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Spectrophotometric Method for Hydroquinone Determination in Skin Whitening Creams

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ABSTRACT

Hydroquinone belongs to the phenolic aromatic organic compound and is famously known as a skin whitening agent in cosmetic products. The presence of hydroquinone that exceeds the permitted level of 2 % in cosmetic products is toxic for humans. Therefore, a sensitive, accurate, simple, rapid and low-cost analytical method is required for hydroquinone determination. In this study, a spectrophotometric method has been proposed for the quantitative analysis of hydroquinone. The calibration curve was linear from 2 mg L^{-1} to 12 mg L^{-1} hydroquinone with a regression coefficient (R^2) of 0.9999. The limit of detection (LOD) was 0.25 mg L^{-1}. The precision in terms of relative standard deviation (RSD) for respective consecutive three days was 4.44 %, 2.22 % and 0.00 % for 2 mg L^{-1} hydroquinone. Meanwhile, the RSDs for 5 mg L^{-1} and 8 mg L^{-1} hydroquinone were ranged between 0.00 % and 2.52 % for consecutive three days. The recoveries achieved for added 2 and 4 mg L^{-1} hydroquinone standard solution into the skin whitening creams were 99.18 % and 94.25 %, respectively. The all-tested skin whitening creams contain hydroquinone below 2 %. It can be concluded that this proposed spectrophotometric method is accurate, simple, fast, low cost and has the potential to be an alternative method for routine analysis of hydroquinone in skin whitening creams involving pharmaceutical industries.

Keywords: *Hydroquinone, Spectrophotometry, Whitening Cream*

1. INTRODUCTION

The cosmetic industry is globally important due to its contribution to the economic growth of countries and generates worldwide income. It was the most successful industry during the Great Depression from the early 1930s till the end of World War II [1]. The cosmetic market in Asia seems to be one of the fastest-growing markets because of the high demand from consumers [2]. Skin whitening products are getting popular day by day. They are sold in the form of creams, gels, lotions and soaps [3], which can be applied on the face, neck, back of the hand and sometimes on the whole body. The purpose of skin whitening products is to treat skin pigmentation. Skin pigmentation is referring to any skin problem such as old acne scars, age spots, freckles or uneven skin tone. It happens due to exposure to ultraviolet (UV) rays, hormonal changes, genetics, medication, pregnancy, skin aging or the wrong use of skincare products. Most people use skin whitening products in order to get fairer skin tone. In our society, most people believe a person with fair skin tone is beautiful and attractive. This kind of thinking leads to the high demand for skin whitening products without considering the safety of the substances used. Typically, hydroquinone and mercury are well-known agents for the whitening purpose [4]. Both agents have proven to be highly toxic and banned in certain

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countries such as Europe [5]. According to the US Food and Drug Administration, the acceptable limit of hydroquinone in cosmetics is 2 % [6].

Hydroquinone, also known as benzene-1,4-diol or quinol, belongs to phenolic aromatic organic compound with the chemical formula of$C_6H_4(OH)_2$ and molecular weight of 110 g mol^{-1}. It was categorized as an important isomer of the dihydroxybenzene compound along with another compound named catechol [7]. Its chemical structure consists of two hydroxyl groups bonded to a benzene ring in a para position, as shown in Figure 1. Hydroquinone is best known as a whitening agent in cosmetics due to its ability to treat various hyperpigmentation disorders by inhibiting the production of melanin in the skin as the action of the enzyme, named tyrosinase is controlled [8].

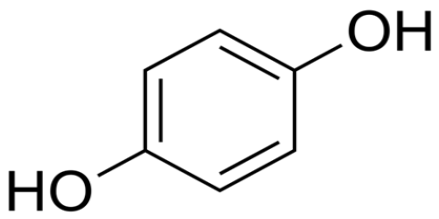

Figure 1. Chemical structure of hydroquinone

Hydroquinone is highly toxic and has been identified as a potential clastogen and mutagen [5]. A clastogen is a toxin that has the ability to cause a break in chromosomes, destroying their sections and leading to rearrangement of the sections. Meanwhile, a mutagen is a substance that causes mutation and damage in deoxyribonucleic acid (DNA) [9]. In addition, overdose application of hydroquinone on the skin might cause skin irritation such as suffering burning sensation, itching and extreme redness, especially to those who are susceptible to allergies or suffer from sensitive skin. More chronic side effects include skin cracking, blistering and the skin turning into a bluish colour. According to the World Health Organization (WHO), 1% of hydroquinone aqueous solution or 5 % of hydroquinone cream caused dermal irritation in humans. Hence, it is very important to have a simple, highly sensitive, precise, accurate, rugged, low cost and fast method for analysing hydroquinone even at a trace amount.

Several methods have been used for the determination of hydroquinone in various samples including spectrophotometry and chromatography, which are particularly high-performance liquid chromatography (HPLC) [10-14] and electrochemistry [15-18]. However, HPLC methods use expensive equipment, require a long time of sample pre-treatment, use toxic organic solvent as mobile phase and various harmful reagents [19]. According to Gao & Legido-Quigley [20], the electrochemistry method is subject to matrix interference, and it makes the quantitative analysis of analyte a bit difficult.

The spectrophotometric method is particularly appropriate to be used for the quality control of whitening creams that contained hydroquinone as an active substance due to its high sensitivity, simplicity, low cost, fast and ability to give reliable results [21]. The spectrophotometric method for hydroquinone determination in skin whitening creams that is available in Libyan markets has shown that the Beer's Law was obeyed in the range from 10 $\mu g\,mL^{-1}$ to 40 $\mu g\,mL^{-1}$ at λ_{max} of 290 nm with R^2 of 0.9994. The hydroquinone concentration in all cream samples was from 0.008 to 0.210 %, which was not exceeding the permissible limit. The LOD was found to be 2.358 $\mu g\,mL^{-1}$ while the LOQ was 7.858 $\mu g\,mL^{-1}$ [22]. Hydroquinone

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determination in pure form, marketed cream and in prepared nanostructured lipid carrier (NLC) formulation by using UV-spectrophotometric technique have also been reported. Phosphate buffer at pH 5.5 has been used as the solvent in the analysis and the λ_{max} for hydroquinone detection was determined at 289.6 nm. Beer's Law was obeyed in the range from 5 $\mu g\, mL^{-1}$ to 40 $\mu g\, mL^{-1}$ hydroquinone concentration with R^2 of 0.998. The intra-day and inter-day precision were found to be less than 2 % [23].

The spectrophotometric method had been developed and validated for the hydroquinone determination in liposomal formulation. The calibration curve was linear from 1 $\mu g\, mL^{-1}$ to 50 $\mu g\, mL^{-1}$ hydroquinone with very good linearity (R^2 of 0.9998) at the λ_{max} of 293 nm. The recoveries of added hydroquinone into liposomal were between 80 % and 120 %. The RSD for intra and inter-day precisions were less than 2 %. The LOD and LOQ were 0.24 $\mu g\, mL^{-1}$ and 0.72 $\mu g\, mL^{-1}$, respectively [24]. Meanwhile, twenty-four different body lotions and creams sold in the Baraton market, Kenya were randomly selected and analysed for the hydroquinone content using UV-Vis spectrophotometric technique. The absorbance was measured at a wavelength of 302 nm. All the products were considered safe because the hydroquinone content was below 2 % [25]. A linear calibration was observed in the range from 0.025 $\mu g\, mL^{-1}$ to 2.00 $\mu g\, mL^{-1}$ hydroquinone at λ_{max} of 245.5 nm with a LOD of 7 ng mL^{-1} and linear regression coefficient (R^2) of 0.9998. A relative standard deviation (RSD) of 1.5 % was observed for 0.5 $\mu g\, mL^{-1}$ hydroquinone standard solution (n=11). The analysed whitening creams were found to contain from 2 % to 4 % of hydroquinone [26]. The purpose of this study, therefore was to develop and validate a UV-VIS spectrophotometric technique for the hydroquinone determination in ten commercial skin whitening creams bought in Jengka, Pahang using 0.05 M sulfuric acid (H_2SO_4) as the solvent throughout the analysis.

2. METHODOLOGY

2.1 Instrumentation

UV-Visible Spectrophotometer, Shimadzu UV-1800 (Japan) was used for the overall analysis of hydroquinone standard solution and hydroquinone in the skin whitening creams. It comes with a 1.0 cm quartz cuvette. The instrument was connected to a computer that has been installed with Spectroscopy Software (Shimadzu®) for data processing.

2.2 Chemicals

All chemicals used in this study were of analytical grade reagent and all solutions were prepared in 0.05 M H_2SO_4. The hydroquinone powder was obtained from Sigma Aldrich, UK. For the preparation of 1000 mg L^{-1} hydroquinone stock solution, 100 mg hydroquinone powder was dissolved with 0.05 M H_2SO_4 in 100 mL volumetric flask. The standard working solution series (2, 4, 6, 8, 10 and 12 mg L^{-1}) were prepared by the appropriate dilution of the hydroquinone stock solution using 0.05 M H_2SO_4 in 100 mL volumetric flask.

2.3 Validation of Proposed Spectrophotometric Technique

An appropriate linear range with acceptable correlation coefficient (R^2), limit of detection (LOD), limit of quantification (LOQ), precision, repeatability, accuracy, ruggedness, robustness and recovery of added hydroquinone into the skin whitening creams were analysed in order to verify the suitability of the proposed spectrophotometric technique for the

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hydroquinone analysis [27]. The linearity was evaluated through a graphical representation of concentration versus absorbance at λ_{max} [28]. Six different concentrations of hydroquinone standard solution ranged from 2 mg L^{-1} to 12 mg L^{-1} were measured at λ_{max}. An appropriate linearity range with an acceptable correlation coefficient (R^2) was then analysed.

The LOD was determined by an additional lower concentration of hydroquinone standard solution until a response that is significantly different from blank (0.05 M H_2SO_4) was obtained. The LOQ was estimated 3.333 times of the obtained LOD. The hydroquinone standard solution at the concentration of 2, 5 and 8 mg L^{-1} was applied for intra-day and inter-day precision, ruggedness and robustness with three replicates (n=3). The precision of the proposed spectrophotometric technique was determined by the relative standard deviation (RSD). The ruggedness was investigated by measuring standard solution using the same instrument, UV-Visible Spectrophotometer, Shimadzu UV-1800 (Japan) but had been conducted by two different analysts under the same optimum parameters. On the other hand, robustness was carried out by small changes of wavelength and scanning time (30 minutes time interval after the standard preparation). Statistical *F*-test was carried out for the ruggedness and robustness.

Three different known concentrations of the hydroquinone standard solution were added into the quartz cell and scanned for three replicates (n=3) measurement in order to determine the accuracy. The obtained absorbance was used to calculate the amount of the hydroquinone standard solution that has successfully recovered by referring to the regression equation from the calibration curve obtained. The percentage of recovery was calculated using the following Equation (1);

$$\% \text{ Recovery} = \frac{\text{Concentration of hydroquinone recovered}}{\text{Concentration of actual hydroquinone}} \times 100 \quad (1)$$

2.4 Collection of Skin Whitening Cream

All of the skins whitening creams were purchased from the shop in Jengka, Pahang. Three skin whitening creams were purchased from a drugstore. Meanwhile, the remaining seven skin whitening products were purchased from the local cosmetic shop in Bandar Jengka, Pahang. Table 1 shows the labelled skin whitening creams purchased for this study.

Table 1: Labelled skin whitening creams purchased in Jengka, Pahang

Product	Source (shop)
SWC-1	Drugstore
SWC-2	
SWC-3	
SWC-4	Local cosmetic shop
SWC-5	
SWC-6	
SWC-7	
SWC-8	
SWC-9	
SWC-10	

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2.5 Pre-treatment of Skin Whitening Cream

1 g of each cream sample was weighed in a beaker and dissolved with 20 mL of 0.05 M H_2SO_4 in the water bath. The solution was then transferred into 25 mL volumetric flask and filled up to the calibration mark with 0.05 M H_2SO_4. The solution was filtered by using a filter paper and 5 mL of the first filtered solution was discarded. Additional 5 mL of H_2SO_4 was used to rinse the filter paper and remove any retained sample [25].

2.6 Recovery and Hydroquinone Determination in Skin Whitening Cream

Recovery of the hydroquinone in skin whitening cream was determined by adding the different known amounts of hydroquinone standard solution into the pre-treated skin whitening cream [11]. This study was carried out with three replicates (n=3) measurements per added concentration. Recovered concentrations of the added hydroquinone standard solution were calculated using the regression equation from the calibration curve. The hydroquinone content in skin whitening cream was determined directly by measuring the absorbance of the sample solution after the required digestion, filtration and dilution steps [22].

2.7 Percentage of Hydroquinone Content in Skin Whitening Cream

The percentage of hydroquinone content in each tested skin cream was calculated using the following Equation (2) [22];

$$\text{Found hydroquinone in sample} = \frac{\text{Amount found (mg L}^{-1})}{\text{Sample weight (mg)}} \times 0.025 \text{ L} \times 100\ \% \qquad (2)$$

3. RESULTS AND DISCUSSION

3.1 Estimation of Maximum Absorption (λ_{max}) of Hydroquinone

The 12 mg L^{-1} of standard hydroquinone solution was scanned by the UV spectrophotometer in order to determine the maximum absorbance. The maximum absorbance of hydroquinone was detected at the wavelength of 288 nm. The λ_{max} was used for further quantitative spectrophotometric measurement of hydroquinone. The obtained λ_{max} in this study was quite similar to the wavelength obtained in spectrophotometric analysis of hydroquinone by different authors. Table 2 shows the value of λ_{max} obtained from the present and literature.

Table 2: The λ_{max} obtained from present and literature review

Researchers	λ_{max} (nm)	References
The present study (2022)	288.0	-
Elferjani *et al.* (2017)	290.0	[22]
Kaur *et al.* (2017)	289.6	[23]
Khoshneviszadeh *et al.* (2015)	293.0	[24]

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3.2 Linearity, Limit of Detection (LOD) and Limit of Quantification (LOQ)

The ability of the proposed spectrophotometric technique as an analytical method for hydroquinone determination had been applied by evaluating the absorbance as the function of hydroquinone concentration. The hydroquinone standard solution with a concentration from 2 mg L^{-1} to 12 mg L^{-1} were measured at the λ_{max}.

A good linear correlation between absorbance and concentration of hydroquinone standard solution was obtained, as shown in Figure 2. The figure shows absorbance for hydroquinone standard solution as the concentration linearly increased from 2 mg L^{-1} to 12 mg L^{-1} at seven concentration levels. The obtained linear equation was y = 0.0243x – 0.0002 with a correlation coefficient (R^2) of 0.9999, as represented by the constructed calibration curve. As the value of R^2 is greater than 0.990, it is acceptable and satisfactory [29]. In addition, if the R^2 is in a range of 0.90 to 1.00, it shows a very high correlation [30]. Table 3 shows the comparison of the regression equation, R^2, LOD and LOQ obtained by the present study and literature.

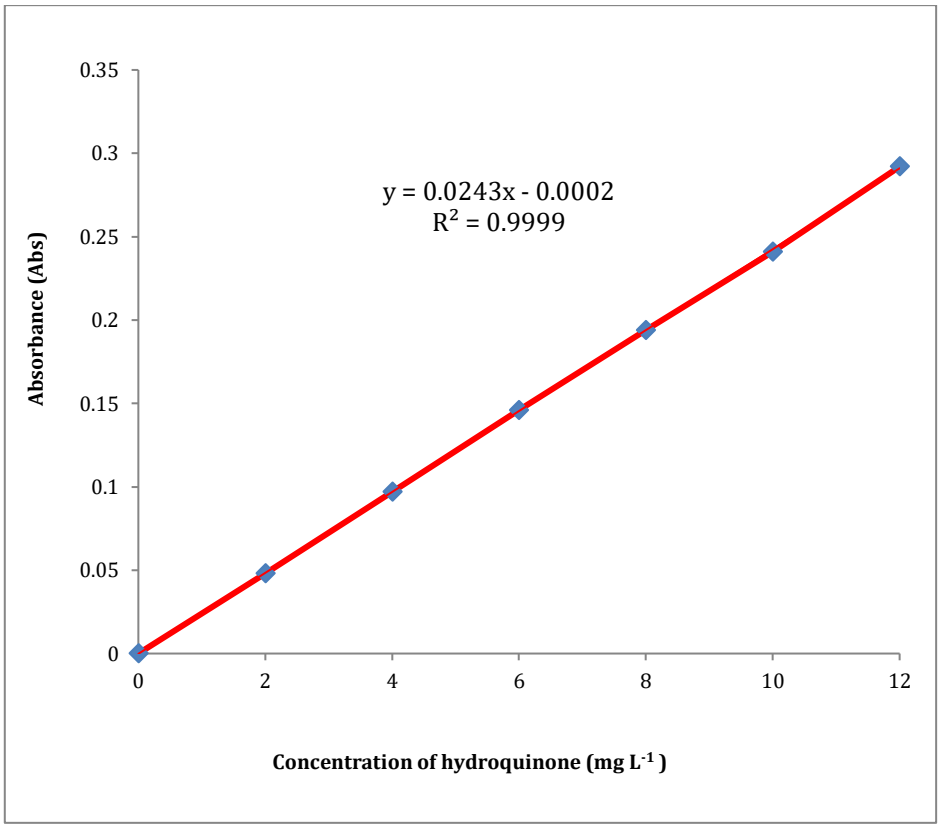

Figure 2: The calibration curve of absorbance against the concentration of hydroquinone from 2 to 12 mg L^{-1} in 0.05 M H_2SO_4 solutions at λ_{max} of 288 nm

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Table 3: The regression equation and R^2 value obtained from this study and by other researchers

Regression Equation	R^2	LOD (mg $\mathbf{L^{-1}}$)	LOQ (mg $\mathbf{L^{-1}}$)	References
y = 0.0243x – 0.0002	0.9999	0.25	0.83	-
y = 0.0220x + 0.007	0.9970	2.36	7.86	[22]
y = 0.0216x	0.9980	0.32	0.96	[23]
y = 0.0274x – 0.0037	0.9998	0.24	0.72	[24]

3.3 Precision and Accuracy

The calculated relative standard deviation (RSD) for the intra-day measurement of 2, 5 and 8 mg L^{-1} hydroquinone standard solution with three replicates (n=3) were 4.65 % 0.86 % and 0.53 %, respectively. Meanwhile, the measurement of 2, 5 and 8 mg L^{-1} hydroquinone standard solution for inter-day measurements (consecutive three days) gave the RSD values of 4.44 %, 0.86 % and 0.00 % for day 1. For day 2, the RSD values were 2.22 %, 2.52 % and 1.05 % for those three concentrations. For day 3, the RSD obtained was 0.00 % for 2 mg L^{-1}, 1.71 % for 5 mg $L^{-1}$and 0.53 % for 8 mg L^{-1} hydroquinone. Both intra and inter-day measurements were acceptable and considered as precise because the RSD values were within the acceptable range, which is less than 5 % [31]. The mean percentage recoveries obtained were 93.00 %, 95.64 % and 98.35 %, respectively for the concentration of 2 mg L^{-1}, 5 mg $L^{-1}$and 8 mg L^{-1} hydroquinone standard solution, as shown in Table 4. These results indicate that the proposed spectrophotometric technique is accurate as acceptable and satisfactory recoveries were successfully obtained [32].

Table 4: Mean values for recovery of hydroquinone standard solution by the proposed spectrophotometric technique (n=3)

Added concentration hydroquinone (mg $\mathbf{L^{-1}}$)	Absorbance (n=3)	Absorbance ± SD (RSD)	Found Concentration Hydroquinone (mg $\mathbf{L^{-1}}$)	Recovery (%)
2	0.043 0.045 0.046	0.045 ± 0.002 (4.44 %)	1.860	93.00
5	0.116 0.116 0.117	0.116 ± 0.001 (0.86 %)	4.782	95.64
8	0.191 0.191 0.191	0.191 ± 0.000 (0.00 %)	7.868	98.35

3.4 Ruggedness and Robustness

The obtained RSD values for the analysed 2 mg L^{-1}, 5 mg $L^{-1}$and 8 mg L^{-1} hydroquinone standard solution with three replicates (n=3) were 2.22 %, 1.71 % and 1.05 %, respectively for the first analyst. For the second analyst, the RSDs were 2.38 %, 0.88 % and 0.53 % for respective hydroquinone concentrations. From the statistical two-tailed *F* test, there were no significant differences between the obtained variances for hydroquinone when the

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measurements were performed by the first and second analysts using the same instrument at a 5 % significance level. Hence, the results indicated that the proposed technique was considered rugged [33].

The robustness of an analytical procedure is a measure of the ability to produce a consistent result even if small changes are made to the experimental conditions [34]. For this proposed spectrophotometric technique, the robustness study was carried out by considering the variation of λ_{max} (286 and 290 nm) and time interval analysis after the standard preparation (30 and 60 minutes). The statistical two-tailed *F* test at 95 % confidence level shows that there is no significant difference of variance by the small changes that were made to the experimental parameters.

3.5 Recovery studies of Hydroquinone in Skin Whitening Cream

The recovery studies of hydroquinone were determined by adding a known amount of hydroquinone standard solution into a pre-treated skin whitening cream sample. The SWC-3 sample was selected to be used in the recovery study as it contained the lowest amount of hydroquinone compared to the others. 2 and 4 mg L^{-1} of hydroquinone standard solution were added into the treated cream sample and analysed by the proposed spectrophotometric technique.

The recovered concentration of added hydroquinone standard solution into the ski whitening cream sample was calculated by using the regression equation, y = 0.0243x – 0.0002 that was obtained from the linearity study. The recovery achieved for respective 2 mg L^{-1} and 4 mg L^{-1} of hydroquinone standard solution were 99.18 % and 94.25 %, as shown in Table 5. According to the *t*-test, there were no significant differences between recovery and added value at the 95 % confidence level with a degree of freedom (n-1 = 2) since all calculated *t* values in the analysis are lower than the theoretical *t* value, which is 4.303 [35].

Table 5: Recovery for added hydroquinone standard solution into the cream sample (n=3)

Added concentration (mg $\mathbf{L^{-1}}$)	Found concentration (mg $\mathbf{L^{-1}}$)	Recovery (%) ± SD	RSD (%)
2	1.98	99.18 ± 0.010	0.51
4	3.77	94.25 ± 0.101	2.69

3.6 Analysis of Hydroquinone in Skin Whitening Cream

The proposed spectrophotometric technique has been applied in this analysis to determine the hydroquinone content in ten different skin whitening creams that were purchased in Bandar Jengka, Pahang. The hydroquinone content in each cream was determined directly after the required digestion, filtration and dilution steps have completed. The content of hydroquinone in percentage for each cream also has been determined to indicate whether the hydroquinone content exceeds the permitted level of 2 % or not [22]. All tested skin whitening creams contained hydroquinone of lower than 2 %, as shown in Table 6.

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Table 6: Hydroquinone content in skin whitening cream by the proposed spectrophotometric technique (n=3)

Brand Name	Absorbance	Concentration hydroquinone found (mg L^{-1})	Percentage concentration (%)
SWC-1	0.265	10.412	0.026
SWC-2	0.223	8.717	0.022
SWC-3	0.071	2.470	0.006
SWC-4	0.068	2.576*10 25.76	0.064
SWC-5	0.213	8.2751*100 82.751	0.206
SWC-6	0.095	3.632*10 36.32	0.091
SWC-7	0.186	7.242*10 72.42	0.181
SWC-8	0.169	6.570*100 657.0	1.643
SWC-9	0.101	3.871*10 3871	0.097
SWC-10	0.088	3.386*10 33.86	0.085

4. CONCLUSION

The proposed spectrophotometric technique had been successfully applied to hydroquinone in the skin whitening creams. The present method has the advantage of requiring a very simple sample pre-treatment. It was also found to be practically rapid, convenient, sensitive, accurate, precise, rugged and low in cost. Therefore, it could be an excellent alternative analytical method for hydroquinone determination in skin whitening creams. In future studies, it is recommended to analyse and compare the hydroquinone content with other established methods such as HPLC with a statistical *F* test.

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