

## Review of Adulterated Herbal Products and Supplements and Methods of Analysis

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Diterima: 24 November 2020; Disetujui : 26 February 2021

**Abstract:** Herbal products and supplements are widely used for primary health care. Many reports of drugs added to these products, such as weight-loss supplements, analgesic herbal products, and erectile dysfunction supplements. This study aims to find out products that are often mixed with drugs and effective methods used for their analysis. The method used in this research is a systematic review. The resources were retrieved through searching the keywords related to the world adulterated herbal products and supplements in the available databases and search engines including Science Direct, PubMed, Springerlink, and Google Scholar. Based on PRISMA flow diagram, a systematic review showed that sibutramine HCl, sildenafil citrate, dexamethasone, and sodium diclofenac are most commonly found in the herbal and supplement products and the ESI-MS method is an effective method for their analysis.

**Keyword:** Analysis methods, drugs, herbal products, supplements, systematic review

### 1. INTRODUCTION

Herbal products are products that contain the main ingredients, namely ingredients herbs (such as parts of a plant) or pharmaceutical preparations (such as essential oils, extracts, and others) (Calahan *et al.*, 2016). Today, the use of herbal products is very wide in various countries. It is noted that around 75-80% of the world's population still makes herbs as a mainstay for primary health care, especially in developing countries. This large population is accompanied by a common belief that it is not only cheap and herbs are available in local, herbal claims to have no side effects (Qazi Majaz and Molvi Khurshid, 2016). Besides herbal products, health supplements with herbal claims are also consumed large. The active ingredients used in health supplements can come from natural ingredients in the form of isolates, fractions, or extracts. One type of health supplement is a supplement with claims for the benefits of weight

loss, male stamina/healthy men, and gym/fitness (Anonym, 2019).

The assumption toward herbal product and supplement which contain primary ingredients from nature is not always been proven correct. This is because there have been reports of mixing of drugs in some herbal products and supplements. In the research of Ching *et al.* (2017) mixing of drugs occurs mainly in three types of herbs indicated to lose weight by 36.8%, analgesics (such as joint pain, gout, and rheumatism) by 22.8%, and for erectile dysfunction as much as 9%. For those three types of herbs and supplements, there are drugs that most commonly found such as sibutramine and orlistat in weight-loss supplements, steroid (dexamethasone) and nonsteroidal (sodium diclofenac) in analgesic herbal products, as well as phosphodiesterase-5 (PDE5) inhibitor (sildenafil citrate and tadalafil) in supplements for erectile dysfunction (ED) (Radu *et al.*, 2015; Hachem *et al.*, 2016; Ching *et al.*, 2017).

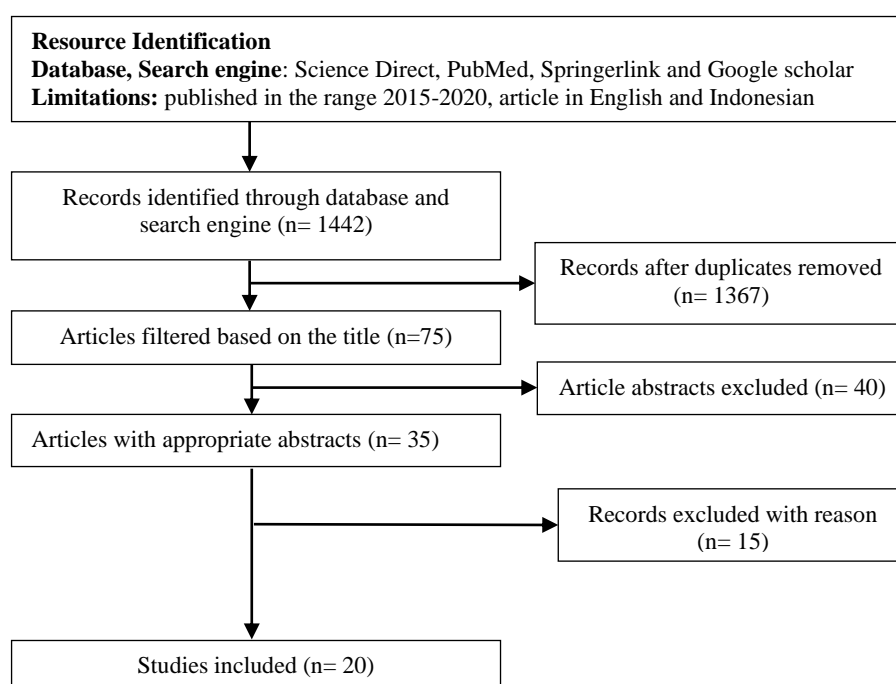
In Indonesia, the National Agency of Drug and Food Control (NADFC/BPOM) also found the presence of herbal products and supplements containing drugs. The findings of herbal products and supplements are dominated by products containing sildenafil citrate, paracetamol, dexamethasone, and phenylbutazone. It is also supported by the issuance of public warning No. HM.01.1.2.07.20.18 (regarding traditional medicine and health supplements containing drugs) mentioned there are 40 types of herbal products and supplements. Based on the regulation of the Indonesian Minister of Health number 007 2012 (regarding the registration of traditional medicine), traditional medicine is prohibited from containing medicinal chemicals that are isolation results or synthetic efficacious drugs. Long-term use of herbal products and supplements containing drugs may pose a risk of serious side effects (Anonym, 2012; Hayun and Karina, 2016; Anonym, 2020).

Herbal products suspected of being mixed with drugs need further identification. Currently, several analytical methods have been developed for the

detection of such products, like High-performance Liquid Chromatography-mass Spectrometry (HPLC-MS), Thin Layer Chromatography (TLC), Liquid Chromatography with tandem mass spectrometry (LC/MS/ MS), NMR spectroscopy, and RAMAN spectroscopy (Radu *et al.*, 2015; Li *et al.*, 2018; Wu *et al.*, 2020). This research conducted a systematic review to see the drugs contained in the herbal product and supplements as well as effective analytical methods based on existing previous research.

## 2. MATERIAL AND METHODS

This research uses a qualitative systematic review method. The data sources are obtained from comprehensive literature through databases such as Science Direct, PubMed, Springerlink and search engines Google scholar. A search for published articles was carried out by using keywords, namely "illegal adulterant", "illegal chemical drug", "detection adulterants", "in herbal medicine", and "chemical adulterations".



**Figure 1. PRISMA Flow Diagram of The Study**

Articles were analyzed using inclusion criteria: journal, proceedings, and e-book used published between 2015-2020; full-text; discussed drugs found in herbal products and supplements for weight loss, analgesics, and dysfunction erection; discussed an efficient, easy, and fast analysis method. Studies are excluded if the article is not published in English and Indonesian; including review articles; not included in the category Q1-Q3 on Scimagojr and Sinta 1 –Sinta 3 on the Sinta web.

The selection of articles was carried out using the PRISMA diagram (Moher *et al.*, 2009) (Figure 1). Based on the results searches in the database and search engine used, 1442 articles match the keyword. After being filtered by title and duplication, 75 were found the appropriate article. Then a total of 35 articles with the appropriate abstract were carried out screening for later stages. Eligibility assessment of 35 articles by inclusion and exclusion criteria was performed, 15 articles were excluded, and 20 were reviewed.

### 3. RESULT AND DISCUSSION

Drugs that are illegally mixed into herbal products and supplements provide fast results not only in Indonesia but also in various countries such as China, Romania, and Egypt. From samples of herbal products and supplements examined in various countries, the results showed that some of the total samples examined still contained a mixture of drugs (Table 1).

#### 3.1 The Most Common Drugs in Weight-Loss Supplements

Sibutramine HCl is the medicinal chemical most commonly added to weight-loss supplements. In this study, sibutramine HCl mentioned in 6 of 11

journals stating that there are drugs in weight-loss supplements. The illegal addition of sibutramine HCl to weight-loss supplements can be attributed to its pharmacological effect that is increasing noradrenaline and serotonin levels in the brain. The increase in levels led to the activation of  $\alpha$ -adrenoceptor,  $\beta$ -adrenoceptor and serotonin receptor 2A and 2C subtypes (5-HT<sub>2A/2C</sub>). This interaction makes the patient feel full after eating and reduces their dietary intake and subsequently, weight loss occurs in patients (Hayun, Maggadani, and Amalina, 2016; Krivohlavek *et al.*, 2016).

#### 3.2 The Most Common Drugs in Analgesic Herbal Products

The most common drugs found in analgesic herbal products are steroid and nonsteroidal drugs. From 6 journals that discuss drugs in analgesic herbal products, 4 journals mention NSAIDs (non-steroidal anti-inflammatory drugs) and steroids in them. NSAIDs and steroids is an anti-inflammatory drug that can be used for the treatment of several diseases, such as rheumatoid arthritis, inflammation, allergies, asthma, and autoimmune diseases (Li *et al.*, 2017; Primpray *et al.*, 2019). These drugs are usually added to analgesic herbal products because it can help suppress the signs and symptoms of inflammation. In the other, the addition of steroids to analgesic herbal products can be caused because steroids are anti-inflammatory which acts directly on the steroid receptors in the nucleus thus making pro-inflammatory substances decrease (Broto, 1999).

#### 3.3 The Most Common Drugs in Supplements for Erectile Dysfunction

Phosphodiesterase-5 (PDE5) inhibitor such as sildenafil, tadalafil, and vardenafil are a medicinal chemical that is often added to supplements herbs to enhance sexual abilities. Among those drugs, sildenafil citrate is the most common found in

supplements for ED. This can be seen from 4 journals that discuss the drugs in supplements for ED, all of them contain sildenafil citrate. The addition of sildenafil citrate to supplements for ED can be associated with a pharmacological effect. Sildenafil citrate added to herbal supplements is used to increase smooth muscle relaxation. The release of nitric oxide in the corpus cavernosum will activate guanylate cyclase. The activation causes an increase in cyclic guanosine monophosphate (cGMP) which will then dilate the blood vessels around the corpus cavernosum and blood can flow towards the penis. Sildenafil citrate works to prolong the erection process by inhibiting PDE5 because it can degrade cGMP (Sutrisno *et al.*, 2017).

### 3.4 Paper-based Analytical Device

There are many indicator strips for the detection of drugs in herbal products developed. Some researchers use polymers as substrate materials. Nowadays, the Paper-based Analytical Devices (PAD) have attracted considerable attention because it is a simple, low operating cost, fast, instrument-free, selective for the detection of several types of drugs and easy-to-use tools for biological and environmental analysis. However, in the colorimetric PAD method, reagents need to be used specific tailored to the chemical drug to be tested so that it can be identified and detect analytes in the sample (Pratiwi *et al.*, 2019).

PAD can be combined with electrochemical detection to improve sensitivity. Electrochemical paper-based analytical device (ePAD) can be used for the analysis of drugs in herbal products and detection of small amounts of target analytes such as glucose, lactate, uric acid, acetylcholinesterase, drug metabolites, and pesticides. This method has a fast analysis time because it can separate the target

from other substances in the herbal extract within 7 minutes. Despite its fast analysis time, ePAD method was not able to detect the compound in some samples when concentrations lower than the limit of quantification (LOQ) of the device (Primpray *et al.*, 2019).

### 3.5 Spectroscopic Method

Fourier-transform Infrared Spectroscopy (FTIR) is analysis spectroscopy which is often used for the analysis of drugs in herbal products and supplements. The screening method using FTIR is very helpful because sample preparation requires a very short time, analysis is completed within 5 minutes/sample, it does not require special reagents, and the costs are minimal. In addition, this method is also very helpful when the number of samples to be examined a lot (Popescu and Radu, 2015). FTIR can be combined with Raman spectroscopy. When compared with TLC, LC-MS/MS, and GC-MS are necessary to sample preparation and analysis are very expensive, Raman spectroscopy and FTIR are the most efficient method (Mateescu *et al.*, 2017).

FTIR can also be combined with two-dimensional correlation spectroscopy (2DCOS). 2DCOS-FTIR is a promising method for mixing monitoring drugs in herbal weight-loss products due to their detection procedures fast, low detection limits, and no treatment on the sample previously. Also, 2DCOS can be applied, one of which is to detect ephedrine and pseudoephedrine drugs whose composition is below 5% (Miao *et al.*, 2016).

In addition to FTIR, there is another spectroscopic analysis, namely near-infrared (NIR) spectroscopy which can be used to characterize the composition of herbal products. NIR spectroscopy combined

with chemometric techniques such as partial least squares discriminant analysis (PLS-DA) can also be used to evaluate the presence or absence of mixing drugs in herbal products. The development of NIR spectroscopy shows that the method is fast, accurate, and non-destructive (da Silva *et al.*, 2015).

Another spectroscopic method is a mass spectrometer (MS). MS method development has been widely done, one of which is high-performance ion mobility spectrometry with electrospray ionization (ESI-HPIMS). The comparison of the ESI-HPIMS method with other methods is very simple because it is not required previous treatment. Besides, the detection procedure is fast (2-3 minutes) and high specificity (Li *et al.*, 2017). Apart from ESI-HPIMS, there is another development, namely fast switching-high-voltage tip-electrospray ionization mass spectrometry (FS-HV tip-ESIMS). The FS-HV tipESI-MS method demonstrates a rapid screening technique (<1 minute/sample) and reliable for analyte identification in complex samples (Yao *et al.*, 2019).

### 3.6 Chromatographic Methods

The chromatographic method can be used for complex mixture analysis because it has a high separation capacity. TLC-densitometry is one of the analysis methods performed through separation or chromatography. This method can be used to identify samples of herbal products and supplements both qualitative and quantitative. Qualitative analysis is carried out by comparing the test samples with the standard from the R<sub>f</sub> value, UV spectrum, and color. Furthermore, the development of the TLC-densitometry method gave the results of specificity, linearity, precision,

and good accuracy. This method is also simpler and the operating costs are low, so it can be used for small laboratories or local health authorities for supervising herbal products and supplements (Hayun and Karina, 2016; Hayun, Maggadani, and Amalina, 2016).

Another widely used chromatographic method is high-performance liquid chromatographic (HPLC). HPLC is a liquid chromatography technique that can be used for the separation of various components in the mixture. The use of HPLC itself aims to separate the components by a time minimum (Annisia, Musfiroh and Indriati, 2019). HPLC can be combined with an ultraviolet detector (UV). HPLC-UV analysis techniques can provide sensitive and reproducible analytical results to determine the number of drugs in dietary supplements, biological fluids, and many other matrices.

HPLC-UV has a fast analysis time with a total analysis time is 7.5 minutes, a low sample requirement (0,2 grams), high accuracy and precision, and cost operations per analysis are low. Moreover, this method has proven to be robust against change several conditions, such as mobile phase, column temperature, and flow rate (Dural, 2020). Reversed-phase high-performance liquid chromatographic with UV detection (RP-HPLC-UV) was also developed as methods with a fast, simple, and procedure reproducible. RP-HPLC-UV is used to detect drugs with a look at the retention times of herbal products and compare them with the retention time's standards (Hemdan and Tawakol, 2018).

**Table 1.** Drugs in Herbal Products and Supplements and their Analysis Methods

Category	Drugs	Adulterated Sample/ Total Sample	Country	Analysis Method	Advantages	Source
Weight-loss supplements	Sibutramine HCl, Fluoxetine	3/10	Romania	FTIR	Short time (5 minutes/sample), special reagents unnecessary, minimal costs	Popescu and Radu (2015)
	Sibutramine HCl	6/7	Indonesia	TLC-densitometric	Simple, low operating costs, can be used for small laboratories	Hayun <i>et al.</i> (2016)
	Sibutramine HCl, Phenolphthalein	2/2	Mesir	RP-HPLC-UV	Fast, simple and reproducible	Hemdan and Tawakol (2018)
	Sibutramine HCl	4/13	Brazil	NIR-spectroscopy	Fast and nondestructive	da Silva <i>et al.</i> (2015)
	Ephedrine HCl, Pseudoephedrine HCl	2/8	China	2DCOS	Fast detection procedure and low detection limit	Miao <i>et al.</i> (2016)
	Sildenafil, Thiosildenafil, Thiodimethylsildenafil	5/5	Australia	GC-QQMS	Rapid identification and quantification were carried out without derivatization step	Mokhtar <i>et al.</i> (2016)
	Hydrocortisone	1/5	China	TLC-SCRS	Simple, fast, specific, sensitive and reliable	Li <i>et al.</i> (2018)
	2,4-DNP, L-Thyroxine, Sibutramine HCl, Phenolphthalein, Norfenfluramine, Ephedrine, Fluoxetine	-/33	India	LC-ESI-MS/MS	Simple, fast and sensitive	Girish <i>et al.</i> (2020)
	Fenfluramine, Phenolphthalein, Sibutramine HCl	4/7	China	Gtip SPE LC-MS/MS	Good specificity, accuracy and reproducibility	Jin <i>et al.</i> (2017)
	Sibutramine HCl, Fluoxetin	29/120	China	UHPLC-LTQ-Orbitrap HRMS	Fast, sensitive and selective	Cheng <i>et al.</i> (2017)
	Sildenafil	37/50	Turki	HPLC-UV	Low cost per analysis, high accuracy and precision, fast retrieval of results and cheap	Dural (2020)

**Table 1.** Drugs in Herbal Products and Supplements and their Analysis Methods

Category	Drugs	Adulterated Sample/ Total Sample	Country	Analysis Method	Advantages	Source
Analgesic herbal products	Paracetamol	4/8	Indonesia	TLC-densitometric	Good specificity, linearity and accuracy while being simpler and cheaper	Hayun and Karina (2016)
	Paracetamol, Naproxen, Sulfamethoxazole, Diclofenac, Phenylbutazone	23/28	China	Fast switching-HV tip-ESI-MS	Simple, fast, reliable and sensitive	Yao <i>et al.</i> (2019)
	Indomethacin	1/5	China	ESI-HPIMS	Simple, very specific, and fast (2-3 minutes with no pretreatment required)	Li <i>et al.</i> (2017)
	Allopurinol	1/4	Indonesia	PAD colorimetric	Simple, fast, instrument-free, and selective	Pratiwi <i>et al.</i> (2019)
	Prednisolon, Dexametason	-/7	Thailand	e-PAD	Low cost, sensitive, and biocompatible	Primpray <i>et al.</i> (2019)
	Dexametason	16/116	Korea	UPLC	Rapid process, high sensitivity, and good accuracy	Kim <i>et al.</i> (2020)
	Supplements for erectile dysfunction	Sildenafil	1/1	Mesir	RP-HPLC-UV	Fast, simple and reproducible
Sildenafil, Tadalafil, Vardenafil		18/26	Romania	LC-MS/MS	Sensitive, selective, and short analysis time (15 minutes/ sample)	Radu <i>et al.</i> (2015)
Sildenafil, Tadalafil, Phenolphthalein		11/50	Romania	Raman spectroscopy-FTIR	Realible, reproducible, easy sample treatment, fast analysis (5 minutes/sample), and low cost	Mateescu <i>et al.</i> (2017)
Sildenafil		2/9	Vietnam	TLC-SERS	Simple, selective and sensitive	Minh <i>et al.</i> (2019)

In addition to HPLC, there is ultra-high-performance liquid chromatography (UHPLC/UPLC). UPLC has a column containing particles smaller than the size which is commonly used HPLC (2.5-5  $\mu\text{m}$ ) (Annissa, Musfiroh and Indriati, 2019). The development UPLC method with a photodiode array (PDA) has advantages in both qualitative and quantitative analysis, such as a fast process, high sensitivity, and good accuracy and precision. The UPLC-PDA method has been successfully developed and applied to the real sample with confirmation of results using LC-quadrupole-time-of-flight (LC-Q-TOF/MS) (Kim *et al.*, 2020).

### 3.7 Hyphenated Techniques

Another analytical method that can be used to analyze drugs in herbal products and supplements is a combination of spectroscopy and chromatography. GC-MS is one of the hyphenated techniques developed for the screening and confirmation of foreign mixtures by specific retention time and spectrum information generated. The identification power of GCMS can improve with a triple quadrupole mass spectrometry (QQQ-MS) instrument for good sensitivity and selectivity. Operations using multiple reaction monitoring (MRM) modes can add an advantage to obtain accurate identification. GC-QQQMS is a method that can analyze rapidly eluted analytes in 11 minutes and it shows sensitivity, selectivity, and can separate without derivatization step (Mokhtar *et al.*, 2016).

TLC that uses the chromatographic analysis method also can be combined with Spot-Concentrated Raman Scattering (SCRS) and Surface-Enhanced Raman Spectroscopy (SERS).

TLC-SCRS is a simple, fast, specific, sensitive, and reliable qualitative screening method. Raman spectroscopy is not a separate method so it cannot be used to distinguish several components in a mixture. This technique uses light refraction whose intensity is proportional to the number of compounds present in the sample. Although TLC-SCRS is less sensitive when compared to HPLC-MS, drugs with effective doses and detection limits above TLC-SCRS can be detected accurately and quickly (Li *et al.*, 2018).

In addition to TLC-SCRS, the development of the TLC combined with SERS significantly increases the selectivity and sensitivity of TLC detection. This method can be used for environmental pollutant analysis, food safety evaluation, forensic analysis, and monitoring analysis of drug therapy in human plasma. The results of the test sample analysis from TLC-SERS have also been proven by confirmation of LC-MS/MS (Minh *et al.*, 2019). UHPLC combined with Linear Ion Trap Quadrupole Orbitrap Mass Spectrometry (LTQ-Orbitrap-MS) is also a combination method between spectroscopy and chromatography. LTQ-Orbitrap can be used for qualitative and quantitative analysis in various fields, such as for the identification of metabolites, drug abuse, pesticide residues, and bioactive compounds in traditional Chinese medicine. Apart from being fast, sensitive, and selective, the development of this method has good accuracy and precision for the weight loss supplement test, which is below 15%, which indicates that this method is reliable (Cheng *et al.*, 2017).

Furthermore, there is a liquid chromatography analysis method combined with tandem mass spectrometry, namely LC-MS/MS. LCMS/MS is a combination of liquid chromatography analysis



techniques with mass spectrometer detection that can separate the sample based on polarity which detects charged ions by a mass spectrometer detector. The mass spectrometer works by identifying ions by mass according to their fragmentation. LC-MS/MS systems generally use

analyzed. LC-MS/MS is a sensitive and selective method for detecting chemical PDE-5 drugs in herbal products and supplements for erectile dysfunction. The use of LC-MS/MS has a period between 20-30 minutes for only one sample. However, a study conducted by Radu *et al.* using

**Table 2.** Comparison of Analytical Methods for Identification of Herbal Products and Supplements a: Hayun and Karina (2016), b: Hayun *et al.* (2016), PCM: Paracetamol, NPX: Naproxen, SMZ: Sulfamethoxazole, DCF: Diclofenac, PBZ: Phenylbutazone, SIB: Sibutramine HCl, PPH: Phenolphthalein, SLD: Sildenafil, PNS: Prednison, DMS: Dexametason

Method	Time Analysis	Cost	LOD	Accuration (%)	Easiness
TLC-densitometry	-	Low	217.5 ng <sup>a</sup> 60.22 ng/spot <sup>b</sup>	99.70 ± 1.22 <sup>a</sup> 99.42-99.46% <sup>b</sup>	Easy
FTIR	5 minutes/ sample	Low	-	-	Special reagents unnecessary
FS-HV tip	< 1	-	0.05 ng/g (PCM), 0.1 ng/g	-	Easy
ESI-MS	minutes/ sample	-	(NPX), 0.01 ng/g (SMZ), 0.01 ng/g (DCF), 0.1 ng/g (PBZ)	-	-
RP-HPLC	Fast	-	-	98.64 ± 1.151 (SIB)	-
UV	-	-	-	98.78 ± 1.537 (PPH)	-
NIR	Fast	-	-	99.11 ± 1.814 (SLD)	-
spectroscopy	-	-	-	-	No pretreatment required
GC-QQQMS	11 minutes/ sample	-	0.03 – 0.3 µg/g (El method)	67.4-91.1% (El method)	No need derivatization step
			0.6 – 1.5 µg/g (Cl method)	83.4-108.8% (Cl method)	
ESI-HPIMS	2-3 minutes/ sample	-	0.33 µg/mL	98.5±0.4 - 99.8±0.2	No pretreatment required
2DCOS-FTIR	Fast	Low	-	-	Can be used for the complex herbal product
LC-MS/MS	15 minutes/ sample	-	-	-	-
e-PAD	7 minutes/ sample	Low	3.59 µg/mL (PNS) 11.98 µg/mL (DMS)	83-108%	Can calculate a small number of the analysis target
TLC-SCRS	Fast	-	4-6 µg	92.3 – 96.1	Easy
UPLC-PDA	Fast	-	0,12 – 1.50 µg/mL	88.06 – 110.50% (solid sample)	-
				89.16 – 110.52% (liquid sample)	
LC-ESIMS/MS	4-12 minutes	-	0.01-0.09 ng/mL	102-114% (solid matrix)	-
				99-109% (liquid matrix)	
PAD	Fast	-	75 mg/mL	-	Instruments-free
Raman	5 minutes/ sample	Low	-	-	Special reagents unnecessary
spectroscopy and FTIR	-	-	-	-	-
UHPLC LTQ-Orbitrap MS	Fast	-	0.3-2 ng/g	98.2-108.6%	-
Gtip SPE	-	-	< 1.8 ng/ml	82.9 - 95.2%	Detect low concentrations
TLC-SERS	Fast	-	10 µg/mL	-	Easy
HPLC	Fast	Low	1.94 ng/mL	87.6 – 111.7%	Easy

several types of ion sources and mass analyzers that are adjusted to the polarity of the compound being

LC-MS/MS has a very short time, which is about

15 minutes (Radu *et al.*, 2015). In addition to identifying herbal products and supplements for erectile dysfunction, LC-MS/MS can identify drugs in weight loss supplements.

In another study, it was stated that the use of LC-ESI-MS/MS had the advantage that the time the analyte was eluted was 4 minutes and extended to 12 minutes. This was done so as not to cause congenital effects. In addition, the LC-ESI-MS/MS method includes fast, simple in the extraction process, sensitive in the detection process and can help with regular monitoring (Girish *et al.*, 2020).

LC-MS/MS with ultra-performance or UPLC can also be combined with Graphene tip solid-phase extraction (Gtip SPE) because it has the advantage of being able to detect at low concentration levels. This method has high extraction efficiency, specificity, accuracy, and good reproducibility, as well as low LOD and LOQ values. However, the Gtip cartridge can only be used for single-use and cannot be used repeatedly because the place to put the solution is easily damaged and can become contaminated if used repeatedly for different samples (Jin *et al.*, 2017).

The analytical method used for the analysis of each medicinal chemical has its advantages and disadvantages. When viewed from the summary of the advantages of each analysis method in table 2, the analysis time of each analysis method varies, ranging from <1 minute-15 minute per sample. Some articles only write that the analysis method is a fast method, without mentioning the time needed to analyze a sample. The ease of using the methods is also quite diverse, such as no need pretreatment

required or special reagents unnecessary. The stated operating costs of the whole method are low. The method used for the analysis of drugs is quite sensitive and accurate because the detected analytes are in the 80-120% range (Riyanto, 2014).

In the final study of 20 articles, it can be concluded that the ESI-MS technique discussed in this study, both ESI-HPIMS, FS-HV tip-ESI-MS, and LC-ESI-MS/MS is an effective analytical method for the identification of medicinal chemical in herbal products and supplements. The analysis time for each method is quite fast, ranging from <1 minute-12 minutes. This method also does not pretreatment required on the test sample. The sensitivity of the ESI-MS technique can be seen from the LOD values which have values in the range of 0.01 ng/g - 0.33 µg/mL. Also, the accuracy of this analysis method ranges from 98.5% - 114%.

#### 4 CONCLUSION

Based on the reviews that have been conducted regarding drugs in world herbal products and supplements and their analysis methods, it can be concluded that the most common drugs found in herbal products and supplements is sibutramine HCl in weight-loss supplements, sildenafil citrate in supplements for erectile dysfunction, as well as dexamethasone and sodium diclofenac in analgesic herbal products. The effective analysis method obtained from the comparison of 20 articles by comparing each of its analysis methods based on the analysis time, LOD value, accuracy, cost, and ease is the ESI-MS technique, both ESI-HPIMS, FS-HV tip-ESI-MS, and LC-ESI-MS/MS.

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