Journal of Applied Pharmaceutical Science Vol. 12(03), pp 191-201, March, 2022
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2022.120320
ISSN 2231-3354

A development method of FTIR spectroscopy coupled with chemometrics for detection of synthetic drug adulterants of herbal products in quaternary mixture

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ARTICLE INFO

Received on: 25/08/2021
Accepted on: 11/11/2021
Available Online: 05/03/2022

Key words:
Jamu, mid-infrared, multivariate analysis, counterfeit, analgesic drugs.

ABSTRACT

Fourier transform infrared-attenuated total reflection (FTIR-ATR) spectroscopy, especially mid-infrared, has fulfilled the need to counter the rising number of adulterated herbal products in society. The non-destructive, rapid, and inexpensive methods are criteria found in FTIR spectroscopy. This study aimed to develop a combination method between FTIR-ATR spectroscopy and chemometrics to analyze the quaternary model of adulterated herbal products claimed as analgesics. The samples consist of three types of analgesic herbal products (Jamu Pegal Linu, Jamu Encok, and Jamu Sakit Pinggang), prednisone, metamizole, diclofenac sodium, and quaternary mixtures were prepared and measured using FTIR spectrophotometer on absorbance mode at wavenumbers range 4,000–650 cm^{-1}. Principal Component Analysis (PCA), Partial Least Square Regression (PLSR), Principal Component Regression (PCR), and Discriminant Analysis were applied for analyzing spectra. The PCA result showed good differentiation between samples. The output of multivariate calibrations was excellent in line with statistical parameter value. The accuracy and precision from PLSR and PCR of quaternary mixtures were shown by a low value of root mean square error of prediction and root mean square error of calibration and $R^2 > 0.99$. Therefore, we suggested the combination method between FTIR-ATR and chemometrics as screening analytical technique to detect any adulterant drugs in herbal products.

INTRODUCTION

Herbal medicine consumption was increasing due to its preventive and treatment functions. Claimed as safe, natural, and with minor adverse effects, herbal medicine has become a promising option to cure and maintain health conditions (de Carvalho Lopes and Neto, 2018; Ernst, 2002). However, there are some findings of adulterated herbal medicine purposefully mixed by synthetic drugs in the market. The adulteration of herbal medicine phenomenon is an unacceptable action to accelerate the fast and effective effect (Popescu and Radu, 2015). Analgesic drugs such as metamizole, diclofenac sodium, and prednisone were commonly found in herbal medicine to reduce pain (Sanzini *et al*., 2011). The improper use of non-steroidal anti-inflammation drugs and steroidal drugs could lead to undesirable adverse effects, in particular tachycardia, gastrointestinal disorder, hypertension, and hyperglycemia (Gan, 2010; Jin *et al*., 2018; Vijayalakshmi and Anbazhagan, 2011).

Some countries from Asia, Europe, Africa, and America had a report about adulteration herbal medicine with a synthetic drug. Indonesia is one of the countries that have a high number of reports about this unethical incident. Some irresponsible manufactured herbal medicine products such as Jamu intentionally alloyed Jamu and synthetic drugs (Ariffin *et al*., 2021; Cebi *et al*., 2017; Ching *et al*., 2018; Snyman *et al*., 2005). The most used methods to detect synthetic drugs in herbal medicine are High performance liquid chromatography (HPLC), thin layer chromatography, LC-MS, and gas chromatography-mass spectrometer (Lee *et al*., 2017; Mustarichie *et al*., 2017; Popescu and Radu, 2015; Vijayalakshmi and Anbazhagan, 2011).

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These techniques use separation as basic concept analysis, which requires substantial time, plenty of samples, and the destruction of samples (Cebi *et al*., 2017).

The studies about vibrational spectroscopic such as mid-infrared (MIR), near-infrared (NIR), and Raman as detecting techniques on adulteration herbal medicines were astonishingly successful. MIR and NIR spectroscopic are distinguished by the range location of each wavenumber. Located wavenumber at 4,000–650 cm^{-1} is the MIR location and at 14,400–4,000 is the NIR location. Since MIR, NIR, and Raman are included in green analytical chemistry, it means that there is reducing solvent usage and no destruction of the sample (Rohman *et al*., 2019). Previous studies report that vibrational spectroscopy could become a technique to control herbal medicine. The wavelength range in the MIR area exhibited the difference spectra between slimming herbal supplement and sibutramine HCl, combined with Partial Least Square Regression (PLSR); the method demonstrated a promising result in the validated test (Lu *et al*., 2007; Rooney *et al*., 2015).

Multivariate analysis, named Principal Component Analysis (PCA), Principal Component Regression (PCR), PLSR, and Discriminant Analysis (DA), could support vibrational spectroscopy data to analyze, detect, and identify synthetic drugs in herbal medicine. The benefits of multivariate analysis on processing vibrational spectroscopy data are simplicity of data interpretation and visualization, easiness of the understanding of the relationship between variables, and giving more information that is simultaneously analyzed (Irnawati *et al*., 2019; Rohaeti *et al*., 2015; Rohman *et al*., 2019).

This study aims for an effective, efficient, and reliable method to analyze adulterated synthetic drugs (metamizole, diclofenac sodium, and prednisone) in a herbal product by developing an analysis technique for identifying and quantifying synthetic drugs in herbal products comprehensively. The structure molecules of synthetic drugs used are shown in Figure 1. These synthetic drugs were chosen as a sample because of the National Agency of Drug and Food Control declaration about the drugs commonly found in herbal products, and metamizole, diclofenac sodium, and prednisone were listed (Sanzini *et al*., 2011). The samples were intentionally composed of three synthetic analgesic drugs. The combination between Fourier transform infrared-

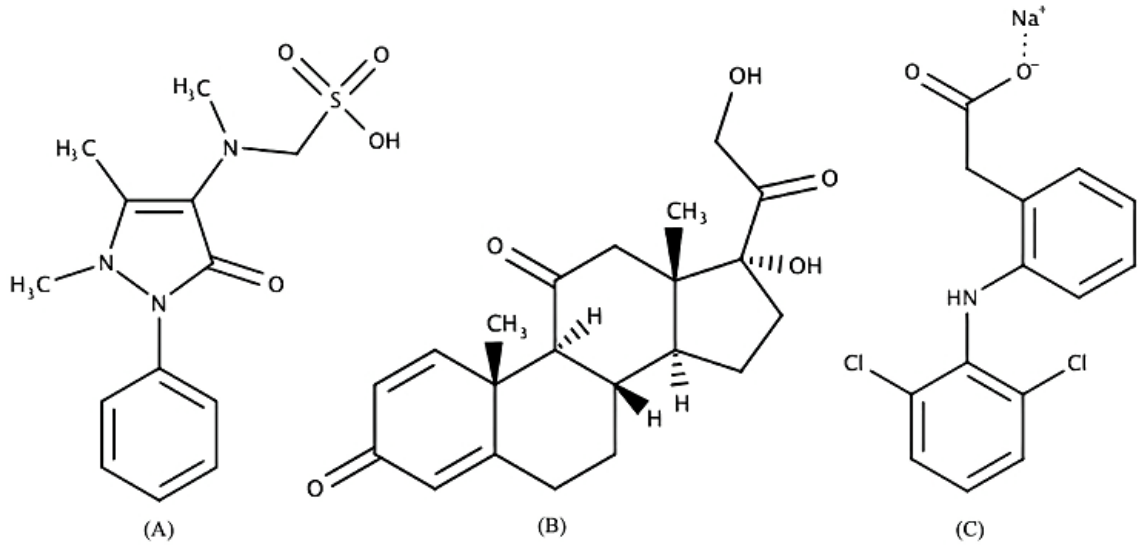

Figure 1. Molecule structures of metamizole (A), prednisone (B), and diclofenac sodium (C).

Table 1. The design of quaternary mixture concentrations.

Synthetic drugs concentration (%b/b)	Herbal products sample (mg)	Metamizole (mg)	Diclofenac sodium (mg)	Prednisone (mg)	Total (mg)
10	270	10	10	10	300
20	240	20	20	20	300
30	210	30	30	30	300
40	180	40	40	40	300
50	150	50	50	50	300
60	120	60	60	60	300
70	90	70	70	70	300
80	60	80	80	80	300
90	30	90	90	90	300

attenuated total reflection (FTIR-ATR) and chemometrics analysis, including PCA, PCR, PLSR, and DA, could classify and quantify unadulterated herbal products and synthetic drugs using calibration and validation tests.

MATERIALS AND METHODS

Sample preparation

Metamizole, diclofenac sodium, and prednisone were granted by PT Phapros, Tbk. Three types of analgesic herbal products (Jamu Pegel Linu, Jamu Encok, and Jamu Sakit Pinggang) were purchased from one of the Indonesian traditional herbal industries. Acetone p.a. 1.0014.2500 as catalog number was obtained from Merck. The quaternary mixture was prepared by combining three synthetic drugs and each herbal product with a range of 0%–100% (wt/wt). The design of various concentrations is shown in Table 1.

FTIR-ATR spectroscopy analysis

The diamond crystal on Nicolet iS10 Spectrophotometer coupled with a detector called deuterated triglycine sulfate was cleaned first using acetone p.a. to prevent any possible noise for collecting data. Collecting background was carried out to reduce the friction between diamond and any reference spectrum in the air. The wavenumber region range for data collection was 4,000–650 using 8 cm^{-1} for resolution conditions and 32 scans/minute.

Table 2. The performance compilation of PCR and PLSR for quantitative analysis of Jamu Pegel Linu in quaternary mixtures with drugs.

Multivariate calibrations	Wavenumber (cm^{-1})	Spectra	Calibration		Validation	
			R	**RMSEC**	***R***	**RMSEP**
PLSR	2,396.09–683.64	Normal	0.9808	6.67	0.9754	8.06
		Derivative 1	0.9990	1.55	0.9986	2.94
		Derivative 2	0.9792	6.94	0.9831	6.42
	1,535.55–649.89	Normal	0.9873	5.43	0.9875	5.72
		Derivative 1	0.9965	2.84	0.9925	4.44
		Derivative 2	0.9892	5.01	0.9830	6.33
	1,829.41–1,095.93	Normal	0.9922	4.27	0.9876	5.57
		Derivative 1	0.9349	12.1	0.9285	12.9
		Derivative 2	0.7693	21.9	0.7314	23.9
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9847	5.96	0.9840	6.45
		Derivative 1	0.9989	1.59	0.9990	2.49
		Derivative 2	0.9994	1.21	0.9978	2.91
	2,396.09–683.64 and 1,829.41–1,095.93	Normal	0.9819	6.48	0.9772	7.78
		Derivative 1	**0.9994**	**1.18**	**0.9986**	**2.49**
		Derivative 2	0.7754	21.6	0.7394	23.5
PCR	2,396.09–683.64	Normal	0.9979	2.22	0.9970	3.28
		Derivative 1	0.9985	1.90	0.9983	3.17
		Derivative 2	0.9972	2.54	0.9955	4.39
	1,535.55–649.89	Normal	0.9979	2.23	0.9956	3.49
		Derivative 1	0.9983	2.02	0.9969	3.13
		Derivative 2	0.9969	2.68	0.9913	5.08
	1,829.41–1,095.93	Normal	0.9922	4.25	0.9876	5.56
		Derivative 1	0.9946	3.55	0.9934	4.46
		Derivative 2	0.9952	3.33	0.9946	4.53
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9976	2.35	0.9972	3.08
		Derivative 1	0.9985	1.85	0.9985	2.77
		Derivative 2	0.9976	2.39	0.9961	4.14
	2,396.09–683.64 and 1,829.41–1,095.93	Normal	0.9982	2.03	0.9957	4.08
		Derivative 1	0.9986	1.80	0.9988	2.96
		Derivative 2	0.9970	2.66	0.9958	4.40

Bold denotes the selected condition.

Samples about 10 mg were located on diamond crystal ATR, and Omnic software was carried out to transform the data from spectrophotometer to spectra in absorbance. Each sample was recorded in triplicate.

Analysis data

The obtained spectra data were further analyzed using PCA, PCR, PLSR, and DA. Minitab 18 was employed to carry out a PCA score plot. Triple quadrupole (TQ) Analyst visualised PCR, PLSR, and DA. The PCR and PLSR were carried out by comparing the value of root mean square error of calibration (RMSEC), root mean square error of prediction (RMSEP), and coefficient determination (R^2). The regions shown in Tables 2, 3, and 4 were selected based on TQ Analyst software suggestion and modified further to obtain optimal conditions. The first and second derivatizations were applied for increasing the resolution of spectra.

RESULTS

Spectra data analysis of FTIR-ATR

Qualified as green analytical chemistry, FTIR-ATR spectroscopy could analyze a complex sample without any solvent used (Moros *et al*., 2010). The MIR region at wavenumbers 4,000–650 cm^{-1} presented visual spectra data containing vibrational bands of metamizole, diclofenac sodium, and prednisone. The spectrum of metamizole exhibited several strong peaks at certain wavenumbers that were 1,656, 1,625, 1,172, 1,152, and 1,047 cm^{-1}. The appeared bands represented stretching C = O, a vibration of C = C, O = S = O stretching, CH_2 out of a plane, and S = O vibration (Mohamed, 2015; Moffat *et al*., 2011; Silverstein *et al*., 1962). The MIR spectrum of diclofenac sodium delivered some unique bands at 3,253, 1,572, and 1,359 cm^{-1}. Those arising vibrations reported the presence of −NH group, symmetric stretch of C = O, and asymmetric stretch of C = O, respectively (Bucci *et al*., 1998; Silverstein *et al*., 1962). Arising peaks of prednisone MIR spectrum at 1,706, 1,665, 1,620, 1,243, and 899 cm^{-1} represented functional groups, namely, C = O stretching vibration, C = C vibrations, C–O vibration, and C–H bending vibration (Chiong *et al*., 1992; Moffat *et al*., 2011; Silverstein *et al*., 1962). The spectra of three types of herbal products, metamizole, diclofenac sodium, prednisone, and the quaternary model are shown in Figure 2.

Qualification analysis using PCA

The application of PCA was used to discriminate the adulterated and unadulterated samples (Miller and Miller, 2010). The chosen region containing significant bands of the drugs built the PCA model. The optimum wavenumber range for PCA was 1,350–850 cm^{-1}. The desired region was full of information about vibrations related to chemical data in samples (Angeline *et al*., 2019). Figure 3 shows the score plot of the model. The quaternary model of this research is located around the unadulterated samples and drugs. Three types of unadulterated samples claimed to reduce pain had similar PC1 and PC2, thus appearing contiguous. The variations of drugs (metamizole, diclofenac sodium, and prednisone) spectrum pattern produced diverse PC1 and PC2 values that came up apart. The PCA performance gave a successful result for the discrimination of the samples without any misclassification.

Multivariate analysis calibration

The performance of quantitative analysis assisted by PLSR and PCR brought the optimum prediction models to analysis drug adulterant in quaternary models. Both of these (PLSR and PCR) were exhibited by regression curve in which responses (calculated value) on the *y*-axis and variables (actual value) on the *x*-axis (Irnawati *et al*., 2019). The quantitative multivariate analysis calibration and validation condition of Jamu Pegel Linu

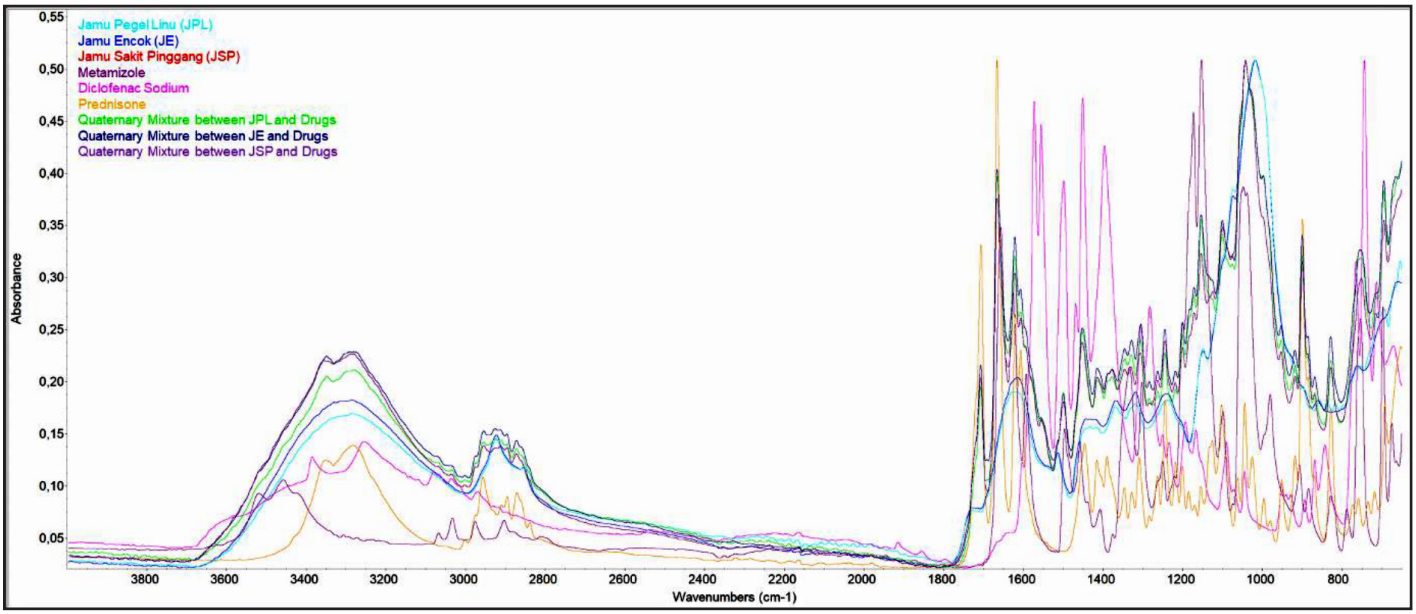

Figure 2. FTIR spectra of three types of herbal pain products, synthetic drugs used, and quaternary mixtures.

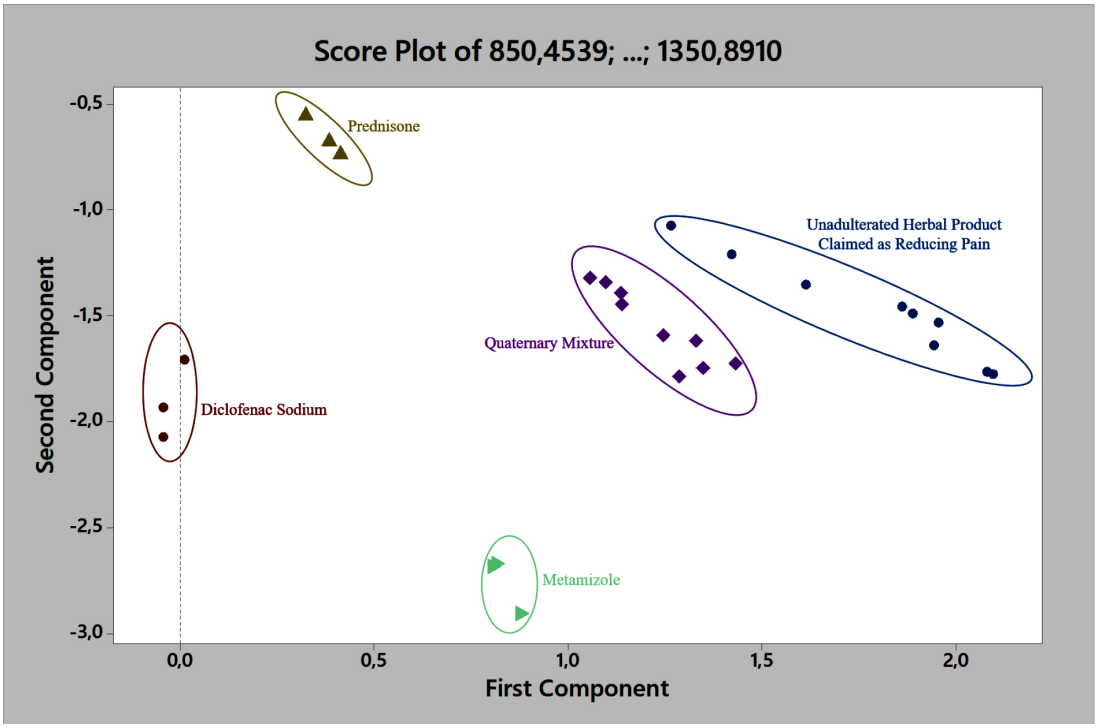

Figure 3. The score plot result of PCA.

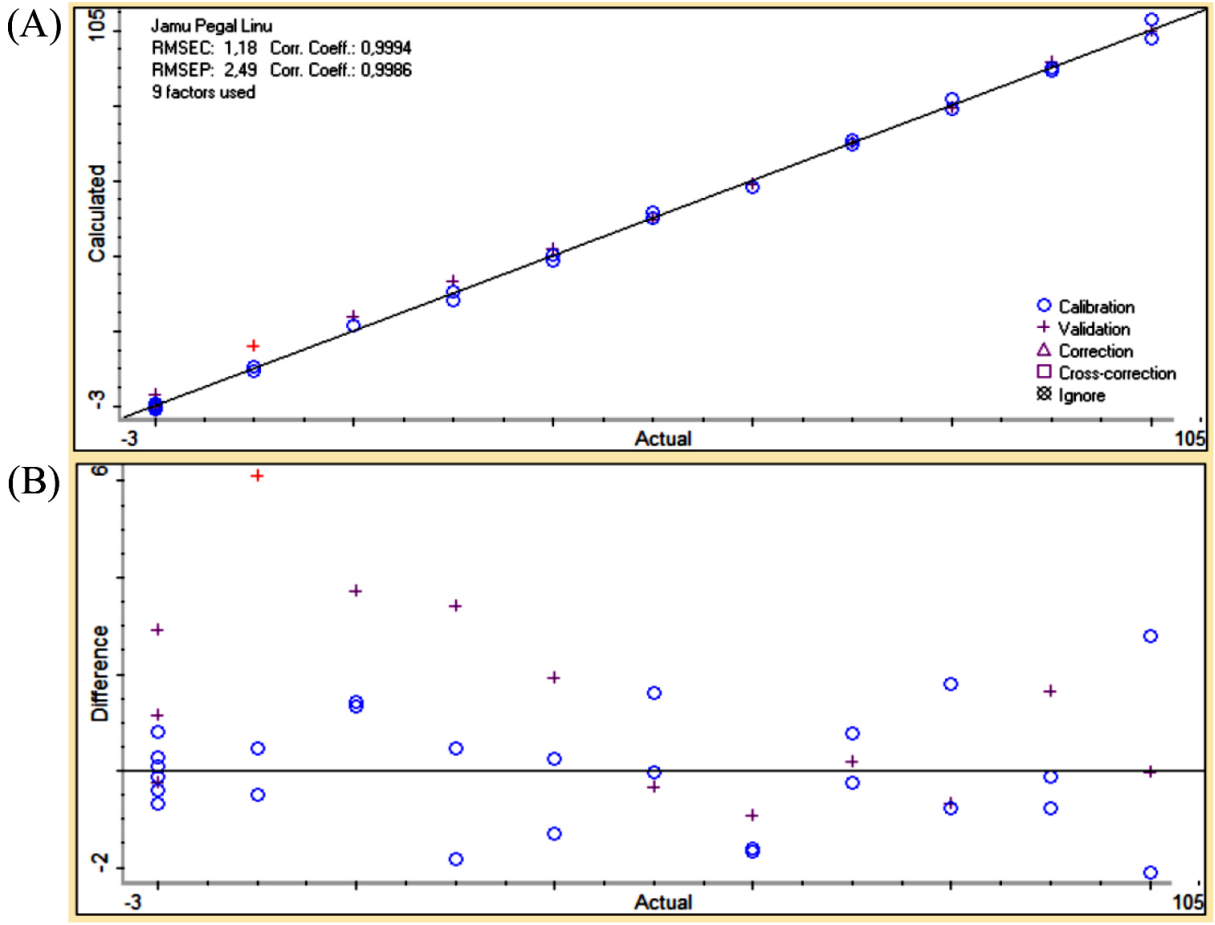

Figure 4. The correlation curve between actual (*x*-axis) and predicted (*y*-axis) values of Jamu Pegel Linu in quaternary mixtures with drugs (A) along with residual analysis (B).

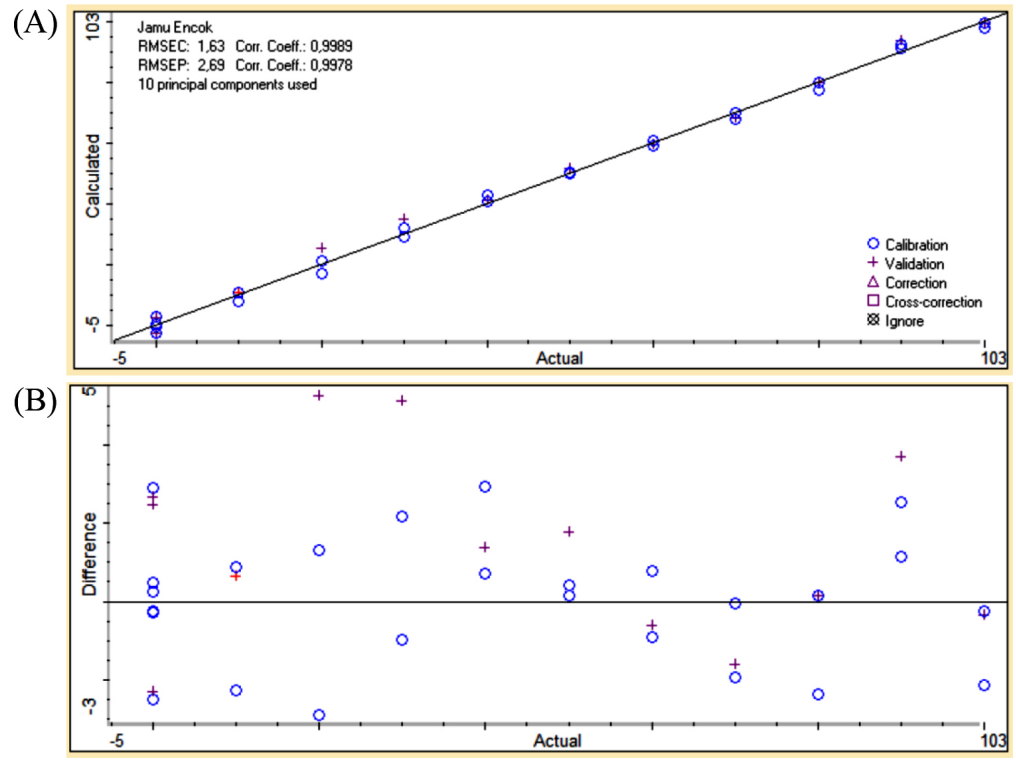

Figure 5. The correlation curve between actual (*x*-axis) and predicted (*y*-axis) values of Jamu Encok in quaternary mixtures with drugs (A) along with residual analysis (B).

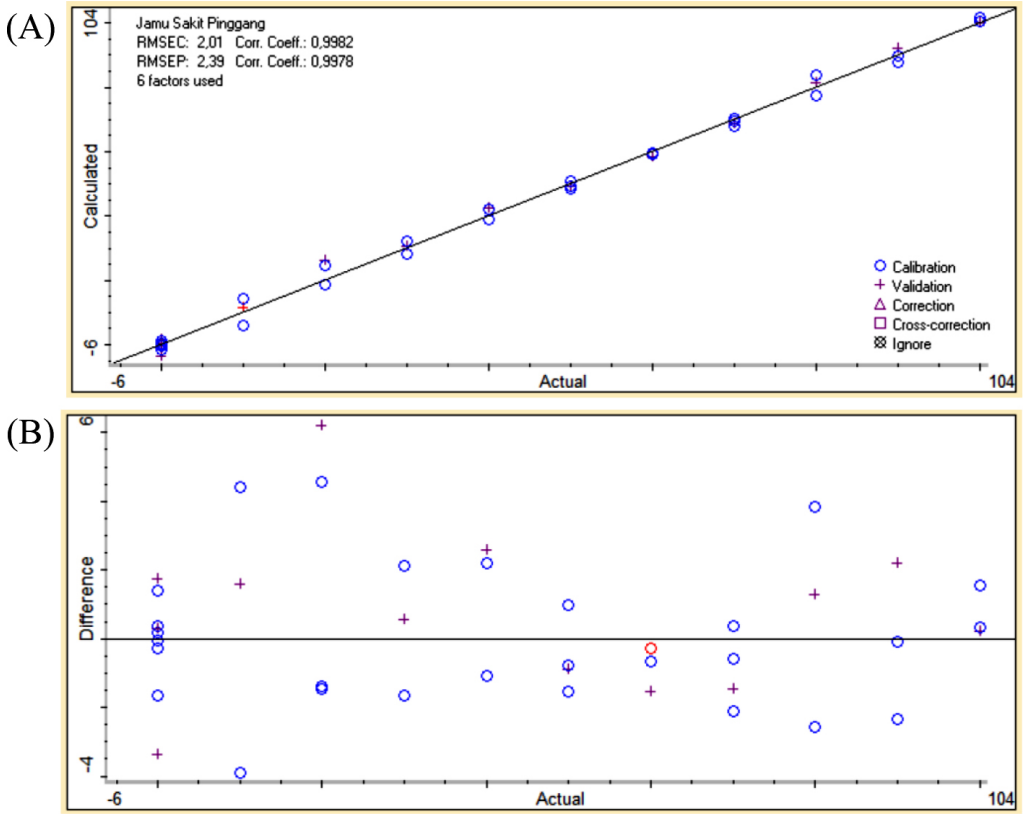

Figure 6. The correlation curve between actual (*x*-axis) and predicted (*y*-axis) values of Jamu Sakit Pinggang in quaternary mixtures with drugs (A) along with residual analysis (B).

Table 3. The performance compilation of PCR and PLSR for quantitative analysis of Jamu Encok in quaternary mixtures with drugs.

Multivariate calibrations	Wavenumber (cm^{-1})	Spectra	Calibration		Validation	
			R^2	RMSEC	R^2	RMSEP
PLSR	2,396.09–683.64	Normal	0.9965	2.85	0.9959	3.93
		Derivative 1	0.9896	4.91	0.9863	6.54
		Derivative 2	0.8452	18.3	0.8688	17.6
	1,535.55–649.89	Normal	0.9966	2.84	0.9974	3.34
		Derivative 1	0.9908	4.63	0.9910	5.37
		Derivative 2	0.9899	4.86	0.9894	5.79
	1,829.41–1,095.93	Normal	0.9956	3.19	0.9934	4.65
		Derivative 1	0.9874	5.42	0.9825	7.33
		Derivative 2	0.9858	5.74	0.9823	7.33
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9937	3.84	0.9956	3.94
		Derivative 1	0.9901	4.80	0.9879	6.17
		Derivative 2	0.9890	5.06	0.9868	6.41
	2,396.09–683.64 and 1,829.41–1,095.93	Normal	0.9891	4.88	0.9836	6.61
		Derivative 1	0.9979	2.12	0.9977	2.52
		Derivative 2	0.9358	11.7	0.9193	14.4
PCR	2,396.09–683.64	Normal	0.9989	1.62	0.9952	4.10
		Derivative 1	**0.9989**	**1.63**	**0.9978**	**2.69**
		Derivative 2	0.9986	1.81	0.9965	3.01
	1,535.55–649.89	Normal	0.9988	1.65	0.9975	3.30
		Derivative 1	0.9987	1.73	0.9966	3.45
		Derivative 2	0.9979	2.23	0.9942	4.39
	1,829.41–1,095.93	Normal	0.9981	2.12	0.9930	4.98
		Derivative 1	0.9982	2.08	0.9937	4.65
		Derivative 2	0.9964	2.89	0.9889	6.02
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9989	1.57	0.9959	3.89
		Derivative 1	0.9988	1.66	0.9975	2.91
		Derivative 2	0.9982	2.06	0.9952	3.93
	2,396.09–683.64 and 1,829.41–1,095.93	Normal	0.9989	1.62	0.9949	4.21
		Derivative 1	0.9988	1.66	0.9978	2.70
		Derivative 2	0.9987	1.77	0.9965	3.08

Bold denotes the selected condition.

in quaternary models with metamizole, diclofenac sodium, and prednisone used PLSR at wavenumbers 2,396.09–683.64 and 1,829.41–1,095.93 in first derivative mode. The powerful result was shown by the low value of RMSEC and RMSEP and the higher value of coefficient determination of each calibration and prediction (R^2) (Manaf *et al*., 2007). The values were 1.18 and 2.49 for RMSEC and RMSEP. The R^2 values were 0.9994 and 0.9986 for calibration and validation (Table 2). The regression curve is displayed in Figure 4A.

PCR at the first derivative on 2,396.09–683.64 wavenumbers on Table 3 was selected as quantitative analysis model for Jamu Encok in quaternary model with drugs based on R^2 values of calibration and validation that were 0.9989 and 0.9978, followed by the values of RMSEC and RMSEP that were 1.63 and 2.69, as shown in Figure 5A. Quaternary model of Jamu Sakit Pinggang for quantitative analysis was carried out by PLSR using the first derivative at 2,396.09–683.64 and 1,535.55–649.89. The result as shown in Figure 6A gave statistical parameter values of 0.9982 and 0.9978 for R^2 calibration and validation, also 2.01 for RMSEC, and 2.39 for RMSEP (Table 4). Minimum errors of calibration and prediction models with no systematic errors observed were confirmed by residual analysis in Figures 4B, 5B, and 6B (Riyanto *et al*., 2019).

Discriminant analysis

As supervised pattern recognition, DA is regularly applied for clustering unadulterated and adulterated samples (Rohman *et al*., 2014). Figure 7 showed Cooman's plot between unadulterated herbal products and quaternary mixtures of samples using wavenumber region at 1,812.34–649.89 cm^{-1} and

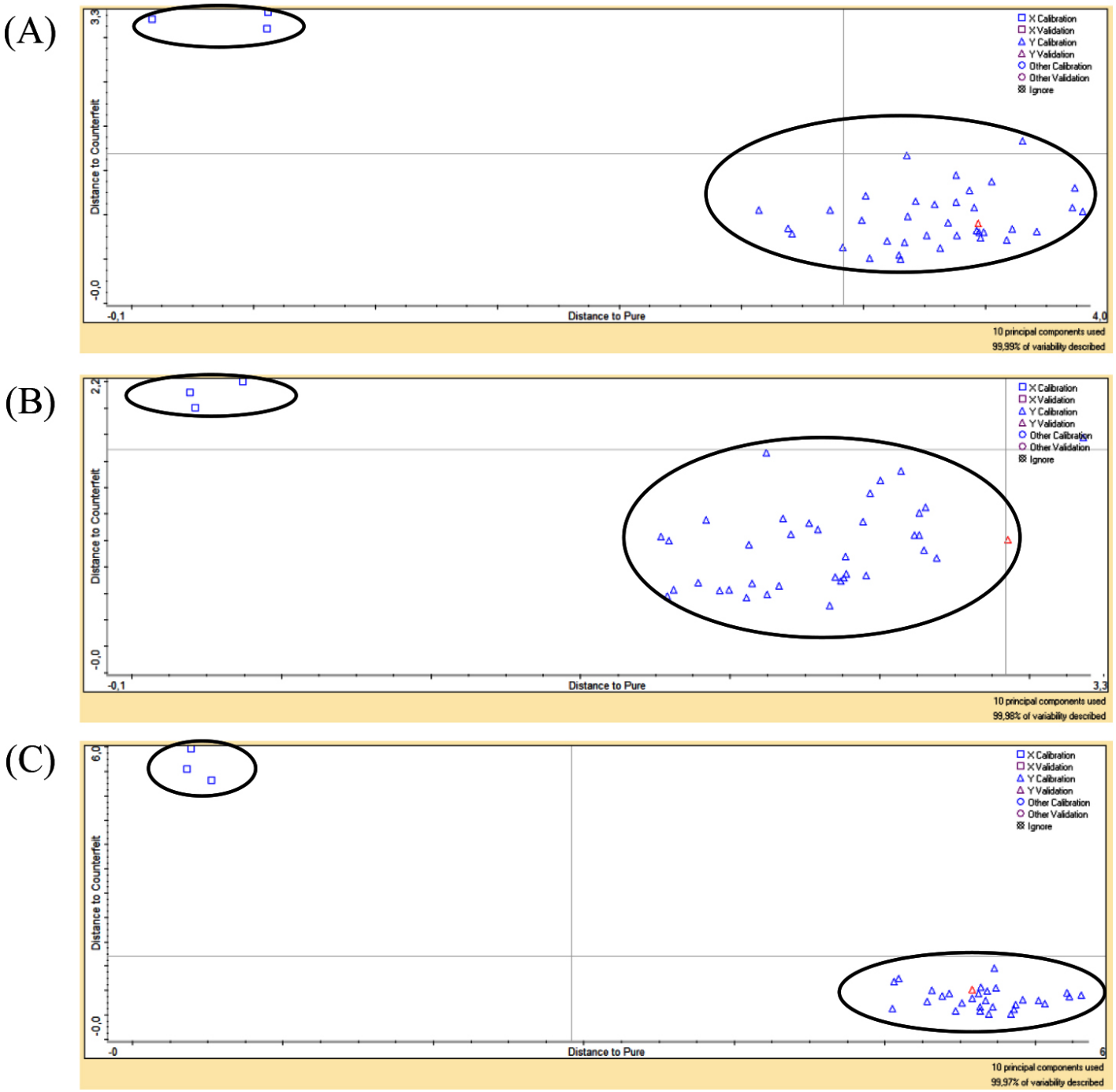

Figure 7. The Cooman plot of samples discrimination between unadulterated herbal products (□) and quaternary mixtures of samples (▲). Jamu Pegel Linu (A), Jamu Encok (B), and Jamu Sakit Pinggang (C).

Mahalanobis distance absorbance units to calculate the distance from each group. As shown, each group was clustered entirely with a 100% accuracy level without misclassification.

DISCUSSION

This method development for combining FTIR-ATR and chemometrics led to rapid, effective, efficient, and reliable analysis for detecting unadulterated herbal products, especially when mixed with synthetic drugs. The use of ATR as a sampling technique in this research made the sample straightforwardly placed on the crystal without any preparation first. The obtained spectra from FTIR-ATR showed unique bands on every collected sample (Rohman *et al*., 2011). These peaks at particular wavenumber contained some critical information like functional groups, type of the functional group, and intensity. However, the data of FTIR spectroscopy alone looked arduous to analyze the adulterant in herbal products because of its limitations (Rohman *et al*., 2019; Popescu and Radu, 2015). Hence, we combine the valuable and

Table 4. The performance compilation of PCR and PLSR for quantitative analysis of Jamu Sakit Pinggang in quaternary mixtures with drugs.

Multivariate calibrations	Wavenumber (cm^{-1})	Spectra	Calibration		Validation	
			R^2	RMSEC	R^2	RMSEP
PLSR	2,396.09–683.64	Normal	0.9814	6.36	0.9749	7.93
		Derivative 1	0.9981	2.03	0.9978	2.40
		Derivative 2	0.9511	10.2	0.9357	13.1
	1,535.55–649.89	Normal	0.9808	6.46	0.9800	7.03
		Derivative 1	0.9572	9.58	0.9441	12.2
		Derivative 2	0.9549	9.83	0.9420	12.3
	1,829.41–876.29	Normal	0.9890	4.90	0.9828	6.77
		Derivative 1	0.9970	2.57	0.9961	3.18
		Derivative 2	0.7763	20.9	0.7497	23.2
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9887	4.97	0.9861	5.99
		Derivative 1	**0.9982**	**2.01**	**0.9978**	**2.39**
		Derivative 2	0.9525	10.1	0.9379	12.8
	2,396.09–683.64 and 1,829.41–876.29	Normal	0.9893	4.84	0.9836	6.60
		Derivative 1	0.9980	2.09	0.9977	2.50
		Derivative 2	0.9520	10.1	0.9373	12.9
PCR	2,396.09–683.64	Normal	0.9974	2.38	0.9958	3.28
		Derivative 1	0.9978	2.18	0.9978	2.39
		Derivative 2	0.9973	2.45	0.9970	2.67
	1,535.55–649.89	Normal	0.9942	3.57	0.9885	5.90
		Derivative 1	0.9974	2.37	0.9967	2.91
		Derivative 2	0.9871	5.30	0.9877	5.38
	1,829.41–876.29	Normal	0.9918	4.23	0.9870	6.17
		Derivative 1	0.9970	2.55	0.9967	2.98
		Derivative 2	0.9924	4.07	0.9928	4.52
	2,396.09–683.64 and 1,535.55–649.89	Normal	0.9975	2.35	0.9960	3.20
		Derivative 1	0.9980	2.09	0.9974	2.58
		Derivative 2	0.9983	1.91	0.9977	2.39
	2,396.09–683.64 and 1,829.41–876.29	Normal	0.9974	2.40	0.9952	3.53
		Derivative 1	0.9978	2.20	0.9977	2.48
		Derivative 2	0.9973	2.43	0.9969	2.70

Bold denotes the selected condition.

robust chemometric technique to assist FTIR spectroscopy in analyzing any contaminant in herbal products.

Regarding the score plot result, PCA, as unsupervised pattern recognition, could classify the samples by processing the data via reduction and extraction of the information on data. Afterward, the more convenient data information would become PCs score and further processed by its similarity (Miller and Miller, 2010). In the previous study, PCA could discriminate the binary mixture between herbal products and metamizole (Fatmarahmi *et al*., 2021). Therefore, the PCA capacity also could classify the quaternary mixtures of herbal products in this research based on the PC1 and PC2 scores.

PCR and PLSR were carried out, compared, and optimized to obtain the quantitative analysis result of samples simultaneously. Derivatization as spectral FTIR treatment could resolve the overlapping peaks limitation on FTIR spectra and yet decrease the sensitivity (Irnawati *et al*., 2019). The statistical parameters on this research exhibited an optimum result to build the best prediction models. Based on the value of RMSEC, RMSEP, R^2, residual analysis, the developed models were accurate and precise.

The DA was included in one of the simple algorithms of supervised pattern recognition. This type of analysis could separate the pure and mixture of samples, yet any misclassification could happen. The high similarity of both samples caused the misclassification that occurred on DA (Riyanto *et al*., 2019; Marina *et al*., 2009).

CONCLUSION

Finding the highlights, the prepared quaternary models were successfully applied to predict adulterants in herbal products.

As green analytical chemistry, this analytical technique did not need any preparation of the sample. Qualitative analysis using PCA and DA could classify and discriminate adulterated analgesic herbal products with synthetic drugs and unadulterated. Moreover, the performance of multivariate calibration analysis gave an optimal result according to the statistical parameter value. Therefore, FTIR-ATR coupled with PCA, PCR, PLSR, and DA fruitfully offered a potential method that is valid, efficient, effective, and reliable for herbal products quality control, especially for screening synthetic drugs adulterant in herbal products.

ACKNOWLEDGMENTS

The authors sincerely acknowledge RTA as one of UGM funding support programs No. 3143/UN1.P.III/DIT-LIT/PT/2021 and also acknowledge PT Phapros, Tbk for supplying the drugs.

CONFLICT OF INTERESTS

Dharmastuti Cahya Fatmarahmi, Ratna Asmah Susidarti, Respati Tri Swasono, and Abdul Rohman as authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

PUBLISHER'S NOTE

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How to cite this article:
Fatmarahmi DC, Susidarti RA, Swasono RT, Abdul Rohman A. A development method of FTIR spectroscopy coupled with chemometrics for detection of synthetic drug adulterants of herbal products in quaternary mixture. J Appl Pharm Sci, 2022; 12(03):191–201.