Clinical Drug Investigation

Advanced Delivery Vectors May Significantly Influence the Utility of Naturally-Derived Hair Growth Compositions

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Manuscript Number:	
Full Title:	Advanced Delivery Vectors May Significantly Influence the Utility of Naturally-Derived Hair Growth Compositions
Article Type:	Review Article
Funding Information:	
Abstract:	A number of well controlled, peer-reviewed, university based, published studies demonstrate safety, efficacy and mechanism of action for naturally-based compounds in the treatment of androgen-mediated disorders. Such disorders include benign prostatic hyperplasia (BPH) and androgenetic alopecia (AGA). Recent advances in nanomaterial manipulation have provided an enhanced platform from which formulators, clinicians and basic scientists may efficiently envelope naturally-derived active chemicals into botanically-based hair growth treatment compounds. These include chitosans, cyclodextrins, nanoparticles and liposomes. Particularly in the setting of a complex trait disorder like AGA, nano-complexed systems may offer enhanced benefit over traditional drug based medical therapy.
Corresponding Author:	Geno Marcovici, Ph.D. Advanced Restoration Technologies Inc. Mahwah, New Jersey UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Advanced Restoration Technologies Inc.
Corresponding Author's Secondary Institution:	
First Author:	Geno Marcovici, Ph.D.
First Author Secondary Information:	
Order of Authors:	Geno Marcovici, Ph.D.
	Alan Bauman, MD
	Glenn Mouser, **Bio-Chemist**
Order of Authors Secondary Information:	
Author Comments:	Thank you in advance for your gracious consideration of this manuscript. As Corresponding Author, please feel free to let me know if any modifications are required prior to acceptance for Review. BR Geno Marcovici dr.marcovici@hairgenesis.com
Suggested Reviewers:	Angela Christiano, Ph.D. Professor, Columbia University amc65@cumc.columbia.edu Strong expertise in gene discovery, drug delivery, ectodermal morphology, pharmacokinetics and related fields.
	Julio Salas, M.D., Ph.D. Director of Research, University of Monterrey drjuliosalas@gmail.com Dr. Salas is a world class expert in skin diseases, hair loss, and related disorders.

	Robert Bernstein, M.D. Clinical Professor, Columbia P & S rbernstein@bernsteinmedical.com Widespread expertise in hair phenotypes and the use of advanced therapeutics in the treatment of androgenetic alopecia

May 19, 2019

Clinical Drug Investigation Journal

Re. submitted manuscript #CDIA-S-19-00218

Dear Editor-

Thank you in advance for your gracious consideration of our Review article submission titled Advanced Delivery Vectors May Significantly Influence the Utility of Naturally-Derived Hair Growth Compositions.

In aiming for the right venue for our submission we took particular note of your highly respected Journal's stated focus upon the "Application of drug-delivery technology in healthcare". Concisely, our Review paper is intended to direct attention to the nanotechnology-enabled drug-delivery paradigm shift now occurring in the medicinal use of naturally-based therapeutic compounds. Moreover, as androgen-mediated disorders are often refractory to traditional methodologies, the deployment of nano-delivered botanical therapeutics represents a 'new way to address an old problem'.

It is our sincere hope that our Review of this exciting and rapidly evolving discipline rises to the level of being worthy for consideration to appear within the pages of your esteemed Journal.

Respectfully,

Geno Marcovici, Ph.D., DABAAHP
Corresponding author / manuscript # CDIA-S-19-00218

Advanced Delivery Vectors May Significantly Influence the Utility of Naturally-Derived Hair Growth Compositions

1st author: Geno Marcovici, ART Inc., 101 Raintree Ln, Mahwah, NJ, 07430, dr.marcovici@hairgenesis.com, 201-785-4061

2nd author: Alan Bauman, Bauman Medical Center, 1450 S. Dixie Hwy, Boca Raton, FL 33432-7359, dr.b@baumanmedical.com

3rd author: Glenn Mouser, Omega Tech Labs Inc., 5858 W. Franklin Rd., Boise, ID, 83709, glenn@omegatechlabs.com

ABSTRACT

A number of well controlled, peer-reviewed, university based, published studies demonstrate safety, limited efficacy and mechanism of action for naturally-based compounds in the treatment of androgen-mediated disorders. Such disorders include benign prostatic hyperplasia (BPH) and androgenetic alopecia (AGA). Recent advances in nanomaterial manipulation have provided an enhanced platform from which formulators, clinicians and basic scientists may efficiently envelope naturally-derived

active chemicals into botanically-based hair growth treatment compounds, further expanding their therapeutic potential. These include chitosans, cyclodextrins, nanoparticles and liposomes. Particularly in the setting of a complex trait disorder like AGA, nano-delivered natural therapeutics may offer enhanced benefit, perhaps even over the traditional drug-based alternatives.

KEYWORDS:

hair loss, advanced drug delivery, nanoparticles, natural hairloss treatment

1. INTRODUCTION

For patients as well as health care practitioners faced with the task of ameliorating androgenetic alopecia (AGA) aka pattern hair loss, each treatment choice comes with limitations and downsides that must be weighed against a desired set of benefits and solutions. In gifted hands, surgical hair restoration may constitute an excellent option, providing density, permanence and esthetics. High capital investment and the potential of donor depletion represent two meaningful caveats. Chasing a

receding hairline is one of the most disheartening issues facing patients and hair restoration surgeons alike (1).

In recent years it has become common for surgical hair restoration providers to avail themselves of multi-mode approaches to treatment, blending transplant surgery with drug-based oral and topical medical therapies. Yet, significant negative side effects have been reported, including loss of libido, teratogenic potential, suicidal ideation, pruritis to name but a few (2). This has led some to formulate and test naturally-based hair growth agonists – which have an inherently more robust safety profile. The liposterolic extract of Serenoa repens (LSESr) constitutes a noteworthy example.

Derived from a scrub palm, and occurring throughout much of the southeast American coast from North Carolina to the Caribbean, LSESr, through fully sustainable harvesting, contains a wealth of fatty acids and sterols --- among these are β-sitosterol, campesterol and stigmasterol (3). While some clinical trials showed limited or no benefit, a number of large, well-controlled European studies have shown positive clinical outcomes for patients using LSESr to treat benign prostatic hyperplasia (BPH) an androgen-mediated disorder that shares a remarkable degree of genetic

homology with AGA (4). Likewise, compared to finasteride, basic science data points to a much greater blockade of the androgen precursor 5 alpha-reductase by LSESr (5).

FIGURE 1

Caption: Serenoa repens berries from which LSESr is derived

Unfortunately, the clinical use of LSESr as a stand-alone treatment against AGA has proven less consistently successful. This is unsurprising due to the multifactorial triggers inherent in a complex trait affliction like AGA. Recent studies point to an inflammatory component as a significant contributing factor in the disease process (6). Here too, naturally-based anti-inflammatory substances have shown activity in downregulating genetic markers linked to pattern hair loss. These include carnitine, lipoic acid, genistein and turmeric. However, as stand-alone agents, none has so far proven demonstrable clinical benefit in blunting or reversing AGA. Recognizing the utility of approaching this disorder with a multi-mode composition, some have sought to combine 5 alpha-reductase inhibitors

with anti-inflammatory compounds (7). In pursuit of this strategy a set of formidable challenges must be recognized and overcome.

From the standpoint of creating safe, stable, multi-mode, botanically-derived hair loss treatment compositions, the formulator is faced with several potential pitfalls. First, it can be difficult to design and combine stable compounds based around lipophilic and hydrophilic substrate. Certain antioxidants are susceptible to rapid degradation. Heat, humidity, air and time can also quickly destroy a putative formula. The skin too poses a daunting barrier to topical delivery (8). From a pharmacokinetic standpoint, naturally-based complex macromolecules also tend to deactivate after first passage or remain largely intact but excreted through urination and evacuation (9). Thus, despite a growing demand for safe, effective naturally-derived hair loss treatment options, a dearth of published research illustrates the intrinsic difficulties involved in deploying, testing and proving candidate compositions.

2. THE HUMAN SCALP HAIR FOLLICLE / STRUCTURE, FUNCTION & PATTERN OF GROWTH

Just as sebaceous glands, apocrine & eccrine sweat glands, and fingernails are ectodermal appendages of the skin, so too are hair follicles (10). Consisting of clearly defined structures, the hair follicle is continuously, genetically, and environmentally driven by a complex interaction between hormones, genes, neuropeptides and immune factors. The scalp hair growth cycle consists of three distinct phases: the anagen phase – a period of hair fiber production which can last for two to seven years, a short catagen or degradation phase, and telogen resting phase - which lasts for approximately ninety days (11) and during which time the hair fiber is ejected. At any given time, eighty to ninety percent of one's scalp hairs are in the anagen growth phase and the remainder, which correspond to ten to twenty percent are either in telogen or catagen. The rate of growth in anagen averages approximately 1.25 cm per month. Unlike some mammals who shed hair in a synchronous 'wave' each hair follicle in a human is tied to its own growth cycle which runs independently of its neighbors, resulting in a mosaic pattern of growth, shedding and quiescence (12).

3. ANDROGENETIC ALOPECIA / A MULTI-FACTORIAL DISORDER

A number of hair loss phenotypes occur in humans with androgenetic alopecia (AGA) -- aka common pattern hair loss – constituting, by far, the most prevalent form (13). Both men and women may be affected, with similar genetic and hormonal triggers. However, the expression pattern differs according to gender-specific variables, including age of onset and speed of progression. Males may begin losing hair in their late teens to early twenties – while it is unusual for a woman to experience AGA prior to her mid to late 30s.

In males, a true pattern of loss is typically evident. Bitemporal recession is often accompanied by thinning of the vertex. In advanced forms of male AGA, the thinning areas can adjoin leading to almost complete denudation with only a thin halo of hair remaining in the supra-auricular and lower occipital fringe. Female AGA generally begins as a progressive, diffuse thinning which may ultimately leave the anterior hairline largely preserved but with a marked loss of density throughout, such that the underlying scalp is readily apparent (14).

There are three principal factors which drive pattern hair loss. The first is age. Prepubescent children for example do not suffer from AGA. The second is genetics. Recent GWAS studies identified seventy-one

susceptibility loci (15). Pattern hair loss exhibits comorbidity with numerous other important pathologies such as cardio-metabolic diseases and prostate cancer suggesting a common underlying biology (16).

The third factor is biochemical. This is evidenced, for example, by androgen insensitivity syndrome wherein affected patients who, despite circulating androgens and a genetic predisposition, do not develop AGA, (17). In AGA susceptible individuals, the onset of the disorder is triggered when 5 alpha dihydrotestosterone (DHT) is metabolized from testosterone (T) by the enzyme 5 alpha-reductase (18). In genetically susceptible scalp hair follicles, membrane-bound androgen receptor binds DHT thereafter translocating to the cell nucleus wherein a pattern of reduced anagen and progressively more frequent telogen transform full thickness terminal scalp hairs into hypo-pigmented vellus hairs by a process of follicle involution. As previously noted, a number of inflammatory markers have been identified that appear to hasten the progression of AGA (19) (20).

FIGURE 2

Caption: Androgenetic alopecia in males

FIGURE 3

Caption: Androgenetic alopecia in females

4. NON-SURGICAL TREATMENT OF PATTERN HAIR LOSS

Until recently, there have been essentially two pharmaceutical treatment options against AGA. The first is minoxidil, a putative modulator of sarcolemmal KATP channels (21). And the second is the oral drug finasteride (22), a preferential inhibitor of type two 5 alpha-reductase. Inasmuch as hair follicles are ectodermal appendages of the integument, they are responsive to both local and systemic treatment. Thus, the concomitant deployment of oral finasteride and topical minoxidil has been attempted with some success. However, the potential of amplified negative side effect may dissuade patients from using both drugs simultaneously.

Laser light therapy offers substantive benefit to some patients, and a number of peer-reviewed clinical trials demonstrate efficacy (23) (24). Recently, whole blood-derived platelet-rich plasma protein (PRP) has been used - both in the setting of hair transplant surgery and also as a stand-alone treatment. Individual case reports point to positive results; but a lack of PRP preparation and application standards as well as a paucity of randomized, controlled trials suggests that here too caution must be exercised when considering this approach (25).

5. SKIN BARRIER FUNCTION, A CHALLENGE TO TOPICAL DRUG DELIVERY

The skin epidermis serves protective and defensive functions (26) and consists of five layers; the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and the stratum corneum. The stratum corneum is composed of 15–20 cell layers of transformed keratinocytes possessing neither nuclei nor viable organelles. Morphologically, the stratum corneum is comprised of corneocytes surrounded by lipid-rich regions. Inasmuch as the skin serves primarily to separate ‘self’ from ‘other’ the highly organized barrier function of the epidermis presents intrinsic

challenges to drug delivery via the transcellular route. As most drugs applied onto the skin permeate thru the lipid-rich regions, a comprehensive understanding of the operative terrain is paramount. Of crucial importance, the hair follicle itself presents a pathway for drug transport, owing to its deep extension into the dermis (27). It thus provides the portal for much deeper penetration and absorption of active compounds beneath the skin than may be achieved via the transdermal route.

FIGURE 4

Caption: Integumentary System / Anatomy & Structure

6. ORAL ROUTE DRUG DELIVERY CHALLENGES

According to the CDC, over half of all adults orally ingest one or more dietary supplements or naturally-based therapies on a daily basis (28). Bioavailability of such treatment compounds must necessarily take into account both the proportion capable of being absorbed and that available for cellular uptake, use, or storage in the target tissue (29).

Stomach acids and enzymes can rapidly break down complex macromolecules rendering them substantially inactivated. In first pass metabolism, the digested subconstituents are absorbed from the GI tract and pass via the portal vein into the liver. Here, superoxide dismutase (SOD), catalase (CAT) and cytochrome (CYP) enzymes convert xenobiotics into non-toxic metabolites which are then shuttled to the excretory system (30).

Adding a further layer of complexity, it has long been recognized that the gut microbiome contributes to digestive biosynthesis thereby influencing the bioavailability of vitamins, supplements and nutrients. However, the magnitude of this contribution—the role of microflora in the gastro-metabolic processes remains, as yet, poorly understood (31).

Despite numerous basic science experiments demonstrating functional metabolic activity in the blockade of androgen and inflammatory pathways linked to pattern hair loss, a dearth of positive clinical data for botanically-based hair growth agonists illustrates the challenge at hand. In sum, without a protective mechanism to shuttle orally and topically administered,

naturally-based therapeutic compounds to the target tissue they may be denatured, converted or simply excreted (32). To those tasked with formulating naturally derived therapeutics intended to treat or prevent pattern hair loss, the digestive system and the integument constitute formidable impediments.

7. NOVEL NANOVECTORS & VEHICLES TO DELIVER NATURALLY-DERIVED DRUGS

TABLE 1: Nanomaterials Successfully Complexed with Natural Compounds

A key objective of nanoparticles is to control, manipulate and introduce biomacromolecular constructs and supramolecular assemblies into living cells, ultimately in order to improve the quality of human health. In recent years this approach has been used widely and successfully to improve the targeted delivery of numerous synthetic drugs (33), however its use in natural medicine has been less well tested. This may be changing (Table 1). Between the years 2000–2018, the natural products field was

estimated to produce or be involved in the research and development of approximately 50% of all small molecules - *i.e. drugs* -, and 10 out of the 44 approved small molecules by the FDA in 2014 were derived from natural substrate (34). Nevertheless, naturally-derived, therapeutic macromolecules present formidable challenges to targeted drug delivery. Nanovectors and vehicles potentially suitable to the task include liposomes, chitosans, and cyclodextrins. Due to their small size, large surface area and design plasticity enabling them to bond with many different kinds of molecules, these materials introduce the potential for significantly enhanced efficacy in naturally-based therapeutic compounds.

- β-Sitosterol encapsulated nanoparticles

Apart from its role in AGA, the androgen receptor (AR) pathway is emerging as a potential therapeutic target in breast cancer (35).

In an intriguing basic science study, poly(lactide-co-glycolic acid) (PLGA) and block copolymers of poly(ethylene glycol)-block-poly(lactic acid) (PEG-PLA) were used to encapsulate β-Sitosterol into nanoparticles with the aim of enhancing in vitro anticancer activity. Neoplastic cell viability was inhibited by up to 80% in a concentration range of 6.64⁻53.08 μg/mL

compared to untreated cells (36). The conclusion demonstrates that β-Sitosterol embedded PLGA nanoparticles represent a promising strategy against cancer. Likewise, the use of cyclodextrin-complexed β-Sitosterol as a sub-constituent of a multi-focal therapeutic formula has also proven beneficial in monolayer gene expression models of benign prostatic hyperplasia (BPH) and androgenetic alopecia (AGA) (37).

- Micellar Epigallocatechin gallate Nanoparticle Complexes

As in breast cancer, the significant role of androgen receptor in ovarian cancer is becoming more widely recognized and understood (38). Epigallocatechin gallate (EGCG), one of the most active antioxidant compounds, is limited by its low chemical stability and inability to efficiently permeate either the gastric mucosa or human epidermis (39). Recently, micellar nanoparticle complexed-EGCG has gained attention as a potent adjuvant to enhance the antitumor efficacy of the chemotherapeutic drug cisplatin while simultaneously mitigating its harmful side effects. Moreover, the nanocomplexes tested exhibited superior antitumor efficacy over free cisplatin while displaying no toxicity in both a

subcutaneous xenograft model and peritoneal metastatic model of human ovarian cancer (40).

FIGURE 5

Caption: Therapeutic tools suitable for incorporation within advanced nanoparticle drug delivery systems:

- Chitosan-loaded Genistein

Genistein has been reported to have antioxidant as well as neuroprotective activity (41). Despite encouraging in vitro and in vivo results, several disadvantages such as poor water solubility, rapid metabolism, and low oral bioavailability limit the clinical application of genistein. In an intriguing published study, genistein-loaded chitosan nanoparticles were prepared for intranasal drug delivery as a potential preventive strategy against neurodegenerative disorders (42). Here, the investigators found that the bulk of chitosan-loaded genistein was successfully transported across the intranasal mucosa --- thus protected the active bolus from enzymatic degradation at the mucosal surface. Notably, the study further concluded that chitosan nanoparticles appear to constitute a novel and efficient

means to transport genistein across the blood-brain barrier, typically the most formidable last-line-of-defense boundary any organism possesses (43).

FIGURE 6

Caption: *β*-cyclodextrin molecular structure

- Cyclodextrins as vitamin delivery vectors

Cyclodextrins (CDs) are cyclic oligosaccharides containing six (*α*-CD), seven (*β*-CD) and eight (*γ*-CD) glucopyranose units, bound by *α*-(1–4) linkages forming a truncated conical structure (44). CDs are used for controlled delivery of organic, inorganic, biological and pharmaceutical molecules due to their ability to form inclusion complexes with diverse guest molecules by encapsulating the non-polar part of the guest into its hydrophobic cavity and stabilizing the polar part by the polar rims. Host–guest inclusion complexes of *β*-cyclodextrin with two vitamins. nicotinic

acid and ascorbic acid in aqueous medium have been explored by reliable spectroscopic, physicochemical and calorimetric methods as stabilizer, carrier and regulatory releaser of the guest molecules. As proof of principal, nicotinic acid and ascorbic acid successfully formed ICs with *β*-CD in aqueous medium, thereby permitting the controlled delivery and release (45).

- Liposomes

Liposomes were the first nanoscale drug vector approved for clinical use in 1995 (46). Since then, the technology has grown considerably, and pioneering recent work in liposome-based delivery systems has brought about positive developments with significant clinical implications. In a recent hair growth study, workers showed that a novel liposome-loaded formulation containing γ linolenic acid, isoflavone and carnitine evinced clinically meaningful improvement in AGA-affected males and females (47).

8. A WORD OF CAUTION

Nanoparticle-augmented therapeutics may confer the ability to overcome biological barriers, effectively deliver novel, amphiphilic drug combinations and preferentially target sites of disease. The complexity of nanoparticles as multi-component three dimensional constructs requires careful design and engineering to achieve a consistent output with the intended physicochemical characteristics, biological behaviors, and pharmacodynamics (48). While the promise of nanotechnology offers many benefits, the use of the new materials is not without risk. To cite but one example, investigators have identified a mechanism by which a class of nanomaterials that is being widely developed for clinical applications may induce lung damage (49). Thus, there is no universal "nanoparticle" to fit all applications --- each must be considered individually and tested critically, always with the intended benefits carefully weighed against the potential risks.

9. CONCLUSION

Due to their pleiotropic mechanisms of action, enhanced safety profile and utility across a spectrum of disorders, naturally-derived chemicals represent an excellent reservoir of future medicinals. A number of steroid-hormone driven diseases, including AGA have shown susceptibility to naturally-based DHT inhibitors, however a key impediment has been the difficulty in delivering the natural-active to the target tissue. Recent studies show that thoughtfully selected nanomaterials may provide utility in overcoming the challenge. Similarly, anti-inflammatory compounds derived from natural substrate have shown unique benefit, for example in the setting of androgen-mediated neoplastic pathology (50). Under careful oversight and guidance, the simultaneous deployment of multi-focal, nanotechnology-enabled, naturally-based, anti-androgen, anti-inflammatory combined formulas may constitute a rational approach.

Advanced delivery vectors now available include liposomes, chitosans, and cyclodextrins. By enveloping, invaginating or otherwise wedding the active compound to the chaperone delivery vector, drug release, stability, uptake and co-packaging of many natural actives is improved. In expert hands, this approach may permit the formulation of safe and efficacious

adjunctives or alternatives to drug-based therapy, even in the setting of a complex trait disorder like AGA.

ACKNOLWEDGEMENT

In assisting the Authors in the pursuit of this dynamic area of research, we gratefully acknowledge the expertise and collaboration of Dr. Yanchun Li, University of Chicago, Department of Medicine, & Professor Sridar Chittur, Center for Functional Genomics, University of Albany, SUNY

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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TABLE 1

Nanomaterial	Successfully Combined with	Indication	Reference
β-cyclodextrin	β-Sitosterol	Benign prostatic hyperplasia & androgenetic alopecia	Phytother Res. 2016 Jun;30(6):1016-20. doi: 10.1002/ptr.5611. Epub 2016 Mar 17.
Hyaluronic acid micellar conjugate nanocomplex	Epigallocatechin-3-O-gallate / cisplatin	Ovarian cancer / reduced toxicity	Biomaterials. 2017 Dec;148:41-53. doi: 10.1016/j.biomaterials.2017.09.027. Epub 2017 Sep 22.
Chitosan	Genistein	Prophylaxis against neurodegenerative sequelae	Pharmaceutics 2019, 11(1), 8; https://doi.org/10.3390/pharmaceutics11010008
Liposomes	γ linolenic acid, isoflavone and carnitine	Androgenetic alopecia	Dermatol Ther. 2019 Jan;32(1):e12778. doi: 10.1111/dth.12778. Epub 2018 Dec 4.

Nanomaterials Successfully Complexed with Natural Compounds

FIGURE 1

Serenoa repens berries from which LSESr is derived

FIGURE 2

Androgenetic alopecia in males

Figure 3

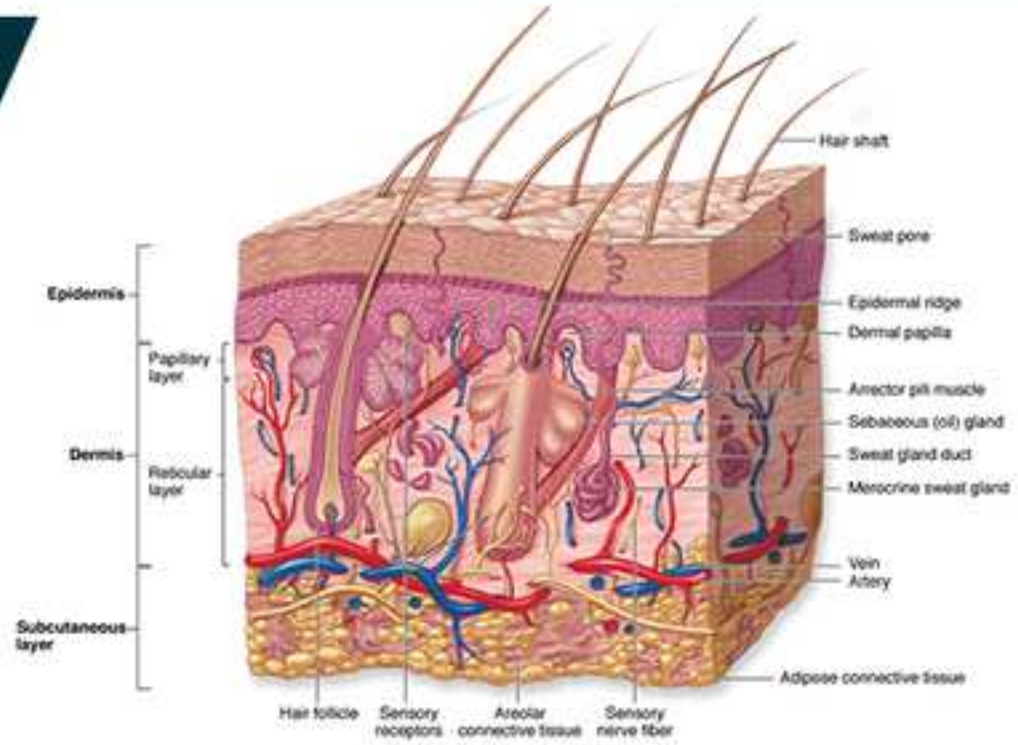
FIGURE 3

Androgenetic alopecia in females

Figure 4

Click here to access/download;Figure;figure4.jpg

FIGURE 4



Integumentary System / Anatomy & Structure

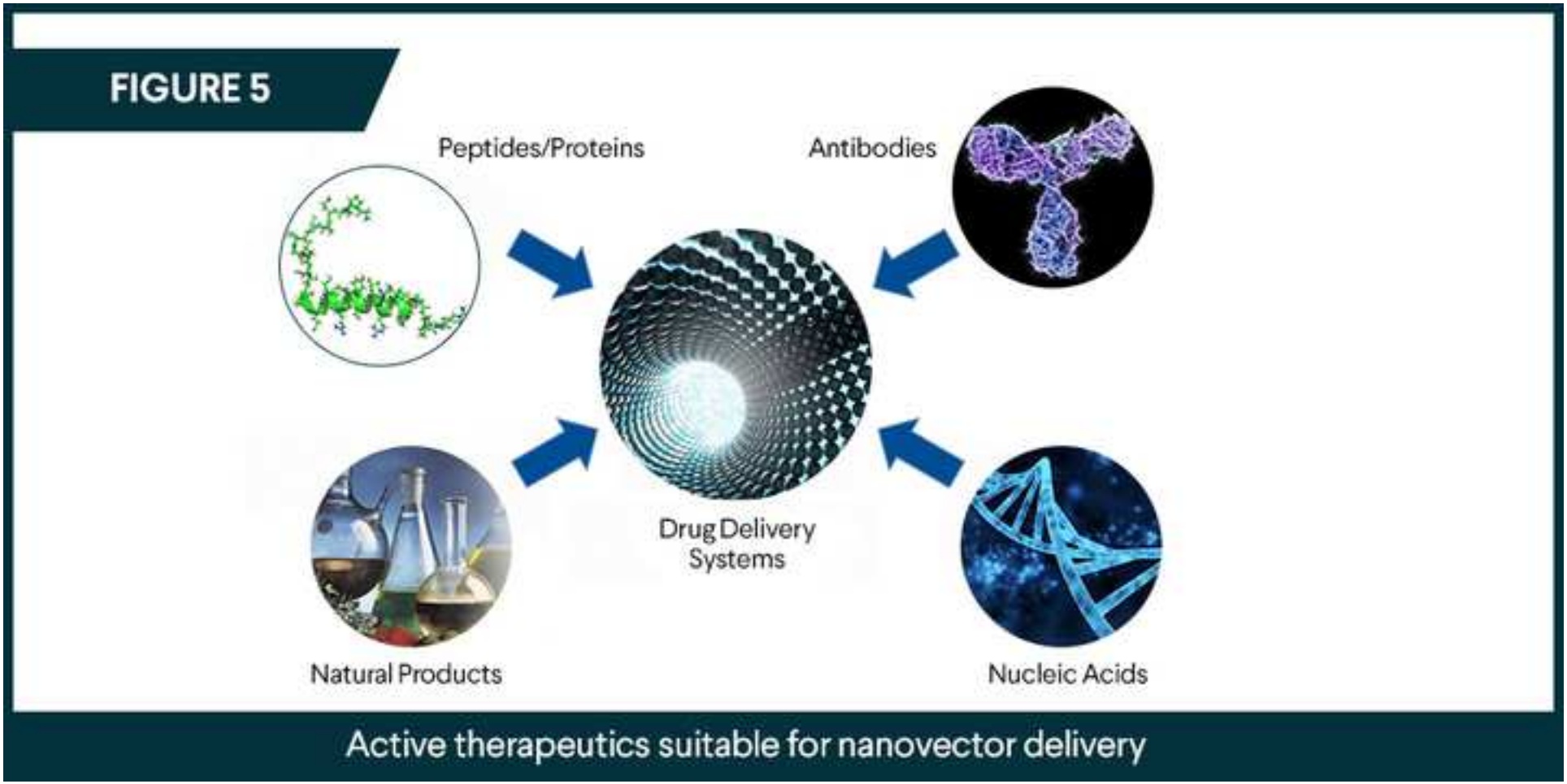
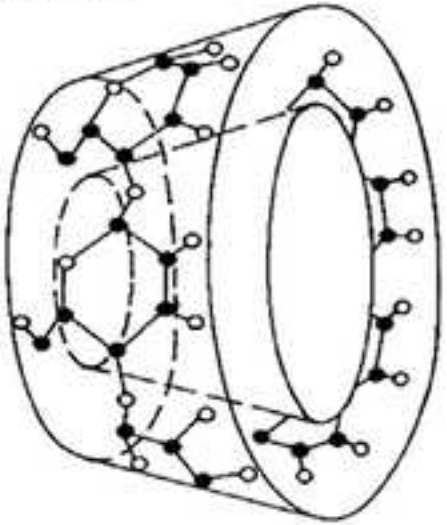
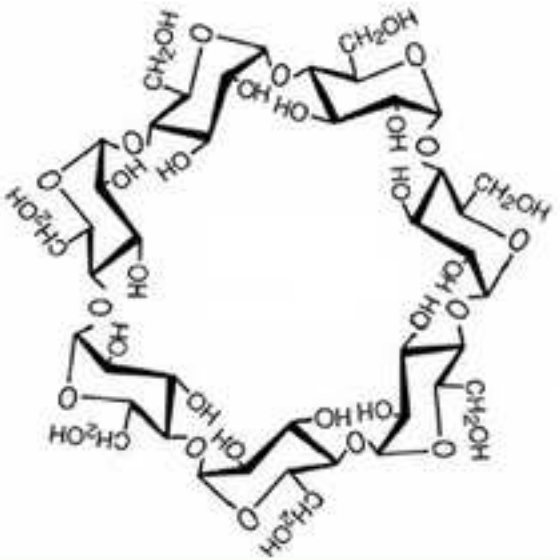


FIGURE 6

The outer surface of the cone is hydrophilic and the center cavity is hydrophobic

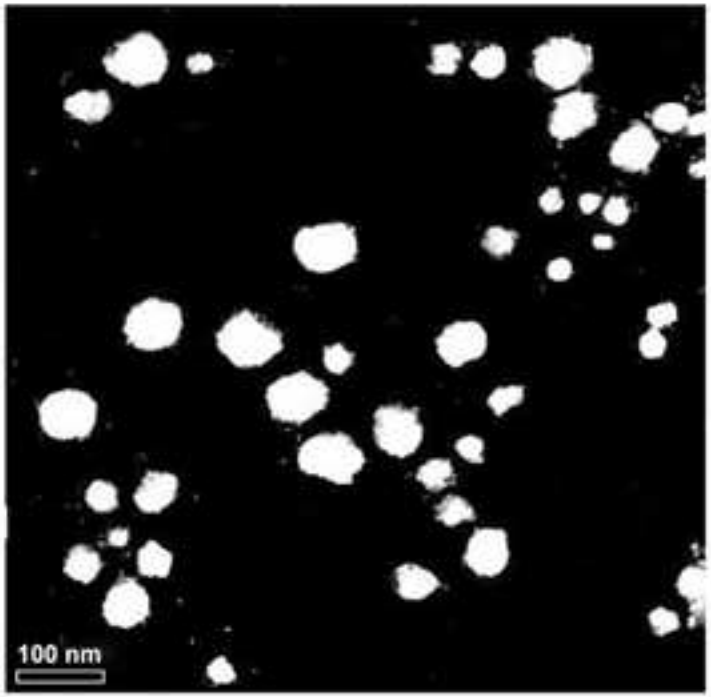


β Cyclodextrin:



Structure of β -cyclodextrin molecule

FIGURE 7



Transmission electron micrograph of genistein nanoparticles.

Adis

AUTHOR DECLARATION FORM

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Journal name: Clinical Drug Investigation Corresponding author: Geno Marcovici

Manuscript title: Advanced Delivery Vectors May Significantly Influence the Utility of Naturally Derived Hair Growth Compositions

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