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Cosmeceuticals: A Practical Approach

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Introduction

The cosmeceutical industry has undergone phenomenal growth over the past decade, and much of this expansion can be attributed to an aging population wanting to sustain a youthful appearance. The availability on drug store shelves of biologically active compounds that exhibit both cosmetic and drug-like effects has created a new group of agents, whose degree of efficacy, in many cases, has been unsubstantiated by science, and they remain unregulated. As such, acquiring a basic knowledge of the major classes of active ingredients that are found in cosmeceuticals will enable healthcare professionals to provide accurate and educational information to consumers.

Categorization and Regulation of Agents

According to US FDA Food, Drug, and Cosmetic Act of 1938:

1. A drug is "intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease," i.e., it affects the structure or function of the body.
2. A cosmetic is intended to be "rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or party thereof for cleaning, beautifying, promoting attractiveness, or altering the appearance of skin," i.e., the product cannot alter the structure or function of skin.

Albert Kligman coined the term "cosmeceutical" and defined it in 1984[1] as a formulation that is used to improve the appearance of skin, but is not for therapeutic purposes. However, it is important to note the following points:

- Many do contain biologically active ingredients.
- Some alter the structure and/or function of skin, thus, according to the regulatory definition, these could be categorized as drugs.
- Most undergo safety testing, but efficacy is not often assessed.
- Categorization and regulation will depend upon how product claims are presented to the public.
- The term "cosmeceutical" is not recognized by the North American regulatory agencies.
- Products considered to be cosmeceuticals circumvent regulation. Under this category, a lower barrier exists for market entry.

Major Classes of Cosmeceuticals

Sunscreens
- Considered as OTC drugs; sun protection factor must be proven by *in vitro* and *in vivo* studies.
- Regarded by dermatologists as the single most important formulation that should be applied daily.
- Products formulated to meet individual preferences, such as scent and feel, can improve compliance.

Retinoids
- Natural and synthetic derivatives of vitamin A
- Drugs: retinoic acid (tretinoin), adapalene, and tazarotene
  - Substantial scientific data confirm their anti-aging and anti-acne benefits.[2]
  - Retinoic acid is considered by dermatologists to be the anti-aging gold standard.
  - Available only through a doctor's prescription
- Cosmeceuticals: retinol, retinaldehyde, retinyl propionate, retinyl palmitate
  - In many cases, bioavailability and activity are unproven when formulated.

Moisturizers
- Include emollients, occlusives, and humectants.
- Considered to be the most useful product for the management of various skin conditions (e.g., atopic dermatitis, psoriasis, pruritus, aging skin).

Antioxidants
- Include vitamins A, C, and E; alpha lipoic acid; ubiquinone (coenzyme Q-10); idebenone; polyphenols (e.g., catechins, flavenoids); kinetin; botanicals (e.g., teas, grapeseed, grape skins and stems, coffeeberry).
- Enhance the skin's natural antioxidant protection system with topical application.
- Reduce free-radical damage by blocking the oxidative processes in cells.
- Inhibit inflammation that causes collagen depletion.
- Protect against photodamage and skin cancer.
- Do not reverse signs of photoaging.

Hydroxy Acids (alpha, beta, poly)
- Include glycolic acid, lactic acid, citric acid, tartaric acid, pyruvic acid, and malic acid.
- Can improve skin texture and dyspigmentation.
- Can induce actual structural changes in skin, so the potential exists for regulatory scrutiny.

Lightening Agents
- At best, depigmenting agents can achieve modest levels of efficacy.
- Hydroquinone is considered to be the most effective.
  - Presently under re-evaluation by the US FDA.
  - Sunscreen use is required due to drug-induced photosensitivity.
- Other examples include kojic acid, glabridin (licorice extract), arbutin, azelaic acid, n-acetyl glucosamine, and vitamin C.

Botanicals/ Plant Extracts
- Have experienced a rapid rise due to the popularity of "natural" compounds.
- Represent the largest group of additives found in marketed products.
- Limited scientific data to support efficacy and safety.

Epidermal Growth Factors
- Naturally occurring chemicals in the body that influence cellular proliferation and differentiation.
- Potential applications include regeneration of damaged or aged skin.

Proteins/ Peptides
- Can trigger skin repair as needed. There are some indications that they can reduce the signs of aging and accelerate the skin's healing processes.[3,4]

Other Vitamins and Minerals

Specific Agents of Recent Interest

OTC Retinoids
- They reduce wrinkles and lentigines.
- Common side-effects include redness, irritation, and an increase in photosensitivity.
- Certain retinoid analogues within the same class of molecules have been shown to provide less irritation, but maintain comparable levels of efficacy.[5]
- 3 classes of retinoids exhibit distinct properties:
  - vitamin A metabolites - trans-retinoic acid, retinaldehyde, adapalene, and tazarotene
  - vitamin A - retinol
  - vitamin A esters - retinyl acetate, retinyl propionate, and retinyl palmitate.
- Randomized, double-blind, placebo-controlled, human studies compared retinol, retinyl acetate, retinyl propionate and trans-retinoic acid.[5]
  - Statistically significant findings showed retinyl propionate exhibited the highest rating when evaluated for efficacy and non-irritation.
  - Furthermore, 0.30% retinyl propionate demonstrated superior reductions in wrinkles, redness and hyper-pigmentation vs. 0.15% retinol.

Niacinamide (vitamin B_3)

Niacinamide is a precursor of NADH and NADPH, which are co-enzymes essential for various metabolic functions. This B-complex vitamin can improve the barrier function of the epidermis and act as an inhibitor of melanosome transfer resulting in reduced hyperpigmentation.
- A left-right randomized, double-blind, placebo-controlled study involved women aged 25-60 years.
  - Patients applied a formulation containing niacinamide twice daily for 8-12 weeks.

Specific Agents of Recent Interest (continued)

- Results showed a decrease in transepidermal water loss through increased barrier layer lipids.[6,7]
- Another placebo-controlled, double-blind, left-right randomized study looked at 60 women of Japanese descent aged 25-60 years.
  - Split-face treatment twice daily for 8 weeks showed substantial improvement on lentiginous lesions.[8]
- A meta-analysis showed significant reduction in fine lines, wrinkles, hyperpigmented spots, blotchiness, sallowness, sebum production, irritation, and improvement to the skin's barrier function.[9]

Topical Peptides (retinoid alternative)

- Regarded as cellular messengers that are formed from amino acids designed to mimic peptide fragments with endogenous biologic activity; one is a 5 amino acid fragment (pentapeptides lysine-threonine-threonine-lysine-serine [KTTKS]).
- KTTKS plays a role in signaling fibroblasts to produce collagen in the skin,[10] which can improve the appearance of wrinkles.
  - One variation, known as palmitoyl-lysine-threonine-threonine-lysine-serine (Pal-KTTKS) was tested in a controlled, double-blind, left-right randomized, split-face study of 92 photoaged women with Fitzpatrick I-III type skin between 35-55 years of age.
  - Pal-KTTKS concentration was 3ppm; both groups were treated twice daily for 12 weeks
  - Improvements in wrinkle appearance and length were observed.
  - When 3ppm pal-KTTKS was combined with 3.5% niacinamide vs. placebo, an even greater reduction in wrinkle length was noted.

N-Acetyl Glucosamine (NAG)

NAG is a more stable form of glucosamine, and research indicates that it may prevent new signs of photodamage from occurring, and fade existing imperfections by interrupting the chemical signals that promote melanin production.

- A placebo-controlled study[11] comparing 3.5% NAG with the combination of 3.5% NAG + 3.5% niacinamide on hyperpigmented spots showed a superior reduction in pigmentation in the combination treatment group vs. both the placebo and NAG only groups.
  - When combined, the agents produced synergistic effects.

Use of Scientific Testing to Forecast Future Discoveries

- High throughput screening is presently in use to identify the next generation of active agents for cosmeceutical applications. This method has the capacity to screen thousands of compounds in a matter of days, or even hours.
- Genomic assays can be used to define all genes expressed in the skin. One application includes identifying targets for the management or prevention of skin and other disorders.
- Proteonics is a method of identifying proteins that are encoded by a genome. By promoting an understanding of the molecular mechanisms that cause human diseases, the development of novel therapeutic agents is possible.
- Metabonomics analyzes alterations in the metabolic end-products and the active pathways that result as a response to drugs, environmental influences, and diseases.

Conclusion

Keeping abreast of the latest findings and newest product offerings has become important for providing accurate advice to patients. Products supported by scientific research can be effective as an adjunct to therapy and/or part of a skincare regime. Actively assessing product clinical results, safety testing, and reviews from independent sources will enable clinicians to assist their patients in making informed product selections.

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Cosmeceuticals: A Panel Discussion About Educating the Public

Introduction

A panel presentation about cosmeceuticals was presented at the 2008 Dermatology Update meeting held April 10-12 in Whistler, BC. The panelists included 4 dermatologists: Jeffrey Dover, MD, Charles Lynde, MD, Catherine Zip, MD, and Jason Rivers, MD, who discussed cosmeceuticals and the role they play in adjunct therapy/effective skincare regimes in current dermatology practice.

They began by noting that on a daily basis they are asked by their patients to recommend skin care products. In order to be better prepared to address consumer queries and to convey practical information, medical professionals should gain fundamental knowledge of the active agents and available product variations. The panelists suggested that the healthcare provider's role can be two-fold: to arm consumers with basic, evidence-based information regarding the science behind various active agents, and to make general recommendations based on a patient's skin-type and individual medical background. They felt that dermatologists' combined understanding of the skin, drug compounding, pharmacodynamics, and pharmacokinetics, placed them in a unique position to influence patient behaviours, and that because of this they must adopt a well-rounded, informed, unbiased approach. While the panel members agreed that professional codes of conduct discourage them from endorsing specific products, they said that, in general, patients actively seek their recommendation and they often make suggestions from each class of skin care products. They concurred that the focus of their recommendations should be placed on providing education about how cosmeceuticals can be incorporated into existing skin care regimes.

Physician Endorsement

The term "dermatologist recommended" is often seen on product labels, and likely, the intended message being conveyed is that a panel of experts has assessed the product's efficacy and validated its claims.* The panelists all agreed that there must be evidence for efficacy, not just the extravagant claims that are frequently made.

Consumer Needs

Individual consumer needs and preferences can greatly assist in dispensing the proper information and narrowing down the types of products for which they can search. Consumer purchasing behaviours are complex and driven by information that is gleaned from multiple sources, as well as being steered by factors such as product efficacy, packaging, and cosmetic acceptability, i.e., patient adherence can be influenced by the product's feel, scent, etc. Because some active agents (e.g., retinoids, acne medications, botanicals, etc.) can produce sensitizing reactions, it is essential for patients to be counselled on expected side-effects, as well as mitigating factors.

The widely accepted skin care regime that these dermatologists recommend for photoaging is a morning application of a sunscreen, followed by use of a prescription retinoid in the evening, provided that tolerability to retinoids is not a concern. It is important to note that this basic regimen cannot be generalized across all populations; recommendations must be individualized.

Moisturizers

Reproducible, scientific evidence has shown that moisturizers yield both therapeutic and cosmetic benefits. Most act by improving barrier function with lipids and oils (decreasing transepidermal water loss) rather than by introducing moisture into the skin. Humectants, such as urea and lactic acid, have some ability to attract water from the dermis and the external environment. The efficacy of moisturizers is mainly derived from their ability to temporarily seal the epidermis and break the dry skin cycle.

Sunscreens and Vitamin D Deficiency

Recently, there has been a great deal of media coverage and published medical literature regarding vitamin D deficiency. As a result, patients are concerned that the use of sunscreens may put them at risk for vitamin D deficiency, and many are asking their physicians for clarification of this pseudo-controversy. There is very little evidence to support the hypothesis that sunscreens modify vitamin D levels. The general consensus in the scientific community is that sufficient levels of vitamin D

Sunscreens and Vitamin D Deficiency (continued)

can be attained from natural sources, i.e., through diet and moderate sun exposure. As this debate is unlikely to resolve in the near future, the panelists recommend continued regular use of a broad spectrum sunscreen with a minimum sun protection factor (SPF) rating of 30, in combination with daily oral vitamin D supplementation at a dose of 800-1,000 IU/day. Daily calcium supplements that include vitamin D are encouraged for women due to their susceptibility to osteoporosis later in life.

The US FDA is currently modifying its monograph on sunscreens, and new guidelines will be released within the next 2-3 years. The current SPF rating system only measures UVB coverage. The changes include an additional methodology that will determine a sunscreen's UVA protection factor using a 4-star rating system.

Contact Sensitivity

The panelists all agreed that contact sensitivities from cosmetics and cosmeceutical products occur, but incidences remain largely unreported to physicians, especially if reactions are mild. Botanical agents are some of the most potent contact allergens. The misperception is that because these cosmetic additives are naturally or plant derived, they pose little or no risk in causing skin sensitivities. Fragrances are also common sources of contact allergens. The present system of ingredient labelling represents an additional layer of confusion when consumers attempt to identify and avoid certain ingredients. For example, a product can claim to be preservative-free; however, the label may disguise an ingredient as a fragrance, when in actuality, it is a preservative with a scent added.

Initiatives by Industry

All the panelists agreed that the cost of any cosmeceutical product is not necessarily a reflection of its efficacy or quality. Increasingly, there is a noticeable effort on the part of larger cosmeceutical manufacturers to engage in clinical studies. The data generated can frequently be found at medical forums as poster presentations and presented at industry-sponsored educational forums/symposia. These attempts to evoke consumer confidence are a first step in the right direction and may form the basis of more accurate product representations.

Education and Information

Most reputable cosmeceutical companies make the scientific data behind specific formulations readily available. However, the panelists stressed that clinicians should be aware that for many cosmeceuticals, much of the scientific data used to support their claims are based on *in vitro* studies, and that while human studies are performed, the final formulation of the product has frequently not been tested in humans. There is a wealth of information on the internet, but panellists warned that clinicians should be aware that much of the content is based on conjecture and inference and they need to pay close attention to the source of the information/data that supports the content. The panel mentioned that it is common to find many of the reputable cosmeceutical manufacturers presenting their research at scientific meetings; these occasions are ideal for assessing the quality of the data used to support product claims, and health professionals are encouraged to participate in/attend such opportunities. Feedback from participants suggests that there is a need for more of these sessions on adjunct therapy.

The panelists concluded by agreeing that based on the myriad of informational sources, an inquisitive and discerning approach is required to assess the available data on cosmeceuticals. Health professionals need to actively seek and evaluate the information being shared, i.e., through well designed *in vitro* and *in vivo* clinical studies. These educational efforts will hopefully contribute to the accurate dissemination of information by medical professionals and to informed decision-making on the part of consumers.

* Editor's note: In response to consumer confusion about cosmeceutical products, SkinCareGuide has established a new professional review process for OTC skincare products to provide professional reviews of skin care product claims. The overall purpose is two-fold. First, the Dermatology Review Panel (DRP) assists consumers and medical professionals to easily identify nonprescription skincare products that meet independent approval standards with regard to product claims. Secondly, the DRP encourages manufacturers to engage in more clinical research. Readers can get more information by going to: http://www.dermatologyreviewpanel.ca.

Management of Recalcitrant Acne

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Background

Acne that is recalcitrant to therapy is a common clinical dilemma. Some of the influencing factors that contribute to treatment challenges include poor adherence, inadequate therapy, and diagnostic mimics.

Diagnostic Considerations

Acne is a common, yet complex skin disorder of the pilosebaceous units that is especially prevalent among people aged 15-24 years, and the associated psychosocial impact can be significant. Acne severity may be classified as minimal, mild, moderate and severe based on the presence of primary acne lesion types, their distribution, and the density of involvement. All forms of acne involve 1 or more of the following pathophysiologic factors:

- hyperkeratinization of the follicular epithelium with comedone formation
- sebaceous gland hyperfunction with increased sebum production
- proliferation of *Propionibacterum acnes (P. acnes)*
- local immune hypersensitivity causing inflammation.

Therapeutic Options

Existing therapies for acne can be divided into 3 categories:

1. Conventional therapies include topical retinoids, antibiotics, benzoyl peroxide (BP), systemic antibiotics, hormonal therapy, and oral isotretinoin. Treatment selection is based on the predominant acne lesion type and overall acne severity. Comedones are most effectively addressed by the comedolytic effect of retinoids. The role of *P. acnes* in inflammatory papules/pustules is the rationale for using topical/oral antibiotics and BP agents. Hormonal therapy reduces sebum secretion, secondarily reducing *P. acnes*. Oral isotretinoin affects all pathogenic factors and is the treatment standard for severe or recalitrant acne. Concerns with *P. acnes* resistance to antibiotics can be addressed by avoiding antibiotic monotherapy, using antibiotics in combination with BP, and avoiding oral antibiotics used for community-acquired infections.
2. Procedural modalities include comedone extraction, intralesional steroid injections, microdermabrasion, and chemical peels.
3. Optical modalities include laser treatment, noncoherent light sources, and photodynamic therapy.

Improving Patient Adherence

Adherence can be directly influenced by the patient-physician relationship and treatment-related issues.[1] More frequent follow-up, ongoing counselling and education can promote adherence, minimize complications, and improve outcomes. Encourage discussion of the impact of acne and gauge the patient's treatment expectations to ensure that their perspective is heard. Tips for encouraging adherence[1] include:

- Reassure patients that acne is a very common skin condition caused by a combination of variables including genetics, hormones, and stress, and it is aggravated by occlusive factors. It is not a result of poor hygiene.
- Explain the pathogenic features of acne and the rationale for the selected treatment regimen. Provide printed material that will educate and reinforce the aims of therapy and the importance of adherence.
- Detail potential side-effects for the medications, modifying the dosing schedule or switching treatments based on tolerance and patient preference.

Clinic Visits

After the initial visit, plan to see patients again at 4 weeks to review medications (i.e., where and how to apply them and how long to use them), encourage maintenance therapy, and counsel patients to expect improvement in 8-10 weeks. By 8-10 weeks, if a patient's acne has not improved, either because the number of lesions has increased or due to patient dissatisfaction with the treatment, evaluate other options.

Acne Mimics

There are multiple factors that engender recalcitrant acne. The primary differentiating feature of acne mimics from acne is the absence of comedones. However, some of these conditions may appear coincidentally with acne, particularly when there has been previous antibiotic therapy for acne.

Acne Mimics (continued)

Skin Disorder	Comments
Miliaria (also referred to as sweat rash or prickly heat)	• Develops from eccrine gland occlusion; can result in extensive minute translucent papules (miliaria), which can become inflamed, leading to inflammatory non-follicular papules (miliaria rubra). • Triggering factors include high ambient heat/humidity, occlusive moisturizers, make-up, hair grooming products, clothing, and headwear. Commonly affects the forehead and hairline. • Can present as extensive, studded, noninflammatory micropapules, and inflammatory papules. These lesions are not centered around a pilosebaceous unit. • To treat, reduce environmental heat and humidity and local aggravating factors. Miliaria rubra will respond to topical therapy with an astringent effect, e.g., gel-based BP preparations.
Demodex Folliculitis	• Results from perifollicular inflammation caused by *Demodex folliculorum*, an otherwise ubiquitous pilososebaceous parasitic resident mite that feeds on sebum and the stratum corneum. • Typically affects an older population than does acne vulgaris. • Follicular papules/pustules exhibit more diffuse background erythema. Comedones are absent. • May also mimic inflammatory rosacea. • Laboratory testing includes a non-invasive skin surface biopsy using cyanoacrylate adhesive and microscope examination; a density of ≥5 mites/cm^2 of skin surface indicates infestation.[2] • Treatment includes topical metronidazole or permethrin. Oral ivermectin 0.2mg/kg q.wk. for 2-4 weeks may help in more extensive or resistant cases.
Malassezia Folliculitis	• Triggered by the lipophilic yeast *Malassezia furfur*. Extension deep into the pilosebaceous follicle is considered to be the cardinal feature.[3] • Typically affects regions rich in sebaceous glands (i.e., scalp, face, upper torso). • Many of the factors aggravating acne and miliaria, e.g., higher sebum production and occlusion, can be triggers. Prolonged antibiotic therapy and immunosupression may also aggravate it. • Presentation is either asymptomatic or seen as itchy, follicular, typically monomorphic papules/pustules in the absence of comedones. • Laboratory evaluation is based on microscopic examination of pustule contents for hyphae and spores (appearing like a spaghetti and meatballs pattern). Skin biopsies may help if pustules are not present. • To treat, correct triggering factors where possible. For milder cases, topical antifungal agents may be adequate (e.g., azole or selenium sulfide, which are formulated in foams, shampoos, lotions). • For more extensive or resistant cases, up to 8 weeks of systemic therapy may be needed, e.g., itraconazole 200mg once weekly; ketoconazole 200mg b.i.d. once weekly; or fluconazole 150mg once weekly.
Gram Negative Folliculitis	• A pilosebaceous unit infection caused by gram-negative organisms. • Patients may present with inflammatory acne unresponsive to antibiotics or previously responsive acne that subsequently worsens. • May be seen as monomorphic papules/pustules or deep indurated nodules and cysts especially on cheeks and chin. • Laboratory confirmation requires bacterial culture of pustules. • Bacteria involved may be *Klebsiella*, *Serratia*, *Escherischia* or *Proteus* species. *Pseudomonas* is more frequently involved with hot tub folliculitis. • For milder cases use topical therapy with BP; for extensive involvement or in the presence of nodules and cysts use oral isotretinoin.[4]

Diagnostic Procedures for Acne Mimics

Diagnosis can be guided by the morphology of the lesions and confirmed through appropriate testing.

- Pustules: bacterial culture; microscopy of pustules with 10%-20% KOH to evaluate for *Malasezzia*
- Papules: cyanoacrylate skin surface biopsy to evaluate for *Demodex*; punch biopsy to evaluate for *Malasezzia*
- Nodules and cysts: bacterial culture; punch biopsy for *Malasezzia*
- Hormonal testing for polycystic ovarian syndrome (testosterone, DHEA-S, LH, FSH, androstenedione), and congenital adrenal hyperplasia (cosyntropin stimulation and 17-hydroxyprogesterone levels)

Conclusion

Acne treatment success involves a comprehensive approach that addresses diagnostic confounders, appropriate therapeutic options and patient adherence. Ongoing education and counselling will assist in meeting patient expectations and establishing a favourable rapport that promotes adherence. A possible contributing factor for inadequate response to acne therapy may be the misdiagnosis or coexistence of other skin disorders that resemble acne. Confirmation of these concurrent conditions with the aid of laboratory evaluations and the withdrawal of triggering factors can mitigate the effects of recalcitrant disease.

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