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COMPARISON OF UV-VIS SPECTROPHOTOMETRIC AND HPLC METHODS IN THE ANALYSIS OF RETINOIC ACID AND HYDROQUINONE CONTENT IN FACE CREAMS: A LITERATURE REVIEW

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ABSTRACT

UV-Vis spectrophotometry and HPLC are commonly used for the analysis of hydroquinone and retinoic acid, as both instruments offer a combination of accuracy, sensitivity, and ease in detecting and quantifying these compounds. UV-Vis is quick and simple to detect the content of materials based on light absorption, while HPLC is superior in separating and analyzing compounds in complex mixtures with high precision. The purpose of this literature review is to compare UV-Vis Spectrophotometry and HPLC methods for analyzing hydroquinone and retinoic acid, and a comparison was performed by examining method validation data between UV-Vis spectrophotometry and HPLC. The method applied involves a review of various related research journals, utilizing the Publish or Perish application using the Google Scholar and Semantic Scholar search engines. The results and conclusions of this study recommend HPLC as the method of choice for the identification of harmful substances, such as retinoic acid and hydroquinone, in face creams.

Keywords: retinoic acid, hydroquinone, face cream, uv-vis spectrophotometry, HPLC

INTRODUCTION

As the outer element of the human body, the skin plays a role in protecting vital organs from harm, regulating body temperature, functioning as a touch sensor or sense of touch, and fulfilling other functions. One type of human skin is facial skin, which protects important organs such as the eyes, mouth, and nose (Wahyuningtyas *et al*., 2015). Facial skin is the main part of the body and shows a person's health (Sanghi and Tiwle, 2016). In addition, facial skin is a type of skin which in daily activities is more often directly exposed to external elements, one of which is ultraviolet light.

Because facial skin tends to be more often exposed to UV rays, care is needed, such as with facial creams. Increased consumer interest in face creams that can brighten and whiten is increasing, and women in Indonesia in the modern era now tend to keep their appearance attractive (Tetha and Sugiarso, 2016). To fulfill this desire, they utilize a variety of skin care methods, ranging from natural to instant, using various types of cosmetics, without often checking more carefully whether the chemicals in these cosmetics can have harmful effects on the skin of the user in the future (Nurjanah *et al*., 2020).

According to BPOM in 2019, cosmetics refer to materials or products used on the surface of the human body, such as the outer skin, hair, nails, lips, external genital organs, teeth, and oral mucous membranes. The purpose of their use is to provide fragrance, clean, change appearance, eliminate body odor, or keep the body in good health (BPOM, 2019).

One of the most commonly used cosmetic products for skin lightening is whitening creams. Whitening creams improve skin color and remove dark spots on the skin (Sarah, 2014). In general, when using whitening creams, people often use these products without

paying close attention to their ingredients and potential side effects. People are more likely to focus on quick results and brighter skin after use (Nugroho *et al*., 2019).

Retinoic acid, also known as tretinoin, is beneficial for acne treatment and is often found in whitening products because of its ability to reduce skin pigmentation (Nursidika *et al*., 2018). Retinoic acid belongs to the category of hard drugs that can only be obtained with a doctor's prescription (Sumarno and Kusumaningtyas, 2018). However, many cosmetic products containing retinoic acid are sold freely without a doctor's prescription. Retinoic acid has potential side effects such as burning sensation on the skin, teratogenic properties, and carcinogenicity (Agustina *et al*., 2019). In addition to retinoic acid, hydroquinone is also a chemical often included in whitening creams (Sarah, 2014). Hydroquinone is a compound with carcinogenic potential that can trigger the growth of cancer cells. Negative effects that often occur include burning sensation, itching, and skin irritation, as well as problems in the ear and fingers. Therefore, it is necessary to closely monitor their long-term use (Arifiyana *et al*., 2019).

Many studies have been conducted on the evaluation of hydroquinone and retinoic acid levels in face whitening creams, some of which utilized analytical methods using UV-Vis spectrophotometry. Such as research conducted by (Syafira, 2022), with samples of night cream products in the Pekalongan City area, (Fariha *et al*., 2023) who also examined samples of face creams purchased online, (Purwanitiningsih *et al*., 2023) tested face whitening creams from Ciracas Market, and (Fajariyani and Huwaid, 2022) examined face whitening creams from Cililitan Wholesale Center, all of which used a UV-Vis spectrophotometer for their analysis. However, these two hazardous substances or ingredients cannot be analyzed using UV-Vis spectrophotometric instruments alone. On the other hand, instruments such as KCKT or High Performance Liquid Chromatography (HPLC) have high selectivity where researchers will get the results as expected, this instrument has also been carried out by previous research in the study (Fertiasari *et al*., 2023) analyzing hydroquinone in cosmetics using HPLC, (Budiarti and Vuqohan, 2016) also examined the content of retinoic acid in night cream using HPLC.

In addition to utilizing UV-Vis spectrophotometry and HPLC, in another study by Fudjayanti and Suarantika (2022) evaluating the levels of hazardous substances such as hydroquinone can also use other quantitative analysis techniques such as High Performance Thin Layer Chromatography-Densitometry (KLTKT-D), and Voltammetry.

Of the several methods described, the author is interested in conducting a review article using two instruments that are most often or commonly used in analyzing hazardous substances in cosmetic products, namely analytical methods with UV-Vis spectrophotometry and HPLC.

RESEARCH METHODS

Researchers conducted a literature search using the Publish or Perish application, Google Scholar, and Semantic Scholar search engines using Indonesian and English. We produced 200 studies and carried out a screening process, setting criteria to select the 20 studies that were most relevant to the problem discussed or in accordance with the topic raised.

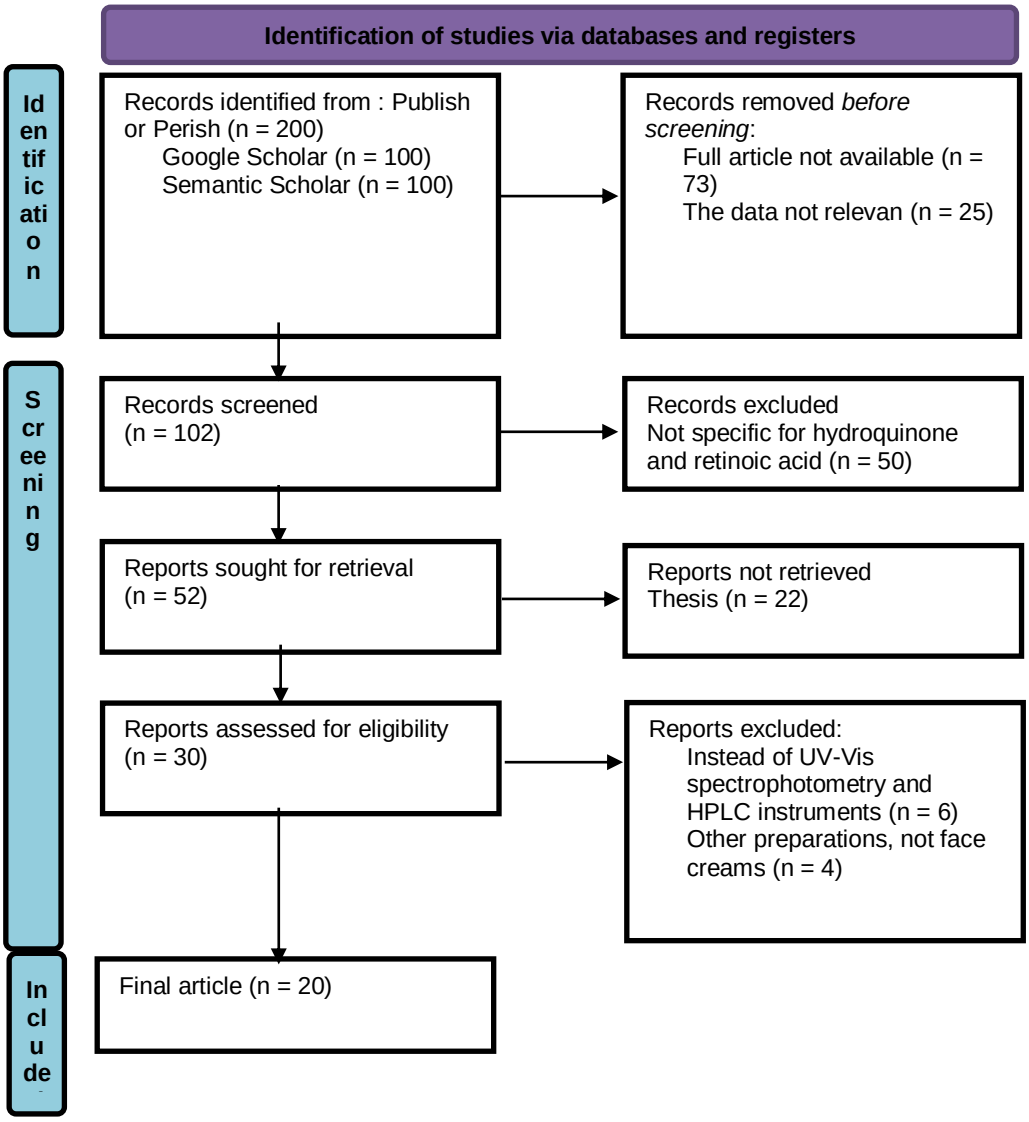

Figure 1. Flow chart PRISMA 2020 *systematic literature review*

The next step was to read the abstractions and select based on the method used, which resulted in 15 studies that met the predetermined criteria. Each selected journal was considered to be relevant to the discussion. Inclusion and exclusion criteria are listed in Table I.

Table I. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Type of literature study	Research articles or journals	Blog, Citation, e-Book
Year of publication	2014-2024	< 2014
Relevance of the study	A study that describes the validation parameters used and discusses the analysis of Hydroquinone and Retinoic Acid using UV-Vis Spectrophotometry and HPLC instruments.	Studies that did not discuss the validation parameters they used in the analysis of the hazardous substances Hydroquinone and Retinoic Acid and used instruments other than UV-Vis spectrophotometry and HPLC.

RESULT AND DISCUSSION

When identifying hazardous substances such as hydroquinone or retinoic acid in cosmetic preparations, namely face creams, the results obtained need to be observed and tested by validating the analysis method (Hadriyati *et al*., 2021). This validation was intended to confirm that the method to be applied meets the criteria for the intended analysis and can account for its accuracy (Rohmah *et al*., 2021). To ensure accurate results from all the methods or test procedures used, validation was carried out by checking certain parameters (Fudjayanti and Suarantika, 2022).

UV-Vis spectrophotometry is an important experimental tool for chemical analysis (Yohan *et al*., 2018). This instrument is often used in chemical field analyses to detect compounds (solid or liquid) based on photon absorbance (Irawan, 2019). Usually, the compounds that can be detected using this method are those with chromophores and auxochrome groups (Sahumena *et al*., 2020). Functional UV-Vis spectrophotometry is used for qualitative and quantitative analyses but is more commonly used for quantitative analysis. The spectrophotometer functions as a tool for measuring the transmittance or absorbance of a sample at a certain wavelength (Miarti and Legasari, 2022).

High Performance Liquid chromatography (HPLC) is a method for separating, identifying, and measuring the components in a mixture (Yulia *et al*., 2021). The function of the HPLC instrument is more or less the same as that of UV-Vis spectrophotometry, which is used for qualitative and quantitative separation analysis techniques, as well as for separation, isolation, and purification (Angraini and Desmaniar, 2020). HPLC has also been used to identify and quantify compounds during the development process (Tumanduk *et al*., 2023). The basic principle of HPLC is the separation of analytes based on their polarity using a column as the stationary phase and a certain solution as the mobile phase (Agustina *et al*., 2019). The advantages and disadvantages of UV-Vis spectrophotometry and HPLC are listed in Table II.

Table II. **Advantages and Disadvantages of UV-Vis Spectrophotometry and HPLC Methods**

No.	Method	Time	Cost	Results
1.	UV-Vis	Fast and accurate, able to determine the quantity of compounds in very small quantities (Rohmah *et al*., 2021).	UV-Vis spectrophotometry is easy to use and simple, costs tend to be efficient because it is cheaper (Nadhila and Nuzlia, 2021).	The resulting absorbance results are influenced by various variables, not always consistent, can be influenced by the type of solvent, pH of the solution, temperature, and the presence of disturbing substances (Mundriyastutik *et al*., 2021).
2.	HPLC	HPLC allows a longer time than UV-Vis spectrophotometry, due to the retention time, which is the time interval required by the analyte to be maximally captured by the detector (Sukma and Fajri., 2019).	Lack of cost efficiency. High flow rates require substantial costs for the purchase and disposal of solvents that have high quality purity (Tumanduk *et al*., 2023).	Another advantage of HPLC is that it only requires a small sample volume, but can produce maximum results (Tumanduk *et al*., 2023). HPLC is a recent development of classical liquid

				chromatography, utilizing columns, more sensitive and fast-responding detectors, and the latest technological advances (Abriyani *et al.*, 2024).

Based on the advantages and disadvantages of UV-Vis spectrophotometry and HPLC instruments above, the results of method validation, namely accuracy, precision, specificity, measurement linearity, IDL, and LOQ, can also be considered to be better and more accurate in identifying certain substances of interest in a preparation, such as hydroquinone and retinoic acid in facial creams. Then, journal data analysis was carried out by comparing the method validation results of the two instruments, which are reviewed in Table III below.

Table III. Journal Review Results

No	Author and Year	Analysis Method	Chemical Substances	Validation Parameters					
				Accuration	Precision (% RSD)	Linearity	LOD (µg/mL)	LOQ (µg/mL)	Selectivity/ Specificity
1.	Budiarti and Vuqohan (2016)	HPLC	Retinoic Acid	99.44%–101.42%	0.37	0.9996	0.16	0.54	Selective
2.	Hadriyati *et al*., (2020)	HPLC	Retinoic Acid	88%–97.90%	0.67	0.9982	0.4689	1.5659	-
3.	(Maggadani *et al*., 2019)	HPLC	Hidrokuinon	99.63%–99.92%	0.20	0.9999	6.86	22.89	Selective
4.	Rejeki and Pramiastusi (2022)	HPLC	Hidrokuinon	-	-	0.9999	-	-	Selective
5.	Lestari and Prasasti (2018)	HPLC	Hidrokuinon	-	0.62	0.9932	-	-	Selective
6.	Erlan *et al*., (2023)	Spektro UV-Vis	Retinoic Acid	98.77%–102.53%	0.47	0.9956	0.0695	0.2317	-
7.	Gabriela *et al*., (2022)	Spektro UV-Vis	Retinoic Acid	-	-	0.9877	0.251	0.853	-
8.	Muadifah and Ngibad (2020)	Spektro UV-Vis	Hidrokuinon	97.5%	0.87	0.9594	3.373	6.704	-
9.	Saraswati and Perwitasa	Spektro UV-Vis	Hidrokuinon	87.42%–98.09%	1.69	0.9986	-	-	-

	ri (2022)								
10.	Sari *et al*., (2023)	Spektro UV-Vis	Hidrokuinon	92.36%–107.22%	0.87	0.9993	0.0747	0.1582	Selective
11.	Irnawati (2016)	Spektro UV-Vis	Hidrokuinon	97.19%–101.4%	0.08	0.9998	0.471	1.570	Not Selective
12.	Kurniawan *et al*., (2022)	Spektro UV-Vis	Hidrokuinon	99.581%–100.68%	0.48	0.9999	0.2742	0.9140	-
13.	Sirait and Widhihastuti (2023)	Spektro UV-Vis	Hidrokuinon	99.962%–100.85%	0.84	0.9973	2.5	8.3	-
14.	Sarah (2014)	Spektro UV-Vis	Hidrokuinon	90.8%–101.73%	-	0.9993	0.06	0.18	-
15.	Rahmadari *et al*., (2021)	Spektro UV-Vis	Hidrokuinon	-	0.38	0.9912	0.2925	0.9749	-

As shown in Table III, to ensure that all the test methods or procedures achieve accurate results, it is necessary to validate the parameters (Fudjayanti and Suarantika, 2022). Validation of this analytical method includes tests for accuracy, precision (% RSD), limit of detection (LOD), limit of quantification (LOQ), selectivity, and specificity. The sample preparation method used in all studies in this journal review used the same sample, namely, the type of cosmetic preparation in the form of a cream. To validate the selectivity or specificity test methods, only a few studies have used selectivity or specificity tests for their analysis.

a. Accuracy

Accuracy is the extent to which test results are close to the true or reference values. Accuracy was measured as a percentage of recovery (Erlan *et al*., 2023). The recovery value was within the acceptable range of 98–102% (Budiarti and Vuqohan, 2016). Some argue that the range of accuracy value requirements can still be said to be good at 80–120% or 70–130%. This is because of the more complex sample preparation and the more difficult the analysis method used, so that the recovery tends to be lower or the range is wider (Erlan *et al*., 2023).

The results obtained from several studies in Table III, the results of recovery, or the value of recovery in hydroquinone chemicals with UV-Vis spectrophotometric instruments and HPLC, the accuracy value obtained meets the requirements, because it is in the range of 80–120%. For the analysis of retinoic acid hazardous substance samples using UV-Vis Spectrophotometry or HPLC, the accuracy value obtained also met good accuracy standards, and the accuracy value of the retinoic acid method validation with UV-Vis spectrophotometry and HPLC instruments was also in the 80%–120% range.

b. Precision

Precision is a measure of the level of uncertainty in analysis results. The precision test was carried out using the repetition method, thus achieving a high level of accuracy (Sahumena *et al*., 2020). This precision was expressed as the Relative Standard Deviation (RSD) value (Muadifah and Ngibad, 2020). The smaller the RSD value, the higher is the accuracy, and vice versa. The greater the RSD value, the lower is the precision. A precision test was declared to have a high level of accuracy if the RSD value was ≤ 1% (Rahmadari *et al*., 2021). Other studies also mentioned that RSD describes the accuracy of the test method: RSD ≤ 1% indicates very high accuracy, 1% < RSD ≤ 2% indicates good accuracy, 2% < RSD ≤ 5% indicates moderate accuracy, and RSD > 5% indicates low accuracy (Sulistyani *et al*., 2021).

Precision tests from several studies that have been reviewed show good results and a high level of accuracy because the average precision test value is in the range of less

than 1%. The results obtained for the analysis of hydroquinone samples using UV-Vis Spectrophotometry showed that the best precision test value was 0.08%, whereas the analysis of hydroquinone using HPLC instruments showed the best precision value at 0.20%. For retinoic acid analysis, the research results obtained, using UV-Vis spectrophotometry in this journal review are 0.47%, for retinoic acid samples with HPLC instruments, the precision value obtained is 0.37%.

Validation of precision test methods when viewed from literature search data in this review, the precision value of UV-Vis Spectrophotometry with hydroquinone samples tends to have better results than using HPLC; on the other hand, for retinoic acid samples, HPLC instruments obtained better precision values than UV-Vis spectrophotometry. The smaller the RSD value, the higher the precision, and vice versa (Rahmadari *et al*., 2021).

c. Linearity

The linearity test aims to determine whether there is a relevant linear relationship between the substance being analyzed and the instrument used (Hutauruk, 2024). A correlation coefficient value close to or reaching 1 indicates that there is a linear relationship between absorbance and analyte concentration (Sari *et al*., 2023).

The linearity results of several reviewed studies obtained the following results: for the analysis of hydroquinone samples using UV-Vis Spectrophotometry, the best linearity value was 0.9999, while the analysis of hydroquinone using HPLC instruments showed the best linearity value of 0.9999. Then, in the analysis using retinoic acid samples, the results of research with UV-Vis Spectrophotometry instruments the best linearity value in this journal review is 0.9877, and for the analysis of retinoic acid samples with HPLC instruments the best linearity value based on the literature in this review is at a value of 0.9996.

Method validation in the linearity test for hydroquinone samples, both methods, namely UV-Vis Spectrophotometry and HPLC, had the same relevant linearity value (0.9999), and both methods had a good relationship between the analyzed substance and the instrument used to analyze hydroquinone samples in facial creams. For retinoic acid samples, the linearity of the HPLC method was better than that of UV-Vis Spectrophotometry because the best value obtained was in the analysis using the HPLC instrument, which was 0.9996.

d. LOD (Limit of Detection) & LOQ (Limit of Quantification)

LOD indicates the smallest limit that can be measured by a device or instrument to detect a certain amount of analyte (Kurniawan *et al*., 2022). The LOQ is the lowest concentration of analyte in a sample that can still be quantified or measured with accuracy and precision using a tool or instrument (Sumarno and Kusumaningtyas, 2018). The analyzed sample must have a value above the LOD and LOQ to ensure that the results can be detected and measured precisely (Erlan *et al*., 2023). Similarly, in a research journal (Rahmadari *et al*., 2021), the calculation of LOD and LOQ that has been calculated through linear regression was compared with the measured concentration of hydroquinone and retinoic acid measured in the cream sample; if it is greater, the measured signal is a signal of hydroquinone and retinoic acid, and the measurement results can be trusted. Conversely, if the concentration obtained was lower than the calculated LOD and LOQ values, the signal obtained was not suspected to be from hydroquinone and retinoic acid (Mundriyastutik *et al*., 2021).

Based on the data from the journal review results in this journal review, on average, almost all of their research validates the LOD and LOQ method, and the validation results for hydroquinone and retinoic acid samples using both UV-Vis Spectrophotometry and HPLC have good results, and the measurement results can be trusted. The samples analyzed had values above the LOD and LOQ, in line with the theory described. As one of the research literature in this journal review describes the value of their samples exceeding the LOD of 0.0695 ppm and LOQ of 0.2317 ppm, it can be concluded that the research results can be detected and measured (Erlan *et al*., 2023).

HPLC and UV-Vis Spectrophotometry have good LOD & LOQ tests, can show the smallest limit they can measure in detecting a number of analytes.

e. Selectivity/Specificity

Selectivity/specificity is the ability of a method to distinguish certain analytes from others (Sulistyani *et al*., 2021). Specificity refers to the ability to accurately measure the intended analyte despite the presence of other components in the sample matrix, such as impurities, degradation products, and other matrix components (United States Pharmacopeial Convention, 2014). In the literature review of this journal, research that includes validation tests of selectivity methods is found in research conducted by Budiarti and Vuqohan (2016) with HPLC instruments (Sari *et al*., 2023) and Irnawati *et al*. (2016), using UV-Vis Spectrophotometry instruments.

In chromatographic techniques, selectivity can be proven through good separation between analytes and other components. A good chromatogram must meet several criteria, namely, a symmetrical peak, a retention time of less than 10 minutes, and a resolution equal to or greater than 1.5. In another journal that examined the characterization of chromatogram peaks in HPLC, the HPLC values are said to be good chromatograms and have met the requirements in their analysis, one of which is indicated by the existing resolution values (Rosydiati, 2019).

The results of this literature review show that only a few studies have used selectivity validation tests for hydroquinone samples with the UV-Vis Spectrophotometer method, and one study with this method showed good selectivity results. Selectivity was measured by determining the maximum wavelength of the hydroquinone standard, sample X, and the blank. The results of UV-Vis Spectrophotometry selectivity can be said to be good because the results of the standard wavelength of hydroquinone 293 nm with a wavelength of sample X 300.1 nm show closeness; therefore, the analysis method has good selectivity in measurement (Sari *et al*., 2023). On the other hand in the literature review of this journal, in research (Irnawati *et al*., 2016), which also used the UV-Vis Spectro method for their hydroquinone analysis, it was found that the selectivity or specificity test showed that this method was not specific for hydroquinone samples. The results obtained were 2 peaks formed with a shift in the maximum wavelength (λ max), the required parameters are 2 peaks formed with λ max which should be exactly or the same as the standard (Sulistyani *et al*., 2021).

Furthermore, for retinoic acid samples, research using selectivity tests is also only a few studies, namely research using HPLC instruments alone that conduct selectivity tests including research conducted (Maggadani *et al*., 2019; Lestari and Prasasti, 2018; Rejeki and Pramiastuti, 2022) the results of selectivity tests in their journals explain that HPLC has good selectivity, indicated by resolution values, and good retention times. The resolution value in one of the studies was ≥ 1.5, and the retention time was less than 5 minutes, indicating good separation. A good chromatogram must meet several criteria, namely, a symmetrical peak, retention time of less than 10 minutes, and resolution of or more than 1.5 (Rosydiati, 2019).

Based on the results of the study, researchers found that the most effective method for the analysis of hydroquinone was HPLC, while for the analysis of retinoic acid, the recommended method or instrument is the same as the hydroquinone sample, namely using the HPLC method, compared to UV-Vis Spectrophotometry. This was observed from the listed method validation parameters. For hydroquinone samples, the precision test results of the UV-Vis Spectrophotometry method were better than those of the HPLC instrument, but in other research journals, the UV-Vis Spectrophotometry method obtained results that were not as effective in selectivity or specificity tests. Therefore, HPLC can be said to provide better results in validating the test method for analyzing hydroquinone in facial creams. However, keep in mind that variations in the results obtained can be caused by several factors, including differences in laboratory environmental conditions, type of instrument used, and accuracy of the analyst (Wardaniati and Taibah, 2019). Each analyst has a different level of expertise; therefore,

the results obtained can also be different (Fudjayanti and Suarantika, 2022). To identify hazardous ingredients in facial cream preparations, the method to be chosen is also re-adjusted to the analyst's own conditions such as cost, available time, availability of laboratory equipment, available materials, and research objectives (Sirait and Widhihastuti, 2023). UV-Vis spectrophotometry, when viewed in the validation of this journal literature review study method, also has quite good results, which can also be considered. If researchers review it in terms of cost, UV-Vis spectrophotometry tends to be efficient because it is cheaper (Nadhila and Nuzlia, 2021). HPLC is a sophisticated tool that is superior in terms of technological advances and the development of chromatography with high-pressure pumps (Rosydiati, 2019).

CONCLUSION

Based on the overall validation results in this literature review, the HPLC method is superior in analyzing harmful substances such as retinoic acid and hydroquinone in facial creams. This is because HPLC has a more sensitive detector, as well as equipment equipped with advanced technology with high pressure pumps, and all validation parameters of each method that have been developed can be compared based on the accuracy, precision, and selectivity test values in accordance with the requirements, so that the final result allows the results to be accurate and as expected.

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