

MS ALEXANDRA R. VAUGHN (Orcid ID : 0000-0003-2975-0983)

Article type : Original Article

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

Running head: Assessment of topical bakuchiol and retinol for facial photoaging

S. Dhaliwal,^{1,*} I. Rybak,^{1,*} S. Ellis,¹ M. Notay,¹ M. Trivedi,² W. Burney,¹ A.R. Vaughn,³ M. Nguyen,⁴ P. Reiter,⁵ S. Bosanac,⁴ H. Yan,¹ N. Foolad,⁴ R.K. Sivamani^{1,6},

1. Department of Dermatology, University of California-Davis, Sacramento, CA
2. School of Medicine, University of Michigan, Ann Arbor, MI
3. Drexel University College of Medicine, Philadelphia, PA
4. School of Medicine, University of California-Davis, Sacramento, CA
5. Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL
6. Department of Biological Sciences, California State University, Sacramento, CA

*These authors contributed equally to this manuscript

Corresponding Author:

Raja K. Sivamani, MD MS AP

3301 C Street, Suite 1400

Sacramento, CA 95816

raja.sivamani.md@gmail.com

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bjd.16918](https://doi.org/10.1111/bjd.16918)

This article is protected by copyright. All rights reserved

Funding Source: Department of Dermatology, University of California - Davis

Conflict of interest disclosures: RKS serves as a scientific advisor for Dermveda and as a consultant for Burt's Bees and Dermala.

1. **Bakuchiol is a plant derived phytochemical that is known to have retinoid like effects in vitro.**
2. **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.**

Abstract

BACKGROUND: Bakuchiol is a phytochemical that has demonstrated cutaneous anti-aging effects when applied topically. Early studies have suggested that bakuchiol is a functional analog 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 to retinol in improving common signs of cutaneous facial aging.

METHODS: This was a randomized, double-blind, 12-week study in which 44 subjects were asked to apply either 0.5% bakuchiol cream twice daily or 0.5% retinol cream daily. A facial photograph and analysis system was used to obtain and analyze high-resolution photographs of subjects at 0, 4, 8, and 12 weeks. Subjects 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.

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

Introduction

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 aging and chronic sun exposure, the skin thins, loses elasticity, and develops wrinkles, uneven pigmentation, and textural irregularities.⁷ Common concerns regarding photoaging 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.^{10,11-13} These side effects typically manifest as cutaneous erythema, pruritus, peeling, stinging or burning, and sensitivity.¹⁰ As the market for over-the-counter anti-aging 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 is also found in other plant sources including *Psoralea grandulosa*,^{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 anti-proliferative,²² anti-inflammatory,^{17,23-25} antioxidant,²⁶ and anti-acne 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 clinically compare to topical retinoids. The goal of this study was to compare the clinical efficacy and side effect profiles of bakuchiol to a commonly used retinoid, retinol, in treating common signs of cutaneous aging. In particular, we hypothesize that bakuchiol will have a similar efficacy in the improvement of wrinkles as retinol.

Materials and Methods

Study Participants

This study was conducted from March, 2017 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 (47±7.2 years) were recruited and screened for eligibility at the UC 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 six months, had used a topical antibiotic or topical retinoid in the 30 days prior to enrollment, or had used products

containing salicylic acid, beta hydroxy acids, or vitamins A, C, or E in the last 14 days. Current smokers, those who smoked within the previous three years as this may serve as a confounder in the assessment of wrinkles, and those who underwent a facial surgical or cosmetic procedure within three 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 pre-randomized 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 *Psoralea 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, USA).

Participants were advised to apply either the retinol or bakuchiol in accordance with how they have been used in previous studies. Specifically, the subjects were instructed either apply 0.5% retinol cream to their full face nightly or the 0.5% bakuchiol 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) 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 comparison to 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 being none or 3 being 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 analyzed 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 based system.

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 greater than 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 subjects in each group with alpha set to 0.05. Statistical analyses were performed using paired t-tests (or Wilcoxon signed-rank test for non-parametric measures) with correction for repeated measures with a Bonferroni correction. P values less than 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 timepoints and

redness, participant reported tolerability (itching, burning, stinging), and in-person clinical assessments (pigmentation, scaling, and erythema) throughout the study.

Results

Of the 50 subjects who were screened, 44 met enrollment criteria and were randomized to receive one of the two interventions: bakuchiol or retinol. Forty-four eligible participants were randomized into two groups: Retinol Group (ages: 31-55; 22 females and 1 male) and Bakuchiol Group (ages: 33-56; 19 females and 2 males); see Figure 2 for CONSORT flow diagram. Of these subjects, 5 subjects dropped out due to nonattendance to study visits, 1 subject was lost to follow-up and unable to be contacted by research team, and 1 subject had to discontinue due to starting chemotherapy. Because an intention to treat analysis was performed, all 44 subjects were included in analysis (mean age 44 years old, range 31-56 years old). The demographic characteristics of each group was similar (Table 1).

Wrinkles

Both bakuchiol and retinol significantly reduced the surface area involvement of fine wrinkles on the face when compared to 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 statistical 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 have a trend toward 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, (Figs. 7a and 7b) though 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 to retinol in its ability to improve photoaging and is better tolerated than retinol. See Figure 8 for 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. Though 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 anti-aging therapy, due to their clinically proven ability to combat signs of aging through collagen production, inhibition of collagen 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 participants in this study agree with previous reports, in that other study subjects also experienced burning, stinging, and scaling.

Bakuchiol exhibits promise to serve as an alternative to retinol with fewer side effects. Both this study, as well as a previous *in vivo* study, show that twice daily bakuchiol application can lead to marked improvements in a number of anti-aging parameters.²⁸ Though retinol and bakuchiol are structurally different, bakuchiol has demonstrated an 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 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 use of either compound.

Though bakuchiol may share some of its anti-aging properties with retinoids, the compound induces its own set of chemical pathways that may also contribute to its anti-aging 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 aging.³⁹ Bakuchiol has been shown to activate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that plays a significant role in cellular resistance to oxidative stress.^{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 alpha-melanocyte stimulating hormone activation as well as 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 anti-aging and anti-hyperpigmentation cosmeceuticals.

Regarding tolerability, bakuchiol subjects had fewer adverse cutaneous side effects than retinol patients, with less stinging and scaling. In addition to its anti-oxidant properties, this may also be related to bakuchiol's anti-inflammatory effects.^{23,45} Furthermore, bakuchiol has not been 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 subjects in the bakuchiol group noted that scaling along the hairline subsided with topical use. While we did not evaluate for treatment of dandruff or seborrheic dermatitis, it is notable that bakuchiol has known antifungal activity.⁴⁷

This study has certain limitations. The sample size is relatively small and done at a single center, 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 the retinol treatment arm applied product once per day, the bakuchiol treatment arm applied 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 7 out 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 other diseases.

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

Acknowledgments: none

References

- 1 Blanco-Davila F. Beauty and the body: the origins of cosmetics. *Plast Reconstr Surg* 2000; **105**: 1196-204.
- 2 Wick JY. Aspirin: a history, a love story. *Consult Pharm* 2012; **27**: 322-9.
- 3 Mahdi JG, Mahdi AJ, Mahdi AJ *et al*. The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. *Cell Prolif* 2006; **39**: 147-55.
- 4 Brook K, Bennett J, Desai SP. The Chemical History of Morphine: An 8000-year Journey, from Resin to de-novo Synthesis. *J Anesth Hist* 2017; **3**: 50-5.
- 5 Onoyovwe A, Hagel JM, Chen X *et al*. Morphine biosynthesis in opium poppy involves two cell types: sieve elements and laticifers. *Plant Cell* 2013; **25**: 4110-22.
- 6 Martin KI, Glaser DA. Cosmeceuticals: the new medicine of beauty. *Mo Med* 2011; **108**: 60-3.
- 7 Kligman DE, Sadiq I, Pagnoni A *et al*. High-strength tretinoin: a method for rapid retinization of facial skin. *J Am Acad Dermatol*; **39**: S93-S7.
- 8 Bruce S, Barkovic S. Open-Label Study Evaluating the Anti-Aging Effects of a 3-Product, 2-Step Retinol-Rejuvenation System Following 3 Months of Treatment in Subjects With Photodamage. *J Drugs Dermatol* 2017; **16**: 23-8.
- 9 Darlenski R, Surber C, Fluhr JW. Topical retinoids in the management of photodamaged skin: from theory to evidence-based practical approach. *Br J Dermatol* 2010; **163**: 1157-65.
- 10 Mukherjee S, Date A, Patravale V *et al*. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging* 2006; **1**: 327-48.
- 11 David M, Hodak E, Lowe NJ. Adverse effects of retinoids. *Med Toxicol Adverse Drug Exp* 1988; **3**: 273-88.

- 12 Culp L, Moradi Tuchayi S, Alinia H *et al.* Tolerability of Topical Retinoids: Are There Clinically Meaningful Differences Among Topical Retinoids? *J Cutan Med Surg* 2015; **19**: 530-8.
- 13 Foti C, Romita P, Borghi A *et al.* Contact dermatitis to topical acne drugs: a review of the literature. *Dermatol Ther* 2015; **28**: 323-9.
- 14 Mehta G, Nayak UR, Dev S. Meroterpenoids .1. Psoralea-Corylifolia Linn .1. Bakuchiol, a Novel Monoterpene Phenol. *Tetrahedron* 1973; **29**: 1119-25.
- 15 Prakasarao AS, Bhalla VK, Nayak UR *et al.* Meroterpenoids .2. Psoralea-Corylifolia Linn .2. Absolute Configuration of (+)-Bakuchiol. *Tetrahedron* 1973; **29**: 1127-30.
- 16 Labbe C, Faini F, Coll J *et al.* Bakuchiol derivatives from the leaves of *Psoralea glandulosa*. *Phytochemistry* 1996; **42**: 1299-303.
- 17 Backhouse CN, Delporte CL, Negrete RE *et al.* Active constituents isolated from *Psoralea glandulosa* L. with antiinflammatory and antipyretic activities. *J Ethnopharmacol* 2001; **78**: 27-31.
- 18 Lystvan K, Belokurova V, Sheludko Y *et al.* Production of bakuchiol by in vitro systems of *Psoralea drupacea* Bge. *Plant Cell Tissue Organ Cult* 2010; **101**: 99-103.
- 19 Choi SY, Lee S, Choi WH *et al.* Isolation and Anti-Inflammatory Activity of Bakuchiol from *Ulmus davidiana* var. *japonica*. *J Med Food* 2010; **13**: 1019-23.
- 20 Krenisky JM, Luo J, Reed MJ *et al.* Isolation and antihyperglycemic activity of bakuchiol from *Otholobium pubescens* (Fabaceae), a Peruvian medicinal plant used for the treatment of diabetes. *Biol Pharm Bull* 1999; **22**: 1137-40.
- 21 Ohno O, Watabe T, Nakamura K *et al.* Inhibitory Effects of Bakuchiol, Bavachin, and Isobavachalcone Isolated from *Piper longum* on Melanin Production in B16 Mouse Melanoma Cells. *Biosci Biotechnol Biochem* 2010; **74**: 1504-6.
- 22 Kim JE, Kim JH, Lee Y *et al.* Bakuchiol suppresses proliferation of skin cancer cells by directly targeting Hck, Blk, and p38 MAP kinase. *Oncotarget* 2016; **7**: 14616-27.

- 23 Ferrandiz ML, Gil B, Sanz MJ *et al.* Effect of bakuchiol on leukocyte functions and some inflammatory responses in mice. *J Pharm Pharmacol* 1996; **48**: 975-80.
- 24 Pae HO, Cho H, Oh GS *et al.* Bakuchiol from *Psoralea corylifolia* inhibits the expression of inducible nitric oxide synthase gene via the inactivation of nuclear transcription factor-kappa B in RAW 264.7 macrophages. *Int Immunopharmacol* 2001; **1**: 1849-55.
- 25 Matsuda H, Kiyohara S, Sugimoto S *et al.* Bioactive Constituents from Chinese Natural Medicines. XXXIII.(1) Inhibitors from the Seeds of *Psoralea corylifolia* on Production of Nitric Oxide in Lipopolysaccharide-Activated Macrophages. *Bio Pharm Bull* 2009; **32**: 147-9.
- 26 Shoji M, Arakaki Y, Esumi T *et al.* Bakuchiol Is a Phenolic Isoprenoid with Novel Enantiomer-selective Anti-influenza A Virus Activity Involving Nrf2 Activation. *J Biol Chem* 2015; **290**: 28001-17.
- 27 Polakova K, Fauger A, Sayag M *et al.* A dermocosmetic containing bakuchiol, Ginkgo biloba extract and mannitol improves the efficacy of adapalene in patients with acne vulgaris: result from a controlled randomized trial. *Clin Cosmet Investig Dermatol* 2015; **8**: 187-91.
- 28 Chaudhuri RK, Bojanowski K. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. *Int J Cosmet Sci* 2014; **36**: 221-30.
- 29 Petukhova TA, Foolad N, Prakash N *et al.* Objective volumetric grading of postacne scarring. *J Am Acad Dermatol* 2016; **75**: 229-31.
- 30 Foolad N, Prakash N, Shi VY *et al.* The use of facial modeling and analysis to objectively quantify facial redness. *J Cosmet Dermatol* 2016; **15**: 43-8.
- 31 Ornelas J, Rosamilia L, Larsen L *et al.* Objective assessment of isotretinoin-associated cheilitis: Isotretinoin Cheilitis Grading Scale. *J Dermatolog Treat* 2016; **27**: 153-5.
- 32 Foolad N, Shi VY, Prakash N *et al.* The association of the sebum excretion rate with melasma, erythematotelangiectatic rosacea, and rhytides. *Dermatol Online J* 2015; **21**.

- 33 Shi VY, Foolad N, Ornelas JN *et al.* Comparing the effect of bleach and water baths on skin barrier function in atopic dermatitis: a split-body randomized controlled trial. *Br J Dermatol* 2016; **175**: 212-4.
- 34 McDaniel DH, Mazur C, Wortzman MS *et al.* Efficacy and tolerability of a double-conjugated retinoid cream vs 1.0% retinol cream or 0.025% tretinoin cream in subjects with mild to severe photoaging. *J Cosmet Dermatol* 2017; **16**: 542-8.
- 35 Proksch E, Segger D, Degwert J *et al.* Oral supplementation of specific collagen peptides has beneficial effects on human skin physiology: a double-blind, placebo-controlled study. *Skin Pharmacol Physiol* 2014; **27**: 47-55.
- 36 Kafi R, Kwak HS, Schumacher WE *et al.* Improvement of naturally aged skin with vitamin A (retinol). *Arch Dermatol* 2007; **143**: 606-12.
- 37 Gendimenico GJ, Mezick JA. Pharmacological effects of retinoids on skin cells. *Skin Pharmacol* 1993; **6 Suppl 1**: 24-34.
- 38 Kim BH, Lee YS, Kang KS. The mechanism of retinol-induced irritation and its application to anti-irritant development. *Toxicol Lett* 2003; **146**: 65-73.
- 39 Rinnerthaler M, Bischof J, Streubel MK *et al.* Oxidative stress in aging human skin. *Biomolecules* 2015; **5**: 545-89.
- 40 Ma Q. Role of nrf2 in oxidative stress and toxicity. *Annu Rev Pharmacol Toxicol* 2013; **53**: 401-26.
- 41 Adhikari S, Joshi R, Patro BS *et al.* Antioxidant activity of bakuchiol: experimental evidences and theoretical treatments on the possible involvement of the terpenoid chain. *Chem Res Toxicol* 2003; **16**: 1062-9.
- 42 Haraguchi H, Inoue J, Tamura Y *et al.* Inhibition of mitochondrial lipid peroxidation by Bakuchiol, a meroterpene from *Psoralea corylifolia*. *Planta Med* 2000; **66**: 569-71.
- 43 Haraguchi H, Inoue J, Tamura Y *et al.* Antioxidative components of *Psoralea corylifolia* (Leguminosae). *Phytother Res* 2002; **16**: 539-44.
- 44 Cheng M, Chen Z. Screening of tyrosinase inhibitors by capillary electrophoresis with immobilized enzyme microreactor and molecular docking. *Electrophoresis* 2017; **38**: 486-93.

- 45 Klebanoff SJ. Myeloperoxidase. *Proc Assoc Am Physicians* 1999; **111**: 383-9.
- 46 Ferguson J, Johnson BE. Retinoid associated phototoxicity and photosensitivity. *Pharmacol Ther* 1989; **40**: 123-35.
- 47 Katsura H, Tsukiyama RI, Suzuki A *et al.* In vitro antimicrobial activities of bakuchiol against oral microorganisms. *Antimicrob Agents Chemother* 2001; **45**: 3009-13.
- 48 Lever L, Kumar P, Marks R. Topical retinoic acid for treatment of solar damage. *Br J Dermatol* 1990; **122**: 91-8.
- 49 Kligman AM, Grove GL, Hirose R *et al.* Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986; **15**: 836-59.

Tables:

Table 1. Demographics of Subjects Enrolled

Demographic Factor	Bakuchiol group (n=21)	Retinol Group (n=23)	p-value
Age, mean±SD	48.1±1.53	47±1.56	0.62
Sex, Male/Female	2/19	1/22	--
Median Baseline Erythema	1	1	0.06
Median Baseline Hyperpigmentation	2	2	0.67

SD, standard deviation; ns, non-significant. Erythema and hyperpigmentation were evaluated on a four-point likert scale.

Figure Legends

Figure 1. Chemical structures of (A) bakuchiol and (B) retinol.

Figure 2. CONSORT Flow Diagram

Figure 3. Participants were treated for 12 weeks with either bakuchiol or retinol. We observed 5.0%, 6.4% and 19.0% decrease in fine wrinkles surface area at 4, 8 and 12 weeks with bakuchiol treatment, respectively, whereas, a decrease of 8.3%, 11.1% and 23.2% was observed at 4, 8 and 12 weeks respectively with retinol treatment (* = $p < 0.05$).

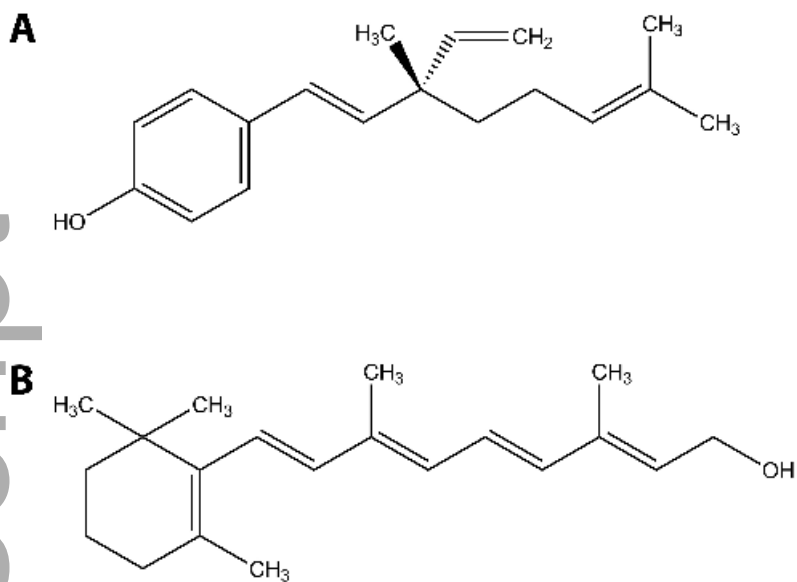
Figure 4. (A) Changes in the clinical grading of hyperpigmentation in comparison to the baseline were assessed at 4, 8, and 12 weeks. Computer analysis based pigment intensity (B) and surface area (c) were measured at 4, 8, and 12 weeks in both treatment groups. (* = $p < 0.05$).

Figure 5. The presence of scaling among the participants was assessed at 4, 8, and 12 weeks. (* = $p < 0.05$).

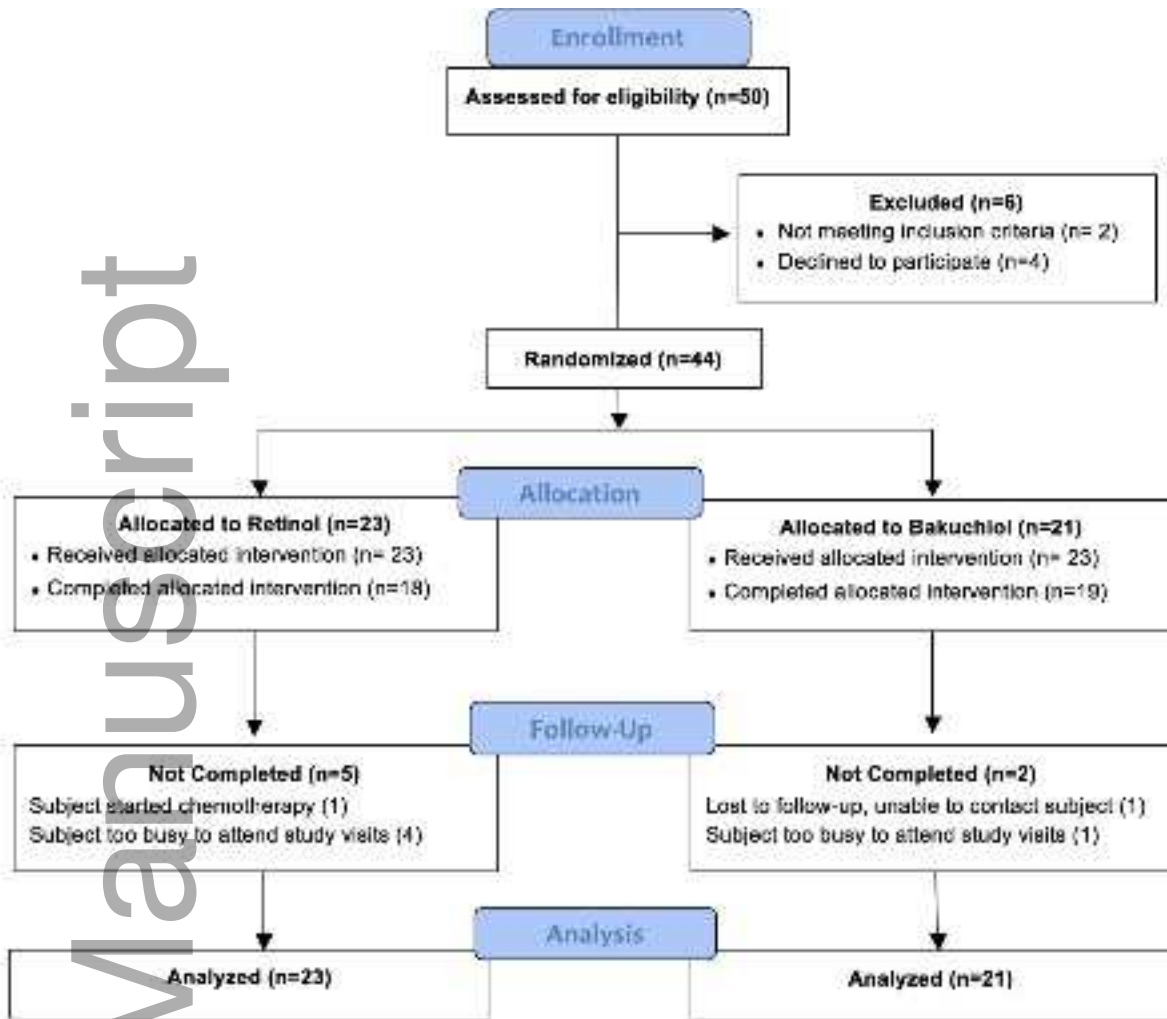
Figure 6. Changes in erythema were assessed by clinical grading (A) and by computer analysis (B) of redness intensity. Clinical grading is reported as a percent of the participants whereas computer grading is noted as changes from the baseline measurements. (Error bars represent \pm SEM, * = $p < 0.05$).

Figure 7. Participant adverse effects were assessed for itching (A), burning (B), and stinging (C). (* = $p < 0.05$)

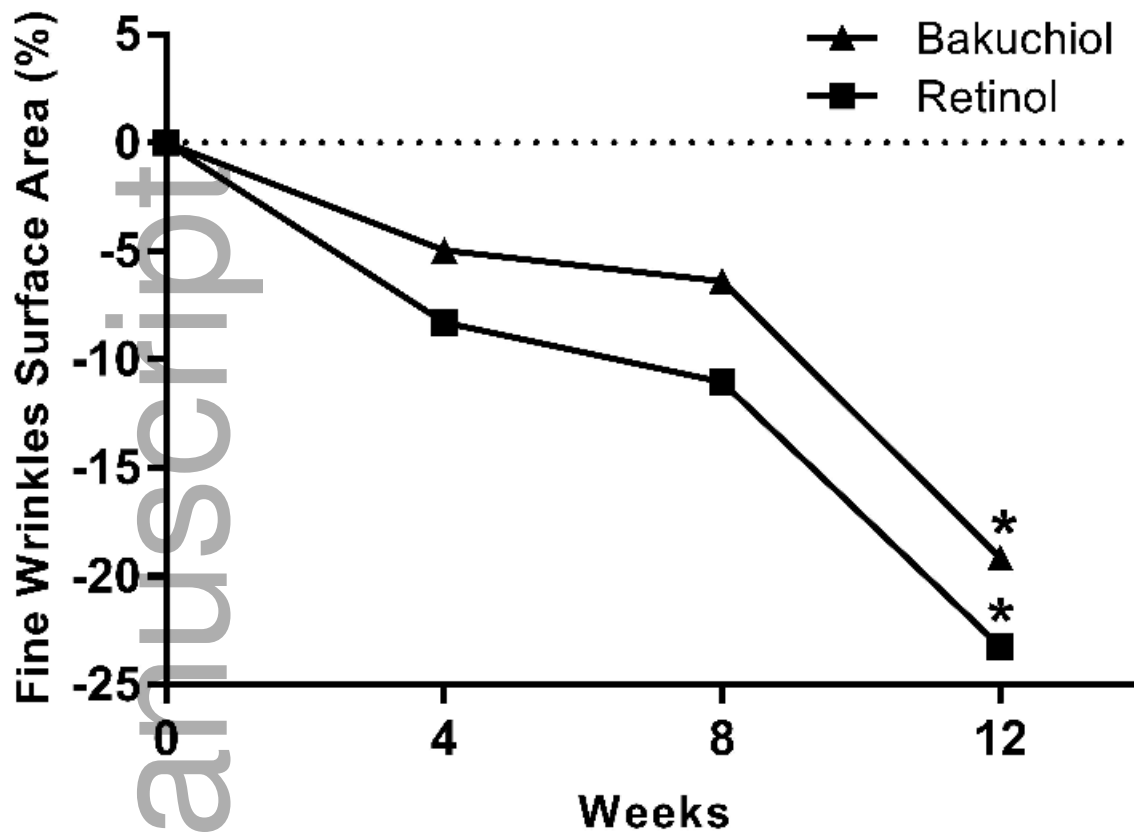
Figure 8. Facial images at baseline and after 12 weeks of topical application of (A) retinol and (B) bakuchiol.



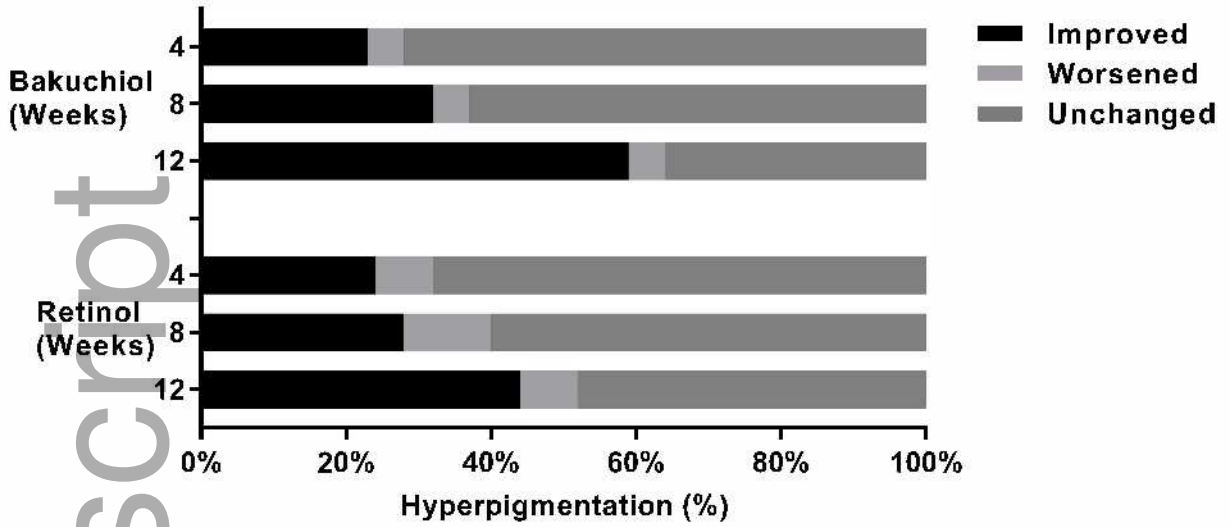
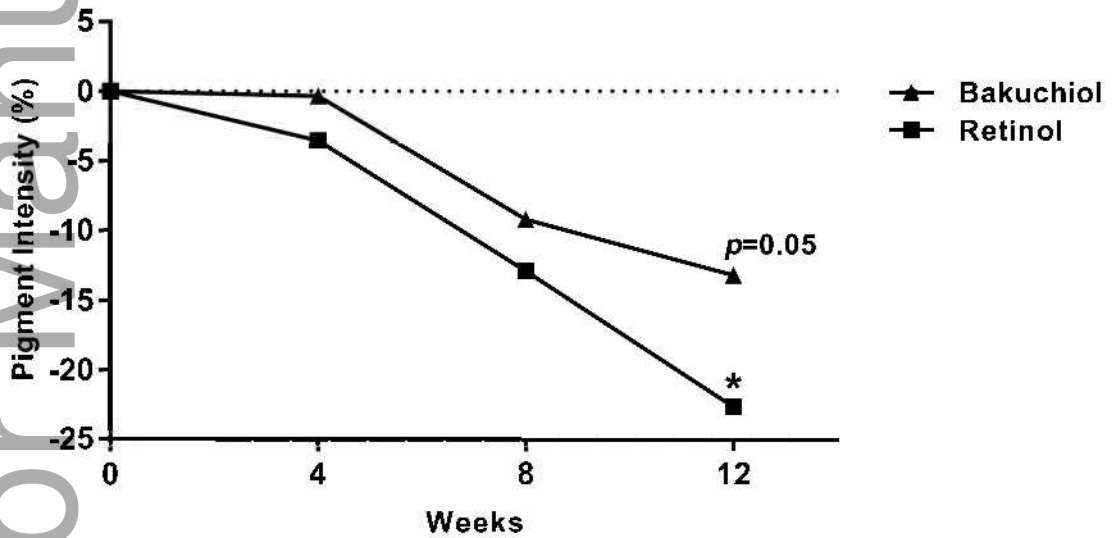
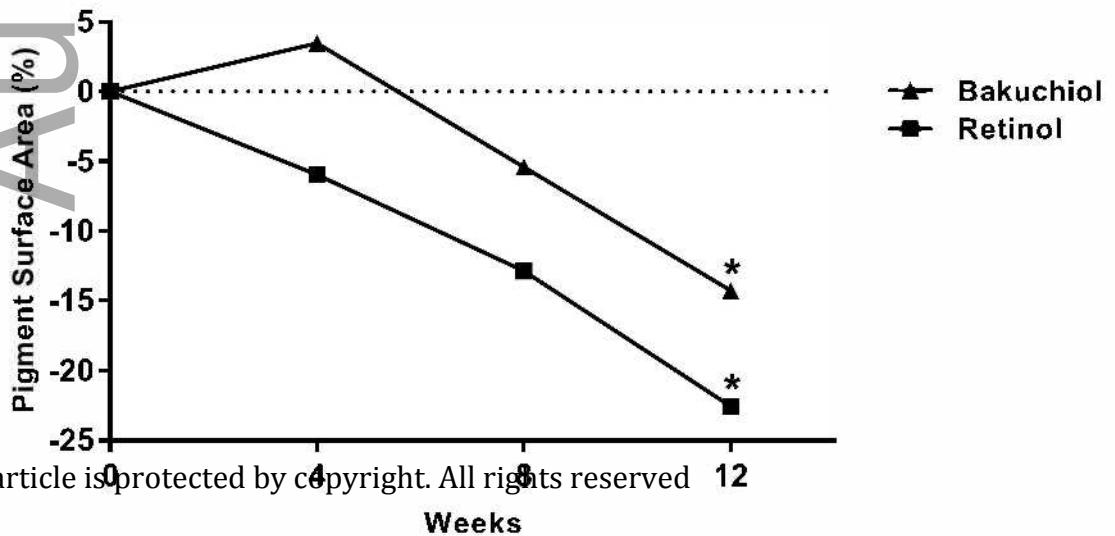
bjd_16918_f1.jpg

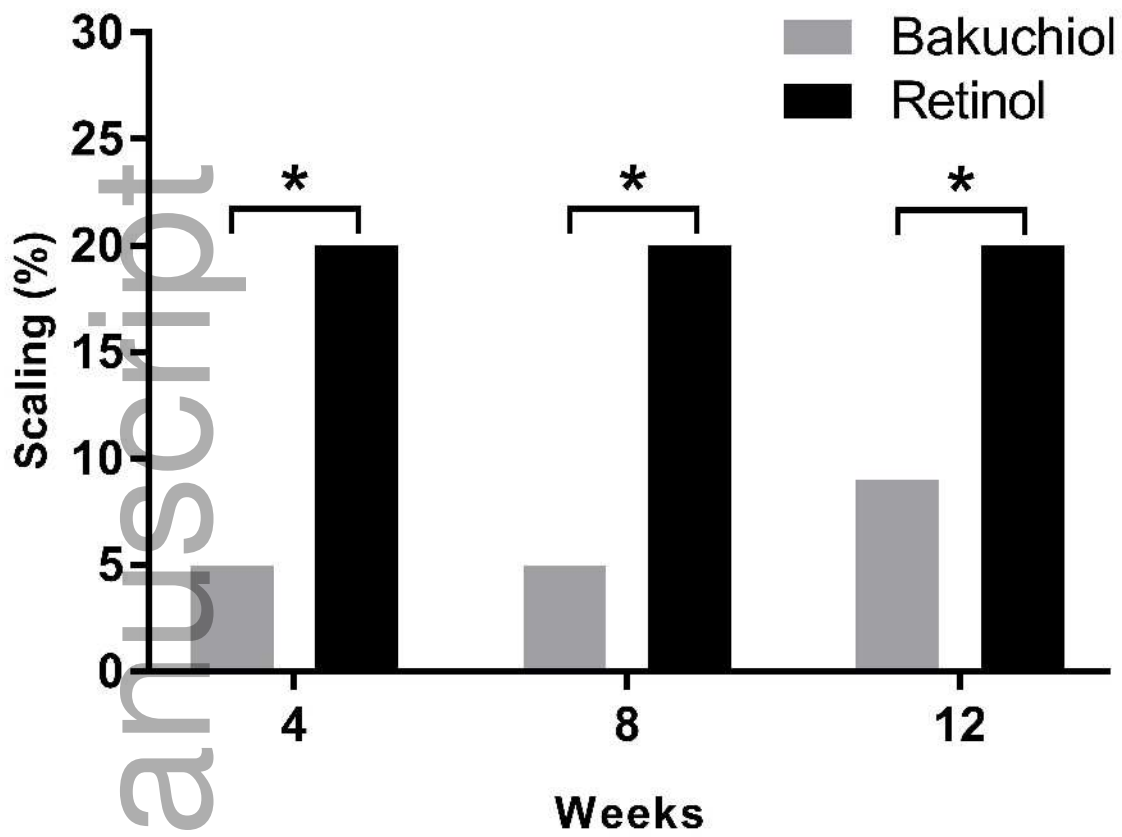


bjd_16918_f2.jpg

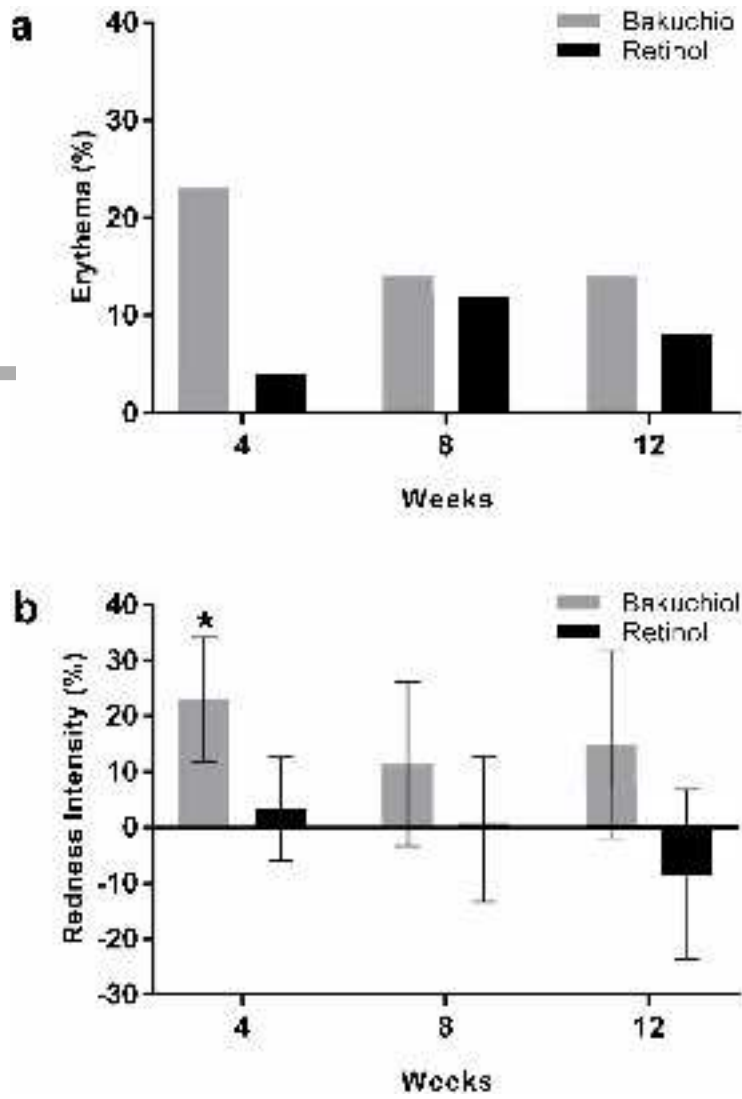


bjd_16918_f3.jpg

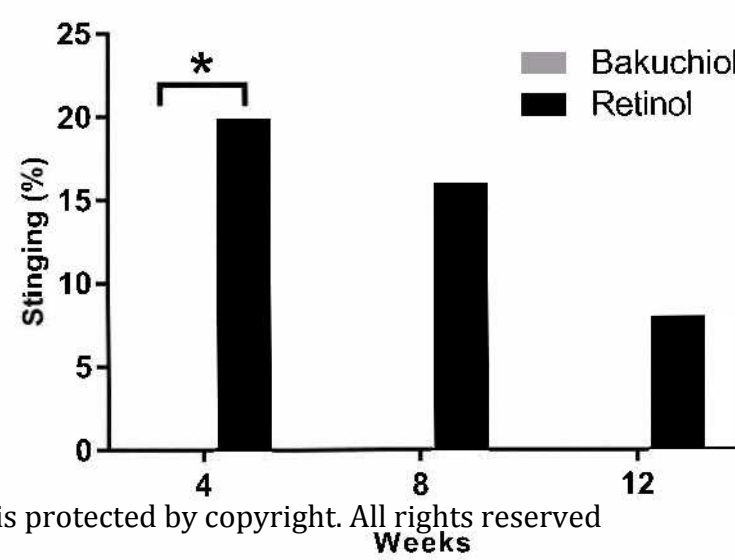
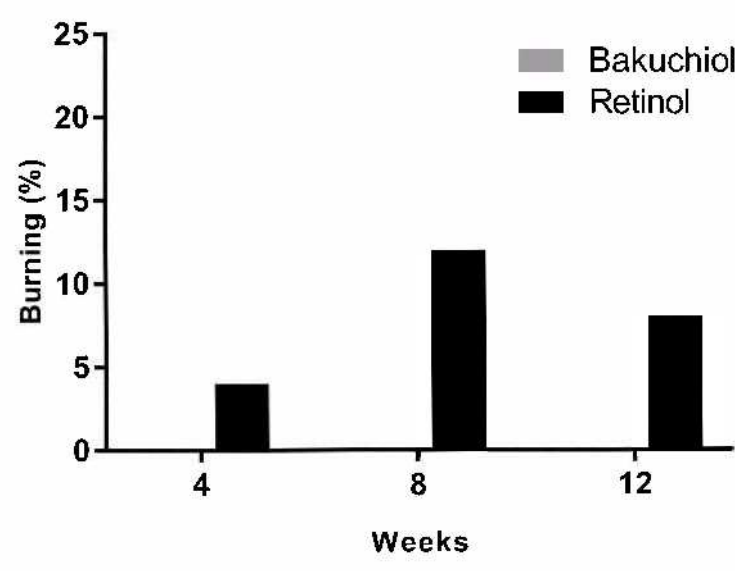
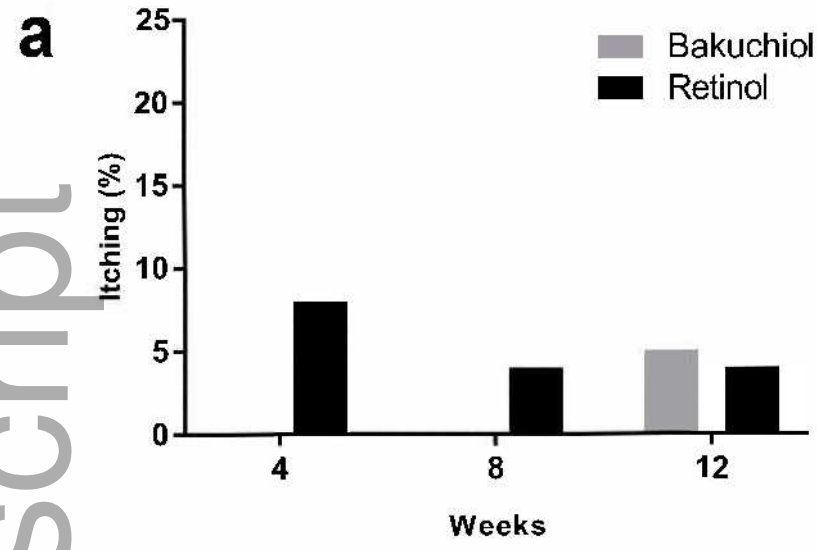
a**b****c**



bjd_16918_f5.jpg



bjd_16918_f6.jpg



a

Retinol

Subject 22



Baseline



12 weeks

Subject 32



Baseline



12 weeks

b

Bakuchiol

Subject 04



Baseline



12 weeks

Subject 37



Baseline



12 weeks

bjd_16918_f8.jpg