A randomized, double-blind, placebo-controlled, comparative study

The safety and efficacy of 0.25% tetrahydrocurcumin (tumeric) cream as depigment agent against 4% hydroquinone cream

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ABSTRACT: Hydroquinone, which is extensively used in the treatment of hyperpigmentary disorders is associated with known side effects. Safer, natural depigmenting actives are therefore being explored. A randomized , placebo controlled study in 50 human subjects, showed that the depigmenting effects of 0.25 percent tetrahydrocurcumin cream and 4 percent hydroquinone cream were comparable in a four week trial. No adverse reactions were noted from 0.25 percent tetrahydrocurcumin cream, while mild to moderate adverse effects were observed with 4 percent hydroquinone cream. 0.25 percent tetrahydrocurcumin cream is therefore an effective and safe alternative to 4 percent hydroquinone cream in depigmenting formulations.

INTRODUCTION

Depigmenting agents, also known as whitening agents or skin tone lighteners, are products used to lighten or "whiten" the skin. In medical practice, such agents are used by dermatologists in the treatment of pigmentation disorders, such as post inflammatory hyperpigmentation secondary to contact dermatitis; widespread *tinea corporis*; disseminated lesions of scabies; conditions like melasma or chloasma; or as a treatment option for patients with widespread, treatment-resistant vitiligo, primarily as a measure to depigment residual normal skin (1). In cosmetics, such agents serve as active ingredients that reduce localized hyperpigmentation, age spots, and sun damage, and help to effect a lighter skin tone. Hydroquinone, an inhibitor of tyrosinase, the rate limiting enzyme in melanin biosynthesis, has been used as an active ingredient in skin tone lightening formulations for over fifty years. The number of cosmetic products containing hydroquinone in the market has escalated, and consumers tend to self-administer these without adequate knowledge of the product and its possible complications and necessary precautions. The incidence of adverse reactions to hydroquinone, including allergic and irritant contact dermatitis; leucoderma, and on prolonged use, an irreversible and unsightly condition, called ochronosis, acneiform lesions, and cancer (2) has therefore become noticeable. These undesirable side effects associated with its use, have resulted in regulatory restrictions, and triggered an increasing interest in safer natural alternatives.

Tyrosinase inhibitors and other agents that affect the melanin biosynthesis pathway are widely distributed in plant materials. These natural actives are safer alternatives to hydroquinone, for use in topical skin lightening compositions, and may offer additional functionalities, as sunscreen boosters, moisturizers, or "anti-aging" ingredients. One such ingredient is derived from the "curry" spice, turmeric.

When natural yellow curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) from *Curcuma longa* (turmeric) roots are hydrogenated, a colour free mixture of Tetrahydrocurcuminoids is obtained (3). This natural blend is valued as a topical antioxidant and antinflammatory agent, with superior free radical scavenging and lipid peroxidation inhibition efficacy as compared to vitamin E. Studies indicate that Tetrahydrocurcuminoids, particularly ultrapure Tetrahydrocurcumin (trademarked SabiWhite®, Sabinsa Corporation) efficiently inhibit tyrosinase (4). The parent compound, Curcumin, is a potent inhibitor of protein kinase C,

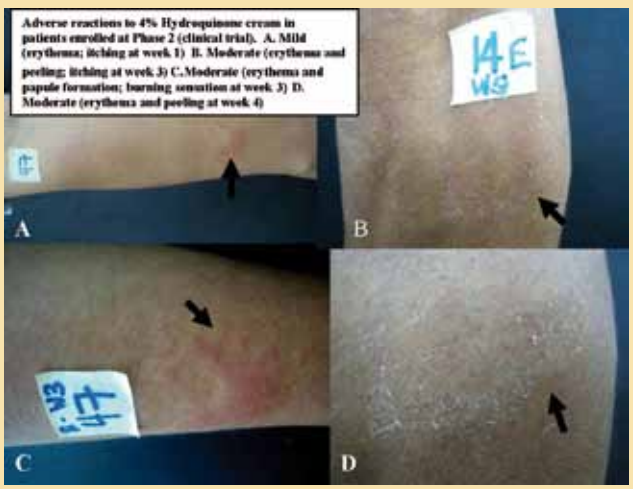

Figure 1.

EGF-receptor tyrosine kinase and IkappaB kinase, and is an effective "bioprotectant" antioxidant (5). Laboratory studies revealed that SabiWhite® is an effective skin lightening agent with multifunctional topical benefits. The extract is safe for topical use with no irritant or sensitization side effects. Ingested curcumin is metabolized into tetrahydrocurcumin *in vivo*. Thus tetrahydrocurcumin is a natural biotransformation product of curcumin.

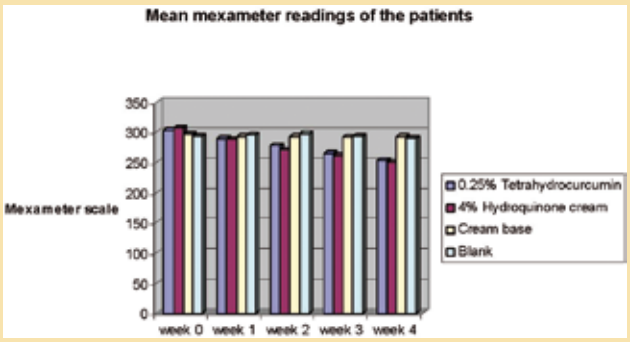

Figure 2.

In vitro studies revealed that SabiWhite® offers effective topical antioxidant "bioprotectant" action, efficiently preventing the formation of free radicals, while quenching pre-formed ones as well. This dual action protects the skin cells from damage by UV radiation and the resulting inflammation and injury, with far reaching beneficial effects on overall health and well being. SabiWhite© efficiently inhibits tyrosinase, and is more effective than kojic acid, 40 percent glabridin (licorice root extract), and vitamin C (ascorbic acid), that are used as natural depigmenting agents, as documented in *in vitro* studies (6). A clinical study was therefore effected, to validate the efficacy of SabiWhite® as a depigmenting agent.

STUDY OBJECTIVE AND DESIGN

The objective of this study is to determine the safety and efficacy of 0.25 percent Tetrahydrocurcumin (THC) cream as a topical depigmenting agent in comparison with 4 percent hydroquinone (HQ) cream in healthy volunteers, using a randomized double-blind placebo controlled trial by quantitatively measuring the depigmenting effect of both substances using a mexameter. Adverse reactions were also recorded.

The study consisted of two phases. A patch test phase (Phase 1) and a clinical trial phase (Phase 2). 50 healthy Filipino volunteers, in the age group of 21 to 45 years, with mexameter readings equal to 200 units or more, taken at the extensor aspect of the forearm, were enrolled in a 48 hour I.Q. Chamber Closed Patch testing. In Phase 1, all subjects were given 0.25 percent Tetrahydrocurcumin cream, 0.5 percent Sodium lauryl sulfate as positive control and water as negative control. The I.Q. Chambers with the test substances were applied at the back (scapular area) of the panelists. The first reading of the patch test was read after 48 hours and a final reading was done after 72 hours. Recording of patch test results was based on the reading used by International Contact Dermatitis Research Group. No subject developed any of the adverse reactions and all proceeded to Phase 2 (Clinical Trial Phase). The Phase 2 trial was a randomized, double-blind, placebo-controlled comparative study on the safety and efficacy of 0.25 percent Tetrahydrocurcumin cream as a depigmenting agent against 4 percent Hydroquinone cream. The percentage of actives in the test cream formulations corresponded with the levels normally used in commercial formulations.

MATERIALS AND METHODS

0.25 percent THC cream was manufactured by Sami Labs Ltd, Bangalore, India and 4 percent HQ cream was compounded by a licensed pharmacist in the Philippines. Both test products were white in colour with similar consistency.

The cream base and the non-treated site served as negative controls. The test products were prepared in four identical white jars (10 grams) and were coded using a computer-generated random allocation scheme. Each subject was given a kit containing four coded jars with a standard template. The subjects were required to visit twice daily at 8am and 5pm during the 4 week period. Prior to the application of the test products, the extensor aspect of the right forearm of each subject was washed with mild soap and water and towel dried. The test products were applied by the investigator using a standard template (one product on each area) touching the reference point (wrist bone) following the order of the coded jars. Subjects were advised to avoid sun exposure, particularly, the extensor aspect of the right forearm. At every visit, the investigator monitored and recorded any adverse reactions using a four-point scale. In this standard scale, a score of "0" corresponds to no adverse reactions; "mild" indicates erythema, itching, dryness, scaling, or stinging; "moderate" indicates burning, tenderness, or pain, with or without erythema, itching, dryness, scaling or stinging; "severe" indicates vesicles, erosion, excoriation (crusting), with or without erythema, itching, dryness, scaling or stinging, burning , tenderness and pain.

Three mexameter readings per test site were taken during each visit and the average was recorded as the final mexameter reading per week, per test site. Using a rectangular template touching the reference point (wrist bone), the sensor of the mexameter was placed at the middle of the opening to make sure the area read was consistent at every visit. Readings were taken on the initial visit (baseline), and on weeks 1, 2, 3 and 4. A decrease in the mexamater value of at least 10 units from baseline was indicative of depigmenting efficacy.

Clinical photographs were taken using a Nikon camera with medical Nikkor lens during the beginning of the study period and in the 4th week. These photographs were also used to document any adverse reactions. Photographs were taken using a black background in a room well lighted with white light. Adverse reactions to the test products administered were monitored and recorded using a four point scale at weeks 1, 2, 3 and 4. All adverse reaction/s were treated accordingly, when necessary, and application of the test product was discontinued if a score of 3 (severe) was noted.

RESULTS AND DISCUSSION

None of the 50 panelists enrolled in Phase 1 of the study showed any adverse reaction to 0.25 percent THC cream. The Primary Irritation Index score of 0.25 percent THC cream is 0, and under the National Institute for Occupational Safety and Health Interpretation of Skin Ratings, the cream is classified as non-irritant, and safe for intact human skin contact.

In Phase 2., a significant decrease (as determined by paired T-test) in the mean mexameter values for both THC and HQ treatments were noted as early as in week 1, and continued through week 4). (p value < 0.001) There was however no significant difference in mean Mexameter readings between the 0.25 percent THC cream and 4 percent HQ cream treated sites. No adverse reactions were noted with 0.25 percent THC cream however for subjects that used 4 percent HQ, 18 percent developed mild adverse reactions as early as week 1. An additional 10 percent developed mild adverse reactions, and another 10 percent developed moderate adverse reactions, in the second week. By the end of the study, 50 percent of these subjects experienced adverse reactions; 30 and 20 percent respectively graded as mild and moderate. The mean mexameter readings showed that 0.25 percent THC cream has significant whitening efficacy as compared to the negative control groups. This evidence supports the preliminary *in vitro* data which showed that THC efficiently inhibits tyrosinase, the rate limiting enzyme in melanogenesis.

Mean mexameter readings of 4 percent HQ cream versus 0.25 percent THC cream treatments were comparable throughout the duration of the study. No adverse reactions were noted with 0.25 percent THC cream. Increasing incidence of adverse reactions to 4 percent HQ cream occurred over time, with 50 percent of the subjects being affected towards the end of four weeks. 0.25 percent THC cream is therefore an effective and safe alternative to 4 percent HQ cream in depigmenting formulations.

Figure 3. Turmeric rhizome.

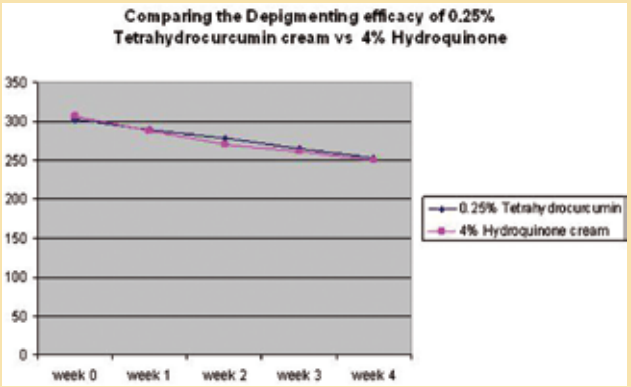

Figure 4.

CONCLUSIONS

0.25 percent THC cream is therefore an effective and safe alternative to 4 percent HQ cream in depigmenting formulations, as demonstrated in this preliminary four week study, in healthy subjects with mexameter readings of 200 units or more (taken at the extensor aspect of the forearm).

A longer study of 12 weeks duration would enable documenting maximum depigmentation effects, in healthy individuals. In view of the promising results of this pilot study, a 12- week randomized, double-blind, placebo controlled trial comparing the efficacy of 0.25 percent THC cream versus 4 percent HQ cream in the treatment of patients with melasma or post-inflammatory hyperpigmentation, and a 4-week controlled use study, monitoring actual use of THC cream on the face and body, as skin lightener in a larger population, are being planned.

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