Archives of Dermatological Research
https://doi.org/10.1007/s00403-022-02514-0

ORIGINAL PAPER

Prospective, randomized, double-blind clinical study of split-body comparison of topical hydroquinone and hexylresorcinol for skin pigment appearance

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Received: 14 January 2021 / Revised: 24 November 2022 / Accepted: 7 December 2022

Abstract

Dyspigmentation is a common cosmetic concern in dermatology. Currently, the first line topical medication in the United States is hydroquinone. Hydroquinone use is associated with potential safety concerns including cytotoxicity to melanocytes, systemic absorption, metabolism in distant organs, and production of potentially carcinogenic metabolites. Hexylresorcinol is an ingredient that has been used in food preservation and as antiseptic has been shown to inhibit tyrosinase in vitro and has been studied as a novel skin-lightening agent. To perform a double-blind randomized split-body investigation of comparison on topical hexylresorcinol and hydroquinone on face and hands to assess for change in the appearance of skin tone and pigmentation. Thirty-two healthy female participants ages 35–65 (50.93 ± 7.37) years old with skin type I–IV were randomized to using either topical 1% hexylresorcinol or 2% hydroquinone on the left or right side of the face and corresponding hand over 12 weeks. The topical preparation was applied twice a day to assigned areas. Standardized photos were taken of the face and colorimetric measurements were taken of both sides of the forehead, cheeks and each hand at baseline (Day 0), week 4, and week 12. Of the 32 participants, 3 were lost to follow-up and the remaining were included in the final analysis. Pigmentation measured by colorimeter and clinical grading were significantly decreased at 4 and 12 weeks relative to baseline with no difference between the HR and HQ groups. No adverse effects were noted with either intervention. Hexylresorcinol 1% is well-tolerated and equivalent to hydroquinone 2% in reducing the appearance of facial and hand pigment. Further studies with an expanded population and longer time course are warranted.
Registration No.: NCT04345094.

Keywords Hexylresorcinol · Hydroquinone · Dyspigmentation · Topical · Facial · Pigmentation · Melasma

Introduction

Uneven skin tone and dyspigmentation are common concerns with photoaging and are accelerated by chronic exposure to the sun or ultraviolet light [1]. There can be many sources for dyspigmentation on the face including melasma or post-inflammatory hyperpigmentation (PIH) that may be the result of acne, ultraviolet damage, or hormonal changes. Dyspigmentation and hyperpigmentation is prevalent with one study estimating the prevalence of hyperpigmentation to be 46% due to melasma, 16% due to PIH, and 8% due to ephilides [2]. There is a female predominance for facial dyspigmentation and is more common in those that are 20–40 years of age [2]. Facial dyspigmentation reduces quality of life and is more emotionally distressing in women than in men [3]. When considering those with skin darker

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Published online: 11 December 2022

pigment, they are more prone to facial dyspigmentation that those with less skin pigment [4].

Currently, one the most common topical ingredients used for dyspigmentation is hydroquinone (HQ), a depigmenting agent that prevents melanin formation by inhibiting tyrosinase activity in the oxidative conversion of tyrosine to dopa during melanogenesis, making it an effective treatment for hyperpigmentation [5].

Despite hydroquinone's efficacy, it has had controversy and poses potential safety risks and has been banned for over-the-counter use in several countries like Japan, Egypt and the European Union. When dosed systemically in mice, hydroquinone has been associated with the development of thyroid follicular hyperplasia and hepatic adenomas [6] although similar findings have not been noted in humans. Nevertheless, hydroquinone is able to penetrate the skin when applied topically and absorption and urinary excretion has been estimated at 45% of the topically applied dose [7] with absorption into the systemic circulation with 30 min after forehead application. When used as a topical treatment, hydroquinone bypasses the liver by being absorbed in the blood and begins to metabolize in other organs [8]. Chronic metabolism of hydroquinone was shown to result in increased concentrations of reactive metabolites such as p-benzoquinone in the bone marrow in animals although similar findings have not been reproduced in humans. Although research is limited as to whether hydroquinone is directly carcinogenic, exposure to benzene was found to play a role in the development of leukemia due to chromosomal damage [9]. Apart from systemic absorption, hydroquinone can also lead to local ochronosis. Finally, hydroquinone is susceptible to photolysis and in an aqueous environment can produce hydrogen peroxide and superoxide anion radicals [10].

As a result of the controversies with hydroquinone, there has been heightened interest for the discovery of hydroquinone alternatives for reduction of skin pigment. An alternative ingredient that has emerged is hexylresorcinol (HR), a substance that may have potential use for evening skin tone and reducing the appearance of fine lines. HR is perhaps one of, if not the, most studied and well-known alkylresorcinols [11]. Alkylresorcinols are also found in nature; alkyl chains C17:0-C25:0 attached to the 5 position are abundant in whole-grain wheat and rye [12]. This ingredient is commonly found in the food industry for its use in food preservation [13] and has been used in medical applications as an oral and urological antiseptic [14, 15]. HR also has a variety of tissue engineering applications because in addition to acting as an antimicrobial and antiseptic, it can increase bone formation by suppressing nuclear factor kappa B signaling, and also promote wound healing by suppressing tumor necrosis factor-α and increasing vascular endothelial growth factor [16]. Hexylresorcinol (also known as 4-hexylresorcinol or 4-hexyl-1,3-phenylenediol) was found to mirror hydroquinone's effects on hyperpigmentation by reducing melanogenesis in primary human melanocytes, murine melanoma cells, and pigmented human epidermal equivalents in a randomized controlled study using in vitro models [17]. Also, it was found that inhibition is reversible and may provide better outcomes in skin lightening than topical use of hydroquinone [17].

HR reduces melanin production by modulating multiple sites in the melanogenesis pathway [11]. It is believed to involve inhibition of tyrosinase and peroxidase enzymes, down-regulation of tyrosinase protein expression in a dose-dependent manner, stimulation of glutathione and E-cadherin, reduction in DNA fragmentation, and inhibition of NF-κB [11, 17].

In light of these findings, the aim of this study is to assess how topical hexylresorcinol may compare to the use of hydroquinone in improvement in the appearance of ultraviolet light induced pigment on the face and dorsal hands, which are both sites that frequently undergo ultraviolet related damage. A secondary objective of this study was to assess the impact of topical hexylresorcinol on fine lines and wrinkles since previous studies with hexyresorcinol containing creams have been shown to improve fine lines [18, 19].

Methods

Participants

Participants ranged in age from 35 to 60 years old (50.93 ± 7.37 years old). Patients who met the inclusion criteria were recruited from dermatology clinics in the Sacramento area within a 50 mile radius. Recruitment and follow-up visits took place from August to December of 2019. The inclusion criteria included: females aged 35–65; individuals with Fitzpatrick skin type I–IV; and no known medical conditions that may interfere with study participation.

Skin types V and VI were excluded from this study as high degree of melanin content would serve as a confounder for fine line and wrinkle based assessments. Males were excluded to remove confounding effects of the effect of hormones as this was a pilot study. Patients were also excluded based on other criteria: individuals who have been on any medication that has caused a change in skin pigmentation; females who are pregnant or are actively breastfeeding or planning a pregnancy within two months; females who had started a new hormonal birth control agent or switched to a hormonal birth control agent within 60 days of study commencement, individuals who have had any medical or cosmetic procedure, such as laser resurfacing or plastic surgery to the test site, within the last 6 months; individuals who were using or had used hydroquinone or retinoids within

30 days of participation; and individuals who had used salicylic acid, beta hydroxy acid, vitamins A,C,E in the 14 days prior to first visit.

Study design and intervention

Each subject applied the topicals for 12 weeks with a baseline, 4 week and 12 week evaluations. Potential candidates were asked to not apply any skin care products for 24 h and not to cleanse their faces and hands for 12 h before the initial visit.

The sample size of 32 for this pilot study was based on > 90% power of detecting a 5% difference between HR and HQ on clinical grading while accounting for 20% dropout. Each subject was then randomized by blinded pre-allocated codes in blocks of 6 participants. 1% Hexylresorcinol—chemical name: 4-hexyl-1,3-phenylenediol (Synovea® HR 1%, Sytheon Ltd., Boonton, NJ) and 2% Hydroquinone (Sytheon Ltd.) were used in split-body experiment and provided in blinded form as A or B to the participants. Both the HR and HQ were formulated in the same vehicle. Participants were randomly assigned to apply left or right side of the body (e.g., Product A used on right side of face and right hand). Subjects were instructed to apply the product to once side of the face and hand and then to wash their hands before applying to the other side. Participants were directed to apply the topical agents twice a day (once in the morning and once at night after cleansing).

A clinical coordinator generated random allocation sequence a priori, enrolled participants, and assigned participants to randomized sided-ness of the split-body application of each intervention. Participants, clinical coordinator, and separate dermatologist evaluator were blinded to product identities until a third-party revealed to the research team the decoding of labels after analysis of data and assessment of outcomes.

Visit procedures

Colorimetric measurements were conducted with a SkinColorCatch (Delfin, Miami, FL) for pigment and redness. Standardized photos, tolerance assessment, and clinical grading of facial skin were performed as described below. Photos were obtained and a subjective skin assessment survey was also administered for each remaining visit. Colorimetric measurements and dermatologist evaluated clinical grading of pigment were the primary outcomes of this study. All additional assessments of erythema and wrinkles were secondary outcomes.

Skin color and wrinkle grading

Erythema and melanin (measurement of pigment) of skin of the face and hand were assessed and recorded through a skin colorimeter (SkinColorCatch, Delfin Technologies). Standardized photographs were taken of the participant's face with BTBP Mini Clarity 3D Facial Modeling and Analysis System (Brigh-Tex BioPhotonics, San Jose, CA) and evaluated.

Tolerability assessment

Subjects were asked on a scale of 0 (none) to 3 (severe) if there was itching, stinging, and burning. A board-certified dermatologist provided clinical grading on scaling, erythema, and pigmentation on right and left sides of the face utilizing the same 0 (none) to 3 (severe) scale.

Statistical analysis

Statistical analyses were performed using repeated measures paired *t* tests for parametric data (i.e., SkinColorCatch and camera output data) with correction for repeated measures with a Bonferroni correction. Wilcoxon signed-rank test was used for nonparametric measures (i.e., Clinical grading). *P* values < 0.05 were considered significant, while values between 0.05 and 0.1 were considered a trend. Means, medians, and standard errors were calculated as appropriate.

Results

The demographics of the study participants is shown in Table 1. Out of 37 participants screened, 32 participants qualified for the study and were enrolled and were randomized to whether they should apply product A or product B on left or right side of the body (hands and face)

Table 1 Demographics of the enrolled patients who finished study

Demographic factor	Hexylresorcinol-applied areas	Hydroquinone-applied areas
Age (years), mean ± SD	50.93 ± 7.37 years old	
Areas measured on SkinColorCatch:	Mean baseline pigmentation (± SD) on SkinColorCatch:	
Forehead	596.28 (± 38.74)	593.34 (± 35.39)
Cheek	447.72 (± 18.36)	590.72 (± 24.72)
Hand	632.54 (± 32.50)	635.96 (± 38.32)

respectively. Of the 32 enrolled participants, 3 dropped out (all lost to follow-up and unable to reach). CONSORT Flow diagram is shown in Fig. 1.

Facial clinical grading

Clinical grading of pigmentation was significantly reduced at 4 and 12 weeks relative to baseline as shown in Fig. 2. There was no statistical difference between the HQ and HR treated sites.

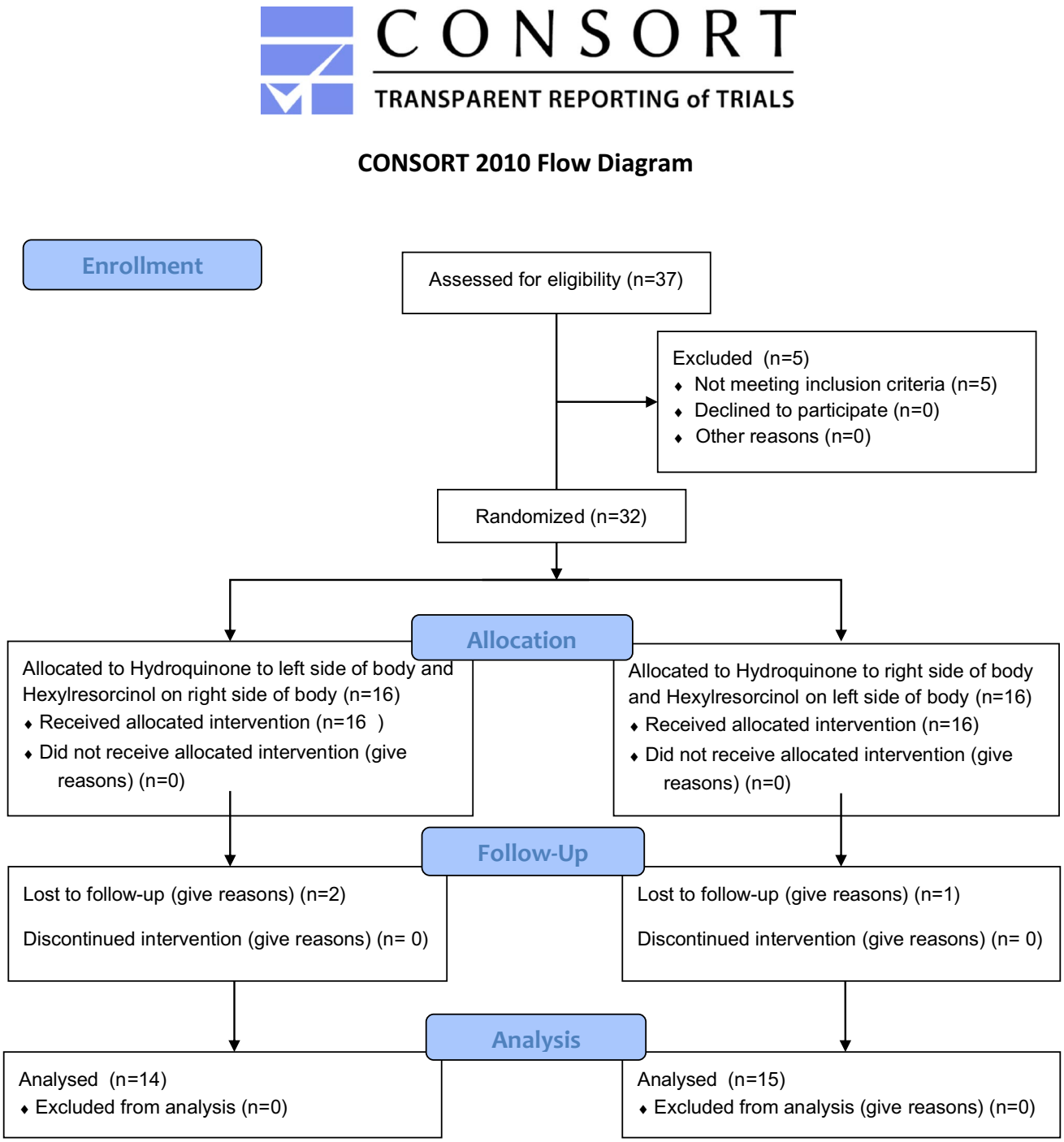

Fig. 1 CONSORT Flow Diagram

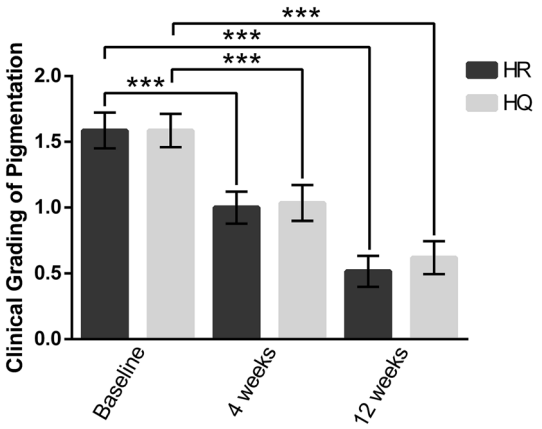

Fig. 2 Facial clinical grading of pigmentation of standardized facial images. *$p < 0.05$, ***$p < 0.001$

Colorimetric measurements

To be able to compare percent change in colorimetric measurements captured by SkinColorCatch for the HR-applied areas and HQ-applied areas, measurements at each timepoint were divided by their baseline values to calculate relative units. Relative pigmentation calculated by taking melanin measurement at each time point divided by melanin measurement at baseline, which was standardized to be 1. The same method applied to calculate relative erythema. Standard error of the mean (SEM) was also calculated. Pigmentation measured by skin colorimetry also was significantly decreased at 4 and 12 weeks relative to baseline and the amount of relative decrease was similar in areas subject to application of HR and HQ (shown in Fig. 3).

Erythema increased slightly at 12 weeks on the cheeks and forehead, while decreasing slightly on the hands in both HQ and HR applied areas (see Fig. 4).

Facial photographs of participants at baseline and week 12 are shown in Fig. 5.

Wrinkles

There was no improvement in the appearance of the wrinkle severity of the lateral canthi in comparison to baseline for either the HQ or the HR groups (Fig. 6).

Adverse effects

Two of the participants developed mild skin irritation (one with "bumps" on cheek and the other with a quarter-sized red, itchy rash at the temple) both on the side treated with hexylresorcinol application appearing after 3 months of use. In both cases, the skin irritation resolved with no sequelae.

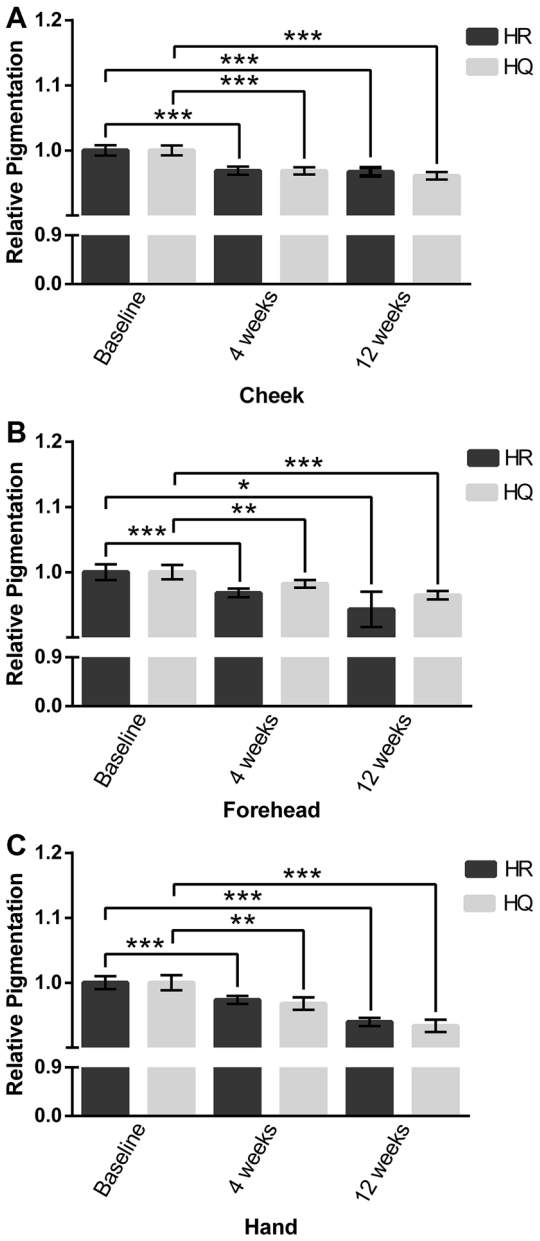

Fig. 3 Relative pigmentation (melanin measurement at time point / melanin measurement at baseline) measured by melanin parameter focally on the cheek (**A**), forehead (**B**), and hand (**C**). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

No other subjects reported irritation including itching, stinging, burning. No other signs of irritation were assessed by evaluator that developed after product usage.

Discussion

Results from this 12 week double-blinded randomized split-body clinical trial comparing the effect of topical hydroquinone (HQ) and topical hexylresorcinol (HR) on face and

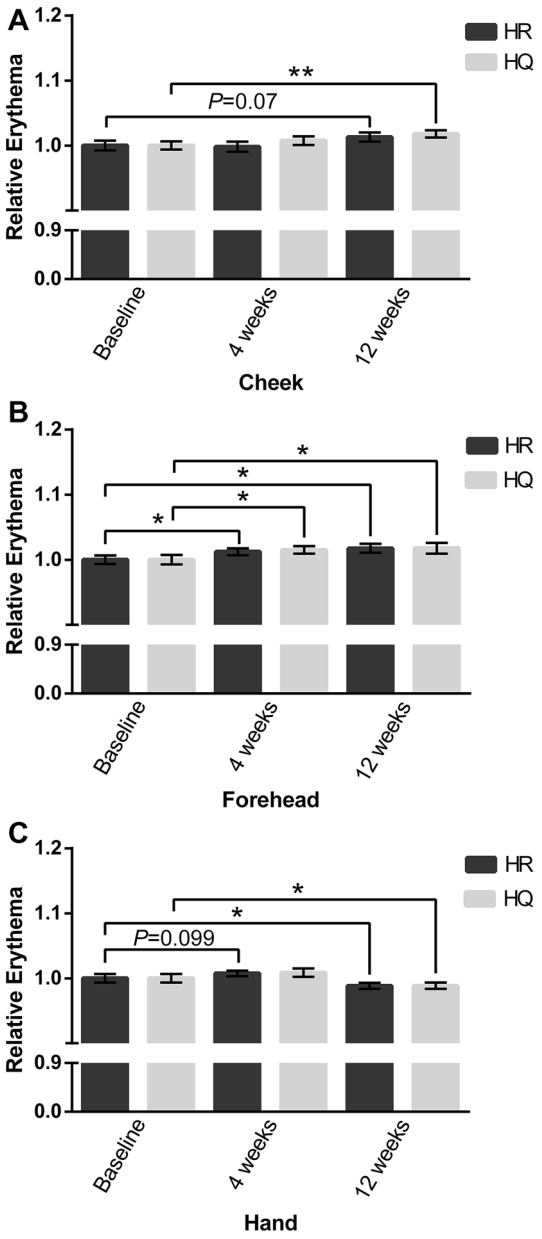

Fig. 4 Relative change in colorimetric erythema measured focally on the cheek (**A**), forehead (**B**), and hand (**C**). $*p < 0.05$, $***p < 0.001$

hands showed that both ingredients significantly decreased the appearance of pigment on clinical evaluation by dermatologist and objective pigment-based measurements. The two ingredients were comparable in magnitude of reduction of the appearance of pigment. Our results suggest that HR may serve as another option for improving the appearance of facial and hand pigment in comparison to HQ.

Our results are in concordance with other studies of HR. HR was shown to be a well-tolerated and efficacious HQ-alternative in previous studies with in vitro with primary human melanocytes, murine melanoma cells, and pigmented human epidermal equivalents and in vivo with randomized controlled trial with Chinese women with mild to moderate solar lentigines [17]. HR was shown to significantly reduce melanogenesis and to be a potent reversible inhibitor of tyrosinase while leaving the melanin synthesis machinery intact without toxicity to melanocytes [17]. Our study expands on these findings by directly comparing HR to HQ.

HR may serve as an alternative to HQ in several ways. HR does not have the same safety controversies as HQ and may also serve as a safer alternative as the concerns with ochronosis and absorption are not the same as HQ [20]. Furthermore, HR does not undergo photolysis or oxidation as easily as HQ and may allow for easier formulation and storage than HQ. Furthermore, hexylresorcinol has GRAS (Generally Recognized as Safe) status [21] and has been used for decades as an oral ingredient in lozenges [22].

There were few side effects noted in this study but there were two cases of mild irritation in the HR group that resolved. Although this was not directly assessed in this study, HR may have an exfoliative mechanism of action in addition to its known actions on the melanogenesis pathway. As a phenolic compound, one potential concern for HR is for xenoestrogen activity and endocrine disruption. However, a recent study showed no estrogen-like effects on neither ERα-positive cells nor in estrogen deficient mice [23], suggesting that HR does not act as a xenoestrogen. Nevertheless, this study serves as a pilot study and additional safety evaluation on long-term topical use of HR are warranted.

In addition to being a potent inhibitor of melanogenesis, HR may have additional benefits as an antioxidant, anti-inflammatory agent, and inhibitor of glycation. It inhibits melanogenesis by competing with tyrosinase enzyme's natural substrate L-tyrosine and is a more potent inhibitor than kojic acid or licorice extract [24]. It is able to inhibit reactive oxygen species formation from UV light exposure [11, 24]. Similar to other natural phenolic compounds, it has anti-inflammatory properties by strong inhibition of proinflammatory NF-kB [24]. It also inhibits the formation of advanced glycation end-products in vitro [11, 24].

We noted that there were only slight changes in erythema. This is not surprising since neither HR or HQ is expected to modulate erythema. The lack of changes in erythema suggest that neither the HR or HQ topical preparations were directly irritating to the face.

While this study did not show an improvement in lateral canthi wrinkles, a previous study with topical HR did record improvement in wrinkles of the lateral canthi with application over 8 weeks [25]. However, the reported data were different between the studies. The previous study reported the response as the percent of people improving rather than individually following each wrinkle. In our study, improvement of wrinkles was measured individually and quantitatively,

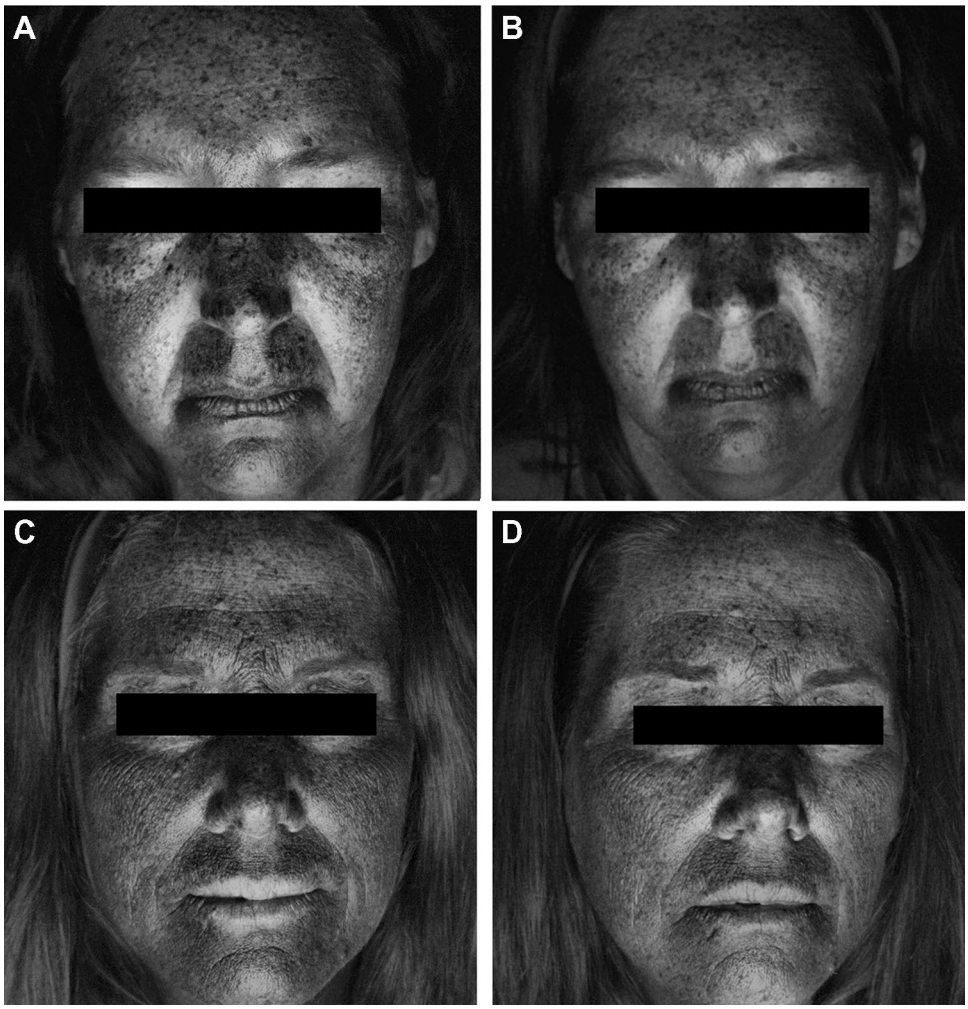

Fig. 5 Clinical photos of participants at baseline (**A** and **C**) and at week 12 for (**B** and **D**)

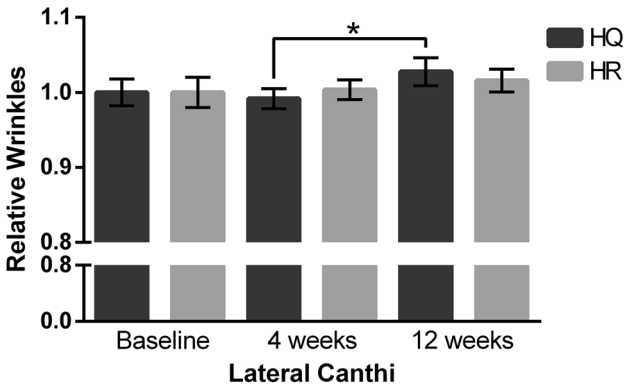

Fig. 6 No improvement in the appearance of the wrinkle severity of the lateral canthi in comparison to baseline for either the HQ or the HR groups

and it may account for the differences in the reporting between the two studies [25].

There were several limitations to this study. This study is pilot in nature and future studies are needed to follow-up on the findings reported here. However, the power of our study is enhanced by the split-body design and by the fact that we also evaluated the dorsal hands in addition to the face so that multiple measures were evaluated. The measurements were made on the lateral forehead and the lateral cheeks but the inclusion of the right and left hands makes cross-contamination even less of a risk and offers more validity to our findings. A second limitation is that we restricted the population to those aged 35–60 years of age without acne and it is unclear how the findings here may extend to use in those with post-inflammatory hyperpigmentation in acne or in those that are older and may have more sun damaged or sensitive skin. This study was limited to 12 weeks in duration and future studies are needed to assess the longer term tolerance and impact of topical HR. This study was limited to skin types I–IV and our conclusions cannot be extended to those with skin types V or VI without further study. The focus of this study was on UV induced dyspigmentation; however, there are other sources for dyspigmentation such as hormonal etiology that should be explored in future studies.

Overall, we showed that HR 1% is similarly efficacious to HQ 2% in reducing the appearance of facial and hand pigmentation with 12 weeks of use. We hope that our findings will promote future studies of HR as a suitable ingredient to address hyperpigmentation and dyspigmentation.

Funding Funding for this study was provided by Sytheon Ltd. The funding source had no role in the collection of data, analysis, manuscript writing, or in the decision to publish.

Declarations

Conflict of interest RKS serves as a scientific advisor for LearnHealth, Codex Beauty, and Arbonne and has received honoraria from Burts Bees, Regeneron, Nutrafol, Sanofi, Galderma, Fotona, Incyte, Novozymes, Novartis, Leo, UCB, Sun Pharma, and Abbvie.

IRB IntegReview has approved the study Approval #HHSOL-1495–125.

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