



Review Article

A comprehensive review of topical bakuchiol for the treatment of photoaging

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Relevance

Photoaging refers to premature aging of the skin due to chronic ultraviolet radiation. Retinoids and retinol are the mainstay treatment for photoaging but come with the potential for cutaneous side effects and concerns of teratogenicity/embryotoxicity. Hence, there is an increasing demand for retinoid-like products without significant adverse effects. Bakuchiol, a phytochemical compound derived from *Psoralea corylifolia*, a medicinal plant widely used in Ayurveda and Traditional Chinese Medicine (TCM), has recently gained traction as a promising natural alternative to topical retinol.

Objective

To review the anti-aging properties, efficacy, tolerability, and safety of topical bakuchiol compared to topical retinol for the treatment of photoaging.

Methods

A comprehensive search of peer-reviewed articles was conducted through PubMed and EMBASE using the key terms “bakuchiol” AND “photoaging.” Six abstracts and titles were screened, four articles underwent full-text review and the reference section of each article was scanned to find additional articles. The search process yielded seven articles from 2014 to 2021, which were included for analysis.

Results

Comparative gene expression profiling revealed that topical bakuchiol can operate as a functional analog of topical retinol *in vitro*, with considerable advantages in safety, photostability, and ease of formulation. Across all studies reviewed, bakuchiol was effective in improving photoaging with minimal side effects on normal and sensitive skin. Bakuchiol demonstrated comparable efficacy and better tolerability than retinol when tested side-by-side. Additionally, there may be an enhanced photoprotective effect when formulated with other antioxidants.

Conclusion

Topical bakuchiol can act as a functional analog of retinol and has additional antioxidant properties that are enhanced when formulated with other antioxidants. It demonstrates clinically significant similarity to topical retinol in efficacy and superiority in tolerability and safety. Topical bakuchiol may be considered as a key ingredient in skincare formulations for individuals who have sensitive skin who may not tolerate topical retinoids and those who are seeking natural antioxidant products. While concrete clinical evidence is insufficient to make definitive claims on pregnancy safety, bakuchiol can be considered a safer option for those who are pregnant, nursing and trying to conceive based on mechanism of action.

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INTRODUCTION

Photoaging, also known as “dermatoheliosis,” is one of the most prevalent dermatological concerns. It is defined as accelerated aging of the skin due to chronic exposure to ultraviolet (UV) radiation (100–400 nm), primarily from the sun, as 80% of facial aging is believed to be the result of solar damage.¹ Solar UV radiation is divided into long wave UVA (315–500 nm), mid wave UVB (280–320 nm), and short wave UVC (200–280 nm).² UVA, which penetrates more deeply into the dermis, is the major cause of photoaging. UVB, which predominantly affects the epidermis, also plays a role in photoaging, sunburn, immunosuppression, and is the major cause of skin cancer.² UVC is a potent mutagen but is mostly blocked by the atmospheric ozone layer.² Photoaging is largely preventable through sun avoidance and sunscreen use; however, this is not realistically achievable at all times as sun damage can occur in as little as 15 minutes of UV exposure to unprotected skin.³ The level of photodamaging depends on the degree of UV exposure and the amount of melanin in the skin.^{3,4} Typically, individuals who are more likely to experience a greater degree of sun damage are those who reside in sunny climates, live outdoor lifestyles, or have lighter skin pigment.^{3,4} Clinical signs of photoaging include wrinkles, uneven pigmentation, loss of skin tone, severe atrophy, roughness, dryness, sallowness, laxity, deep furrows, leathery appearance, telangiectasias, solar elastosis, actinic purpura, precancerous lesions, and even skin cancer.⁴ Repeated, long-term exposure to UVA and UVB induces changes in the skin through several molecular processes, including formation of reactive oxygen species (ROS), degradation of collagen, and dysfunction of the skin mechanical barrier.

DAMAGE BY OXIDATIVE STRESS

UVA is responsible for the formation of ROS, such as singlet oxygen, superoxide anion, and peroxy and hydroxyl radicals unstable oxygen molecules with unpaired electrons that readily react with endogenous and exogenous factors, causing cellular damage.² UV-induced ROS are known to be associated with the development of skin aging, skin cancer, and other inflammatory skin disorders.² The generation of ROS causes photoaging by inducing oxidative stress in the skin. While the skin is normally equipped with a myriad of endogenous antioxidant defense mechanisms in order to protect itself from ROS damage, chronic UVA exposure can overwhelm the capacity of these detoxification pathways, causing an imbalance in the antioxidant immune system.^{2,5} Additionally, ROS further cause photoaging by inducing alterations in gene expression pathways that contribute to collagen degradation and elastin accumulation, which may contribute to elastin deposition in photoaged skin.⁶

COLLAGEN DEGRADATION

Collagen plays an important role in maintaining the structure and function of the skin. Within hours of exposure, UVA significantly upregulates the synthesis of several collagen-degrading enzymes called matrix metalloproteinases

(MMPs), specifically collagenase and gelatinase.^{6,7} Repeated exposure leads to a sustained induction of MMPs, causing long-term elevations in collagenase and subsequently resulting in the degraded, disorganized collagen fibrils characterized in photoaged skin.^{6,7}

Collagen types I and III are important components of the extracellular matrix (ECM). Collagen I, the most abundant collagen in the body, is integral to providing strength and resilience to the skin. Collagen III, which is thinner than collagen I, also plays a contributing role. UVA inhibits the synthesis of collagen I, leading to an increase in the collagen III to I ratio, consistent with changes observed in older skin.⁶ This, along with the upregulation of MMPs, results in a net loss of collagen in the dermis, leading to the visible clinical signs of photoaging in the skin.⁶

It is also believed that wrinkle formation may occur as a result of compromised bond between the epidermis and the dermis.⁶ Collagen IV is important for maintaining mechanical stability in the dermoepidermal junction (DEJ), while collagen VII anchors fibrils to the basement membrane zone to the underlying papillary dermis.⁶ Lower levels of collagen IV and collagen VII have been observed in the base of wrinkles compared to the flanks of the same wrinkles.⁸ Although there is not a clear link between UV radiation and the degradation of collagen IV and VII, the loss of collagen in the base of wrinkles may be implicated in compromising the mechanical barrier, and thereby contributing to wrinkle formation.^{6,8}

MECHANICAL BARRIER DYSFUNCTION

UVB can impair the skin by altering the mechanical barrier function.⁹ The stratum corneum, the outermost layer of the epidermis, provides critical mechanical protection and is a highly efficient permeability barrier to the external environment. UVB-induced barrier impairment causes morphological changes in lipids and decreased hydration in the stratum corneum, as well as increased transepidermal water loss (TEWL).⁹ TEWL is the most widely used method of assessing the integrity of the skin barrier and is quantified by the amount of condensed water that diffuses across a fixed area of the stratum corneum to the skin surface per unit time. Elevated TEWL indicates a disturbed skin barrier and has been associated with skin diseases such as atopic dermatitis, contact dermatitis, psoriasis, and ichthyoses.¹⁰

TOPICAL BAKUCHIOL FOR THE TREATMENT OF PHOTOAGING

Psoralea corylifolia (Leguminosae) is an erect annual herb that can be found in India as a common weed during the winter season, throughout the Himalayan regions of Pakistan and China, Southern Africa, and the Southern United States, west of the Allegheny Mountains.^{11,12} It has been widely valued as a therapeutic agent in many indigenous medicine systems, most notably in Ayurveda and TCM, where it is commonly known as babchi and bǔ gǔ zhī, respectively.^{11,12} The name of the plant originates from the Greek word psoraleos, meaning “affected with itch or leprosy.”^{11,12} As its name indicates, *Psoralea corylifolia* has

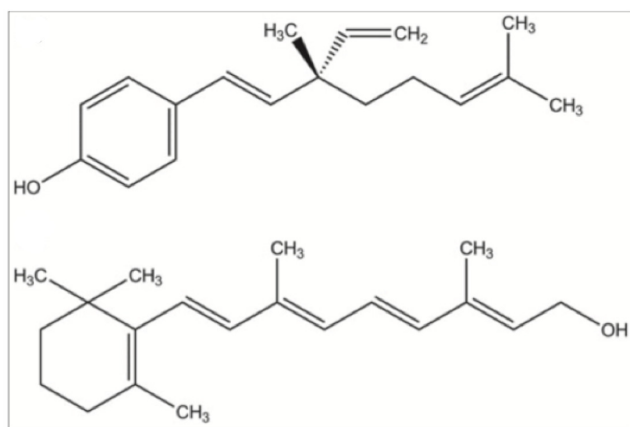


Figure 1. Chemical structures of bakuchiol (top) and retinol (bottom). Bakuchiol and retinol do not share structural similarity.

Note: This figure is from the original study by Dhaliwal et al.³⁸

been used both internally and externally in Ayurveda for various ailments such as leprosy, leukoderma, psoriasis, eczema, alopecia, and inflammation.^{11,12} In TCM, the plant is considered warm by nature and therefore demonstrates therapeutic actions on the kidney and spleen meridians.¹³

Approximately 100 bioactive compounds have been isolated from *P. corylifolia* so far,¹² and the most important compounds identified belong to the coumarin, flavonoid, and meroterpene groups.¹⁴ Among these is bakuchiol, a meroterpene phenol that was first isolated from the seeds of the plant in 1966.¹⁵ It was biosynthesized in 1983 and concluded to be a derivative of the phenylpropane pathway.¹⁶ Bakuchiol possesses a diverse range of pharmacological activities, including anti-acne,^{17,18} antioxidant,¹⁹ anti-inflammatory,^{20–22} anti-cancer,^{23–25} antimicrobial,^{26,27} estrogenic,^{28,29} and organ-protective properties.^{30–33} It has been studied in a variety of conditions, such as acne,^{17,18} psoriasis,^{34,35} neurodegenerative disease,²² osteoporosis,²⁸ acute kidney injury,³¹ myocardial ischemia reperfusion injury,³² and several types of cancer.^{23–25}

Over the last decade, the topical use of bakuchiol has emerged in the literature as a promising cosmeceutical agent, gaining traction in the skincare industry as a natural alternative to topical retinol (all-*trans*-retinol), a 20-carbon molecule with a cyclohexenyl ring, a side chain with all four exocyclic double bonds in *trans* configuration, and an alcohol end group³⁶ (Figure 1). Topical retinol has been well-studied and is considered the mainstay treatment for photoaging. Bakuchiol, like retinol, has been suggested to have significant cutaneous anti-aging benefits, but unlike retinol, it is considered to cause less irritation and have a more favorable safety profile.³⁷ Clinical research on bakuchiol, however, is still in its infancy compared to retinol. The aim of this review was to examine the current literature assessing the effects of topical bakuchiol on photoaging in order to determine whether it is a comparable alternative to topical retinol.

METHODS

In order to ensure a thorough and unbiased review of the literature on bakuchiol, a comprehensive search of peer-reviewed articles was conducted through two databases: PubMed and EMBASE. The following key terms were used to generate a search: “bakuchiol AND photoaging.” Titles and abstracts of the resulting six articles were screened. Two articles were excluded as they were not clinical studies. Four articles underwent full-text review and the reference section of each article was scanned to find additional sources. The search process yielded seven articles from 2014 to 2021 that were included for analysis on the use of topical bakuchiol for treatment of photoaging.

RESULTS

In vitro, *in vivo*, and *ex vivo* studies were examined, and each had a different study design (Table 1). Data regarding anti-aging properties, efficacy, tolerability, and safety were extracted from each article and summarized (Table 2). Bakuchiol was the primary active ingredient in three studies, while the other four studies formulated bakuchiol in combination with other antioxidants.

COMPARATIVE ANALYSIS OF BAKUCHIOL AND RETINOL

Chaudhuri and Bojanowski³⁷ conducted a three-part study, using comparative gene expression profiling in the Epiderm full thickness skin substitute model, human dermal fibroblasts (HDFs), and human subjects. In the comparative gene expression analysis, bakuchiol and retinol showed similarity in overall shapes on volcano plots and in numerous retinoid-binding and metabolizing genes despite bearing no structural similarity (Figure 1).

There were several findings that demonstrated potential for clinical applicability that were detailed by Chaudhuri and Bojanowski³⁷ (Table 3). Retinoid acid receptors (RAR), specifically RAR- β and RAR- γ , were both only upregulated by retinol, suggesting bakuchiol may have a possible advantage over retinol in terms of side effects. Namely, RARs are involved in various processes of the fetal development⁴⁴ and the reason why retinoid products are considered teratogenic. N-6 adenine-specific DNA methyltransferase 2 (N6AMT2) was only downregulated in bakuchiol, suggesting that bakuchiol used in combination with retinol may reduce retinoic acid-induced toxicity. Lecithin-retinol acyltransferase (LRAT), which plays a key role in the absorption and storage of retinol, was upregulated in both retinol and bakuchiol but dramatically higher in the latter, suggesting bakuchiol may enhance the availability of endogenous retinol. Tazarotene-inducible gene (TIG1), which is downregulated in acne, rosacea, psoriasis, and many human cancers, was upregulated by both retinol and bakuchiol, suggesting bakuchiol, like retinol, may be effective for other skin disorders as well.³⁷

Retinol is known to inhibit the processes that deteriorate the ECM and the DEJ, which are important for maintaining skin elasticity, hydration, and barrier recovery and prevent-

Table 1. An overview of studies on bakuchiol or bakuchiol-containing formulas

Study	Design	Duration	Intervention	Model	No. of Human Subjects	Age (Years)	Fitzpatrick phototypes
Chaudhuri and Bojanowski, 2014 ³⁷	Comparative gene expression analysis and open-label clinical pilot study	12 weeks	Bakuchiol cream	Skin substitutes HDFs Humans	16	40-65	Not specified
Dhaliwal et al, 2019 ³⁸	Randomized, double-blind clinical study	12 weeks	Bakuchiol cream vs retinol cream	Humans	44	40-65	Not specified
Draelos et al, 2020 ³⁹	Open-label clinical study	4 weeks	Bakuchiol cleanser and moisturizer	Humans	60	40-65	I-V
Goldberg et al, 2019 ⁴⁰	Five open-label clinical studies	28 to 84 days	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	Humans	103 total	43-65	I-IV
Goldberg et al, 2020 ⁴¹	Open-label clinical study	12 weeks	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	Humans	24	40-75	I-V
Narda et al, 2020 ⁴²	Immuno-cytochemical analysis	N/A	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	HEKs HDFs Skin explants	N/A	30-32	II
Bacqueville et al, 2020 ⁴³	Histological analysis and open-label clinical study	56 days	Bakuchiol and <i>Vanilla tahitensis</i> extract serum	HDFs Skin explants Humans	43	45-65	II, III

Abbreviations: NFS, night facial serum; HDFs, human dermal fibroblasts; HEKs, human epidermal keratinocytes

ing skin thinning and morphological flattening. Retinol and bakuchiol both upregulated several genes important for the integrity of the ECM and the DEJ, such as E-Cadherin, laminin, aquaporin 3 (AQP3), and several types of collagen (COL1A2, COL4A6, COL9A2, COL9A3, COL4A6, COL17A1),³⁷ suggesting that bakuchiol may also be able to inhibit the deterioration of the ECM and DEJ (Table 3). Bakuchiol demonstrated a higher upregulation in AQP3 in skin substitutes, and an increase in the expression of AQP3 by bakuchiol and retinol was confirmed in HDFs.³⁷ Chaudhuri and Bojanowski³⁷ also observed an upregulation in collagen I, III, and IV in HDFs but attributed these findings to the selective metabolic activation of collagen synthesis in fibroblasts.

Bakuchiol was further evaluated in a clinical trial, assessing 16 female subjects aged 40-65 years old over 12 weeks on the following parameters: fine lines/wrinkles, roughness and dryness, skin tone, skin elasticity and firmness, radiance, brightening, and overall eye area appearance. Chaudhuri and Bojanowski³⁷ found a statistically significant reduction in wrinkle depth at all three checkpoints compared to baseline ($P \leq 0.01$), but the reduction was observed to be considerably more significant at 8 weeks and

even greater at 12 weeks compared to at 4 weeks. Improvement in skin roughness was statistically significant at 8 and 12 weeks ($P \leq 0.004$). These findings were consistent in most of the parameters, indicating that topical application of bakuchiol may result in a cumulative beneficial effect over time.

RANDOMIZED, DOUBLE-BLIND TRIAL COMPARING BAKUCHIOL AND RETINOL

In a randomized, double-blind trial assessing clinical efficacy and tolerability of topical bakuchiol and retinol in 44 subjects over 12 weeks, Dhaliwal et al.³⁸ found that at week 12, subjects in the bakuchiol group had a higher reduction in hyperpigmentation from baseline than retinol. Subjects from both the bakuchiol and retinol groups had significant improvements in pigment intensity, pigment surface area, and wrinkle surface area at 12 weeks ($P < 0.05$) with no significant difference between the two.

Subjects in the retinol group³⁸ reported significantly more scaling and burning at all follow-up time points. Those in the retinol group also reported more itching and burning, though this finding was not statistically signifi-

Table 2. Key findings in studies on bakuchiol or bakuchiol-containing formulas

Study	Intervention	Efficacy	Tolerability and Safety
Chaudhuri and Bojanowski, 2014 ³⁷	Bakuchiol cream	There was a statistically significant reduction in wrinkle depth and skin roughness, which was observed to be highest at 12 weeks.	Not measured
Dhaliwal et al, 2019 ³⁸	Bakuchiol cream vs retinol cream	Both bakuchiol and retinol groups both showed significant improvements in wrinkle surface area, pigment surface area, and pigment intensity at 12 weeks. The bakuchiol group had a slightly higher improvement in hyperpigmentation.	Retinol group had significantly more reports of scaling and burning at all measurements. Bakuchiol had more redness at week 4. There were no reports of photosensitivity in either group.
Draelos et al, 2020 ³⁹	Bakuchiol cleanser and moisturizer	60/60 participants showed improvement in smoothness, clarity, radiance, overall appearance, and global anti-aging at 4 weeks. There was an increase in skin moisture content and no change in TEWL.	10% of the eczema group reported minimal stinging immediately after application that persisted into week 4. There were no other reports of intolerability.
Goldberg et al, 2019 ⁴⁰	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	There was significantly increased skin firmness, reduced wrinkle depth, and uneven pigmentation.	One subject showed signs of slight red papules on the right crow's feet areas of both cheeks, and another of moderate erythema, dryness, and desquamation on the cheek, around lips, and chin. The formula was otherwise well-tolerated.
Goldberg et al, 2020 ⁴¹	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	There were statistically significant improvements skin texture, pigmentation, erythema, skin tone, complexion, lines, and wrinkles at 24 weeks. The greatest changes were in radiance at 12 weeks and youthful appearance at 24 weeks.	One subject had mild dryness and scaling at week 6. There were two reports of mild tingling, as well as mild itching, at week 12 and another at week 24. There were no other reports of intolerability.
Narda et al, 2020 ⁴²	Bakuchiol, vitamin C, and melatonin in 3-in-1 NFS	There were increased levels of filaggrin and aquaporin 3 in HEKs, collagen I and III in HDFs, procollagen I and tropoelastin in skin explants.	Not measured
Bacqueville et al, 2020 ⁴³	Bakuchiol and <i>Vanilla tahitensis</i> extract serum	There was a significant improvement in facial sagging, depth and volume of skin deformation, skin firmness, and skin radiance at day 56.	Global tolerance and safety were rated as "very good" for skin evaluation and "excellent" for ophthalmologic evaluation.

Abbreviations: TEWL, transepidermal water loss; HEKs, human epidermal keratinocytes; HDFs, human dermal fibroblasts

cant. At week 4, subjects in the bakuchiol group showed more redness; however, neither group reported significant changes in redness at week 8 or 12. There were no reports of photosensitivity in either group.

BAKUCHIOL ON SENSITIVE SKIN

Topical retinol use is often not poorly in individuals with sensitive skin due to irritation and side effects.³⁹ In order to test if bakuchiol would be well-tolerated by these individuals, Draelos et al.³⁹ enrolled 60 female subjects with Fitzpatrick skin types I-V age 40 to 65 years with sensitive mild to moderate photodamaged skin in a 4-week study. The sensitive skin panel comprised of subjects with eczema, rosacea, and cosmetic intolerance syndrome. Using a cleanser and moisturizer containing 1% bakuchiol twice daily, Draelos et al.³⁹ found that all 60 subjects showed highly statistically significant improvement in all parameters of visual smoothness, tactile smoothness, clarity, radiance, overall appearance, and global anti-aging in both investigator and subject ratings ($P < 0.001$).

Draelos et al.³⁹ discovered that there was a statistically significant increase in skin moisture content ($P < 0.001$), and there was no change in TEWL, suggesting that the skin barrier remained preserved—an important finding that is crucial to skin health in individuals with sensitive skin. In tolerability assessments, 10% of subjects with eczema reported minimal stinging immediately after application ($P = 0.008$) that persisted into week 4 ($P = 0.031$). Minimal tightness was also reported at week 4 ($P = 0.017$). There were no other reports of intolerability. Given that the sensitive skin panel comprised of subjects with eczema, rosacea, and cosmetic intolerance syndrome, bakuchiol may be well-tolerated in individuals who report to have sensitive skin.³⁹

BAKUCHIOL, VITAMIN C, AND MELATONIN

The antioxidant synergism between vitamin C and melatonin has previously been reported.⁴⁵ Three articles examined the combination of ascorbyl tetraisopalmitate—a direct antioxidant, melatonin—an indirect antioxidant, with bakuchiol—a polyphenol, in a 3-in-1 night facial serum

Table 3. Comparative gene expression analysis between retinol and bakuchiol

Gene	Full name	Retinol	Bakuchiol
CRBP I	Cellular retinol binding protein I	2.6	4.2
CRBP II	Cellular retinol binding protein II	NS	4.1
CRBP IV	Cellular retinol binding protein IV	NS	3.1
N6AMT2	N-6 adenine-specific methyltransferase 2	NS	-2.1
TIG1	Tazarotene-inducible gene 1	13.2	12.9
LRAT	Lecithin-retinol acyltransferase	12.3	82.2
CYP1A1	Cytochrome P450	4	4.9
CYP1A2	Cytochrome P450	3.6	6.7
RAR-β	Retinoic acid receptor beta-1	5.6	NS
RAR-γ	Retinoic acid receptor gamma-1	1.8	NS
COL1A2	Collagen 1A2	3.3	1.9
COL4A6	Collagen 4A6	6.4	11.2
COL9A2	Collagen 9A2	5.6	6.7
COL9A3	Collagen 9A3	4.1	5.8
EMILIN3	Elastin microfibril interface-located protein 3	2.2 (NS)	9.1
EMILIN1	Elastin microfibril interface-located protein 1	-3.4	-2.4
HAS3	Hyaluronan synthase 3	10.8	19.2
AQP3	Aquaporin 3	3.5	4.3
COL4A6	Collagen alpha-6 (IV)	6.4	11.2
COL17A1	Collagen alpha-1 (XVII)	3.6	8.7
LAMA3	Laminin subunit alpha-3 precursor	4.7	11
LAMC2	Laminin subunit gamma-2 precursor	2.7	7.8
CDH1	E-Cadherin	9.4	21.6

Note: This table has been adapted from the original study by Chaudhuri and Bojanowski.³⁷

(NFS).^{40–42} The majority of these studies were performed using combination formula rather than bakuchiol alone.

Goldberg et al.⁴⁰ investigated the 3-in-1 NFS in five clinical studies on efficacy and tolerability, hydration kinetics, TEWL, oily skin, and non-comedogenesis on a total of 103 subjects treated from 28 to 84 days. In the efficacy and tolerability study, 39 healthy female subjects of ages 40 to 65 years with the presence of “crow’s feet” wrinkles, moderate skin aging, Fitzpatrick phototypes I–IV, and at least one pigmented spot on the face, were given the NFS to use at home each evening for 84 days. Dermatological assessment showed significantly increased skin firmness, reduced wrinkle depth, and uneven pigmentation. The NFS was reported to be well-tolerated overall. One subject showed signs of slight red papules on the crow’s feet of both cheeks, which was deemed unlikely attributable, and another showed moderate erythema, dryness, and desquamation on the cheek, around lips, and chin, which were also deemed not clearly attributable.⁴⁰

In the hydration studies,⁴⁰ there was a statistically significant difference in hydration between treated and untreated areas from 30 minutes until the end of 12 hours. A peak in hydration was observed in the treated area at 4 hours. There was a decrease in TEWL values that became statistically significant at 4 hours and 6 hours after application. Sebum secretion decreased significantly ($P < 0.01$), suggesting that the NFS was suitable for individuals with

oily skin. The product was also categorized as noncomedogenic, as 82% of subjects had fewer comedones at day 14 and 85% at day 28 compared to baseline. There were no cutaneous adverse effects reported in these studies.

Goldberg et al.⁴¹ then conducted another study to further examine the clinical changes observed in the first series of studies⁴⁰ on the 3-in-1 NFS and to seek a histological explanation for these effects. In this study,⁴¹ 24 subjects of ages 40–75 years with moderate skin aging and Fitzpatrick skin types I to V were evaluated over 12 weeks, based on clinical assessment and histological analysis via punch biopsy. In investigator assessments,⁴¹ there were statistically significant improvements in skin texture, pigmentation, erythema, skin tone, complexion, lines, and wrinkles at 24 weeks ($P < 0.05$). The greatest changes were in radiance at 12 weeks and youthful appearance at 24 weeks ($P < 0.01$). There were significant reductions in photodamage and hyperpigmentation scores reported at 12 weeks compared to baseline. There were also significant reductions in wrinkle lines on all locations of the face measured ($P < 0.05$). In self-assessments, 23 out of 24 subjects scored an improvement from baseline, and all subjects reported being either satisfied or very satisfied by the end of the treatment. In tolerability assessments, no serious adverse effects occurred. At week 6, one subject had mild dryness and scaling. There were two reports of mild tingling, as well as mild itching, at week 12 and another at week 24.

Histological examination⁴¹ revealed an increase in epidermal thickness in all treated forearms at 12 weeks, compared to a reduction in the thickness of the control forearm over the same period. Four of five treated forearms also demonstrated an increase in dermal thickness, higher than that of the control forearm. Levels of hyaluronic acid (HA) increased slightly in the treated samples, while HA in the untreated samples decreased. Levels of collagen III increased significantly in the treated arm ($P < 0.05$), while levels of procollagen I, elastin, and fibronectin increased in both treated and untreated arms to a similar extent.

These histological findings⁴¹ were tested further by Narda et al.,⁴² using the 3-in-1 NFS at 0.05%, 0.1%, 0.5%, and 1% concentrations on primary epidermal keratinocytes (HEKs) and HDFs *in vitro*, and UV-exposed skin explants *ex vivo*. *In vitro*, Narda et al.⁴² observed a reduction in TEWL and an increase in hydration levels in HEKs, suggesting the 3-in-1 NFS may influence the expression of key molecules, such as filaggrin and AQP3, that are involved in skin barrier formation and epidermal water transport. The greatest effects were observed with 0.05% and 0.1% concentrations, indicating a dose-dependent increase in AQP3 expression.

In HDFs, there was an increased expression of collagen I and III with the 0.05% and 0.1% concentrations, suggesting the NFS may have the ability to stimulate new collagen synthesis.⁴² However, collagen was inhibited at higher concentrations of 0.5% and 1% NFS. The expression of laminin, a major constituent of basement membrane that is essential for its function, was increased when treated with 0.5% concentration NFS. There was no impact at 0.5% in the expression of fibronectin, a multifunctional adhesive glycoprotein that plays an important role in the organization and maintenance of the ECM, but it was inhibited at all other concentrations.

Sunburn cells (SBCs) are keratinocytes undergoing apoptosis from irreparable DNA damage—a hallmark characteristic of UV exposure.⁴² In the *ex vivo* study, explants treated with the NFS showed significantly fewer SBCs in the epidermis following UV exposure than untreated skin explants. There were also increases in the expression of procollagen I—a collagen precursor, and tropoelastin—an elastin precursor, observed in the skin explants treated with the NFS following UV exposure, beyond that of the untreated skin explants.

Interestingly, Narda et al.⁴² noted that there was no significant change in the number of SBCs or procollagen I levels in skin explants treated with the individual components of the NFS or with the combination of melatonin and bakuchiol—suggesting there may be a synergistic effect from all three ingredients combined. There was, however, an increase in tropoelastin expression in skin explants treated with the combination or melatonin and bakuchiol but not with the individual components.

BAKUCHIOL AND *VANILLA TAHITENSIS* EXTRACT

Vanilla tahitensis extract (VTE), like bakuchiol (BK), is rich in antioxidants and polyphenols that are known to improve the signs of skin aging.⁴³ Bacqueville et al.⁴³ tested a combination of these two active ingredients *in vitro*, *ex vivo*,

and *in vivo*. The majority of the data in this study was on the combination formula of BK+VTE, rather than bakuchiol alone.

In vitro,⁴³ there were notable changes in three major markers associated with skin aging in HDFs—morphology (actin), inflammation (IL-8), and senescence (*p16*). Actin staining showed that treatment with both individual compounds and the combination formula BK+VTE prevented morphological changes induced by acute UVA exposure, resulting in improved fibroblast morphology. In HDFs treated with BK or VTE individually, there were reductions seen in the expression of IL-8 following UVA irradiation for both active ingredients at 88.3% and 83.8%, respectively ($P < 0.05$).⁴³ The protection observed was slightly higher in BK than VTE. In HDFs treated with the BK+VTE combination, however, there was a significant synergistic reduction of IL-8 expression to levels that were identical to the control, reaching 95.1% ($P < 0.05$). Treatment with BK or VTE also demonstrated a tendency to prevent *p16* expression, at 44.4% and 29.2%, respectively ($P > 0.05$). This again was observed to be significantly higher in combination at 95.2% ($P < 0.001$) than the addition of the individual effects.⁴³

In the *ex vivo* study,⁴³ photodamaged human skin explants were used to mimic the changes induced from chronic UVA exposure, demonstrating a loss of ECM, especially of glycosaminoglycans (GAGs). Treatment with BK+VTE demonstrated an improvement in dermal density associated with a recovery of GAGs, comparable to the control samples, suggesting that BK+VTE can protect the skin from alterations in GAGs and loss of dermal density from chronic UVA exposure.

In the clinical trial,⁴³ measures for skin remodeling, firmness, radiance, global tolerance and safety were evaluated in 43 Caucasian females with Fitzpatrick prototypes II or III with naturally aged skin over 56 days. Bacqueville et al.⁴³ found that at day 56, subjects using BK+VTE saw a significant reduction in facial sagging (63% of subjects), improvement in depth of skin deformation (73% of subjects) and volume of skin deformation (78% of subjects), significant improvement in skin firmness (95% of subjects), and increase in skin radiance (80% of subjects). Overall, global tolerance and safety were rated as “very good” for skin evaluation and “excellent” for ophthalmologic evaluation.

DISCUSSION

This review found two main properties of topical bakuchiol that support the reduction of photoaging: retinol-like functionality and synergistic antioxidant photoprotection.

RETINOL-LIKE FUNCTIONALITY

Chaudhuri and Bojanowski³⁷ postulated that despite bearing no structural resemblance to retinol, bakuchiol can perform as a functional analog of retinol and that these similarities in gene expression show promise for similar bioactivity *in vivo*. This was confirmed in a randomized, double-blind trial by Dhaliwal et al.³⁸ Bakuchiol or bakuchiol-containing formulas may have the ability to stimulate

new collagen synthesis and^{37,42} inhibit the same processes that retinol inhibits to prevent ECM and DEJ degradation.³⁷

Topical retinol is known to inhibit UV-induced upregulation of MMPs, preventing collagen degradation, while concomitantly increasing fibroblast growth and collagen synthesis, resulting in a net increase of collagen in the skin.⁴⁶ Retinol also penetrates into the stratum corneum of the epidermis and into the dermis to a smaller degree, promoting keratinocyte proliferation, strengthening the protective function of the epidermis, and reducing excess TEWL.⁴⁷ These mechanisms work in interaction with one another to significantly improve the clinical signs of photoaging, resulting in a more homogeneous pigmentation, increase in skin elasticity, and reductions in wrinkle depth as well as atypical cells that are responsible for the development of precancerous lesions.

Similar to retinol, there were statistically significant improvements following the use of bakuchiol in the parameters that define photoaging.³⁸ Most subjects reported greater improvements after 12 weeks, likely due to cumulative beneficial effects of bakuchiol. While topical retinoids are already well-established for the treatment of acne, rosacea, and psoriasis, there are a limited but growing number of studies on bakuchiol for acne,^{17,18} psoriasis,^{34,35} and even skin cancer.²⁵ Given functional similarity to retinol, the effect of bakuchiol on these skin conditions should be further explored.

The main advantage of bakuchiol over retinol in terms of adverse effects involves their effect on RARs. In gene expression profiling, RAR- β and RAR- γ were upregulated by retinol, but not by bakuchiol.³⁷ This finding was consistent with the studies in this review as bakuchiol and bakuchiol-containing formulas were generally well-tolerated, and no serious adverse effects were reported in any of these studies. Subjects in the retinol group had significantly more scaling and burning in side-by-side comparisons,³⁸ and there was notable reduction in IL-8 in HDFs treated with bakuchiol, indicating reduced inflammation after UVA irradiation.⁴³ The local skin irritation caused by topical retinoids, termed “retinoid reaction,”³⁶ is characterized by pruritus, erythema, peeling, and burning sensation at the site of application, and it is thought to be initiated by the release of pro-inflammatory cytokines IL-1, TNF- α , IL-6, IL-8, and MCP-1.⁴⁸

Two separate case reports^{49,50} have documented allergic contact dermatitis following topical application of products containing bakuchiol that were not a part of any of the studies discussed in this review. The first reaction was reported in 2019,⁴⁹ when a 33-year-old female patient presented with a one-year history of erythematous plaques on both of her eyelids, the perioral area, and the neck. Patch testing demonstrated that it may have been an allergic reaction to a cosmetic product containing bakuchiol 0.1%. A second case⁵⁰ was reported in 2020 regarding a 23-year-old female with presenting with recurrent facial eczema and a history of seasonal rhinoconjunctivitis and aquagenic urticaria. Patch testing was again positive with bakuchiol 0.1% in this patient. These two are the only known cases of

allergic reactions to bakuchiol that are reported in the literature.

The finding that RAR- β and RAR- γ were not upregulated by bakuchiol is also pertinent to the safety of bakuchiol as RARs are implicated in various processes of fetal development, demonstrating that bakuchiol mechanistically is not expected to play a role in embryogenesis like retinol does.⁴⁴ It is from this key difference in mechanism of action that bakuchiol’s safety claims on pregnancy is made. Across all studies reviewed, bakuchiol was concluded to be safe to use in pregnancy. There have been no reports of systemic side effects from the topical application of bakuchiol. However, it is important to note that no clinical studies have been performed on individuals who were pregnant or nursing to verify the safety in this population. Multiple safety data sheets, however, were found online for bakuchiol.^{51–53} The safety profile of bakuchiol indicates there is an acute toxicity for oral use of category five, indicating relatively low acute toxicity but may pose a hazard to vulnerable populations. In rats, there was acute toxicity at 2,560 mg/kg when consumed orally. There was no detectable irritation or sensitization in humans. There was no information available on teratogenicity or carcinogenicity. In contrast, the safety profile of topical retinoids warrants caution for use in individuals who are pregnant, nursing, or trying to conceive, due to the potential for teratogenicity and embryotoxicity. Although fetal malformations have only been observed with systemic retinoid exposure,⁵⁴ it is generally advised to avoid all retinoid products in this population.

SYNERGISTIC ANTIOXIDANT PHOTOPROTECTION

Bakuchiol has additional antioxidant properties, not shared with retinol, that allow it to target the third mechanism. Antioxidants play a crucial role in photoaging and skin carcinogenesis by supplying another electron to neutralize ROS, stabilizing the molecule.⁴ Exogenous antioxidants complement the photoprotective endogenous antioxidants in the skin and protect against ROS damage from acute and chronic sun exposure.⁴

Bakuchiol is thought to possess antioxidant properties, largely due to its terpenoid moiety.¹⁹ Bakuchiol previously demonstrated scavenging activity against oxidizing radicals such as $\text{Cl}_3\text{CO}_2\bullet$, linoleic acid peroxyl radicals, $\text{LOO}\bullet$, DPPH radicals, $\bullet\text{OH}$, and glutathionyl radicals, revealing that its antioxidant ability via radical scavenging.¹⁹ In another study investigating *P. corylifolia* seed (PCS) extract in the hepatocytes of aged mice and HDFs,⁵⁵ bakuchiol, a major component of PCS, demonstrated an ability to recover mitochondrial dysfunction from H_2O_2 treatment. This finding pertinent is pertinent to aging as many age-related pathologies are suggested to be a result of ROS damage that largely target the mitochondria. This study⁵⁵ concluded that PCS extract had protective effects against ROS damage in mitochondrial DNA and that bakuchiol played a main role in these effects.

Bakuchiol has also been shown to activate nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator that protects cells from oxidative and electrophilic stress.⁵⁶ Nrf2 modulation plays an important role in cancer therapies due

to the interplay of ROS and Nrf2 signaling pathways with carcinogenesis.^{57,58} This shows there is a possible role that bakuchiol can play in the prevention of skin carcinogenesis.

Additionally, antioxidants are most effective when used in combination because they provide a synergistic effect.⁴ This was demonstrated in the studies that showed that bakuchiol was more effective when combined with other antioxidants, confirming this enhanced and synergistic effect in photoprotection.^{40–43}

Another interesting finding suggested that bakuchiol may reduce the oxidative stress caused by retinol and may even allow retinol to be used at higher concentrations than the physiological limit when used together.³⁷ It has been documented that concomitant application of natural agents or extracts could counteract the irritant effects produced by topical retinoids by reducing the secretion of MCP-1 and IL-8.⁴⁸ Bakuchiol was also suggested to enhance the availability of endogenous retinol.³⁷ This has been supported by evidence that bakuchiol has demonstrated an activity-enhancing and stabilizing effect on retinol.⁵⁹ In a study on the efficacy and tolerance of retinol and vitamin C in mild to moderate hyperpigmentation and photodamaged facial skin,⁶⁰ bakuchiol was added to a formulation with retinol for its complementary effects on retinol, in addition to its broad-spectrum antioxidant, anti-inflammatory, antibacterial, and other properties. These findings support that topical bakuchiol may not only be effective as an alternative to topical retinol, but that it can also be beneficial used in conjunction with retinol to mitigate side effects and improve efficacy.

LIMITATIONS AND RECOMMENDATIONS

There were several limitations in these studies, particularly the size, duration, and lack of control group. The largest sample size collected was 60 participants,³⁹ and the longest duration was 12 weeks.^{37,38,40,41} Only one human study used a control group.³⁸ Studies on combination formulas containing bakuchiol^{40–43} strengthened the argument for the synergistic benefits of antioxidants but not for the argument for bakuchiol as a solitary ingredient. There were also potential conflicts of interest in these studies. Investigators of the 3-in-1 NFS were employees or consultants of ISDIN, which manufactures the 3-in-1 NFS, or employees of Matriscience who were paid by ISDIN to perform the studies.^{40–42} Draelos et al.³⁹ received funding from Burt's Bees, and Chaudhuri and Bojanowski³⁷ received funding from Syntheon Ltd.

Additionally, the majority of the studies were either conducted on lightly-pigmented skin or did not indicate what skin types were used. The effects of bakuchiol on individ-

uals with darker skin pigment should be further studied. The randomized controlled trial by Dhaliwal et al.³⁸ should serve as a jumping-off point for further research as it is the only one that includes a control group using retinol.

CONCLUSION

Topical bakuchiol demonstrates efficacy in preventing and treating photodamage through its retinol-like functionality and antioxidant properties. Additionally, bakuchiol has anti-inflammatory and antimicrobial properties that could provide added benefit against a variety of skin disorders. Bakuchiol demonstrates clinically significant similarity to topical retinol in efficacy and superiority in terms of tolerability and safety. Bakuchiol also has the advantage of being able to be used during the day due to its excellent photostability, and it is easy to formulate due to its miscibility with many other active ingredients. When seeking bakuchiol-containing formulas, products that contain other antioxidants may be most beneficial due to a synergistic effect in photoprotection. It may also be used as a complementary product to use in conjunction with topical retinol as it has an activity-enhancing and stabilizing effect on retinol. In conclusion, topical bakuchiol may be considered as a key ingredient in skincare formulations for individuals who have sensitive skin who may not tolerate topical retinoids and those who are seeking natural antioxidant products. While concrete clinical evidence is insufficient to make definitive claims on pregnancy safety, bakuchiol can be considered a safer option for those who are pregnant, nursing and trying to conceive based on mechanism of action.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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