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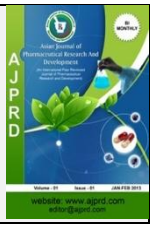

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Review Article

Analysis of Medicinal Chemicals Contained on *Jamu*: A Review

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ABSTRACT

Background: *Jamu* is commonly known as an Indonesian traditional herbal medicine that contains ingredients or ingredients derived from plants, animals, minerals, galenic, or mixtures of these ingredients that have been hereditary for medicinal use. Some studies reported the presence of medicinal chemicals that are deliberately added to *jamu*. *Jamu* that containing medicinal chemicals usually had a faster healing effect compared to *Jamu* that do not contain medicinal chemicals. *Jamu* added medicinal chemicals cause serious side effects if it is consumed regularly, overdose, and long period consumption with uncontrolled dosage or its interaction with other substances on *jamu* formulation.

Purpose: This review article aims to summarize several methods used to analyze medicinal chemicals contained in *jamu*.

Data source: The author created thisreview article by conducting literature studies. The literature was collected from national and international journals published in the last ten years (2010-2020). The works of literature were collected from trusted online journal sites such as the digital library, Google, Google scholar/Google Cendekia, PubMed, Science Direct, NCBI, Researchgate, and other E-resource with the keyword "*Jamu*", "medicinal chemicals", and "analysis of medicinal chemicals".

Conclusion: *Jamu* products that containing medicinal chemicals are *jamu pegal linu*, weight loss, stamina enhancer, diabetes, antihypertensive and dietary supplements. The medicinal chemicals used are sodium diclofenac, paracetamol, piroxicam, ibuprofen, dexamethasone, mefenamic acid, phenolphthalein, sibutramine, fenfluramine, sildenafil, tadalafil, thiosildenafil, caffeine, ephedrine, nifedipine, glibenclamide. Herbal medicine was analyzed by the TLC method (thin layer chromatography), Densitometry-chromatography, thin-layer chromatography-Spectrophotometry, SERS-thin layer chromatography, Spectrophotometry, HPLC (High-Performance Liquid Chromatography), HPLC-ESI-MS/MS (high-performance liquid. chromatography/electrospray ionization tandem mass spectrometry), HPLC-Densitometry (High-Performance Liquid Chromatography-densitometry), UHPLC-Q-ORTIP HERMS (ultra-high-performance liquid chromatography-Quadrupole-orbitrap high-resolution mass spectrometry), UPLC/Q-TOF MS (ultra-performance liquid chromatography (UPLC) coupled with quadrupole-time-of-flight mass spectrometry (Q-TOF MS), Capillary electrophoresis (CE), GC-MS (Gas Chromatography-Mass Spectrometry), LC-MS (Liquid Crhomatogaph Mass) Spectrometry), Prototype Test-Strip, Infrared spectroscopy.

Keyword: Analysis, Medicinal chemicals, *Jamu*.

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INTRODUCTION

Jamu (herbal medicine) is one of the traditional medicines in Indonesia that has been used empirically for medicine. Generally, *Jamu* was made from plants, animals, minerals, sarian preparations, and mixtures of these ingredients[1,2,3]. In Indonesia, *jamu* have been well known for up to 15-16 decades or longer[4]. The result of research studies showed the use of herbal medicine in Indonesia amounted to 49.53% to maintain health and 95.6% of them felt the benefits of consumption of *jamu*. Globally, *jamu* are widely consumed because it is considered a natural alternative medicine and affordable cost[6,7]. The increasing demand for *Jamu* has led some producers to add medicinal chemicals to herbal products[8,9,10].

Medicinal chemicals can consist of active chemicals or finished drugs. *Jamu* cannot provide an instant medicinal effect, because it comes from natural ingredients.

*Jamu*that containing medicinal chemicals usually had a faster healing effect compared to *Jamu* that do not contain medicinal chemicals [11,12].*Jamu* added medicinal chemicals cause serious side effects if it is consumed regularly, overdose, and long period consumption with uncontrolled dosage or its interaction with other substances on *jamu* formulation[13,14,15].

Ensuring safety factors before consuming herbal medicineis very important for consumers[16]. Identification and quantification are essential for the safety of traditional medicines[17,18]. According to the regulations of the Ministry of Health of Indonesia and the National Food and Drug Agency, *Jamu* should not contain synthetic medicinal chemicals[19]. Although it has been determined, medicinal chemicals are still found in herbal products[20]. *Jamu* products that containing medicinal chemicals are jamu pegal linu, weight loss, stamina enhancer, diabetic, antihypertensive, and dietary supplements. The medicinal chemicals used were sodium diclofenac, paracetamol, piroxicam, ibuprofen, dexamethasone, mefenamic acid, phenolphthalein, sibutramine, fenfluramine, sildenafil, tadalafil, thiosildenafil, caffeine, ephedrine, nifedipine, glibenklamid[21].

To measure levels of medicinal chemicals, some studies used qualitative and quantitative methods, among other TLC method (thin layer chromatography), Densitometry-chromatography, thin-layer chromatography-Spectrophotometry, SERS-thin layer chromatography, Spectrophotometry, HPLC (High-Performance Liquid Chromatography), HPLC-ESI-MS/MS (high-performance liquid. chromatography/electrospray ionization tandem mass spectrometry), HPLC-Densitometry (High-Performance Liquid Chromatography-densitometry), UHPLC-Q-ORTIP HERMS (ultra-high-performance liquid chromatography-Quadrupole-orbitrap high-resolution mass spectrometry), UPLC/Q-TOF MS (ultra-performance liquid chromatography (UPLC) coupled with quadrupole-time-of-flight mass spectrometry (Q-TOF MS), Capillary electrophoresis (CE), GC-MS (Gas Chromatography-Mass Spectrometry), LC-MS (Liquid Crhomatogaph Mass) Spectrometry), Prototype Test-Strip, Infrared spectroscopy[22,23]. This review article aims to summarize several methods used to analyze medicinal chemicals contained in *jamu*.

METHODS

The author was created this article review by conducting literature studies. The works of literature were collected from pharmaceutical scientific official books, national and international journals published in the last ten years (2010-2020). The literature was collected from trusted online journal sites such as Science Direct, NCBI, Researchgate, PubMed, Google Scholar/Google Cendekia, and other E-resource with the keyword "*Jamu*", "medicinal chemicals", and "analysis of medicinal chemicals".

RESULTS AND DISCUSSION

Herbal medicine has been used to reduce pain, fatigue, muscle and bone pain, circulate blood circulation and reduce pain throughout the body. Common medicinal chemicals added to herbal medicine are sodium diclofenac, paracetamol, ibuprofen, mefenamic acid, phenylbutazone, pyroxykam[24,25]. Paracetamol is one of the drugs that are categorized as non-opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAID)[26]. Paracetamol inhibits COX-1 and COX-2 cyclooxygenase enzyme activity, which results in the inhibition of prostaglandin synthesis, which acts to regulate hypothalamic pain[27,28]. Paracetamol is the most commonly used drug in most countries, available without a doctor's prescription[29].

Diclofenac sodium is a non-steroidal anti-inflammatory (NSAID) drug that has analgesic, anti-inflammatory, and antipyretic effects[30,31]. Diclofenac sodium and mefenamic acid-binding to cyclooxygenase (COX), resulting in decreased formation of prostaglandins, which are biomarkers responsible for inflammation and pain[32,33]. Dexamethasone is a synthetic glucocorticoid used for anti-inflammatory and analgesic effect[34]. Dexamethasone suppresses bradykinin formation and also releases neuropeptides from nerve endings. Inhibition of prostaglandin production by dexamethasone would produce an analgesic effect through inhibition of the enzyme cyclooxygenase synthesis in the body's peripheral tissues[35,36].

The pharmacological effect of sibutramine used in weight loss herbs is reduced appetite and satiety by inhibiting the reuptake of noradrenaline (NA) and 5-hydroxytryptamine or serotonin (5-HT)[37,38]. Side effects of the use of sibutramine have been observed such asheadache, insomnia, anorexia, dry mouth, shivering, mood swings, hypertension, and tachycardia[39,40]. The drugs commonly added to the herbal weight gain are cyproheptadine and dexamethasone[41].

Medicinal chemicals such as sildenafil and tadalafil are commonly found in *jamu kuat* (men vitality herbal products) to the enhancement of sexual function. sildenafil was the inhibitor drug of PDE5 (Phosphodiesterase-5) that use to treat erectile dysfunction[42]. Phosphodiesterase type 5 (PDE5) is a regulator of vascular smooth muscle contraction in all smooth muscle districts and especially in the penis, and PDE5 inhibitors are currently the first-line therapy for erectile dysfunction [42], by inhibiting the cyclic guanosine monophosphate (cGMP). Inhibitor PDE-5 works by increasing the levels of cyclic guanosine monophosphate (cGMP) in the *corpus cavernosum* indirectly by inhibition of the enzyme PDE-5 by increasing nitrogen oxide (NO). This leads to the effect of smooth muscle relaxation and an increased inflow of blood in the corpus cavernosum[43]. Side effects of consumption of herbs containing Sildenafil are irregular heartbeat, shortness of breath, angina, myocardial infarction, stroke, priapism, sudden hearing loss, and blindness[44].

Glibenclamide is sulfonylurea antidiabetic[45]. It has the mechanism of action in lowering blood glucose like Sulfonylurea's which acts by stimulating the release of insulin from the B-cell of the pancreas through inhibiting ATP-sensitive K channels, thereby activating the Ca++ channel with an increase in intracellular calcium to release insulin[46,47]. Glibenclamide is one of the synthetic added to anti-diabetic herbs to increase its effect. Generally, the herbs containing glibenclamide have side effects that include liver failure and gastrointestinal[48].

Nifedipine (Calcium Channel Blocker) is the most widely used drug for hypertension[49]. Nifedipine binds to L-type calcium channels in blood vessels, selectively. There by it does not reduce the activity of the sinuses, causing vasodilatation and lower blood pressure[50,51].

Table: 1. Analysis of medicinal chemicals in herbal medicine using the thin layer chromatography method.

No	Medicinal chemicals detected	Stationary phase	Mobile phase	Results and discussion	References
1	Diclofenac sodium	Silica gel GF254 (7x8)	Toluene : ethyl acetate: glacial acetic acid (60:40:10)	Jamu A, C, G positively contains sodium diclofenac with the same Rf value of 0.69	52
2	Paracetamol	Silica gel GF254	Chloroform : ethanol (90:10)	Jamu D positively contains sodium diclofenac with Rf value of 0.313	53
3	Piroxicam	Silica gel GF254	Chloroform : acetone (80:20)	A total 8 samples positive containing piroxicam	54
4	Mefenamic acid	Silica gel GF254	Ethyl acetate : methanol : ammonia (80:10:10)	Jamu J positively contains sodium diclofenac with rf value equal to comparison of 0.32	55
5	Phenylbutazone	Silica gel GF254	N-heksan : ethyl acetate (4:1)	The Rf value of sample A was 0.71, B 0.7, C 0.7 and D 0.71. It had the same Rf value as phenylbutazone, thatis 0.7	56
6	Ibuprofen	Silica gel GF254 (10x10)	Ethyl acetate : Methanol : ammonia (85:10:5)	A total 14 of the 15 samples positively contained ibuprofen with the same Rf value as ibuprofen, that is 0.87	57
7	Sildenafil	Silica gel GF254 (20 x 20)	Ethyl acetate : methanol : ammonia (85:10:5)	Samples A, B, D, E, G were positive for sildenafil because the Rf values are 0.53, 0.53, 0.53, 0.52, and 0.52, have the same Rf value with the sildenafil that is 0.53	58

The thin-layer chromatography method can be used for qualitative analysis of the presence of sodium diclofenac in herbal products[59]. Seven ethanol extracts of herbal products A, B, C, D, E, F, and G spotted on silica gel and eluted with the mobile phase. For visualization of the spots using ultraviolet at wavelength 254 nm and 366 nm. Herbal medicine products A, C, G positively contain sodium diclofenac because the Rf value obtained is equal to the value of Rf comparison, which is 0.69. However, herbs B, D, E, and F not contained diclofenac sodium[52].

The presence of paracetamol in herbal products can be analyzed using the thin layer chromatography method with a mobile phase of a mixture of ethyl acetate: acetone and silica gel as the stationary phase. The spots of the sample and its comparators were observed at a wavelength of 254 nm, the result is that the Rf value of the herbal product code A was 0.155 and the comparison was 0.158[53]. Two spots with almost the same wavelength and Rf value, it follows that the two components are the same molecules[60].

Medicinal products containing piroxicam can be analyzed using TLC used eluent from chloroform and acetone as well as the stationary phase used silica gel.From 114 herbs analyzed at a wavelength of 254 nm was obtained 8 positive herbal products containing piroxicam. TLC can be used for qualitative tests for large samples and does not take a long time[54].

Mefenamic acid was analyzed using silica gel F254 and eluent from mixtures of ethyl acetate: methanol: ammonia with a ratio of 80:10:10 as mobile phase. The results of observations using UV 254 nm UV, it was found that sample J was positive for containing mefenamic acid with an Rf value of 0.32[55].

Phenylbutazone content in herbal products can be analyzed qualitatively using TLC. The n-hexane: ethyl acetate (4: 1) solvent was used as the mobile phase and 254 nm silica gel as the stationary phase. Extracts of sample A, B, C, D, E, F compared with Rf value comparison, then observed at 254 nm UV light. the results obtained are the values A, C, D, E have the same Rf value as the comparison (0.7), namely 0.71, 0.7.0.7, and 0.71[56].

TLC is a simple method for analyzing samples of herbal products containing ibuprofen. TLC analysis used eluent from mixtures of ethyl acetate: methanol: ammonia (85: 10: 5) and silica gel F254 with a size of 10x10 cm for the stationary phase. From the sample

spots observed under UV 254 nm, 14 samples were positive for the presence of ibuprofen *jamu* stiff and gout from 15 samples of herbal products with an Rf value of 0.87.[57]

Jamu containing sildenafil can be analyzed qualitatively by the TLC method. The mobile phase used a mixture of ethyl acetate: methanol: ammonia (85: 10: 5), and for the stationary phase used Silica gel F254 with a size of 20 x 20 cm. From the sample and comparison spots, the Rf values of samples A, B, D, E, G were 0.53, 0, 53, 0.53, 0.52, 0.52, and the Rf value of 0.53 from the sildenafil comparators respectively[58].

Table: 2. Analysis of medicinal chemicals using the TLC-Densitometric method, TLC-spectrophotometry, and TLC - SERS

No	Medicinal chemicals detected	Stationary phase	Mobile phase	Densitometry and SERS	Results and discussion	References
1.	Paracetamol	Silica gel F_{254} nm	Chloroform : ethanol (8:1)	Camag TLC scanner 4	Samples 3 (SM), 7 (US) 10 (JE) positively contained Paracetamol with the Rf value and color spots the same as the comparison with levels of 0.04%, 0.30%, and 0.13%	61
2.	Sibutramine	Silica gel F_{254} nm	Toluene : diethylamine (10 : 0,3)	Camag TLC scanner 3	Herbal products positively contain sibutramine which has the same rf value of 0.58 as 2.45-26.24 mg	62
3.	Sibutramine	Silica gel F_{254} nm	Toluene : n- heksan : diethylamine (9 : 1 : 0,3)	Camag TLC scanner 3 225 nm	samples S10 and S 19 were found sibutramine with levels of 20.63 mg and 24.16 mg	63
4.	Efedrin	Silica gel F_{254} nm	Chloroform : methanol : ammonium hydroxide	Spectrometer raman portable	Eight common raman peaks ($\Delta\upsilon$=620, 1003, 1030, 1159, 1181, 1205, 1454, 1603 cm−1) were extracted experimentally and statistically to characterize the common feature of ephedrine analogues	64
5.	Fenilbutazon	Silica gel F_{254} nm	acetate: Chloroform (2:1)		Silica gel F254 nm 5 samples positively contained phenylbutazone, namely j, k, s, u, v with a percentage level of 9, 053%; 10, 6138%; 62, 8776%; 42, 8839% and 24, 9238%, respectively.	65

The TLC-Densitometry method can be used to analyze the presence of paracetamol in herbal products. It was used silica gel F254 as the stationary phase and using a UV lamp 254 for observation. From the results of the analysis obtained that samples 3 (SM), 7 (U.S.), 10 (JE) positive containing paracetamol with Rf values 0.43, 0.49 0.45 respectively. Then continued with the densitometry test to determine the paracetamol levels in the samples. From the densitometric test results, the paracetamol content of each sample was 0.04%, 0.30%, and 0.13%[61].

Analysis of sibutramine contained in herbal products could be done using the TLC-Densitometry method with a detection limit of 3.3 ng and a quantification limit of 10 ng. As a result, a total of 6 herbal products with sample codes AR, SU, DI, SL, LK, MN contained sibutramine with levels of 9.83 mg, 2.35 mg, 26.24 mg, 20.47 mg, 15.97 mg, and 3.43 mg respectively. This method has good specificity and there were no interferences by other components of the sample in analyzing sibutramine [62].

The TLC-Densitometry method was used to analyze sibutramine added to herbal products, using a stationary phase of silica gel 60 F_{254}, but weakly detected under UV at 254. The intensity of spot detection was enhanced by dipping the plate in the dragendorff reagent. The orange-colored band corresponding to SH was observed and well separated from other components in the samples. Two herbal products, samples S10 and S19 positive for containing sibutramine with levels of 20.63 mg and 24.16 mg63 respectively[63].

Analysis of herbal products using TLC under UV light 254 nm with a mobile phase of chloroform: methanol: ammonium hydroxide obtained an Rf value of 0.30. To differentiate between components with other components, the SERS spectrum method was followed. As a result, the peak characteristics of ephedrine compounds and their analogs are (△ υ = 620, 1003, 1030, 1159, 1181, 1205, 1454, 1603 cm − 1)[64].

The TLC method with ethyl acetate: chloroform (2: 1) eluent, with absorption of 254 nm, can be used to detect the presence of phenylbutazone in herbal medicine. As a result, an Rf value of 0.88 was found.The maximum wavelength of phenylbutazone was 237 nm. Linearity with an R-value of 0.9719, the detection limit of 12200.28 g/mL, and a quantification limit of 40667 g/mL. In the 30 herbal medicine samples tested, 5 samples positive containing phenylbutazone were sampled with the code j, k, s, u, v with a percent content of 9.5053%; 10,6138%; 62,8776%; 42.8839%, and 24.9238%, respectively[65].

Table: 3. Analysis of medicinal chemicals in herbal medicine using the Spectrophotometric method

No	Medicinal chemicals detected	λ Max	Absorbantion	Results and discussion	References
1.	Diclofenac sodium	276 nm	S3 = 0.3880 nm S4 = 0.3284 nm S7 = 0.2653 nm	Three samples of *jamu* contained diclofenac sodium with levels of S3 = 135,1982 mg, S4= 110,0334 mg and S7= 6.0968 mg	66
2.	Paracetamol	254,5 nm	SD= 3,350 nm SE=2,872	SD and SE herbal product samples contained paracetamol with levels of 47.21 mg and SE = 40.47 mg	67
3.	Mefenamic acid	285 nm	0,815 nm	Mefenamic acid was contained in the herbal product of 0.8%	68
4.	Phenylbutazone	265,2 nm	-	Three samples contained phenylbutazone with levels of SB = 33.55 mg, SC = 476.23 mg and SD 507 mg	69

Spectrophotometry (UV-Vis) can detect quickly and sensitively[70]. Diclofenac sodium has a chromophore group or conjugated double bonds that can absorb UV rays. The maximum wavelength of diclofenac sodium was 276 nm. The binding force auxochrome the chromophore group in a shift of the absorbance band larger wave (bathochromic shift) and increased intensity (hyperchromic effect). By measuring the absorbance of the sample obtained 0.3880, 0.3284, and 0.2653 with the linear regression equation y = 0.038x - 0.011, it was found that the levels of diclofenac sodium in herbal products were 133.1982, 110, 0334, and 6.0968[66].

The absorbance of paracetamol can be measured using the spectrophotometric method at a wavelength of 254.5 nm.The absorbance results of samples D 3,350 and E 2,872 with linear regression equation y = 0.0708x – 0.00557, obtained the absorbance values of SD = 47.21 mg and SE = 40.47 mg[67]. The spectrophotometric method is a rapid test method for quantitative analysis. The wavelength for mefenamic acid is 285 nm, linearity 0.998 over a concentration range of 1-9 µg/mL, the limit of detection of 0.48µg/mL, and the limit of quantification of 1.63µg/mL.As a result, the absorption value of the herbal product sample was 0.815 and

mefenamic acid content in the herbal product was 0.8%[68].

Spectrophotometric methods are used for phenylbutazone analysis in herbal products. Absorbance was measured at 265.2 nm with a correlation coefficient (r) of 0.997. Based on the results, it is concluded that the positive correlation between levels and absorption and indicates increased concentration, the absorption will also increase. From the results, the levels of phenylbutazone in herbal products B, C, and D were 33.55 mg, 475.23 mg, and 507.50 mg, respectively HPLC is a rapid test method for the analysis of a compound[87]. HPLC method was used to analyze paracetamol with Column C18 (5.0 µm, 300 mm × 4.6 mm), the mobile phase was methanol: aquadest with a flow rate of 1.0 ml/min. Absorption of paracetamol was measured at 254 nm, the limit of detection and limit quantification were 3,024 ppm and 10,079 ppm, values (r) 0,999 and linearity in the range of 10-100 ppm on paracetamol contained in herbal products[71].

The HPLC method is selective and effective in analyzing diclofenac sodium in herbal products. The columns used are C18 Phenomenex Luna (250 mm × 4.5 mm), Phosphate Buffer: Acetonitrile (45:55 v/v) as the mobile phase, for detection using a Diode array detector (DAD) at a wavelength of 254 nm. The detection limit for diclofenac sodium was 3.10 µg/ml and the correlation coefficient was 0.997. The results showed that an excellent correlation existed between the peak area and concentration of the analytes[72].

The mobile phase used is acetonitrile: water (7:3), which is polar. It has flowed through the column C18 to the detector with the wavelength used in the measurement is 254 nm, then be detected by a detector in the form of a chromatogram. The retention times of the herbal products A, B, C, E, and G are 1.988, 1.573, 1.561, 1522, and 1.784, respectively, with the equation y = 43425x - 8780 and an R-value of 0.9815. The analysis obtained 5 samples of herbal medicine containing dexamethasone, respectively 0.0979%, 0.222%, 0.4521%, 0.5131%, and 0.2809%[73].

The RP HPLC method uses a non-polar stationary phase i.e. Eurospher column, the mobile phase from Dihydrogen phosphate 50 mM: acetonitrile pH 5.5 with the addition of 10% orthophosphoric acid) (30:70), then be detected by a detector UV-Vis 225 nm. The limit of detection of sibutramine in herbal products was 16 ppm. The retention time of sibutramine was 4.69 min. The observations showed two herbal medicine i.e. brand A and brand B contain sibutramine of 15.39 mg and 12.83 mg, respectively[74].

The HPLC method was specific, sensitive, fast, reliable, and useful for analysis of illegally added sibutramine in herbal weight loss products. The mobile phase of acetonitrile: water: formic acid (45:55:0.78,) was used, a phenyl column (5.0 mm, 150 mm × 4.6 mm) and detected was carried out FLD 225 nm. The calibration curve area was found to be linear in the range 5–200 µg/ml and the limit of quantification was calculated as 1.71 ± 0.14 µg/ml and peak area 0.997[75].

UHPLC can offer 3–10-fold increases in analysis speed with similar resolution using the geometrical scaling approach. Analysis of sibutramine in herbal products using Column Vision HT C18 (2 mm x 100 mm, 1.5 m), cellular phase Ammonium acetate buffer: water: acetonitrile, detected by a Diode Array Detector (DAD) flow rate of 0.5 ml/min and the injection volume of 5 µl. As a result, 5.90 mg of sibutramine were found in herbal medicine products[76].

The HPTLC isa simple method, cost-efficiency, and good speed of analysis. HPTLC was sufficiently sensitive to detect 0.3 mg of sibutramine/capsule. The mobile phase was a mixture of 10% of methanol: ammonium formate buffer and UV-Vis as a detector. As a result, 5 weight loss herbal medicine products were found containing sibutramine with levels of 10 mg, 29 mg, 30 mg, 30 mg, and 32 mg, respectively[77].

UHPLC is a simple, fast, and selective method to determine the presence of phenolphthalein in herbal weight loss products (fat cut). UHPLC using a C18 column (Acquity BEH C18, 1.7 µm, 100 mm x 2.1 mm), The mobile phase was composed of phosphate: acetonitrile buffer. The Photodiode Array Detector (PDA) was used to determined phenolphthalein in herbal medicine. As a result, 60 mg phenolphthalein is contained in herbal products[78].

HPLC method used for the analysis of phenolphthalein, by comparing the maximum wavelength between the sample and the comparison. The mobile phase used methanol: water: glacial acetic acid (50: 50: 1) and the column was made of stainless material, in diameter 4.6 mm, containing octadecyl silane (C18).The wavelength was detected using ultraviolet. From the results obtained λ max sample = 275 nm and λ max comparison = 276 nm and retention values 1,877, 2,488, 3,600 and 1,860, 2,451, 3,568 and the levels of phenolphthalein were 133.2 mg[79].

To detect phenolphthalein, the mobile phase used potassium phosphate buffer pH 4, with a maximum HPLC wavelength of 225 nm, Linearity 27.22-56.7 µg/ml, the value of (r) 0.9991 and the content of phenolphthalein determined was 48.20 mg[80].

The HPLC method is a fast and simple method for quantitative analysis of sildenafil in herbal medicine products. Analysis using reversed-phase column C18 (4.6 × x250 mm, particles 5 µm) was performed isocratically with a flow rate of 1 ml/min. The mobile phase consisted of 10mM phosphate buffer (containing 0.1% triethylamine) and acetonitrile (65:35).The mobile phase pH was adjusted to 3.5 by 1 phosphoric acid. The method showed good linearity and correlation with a limit of quantification of 6.5 ng/ml. Sildenafil content was found to range from 0.01 to 465.47 mg/g[81].

To analyze the presence of sildenafil, the HPLC method was used. The mobile phase used was acetonitrile: 50

mmol of potassium dihydrogen phosphate (10:90) and the stationary phase was column C18.As a result, obtained the value (r) of 0.9997 ± 0.0005, the limit of detection 0.02 mg, and the limit of quantification 0.07 µg. The same retention time between sildenafil and herbal product samples was 13.6 min. The content of sildenafil citrate in herbal medicine with syrup forms A, B, C, D, E, F, G, H and I were 17 mg, 22 mg, 26 mg, 25 mg, 10 mg, 24 mg, 29 mg, 22 mg and 17 mg/100 ml, respectively[82].

The HPLC method was used to determine the tadalafil adulterated in herbal products. The mobile phase used was methanol/water: diethylamine (65: 35) and column C18. To detect using UV detector 290 nm. The results showed limit of detection 0.41 µg/ml, limit of quantification 1.25 µg/ml with Y value = 4421.1x + 14119. Tadalafil was contained in Max man (8µg/ml per pill) and Magna RX (5µg/ml per pill)[83].

To analyze the presence of sildenafil, the herbal medicine products have been extracted first with methanol before being tested. The stationary phase used was the C18 HPLC column, 50 × 4.60 mm, 2.6 µm (Phenomenex, USA). The mobile phase consisted of acetonitrile and ultrapure water flowing at 1.2 mL/min. Photodiode Array Detector (PDA) was used for the analysis at 230 nm. The result showed Tadalafil was contained in herbal medicine (12 mg)[84].

HPLCis a valid methodfor qualitative and quantitative analysis of glibenclamide in antidiabetic jamu. HPLC separation was carried out with a Kromasil 100 C18 column (150 x 4.6 mm i.d, 5 µm particle size) using methanol: water (75:25) v/v as the mobile phase at a flow rate of 0.5 mL/min, UV detection was set at 301 nm. There was no potential interference from other compounds at the glibenclamide retention time (retention time of 5.234 ± 0.056 min). The method has good linearity (r = 0.9936) in the range 10-50 µg/mL. The detection limit of the method was 6.21 µg/mL while the quantitation limit was 20,71 µg/mL.The resultshowed that glibenclamide was detected in one sample with a level of 1.88 ± 0.25 µg/g[85].

The HPLC analysis was isocratically conducted on a C18 column (250 mm×4.0 mm ID., 5 µm, Euro- spher II ®100-5). The samples were detected by the detector Diode Array Detector (DAD, S2800). The mobile phase was a mixture of acetonitrile and phosphate buffer (pH=2.3) (63:37 v/v) was used as elution solvents. A 20-µL sample was injected into the column and eluted at room temperature with a flow rate of 1.0 mL/min. The result showed herbal products brand (cravil) contain medicinal chemicals (caffeine)[86].

Table: 4. Analysis of medicinal chemicals using the HPLC (High-Performance Liquid Chromatography) methods

No	Medicinal chemicals detected	Column	Mobile phase	Detector	Chromatographic conditions	Result	References
1.	Parasetamol	C18 column (5.0 µm, 300 mm × 4.6 mm)	methanol: aquadest	UV detector 254 nm	Flow rate 1.0 ml / min, injection volume 20 µl	Standard curve linearity for acetaminophen is in the range of 10 - 100 ppm	71
2	Natrium Diklofenak	C18 Phenomax Luna (250 mm × 4.5 mm)	Phosphate Buffer: Acetonitrile (45:55 v/v)	Diode array detector (DAD)	Flow rate 1.0 ml / min, injection volume 20 µl at room temperature using water diluent	accuracy and precision according to the linearity range of 10 µg / ml to 60 µg / ml and the correlation coefficient of diclofenac sodium is 0.997	72
3	Dexamethasone	Column C18 µm	Acetonitrile : water (7:3)	UV detector 254 nm	Induced volume was 10.00 µl	5 samples of herbal medicine containing dexamethasone with levels of 0.0097%, 0.222%, 0.4521, 0.5131%, and 0.2809% respectively	73
4	Sibutramine	Eurospher C18 (5 µm, 4,6 x 250 mm)	DihydrogenPhosphate 50 mM : acetonitrile (30:70)	UV-vis wavelength 255 nm	Flow rate 1 mL / minute, injection volume 20 µL, column temperature 25 ° C	herbal products A and B contain sibutramine with levels of 15.39 mg and 12.83 mg.	74
5	Sibutramine	Phenyl column (5.0 m, 150 mm × 4.6 mm)	Acetonitrile: water : formic acid (pH 3.0; 0.19 M) (45:55:0.78, v/v/v).	Fluorescence cence detector (FLD)	Flow rate 1.0 ml / min, injection volume 5 µL	The area of the calibration versus concentration curve was found to be linear 5-200 µg / ml	75
6	Sibutramine	Column Vision HT C18 (2 mm x 100 mm, 1.5 m)	Buffer ammonium asetat : water: acetonitrile	Diode array detector (DAD)	Flow rate 0.5 ml / min, injection volume 5 µl	Weight loss herbs contain Sibutramine with levels of 5.90 mg	76

7	Sibutramine	Column synergi polar-Rp	Methanol 10% : ammonium formate buffer	Uv 225 nm	Flow rate 250 µl / min	5 samples contained sibutramine at levels of 10 mg, 29 mg, 30 mg, 30 mg and 32 mg, respectively.	77
8	Fenolftalein	Column Acquity BEH C18 (1,7 µm 100 mm x 2,1 mm)	buffer phosphate : acetonitrile	Diode array detector (DAD)	Flow rate 0.35 ml / min, injection volume 1 µl	The fut cut sample contained phenolphthalein at a level of 60 mg	78
9	Fenolftalein	-	Methanol p : water: glacial acetic acid (50:50:1)	UV 276 nm.	Flow rate 1.5 ml / min,	Chromatogram of Sample F with phenolphthalein very similar to levels of 47.133 ± 0.0058%	79
10	Fenolftalein	column (Macherey-Nagel), 100-5 CN, 125 x 4.6 mm.	Buffer phosphate pH 4 : acetonitrile	diode-array detector	Flow rate 2.5 ml / min, injection volume 20 µL	The phenolphthalein level was found to be 48.20 mg / capsule	80
11	Sildenafil	Reversed phase Column C18 4,6 × 250 mm	Buffer phosphate pH 3,5 : acetonitrile (65 : 43)	293 nm	Flow rate 1 ml / min	0.01 to 465.47 mg / g	81
12	Sildenafil	Column C18	acetonitrile: 50 mmol potassium dihydrogen phosphate (10:90)	Photodiode Array Detector (PDA) 190-400 nm	Flow rate 1 ml / min, injection volume 20 µl	The content of sildenafil Citrate in herbal medicine in the form of syrup A, B, C, D, E, F, G, H and I was found 17 mg, 22 mg, 26 mg, 25 mg, 10 mg, 24 mg, 29 mg, 22 mg and 17 mg / 100 ml, respectively	82
13	Tadalafil	Column C18 (C18, 5µm, 150 mm x 4,6 mm)	methanol/ water (65:35 v/v, dietil amina (100µl/l, pH 3,5)	UV pada 290 nm	Flow rate 1.5 ml / min	contained in King man (10 mg / ml per pill), Max man (9 mg / ml per pill) and green Viagra (8mg / ml per pill).	83
14	Tadalafil	C18 (50 × 4.60 mm, 2.6 µm)	Acetonitrile and ultrapure water	Photodiode Array Detector (PDA)	Flow rate 1.3 ml / min, injection volume 15 µL	Herbal medicine containing detectable levels of 12.21 mg of tadalafil with	84
15	Glibenklamid	Column C18 (150 x 4.6 mm i.d, 5 µm particle size)	methanol: water (75:25) v/v	UV 301 nm.	Flow rate 0.5 mL / min, injection volume 20 µL	Glibenclamide levels in the herbal medicine 1.88 ± 0.25 µg / g	85
16	Kafein	Column 5 C18	Acetonitrile : buffer phosphate (62:37)	diode-array detector	Flow rate 1.0 ml / min, injection volume 20 µL	Caffeine was contained in cravil weight loss herbal products	86

Table: 5. Analysis of medicinal chemicals using the HPLC - ESI-MS/MS method

No	Samples	Chromatographic conditions	Spectrophotometric conditions	Results and discussion	References
1.	Fenfluramine	Column C18, mobile phase : methanol : ammonium formate buffer, at a flow rate 250 µl/min	Electrospray Ionization(ESI) used for ionization , spray voltage of 3500 (+)/3000 (-) V	A total 3 herbal products contain Fenfluramine with a level of 1.27 mg, 7,65 mg, 31,3 mg	89

System of HPLC – ESI-MS/MS with Chromatographic conditions by using a C18 column. The mobile phase was methanol : ammonium formate buffer, flow rate 250 µl/min and spectrometric conditions used electrospray ionization (ESI) was used for ionization. Spray voltage 3500 (+)/3000 (-) V. Retention time 13.76 min. To analyze the presence of Fenfluramine in herbal products, the HPLC-ESI-MS/MS method was used. The value (r) of 0.9942, linearity range of 2-100 µg/l, the limit of detection was0.0660 mg/kg, the limit of quantification was 0.20. Three samples of herbal medicine contained Fenfluramine with levels of 1.27 mg /, 7.65 mg, 31.3 mg, respectively[89].

Table: 6. Analysis of medicinal chemicals using the HPLC - Densitometry method

No	Medicinal chemicals detected	HPLC conditions - Densitometry	Results and discussion	References
1	Dexamethasone	Stationary phase: silica gel 60 F 254 Mobile phase: methanol: cloform (9: 1)	A total two samples (A and B) were detected to contain dexamethasone with levels of 0.23% and 0.25%	40

HPLC method-densitometry was used to analyze herbal products containing dexamethasone. The limit of detection was 9.1932µg/mL and the limit of quantification was 30.6440µg/mL. The result showed that the detector response was linear for concentrations between 100-500 µg/mL (r =0.998). The limits of detection and quantitation were 9.19 µg/mL and 30.64 µg/mL, respectively. The result showed that two samples A and B were containing dexamethasone with levels of 0.23% and 0.25%, respectively[40].

Table: 7. Analysis of medicinal chemicals using the UHPLC - Q-Orbitrap and UPLC/Q - TOF MS methods

No	Samples	Chromatographic conditions	Mass spectrophotometric conditions	Results and discussion	References
1.	Nifedipine	Thermo hypersil gold column c18, mobile phase 0.01 mol / L ammonium acetate: acetonitrile, flow rate 400 µl / min, injection volume 5 µl	Electrospray 3.0 kG for positive and 2.5 kV negative. MS resolution 70,000 FWHM, maximum injection (IT) 200 ms	Samples 9 and 20 containing nifedipine with levels of 22.7 mg and 15 mg, respectively.	90
2	Tadalafil	Waters acquity UPLC C18, mobile phase 0.1% formic acid: 0.1% formic acid in acetonitrile, injection volume 10 µl	Voltage capillary 4.5 kv, nebulizer 0.3 gs dry flow 4.0 L / min	Q - TOF calculates the molecular weight of tadalafil is 390.14, samples contains tadalafil at a level of 11.08 mg and 47.8 mg	91

To analyze the presence of nifedipine, the UPLC/Q - TOF MS method was used. Hypersil Gold column was used for sample separation. The mobile phase is made of 0.01 mol/L ammonium acetate: acetonitrile at a flow rate of 400 µl/min. The injection volume of 5µL was used and Electrospray mass spectrophotometric conditions of 3.0 kV for positive and 2.5 kV for negative. The MS resolution was set to 70,000 FWHM, with a maximum injection time (IT) of 200 ms. The results showed that nifedipine was detected in the herbal medicine with levels of 22.7 mg and 15 mg[90].

The UPLC/Q-TOF MS method with the chromatographic column was a Waters ACQUITY UPLC C18, a mobile phase consisting of 0.1% formic acid and 0.1% formic acid in acetonitrile and capillary voltage of 4.5 kV, nebulizer pressure of 0.3 bar; the dry gas flow of 4.0 L/min with Q-TOF. The chromatogram results showed that the tadalafil molecular weight was 390.14 with a retention time of 9.3 min. The limit of detection was0.4 µg to 2.0 µg and samples contain tadalafil at a level of 11.08 mg and 47.8 mg[90].

Table: 8. Analysis of medicinal chemicals using the capillary electrophoresis method

No.	Medicinal chemicals detected	Detector	Capillary Electrophoresis Conditions	Stationary phase	Results and discussion	References
1.	Glibenclamide	C^4 D conductivity with a frequency of 400 kHz	Voltage 15 kV, frequency 400 kHz.	Silica fused	Glibenclamide contained in the herbal medicine was 0.15 mg	91
2	Sibutramine	Conductivity detector (C^4 D)	Voltage 15 kV,	Silica fused	Sample D contains sibutramine with a level of 3563.47 mg	93

The capillary zone electrophoretic method using sodium acetate as an electrolyte solution for improving the solubility of the analyte with a voltage of 15 kV and a frequency of 400 kHz provided the best signal/noise ratio for the detection of the medicinal chemical and operation frequency of the conductivity detector in C^4D. The results showed 0.15 mg of glibenclamide contained in herbal products[92].

The capillary electrophoresis method was able to detect and measure the levels of sibutramine in herbal products. The analysis using a conductivity detector (C^4D) with a voltage of 15 kV. As the result of the analysis, sample D contains sibutramine with a level of 3563.47 mg. The capillary electrophoresis method is a fast and selective method for detecting sibutramine in herbal products[93].

Table: 9. Analysis of medicinal chemicals using the GC-MS method

No	Medicinal chemicals detected	Stationary phase	Chromatographic conditions	Mass spectrophotometric conditions	Results and discussion	References
1.	Sibutramine	capillary [HP-5ms, 30 m (length), 0.25 mm (diameter), 0.25 µm (film)	The carrier gas helium, flow rate 1 mL/min, injection volume 1 µL.	Ionization energy 70 eV, mass range 25-1000 amu and electron impact ionization technique	Herbal products include Herbaceous Essence, magic slim, green lean super slim, original super slim, fast slim, fat loss positive containing sibutramine with levels of 30 mg, 6 mg, 15 mg, 78 mg, 57 mg and 4 mg, respectively.	93
2	Sildenafil	capillary HP5-MS 30 m length x 0.25 mm ID x 0.25 µm film thickness	Agilent gas chromatography	Electron (70 ev) is positive full scan mode (50-550 m /z)	A total 80 samples, 23% were sampled contains sildenafil	95

The presence of sibutramine was analyzed using the GC-MS method. The carrier gas helium, at a working flow rate of 1 mL/min and the injection volume was 1 µL. The MS conditions were: ionization energy 70 eV, mass range 25 - 1000 amu and ionization technique was electron impact and retention time of 18.557 min. Six brands of herbal products include Herbaceous Essence, magic slim, Green Lean Super Slim, Original Super Slim, Fast Slim, Fat Loss positive containing sibutramine with levels of 30 mg, 6 mg, 15 mg, 78 mg, 57 mg, and 4 mg, respectively[94]. To analyze sildenafil, the GC-MS method was used with HP 5-MS capillariesat a retention time of 1.31 min. The result showed of 80 herbal products tested, 3 samples contained sildenafil[95]

Table: 10 Analysis of medicinal chemicals using the LC / MS / MS method

No	Medicinal chemicals detected	Mobile phase	LC/MScondition	Result and discussion	References
1	Thiosildenafil	0.1% formic acid: methanol (35:66)	Flow rate 0.3 ml/min, injection volume 2 µl, capillary voltage 3 kV, ionization mode ES +	The results indicated that there were compounds that had similar structural properties to thiosildenafil (C 22 H 30 N 6 O 3 S 2) with fragmentation of [TSLD + H] + at 491 m/z	96
2	Phenylbutazone	ultrapure water : acetonitrile (90:10% v/v)	Column C18, flow rate 200 µL/min. Injection volume 10µL, ionization mode: Positive ion (M +)	phenylbutazone formed fragmentation patterns at ratios of 309 m / z, 188 m / z, 170 m / z, 114 m / z. The four herbal samples analyzed also formed a fragmentation pattern of 309 m / z, 188 m / z, 170 m / z, 114 m / z.	56

The Spectroscopy LC/MS/MS analysis using electron spray ionization (ESI-MS/MS) showed that the isolate has a similar spectra with thiosildenafil compound [TSLD+H]+ at 491 m/z and [TSLD+Na]+ at 513 m/z[96]. The molecular weight of a generated compound can provide important information, in which the analytical ions will be fragmented by the presence of colliding molecules.The voltage applied to the analytical ions increases energy, to be able to collide to create more fragmentation[96].

To analyze herbal products containing phenylbutazone, the LC/MS method was used. The mobile phase was prepared of ultrapure water: acetonitrile (90: 10% v/v), and the other LC/MS conditions were column C18, at a flow rate of 200 2 mL/min, injection volume 10 mL, and positive ions (m +) for ionization. From the results of LC obtained retention time phenylbutazone with an average of 1.89/min with a concentration of 5-25 mg/ml. For the herbal product samples A, C, D, E with a concentration range of 10-30 µg/ml, the retention times obtained were 2.05 minutes, 2.00 minutes, 2.06 minutes, and 1.96 minutes, respectively. From the results of GC, phenylbutazone formed a fragmentation pattern at the ratios of 309 m/z, 188 m/z, 170 m/z, 114 m/z[56].

Table: 11. Analysis of medicinal chemicals using the color test strip methods

No	Medicinal chemicals detected	Color reaction	Prototype color test strips	Results and discussion	References
1	Paracetamol	**10% Reaction Iron (III) Chloride:** greenish brown **Folin Ciocalteu reaction:** light green color	(III) 10% chloride reagent, ciocalteu reagent: light green will turn dark green	samples D, F, I were positive for the presence of paracetamol in herbal medicine	97

The color test-strip an inexpensive method and does not need to use hazardous combined solvents. First, iron (III) 10% chloride reagents show visually greenish-brown and the reaction of folin Ciocalteu formed a light green color and formed a precipitate. Second, the prototype test-strip which contains a yellow iron (III) chloride reagent of 10% will turn grayish-green and the prototype test-strip which contains a light green focal ciocalteu reagent will turn to dark green. Based on the analysis results, from10 samples studied obtained 3 samples, namely samples D, F, and I positively contained paracetamol.[97]

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Table: 12. Analysis of medicinal chemicals using infrared spectroscopy methods

No	Medicinal chemicals detected	Detector	Infrared spectroscopic conditions	Results and discussion	References
1.	Dexamethasone	Triglycerine sulfate (DTGS) and Interferometer Dynascan	Spektrofotometer spectrum 10 4000-400 cm-1, with resolution 1 cm-1, and the number of scans 32	Infrared spectroscopy revealed the R2 values of 0.9988. The RMSEC values obtained 0,009455, The PRESS and RMSECV value obtained as the results of cross-validation model selection for dexamethasone in herbal medicine were 0,0022721 and 0,02902, respectively.	98
2	Sildenafil	-	IR spectrum EM (4000 - 400 cm^{-1}	35% of the total sample without any label, 20% (Sam. No. 8, 9, 11, 12 and 13) traditional medicines and 70% (Sam. No. 26, 28, 29, 31, 33, 34, and 35) of the dietary supplements containing sildenafil, 11% of the sample (Sam. no.9, 28, 29 and 31) were found to be in excess of the highest recommended dosage.	99

The infrared spectroscopy method combined with Partial Least Square (PLS) has been developed for the dexamethasone quantification in joint- pain killer traditional herbal medicine. Infrared spectroscopy revealed the R2 values of 0.9988. The RMSEC values obtained 0,009455, The PRESS and RMSECV value obtained as the results of cross-validation model selection for dexamethasone in herbal medicine was 0.0022721 and 0.02902, respectively[98].

Fourier-transform infrared spectroscopy (FTIR) is a method by marking the functional group of a compound from the infrared absorbance used for the compound[100].Among the identified groupsin the sildenafil analysis, theketonic carbonyl group and the secondary amine group produced intense bands in the spectrum at 1702.21 cm-1 and 3299.3 cm-1 regions, respectively[99] .

CONCLUSION

Medicinal chemicals obtained in herbal medicine include diclofenac sodium, paracetamol, piroxicam, ibuprofen, dexamethasone, mefenamic acid, phenolphthalein, sibutramine, fenfluramine, sildenafil, tadalafil, thiosildenafil, caffeine, ephedrine, nifedipine, glibenclamide. Side effects of medicinal chemicals added in herbal medicine were increased risk of cardiovascular disease, hepatotoxic, gastric ulcers, moonfaced.

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