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Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing*

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Summary

Background Bakuchiol is a phytochemical that has demonstrated cutaneous antiageing effects when applied topically. Early studies have suggested that bakuchiol is a functional analogue of topical retinoids, as both compounds have been shown to induce similar gene expression in the skin and lead to improvement of cutaneous photodamage. No *in vivo* studies have compared the two compounds for efficacy and side-effects.

Objectives To compare the clinical efficacy and side-effect profiles of bakuchiol and retinol in improving common signs of cutaneous facial ageing.

Methods This was a randomized, double-blind, 12-week study in which 44 patients were asked to apply either bakuchiol 0·5% cream twice daily or retinol 0·5% cream daily. A facial photograph and analytical system was used to obtain and analyse high-resolution photographs of patients at 0, 4, 8 and 12 weeks. Patients also completed tolerability assessment questions to review side-effects. During study visits, a board-certified dermatologist, blinded to study group assignments, graded pigmentation and redness.

Results Bakuchiol and retinol both significantly decreased wrinkle surface area and hyperpigmentation, with no statistical difference between the compounds. The retinol users reported more facial skin scaling and stinging.

Conclusions Our study demonstrates that bakuchiol is comparable with retinol in its ability to improve photoageing and is better tolerated than retinol. Bakuchiol is promising as a more tolerable alternative to retinol.

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S.D. and I.R. contributed equally to this manuscript.

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What's already known about this topic?

- Bakuchiol is a plant-derived phytochemical that is known to have retinoid-like effects *in vitro*.

What does this study add?

- This clinical study suggests that topical bakuchiol is similar to topical retinol in improving facial wrinkles and pigmentation.
- Bakuchiol was better tolerated with fewer side-effects.

For centuries, botanicals were the fundamental basis of treatment for various ailments.[1] Even now, many well-known medications are derived from plants. For example, aspirin is derived from salicin, a compound found in the bark of the willow tree,[2,3] while morphine comes from *Papaver somniferum*, more commonly known as opium poppy.[4,5] Patients are still

turning to botanicals and natural compounds as alternative treatment options, providing an impetus to advance and progress the scientific knowledge regarding botanically derived phytochemicals and compounds. One sector of growing interest and research has been in cosmeceuticals, where natural products are being evaluated for their use as cosmetic agents.[6]

With ageing and chronic sun exposure the skin thins, loses elasticity and develops wrinkles, uneven pigmentation and textural irregularities.[7] Common concerns regarding photoageing include the development of wrinkles and dyspigmentation. Currently, topical retinoids are utilized as an effective preventative and therapeutic intervention.[8,9] However, their significant cutaneous side-effects are common and well documented in the literature.[10–13] These side-effects typically manifest as cutaneous erythema, pruritus, peeling, stinging or burning, and sensitivity.[10] As the market for over-the-counter antiageing products expands, the desire for retinoid-like products, but with limited side-effect profiles, is growing.

Bakuchiol is an alternative agent to topical retinoids that has recently gained more exposure in the literature (Fig. 1). Bakuchiol is a purified meroterpene phenol found mainly in the seeds of the Indian plant *Psoralea corylifolia* (babchi),[14,15] but it is also found in other plant sources including *Psoralea glandulosa*,[16,17] *Pimelea drupaceae* (cherry riceflower),[18] *Ulmus davidiana* (Father David elm),[19] *Otholobium pubescens*[20] and *Piper longum* (long pepper).[21] The compound has been found to have antiproliferative,[22] anti-inflammatory,[17,23–25] antioxidant[26] and antiacne activity.[27]

Mechanistically, bakuchiol appears to target several cellular pathways similar to those targeted by retinoids, including the modulation of retinoic acid receptors genes and upregulation of collagen and extracellular matrix synthesis enzymes.[28]

One clinical study evaluated the effect of topical bakuchiol twice daily and found a statistically significant improvement in wrinkles, pigmentation and firmness.[28] However, this study did not involve a control group, and it is unclear how bakuchiol would compare clinically with topical retinoids. The goal of this study was to compare the clinical efficacy and side-effect profiles of bakuchiol against a commonly used retinoid, retinol, in treating common signs of cutaneous ageing. In particular, we hypothesize that bakuchiol will have a similar efficacy to retinol in the improvement of wrinkles.

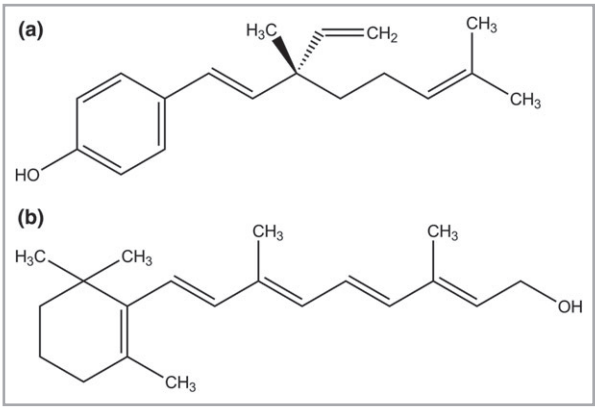

Fig 1. Chemical structures of (a) bakuchiol and (b) retinol.

Patients and methods

Study participants

This study was conducted from March to November 2017 as a randomized, double-blinded, rater-blinded, 12-week study. This study was approved by the institutional review board at the University of California – Davis and registered on ClinicalTrials.gov (NCT03112863). All participants provided written informed consent prior to participation and received financial compensation ($100 for the entire study). Fifty healthy participants (age 47 ± 7·2 years) were recruited and screened for eligibility at the University of California – Davis dermatology clinic. Participants were excluded if they were pregnant or breastfeeding, had a known sensitivity to retinol or bakuchiol, or had a cutaneous disease that affected the face. Participants were also excluded if they had used isotretinoin in the previous 6 months, had used a topical antibiotic or topical retinoid in the 30 days prior to enrolment, or had used products containing salicylic acid, β-hydroxy acids or vitamins A, C or E in the last 14 days. Current smokers and those who had smoked within the previous 3 years (as this may serve as a confounder in the assessment of wrinkles) and those who had undergone a facial surgical or cosmetic procedure within 3 months prior to participation were excluded.

Study design and intervention

The study was conducted over 12 weeks and consisted of four visits. All treatments were prerandomized using a computer-based randomization generator with blinded allocation via sealed envelopes. Participants were enrolled and assigned interventions by the clinical research coordinator.

The bakuchiol used in this study was isolated from edible seeds of *P. corylifolia*, a psoralene-depleted bakuchiol {INCI name: bakuchiol; chemical name: phenol, 4-[(1E,3S)-3-ethenyl-3,7-dimethyl-1,6-octadienyl], optically active} with a purity of over 99%. The topical retinol was formulated in the same vehicle as the bakuchiol (Sytheon Ltd, Boonton, NJ, U.S.A.).

Participants were advised to apply either the retinol or bakuchiol in accordance with how they have been used in previous studies. Specifically, the patients were instructed to apply either retinol 0·5% cream to their full face nightly or bakuchiol 0·5% cream to their full face twice daily as a thin layer. At each visit the BTBP 3D Clarity Pro® Facial Modeling and Analysis System (Brigh-Tex BioPhotonics, San Jose, CA, U.S.A.) was utilized to obtain high-resolution facial photographs for all study participants. The photographic instrumentation takes automated photographs in zero ambient lighting with reproducible placement of the face and identical photographic exposures. This system has been validated in

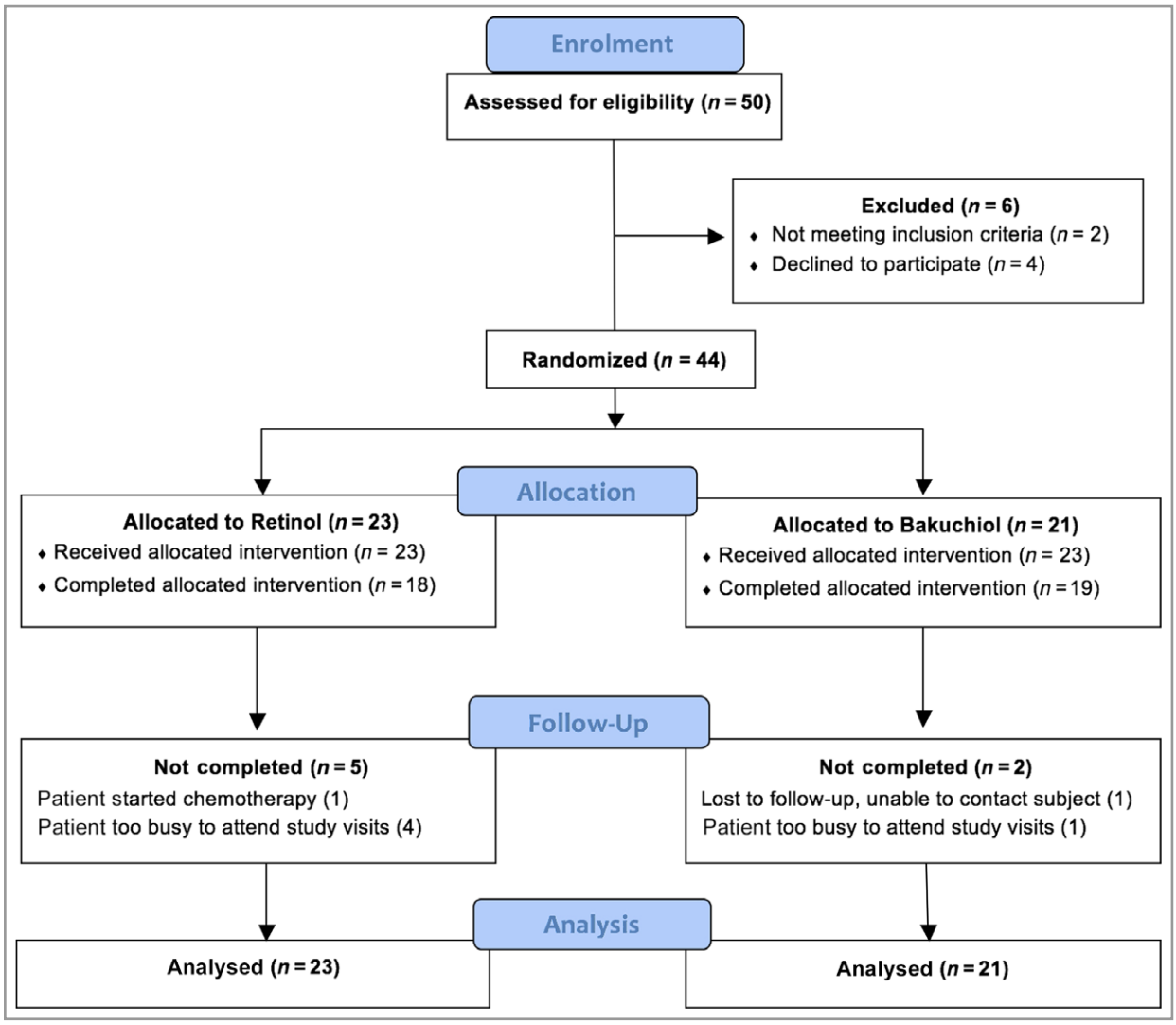

Fig 2. CONSORT flow diagram.

Table 1 Demographics of the enrolled patients

Demographic factor	Bakuchiol group (n = 21)	Retinol group (n = 23)	P-value
Age (years), mean ± SD	48·1 ± 1·5	47 ± 1·6	0·62
Sex, male/female	2/19	1/22	–
Median baseline erythema	1	1	0·06
Median baseline hyperpigmentation	2	2	0·67

Erythema and hyperpigmentation were evaluated on a four-point Likert scale.

comparison with clinical grading of multiple facial features in previous work.[29–32] Participants were also directed to answer a set of subjective tolerability assessment questions of the skin at each follow-up visit. Participants were asked on a scale of 0 (none) to 3 (severe) if they had any itching, burning or stinging. After completion of all study visits, a board-certified dermatologist, blinded to study group assignment, graded scaling, pigmentation and redness.

Facial grading and analysis

Facial photographs were analysed by a computer. Computer-based grading utilized facial computational algorithms that have been previously validated for assessment of cutaneous pigment, redness and wrinkles.[32,33] In-person grading for pigmentation, erythema and scaling was performed at each visit by a board-certified dermatologist and the same grader was used throughout the study to maintain consistency.

Tolerability assessments

Product tolerability was assessed at each follow-up, where participants were asked to grade their experience of itching, burning and stinging along a four-point Likert scale.

Statistical analysis

Previous studies have reported relevant changes in wrinkles to be approximately 20%.[34,35] An *a priori* power analysis showed that there was > 90% power to detect a 20% difference in wrinkle severity between the bakuchiol and retinol treatments at week 12, with recruitment of at least 17 patients in each group with alpha set to 0·05. Statistical analyses were performed using paired t-tests (or Wilcoxon signed-rank test for nonparametric measures) with correction for repeated measures with a Bonferroni correction. P-values < 0·05 were considered significant, while values between 0·05 and 0·1 were considered a trend.

Outcomes measured

The primary outcome measure was image-analysis-based assessment of wrinkle severity and pigmentation at 12 weeks. Secondary outcome measures included image-based analysis of wrinkles and facial pigmentation at earlier time points, and redness, participant-reported tolerability (itching, burning and stinging) and in-person clinical assessments (pigmentation, scaling and erythema) throughout the study.

Results

Of the 50 patients who were screened, 44 met the enrolment criteria and were randomized to receive one of the two interventions: bakuchiol or retinol. Forty-four eligible participants were randomized into two groups: the retinol group (age 31–55 years; 22 female and one male) and the bakuchiol group (age 33–56 years; 19 female and two male). The CONSORT flow diagram is shown in Figure 2. Of these patients, five dropped out due to nonattendance to study visits, one was lost to follow-up and unable to be contacted by the research team, and one had to discontinue due to starting chemotherapy. Because an intention-to-treat analysis was performed, all 44 patients were included in the analysis (mean age 44 years, range 31–56). The demographic characteristics of each group were similar (Table 1).

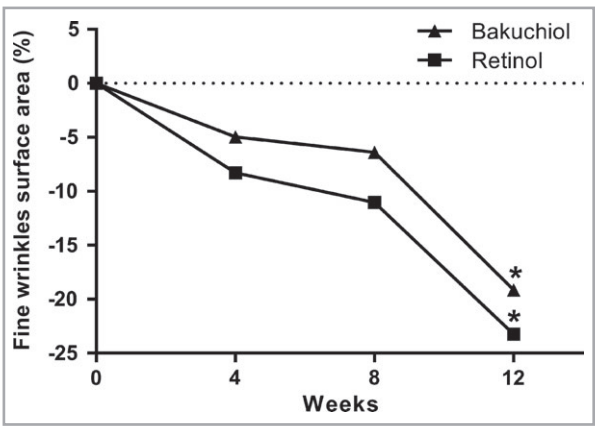

Fig 3. Participants were treated for 12 weeks with either bakuchiol or retinol. We observed 5·0%, 6·4% and 19·0% decreases in fine wrinkles surface area at 4, 8 and 12 weeks, respectively, with bakuchiol treatment, whereas decreases of 8·3%, 11·1% and 23·2% were observed at 4, 8 and 12 weeks, respectively, with retinol treatment. *P < 0·05.

Wrinkles

Both bakuchiol and retinol significantly reduced the surface area involvement of fine wrinkles on the face compared with baseline (Fig. 3). Notably, significant changes from baseline were found at the 12-week time point. There were no significant differences between bakuchiol and retinol.

Pigmentation

Pigmentation was assessed through clinical grading and through facial analysis of the surface area of involvement and overall pigment intensity. Clinical grading showed that 59% of the participants in the bakuchiol group had improvement in their hyperpigmentation, while 44% of those in the retinol group had improvement in their hyperpigmentation at week 12 (Fig. 4a). Retinol and bakuchiol improved both pigment intensity (Fig. 4b) and surface area of involvement (Fig. 4c) at week 12. There were no statistically significant differences between bakuchiol and retinol in the facial analysis or the clinical grading.

Adverse effects

There was significantly more scaling noted in the retinol group at all follow-up time points (Fig. 5). Bakuchiol appeared to show a trend towards more redness on clinical grading at week 4 (Fig. 6a) and an increase in redness intensity by computer analysis at week 4 (Fig. 6b). There were no significant changes in redness in either group at weeks 8 or 12.

There were more subjective reports of itching and burning in the retinol group (Fig. 7a, b), although this was not statistically significant. There were more statistically significant subjective reports of stinging in the retinol group (Fig. 7c).

Discussion

Our study demonstrates that bakuchiol is comparable with retinol in its ability to improve photoageing and is better tolerated than retinol. Figure 8 shows facial images at baseline and after 12 weeks of application of either retinol or bakuchiol. In particular, for consumers who value natural products, bakuchiol provides appeal due to its origin in several plant species. Although retinol may also be derived from various natural sources, much of what is on the market is manmade and quite potent, causing unwanted side-effects.

Topical retinoids have become a staple in antiageing therapy, due to their clinically proven ability to combat signs of ageing through collagen production, inhibition of collagen

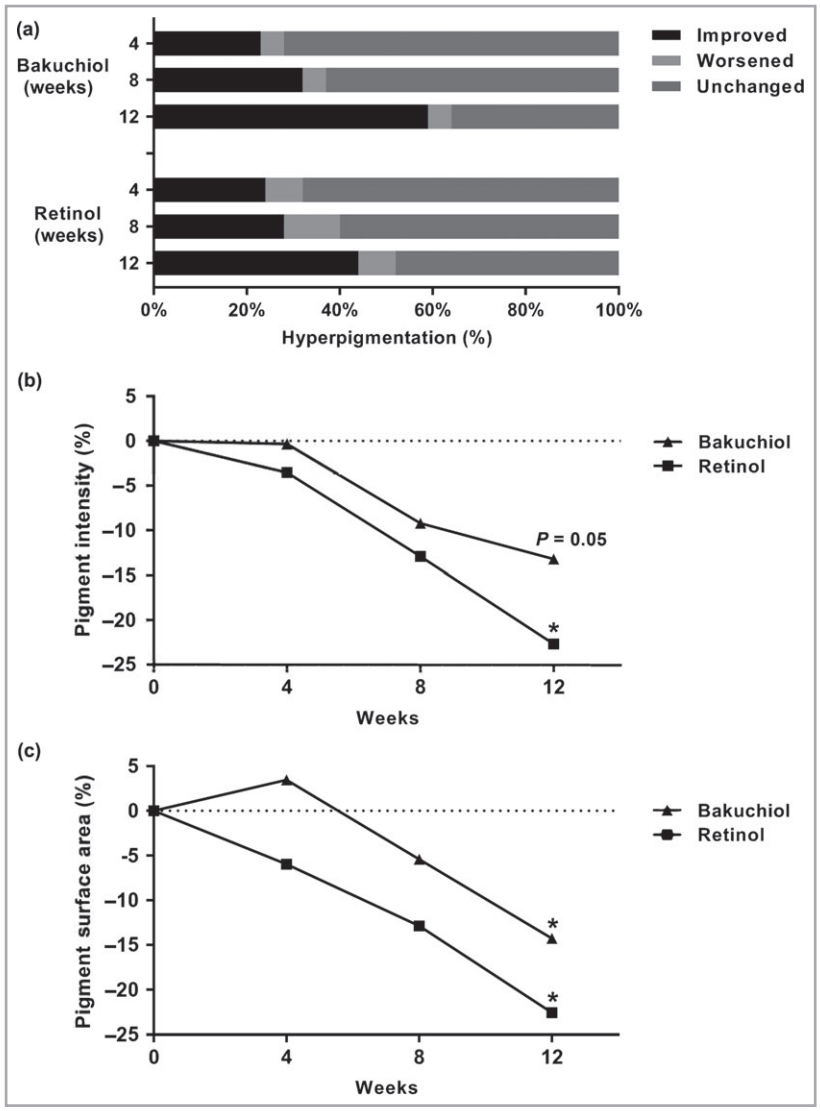

Fig 4. (a) Changes in the clinical grading of hyperpigmentation in comparison with baseline were assessed at 4, 8 and 12 weeks. (b) Computer-analysis-based pigment intensity and (c) surface area were measured at 4, 8 and 12 weeks in both treatment groups. *P < 0·05.

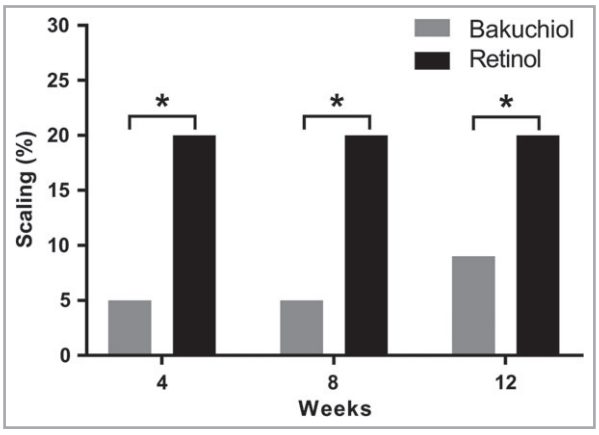

Fig 5. The presence of scaling among the participants was assessed at 4, 8 and 12 weeks. *P < 0·05.

degradation, angiogenesis and alteration of melanin synthesis.[7,36,37] The 'retinoid reaction' is an adverse event associated with all topical retinoids, and is likely a result of the upregulation of inflammatory mediators in the skin during therapy.[38] The experiences of participants in this study are consistent with those in previous reports, in that other study patients also experienced burning, stinging and scaling.

Bakuchiol exhibits promise to serve as an alternative to retinol with fewer side-effects. Both this study and a previous *in vivo* study show that twice-daily application of bakuchiol can lead to marked improvements in a number of antiageing parameters.[28] Although retinol and bakuchiol are structurally different, bakuchiol has demonstrated the ability to serve as a functional analogue to retinol. Specifically, both compounds induce highly similar gene expression in human skin. This includes genes involved in the cellular uptake of endogenous retinol, the activation of retinol in the skin and the production

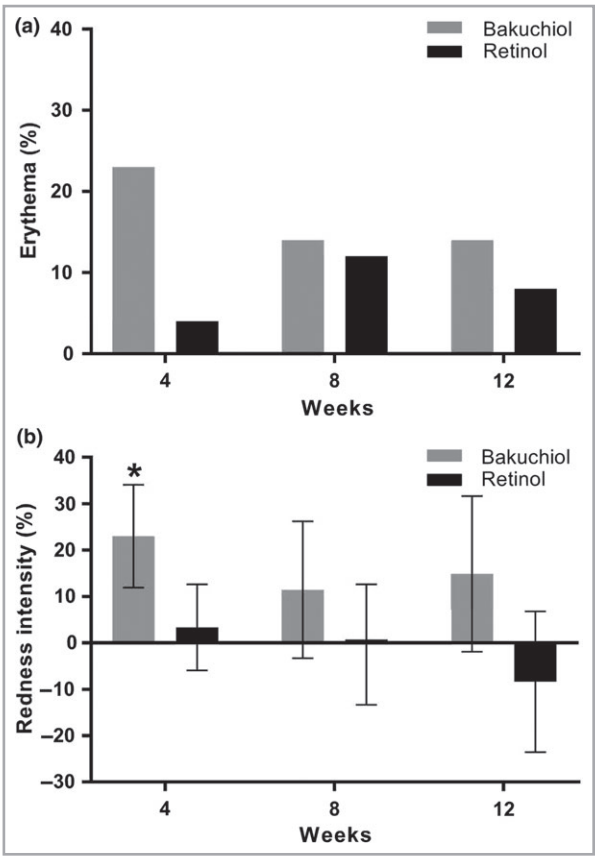

Fig 6. Changes in erythema were assessed by clinical grading (a) and by computer analysis (b) of redness intensity. Clinical grading is reported as the percentage of the participants, whereas computer grading is measured as the change from the baseline measurement. Error bars represent the SEM. *P < 0·05.

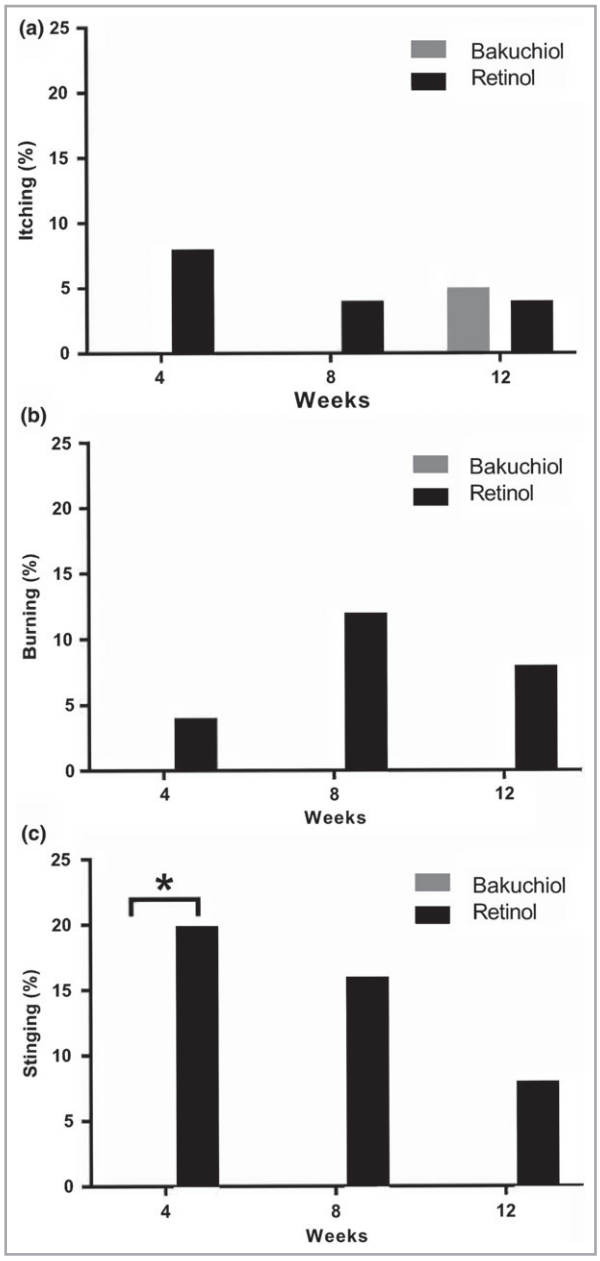

Fig 7. Adverse effects were assessed in the participants: (a) itching, (b) burning and (c) stinging. *P < 0·05.

of extracellular matrix proteins that provide epidermal support and integrity.[28] These molecular findings translate to clinical outcomes, as our study shows comparable improvements in wrinkles and hyperpigmentation with the use of either compound.

Although bakuchiol may share some of its antiageing properties with retinoids, the compound induces its own set of chemical pathways that may also contribute to its antiageing effects. Perhaps most notably, bakuchiol influences several antioxidant processes. Oxidative stress on skin cells, from both internal metabolic processes and external environmental toxins and stressors, is known to contribute significantly to cutaneous ageing.[39] Bakuchiol has been shown to activate nuclear factor erythroid 2-related factor 2, a transcription factor that plays a significant role in cellular resistance to oxidative stess.[26,40] Additional antioxidant capabilities include its capacity for scavenging oxygen free radicals and its significant role in preventing mitochondrial lipid peroxidation.[41–43]

In addition to improving wrinkle depth, bakuchiol also decreased pigment intensity and surface area over the 12-week treatment course. This may be attributable to bakuchiol's antioxidant effects, as well as its ability to disrupt melanin synthesis. Interestingly, bakuchiol can interfere with two steps of the melanin synthesis pathway, blocking both α-melanocyte-stimulating hormone activation and tyrosinase (the rate-limiting enzyme in melanin synthesis).[21,44] Bakuchiol's suppressive effects on cutaneous melanin production prime the compound for use in both antiageing and antihyperpigmentation cosmeceuticals.

Regarding tolerability, the patients receiving bakuchiol had fewer adverse cutaneous side-effects than those taking retinol, with less stinging and scaling. In addition to its antioxidant properties, this may also be related to bakuchiol's anti-inflammatory effects.[23,45] Furthermore, bakuchiol has not been

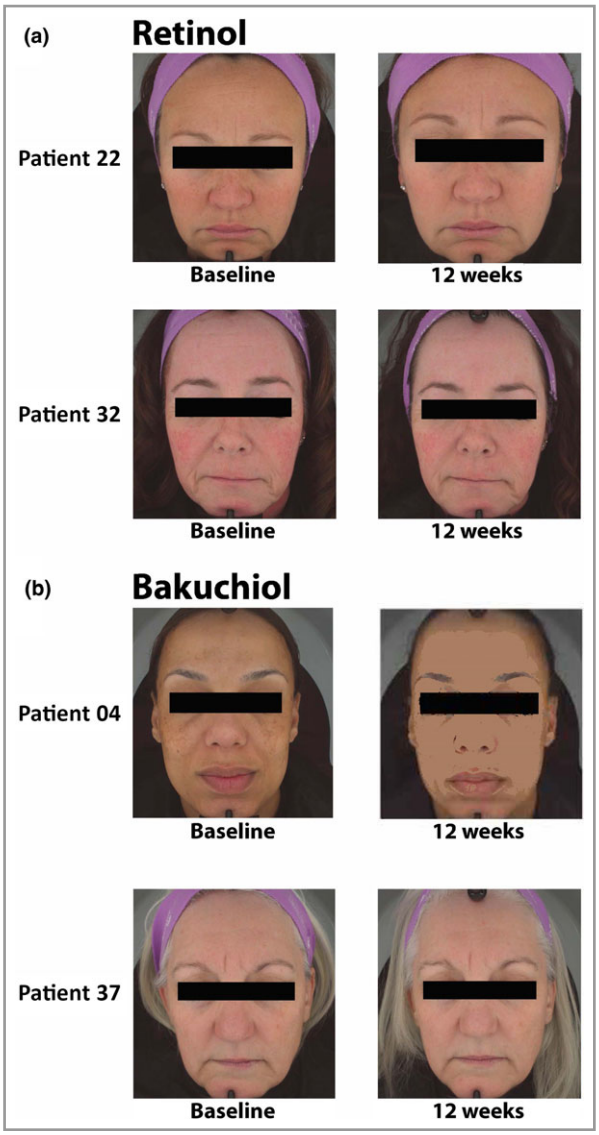

Fig 8. Facial images at baseline and after 12 weeks of topical application of (a) retinol and (b) bakuchiol.

shown to increase photosensitivity, as retinoid products are known to do.[46] There were no reports of photosensitivity in this study.

Interestingly, one of the patients in the bakuchiol group noted that scaling along the hairline subsided with topical use. While we did not evaluate for treatment of dandruff or seborrhoeic dermatitis, it is notable that bakuchiol has known antifungal activity.[47]

This study has certain limitations. The sample size is relatively small and the study was done at a single centre; however, the number of study participants is double that of early trials for topical retinoids.[48,49] Our study is limited to cosmetic evaluation, and no evaluations were made regarding collagen production. While patients in the retinol treatment arm applied the product once per day, those in the bakuchiol treatment arm applied the product once in the morning and once in the evening. However, this is consistent with the products' respective standard treatment regimens outside of a clinical trial setting and reflects that bakuchiol is well tolerated during daytime use without photosensitivity. Another limitation was that seven of the 44 enrolled participants dropped out, but we utilized an intention-to-treat analysis to account for this. Our study was limited to assessments over 12 weeks and an assessment of longer time periods would need further study. Finally, our study did not evaluate any diseases, and our results are limited to otherwise generally healthy adults. Therefore, the results cannot be generalized to patients with other diseases.

Overall, our results suggest that bakuchiol is an effective option for improvement of photoageing and is a better-tolerated alternative to retinol. Our results warrant future studies with an expanded population.

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