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Implementation of Thin Layer Chromatography to Detect Dihydroxybenzene Isomers for Cosmetic Product Regulatory Enforcement

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***Abstract*—**Thin Layer Chromatography (TLC), used in forensic analysis, has many advantages: simple, cheap, and efficient. This study aimed to separate dihydroxybenzene isomers in whitening creams in the market and online shops using the BPOM label or not. Of the six eluent mixtures, this research used Toluene: Diethyl Ether: Acetic Acid with a ratio of 80:20:1 after optimization and validation test. In this case, the recovery percentages of resorcinol and hydroquinone were 51-66% and 80-87%. Of the 20 samples tested, 12 whitening creams were added with resorcinol, and 4 were added with hydroquinone. The addition of resorcinol and hydroquinone based on the regulation in Perka BPOM no 18 of 2015 was 5%. Furthermore, 2 out of 20 samples were added with hydroquinone within the regulated threshold, while the remaining 2% were accepted and the other six were undetected. In this case, adding hazardous substances has violated the rules of consumer protection laws and regulations.

***Keywords*—** TLC; Isomer; Hydroquinone; Law regulation

1. INTRODUCTION

Hydroquinone (HQ) and resorcinol (**Fig. 1**) are dihydroxybenzene isomers considered as hazardous environmental pollutants because of their high toxicity and low degradability in ecological systems. Both dihydroxybenzene isomers are used in various fields, such as cosmetics, tanning, antioxidants, dyes, and photographic chemicals. HQ is a bleaching agent, especially for melasma and hyperpigmentation disorders.

HQ is still the best option for treating melasma and post-inflammatory hyperpigmentation. The widely recognized components of Kligman's formula contain a combination of 5.0% HQ and other additives. For daily use, it can be used for no more than six months and must be under supervision [1]. HQ can stop the conversion of DOPA into melanin by inhibiting the tyrosinase enzyme activities. Other processes are the DNA and RNA synthesis inhibition, melanosome degradation, and melanocyte destruction [2]. HQ is directly detected at the concentration of preparation, carrier, and stability of the final chemical products.

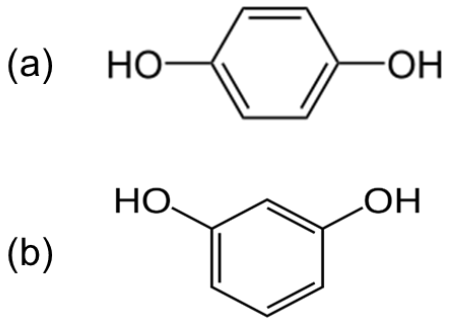

Fig. 1. Chemical structure of HQ (a) and resorcinol (b)

Resorcinol derivates have similar utility as HQ in hyperpigmentation disorders. Resorcinol (N-Hydroquinone) is used in cosmetic products as an acne treatment, antipruritic, exfoliating agent, or keratolytic in a concentration of 2.5% to 5%. Retinoic acid and resorcinol form a mixture that can regulate the formation and destruction of skin cells. It can regulate the cell life cycle which is also utilized by

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anti-aging cosmetics to overcome the effects of aging [3].

HQ frequently irritates allergies, requiring rapid therapy based on diagnostic results. HQ can be harmful in both acute and chronic forms. HQ can also harm the kidneys (nephropathy), induce cell growth, and is carcinogenic and teratogenic [4]. These side effects may develop if resorcinol is applied to the skin and transferred into the blood vessels making the heart or breathing slow down, feeling weak, feeling a painful headache, nausea, vomiting, and restlessness, or thoughts.

Every cosmetic sold in Indonesia must comply with the norms and/or regulations outlined in the legislation, and possess a distribution permit. This provision is based on Article 105 verse (2) and Article 106 verse (1) of Law No. 36 of 2009 on Health (2). Therefore, any cosmetic product that does not meet the legislation's criteria and/or regulations, such as containing dangerous substances or without a distribution authorization (notice), is classified as unlawful. Crimes are manifested in-abstracto criminal standards in the normative legal sense. Clause 197 of the Indonesia Health Law punishes anyone who illegally produces or distributes pharmaceutical preparations and/or medical products without a distribution permit, as defined in article 106 point (1), with a maximum penalty of IDR 1,500,000,000.00 (one billion and five hundred million rupiahs) and a maximal term of 15 (fifteen) years. To authorize it, a legal inquiry is required [1].

Forensic toxicology uses the science of toxicology and other disciplines such as analytical chemistry, pharmaceutical science, and clinical chemistry to assist in the investigation of deaths, poisonings, and others. Not only toxicological results, but forensic toxicology also builds some technologies or techniques to analyze samples. In forensic inquiries, thin-layer chromatography is commonly used. Much work has been done to select the finest Thin Layer Chromatography (TLC) system for general screening and identify purposes to build some standardized systems during the previous few years. The benefits of standardization include (a) more efficient and effective analyses, (b) easy transferability of chromatographic data from one laboratory to another, and (c) fewer discrepancies between the findings of two or more laboratories studying the same sample [5].

The highly toxic isomers of dihydroxybenzene, HQ, and resorcinol have similar chemical characteristics. Thus, it makes the qualitative and quantitative analysis challenging. A simple or quick method is needed to analyze the combinations of HQ and resorcinol in cosmetic formulations. Chromatography analysis is part of the separation method that can separate a mixture of HQ and resorcinol. High-resolution liquid chromatography, gas chromatography, and thin-layer chromatography are examples of chromatography. De et al. reserved a high-performance liquid chromatography method for evaluating resorcinol in hair tonic solutions [5]. However, only resorcinol was tested in this study, not a mix of HQs. Using a voltammetric technique, the combination of isomeric chemicals was examined by Arago [6].

In Indonesia, unregistered cosmetics or without Indonesia Food and Drug Authority (FDA) licenses are common. They sell products through online and/or offline markets. Preferring for profit only, sellers do not care about safety and health ingredients. Yunianto et al. present facial creams containing HQ with levels of 9.74% and 3.48% [7]. Arifiyana found that the concentration of HQ in some whitening cream products in Sidoarjo was 4.05% and 3.09%, respectively [8]. Some consumers are not aware of the side effects without the harmful ingredients. After using the product for a long time, side effects will appear. This is detrimental to the consumers, and sellers can be subject to sanctions.

This article presents an analytical method using TLC. This article describes the use of TLC to separate HQ and resorcinol isomers. These two have similar physical and chemical properties, making them difficult to separate. Forensic examinations can be assisted with easy, inexpensive, and high-precision tools. In addition, it is necessary to optimize and validate the eluent that is easier.

2. EXPERIMENTAL SECTION

2.1. Materials

The materials used in this research were TLC Plate GF 254 (CAMAG), HQ (pharmaceutical grade), $AgNO_3$ powder, resorcinol (pharmaceutical grade), ten whitening creams without FDA licenses (sample 1-10), placebo face whitening cream, and ten whitening creams with BPOM (sample 11-20). The solutions used in this study had high purity provided by Merck®: HCl 4N, Na_2SO_4, Ethanol, Aquades, Diethyl ether, Glacial acetic acid, Toluene, and Chloroform.

2.2. Instrumentations

The tools used in this research were spatulas, micropipette, microhematocrit tube without anticoagulant, analytical balance, TLC densitometer toolkit (CAMAG TLC Scanner 4), measuring flask, hot plate, beaker glass, and glass plate.

2.3. Procedure

2.3.1 Optimization and condition analysis

Optimization of the mobile phase selection with the composition of the mobile phase was presented in **Table 1.** HQ, resorcinol, and their mixtures each contained 0.050 gr in 1 mL of ethanol and then 1 mL of a 0.02 g/mL of $AgNO_3$ solution was added. The solution was spotted at a distance of 1.5 cm on the plate. Then, the plate was TLC eluted using the above mobile phase components. The value of Rs' was further calculated from the Rf of each peak.

Table 1. Ratio composition of the mobile phase

No	Composition	Ratio
1	Toluene/acetic acid	70:30
2	Chloroform/acetic acid	80:20
3	Toluene/Acetic acid ratio	80:20
4	Toluene/diethylether/acetic acid	80:20:1
5	Toluene/diethylether/acetic acid	90:10:1
6	Toluene/diethylether/acetic acid	70:30:1

2.3.2 Optimization of colouring plate

The plate staining process was optimized using Rhodamine-B solution, vanillin HCl in 0.02 % v/v ethanol, and UV light. The efficiency of the chromatogram was then studied using the staining plates technique using these solutions (viewed from the results of the chromatogram baseline display).

2.3.3 Validation and sampling anlysis

Validation. The samples were then given $AgNO_3$ solution with a solution of each vial spaced 1.5 cm on a GF254 silica gel TLC plate. The sample was then eluted in the mobile phase. Then, the mean area, standard deviation (SD), Coefficient of Variation (CV), recovery (%), linearity curve for sampling, and precision and accuracy were calculated. The observed area at the selected wavelength was also determined using a densitometer.

Sampling Analysis. The samples were prepared as in the validation test, then a solution of 1–20 was spotted on a TLC plate. The stains formed were read at a wavelength of 254nm. HQ and resorcinol levels of the peak area in Rf were suitable for both compounds.

3. RESULT AND DISCUSSION

3.1. Optimization Result

The eluent optimization aims to determine the right solvent mixture in this study. The use of a solvent mixture is affected by the polarity of the solvent. In this study, mixtures with different polarities were selected. The aim is that the two isomers can be separated properly [9].

Variations in the mobile phase of toluene, chloroform, diethyl ether, and acetic acid are often mentioned in several studies. This is due to the influence of the polarity of the two different compounds (resorcinol is more polar). The polarity of the mobile phase is expected can separate the two isomers. Two things were elucidated, producing a point when rising with the solvent. The eluent optimization data can be seen in **Table 2.**

The calculation of the Rf value was assisted by the optimization of color assignment. Using the comparison, the dye was applied to the TLC plate between rhodamine-B, and vanillin HCl in ethanol, and tested under UV light as in **Fig 2.** To facilitate the determination of the point of separation between the two, this research used UV light to detect spots.

Table 2. Eluent optimization data

No	Optimization Solvent Mixture		
	Solvent	Sample	Rf
1	Toluene: Acetic acid 70:30	resorcinol hydroquinone	0.92 0.95
2	Chloroform: Acetic acid 80:20	resorcinol HQ	0.15 0.61
3	Toluena: Acetic acid 80:20	resorcinol HQ	0.26 0.59
4	Toluene:Diethylether:Acetic acid 80:20:1	resorcinol HQ	0.26 0.69
5	Toluene:Diethylether:Acetic acid 90:10:1	resorcinol HQ	0.41 0.37
6	Toluene:Diethylether:Acetic acid 70:30:1	resorcinol HQ	0.33 0.28

Fig. 2. Optimization colouring using Rhodamine-b (pink) and vanillin-HCl (brown)

3.2. Validation Result

In validating the method, toluene: diethyl ether: acetic acid 80:20:1 was used. From the results of the optimization test using densitometry to see the separation between the two, the data was obtained as presented in **Fig. 3.** The calculated value of Rs was 1.67.

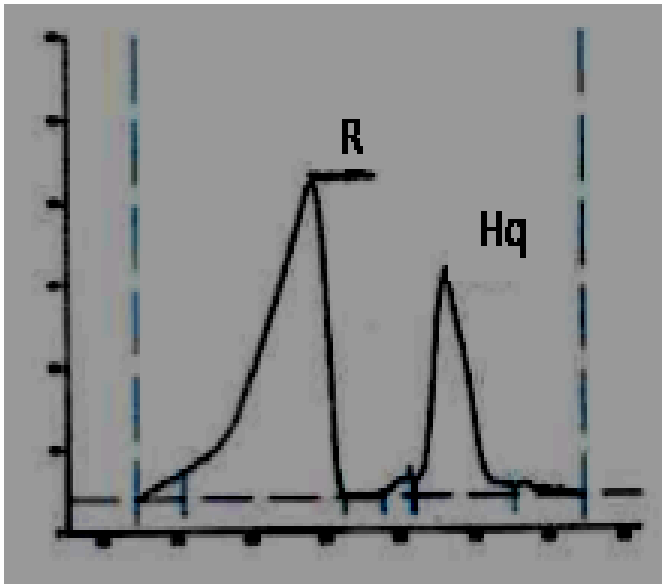

Fig. 3. Peaks of Resorcinol and hidroquinone using TLC-densitometer

Validation continued with the standard measurements and calculating the extract percentage

to determine the level of precision and accuracy of the concentration of the two isomers after being spotted on the TLC plate. In this case, the concentration percentage of the extract was 51% for HQ and 87% for resorcinol. The results from the validation test for HQ were: standard deviations from 80%, 100%, and 120% were 4.4; 3.4; and 1.76. Coefisient of Variation or KV were 1.8; 1.1; and 1.82.

From the results of the validation test for resorcinol were: standard deviations from in 80%, 100%, and 120% were 4.6; 3.8; and 2.02. Coeffisient of Variation or KV were 3.04, 1.28, and 2.43. Then, the minimum detection limit was calculated at 6-21 mg for HQ and 7-23 mg for resorcinol.

3.3. Sample

The use of TLC was applied to the sample. Of the 20 samples tested qualitatively using staining and lighting as in optimization, 12 of 20 samples used resorcinol and 6 of 20 samples contained HQ in skin whitening cream. To confirm the concentration, the TLC plate was tested in a TLC-densitometer. As a result, the percentage of 1,25 g HQ concentration in 20 samples ranged from 1-15%, while the resorcinol was 1-36%. The results can be seen in **Table 3.**

Table 3. Resulf of analysis

Sample	Indonesia FDA lisence	Place of market	Result of Detection			
			Resorcinol		HQ	
			Qualitative	Quantitative (%)	Qualitative	Quantitative (%)
1	unregistered	Modern	V	35	V	11
2	unregistered	Modern	-	0	V	2
3	unregistered	Modern	-	0	V	1
4	unregistered	Traditional	V	23	-	0
5	unregistered	Traditional	V	20	V	13
6	unregistered	Traditional	V	20	-	0
7	unregistered	Online	V	10	-	0
8	unregistered	Online	V	36	-	0
9	unregistered	Online	V	17	-	0
10	unregistered	Online	-	0	-	0
11	registered	Modern	V	2	V	2
12	registered	Modern	-	0	-	0
13	registered	Modern	-	0	-	0
14	registered	Traditional	V	1	-	0
15	registered	Traditional	-	0	-	0
16	registered	Traditional	V	22	V	1
17	registered	Online	V	19	-	0
18	registered	Online	-	0	-	0
19	registered	Online	V	36	V	15
20	registered	Online	-	0	-	0

3.4. TLC and Sample

The most common approach for whitening agents analysis in skin whitening products is HPLC. Other techniques that have been used include TLC and GC/MS [10]. In general, dihydroxybenzenes isomers have similar chemical formula of $C_6H_6O_2$. The physical properties of the two mixtures are similar, including a molecular weight of 110.11, a boiling point of 277-287 ^{0}C, and a melting point between 109-112 ^{0}C. Although they have similar parts, they have different levels of polarity. Different position of Hidroxyde chain in resorcinol and hidroquinone affects the dipole moment, polarity, and solubility. The most soluble compounds will be separated by the furthest mobile phase on the TLC plate. The less soluble compounds in the mobile phase and have a higher affinity for the particles on the TLC plate will stay behind [11]. The mixture has a different polarities which affect the separation of resorcinol and HQ. However, all five solvents were able to separate the two compounds well.

The election of eluent is appropriate if the difference in values between compounds is significant enough so that the separation can be seen. In addition, the exact value of rf was in the range of 0.2-0.8. The mixtures no. 1, 5, and 6 in this study showed a small Rf difference, making it difficult to proceed to validation. The mixtures of 2, 3, and 4 were quite good in providing the value of the distance between the two Rfs. In mixture 2, the range did not fall within the required range, so in the mixture, it was continued to use mixtures 3 and 4. The selectivity parameter was solvent 3, greater than 4, with Rs of 1.67. In this project, solvent number 3 was elected.

A good spot viewer uses UV light because both dyes still need UV light to explain the stains on the TLC plate. The HQ compounds were dark in color under UV light, purple in Rhodamine-B, and colorless in vanillin HCl. Meanwhile, resorcinol compounds were dark in color under UV light, colorless in rhodamine-B, and brown in vanillin-HCl.

Validation is used to detect the accuracy of this method before it is applied to the sample. Placebo is a

basic ingredient of facial cream without active ingredients. The samples and placebo were tested without extraction Thus, it can be seen that the method's performance is good. The HQ concentration is only 56% which will affect the sample concentration. Further theoretical calculations are also utilized to determine the actual concentration of the sample. In this case, the placebo was mixed with resorcinols, HQ, and both. In the method validation, the concentration percentage obtained in HQ was tiny. The method was used to test 20 samples of whitening cream purchased from online, traditional, and modern markets.

As a result of the thematic of optimization and validation to sample analysis, TLC can assist in forensic investigations. Time efficiency and usefulness were used to detect something in a place, and it did not take long to bring justice. Easy-to-use and efficient tools are useful in the forensic field. The development of chemical methods that are easy to use and environmentally-friendly will make it easier for investigators to conduct on-site inspections. The development of deep TLC as a technique for separating dihydrobenzene isomers (HQ and resorcinol) is one of the efforts in national defense against threats. In Indonesia, which consists of a number of islands, not all regions have modern and advanced tools such as GC-MS and HPLC. The use of TLC is an alternative method of inspection in remote areas. In addition to using the TLC-Densitometer, simple extraction of the separation results through the TLC plate can assist investigators to detect fraud in their area. Research on other hydrocarbon samples, especially in explosives, also requires easy and simple tools such as TLC, and it is possible.

The use of these tools needs further research on other eluents that can separate the two without destroying nature. In addition, further research is needed to validate the much larger extraction percentage than this study. Thus, high accuracy values can be obtained. In this study, researchers still use less environmentally-friendly eluents but is easy to find and often used.

Isomers have a similar effect on the skin in more ways than one. Excessive content causes harm to consumers. There are indications of fraud and unlawful acts. This whitening cream impacts health conditions and can be detrimental to consumers.

3.5. Impact of Using High Resorcinol and Hydroquinone for Consumer

Skin whitening chemicals work by interfering with melanin formation, transport, and elimination via skin turnover at several enzymatic stages in the melano genesis pathway. Melanins are black or brown pigments in the skin that play a crucial role in protecting human skin from exposure to ultraviolet (UV) radiation [12]. Tyrosinases are important enzymes in the melanogenesis process found in melanocytes.

Melasma, actinic, senile lentigines, and postinflammatory hyperpigmentation are all hyperpigmentation disorders in which melanin is generated in excess. Melanin is produced in melanocytes and transferred to melanosomes, then carried to keratinocytes through melanocyte dendrites. Numerous enzymes make the physiological process known as melanogenesis. Tyrosinase is the rate-limiting enzyme that catalyzes the conversion of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to dopaquinone. Microphthalmia-associated transcriptional factor (MITF), a dimeric transcription factor with a primary helix-loop-helix-leucine zipper domain in its structure, also regulates tyrosinase. By attaching to an M-box pattern in the promoter sites of tyrosinase, tyrosinase-related protein 1 (TRP-1), and TRP-2, MITF increases their expression. MITF also controls the pigmentation, proliferation, and survival of melanocytes. As a result, MITF and tyrosinase play a significant role in cell melanogenesis regulation.

Natural skin whitening chemicals work by decreasing the expression and action of TYR and suppressing the absorption and dispersion of melanosomes, among other methods. Because natural skin-whitening substances are more attractive to consumers, there is a higher demand for inhibitors of melanogenesis derived from whitening cream with active ingredients that prevent hyperpigmentary diseases in the cosmetic business. The inhibition of tyrosinase (key enzyme responsible for melanin production) synthesis, the inhibitory effect on this enzyme, the destruction of melanocytes by the production of free radicals, and interference with melanin-containing organelles (melanosomes) are instrumental in making this ingredient an effective depigmentation agent. Competitive and noncompetitive tyrosinase inhibitors have become the most common whitening agents in commercial skin whitening solutions due to their selectivity and importance in melanin synthesis. HQ is a tyrosinase inhibitor first used in medicine in 1961. Hydroquinone derivatives have added to skin whitening treatments until today.

Lower quantities of hydroquinone inhibit tyrosinase in a research by Chen and Chavin [12], but greater amounts increase it. The tyrosinase enzyme is activated, resulting in an increase in melanin production. The oxidized by-products of hydroquinone, according to Engasser [13], might be fault for tyrosinase activation. Exogenous ochronosis has been linked to at least 30 distinct formulations of hydroquinone. Others argue that hyperpigmentation cannot be caused by oxidized or contaminated breakdown products [14]. The melanocyte-free regions on the face of patients with ochronosis and vitiligo are not hyperpigmented in a study by Hull and Procter, suggesting that melanocytes have a role in ochronosis development [15].

As hidroquinone, resorcinol topical (for the skin) is used to treat small cuts and scrapes, burns, bug bites,

poison ivy, sunburn, and other skin irritations that cause pain and itching. In addition, acne, eczema, psoriasis, seborrhea, corns, calluses, warts, and other skin conditions are also treated with resorcinol topical.

The inhibition effects of tyrosine by resorsinol are detected in 2018 [16]. There are three forms of protein kinases in the MAPK family: p38 MAPK, p42/44 MAPK, and JNK. p42/44 MAPK, for example, causes MITF phosphorylation, which is then destroyed by the proteasome. Tyrosinase has also been observed to be degraded by activated p38 MAPK through proteolytic degradation. MITF regulates melanogenesis by controlling the expression of the genes tyrosinase, TRP-1, and TRP-2. The expression of these melanogenic genes is aided by many signaling pathways. The anti-melanogenic actions of resorcinol were discovered to be mediated through the cAMP-PKA-CREB and p38 MAPK signaling pathways in this study. Resorcinol inhibits cAMP generation and phosphorylated p38 MAPK, but not p42/43. MAPK, JNK, or NF-B. SB2035809, a p38 MAPK inhibitor, also reduces resorcinol's anti-melanogenic effects, demonstrating that p38 MAP is involved in the anti-melanogenic process.

Any HQ prescription given to a patient should be accompanied by information on the drug's potential side effects, and the fact that it should only be used for a short time and under medical supervision. In addition, it also has a function for melanogenesis. There are many side effects of using much hydroquinone and resorcinol for the body. Hydroquinone causes the same type of genetic damage as leukemia. Quinones produced from phenol, catechol, hydroquinone, and 1,2,4-benzenetriol induce genetic harm in various ways.

Aneuploidy and chromosomal breakage are both symptoms of leukemia. Aneuploidy is a clonal aberration in which complete chromosomes are lost or gained. It is a common clonal aberration in leukemia. Trisomy of chromosome 8 and monosomy of chromosomes 5 and 7 are common aneuploidies. In vitro grown human cells, including CD34+ progenitor cells, the phenolic metabolites of benzene have been found to produce trisomy 8 and monosomy 5 and 7.

As a side effect of hydroquinone, high use resorcinol causes some toxicity. Resorcinol, once used to treat leg ulcers, is now widely utilized as a peeling agent in the treatment of acne vulgaris. It is also used in hair dyes as a coupler. Several examples of systemic toxicity via percutaneous absorption have been recorded in the older literature, including deaths. Pallor, dizziness, cold sweat, collapse, cyanosis; tremor; hypothyroidism, methem-globinemia, hemolytic anemia; hemoglobinuria, violet-black urine, maculopapular eruptions, ochronosis are all signs and symptoms of resorcinol intoxication.

Resorcinol is a primary irritant and a fairly strong sensitizer to cause allergic contact dermatitis in a small percentage of people. The use of resorcinol in acne preparations may be the source of most people's exposure to it in the United States and Spain. There is no evidence of systemic toxicity or carcinogenic consequences after twice-weekly topical treatment of groups of 50 female Swiss mice with 0.02 mL of 5; 25; and 50% resorcinol in acetone for 110 weeks. Ulceration, inflammation, and reactive hyperplasia of the skin were all observed at the application site. The administration of resorcinol in arachis oil for 47 or 69 days increases thyroid weight and causes hyperemia, cellular hyperplasia, and colloid depletion, all of which are indicators of goitrogenic potential.

In addition to each of these effects, long-term use of hydroquinone and resorcinol can cause exogenous ochronosis (EO), which is a rare condition well-known for the side effects of hydroquinone topical therapy. As a result of the extended usage of this drug, a microscopic buildup of ocher-colored pigment is detected in the dermis in this pathology. It is a clinical and histopathological condition similar to endogenous ochronosis, also known as alkaptonuria. The difference is that it has no systemic symptoms like dark urine, gray-blue or gray-brown coloration of cartilages, conjunctive, and arthropathy. Meanwhile, EO's affected area is limited to the area treated with HQ [17]. Hydroquinone use is the most common cause of ochronotic discolouration. However, resorcinol, phenol, mercury, picric acid, and antimalarials have all been linked [18].

Of these effects, only prescription skin lightening medications with a concentration of 2–4% HQ are approved in the United States, while cosmetic goods with a concentration of 2 percent or fewer are permitted. The US Cosmetic Ingredient Review recently found that HQ is safe in cosmetic formulations designed for discontinuous, short application followed by washing skin and hair at concentrations less than 1%. In Japan, however, HQ is not classified as a prohibited or restricted cosmetic component, and several types of skin-lightening cosmetics containing HQ are available. Some of theme even contain up to 10% HQ. Since March 1, 2000, hydroquinone has been prohibited in European cosmetics for skin use. This does not prevent some companies from breaking the rules and using hydroquinone in topical treatments without first obtaining marketing approval. Since 1982, the dose "Generally Recognized As Safe and Effective" (GRASE) has been set at 1.5 to 2.0 percent. However, there are still many preparations on the American market containing larger doses of hydroquinone.

In Indonesia, the permitted hydroquinone level is two percent, as specified in the Regulation of the Head of the Food and Drug Supervisory Agency no. 18 of 2015, which is in shampoos and other preparations, not found in lightening creams. Furthermore, the maximum amount allowed of resorcinol in hair dye is 5%. Resorcinol is included in the FDA's final rule list of all permitted active ingredients for OTC topical acne treatments. An authorized combination active-component product is resorcinol at a concentration of 2% in combination with sulfur at a concentration of 3 to 8%.

Cosmetics containing hydroquinone are prohibited, according to a circular letter from the FDA in Indonesia. Excepting in the creation of 0.3 percent hair color, materials containing hydroquinone must be destroyed, according to circular letter No. PO.02.05.43.4496. This letter supports the previous regulation number HK.00.05.42.1018 dated 25 February 2008 about cosmetic ingredients, as well as the Circular Number PO.01.04.41.120 dated 27 September 2006 concerning cosmetic products containing hydroquinone [1, 19]. **Table 3** shows that 10 samples have high levels of resorcinol, with three having high levels of hydroquinone. This demonstrates that production fraud is still a problem.

Articles 8-17 of the Consumer Protection Law No. 8 of 1999 ban corporate actors or consumers to: not in accordance with the substance of the net weight and the image being promoted. There is no indication of when the product will expire. There is no indication of how to utilize the halal mark, and producers are barred from selling faulty items. To develop a product or a number of medications involving chemical compounds in Indonesia, a license is needed from the Food and Drug Supervisory Agency (BPOM) or a halal test from the Indonesian Ulema Council (MUI) is required. The product's marketing license can be cancelled if one of the licenses is not registered, as it violates the law.

The Consumer Protection Laws the government's endeavor to improve public welfare while protecting consumers and their rights, in accordance with Article 3 of the Consumer Protection Law, as the government's responsibility and protecting its people from this condition. A consumer of products and services must be able to determine if a consumable product is legal because this determines the quality of an item is guaranteed or not. Therefore, a consumer must have knowledge so as not to become a victim of consumption goods that violate the law.

4. CONCLUSION

Using whitening creams that do not have FDA or MUI labeling carries a significant danger. Although it produces rapid effects, it has a negative impact on users' health. Not all customers are aware of the negative consequences of using it. The presence of resorcinol and hydroquinone in excessive concentrations is harmful to the body. In the investigation, a quick and precise examination is crucial. TLC plates were very efficient for investigations in remote areas with high accuracy and precision. After the optimization and validation testing, it was determined that the eluene was Toluene: Diethyl Ether: Acetic Acid 80:20:1. Resorcinol and hydroquinone showed recovery rates of 51-66% and 80-87%, respectively. A total of 20 samples were examined. Resorcinol was found in 12 of the 20 whitening cream samples, while hydroquinone was found in four samples. The inclusion of resorcinol and hydroquinone increased the percentage of resorcinol and hydroquinone in Perka BPOM no. 18 of 2015 by 5%. Companies that break the rules must be held accountable. In this case, hydroquinone-containing chemicals in the facial whitening creams must be destroyed, according to regulation number PO.02.05.43.4496.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest among authors.

AUTHOR CONTRIBUTIONS

All authors contributed in conducting the experiment, writing, and revising the manuscript. All authors agreed to the final version of this manuscript.

REFERENCES

[1] Regulation of the Head of the Food and Drug Supervisory Agency of the Republic of Indonesia. 2013. Rule Number 34 Year 2013 concerning Amendments to the Regulation of the Head of the Food and Drug Supervisory Agency Number Hk.03.1.23.12.10.11983 of 2010 concerning Criteria and Procedures for Submitting Cosmetic Notifications.

[2] Pérez-Rueda, E., & Collado-Vides, J. 2000. The repertoire of DNA-binding transcriptional regulators in Escherichia coli K-12. *Nucleic Acids Res*. 28(8). 1838-1847. doi: 10.1093/nar/28.8.1838.

[3] Sari, S.D., Budiono, A., & Yulianie, D.A. 2020. Legal protection for skincare users that does not have a production license review of the consumer protection act. Media Keadilan: Jurnal Ilmu Hukum. 11(2). 156-168. doi: 10.31764/jmk.v11i2.3256.

[4] Astuti, D.W., Prasetya, H.R., & Irsalina, D. 2016. Identification in Whitening Creams Sold at Minimarkets in Minomartini, Yogyakarta. *Journal AMS*. 2(1). 13-19.

[5] De, A.K., Chowdhury, P.P., & Chattapadhyay, S. 2014. Quantitative analysis of resorcinol from marketed hair tonic using liquid chromatographic technique. *Int. Sch. Res. Notices*. 2014(632591). 1-5. doi: 10.1155/2014/632591.

[6] Aragó, M., Ariño, C., Dago, À., Díaz-Cruz, J. M., & Esteban, M. 2016. Simultaneous determination of hydroquinone, catechol and resorcinol by voltammetry using graphene screen-printed electrodes and partial least squares calibration. *Talanta*. 160. 138-143. doi: 10.1016/j.talanta.2016.07.007

[7] Yunianto, E.P., & Anggoro, Y. 2021. Understanding Illegal Cosmetic Circulation in Indonesian Online Marketplace through Problem Analysis Triangle. *JICP*. 4(3), 34-41. doi: 10.32535/jicp.v4i3.1297

[8] Arifiyana, D. Harjanti, Y.S. & Ebtavanny, T.G. 2019. Quantitative Analysis of Hydroquinone on Whitening Cream Cosmetic Products Circulating in Central Surabaya and North Surabaya using UV-Vis Spectrophotometry Method. *Akta Kimindo*. 4(2). 107-117. doi: 10.12962/j25493736.v4i2.5532

[9] Wang, Y.H., Avonto, C., Avula, B., Wang, M., Rua, D., & Khan, I.A. 2015. Quantitative determination of α-arbutin, β-arbutin, kojic acid, nicotinamide, hydroquinone, resorcinol, 4-methoxyphenol, 4-ethoxyphenol, and ascorbic acid from skin whitening products by HPLC-UV. *J. AOAC Int.* 98(1). 5–12. doi: 10.5740/jaoacint.14-123

[10] Kirkwood, K., & David Jackson, S. 2020. Hydrogenation and hydrodeoxygenation of oxygen-substituted aromatics over

rh/silica: Catechol, resorcinol and hydroquinone. *Catalysts*, 10(5). 1-17. doi: 10.3390/catal10050584

[11] Akyol, A., Can, O.T., Bayramoglu, M. 2015. Treatment of hydroquinone by photochemical oxidation and electrocoagulation combined process. *J. Water Process Eng.* 8. 45–54. doi: 10.1016/j.jwpe.2015.09.001

[12] Chen, Y.M., & Chavin, W.A.L.T.E.R. 1976. Hydroquinone activation and inhibition of skin tyrosinase. *Pigment Cell.* 3,.105-112.

[13] Engasser, P. G. 1984. Ochronosis caused by bleaching creams. *J. Am. Acad. Dermatol.* 10(6).1072-1073. doi: 10.1016/s0190-9622(84)80351-5

[14] Bellmaine, S., Schnellbaecher, A., & Zimmer, A. 2020. Reactivity and degradation products of tryptophan in solution and proteins. *Free Radic. Biol. Med..* 160. 696-718. doi: 10.1016/j.freeradbiomed.2020.09.002

[15] Hull, P.R., & Procter, P.R. 1990. The melanocyte: an essential link in hydroquinone-induced ochronosis. *J. Am. Acad. Dermatol.* 22(3). 529-531. doi: 10.1016/S0190-9622(08)80401-X

[16] Pillaiyar, T., Manickam, M., & Namasivayam, V. 2017. Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors. *J. Enzyme Inhib. Med. Chem.* 32(1). 403–425. doi: 10.1080/14756366.2016.1256882

[17] Levin, C.Y., & Maibach, H. 2001. Exogenous ochronosis. *Am. J. Clin. Dermatol.* 2(4), 213-217.

[18] Qian, W., Liu, W., Zhu, D., Cao, Y., Tang, A., Gong, G., & Su, H. 2020. Natural skin-whitening compounds for the treatment of melanogenesis. *Exp. Ther. Med.* 20(1) 173-185. doi: 10.3892/etm.2020.8687

[19] Kang, M., Park, S. H., Oh, S. W., Lee, S. E., Yoo, J. A., Nho, Y. H., Lee, S., Han, B. S., Cho, J. Y., & Leea, J. 2018. Anti-melanogenic effects of resorcinol are mediated by suppression of cAMP signaling and activation of p38 MAPK signaling. *Biosci. Biotechnol. Biochem.* 82(7). 1188–1196. doi: 110.1080/09168451.2018.1459176