He, H.; Xie, B.; Xie, L. Male pattern baldness and incidence of prostate cancer: A systematic review and meta-analysis. *Medicine* **2018**, *97*, e11379. [CrossRef]
3. Starace, M.; Orlando, G.; Alessandrini, A.; Piraccini, B.M. Female Androgenetic Alopecia: An Update on Diagnosis and Management. *Am. J. Clin. Dermatol.* **2020**, *21*, 69–84. [CrossRef]
4. Martinez-Jacobo, L.; Villarreal-Villarreal, C.D.; Ortiz-López, R.; Ocampo-Candiani, J.; Rojas-Martínez, A. Genetic and molecular aspects of androgenetic alopecia. *Indian J. Dermatol. Venereol. Leprol.* **2018**, *84*, 263–268.
5. Singh, S.; Ilyayeva, S. *Androgen Insensitivity Syndrome*; StatPearls: Treasure Island, FL, USA, 2020.
6. Lolli, F.; Pallotti, F.; Rossi, A.; Fortuna, M.C.; Caro, G.; Lenzi, A.; Sansone, A.; Lombardo, F. Androgenetic alopecia: A review. *Endocrine* **2017**, *57*, 9–17. [CrossRef]
7. Sinclair, R.; Torkamani, N.; Jones, L. Androgenetic alopecia: New insights into the pathogenesis and mechanism of hair loss. *F1000Research* **2015**, *4*, 585. [CrossRef]
8. Said, M.A.; Mehta, A. The Impact of 5α-Reductase Inhibitor Use for Male Pattern Hair Loss on Men's Health. *Curr. Urol. Rep.* **2018**, *16*, 65. [CrossRef]
9. Badri, T.; Nessel, T.A.; Kumar, D.D. *Minoxidil*; StatPearls: Treasure Island, FL, USA, 2020.
10. Suchonwanit, P.; Thammarucha, S.; Leerunyakul, K. Minoxidil and its use in hair disorders: A review. *Drug Des. Dev. Ther.* **2019**, *13*, 2777–2786. [CrossRef]
11. Barbareschi, M. The use of minoxidil in the treatment of male and female androgenetic alopecia: A story of more than 30 years. *G. Ital. Dermatol. Venereol.* **2018**, *153*, 102–106.
12. Colamarino, R.; Dubost, J.J.; Brun, P.; Flori, B.; Tournilhac, M.; Eschalier, A.; Sauvezie, B. Polymyalgia Induced by Minoxidil. *Ann. Med. Interne* **1990**, *141*, 425–428.
13. Tennstedt, D.; Herman, A.; Lachapelle, J.M. Adverse effects of hair care in users. *Ann. Dermatol. Venereol.* **2018**, *145*, 521–531. [CrossRef]
14. Lee, S.W.; Juhasz, M.; Mobasher, P.; Ekelem, C.; Mesinkovska, N.A. A Systematic Review of Topical Finasteride in the Treatment of Androgenetic Alopecia in Men and Women. *J. Drugs Dermatol.* **2018**, *17*, 457–463.
15. Iamsumang, W.; Leerunyakul, K.; Suchonwanit, P. Finasteride and Its Potential for the Treatment of Female Pattern Hair Loss: Evidence to Date. *Drug Des. Dev. Ther.* **2020**, *14*, 951–959. [CrossRef]

16. Traish, A.M. Post-finasteride syndrome: A surmountable challenge for clinicians. *Fertil. Steril.* **2020**, *113*, 21–50. [CrossRef]
17. Zhou, Y.; Chen, C.; Qu, Q.; Zhang, C.; Wang, J.; Fan, Z.; Miao, Y.; Hu, Z. The effectiveness of combination therapies for androgenetic alopecia: A systematic review and meta-analysis. *Dermatol. Ther.* **2020**, e13741. [CrossRef]
18. York, K.; Meah, N.; Bhoyrul, B.; Sinclair, R. A review of the treatment of male pattern hair loss. *Expert Opin. Pharmacother.* **2020**, *21*, 603–612. [CrossRef]
19. Katzer, T.; Leiter, A., Jr.; Beck, R.; Da Silva, C.; Silva, C.B. Physiopathology and current treatments of androgenetic alopecia: Going beyond androgens and anti-androgens. *Dermatol. Ther.* **2019**, *32*, e13059. [CrossRef]
20. Shoji, Y.; Nakashima, H. Nutraceutics and Delivery Systems. *J. Drug Target.* **2004**, *12*, 385–391. [CrossRef]
21. Jafari, S.M.; McClements, D.J. Nanotechnology Approaches for Increasing Nutrient Bioavailability. *Adv. Food Nutr. Res.* **2017**, *81*, 1–30.
22. Speranza, B.; Petruzzi, L.; Bevilacqua, A.; Gallo, M.; Campaniello, D.; Sinigaglia, M.; Corbo, M. Encapsulation of Active Compounds in Fruit and Vegetable Juice Processing: Current State and Perspectives. *J. Food Sci.* **2017**, *82*, 1291–1301. [CrossRef]
23. Balic, A.; Vlašić, D.; Žužul, K.; Marinović, B.; Mokos, Z.B. Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 741. [CrossRef]
24. Cabeza, M.; Bratoeff, E.; Heuze, I.; Ramírez, E.; Sánchez, M.; Flores, E. Effect of beta-sitosterol as inhibitor of 5 alpha-reductase in hamster prostate. *Proc. West. Pharmacol. Soc.* **2003**, *46*, 153–155.
25. Andreu-Fernández, V.; Serra-Delgado, M.; Pizarro, N.; Navarro-Tapia, E.; Gomez-Roig, M.D.; De La Torre, R.; García-Algar, O. Bioavailability of Epigallocatechin Gallate Administered with Different Nutritional Strategies in Healthy Volunteers. *Antioxidants* **2020**, *9*, 440. [CrossRef]
26. Shin, S.; Kim, K.; Lee, M.J.; Lee, J.; Choi, S.; Kim, K.-S.; Ko, J.-M.; Han, H.; Kim, S.Y.; Youn, H.J.; et al. Epigallocatechin Gallate-Mediated Alteration of the MicroRNA Expression Profile in 5α-Dihydrotestosterone-Treated Human Dermal Papilla Cells. *Ann. Dermatol.* **2016**, *28*, 327–334. [CrossRef]
27. Merlotto, M.R.; Ramos, P.M.; Miot, H.A. Pattern hair loss: Assessment of microinflammation in miniaturized and terminal hair follicles through horizontal histologic sections. *J. Am. Acad. Dermatol.* **2020**. [CrossRef]
28. Lippens, S.; Hoste, E.; Vandenabeele, P.; Agostinis, P.; Declercq, W. Cell death in the skin. *Apoptosis* **2009**, *14*, 549–569. [CrossRef]
29. Bae, M.; Woo, M.; Kusuma, I.W.; Arung, E.T.; Yang, C.H.; Kim, Y.-U. Inhibitory Effects of Isoflavonoids on Rat Prostate Testosterone 5α-Reductase. *J. Acupunct. Meridian Stud.* **2012**, *5*, 319–322. [CrossRef]
30. Yao, Q.; Lin, M.T.; Lan, Q.H.; Huang, Z.W.; Zheng, Y.W.; Jiang, X.; Zhu, Y.D.; Kou, L.; Xu, H.L.; Zhao, Y.Z. In Vitro and in Vivo evaluation of didymin cyclodextrin inclusion complexes: Characterization and chemosensitization activity. *Drug Deliv.* **2020**, *27*, 54–65. [CrossRef]
31. Frigerio, G.; Campo, L.; Mercadante, R.; Santos, P.M.; Missineo, P.; Polledri, E.; Fustinoni, S. Development and validation of a liquid chromatography/tandem mass spectrometry method to quantify metabolites of phthalates, including di-2-ethylhexyl terephthalate (DEHTP) and bisphenol A, in human urine. *Rapid Commun. Mass Spectrom.* **2020**, *34*, e8796. [CrossRef]
32. Carneiro, B.; Duarte, F.; Heimfarth, L.; Siqueeira, J.; Quintens-Jr, L.; da Veiga, V.; Neves de Lima, A. Cyclodextrin–Drug Inclusion Complexes: In Vivo and In Vitro Approaches. *Int. J. Mol. Sci.* **2019**, *20*, 642. [CrossRef]
33. Manca, A.; Cabboi, M.P.; Ortu, E.; Ginatempo, F.; Dragone, D.; Zarbo, I.R.; De Natale, E.R.; Mureddu, G.; Bua, G.; Deriu, F. Effect of Contralateral Strength Training on Muscle Weakness in People With Multiple Sclerosis: Proof-of-Concept Case Series. *Phys. Ther.* **2016**, *96*, 828–838. [CrossRef]
34. Brotzu, G.; Fadda, A.M.; Manca, L.; Consolaro, F. A liposome-based formulation containing equol, dihomo-γ-linolenic acid (DGLA), and propionyl-L-carnitine to prevent and treat hair loss: A prospective investigation. *Dermatol. Ther.* **2019**, *32*, e12778. [CrossRef]