Comparison of 2% deoxyarbutin and 4% hydroquinone as a depigmenting agent in healthy individuals: A double-blind randomized controlled clinical trial

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ORIGINAL CONTRIBUTION

Comparison of 2% deoxyarbutin and 4% hydroquinone as a depigmenting agent in healthy individuals: A double-blind randomized controlled clinical trial

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Abstract

Background: Hydroquinone, which is considered the gold standard skin depigmenting agent, has been associated with multiple side effects. Lately, deoxyarbutin has been suggested to be an alternative of hydroquinone with better safety profile.

Objective: To compare the depigmenting effect of 2% deoxyarbutin and 4% hydroquinone sera.

Methods: This double-blind randomized controlled study was done on the right and left arms of healthy participants. Subjects were instructed to apply either 2% deoxyarbutin or 4% hydroquinone serum on each arm, which were randomly labeled as group A and B, every day for 12 weeks. Chromameter and mexameter analysis were done every 2 weeks to assess the color change. Paired and independent *t*-tests were used to assess the color change within and between both groups, respectively.

Results: A total of 59 females participated in this study. Both groups showed significant improvement in skin depigmentation as shown by the chromameter (increase in L^* value) and mexameter (decrease in melanin index) analysis at the end of the study ($p < 0.05$). No significant difference in both parameters was observed between both groups ($p > 0.05$). No side effects were reported in either groups.

Conclusion: 2% deoxyarbutin and 4% hydroquinone sera showed comparable depigmenting efficacy.

KEYWORDS
chromameter, deoxyarbutin, depigmenting agent, hydroquinone, mexameter

1 | INTRODUCTION

Skin whitening products market is a vast and rapidly growing industry which is estimated to worth US$ 31.2 billion by 2024.[1] The desire to obtain a fair complexion to achieve a certain standard of beauty has been in practice for ages in various countries and cultures.[2] In addition, this appearance also serves as an expression for the "good," "holy," and virtuous attributes in multiple religious worldviews.[3] As a result, it is not surprising that attempts to make the skin fairer, both through certain practices or products, continue to thrive and expand up until now.

Unfortunately, the vast growth of skin whitening market is also accompanied by an increasing number of side effects resulting from the application of such products. Hydroquinone is a type of whitening products with high efficacy and is widely regarded as the gold standard topical treatment of hyperpigmentation disorders.[4,5] However, it has also been associated with side effects such as irritation, leukoderma, and even a potential risk of carcinogenesis.[6] Thus, once was the most widely used whitening agent, hydroquinone is now banned for cosmetic use in European countries, the United States of America, and some Asian countries.[7] Furthermore, these adverse effects have also caused scientists and healthcare practitioners to reconsider its use in hyperpigmentation disorders, prompting a quest to find an alternative skin depigmenting agent.

Deoxyarbutin is a derivative of arbutin, which is a glucoside derivative of hydroquinone.[8] It can be found naturally in fruits such as pear and cranberry.[9] Some studies have suggested its melanogenesis inhibitory effect and superior safety profile relative to hydroquinone.[8,10] However, clinical trials assessing the whitening effect of deoxyarbutin are still scarce and limited in sample size and assessment methodology.[10,11]

This study aims to assess the whitening effect of 2% deoxyarbutin serum in comparison with hydroquinone as a depigmenting agent in healthy population.

2 | METHODS

2.1 | Study design

This double-blind randomized controlled clinical trial was done at Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia, between November 2019 and March 2020.

2.2 | Participant

Healthy females aged 25–45 years with Fitzpatrick skin type III and IV without history of intense UV exposure were included in this study. Subjects with diabetes, cardiovascular disease, history of skin cancer, application of topical or systemic agents that contained hydroquinone, deoxyarbutin, or any antioxidant agents in the past month, hormonal contraception, active dermatoses, and allergic reaction to the study materials were excluded. Participants were only included if they agreed to comply to the study protocol and sign an informed consent form.

2.3 | Study protocol

Two sera each containing 4% hydroquinone and 2% deoxyarbutin (PT. LipiWih SynergyLab), randomly labeled as serum A and serum B by an independent party, were applied to the volar aspect of either the right (serum A) and left (serum B) lower arm. The volar instead of the dorsal side was used as the former due to its location being more protected against UV radiation would allow a more accurate analysis and better estimate of the facultative skin color. Both sera were identical in color and consistency and were put in similar containers. A special sleeve made of elastic material consisted of two holes each sized 4 × 4 cm was placed on each arm in order to ensure consistent application sites: Hole A was placed 4 cm from the cubital fossa, and hole B was placed 4 cm from hole A. Two drops of each serum were applied once daily before bedtime to the area enclosed by the special sleeve for 12 weeks. Neither the examiner nor the participants knew the content of the serum applied. In addition, the patients were instructed to apply SPF 35 sunscreen in the morning and avoid using other applied lotions or creams. The study flow is depicted by Figure 1.

The skin brightness of the subjects was assessed every two weeks for a total of eight weeks (T0, T2, T4, T6, and T8) by using Chromameter (Konica Minolta) and Mexameter® MX 16 (Courage+Khazaka, Electronic GmbH). In addition, standardized photographs under standard lighting were taken using 16.1-megapixel Canon® digital camera from a distance of 20 cm at each meeting. The occurrence of adverse events was also recorded.

Ethical clearance had been obtained from the local ethical board committee prior to commencing the study. This study was done according to the Declaration of Helsinki guideline.

2.4 | Quantitative skin color examination

2.4.1 | Chromameter

This instrument worked by emitting three wavelengths of 450, 560, and 600 nm to the skin surface. Once the light was reflected back and absorbed by the probe of device, three parameters, L^* (black-white spectrum), a^* (red-green spectrum), and b^* (blue-yellow spectrum), were produced. The L^* value represented skin brightness and ranged from 0 (black) to 100 (white).[12] In this study, we focused our assessment on the L^* value as skin brightness was the main objective of this study.

2.4.2 | Mexameter

The probe of this device emitted light at 568 (green), 660 (red), and 880 (infrared) nm on an area of 20 mm^2. A computerized assessment of the reflected light eventually resulted in melanin index (MI), which denoted the skin melanin level, and erythema index (EI), which referred to cutaneous hemoglobin content). The MI was determined through analysis of the red and infrared wavelengths where higher value corresponded to higher melanin level (darker skin).[13]

FIGURE 1 Study flowchart

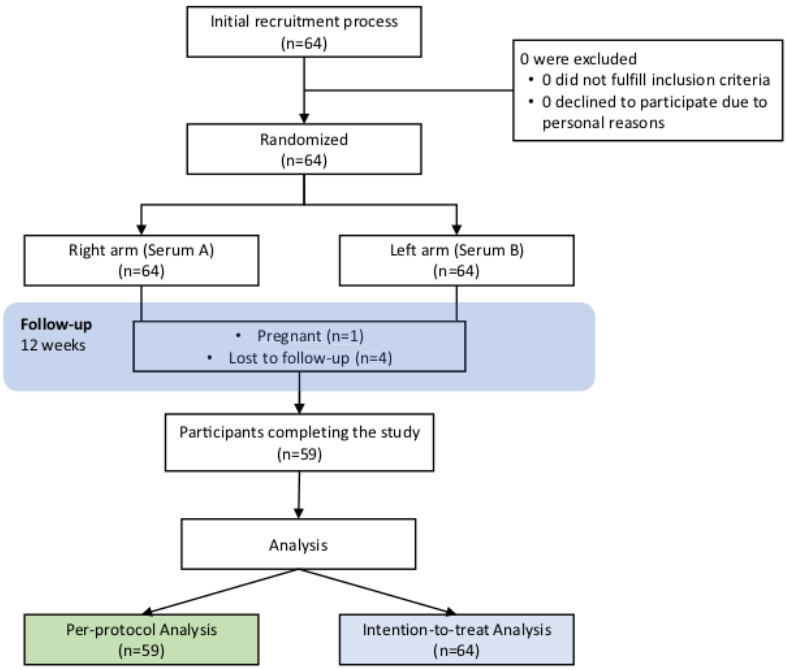

TABLE 1 Demographic characteristics

Variable	Total
Age (years)	
Mean ± SD	29.4 ± 10.1
Range	25–45
Gender	
Male (%)	0 (0)
Female (%)	59 (100)
Fitzpatrick skin type	
III (%)	25 (42.4)
IV (%)	34 (57.6)

2.5 | Safety profile assessment

The occurrence of erythema, edema, stinging sensation, itching, and hyperpigmented lesions was assessed during each follow-up period. In addition, the participants were allowed to contact the researchers anytime to report the occurrence of such complaints.

2.6 | Statistical analysis

Standard descriptive analysis for population demographic data and characteristics was conducted by calculating the number of values, mean, standard deviation, and percentage. Intragroup analysis of change in skin brightness over time was assessed using paired *t*-test. Unpaired *t*-test was used to compare the difference in skin brightness between the 4% hydroquinone and 2% deoxyarbutin groups. All analysis was performed for both per protocol (PP) and intention-to-treat (ITT) analysis using SPSS version 22 (SPSS Inc.).

3 | RESULT

3.1 | Demographic data

During the recruitment process, out of 64 participants enrolled, 5 subjects dropped out (4 were lost to follow-up and 1 subject became pregnant during the study) leaving a total of 59 females (Figure 1). The demographic characteristics of the participants are shown in Table 1. The majority of participants were between 25 and 35 years old (40 subjects, 67.8%). Overall, 42.4% of the participants had a Fitzpatrick skin type III and 57.6% had a Fitzpatrick skin type IV.

3.2 | Efficacy analysis

The average L^* values and MI of each group at baseline, during, and after therapy are presented in Table 2. There was no significant difference in L^* values and MI between both groups at baseline, during, and at the end of the study ($p > 0.05$). The L^* values and MI of the deoxyarbutin and hydroquinone group during and after the study were significantly lower compared to the baseline data of each

TABLE 2 L^* values and melanin index of both groups at baseline and each follow-up session

	Melanin index (mean ± SD)			L^* value (mean ± SD)		
Time	Deoxyarbutin	Hydroquinone	*p*-Value	Deoxyarbutin	Hydroquinone	*p*-Value
Week 0	246.88 ± 57.90	244.22 ± 55.61	0.695	52.41 ± 3.41	52.58 ± 3.53	0.886
Week 2	238.61 ± 56.57*	233.79 ± 54.57*	0.718	52.80 ± 3.27*	52.85 ± 3.42*	0.841
Week 4	230.17 ± 51.66*	234.00 ± 56.74*	0.369	53.00 ± 3.29*	53.06 ± 3.33*	0.744
Week 6	223.42 ± 51.13*	224.34 ± 55.76*	0.444	53.24 ± 3.30*	53.25 ± 3.41*	0.824
Week 8	213.00 ± 47.11*	217.42 ± 56.43*	0.190	53.50 ± 3.11*	53.41 ± 3.35*	0.480
Week 10	208.22 ± 49.34*	214.54 ± 57.62*	0.246	53.67 ± 3.10*	53.45 ± 3.38*	0.359
Week 12	199.61 ± 48.02*	203.98 ± 55.20*	0.255	54.08 ± 3.11*	54.08 ± 3.40*	0.426

Note: No significant difference was observed between both groups at any given time during the study ($p > 0.05$). The melanin index and L^* value of each group during the study were significantly lower compared to the baseline value of each group ($p < 0.05$, denoted by *).

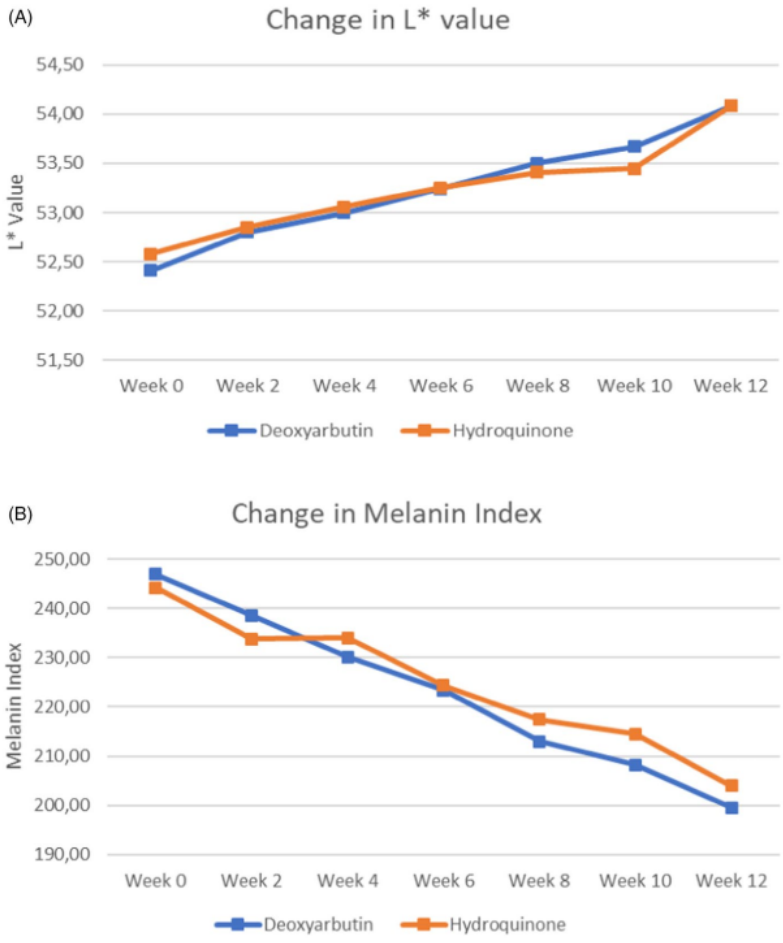

FIGURE 2 Change in L^* value (A) and melanin index (B) during the 12-week study period

group ($p < 0.05$). This result was accompanied by a consistent decreasing pattern of L^* values and MI in both groups during the 12-week study period (Figure 2). Similar results were found for the ITT analysis (Table S1).

The increase in L^* value and decrease in MI at each follow-up session are shown by Figure 3. When compared to the baseline data, a L^* value increase and of MI decrease was shown by both groups at each follow-up session, with the greatest improvement being observed at the twelfth week of the study. No significant difference of L^* value and MI improvement between both groups at any time point during the study were observed ($p > 0.05$). Similar results were found for the ITT analysis (Figure S1).

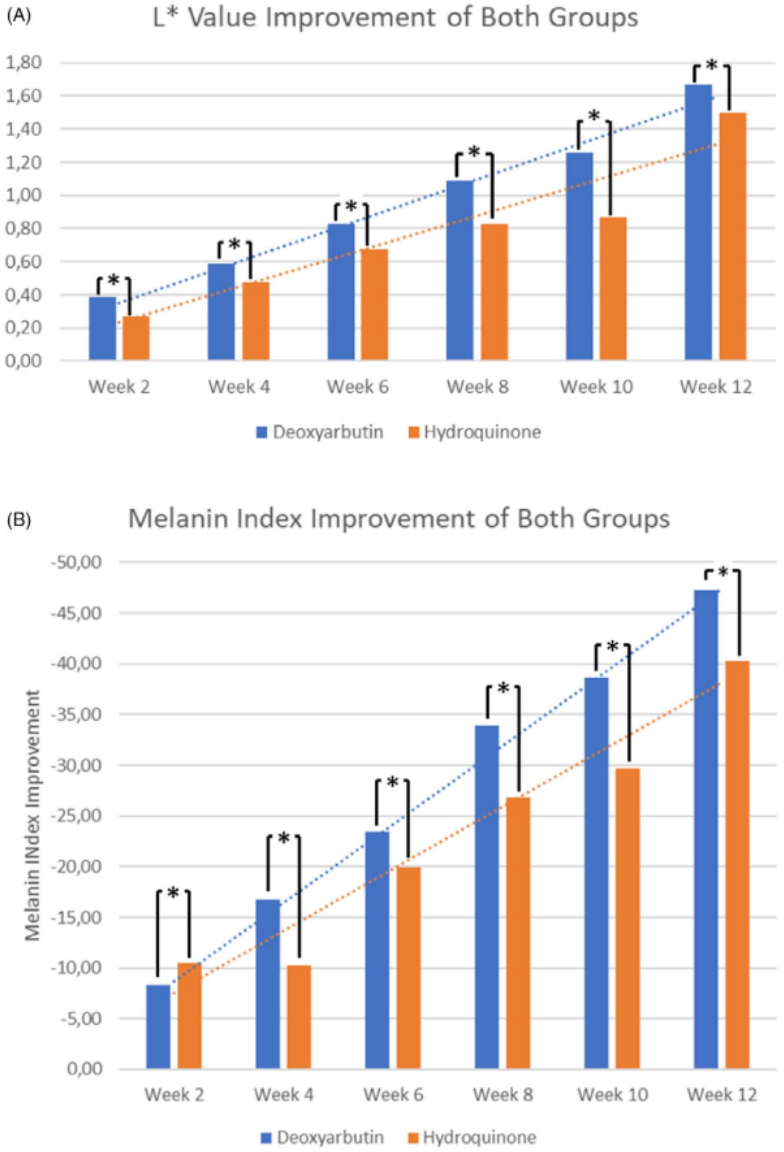

FIGURE 3 The *L** value and melanin index improvement of both groups at each follow-up session. The baseline data served as the reference value for each analysis. No significant difference in melanin index improvement was observed between both groups at each follow-up ($p > 0.05$, denoted by *)

3.3 | Tolerability

Erythema, edema, stinging, itching, or development of hyperpigmented spots were not observed nor reported by any of the participants during this study. No systemic side effects were observed nor complained during this study.

4 | DISCUSSION

This double-blind, randomized controlled clinical trial aimed to compare the depigmenting effect of 2% deoxyarbutin and 4% hydroquinone. This study demonstrated that 12-week topical application of deoxyarbutin resulted in a comparable depigmenting effect compared to 4% hydroquinone, which served as a gold standard depigmenting agent.

Deoxyarbutin and hydroquinone have similar chemical structure to tyrosine, the main substrate for melanogenesis, in which all three compounds have phenolic moiety.[11] Thus, deoxyaburtin and hydroquinone may act as a substitute substrate for tyrosinase, the rate-limiting enzyme of melanogenesis, resulting in diminished melanin synthesis.[8] The depigmenting potential of deoxyarbutin has been elucidated in several in vivo and in vitro studies,[8,10,11] where all studies demonstrated a comparable tyrosinase inhibitory effect to hydroquinone.

In terms of clinical trial, to our knowledge, only two studies examining the whitening effect of deoxyarbutin, which are limited in several parameters, are available.[10,11] In both studies, despite the

well-demonstrated significant L^* value increase in deoxyarbutin and hydroquinone groups compared to the baseline values, no intergroup analysis comparing the L^* values nor the increase in L^* values of both groups was available. As a result, a direct comparison of both agents could not be drawn. This limitation was tackled in our study, where we managed to demonstrate that the increase in L^* value between both agents was consistent and insignifcant ($p > 0.05$), implying that the whitening effect of deoxyrbutin and hydroquinone was comparable. Our study was also done on more participants and with longer follow-up period as compared to the study by Hamed et al[11] (25 participants and 5-week follow-up, respectively). An interesting result was shown by Boissy et al.,[10] where the increase in L^* value was only significant in the Caucasian subgroup and was not significant in the dark skin population. Although this study was also done in the same duration as our study (12 weeks), the different result obtained might be attributed to the small number of participants with dark skin (16 subjects compared to 34 subjects of the Caucasian group) as compared to our study (59 subjects).

In order to strengthen our result, we also included mexameter analysis in this study. To our knowledge, this was the first human clinical trial of deoxyarbutin which combined two colorimeter measurements. Our result showed consistent findings with that of chromameter where the MI values of both groups at the end of the study were significantly lower than the baseline values and that the MI values of both groups were not significantly different. The clinical significance of mexameter in melanin level assessment has been demonstrated in various studies.[14,15] The readings from mexameter further corroborated our findings that deoxyarbutin, as hydroquinone, decreased melanin synthesis and improved skin pigmentation.

Despite having a similar mechanism of action and depigmenting effect, the proposed superior safety profile of deoxyarbutin needs to be considered with great attention. Although no adverse events occurred in our study, the side effects of hydroquinone have been well documented.[7] These effects are thought to arise from the rapid oxidation of hydroquinone upon binding with tyrosinase which results in the formation of quinones[16] and free radicals[17] that might lead to skin irritation and damage to cells such as melanocytes.[18] On the contrary, in vitro studies have shown that deoxyarbutin did not cause oxidative damage to melanosomes.[8,11]

In addition, the presence of pyran ring and acetyl group in deoxyarbutin is also associated with high affinity toward tyrosinase and resistance to oxidation, respectively.[19] The hydrophobic nature of the pyran ring enables greater affinity to the copper active site of tyrosinase, which plays a central role in tyrosinase activation and activity.[20] This was shown by the much lower inhibition coefficient of deoxyarbutin compared to hydroquinone,[10] which corresponded to higher tyrosinase inhibitory effect.[21]

However, despite of these encouraging data, it is worthy to note the concern of the European Scientific Committee on Consumer Safety (SCCS) regarding the potential safety profile of deoxyarbutin.[22] This report stated that, although dermal absorption of deoxyarbutin resulted in no detectable hydroquinone, partial degradation of deoxyarbutin to hydroquinone might still occur when applied to the skin, possibly due to high temperature and acid condition of the skin.[23] While we definitely need to be alarmed and cautious of this issue, it is also important to note that clinical data for this phenomenon is yet to be available and that all calculations were derived from approximations from stability tests. In addition, the 2% concentration used in our study, compared to the 3% concentration the SCCS investigated, when assessed using the calculation elaborated in the full report, would yield in a considerably lower hydroquinone level, and thus, putatively, wider margin of safety. Provided with these data, further and more extensive clinical evaluation are warranted to confirm this issue.

Future studies assessing deoxyarbutin with longer follow-up duration in subjects with Fitzpatrick skin type V and VI will be interesting to explore the long-term side effects and safety profile. In addition, as this study was done in subjects with normal skin, clinical trials done in patients with hyperpigmentation disorders would be required to confirm its therapeutic efficacy.

5 | CONCLUSION

This study showed that the depigmenting effect of 2% deoxyarbutin and 4% hydroquinone sera were comparable.

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CONFLICT OF INTERESTS

None to disclose.

AUTHOR'S CONTRIBUTION

Prof. Anis Irawan Anwar, MD, PhD is the head of research team, initiated the research topic, devised the study design, and devised the manuscript. Yulia Asmarani, MD involved in data collection, study products, wrote and reviewed the manuscript. Asnawi Madjid, MD provided expert opinion on the result interpretation, conducted literature review, and reviewed the manuscript. Ilham Jaya Patellongi, MD, PhD provided expert opinion on the statistical methodology, conducted the statistical analysis, and interpreted the statistical result. Anni Adriani, MD, PhD critically reviewed the manuscript, conducted literature review, and provided expert opinion on the study product and ingredient. Prof. Suryani As'ad, MD, PhD provided expert opinion on the study design and critical review of the manuscript, approved the final version of the manuscript. Ivan Kurniadi, MD, BMedSci(Hons) provided expert opinion on study design, wrote the manuscript, advise on academic English, and approved the final version of the manuscript.

ETHICAL APPROVAL

This study had obtained ethical clearance from the local ethical board committee.

DATA AVAILABILITY STATEMENT

Available upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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