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Validation of RP-HPLC Method for Determination of Curcumin Content Obtained from E-Commerce

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ABSTRACT

Among the curcuminoid compounds, curcumin is the dominant component and has promising hepatoprotective activity. Although the curcumin content in turmeric rhizomes varies, it is not less than 3.82%. The pharmacological effectiveness of curcumin is highly dependent on accurate and consistent dosage. Along with the rise of traditional medicine sales through e-commerce, determining curcumin levels is crucial to ensure product safety, efficacy, and quality. This study aims to measure the curcumin content in turmeric capsules obtained from e-commerce using the reversed-phase HPLC method with octadecylsilane stationary phase (C18), mobile phase HPLC grade methanol: 0.5% phosphoric acid (60:40), flow rate 0.8 ml/min with a wavelength of 425 nm. The validation parameters tested were selectivity, linearity, accuracy, precision, LOD and LOQ. The results showed that the reversed phase HPLC method has good selectivity with the same Rt value 2.624 and Rs ≥ 1.5 on curcumin standard obtained RS of 1.70 and 1.88 on the sample. The linearity test results obtained an R value of 0.9999 means that it meets the requirements of R > 0.99. The accuracy test with 80% addition is 96.141% ± 0.682, 100% addition is 94.081% ± 5.789 and 120% addition is 94.591% ± 5.723. In the repeatability test % RSD values obtained were 0.789%, 6.153%, and 5.500% respectively, which means that the %RSD < 8% is qualified. In the LOD and LOQ results obtained 0.917 µg/mL and 3.058 µg/mL. Validation of analytical methods in accordance with established requirements. The curcumin content produced in samples that have a BPOM license is higher at 12.757% ± 0.7177 than those that do not have a BPOM license which is 0.187633% ± 0.00583.

INTRODUCTION

In Indonesia, traditional medicinal herbs are the main choice for maintaining health. The use of traditional medicine is considered safer than the use of modern medicine because it has relatively fewer side effects (Sumayyah *and* Salsabila, 2017). Among various medicinal plants, turmeric *(Curcuma longa L.)* from the Zingiberacea family is one of the best known (Farmakope Herbal Indonesia Edisi II, 2017).

Turmeric rhizome has several benefits for overall health. Turmeric has an essential oil content of 1.85% and a curcumin content of 3.82%. Curcumin has health properties as immune modulation, cardiovascular, and neuroprotection (Fu *et al.*, 2021). In the market, many turmeric extract products have been circulated, the most famous of which is the capsule form (Hamidah *et al.*, 2024). These capsules are marketed in traditional medicine stores, pharmacies, markets, and e-commerce

E-commerce is a solution for small companies to adapt and improve efficiency. The platform allows them to produce flexibly, take orders quickly, and deliver products to customers

efficiently, thereby increasing their competitiveness in the market (Riswandi, 2019). But the existence of e-commerce also provides a loophole for irresponsible manufacturers, by selling their products without having a license from Food and Drug Administration of the Republic of Indonesia (BPOM).

In January to April 2023, BPOM has found 9,597 links to the sale of illegal traditional medicines in online stores (BPOM RI, 2023). Entrepreneurs are obliged to ensure that products circulated online meet the requirements of safety, efficacy, and quality in accordance with the provisions of laws and regulations. To fulfill the requirements of safety, efficacy and quality, it is necessary to know the quality of the products sold in e-commerce. As an effort to maintain the safety, efficacy and quality of herbal medicines, especially those sold in e-commerce, it is necessary to know the levels contained in the herbal medicine products (Hanwar *et al.*, 2021).

To establish levels, validated methods need to be used, to confirm and confirm. Method validation ensures that the procedure is capable of producing results that are accurate, reliable and fit for their intended use (2020). The main objective of method validation is to ensure that the methods we use can produce accurate and reliable data (Ulfa *and* Winahyu, 2017).

Some of the methods used in identifying and determining the levels of curcumin in turmeric are uv-vis spectrophotometry, IR spectroscopy, thin layer chromatography, and high performance thin layer chromatography, high performance liquid chromatography, UHPLC (Ultra high-performance liquid chromatography) and liquid chromatography-mass spectrometry (Kotra *et al.*, 2019).

Reversed-phase HPLC (RP-HPLC) is the most commonly used HPLC and as the name suggests this type is the opposite of normal phase HPLC (NP-HPLC), where the stationary phase is nonpolar and the mobile phase is polar (Sarker *and* Nahar, 2015). The more hydrophobic a molecule is, the higher its tendency to remain in the stationary phase because the energy gain by its removal from the mobile phase is higher, since the "retention" of analytes with nonpolar molecules in RP-HPLC is actually a "rejection" from the mobile phase (Moldoveanu *and* David, 2017).

Previous research by (Hanwar *et al.*, 2020), has conducted a validation test of the HPLC method for curcumin analysis in Curcuma zanthorrhiza using an Alliance 2998 HPLC instrument equipped with a SunFireTM C18 column. A mixture of acetonitrile (60%) and 0.5% phosphoric acid (40%) with the aim of ensuring the quality of curcumin extract both as raw material and as a final product. The validity test results were valid as seen from the good validation parameter values.

The next research by (Hanwar *et al.*, 2021), intends to measure the curcumin content in temulawak extract sold in the market and compare the measurement results with the claims written on the product label using the HPLC method. Analysis of curcumin content was carried out on Curmino products which claimed 5 mg of curcumin and Diapet which claimed 120 mg of Curcuma domestica. The results showed that Curmino contains 4,996 mg curcumin or equivalent to 99.91% of the claim, indicating that the measured levels are close to the claim.

The aim of this study was to examine the curcumin content in turmeric capsules sold online and ensure their quality. For this reason, testing of the analytical methods used was carried out so that the results were accurate and reliable.

METHODS

The type of research is laboratory experimental using samples of curcumin extract capsules licensed by BPOM and not licensed by BPOM with the RP-HPLC method to separate curcumin compounds from other compounds contained in the sample. The parameters tested include linearity, accuracy, precision, selectivity, limit of detection, and limit of quantification are expected to provide good values so that they can be used for determining curcumin levels in capsule preparations.

Materials and Equipments

Turmeric extract capsules with BPOM license, turmeric extract capsules without BPOM license, curcumin standard (Merck), acetonitrile grade HPLC (Merck), methanol grade HPLC (Merck), Orthophosporic acid grade pro analysis (Merck).

Agilent 1220 infinity II HPLC instrument, Column EC-C18 2.7 µm size 4.6 x 100 mm (Poroshell 120), software OpenLab CDS

v.2.7.0.683, ultrasonic bath (GT Sonic), glass stirrer, micropipette (Dragonlab), 10 mL volumetric flask (Herma), beaker glass (Herma), 5mL syringe (terumo), micron syringe filtre 25mm x 0.45 µm.

Preparation of Standard and Reference Solutions

Curcumin standard (Merck) was weighed as much as 25 mg, then dissolved with methanol grade HPLC until the mark in a 25 mL measuring flask, so that a concentration of 1000 µg/mL was obtained, then sonicated for 10 minutes with an ultrasonic bath. Working standard solutions were made with concentrations of 50, 60, 70, 80, 100 and 110 µg/mL. Taken from the dilution of 1000 µg/mL standard solution.

Sample Preparation

The sample was selected in e-commerce with a store that already sells the product, with a price comparison that is cheaper than turmeric extract that has a permit from BPOM. Twenty capsules were taken and weighed one by one. The contents of the capsule were removed, weighed all parts of the capsule shell, the weight of the capsule contents and the average weight of each capsule contents were calculated, then taken as much as the average weight of 20 capsules. Then dissolved in a 10 mL volumetric flask by adding methanol until the 10 mL limit mark, then sonicated for 10 minutes using an ultrasonic bath (GT sonic).

RESULT

Chromatography System

In this research, a mixture of acetonitrile (Merck) grade HPLC and phosphoric acid 0.5% (Merck) grade pro analysis in a ratio of 60:40 was used as the mobile phase with isocratic elution. Before use, the mobile phase components were filtered twice using a 25mm x 0.45 µm microfilter filter and degassing by ultrasonification. Column EC-C18 2.7 µm size 4.6 x 100 mm (poroshell 120) was used as the column. The wavelength was 425 nm and the flow rate was 0.8/min. The running time of 3 minutes was used because the curcumin chromatogram had been detected optimally marked by the absence of a chromatogram that was read after 3 minutes as shown in **Figure 1**.

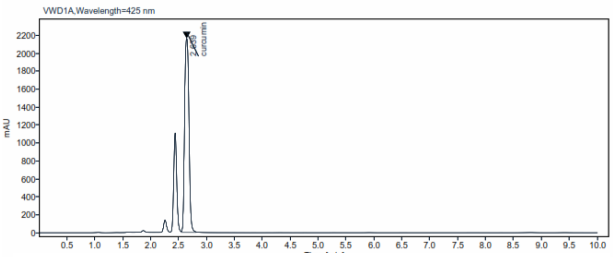

Figure 1. Chromatogram of curcumin standart

In curcuminoids there are 75% curcumin compounds, 20% demethoxycurcumin and 5% bisdemethoxycurcumin. it indicates that the highest peak is the curcumin compound (Wahyuni *et al.*, 2018).

Linearity

Linearity aims to ensure that the analytical method is able to produce results that are proportional to the concentration of the analyte in the sample. The R value in Linear Regression expresses the linear relationship between grade and area. An R value of more than 0.99 indicates that the relationship is highly correlated and reliable (Riyanto, 2014). Linearity parameters were taken from curcumin standard using RP-HPLC with C-18 column and acetonitrile : methanol (60 : 40) mobile phase.

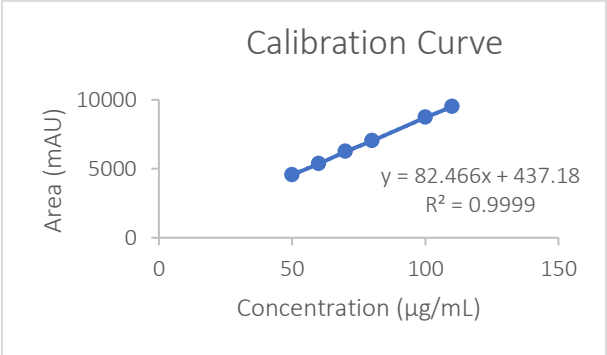

Figure 2 Calibration curve

A series of standard working solutions with concentrations of 50, 60, 70, 80, 100, and 110 µg/mL were prepared. Each concentration was taken 10 µl and injected into the HPLC instrument. The standard curve is a reference in Inaccuracy in making the standard curve will cause systemic errors in determining the sample content. In **Figure 2**, illustrates good linearity results with a value of y = 82.466x + 437.18; R = 0.9999 which means it has a good correlation between concentration and response, this shows that with increasing concentration it will increase the area produced (Setyaningsih *et al.*, 2021).

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

LOD is the lowest limit of a substance that can still be detected by the device, while LOQ is the lowest limit of a substance that can still be measured accurately and precisely (Farida & Muliya, 2023). In this research using the calibration curve method to determine the LOD and LOQ values by taking the y value obtained from linearity. This can be expressed in a model such as y = bx + a. This model is used to calculate sensitivity b and LOD and LOQ (Riyanto, 2014). Calculation of LOD and LOQ using **equation 1-3.**

$$LOD=(3 \times S(y/x))/slope \quad \textbf{(1)}$$

$$LOQ = (10 \times S(y/x))/slope \quad \textbf{(2)}$$

$$S(y/x)=\sqrt{(y-yi)2/(n-2)} \quad \textbf{(3)}$$

LOD and LOQ tests using curcumin samples that are licensed by BPOM with test concentrations of 50, 60, 70, 80, 90, 100 and 110 µg/mL. Each concentration was taken 10 µL and injected into the HPLC instrument.

In **Table 1**, the LOD result is 0.917 µg/mL and LOQ is 3.058 µg/mL. The LOD value indicates the smallest amount of analyte that can still be measured by HPLC while LOQ is the lowest concentration of analyte that can be reliably measured through analytical procedures (Riyanto, 2014). Therefore, the analysis of curcumin levels by HPLC method can still be read with a limit of 0.917 µg/mL and the lowest analyte concentration that can be reliably measured is 3.058 µg/mL.

Table 1 Test results of limit of detection, limit of quantity

Concentration (µg/mL)	Area	Area
51.704	4555.795	4560.480
61.542	5375.963	5385.140
71.907	6240.149	6209.800
81.144	7010.360	7034.460
101.516	8708.911	8683.780
110.896	9491.007	9508.440
Average		6897.017
S/y		25.217
LOD		0.917 µg/mL
LOQ		3.058 µg/mL

Repeatability

Repeatability measures the agreement between measurement results obtained from repeated tests on identical samples, under the same test conditions, and within a short time interval (Peris-Vicente *et al.*, 2015). Reproducibility indicates how consistent test. The precision of a measurement is usually expressed by the value relative standard deviation (RSD). The smaller the RSD value, the more precise the measurement results (Arbianto *et al.*, 2019).

In this research using the repeatability method, using 3 concentrations and 3 repetitions of each concentration (United States Pharmacopeia, 2023). Concentrations of 90 µg/mL, 100 µg/mL, and 110 µg/mL were made using sample A Each concentration was taken 10 µl and injected into the HPLC instrument with the condition that the RSD value was ≤ 8%.

Table 2 Precision results

Concentration (µg/mL)	Respon		Average (µg/mL)	SD	RSD (%)
	Concentration	Area			
90	87.312	7524.614	86.527	0.682	0.789
	86.197	6066.387			
	86.073	7421.328			
100	88.465	7620.777	94.084	5.789	6.153
	100.03	8585.023			
	93.757	8061.966			
110	105.206	9016.62	104.050	5.723	5.500
	97.837	8402.159			
	109.106	9341.771			

Table 3 Accuracy results

Adition (%)	Area	Concentration (µg/mL)	Average (µg/mL) ± SD	recovery (%)
80	7524.614	87.312	86.527 ± 0.682	96.141
	6066.387	86.197		
	7421.328	86.073		
100	7620.777	88.465	94.084 ± 5.789	94.084
	8585.023	100.03		
	8061.966	93.757		
120	9016.620	105.206	104.050 ± 5.723	94.591
	8402.159	97.837		
	9341.771	109.106		

Table 2 is the result of the precision test with RSD values at concentrations of 90, 100 and 110µg/mL respectively being 0.789%, 6.153% and 5.5%. From the RSD results, the precision test is declared to meet the RSD <8% requirement (Riyanto, 2014).

Accuracy

The accuracy of an analytical method can be determined through two methods, namely the spike recovery method, which involves adding a certain amount of standard substance to the sample, and the standard addition method, which involves creating a calibration curve by adding a different amount of standard substance to the sample matrix (Yantih *et al.*, 2022). Accuracy is expressed by the Percent recovery value which shows how much the analytes are lost or degraded during the analysis process (Yohana Chaerunnisa *et al.*, 2018).

In this experiment, the accuracy of the method can be measured by the recovery value or the percentage of recovery. The standard addition method is 80%, 100%, 120%. With an acceptability requirement of 90% - 107% (Riyanto, 2014).

In **Table 3**, the accuracy test results obtained in the addition of 80% obtained a recovery value of 96.141% ± 0.682, in the addition of 100% obtained a recovery value of 94.084% ± 5.789, and at the addition of 120%, the recovery value is 94.591% ± 5.723, the accuracy test results are declared to meet the requirements with a percent recovery value between 90% - 107%.

Selectivity

Selectivity is determined through the calculation of its resolving power (Rs) (Riyanto, 2014), With the condition that the value of Rs ≥ 1.5 and Rt are the same as the standard curcumin standard (Bose, 2014).

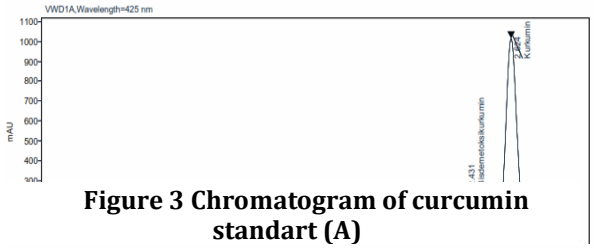

Figure 3 Chromatogram of curcumin standart (A)

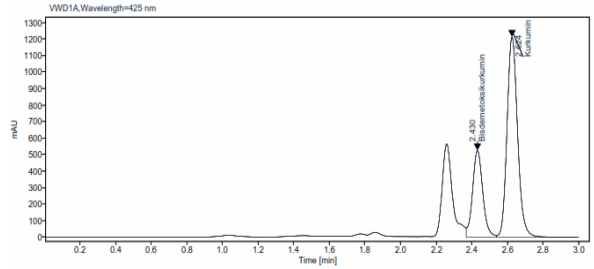

Figure 4 Chromatogram of curcumin sample BPOM without license (B)

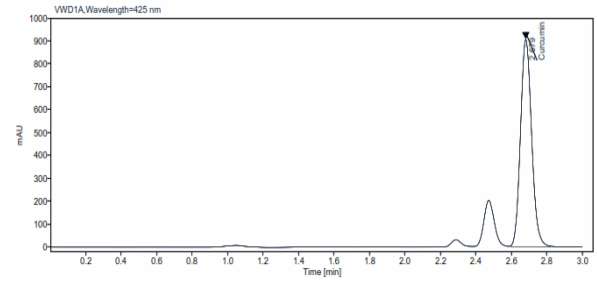

Figure 5 Chromatogram of curcumin sample BPOM license (C)

In **Figure 3**, **Figure 4**, and **Figure 5,** it can be seen that the results of peak chromatogram separation between curcumin standard (A), sample whitout BPOM license (B) and sample with BPOM license (C) show a very identical chromatogram pattern because both contain curcumin compounds (Hanwar *et al.*, 2021). The results of the chromatogram of the curcumin standard and the sample obtained the same Rt value of 2.624 and the Rs value of the curcumin standard was 1.70 while the Rs value of the sample was 1.88. The test results show that this method is able to distinguish curcumin from other compounds, so it can be said that this method is meet requirement of selectivity.

Content Determination

The level determination procedure was carried out using a concentration of 50 µg/mL obtained from the results of the selected optimization test and was carried out 3 times. Sample preparation was equalized by weighing 4 mg of samples that had BPOM license and did not have BPOM license then dissolved with methanol until the limit mark of a 10 ml volumetric flask. The regression equation value obtained from linearity was used to calculate the curcumin content in the capsule so as to obtain the curcumin content in % w/w.

Table 4 Determination of curcumin content in the sample

	Sample A	Sample B
	Concentration	
Replication 1	12.237%	0.188%
Replication 2	12.609%	0.182%
Replication 3	13.425%	0.193%
Average ± Sd	12.757% ± 0.7177	0.187633% ± 0.00583

In **Table *4*** shows the acquisition of levels in samples registered from BPOM (sample A) of 12.757% ± 0.7177 while in sample without registered from BPOM (sample B) of 0.187633% ± 0.00583. This indicates that sample A meets the requirements of the FHI where the curcumin content in turmeric rhizomes is not less than 3.82% (Farmakope Herbal Indonesia Edisi II, 2017). Meanwhile, sample B does not meet the requirements because the amount of curcumin content is lower than the requirements in the Farmakope Herbal Indonesia.

CONCLUSIONS

Based on the results obtained, it can be concluded that the validation of the HPLC method used to analyze curcumin compounds meets all validation parameters including linearity, accuracy, repeatability, selectivity, detection limit, and quantification limit. The results of the study obtained a value of R = 0.9999, accuracy test obtained a recovery value of 96.141%; 94.084%; 94.591%, repeatability test obtained RSD values of 0.789%; 6.153%; 5.5%. Selectivity value obtained Rt 2.624 and Rs of $\geqslant$ 1.5, LOD value of 0.917 µg/mL and LOQ value of 3.058 µg/mL. Based on these results, the reversed phase HPLC method has good validity for the determination of curcumin content in capsule preparations.

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AUTHORS' CONTRIBUTIONS

Conception and design of the study were done by Indra Dwi Framono, Prisma Trida Hardani, Ira Purbosari; data analysis and interpretation were done by Indra Dwi Framono, Prisma Trida Hardani, Ira Purbosari; critical revision of the article for important intellectual content was done by Indra Dwi Framono, Prisma Trida Hardani, Ira Purbosari; all authors contributed to the drafting of the article and approved the final version.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this review article.

ETHICAL CONSIDERATION

All ethical issues, including plagiarism, data fabrication, falsification, and duplicate publication, have been thoroughly observed and adhered to by the authors during the preparation of this review article.

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