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The effects of topically applied glycolic acid and salicylic acid on ultraviolet radiation-induced erythema, DNA damage and sunburn cell formation in human skin☆

Andrija Kornhauser[a,1,*], Rong-Rong Wei[a], Yuji Yamaguchi[b], Sergio G. Coelho[b], Kays Kaidbey[c], Curtis Barton[a], Kaoruko Takahashi[b], Janusz Z. Beer[d], Sharon A. Miller[d], Vincent J. Hearing[b]

[a] Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, College Park, MD 20740, USA
[b] Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
[c] Ivy Laboratories (KGL Inc.), 505 Parkway, Broomall, PA 19008, USA
[d] Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD 20993, USA

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ABSTRACT

Background: α-Hydroxy acids (αHAs) are reported to reduce signs of aging in the skin and are widely used cosmetic ingredients. Several studies suggest that αHA can increase the sensitivity of skin to ultraviolet radiation. More recently, β-hydroxy acids (βHAs), or combinations of αHA and βHA have also been incorporated into antiaging skin care products. Concerns have also arisen about increased sensitivity to ultraviolet radiation following use of skin care products containing β-HA.
Objective: To determine whether topical treatment with glycolic acid, a representative αHA, or with salicylic acid, a βHA, modifies the short-term effects of solar simulated radiation (SSR) in human skin.
Methods: Fourteen subjects participated in this study. Three of the four test sites on the mid-back of each subject were treated daily Monday–Friday, for a total of 3.5 weeks, with glycolic acid (10%), salicylic acid (2%), or vehicle (control). The fourth site received no treatment. After the last treatment, each site was exposed to SSR, and shave biopsies from all four sites were obtained. The endpoints evaluated in this study were erythema (assessed visually and instrumentally), DNA damage and sunburn cell formation.
Results: Treatment with glycolic acid resulted in increased sensitivity of human skin to SSR, measured as an increase in erythema, DNA damage and sunburn cell formation. Salicylic acid did not produce significant changes in any of these biomarkers.
Conclusions: Short-term topical application of glycolic acid in a cosmetic formulation increased the sensitivity of human skin to SSR, while a comparable treatment with salicylic acid did not.
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1. Introduction

Formulations containing hydroxyacids (HAs) have been used in clinical practice for decades to treat a variety of skin conditions. The most prominent representatives in this class of compounds are glycolic, lactic and salicylic acids. They have been used, typically in concentrations ranging from 2 to 70%, to treat acne, ichthyosis, keratosis, warts, psoriasis, photoaged skin and other disorders. In the last two decades, αHAs have been widely incorporated into a variety of cosmetic products for daily use over long periods of time [1]. Currently, glycolic acid, lactic acid and salicylic acid (the latter is frequently called a βHA) are commonly used in cosmetics. One of the most cited beneficial effects of HAs is the reported improvement of photoaged skin. These improvements have been measured as decreases in roughness, discoloration, solar keratoses, overall pigmentation, and also as increased density of collagen and improved quality of elastic fibers [2]. The antiaging effects of HAs have become a prominent factor in cosmetic dermatology, leading to proliferation of HA-containing cosmetic products and skin care systems [3].

Questions have been raised about the safety of prolonged use of HA-containing products on sun-exposed skin. A number of clinical studies have reported that topical application of glycolic acid can

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* Corresponding author at: Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, 5100 Paint Branch Parkway, HFS-717, College Park, MD 20740, USA. Tel.: +1 703 941 4221.
E-mail address: akornhause@aol.com (A. Kornhauser).

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increase the skin's sensitivity to solar simulated radiation (SSR) [4,5], however most of these studies used vehicles which differ significantly from those used in cosmetic products. In addition, a single cutaneous marker for UV-induced damage was usually measured. In the few cases in which multiple endpoints were used, they were not evaluated in the same subjects [4]. In 1998, the Cosmetic Ingredient Review Expert Panel evaluated the available studies [6] and concluded that αHA ingredients are not mutagenic or carcinogenic, are not reproductive or developmental toxins, and are not skin sensitizers. To reduce the risk of skin irritation, the Panel recommended limitations on the concentration of αHA (less than 10%) and the pH (at or above 3.5) of cosmetic products containing αHA [6]. In addition, the Panel recommended that αHA-containing products should be formulated to avoid enhancing sun sensitivity and that consumers should be advised to use daily sun protection [6]. Salicylic acid is added to cosmetic products at concentrations usually less than 3% [7]. The Cosmetic Ingredient Review Expert Panel has similarly recommended that effects on the skin's sensitivity to sunlight be considered in the formulation and use of products containing salicylic acid and salicylates [7]. The doses of glycolic acid and salicylic acid used in this study reflect the doses actually used in cosmetic products.

The present study was devised to address still unanswered questions about the effects of HAs on the SSR-induced sensitivity of human skin. In particular, this study is the first to evaluate a number of prominent biomarkers for SSR-induced damage in the same subject, with each subject serving as his/her own control. This approach makes it possible to examine quantitative correlations among a number of independent biomarkers. In addition, the study was designed to determine the effects of both glycolic acid and salicylic acid on each subject's sensitivity to UV radiation.

2. Materials and methods

2.1. Test products

The test products investigated in this study resembled standard cosmetic formulations containing nonionic emulsifiers (Steareth-21, ceteareth-20 and PEG-100 stearate), glycerin, surfactants, thickeners (xanthan gum), and preservatives (parabens and diazolydinyl urea). These products had minimal absorption of UV and were formulated by and obtained from Cosmetech Laboratories, Inc. (Fairfield, NJ) [8]. One test product contained 10% glycolic acid (pH 3.5). A second test product contained 2% salicylic acid (pH 3.5). The third test product was a vehicle control and was the same as the other test products but lacked glycolic acid or salicylic acid. Prior to use, we confirmed the concentrations of the glycolic acid and salicylic acid and the pHs using a previously published analytical method [9]. All test products were supplied in identical containers labeled A, B, or C for double-blinded application.

2.2. Subject selection criteria

This study involved 14 healthy Caucasian volunteers of both sexes, ages 24–59 years. All were in good health and without any internal or dermatological diseases. Volunteers were excluded from the study if they had any skin conditions or allergies that might interfere with the study (e.g., atopic eczema or psoriasis). In addition, they were also excluded if they had used sunscreens or any α- or β-hydroxy acid containing preparations in the past 4 weeks that might alter their skin condition. All qualified candidates were of skin types II to III, as determined by the Fitzpatrick classification [10]. All subjects submitted the required questionnaires and signed the Clinical Investigation Consent Document. Prior to the beginning of the study, the attending dermatologist interviewed each subject about their health history and examined their back. The study protocol was approved by the FDA Research Involving Human Subjects Committee.

2.3. Product application

The test sites were located in the mid-back region of each subject. The designated test sites each consisted of a 7 cm × 14 cm rectangular area that was marked off by gentian violet pens and ink markers. There were four test sites on each subject, located on two opposite symmetrical areas of the mid-back (Fig. 1A). Three test sites served for test product application, while the fourth site served as a control without topical treatment. Within each test site, five subsites were designated for determination of the minimal erythema dose (MED) and two for obtaining biopsies. One additional subsite was assigned as an untreated, dark (unirradiated) control (Fig. 1A). To minimize potential effects of the site location on the outcome, the topical treatment applied at each test site was established using a randomization procedure for each subject.

The formulations were administered once daily (Monday through Friday) for each subject for 3.5 weeks by an investigator in the study facility. Each test product was dispensed from a 1-ml disposable plastic tuberculin syringe. The topical daily dose was 120 μl to each test site. The investigator uniformly rubbed in each product throughout the designated test site using a finger cot. The

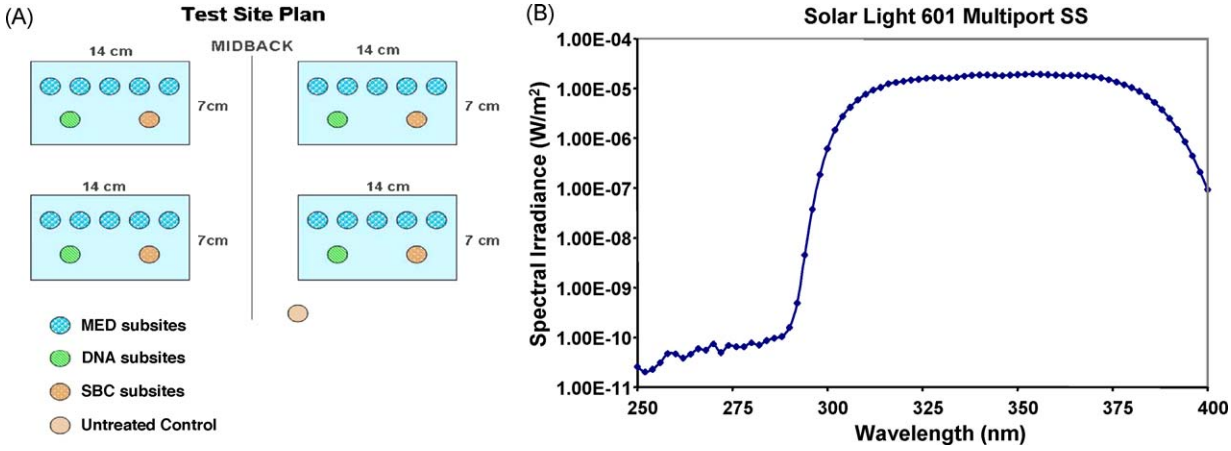

Fig. 1. (A) The test site plan for the four treatment areas with the respective subsite locations used in this study. (B) Emission spectrum of the SSR source. The signal below 300 nm is slightly above the noise level of the spectroradiometer but is very low, 6 orders of magnitude below the peak intensity level (note this is on a semi-log plot).