Received: 14 February 2021 | Revised: 10 May 2021 | Accepted: 11 May 2021

DOI: 10.1096/fba.2021-00022

FASEB BioAdvances Open Access WILEY

REVIEW

Topical and nutricosmetic products for healthy hair and dermal antiaging using "dual-acting" (2 for 1) plant-based peptides, hormones, and cannabinoids

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Abstract

One of the side effects of oral antiaging retinoids is increased hair shedding. Retinoids promote the expression of TGF-β2 from fibroblasts, which stimulate collagen expression but silences keratinocytes. Since keratinocytes normally influence differentiation of dermal papilla cells at the base of the hair follicle, retinoids feasibly inhibit hair growth via the increased expression of TGF-β2, which inhibits Wnt/β-catenin signaling. Fortunately, the plant kingdom provides an array of alternatives as dual-acting nutricosmetics and topicals that work independently of TGF-β2 to confer dermal antiaging and hair health effects. These alternatives include "plant hormones" such as cytokinins and phytoestrogens. Many cytokinins are agonists of the G-coupled adenosine receptors. Partial agonism of adenosine receptors promotes collagen synthesis independently of TGF-β2 signaling. Adenosine expression is potentially also the mechanism of minoxidil in promotion of scalp hair growth. Because of crosstalk between adenosine and cannabinoid receptors it makes sense to try combinations of specific CB2 agonists and cytokinins (or phytoestrogens). However, dual-acting cosmetics including peptides with high numbers of positively charged amino acids, such as lysine or arginine, offer real potential as they can be processed from multiple botanical candidates, including almond, fenugreek, pea sprouts, soy, and seaweeds. The current review summarizes much of what is known about retinoid alternatives in the plant kingdom and identifies potentially fruitful new areas of research.

KEYWORDS

alopecia, antiaging, collagen, dermis, fibroblast, hair, keratinocyte, peptides

1 | INTRODUCTION

While retinoids have long been the primary dermal antiaging ingredients of choice in cosmetics, it is well known that mild to moderate side effects have persuaded researchers to develop alternatives. Negative effects of topical retinoids include dryness, tightness, peeling, and redness, while oral or systemic retinoids can cause excessive hair shedding. This presents a paradox: retinoids are necessary for the continued growth and health of the hair follicle,[1] but at higher doses lead to hair loss.[2] Thus, oral use of retinoids to achieve younger skin may be at the cost of healthy hair and topical

use can cause undesirable side effects. Furthermore, there is a risk that consumers will exceed prescribed topical applications, which is predicted to cause hair shedding if applied to the scalp. Natural products that are functional analogues of retinol, with yet to be determined optimal doses, risk similar negative outcomes. Hence, to identify natural products that serve the dual purpose of providing hair and skin improvements, it will be necessary to utilize non-retinoid products. Active natural products could be ideally delivered via both topical and nutricosmetic applications.

The cosmetics industry is experiencing a paradigm shift toward the "inside-out" ethos. In this regard, dermatologists are acknowledging that hair and skin quality are dependent upon both external (topical) and internal (dietary) factors. The exciting new developments are collectively known as nutricosmetics. Although nutricosmetics is still being defined and legislated, it advocates nutritional factors as necessary for cosmetic improvements to hair and skin.[3] It is the contention of this narrative that topical and nutritional initiatives that utilize plant-based ingredients are of interest, comparable to retinoids but with less pronounced negative outcomes.

While it is well known that oral retinoids can negatively impact scalp hair, such effects may be exaggerated in individuals with hair loss pathologies. Research demonstrates that scalps afflicted with hair loss pathologies express high amounts of transforming growth factor beta isotype 1 (TGF-β1),[4] and low amounts of isotype 2 (TGF-β2). Normalization of these isotypes is considered a positive outcome.[5] Thus, therapeutic intervention with retinoids is expected to bring about an improvement to hair health[1] by upregulation of TGF-β2.[6] But topical application may be considered a risk, because in normal metabolism the dermal concentration of retinoic acid is maintained within a safe threshold by forward and reverse conversion from retinol to retinyl esters.[7] The problem with topical retinoic acid is that excess can interfere with this natural balance, which increases TGF-β2 to above homeostatic levels and causes hair loss[2] (Figure 1).

Both of the TGF-β cytokines promote the expression of collagen in dermal fibroblast cells[8] (Figure 2) and create fibrosing effects in the long term. Purportedly, TGF-β1 and -2 induce matrix metalloproteinase expression and senescence in keratinocytes stem cells,[9] which normally influence differentiation of dermal papilla cells that create hair shafts in hair follicles, in modulation with the Wnt/β-catenin signaling pathway.[10,11] Because this pathway is inhibited by overexpression of both TGF-β1 and -2,[12] then the use of retinoids and functional analogues in hair loss therapy poses a risk. Hence, it is necessary to find oral and topical products that promote dermal antiaging effects (collagen synthesis) independently of TGF-β to avoid negative effects to scalp hair. For example, products that promote collagen expression by partial agonism of adenosine receptors may simultaneously benefit hair. It has been demonstrated that dermal papilla cells have adenosine receptors and it is thought that increased expression of adenosine synthesizing genes from the sulfonylurea gene battery is the mechanism of hair growth promotion by minoxidil.[13] By way of example, adenosine and functional analogues of adenosine may support hair growth in a similar way to minoxidil.[14]

Recently, peptides, which are short chains made up of amino acids, have been introduced to the market as topical and oral cosmetics in both contexts, i.e., hair health[15] and dermal rejuvenation.[16] The efficacy of peptides in promotion of cellular turnover is conceded to be an adaptive response to "signs" of tissue damage. Another example of overlap between hair and dermal rejuvenation comes from studies of cannabinoids as agonists for cannabinoid receptor 2 (CB2). Specific agonists of CB2 are finding a place in dermal treatments by promotion of lipogenesis out of the sebaceous gland, where CB2 receptors are expressed.[17] This has the effect of enhancing barrier water content and hence skin hydration. However, preliminary evidence is also in favor of use in promotion of hair follicle bulge stem cells. Preliminary studies have conveyed that caryophyllene has this effect.[18]

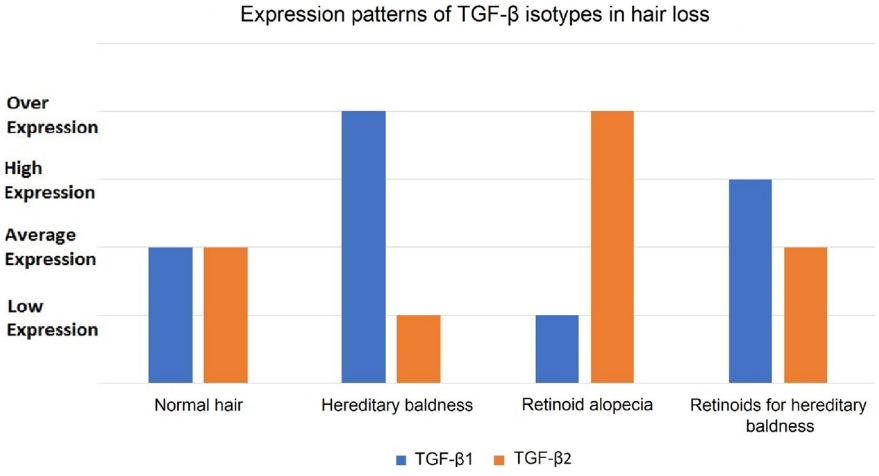

FIGURE 1 TGF-β isotypes are expressed in equilibrium. In hereditary hair loss TGF-β1 is over expressed and TGF-β2 is under expressed. Because retinoic acid promotes expression of TGF-β2 it can be used as a therapy for this type of hair loss. But normal hair types are negatively affected by retinoic acid, paradoxically by the same mechanism

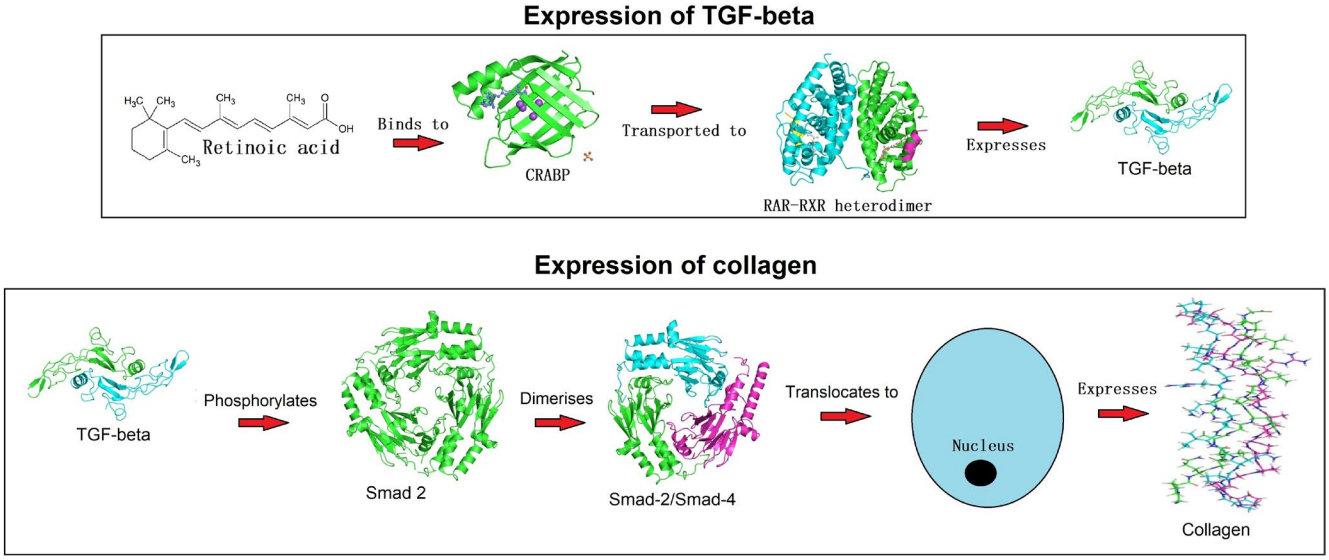

FIGURE 2 The biochemical cascade that triggers collagen synthesis from the dermal fibroblast, initiated by retinoic acid; Retinoic acid binds to CRABP which transports it to the RAR-RXR receptor, causing transcription of TGF-beta. Then TGF-beta phosphorylates Smad 2, which dimerizes with Smad-4 and translocates to the nucleus of a fibroblast. This causes expression of collagen

The plant kingdom expresses a diverse array of metabolites that are selective agonists for CB2. Furthermore, some plant-derived metabolites have the potential to enact dual therapies for skin and hair by various mechanisms, including peptide signaling and promotion of keratinocyte proliferation/differentiation. The current review gives an overview of the diverse metabolites expressed by plants that can fill the same niche as the classic retinol in dermal antiaging therapies and improve, rather than negate, hair quality.

2 | HISTORICAL PERSPECTIVE: INSPIRATION FOR MODERN CYTOKINE MIMETICS

The therapeutic potential of endogenous bioactive peptides has been recognized since the discovery of insulin for the treatment of type 1 diabetes in the 1920s.[19] Since then, more bioactive peptides have been identified. For example, in 1973 Loren Pickart published the discovery of an endogenous metallopeptide known as "copper peptide" or GHK-Cu (glycyl-L-histidyl-L-lysine), which he isolated from human plasma. Pickart demonstrated that this tripeptide conferred pronounced rejuvenating effects in a neoplastic liver.[20] The same peptide has since been demonstrated to be of substantial value in the rejuvenation of human tissues, particularly the dermis.[21]

More importantly, GHK-Cu has been shown to promote fibroblast proliferation together with the expression of ECM proteins and proteoglycans.[21] But unlike retinol, keratinocyte cells are modulated via a conservative orchestration of cellular signaling, with no significant change to interleukin-1α expression[22] and moderate proliferation that is thought to derive from regulation of the epidermal extracellular matrix proteins, integrins α6 and β1. Integrin α6 is a marker of extracellular adhesion receptors common in the dermal-epidermal junction. Integrin β1 is expressed in the basal cell plasma membrane.

These results demonstrate that GHK-Cu increases cell adhesion and integrity of the dermal-epidermal junction,[23] providing mechanical tension on the fibroblasts, which is known to enhance production of collagen, ECM proteins and proteoglycans.[24] The mechanism of GHK-Cu is unclear, because at times it appears to be merely a vehicle for copper transport, whereas it can also be argued that it is a signaling molecule in its own right.[25]

Despite being a promoter of wound healing and collagen synthesis, GHK-Cu suppresses the expression of TGF-β1,[26] which is overexpressed in balding scalps. This is probably the mechanism of hair shaft thickening and hair growth support observed from subcutaneously delivered GHK-Cu. A similar tripeptide, AHK-Cu, also yielded the same outcome in vitro, that includes reduced expression of TGF-β1 and increased hair shaft elongation, increased expression of vascular endothelial growth factor and reduced negative growth factors.[27]

The unusual peptide sequence of GHK is found in collagen-1, from where it is released during degradation of the ECM.[28] From an evolutionary perspective, the GHK sequence appears to be built into the protein as a sentinel defense against the destructive force of extrinsic factors. It is thought, however, that there are many more such biomimetic

peptides significantly involved in the complex orchestration of ECM restoration, as demonstrated in the previous example.

While the positive effects of GHK-Cu are promising, its high hydrophilicity and poor transdermal penetration makes it uncertain that topical non-invasive applications would have the same efficacy as compared to injection or microneedling.[29] Alternatives that have better pharmacokinetics can be sourced from the animal or invertebrate kingdoms. For example, Schagen[16] provides a summary of animal-derived peptides and associated roles in dermal remodeling.

However, the current review is focused on plant-based ingredients because the cosmetics industry has recognized that consumer preference has shifted toward plant-based alternatives.[30] Fortunately, in the past few decades research has started to indicate that plant-derived peptides can also confer positive effects[31] consistent with the endogenous cytokines, such as GHK-Cu, but with better pharmacokinetics.

Aside from the unique sequence, the communicating power of GHK may be related to the presence of the uncommon amino acid L-lysine, which is the "K" in GHK (or AHK). Thus, a strategy for identifying biomimetic peptides from plant protein digests is to narrow the investigation to species with high contents of amino acids that are positively charged at homeostatic pH (Table 1), such as lysine, or the structurally related arginine (Figure 3). The merit of this observation will become evident in the following examples. The feasibility of this selection criteria is validated by interrogation of anecdotal claims of efficacy based on historical empirical strategies. One of the best-known historical antiaging therapies is the unique extract from seed and seed-coat of "hemayet," which was originally translated as fenugreek, but later realized by Professor JP Allen to mean bitter almond,[32] a known source of arginine and lysine-rich peptides. Allen relates the details of the extraction process and intended application, giving an up to date translation from the "Edwin Smith Papyrus," an Egyptian medical document dated to over 3500 years BC (>5000 years BP),[32] now located at the New York Academy of Medicine.

Motivated by the marketability of the papyrus story, the oil of bitter almond is sold as an age reversing therapy. However, the oil is generally manufactured by cold pressing or supercritical extraction of fresh seed, which is very different from the old recipe.[32] By following the steps as translated by Allen[32] and adhering to strict protocols prescribed by the papyrus' author, the derived oil is likely to contain the lipophilic portion of the protein and/or peptide in the kernel. The leaching process removes the hydrophilic cyanogenic toxins or "bitters" but the lipophilic protein/amino acids are conserved and dissolve into the oil layer that is collected following the extraction.

Proteins and peptides appear at a lower concentration in common oils, such as rapeseed, following the routine industrial extraction process,[33] but due to the heat used, which drives aqueous solubility or liquidation, protein derivatives will be at a much higher concentration in the end product specified in the papyrus. More importantly, both arginine and lysine are chemically characterized by slightly longer methylene series (carbon chains), which increases lipophilicity of the respective peptide, increasing solubility in oils and affinity for lipophilic binding domains in cellular receptors.

An entrepreneurial plastic surgeon eventually discovered mandelic acid in bitter almond, which was demonstrated to

TABLE 1 The ionic states of amino acids that form peptides

Ionic states of amino acids at homeostatic pH (pH 7.3–7.4)	
Low polarity	Moderate polarity
Gly = glycine	Ser = serine
Ala = alanine	Thr = threonine
Val = valine	Tyr = tyrosine
Cys = cysteine	Asn = asparagine
Pro = proline	Gln = glutamine
Leu = leucine	
Ile = isoleucine	
Met = methionine	
Trp = tryptophan	
Phe = phenylalancine	
Positive charge	Negative charge
Lys = lysine	Asp = aspartic acid
Arg = arginine	Glu = glutamic acid
His = histidine	

Note: The amino acids that are important in therapeutic and cosmetic peptides are the ones that have a positive net charge at homeostatic pH level. Only three are common, and these include arginine, histidine, and lysine.

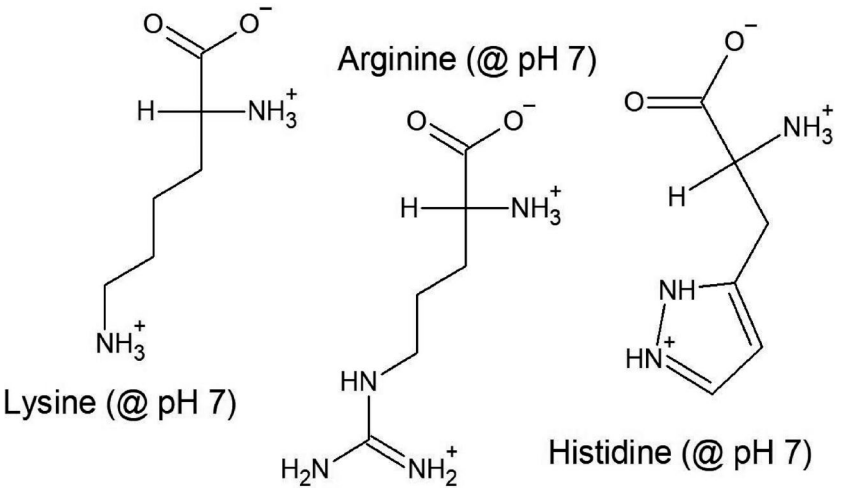

FIGURE 3 The three amino acids that have positive net charge at homeostatic pH

give a significant aesthetic improvement to aged skin,[34] and no mechanism has been explained till now. But bioactive peptides have also been discovered in the hydrolysate of the protein fraction of almond flesh and the activity of these peptides is dependent upon the presence of arginine and lysine at the C-terminal end of the peptide.[35] Although these peptides are known as inhibitors of angiotensin-1-converting enzyme, significant in the context of hypertension, several patents have also been filed on the use of these peptides in dermal rejuvenation cosmetics,[36] and there are now many peptide-based cosmetic products on the market.[37]

Today research on plant-derived protein hydrolysates utilize industrially available peptidases (pepsin, trypsin, chymotrypsin, alcalase, and flavourzyme),[35] which may be described as a "shot gun" approach to the creation and identification of bioactive peptides. However, it is possible that by soaking grains or seeds in water and allowing them to approach germination the cytokinin levels and bioactive peptides increase naturally.[38] This process is known as "imbibing" the seeds, which activates hydrolytic enzymes that drive the conversion of whole proteins into peptide fragments and free amino acids.[39] Thus, out of the naturally occurring hydrolytic products the proportion of bioactive metabolites would be much higher, since the process follows the biomimetic route. It is possible that the previously mentioned Egyptian protocol for the manufacture of oil out of bitter almond induces these imbibing effects, known today as "activating" the almonds, which in actuality is "activating" hydrolytic enzymes.

The almond skins are also the site for the accumulation of several antioxidant flavonols and isoflavonoid glycosides. The glycosides will be inevitably cleaved into their aglycone form during extended cooking and boiling steps, making them lipophilic and soluble in the oil layer described in Allen's translation of the papyrus.[32] Recently it was demonstrated that the inclusion of antioxidants with collagen peptides promotes elastin and collagen synthesis further than with collagen peptides alone.[24] The activity was thought to derive from protection against matrix metalloproteinase (MMP) expression by antagonizing reactive oxygen species, which are thought to be a major driving force behind the increase in MMP levels in aged skin.[40]

Other sources of lysine and arginine-rich proteins include: the seed of soy (*Glycine max* L.), which yields peptides upon hydrolysis that promote collagen-1 expression in fibroblasts[41]; fenugreek (*Trigonella foenum-graecum* L.), a lysine, β-carotene and protein-rich organ,[42] also a source of the antidiabetic amino acid 4-hydroxyisoleucine[43]; the extract of pea sprouts (*Pisum sativum*),[44] which has not yet been popularized in the context of dermal restoration; and *Pyropia yezonensis* (seaweed), which produces a peptide upon protein hydrolysis, with a lysine-dense region near the n-terminus (D-P-K-G-K-Q-Q-A-I-H-V-A-P-S-F: K = lysine), which nevertheless promotes expression of collagen in fibroblasts by activation of the TGFβ/smad pathway.[45]

The previously mentioned peptide derived from the seaweed *P. yezonensis*, was also associated with decreased MMP-1 and upregulation of the expression of "tissue inhibitors of metalloproteinase," TIMP-1 and TIMP-2.[45] By upregulation of TIMP a more efficient modulation of the protein degradation and rejuvenation cycle can be enacted.[46] Upregulation of TIMP enzymes is albeit a downstream effect of the TGF-β/smad pathway,[9] but this outcome appears to work independently of TGF-β signaling.

In today's modern market "multi-peptide" formulations are the dominant active components of a wide range of antiaging serums. These same multi-peptide compositions are repackaged as hair growth topicals. One of the most common compositions include "acetyl tetrapeptide-3" (Capixyl™) which is comprised by the amino acid sequence of acetyl-K-G-H-K-NH_2, including two lysine groups. Compositions usually also include the previously mentioned pea sprout extract of *Pisum sativum* (Anagain™), which will create many lysine-rich peptides[44] in the sprouting process.

Something that has not yet received serious consideration with respect to plant-derived peptides is the possibility of synergistic effects derived from plant specialized

metabolites that are included as a by-product of the extraction process.[30] Plant-derived bioactive peptides differ from those sourced via synthetic and animal manufacturing processes in that the specialized metabolites of the plant kingdom, that are known to have numerous positive and negative effects in human health,[47] may be present in the protein hydrolysates. Since many of the protein hydrolysates are derived from plant stem cell or tissue cultures,[30] then endogenous plant ligands or cytokinins may be extracted at detectable and hence bioactive concentrations. Plant-derived cytokinins may confer additive effects, due to agonism of membrane receptors.

3 | "PHYTOHORMONES": AGONISM OF THE ADENOSINE A_{2A} MEMBRANE RECEPTOR

The phenomena of partial agonism as a means of modulating genes out of receptor-ligand complexes, and agonist-specific effects on downstream phosphorylation steps,[48,49] conveys the need to assess gene arrays of known receptor ligands to have any idea of their effects. Just like nuclear receptors, the adenosine A_{2A} membrane receptor ($A_{2A}R$) modulates effects that are specific to the concentration and degree of agonism of the ligand. The endogenous ligand, adenosine, is released in stress and injury. The expression of collagen types is modulated by the concentration of adenosine in tissues, with higher concentrations in damaged tissue.[50] Full agonism of the adenosine $A_{2A}R$ receptor occurs with elevated levels of adenosine, occurring shortly after dermal assaults that require rapid tissue growth to close wounds. During wound recovery, the $A_{2A}R$ modulates the ratio of collagen-1/collagen-3, which is normally 4:1 in non-scarred tissues but reduced to 2:1 (increased collagen-3) in scar tissue.

Adenosine has been trialed on non-injured skin as a topical antiwrinkle treatment, with indication of beneficial effects.[51] However, modern dermal treatments incorporate microneedling into topical treatments, so there is some concern that adenosine in such contexts may lead to the formation of scars. It has been shown that the synthetic partial agonist of the $A_{2A}R$, known as CGS21680, did not activate Smad2/3 and instead modulated the expression of other $A_{2A}R$ effectors, increasing the ratio of collagen-1/collagen-3.[50] This outcome demonstrates that it is feasible to search for partial agonists of the $A_{2A}R$ in the plant kingdom to promote a similar outcome to that achieved by the synthetic CGS21680.

Dermal papilla cells have adenosine receptors. Increased expression of adenosine by agonism of the sulfonylurea receptor is thought to be the mechanism of minoxidil in hair growth.[13] Hence, it is possible that partial agonists of the $A_{2A}R$ may not only benefit aged skin but could promote the growth of scalp hair.

Adenosine is an endogenous purine nucleoside. The ribose moiety enhances the polar headspace, making it a relative polar molecule that is consequently concentrated in the extracellular spaces where it acts on its endogenous membrane bound receptor. The functional equivalents in the plant kingdom are cytokinins, which are found at high concentrations in imbibed seeds (post dormant, pre-germinated seeds), peaking at up to 40 h during the pre-germination phase, following by a dramatic reduction at the start of the germinating phase.[38] Cytokinins are also found in plant root tips, shoots[52] and stem cell extracts, which have been shown to promote collagen production out of human fibroblasts.[53] The purine alkaloid kinetin (6-furfuryladenine) is identified as important in accommodating this effect, and the authors discuss the importance of kinetin's antioxidant activity to derive these effects. However, partial agonism of the $A_{2A}R$ by kinetin or a related derivative has not yet been considered as a possible mechanism.

Agonists and antagonists of the $A_{2A}R$ have been of interest in the context of cancers, inflammatory etiologies, and neurodegenerative conditions, such as Parkinson's and Alzheimer's disease.[52,54] A cross-examination of agonists and antagonists of the $A_{2A}R$ provided by Müller and Jacobson[54] gives a clear indication of the importance of a ribose moiety in full affinity. The plant-derived $A_{2A}R$ agonist identified by Lee et al.,[52] zeatin riboside from chicory root,[55] is an $A_{2A}R$ agonist as expected. Also as expected, in a lymphocyte model cAMP levels were elevated significantly above vehicle treatment controls,[56] which as previously mentioned is the same outcome derived by the endogenous ligand adenosine.[50] Hence, less analogous cytokinins as compared to adenosine would be a preferred alternative. It is not obvious what the structural requirements are for mere partial agonism, or if the ribose unit is necessary for this.

Many cytokinin bases, ribosides, and ribotides are found in plants.[57] Research on the treatment of human cells with plant-based cytokinins is immature but may generate interesting outcomes. Thus, studies that show collagen expression in fibroblasts treated with extracts from plant stem cell cultures require more comprehensive investigation, seeking complementary active ingredients, such as cytokinins. For example, a study that examined a cell culture extract of *Nicotiana sylvestris* demonstrated collagen-1 and collagen-3 upregulation in human dermal fibroblasts, with the effects attributed to the peptides and "sugars".[58] Tomato (*Lycopersicon esculentum*) stem cell extracts protect skin cells from heavy metal-induced damage via metal chelating factors and "antioxidants".[59] Stem cell extracts of *Coffea bengalensis*[60] and *Vitis vinifera*[61] both promoted collagen synthesis in human dermal fibroblast cells with no mechanism defined. Since, allegedly, plant stem cells are a rich source of cytokinins[53] then it is reasonable to

encourage chemical characterization of stem cell extracts in these kinds of studies to identify co-contributing chemical species.

4 | CUTANNABINOIDS

While CB2 agonism leading to lipogenesis promotion can create aesthetically pleasing effects in scalp hair, it may be contraindicated in cases of androgenetic alopecia,[62] which is characterized by aberrant lipogenesis and chronic agonism of the peroxisome proliferator activated receptor gamma (PPAR-γ).[63,64] However, because there are no CB2 receptors expressed in the human hair follicle epithelium, there is scope to take research using CB2 therapies further. In contrast, cannabinoid receptor 1 (CB1) is expressed in this region, and it has been shown that agonists for the CB1 receptor are negative growth regulators.[65] Thus, dermal treatments with cannabinoids need to be specific agonists for the CB2 receptor, with no binding affinity for CB1, before considered as worthy research candidates.

It is also possible that antagonism of the CB1 receptor could improve contiguous therapies by negating negative effects. For example, full agonism of the adenosine receptor 2A ($A_{2A}R$) can create fibrosis, whereas partial agonism can have antiaging effects.[50] Because these profibrotic effects derived from full agonism of the $A_{2A}R$ are related to a crosstalk with CB1,[66] antagonism of the CB1 receptor could alleviate the fibrotic problem. Hence, this creates an avenue for the use of $A_{2A}R$ agonists in dermal antiaging therapy and hair health. This reiterates that it is necessary to avoid agonists for CB1 as they may derive negative effects, rather than positive, particularly in combination therapies. For example, the best known endogenous ligand (endocannabinoid) of CB1 is anandamide, a derivative of arachidonic acid,[67] which is expected to confer negative effects to hair follicles.

Hence, dermal and hair treatments that use cannabinoids that are specific agonists for the CB2 receptor, with no binding affinity or are antagonists for CB1, are regarded as worthy of further research. Specific cannabinoid agonists for CB2 are already finding a place in dermal treatments. As mentioned earlier, the main positive effect is promotion of lipogenesis out of the sebaceous gland, a place where CB2 receptors are concentrated,[17] which has the effect of enhancing barrier water content and hence skin hydration.

The view that cannabinoid signaling in the skin can be used as a therapeutic antiaging target has been expressed, and the term "cutannabinoid" has been used to denote cutaneous cannabinoid.[68] The discovery of plant-derived compounds acting on the cannabinoid receptors is without a doubt feasible, since numerous natural cannabinoids have been described.[69] Several applications for patents that incorporate cannabinoids into skin care products have been lodged in the last few years.[70,71] The best known example of a specific CB2 agonist is caryophyllene.[72] It has already been demonstrated to improve wound healing in dermal skin models through multiple routes. The anti-inflammatory effects are alleged to be important in this outcome, but the observation of higher rates of re-epithelialization and the upregulated expression of hair follicle bulge stem cells conveys strong benefit to both dermis and hair.[18] This is because hair follicle stem cells promote wound healing by migration from the hair follicle bulge to the epidermis then into healing wounds.[73] Hence, the CB2 agonist stimulates hair follicle bulge stem cell proliferation in wound healing, which may conceivably improve hair health. Hence, scalp microneedling may promote this effect by creating sites of "tissue healing."

The crosstalk between $A_{2A}R$ and cutannabinoid receptors may explain the efficacy of many plant-based therapies that attenuate the effects of dermal aging, but the complexity of plant extracts beckons researchers to acknowledge the possibility of multiple pathways occurring in concert. For example, combinations of cutannabinoids and phytoestrogens should be examined, as described in the next section.

5 | PHYTOESTROGENS

As previously mentioned, imbibed seeds are often rich in peptides, amino acids, isoflavonoids, and cytokins. Almond kernels fall into this category, as does the date palm kernel. A promising trial was conducted using extracts of the date palm kernel to treat skin wrinkles, wherein significant reductions in skin wrinkles after 5 weeks of treatment was observed.[74] The authors attribute the effects to "phytohormones." Although cytokinins may be regarded as "phytohormones," the discussion was directed at the importance of isoflavones or phytoestrogens.

A role for the estrogen receptors in dermal aging has been very clearly motivated, where the nuclear estrogen receptors alpha (ERα) and beta (ERβ) have been described in dermal fibroblasts of mice,[75] and also in the hair follicle.[76] In bronchial epithelial cells estrogen receptor agonism and TGF-β1 inversely modulated ECM turnover,[77] indicating the possibility that TGF-β1 secretion is modulated by estrogen receptor agonism. This is interesting because the previous mentioned study that demonstrated re-epithelialization of dermal wounds in mice using the CB2 agonist caryophyllene only conveyed results for female mice, not male mice. It is therefore necessary to re-examine this effect in male mice by including a phytoestrogen, such as equol, in the treatment.

The phytoestrogen equol is a derivative of the soy isoflavone daidzein, which is biotransformed to S-equol in a gut microbe-mediated reaction.[78] This phytoestrogen is thought to be an important contributor to the youthful skin and hair of Asians that include soy as a part of their diets.[78,79] Despite

the positive effects of equol in ECM reconstruction, the reproducibility of these results is contentious in the wider scientific community, and the mechanism has not been explained[80] but estrogen receptor agonism is evidently important. In vivo trials convey that equol promotes collagen-1, elastin and TIMP-1 expression in dermal fibroblasts, and antagonizes interleukin-1α, MMP-1, -3 and -9.[80] However, by extrapolation of generalizations made for estrogens, these effects are thought to be achieved in sun protected skin only. This is because in the last decade the beneficial effects of estrogens (and phytoestrogens) in sun-protected vs sun-damaged skin have been demonstrated to be one-sided. Allegedly, estrogen treatment is beneficial to sun-protected skin, but no positive outcome is observed in sun-damaged skin. Although negative cosmetic effects were not observed, increased measures of matrix metalloproteinase-1 indicates the possibility of accelerated collagen degradation.[81] However, estrogen or estradiol are agonists for ERα, whereas phytoestrogens tend to be agonists for ERβ, which conveys the possibility of a difference in outcome. Furthermore, it has been shown that ERα (not ERβ) is involved in the telogen-anagen shift in scalp hairs and topical estrogen may delay the emergence of new hairs.[76] Since phytoestrogens are generally not agonists for ERα it is feasible that typical estrogenic effects to hair are unlikely. Although these effects have not been demonstrated specifically for equol, a new research direction may be necessary. Hence, the crosstalk with cannabinoid receptors should be examined to generate new data, using combinations of cannabinoids and phytoestrogens.

6 | CONCLUSION

Finding plant-based cosmetics that cater to the desire of the community to experience both dermal and hair rejuvenating effects in the one, dual-acting therapy is given impetus by the negative publicity that retinoids have received in anti-ging therapies. Retinoids promote the expression of TGF-β from fibroblasts, which cascade into collagen expression at the cost of keratinocyte function. Since keratinocyte stem cells influence differentiation of dermal papilla cells that dwell at the base of the hair follicle, retinoids can interrupt hair growth. This is typically a problem in cases of oral retinoids, which excludes it from nutricosmetic initiatives. Fortunately, the plant kingdom provides us with a diverse array of specialized metabolites and fermentation derivatives that cater to the need to promote collagen synthesis independently of this pathway. The best candidates are lysine or arginine-rich peptides from several species, including almond, fenugreek, pea sprouts, soy, and seaweeds. However, "plant hormones" such as cytokinins and phytoestrogens are also potentially interesting. Many cytokinins are agonists of the G-coupled adenosine receptors which not only modulate collagen synthesis in the dermis but are also thought to be the mechanism of minoxidil in promotion of scalp hair growth. Hence, because of crosstalk between adenosine and cannabinoid receptors it makes sense to try combinations of agonists/antagonists for both receptors. Lastly, it is possible that the activity of standalone CB2 agonists in promotion of dermal epithelialization may be counteracted by the expression of other cytokines in male metabolism. In this regard it is of interest to try coadministration of a phytoestrogen to observe a changed outcome on male mice. It is also of interest that estrogen agonism can potentially attenuate the expression of TGF-β, but this needs to be examined in further detail.

ACKNOWLEDGEMENTS

The authors acknowledge input from colleagues at Royal Botanic Gardens, Kew into the topics covered in this review.

CONFLICT OF INTEREST

Monique Simmonds has received research grants from companies involved in skin research such as Procter and Gamble and Boots UK. However, this review was undertaken independently from any input from researchers in these companies. The authors state explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Monique Simmonds initiated the review, Nicholas Sadgrove provided the first draft and both authors reviewed and modified the manuscript.

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How to cite this article: Sadgrove NJ, Simmonds MS. Topical and nutricosmetic products for healthy hair and dermal antiaging using "dual-acting" (2 for 1) plant-based peptides, hormones, and cannabinoids. *FASEB BioAdvances*. 2021;3:601–610. https://doi.org/10.1096/fba.2021-00022