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Chemical analysis of Cyproheptadine Hydrochloride in appetite-stimulating herbs marketed in Banyumas regency: ensuring consumer safety

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ABSTRACT

Jamu, a traditional Indonesian herbal medicine, is widely used in traditional healing practices nationwide, including the Banyumas Regency. The Indonesian government has implemented restrictions that forbid the inclusion of medicinal compounds in jamu, as their unregulated usage poses possible health hazards. Cyproheptadine hydrochloride is a frequently encountered medicinal component in appetite-stimulating herbs. However, the extent of adulteration of cyproheptadine hydrochloride in appetite-stimulating herbs marketed in Banyumas Regency is undisclosed. This study purposed to analyze and quantify the presence of cyproheptadine hydrochloride in appetite-stimulating herbs that are available for sale in the Banyumas Regency. The aim was to inform customers about these herbs' possible pharmaceutical ingredient content. The study utilized a qualitative analysis of thin-layer chromatography (TLC) and a quantitative analysis with a UV-Vis spectrophotometer. Fourteen samples of appetite-stimulating herbs in powdered, capsule, and tablet forms were gathered from different areas within the Banyumas Regency. Qualitative analysis revealed cyproheptadine hydrochloride in two herbal samples, SNM TG and SNM AM. The quantitative examination revealed that the content of cyproheptadine hydrochloride in SNM TG was 10.92 mg/5g, whereas in SNM AM, it was 7.93 mg/5g. These findings indicate that there have been breaches of regulations, and individuals who ingest these herbs may be susceptible to health problems. Further investigation is required to analyze a broader range of appetite-stimulating herbal samples, particularly those in liquid form, to ascertain the level of contamination with cyproheptadine hydrochloride and provide essential data for health regulations.

Keywords:
Cyproheptadine Hydrochloride; Herbs; TLC; UV-Vis Spectrophotometry.

Introduction

The utilization of appetite-stimulating herbs as traditional medical remedies in Indonesia is a significant cultural legacy, providing an alternative method to promote weight gain while reducing the possible negative impact on the digestive system that is often linked with modern medications (Marzuki & Nova, 2018). Herbs with appetite-stimulating properties have been found to enhance metabolic activity, repress and prevent gastric acid production, accelerate food release, and increase appetite (Sefriadi, 2018). The plants commonly used as primary constituents in appetite-stimulating herbs due to their capacity to enhance appetite include *Curcuma zanthorrhiza, Curcuma aeruginosa, Boesenbergia rotunda, Alpinia galanga, Curcuma longa, Zingiber officinale, Tinospora cordifolia, Solanum lycopersicum*, and *Foeniculum vulgare* (Kurniarum & Novitasari, 2016).

According to Regulation No. 007 of 2012 from the Ministry of Health of the Republic of Indonesia, traditional medicines are subject to a few restrictions. Article 7(1) letter b of this regulation explicitly prohibits the addition of medicinal compounds obtained by isolation and

synthetic medicinal characteristics to traditional medicines (Permenkes RI, 2012). However, numerous producers or business entities generate rivalry by primarily emphasizing herbal medicine products' immediate benefits and effectiveness by incorporating medicinal ingredients (Putri et al., 2021). The presence of pharmaceutical ingredients, including their type and quantity, is not disclosed on the packaging of these herb products, leaving consumers unaware of their content. The uncontrolled use of pharmaceuticals in herb products can pose significant health risks to consumers. Long-term use of cyproheptadine hydrochloride causes hyperglycemia-diabetes, edema, obesity, hypertension, and a decreased immune response (Longui, 2007). More than 15 times the therapeutic dose of cyproheptadine hydrochloride can cause death (Graham et al., 2008).

Previous research has shown instances of regulatory non-compliance in certain herbal products. In 2021, it was discovered that cyproheptadine hydrochloride was detected in two herbal medicines: Tabib Guna Gemuk Sehat Sempurna, manufactured by PT Tunggal Wulung Jateng, and Ginseng Kianpi Pil, produced by Green herb Medica (M) SD BHD 22-26 Sarawak, Malaysia, and imported by PT Sehat Anugrah (BPOM RI, 2021). In 2022, it was discovered that two herbal items, namely Gaining Weight Capsule manufactured by Sanming Pharmaceutical Factory in Fujian, China, and GS Powder Guna Sehat, contained Cyproheptadine Hydrochloride. The herbal medicine is not registered with the Food and Drug Administration and has a fictitious distribution license number (BPOM RI, 2022).

Many appetite-stimulating herbs in Banyumas Regency are sold in every drugstore and pharmacy. Based on the direct survey results, around 14 appetite-stimulating herbal products are circulating in drug stores and pharmacies in the Banyumas Regency. A total of 14 kinds of appetite-stimulating herb products are circulating in capsule, tablet, powder, and liquid dosage forms. The 14 appetite-stimulating herbs have the herbal logo and a BPOM registration permission number. Additionally, it is essential to mention that not all registration permit numbers inscribed on each container are officially registered with BPOM. This study aims to conduct a thorough investigation into the presence of cyproheptadine hydrochloride in appetite-stimulating herb products that are being sold in the Banyumas Regency. This research is based on previous studies that have indicated the possibility of regulatory violations related to adding pharmaceutical ingredients to herbs.

Cyproheptadine hydrochloride has been chemically identified using fattening herbal medicines from herbal shops, especially in Air Putih Village, Samarinda. The research used a thin-layer chromatography method, and one of the four samples of fattening herbs contained the therapeutic compound cyproheptadine hydrochloride (Ramadhani, 2017). Another study at the Rengel District Market utilized the thin-layer chromatography method to examine samples of appetite-stimulating herbs. Analysis revealed the presence of Cyproheptadine in three out of the six herb samples (Lani et al., 2020). Thin-layer chromatography (TLC) is a cost-effective, simple-to-use, and sensitive technique to detect tiny levels of chemical components in samples, such as cyproheptadine hydrochloride.

This study aimed to examine Cyproheptadine Hydrochloride's presence in appetite-stimulating herbs marketed in the Banyumas Regency. The thin-layer chromatography method was used to detect the presence of Cyproheptadine Hydrochloride in the herbs. The UV-Vis Spectrophotometry method was employed to measure the Cyproheptadine Hydrochloride content in the herbs accurately. The results of this study are expected to be an essential resource for consumers, improving their comprehension and consciousness of the safety of traditional medicine. Additionally, it will provide the government with information for better supervision and regulation of traditional medicines in the Banyumas Regency.

Methods

Materials

The tools used in this research are glassware, analytical balance (Fujitsu FS), silica gel 60 GF254 KLT plate (Merck), UV-Vis spectrophotometer (BIOBASE BK-D590), UV lamp 254 nm and 365 nm (local), pH meter (ISW 900), water bath (Mamert), magnetic stirrer (Thermo), scaled

micro syringe pipette (Dragonlab), and preparative KLT plate (local). The materials used in this study are 14 samples of appetite-stimulating herbs obtained from drug stores in Banyumas Regency, Cyproheptadine Hydrochloride BPFI, distilled water, methanol p.a (Merck), NaOH (Merck), diethyl ether p.a (Merck), H_2SO_4 p.a (Merck), chloroform p.a (Merck), and silica gel 60 powder (Merck).

Procedure

Sample Preparation

The samples used in this study were appetite-stimulating herbal products in powder form or those that can be powdered, which had an herbal product logo on the packaging and were widely purchased and consumed by consumers in Banyumas Regency. Appetite-stimulating herbs samples were accurately weighed (5 g), dissolved in 30 mL of methanol, and shaken for 30 minutes. Following this, the solution was evaporated until completely dry. The residual was added with 50 mL of distilled water, shaken for 30 minutes, and filtered with a filtering paper. The residual solution was added with 1 N NaOH until pH 9. Liquid-liquid extraction was conducted by extracting the solution thrice with 25 mL of diethyl ether using a separatory funnel. The water phase was separated from the diethyl ether phase. The water phase was evaporated until completely dry and dissolved with 5 mL of methanol to create a sample solution (Mardiana, 2009).

Preparation of Cyproheptadine Hydrochloride Comparative Standard

The standard for Cyproheptadine Hydrochloride was weighed accurately at 5 mg and put in a volumetric flask. It was dissolved with 5 mL of methanol to create a comparative standard solution (Nurfadillah, 2019).

Qualitative Analysis using Thin-layer chromatography

Sample solutions and cyproheptadine hydrochloride standard solutions were applied to the TLC plate. The plate was placed into the chamber and eluted with the chloroform: methanol (9: 1) mixture until it reached the topmost, approximately 30 minutes. The TLC analysis was conducted at room temperature using a 10 x 20 cm glass chamber without sharp corners. The spots were observed under ultraviolet light at 254 nm, and the Rf value of each spot was calculated. The sample spot was then compared to the cyproheptadine hydrochloride standard spot.

Quantitative Analysis using UV-Vis Spectrophotometry

1) Determination of Maximum Wavelength

Determination of the maximum absorption wavelength of the Cyproheptadine Hydrochloride standard solution (20 ppm) was carried out using a UV-Vis Spectrophotometer at a wavelength of 200-400 nm (Madhu et al., 2016).

2) Calibration Curve

A series of Cyproheptadine Hydrochloride, standard solutions with concentrations of 5, 10, 15, 20, and 25 ppm, was prepared from the Cyproheptadine Hydrochloride stock solution using methanol as the solvent. The absorption of Cyproheptadine Hydrochloride standard solution was measured using a UV-Vis spectrophotometer at the maximum wavelength. The linear regression equation ($y = bx + a$) was derived from the collected data (Mardiana, 2009).

3) Determination of Cyproheptadine Hydrochloride Level in Samples

The Cyproheptadine Hydrochloride included in the sample was isolated using a TLC-preparative technique. The sample solutions were spotted along the line at the lower limit of the TLC-preparative plate that had been previously activated. The TLC-preparative was then eluted using eluent, a mixture of chloroform: methanol (9: 1), until reaching the upper limit. The spot bands formed were observed under UV light 365 nm and scraped with a spatula. The collected

samples were subsequently dissolved with 5 mL of 1 N H_2SO_4. The solution was shaken until homogenous and then filtered using a filtering paper. The filtrate was collected, transferred into a cuvette, and measured with a UV-Vis Spectrophotometer at the maximum wavelength.

Validation Method

1) Linearity

A standard solution of Cyproheptadine Hydrochloride was prepared with concentrations of 5, 10, 15, 20, and 25 ppm. The absorbance of each concentration was measured using a UV-Vis spectrophotometer at the maximum wavelength. A standard curve represents the correlation between the absorbance (y) and the concentration of the standard solution (x). The correlation coefficient, denoted as r, has been derived from the standard curve. Linearity is considered good when the resulting correlation coefficient value approaches 1 (0.999) (Harmita, 2004).

2) Precision

A standard solution of Cyproheptadine Hydrochloride, with a concentration of 20 ppm, was analyzed using a UV-Vis Spectrophotometer at the maximum wavelength. The measurement was repeated five times, and the relative standard deviation (RSD) value was calculated. A % RSD value is considered to have good precision if it is less than or equal to 2% (Harmita, 2004).

$$\text{RSD} = \frac{\text{SD}}{\text{Average measured levels}} \text{ x } 100\% \quad (1)$$

3) Accuracy

A standard solution of Cyproheptadine Hydrochloride, with concentrations of 5, 15, and 25 ppm, was measured using a UV-Vis Spectrophotometer at the maximum wavelength. This process was repeated five times. Percent recovery was determined to determine accuracy. The % recovery result for analytical purposes is considered to meet the requirements if it shows a percentage value between 80-110% (Lovianasari et al., 2021).

$$\%\ recovery = \frac{\text{Measurable concentration}}{\text{Real concentration}} \text{ x } 100\% \quad (2)$$

4) LOD (Limit of Detection) and LOQ (Limit of Quantification)

Five concentrations of Cyproheptadine Hydrochloride standard solutions (5, 10, 15, 20, and 25 ppm) were measured using a UV-Vis Spectrophotometer, repeated five times at the maximum wavelength. The concentration of the Cyproheptadine Hydrochloride standard solution was correlated with the absorbance. This correlation allowed for the creation of a linear regression equation, y = bx + a. This equation was subsequently utilized to determine the LOD (Limit of Detection) and LOQ (Limit of Quantification) (Wahyuni et al., 2022).

$$\text{SD} = \sqrt{\frac{(x-\bar{x})^2}{n-1}} \quad (3)$$

$$\text{LOD} = \frac{3 \text{ X SD}}{\text{S}} \quad (4)$$

$$\text{LOQ} = \frac{10 \text{ X SD}}{\text{S}} \quad (5)$$

Results and Discussions

Jamu is an Indonesian herbal medicine with various natural ingredients and must not contain medicinal chemicals such as Cyproheptadine Hydrochloride. This study was conducted to identify and determine the levels of Cyproheptadine Hydrochloride in appetite-stimulating herbs sold in Banyumas Regency. Analysis of Cyproheptadine Hydrochloride content was performed using thin-layer chromatography and UV-Vis Spectrophotometer.

Identification of Cyproheptadine Hydrochloride in Samples

Qualitative analysis using thin-layer chromatography was conducted to identify whether the sample of appetite-stimulating herbs contained Cyproheptadine Hydrochloride. The results show that 2 out of 14 sample appetite-stimulating herbs are known to be positive for Cyproheptadine Hydrochloride, namely samples SNM TG and SNM AM (Figure 1). The two samples exhibited prominent bright blue fluorescence spots under the UV light 254 nm. Additionally, the Rf value of both samples was found to be nearly identical, measuring 0.56, in comparison to the Cyproheptadine Hydrochloride comparative standard, which has an Rf value of 0.57 (Departemen Kesehatan RI, 2014; Ramadhani, 2017; Soebagio et al., 2005)

The mobile phase used in this study was chloroform: methanol (9: 1), which provides the best separation. The polarity of a mixture of two organic solvents can be easily regulated so that separation can occur optimally (Gandjar & Rohman, 2007). A mobile phase with a similar polarity range is chosen for TLC analysis to achieve optimal separation (Figure 2). The mixture of chloroform: methanol (9: 1) has a similar polarity with Cyproheptadine Hydrochloride. Cyproheptadine Hydrochloride is semi-polar due to amine and polar methyl groups. The combination of non-polar chloroform and polar methanol (9: 1) results in a semi-polar mobile phase. This mobile phase is appropriate for this study, as it facilitates the separation of semi-polar compounds. The semi-polar mobile phase enables efficient elution of semi-polar compounds. This study utilized polar silica gel GF254 nm as the stationary phase. Due to its strong adsorption properties, silica gel is a polar stationary phase commonly used in TLC. It can effectively interact with various types of compounds, including cyproheptadine hydrochloride. Therefore, it is an effective material for separating compounds with semi-polar properties (Lani et al., 2020).

Samples with positive Cyproheptadine hydrochloride were further analyzed using a UV-Vis Spectrophotometer to determine Cyproheptadine hydrochloride levels. Herbal medicine samples that did not contain Cyproheptadine hydrochloride were not subjected to further analysis. UV-Vis spectrophotometry is a valuable tool for researchers studying the presence and amount of cyproheptadine hydrochloride in herb samples because of its specificity, simplicity, affordability, sensitivity, quantitative capabilities, and rapid analysis (Sayanna et al., 2015). A calibration curve is necessary for quantitative analysis (Table 1). The measured absorbance of the herbs sample is then compared to the curve. The corresponding concentration of cyproheptadine hydrochloride in the herbs sample can be interpolated from the curve.

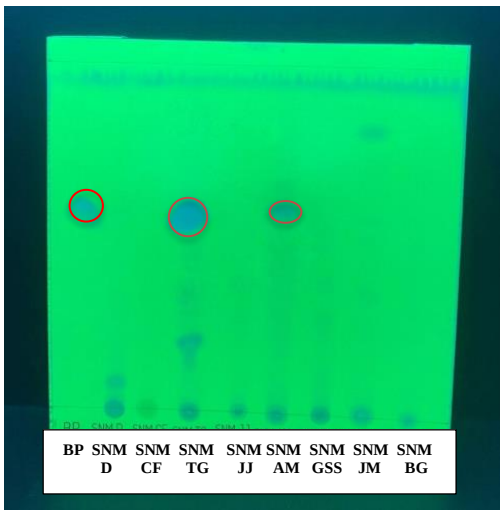

Figure 1. TLC analysis of BP (Comparative Standard) and Sample SNM (D, CF, TG, JJ, AM, GSS, JM, BG)

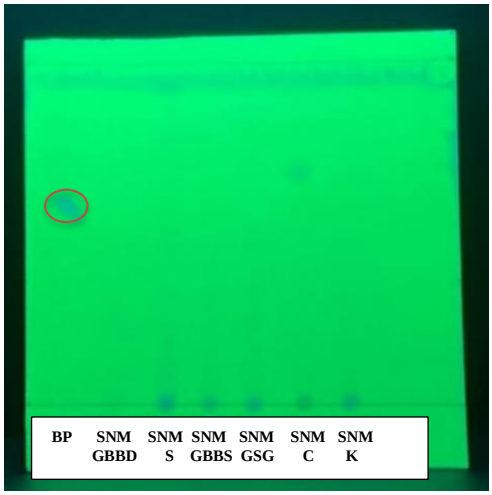

Figure 2. TLC analysis of BP (Comparative Standard) and samples (GBBD, S, GBBS, GSG, C, K)

Table 1. Qualitative Analysis of Appetite-stimulating Herbs

Sample	Results		
	Fluorescence	**Rf**	**Conclusion**
Cyproheptadine hydrochloride	Light blue	0.57	
SNM D	Blue	0.08	(-)
SNM CF	-	-	(-)
SNM TG	Light blue	0.56	(+)
SNM JJ	-	-	(-)
SNM AM	Light blue	0.56	(+)
SNM GSS	-	-	(-)
SNM JM	Blue	0.81	(-)
SNM BG	-	-	(-)
SNM GBBD	-	-	(-)
SNM S	-	-	(-)
SNM GBBS	-	-	(-)
SNM GSG	-	-	(-)
SNM C	Blue	0.68	(-)
SNM K	-	-	(-)

Analysis of Cyproheptadine Hydrochloride Level in Samples

Quantitative analysis begins with the determination of the maximum wavelength of Cyproheptadine Hydrochloride. The result shows that the maximum wavelength of Cyproheptadine Hydrochloride is 286 nm (Figure 3). These results are consistent with the literature, which indicates that Cyproheptadine hydrochloride BPFI absorbs at a maximum wavelength of 286 nm, with a maximum deviation of 3.0% (Departemen Kesehatan RI, 2014).

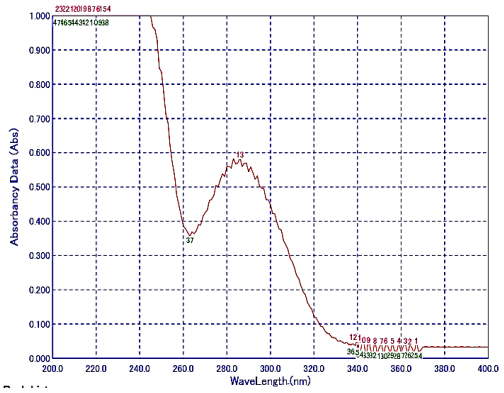

Figure 3. Maximum wavelength Cyproheptadine Hydrochloride (286 nm)

The results showed that the level of Cyproheptadine Hydrochloride in appetite-stimulating herb samples labeled as SNM TG was 10.92 mg/5 g sample, whereas SNM AM was 7.93 mg/5 g sample (Table 2).

Table 2. Cyproheptadine Hydrochloride Level in Appetite-stimulating Herbs

Sample	Replication	Concentration (ppm)	Level (mg/5g)
SNM TG	1	22.34	11.17
	2	22.34	11.17
	3	21.30	10.65
	4	21.37	10.69
	5	21.87	10.94
	$\bar{x}$	**21.84**	**10.92**
SNM AM	1	16.26	8.13
	2	15.90	7.95
	3	15.54	7.77
	4	15.40	7.70
	5	15.90	7.95
	$\bar{x}$	**15.80**	**7.93**

The typical therapeutic dosage range for Cyproheptadine Hydrochloride is 8 mg/day to 12 mg/day (Bertrand et al., 2021). Even though the levels present in the two samples fall within the typical dosage range of at least 1 x 5 g/day, their consumption remains prohibited due to non-compliance with the prevailing legal regulations stipulated in the Regulation of the Minister of Health of the Republic of Indonesia No. 007 of 2012, specifically, Article 7 (1) letter b, which pertains to the Traditional Medicine Registration.

The presence of cyproheptadine hydrochloride in herbs can pose various health risks. Due to the lack of proper dosage information, consumers may unknowingly consume excessive amounts, leading to potential side effects like drowsiness, dry mouth, dizziness, constipation, and blurred vision. Additionally, unexpected and potentially harmful interactions can occur with undisclosed cyproheptadine hydrochloride in herbs. Furthermore, cyproheptadine hydrochloride can cause adverse reactions, such as allergic reactions with rashes, sneezing, runny nose, watery eyes, etc. (Lee et al., 2021; Product Information: Periactin, 1999).

This study has some potential limitations. The sample size of appetite-stimulating herbs may not fully represent the prevalence of Cyproheptadine Hydrochloride in all available products. Additionally, the study only focused on a powdered form or in forms that can be powdered, such as capsules or tablets and did not include liquid herbal formulations. Further research employing various appetite-stimulating herbs and encompassing different herb types would be beneficial.

Validation Method

The validation method assesses the analytical accuracy, specificity, reproducibility, and robustness of the analytical process, ensuring its suitability for the analysis of Cyproheptadine Hydrochloride. Validation of the analytical method involves assessing the generated value based on specific parameters utilized and determining if it conforms to the prescribed standards for its application (Harmita, 2004).

1.) Linearity

Linearity is the ability of an analytical method to provide a response or produce a test that is directly proportional to the concentration of the analyte in the sample in the given range. The purpose of the linearity test is to ascertain whether or not the concentration of the substance to be analyzed by UV-Vis Spectrophotometry exhibits a linear relationship (Gandjar & Rohman, 2007).

The result shows that this method's correlation coefficient (r) was 0.9991. This value suggests a linear relationship exists between the analyte concentration and the absorbance. The correlation coefficient in this study corresponds to the criterion for high linearity, as it is close to 1 (0.999) (Harmita, 2004).

2.) Precision

Precision is a quantitative indicator that assesses the extent to which an analytical procedure can produce consistent and reproducible results over multiple iterations of tests. The determination of the accuracy value can be accomplished by assessing the Relative Standard Deviation (RSD) or Coefficient Variation (CV) value of the specified acceptance criteria (Harmita, 2004).

The % RSD for the precision parameter is 1.5% (Figure 4). The % RSD value observed in this study satisfies the established criteria for a reliable precision test since it falls below the threshold of <2% (Harmita, 2004). This result indicates that the procedure employed exhibits a satisfactory level of precision (Table 3).

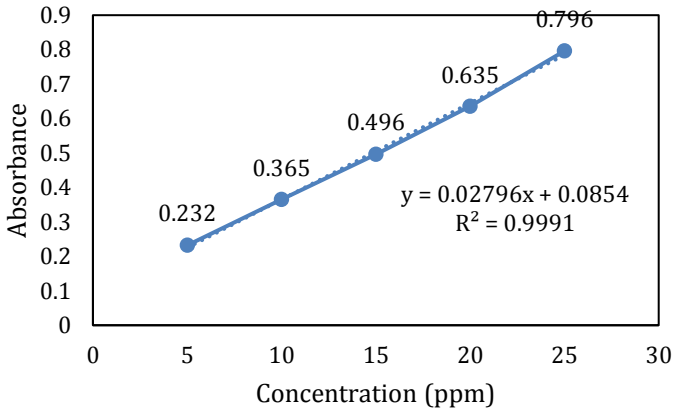

Figure 4. The standard curve between concentration and the absorbance of Cyproheptadine Hydrochloride standard solution

Table 3. Precision test results

Replication	Absorbance	Measured Concentration (ppm)
1	0.625	19.2989
2	0.641	19.8712
3	0.637	19.7281
4	0.623	19.2274
5	0.638	19.7639
SD		0.2930
RSD		1.5%

3.) Accuracy

Accuracy is a quantitative measurement that indicates the extent to which the results of an analysis align with the proper amounts of the analyte being studied. The objective of the accuracy test is to assess the degree of agreement between the measured findings obtained through an analytical method and the actual results. Accuracy is expressed as % recovery, which must be within the specified range of 90%-110% (Harmita, 2004).

According to the calculation results, the %recovery values for the standard solution concentration of 5, 15, and 25 ppm are 99.44%, 97.468%, and 95.9072%, respectively. The

%recovery is within the acceptable range of 90-110%, suggesting that the UV-Vis Spectrophotometer accurately analyzed Cyproheptadine Hydrochloride (Harmita, 2004).

4.) LOD (Limit of detection) and LOQ (Limit of quantification)

LOD and LOQ tests aim to determine the minimum concentration and quantity of analyte present in the sample that can be accurately quantified using UV-Vis Spectrophotometry (Gandjar & Rohman, 2007). The determination of the detection limit and amount limit in the UV-Vis Spectrophotometry method is based on the standard deviation (SD) and intercept (S) derived from the calibration curve (Widiyana, 2021).

The LOD value in this study indicates that the UV-Vis Spectrophotometry can detect a minimum concentration of 10.292 ppm of Cyproheptadine Hydrochloride in the sample (Table 4). Furthermore, the LOQ value indicates that 34.309 ppm is the smallest amount of Cyproheptadine Hydrochloride standard solution that can still be observed by a UV-Vis Spectrophotometer and still meet the criteria for precision and accuracy.

Table 4. Accuracy test results

True concentration (ppm)	Measured concentration (ppm)	% Recovery
5	4.957	99.1
	4.850	97.0
	5.136	102.0
	5.064	101.3
	4.885	97.7
Average		**99.44**
15	14.506	96.7
	14.578	97.2
	14.685	97.9
	14.721	98.1
	14.613	97.4
Average		**97.47**
25	23.912	95.6
	24.020	96.0
	23.877	95.5
	24.091	96.3
	23.984	95.9
Average		**95.90**

Conclusion

Cyproheptadine Hydrochloride was detected in two samples of appetite-stimulating herbs sold in Banyumas Regency. The concentration of Cyproheptadine Hydrochloride in the sample SNM TG is 10.92 mg/5 g, while in the sample SNM AM, it is 7.93 mg/5 g. This study raises public health concerns due to potential side effects and drug interactions of Cyproheptadine Hydrochloride. These findings highlight the need for stricter regulations and enforcement mechanisms to ensure the safety and quality of herbal products, apart from enhanced consumer awareness. Further research on contamination prevalence and regulatory effectiveness would be beneficial.

Acknowledgments

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Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Bertrand, V., Massy, N., Vegas, N., Gras, V., Chalouhi, C., Tavolacci, M. P., & Abadie, V. (2021). Safety of Cyproheptadine, an Orexigenic Drug. Analysis of the French National Pharmacovigilance Data-Base and Systematic Review. *Frontiers in Pediatrics*, *9*(September). https://doi.org/10.3389/fped.2021.712413

BPOM RI. (2021). *Public Warning NO.HM.01.1.2.10.21.45; Obat Tradisional Mengandung Bahan Kimia Obat*.

BPOM RI. (2022). *Penjelasan Publik No.PW.02.04.1.4.10.22.166; Tentang Obat Tradisional Mengandung Bahan Kimia Obat*.

Departemen Kesehatan RI. (2014). *Farmakope Indonesia Edisi V*. Departemen Kesehatan Republik Indonesia.

Gandjar, I. G., & Rohman, A. (2007). *Kimia Farmasi Analisis*. Pustaka Pelajar.

Graham, M. R., Davies, B., Grace, F. M., Kicman, A., & Baker, J. S. (2008). Anabolic steroid use: Patterns of use and detection of doping. *Sports Medicine*, *38*(6), 505–525. https://doi.org/10.2165/00007256-200838060-00005

Harmita, H. (2004). Petunjuk Pelaksanaan Validasi Metode Dan Cara Perhitungannya. *Majalah Ilmu Kefarmasian*, *1*(3), 117–135. https://doi.org/10.7454/psr.v1i3.3375

Kurniarum, A., & Novitasari, R. A. (2016). Penggunaan Tanaman Obat Tradisional Untuk Meningkatkan Nafsu Makan Pada Balita. *Jurnal Kebidanan Dan Kesehatan Tradisional*, *1*(1). https://doi.org/10.37341/jkkt.v1i1.75

Lani, D. N., Dewi, Belinda, A. D., Anugerah, B., & Rosita, F. (2020). Identifikasi Bahan Kimia Obat Siproheptadin Hidroklorida dalam Jamu Penambah Nafsu Makan di Pasar Kecamatan Rengel dengan Metode Kromatografi Lapis Tipis. *Jurnal Ilmiah Kesehatan*, *1*(1), 18–23.

Lee, C., Wu, H., Kuan, M., Hung, C., Chi, C., & Fan, H. (2021). Central Anticholinergic Syndrome Due to Cyproheptadine Overdose in a Child : A Case Report and Literature Review. *Tungs' Medical Journal*, *15*, 40–44. https://doi.org/10.3966/207135922021061501008

Longui, C. A. (2007). Glucocorticoid therapy: minimizing side effects. *J Pediatr (Rio J)*, *Nov*(83), 163–177.

Lovianasari, E., Fitriana, A. S., & Prabandari, R. (2021). Identifikasi Kandungan Bahan Kimia Obat Deksametason dalam Obat Tradisional Penggemuk Badan yang Dijual di Banyumas. *Seminar Nasional Penelitian Dan Pengabdian Kepada Masyarakat (SNPPKM)*, 133–139.

Madhu, M., Chanti, N. M., Gireesh, K. E., Chand, B. S., & Gopinath, C. (2016). Development and Validation of Spectroscopic Method for The Estimation of Cyproheptadine HCl in Tablet Dosage Form. *Journal of Global Trends in Pharmaceutical Sciences*, *7*(1), 2982–2986.

Mardiana, E. (2009). *Identifikasi Siproheptadin Hidroklorida Dan Deksametason Dalam Sediaan Jamu Gemuk Yang Dijual Di Kios Jamu Seduhan Secara Spektrofotometri UV-VIS*. Universitas Muhammadiyah Prof. Dr. Hamka.

Marzuki, R. D., & Nova, A. (2018). Pembinaan Masyarakat Tentang Pemanfaatan Tanaman Binahong (Anredera cordifolia) Sebagai Obat Tradisional Di Gampong Sidorejo Langsa Lama. *Jurnal Jeumpa*, *5*(2), 112–118. https://doi.org/10.1098/rspb.2014.1396%0Ahttps://www.uam.es/gruposinv/meva/publicaciones jesus/capitulos_espanyol_jesus/2005_motivacion para el aprendizaje Perspectiva alumnos.pdf%0Ahttps://www.researchgate.net/profile/Juan_Aparicio7/publication/253571379

Nurfadillah, S. (2019). *Identifikasi Bahan Kimia Obat Siproheptadin Hidroklorida Dalam Jamu Penggemuk Badan Yang Beredar di Pasar Bintara dengan Metode Kromatografi Lapis Tipis dan Reaksi Warna Periode Mei-Agustus 2019*. Akademi Farmasi IKIFA Jakarta.

Permenkes RI. (2012). *Peraturan Menteri Kesehatan Republik Indonesia No.007 Tahun 2012 Tentang Registrasi Obat Tradisional*. Menkes RI.

Product Information: Periactin, C. hydrochloride. (1999). *Product Information: Periactin, Cyproheptadine hydrochloride* (Vol. 01).

Putri, R. E., Zamroni, M., & Huda, M. K. (2021). Tinjauan Hukum Obat Tradisional Berbaha Kimia Obat. *Jurnal Hukum Magnum Opus*, *4*(1), 1–11.

Ramadhani, M. (2017). *Identifikasi Bahan Kimia Obat Siproheptadin Hidroklorida dalam Jamu Penggemuk Badan dengan Metode Kromatografi Lapis Tipis*. Akademi Farmasi Samarinda.

Sayanna, Veeraiah, T., & Reddy, C. V. R. (2015). Determination of cyproheptadine hydrochloride in pure and pharmaceutical forms: A spectrophotometric study. *Oriental Journal of Chemistry*, *31*(3), 1779–1786. https://doi.org/10.13005/ojc/310360

Sefriadi, M. (2018). *Penambahan Berbagai Konsentrasi Tepung Agar-agar Terhadap Sifat Sensori dan Kimia Permen Agar-agar Jamu Cekok*. Universitas Lampung.

Soebagio, Ibnu, M. S., Widarti, H. R., Munzil, & Bidiasih, E. (2005). *Kimia Analitik 2*. Universitas Negeri Malang.

Wahyuni, A. M., Afthoni, M. H., & Rollando, R. (2022). Pengembangan dan Validasi Metode Analisis Spektrofotometri UV Vis Derivatif untuk Deteksi Kombinasi Hidrokortison Asetat dan Nipagin pada Sediaan Krim. *Sainsbertek Jurnal Ilmiah Sains & Teknologi*, *3*(1), 239–247. https://doi.org/10.33479/sb.v3i1.181

Widiyana, A. P. (2021). Validasi dari Spektrofotometri UV-Vis dan Kandungan Total Flavonoid Ekstrak Etanol dari Akar Alang-Alang (Imperata cylindrica) dan Daun Pegagan (Centella asiatica) Validatian of UV-Vis Spectrophotometry and Total Flavonoid Content Ethanolic Extract from I. *Journal of Pharmaceutical Care Anwar Medika*, *3*(2), 126–136.