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### Pharmacovigilance of herbal medicine in two public health centers of Yogyakarta

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#### ABSTRACT

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**Background :** The use of herbal medicine in Indonesia is getting increase. People try to keep their health or to prevent some diseases using herbal medicines. However, the safety of herbal medicine used in community has not known yet, due to the limited data and believe that herbal medicine is safer than modern medicines.

**Objective :** This study was aimed to understand the safety of herbal medicine used in Yogyakarta.

**Methods :** We used retrospective data of patients who were prescribed herbal medicine by the physicians in two public health centers in Yogyakarta. We searched for the patients identity in the medical records then we did the interview and gave questionnaire to the patients at their homes. The Adverse Drug Reaction was identified using Naranjo algorithm. This study has been approved by ethical committee of Universitas Ahmad Dahlan, Yogyakarta.

**Results :** We identified 47 patients prescribed with herbal medicine as complementary treatment. There are 10 patients (21.3%) experienced ADR. The category of ADR are: probable (7 patients) and possible (3 patients). Tensigard is the most phytopharmaca cause pruritus in this study.

**Conclusion :** Around 20% patients experienced ADR due to the herbal medicine prescription in complementary treatment. Thus, the study of pharmacovigilance is needed to be conducted in bigger sample size and cohort design to understand the safety profile of herbal medicine used.

**Latar belakang:** Penggunaan herbal saat ini semakin meningkat di Indonesia. Masyarakat menggunakan obat herbal untuk menjaga kesehatan maupun untuk mencegah penyakit. Namun sampai saat ini, keamanan penggunaan obat herbal di masyarakat belum banyak diketahui karena terbatasnya data dan adanya kepercayaan bahwa obat herbal itu aman.

**Tujuan:** Penelitian ini bertujuan untuk mengetahui keamanan penggunaan obat herbal di Yogyakarta.

**Metode:** Pengambilan data pada penelitian ini adalah secara retrospektif pada pasien yang mendapatkan resep obat herbal di dua puskesmas di Yogyakarta. Identitas pasien ditelusuri melalui rekam medik, kemudian wawancara dan pengisian kuesioner dilakukan di rumah pasien. Reaksi Obat yang tidak diinginkan (ROTD) ditelusuri menggunakan algoritma Naranjo. Penelitian ini telah disetujui oleh komite etik penelitian Universitas Ahmad Dahlan.

**Hasil:** Terdapat 47 pasien yang bersedia berpartisipasi dalam penelitian ini. Sejumlah 10 pasien (21.3%) mengalami ROTD. Kategori ROTD adalah probable (7 pasien) dan possible (3 pasien). Tensigard merupakan fitofarmaka yang paling banyak menimbulkan ROTD berupa pruritus.

**Kesimpulan:** Sejumlah 20% pasien mengalami ROTD karena peresepan obat herbal. Oleh karena itu, perlu dilaksanakan studi farmakovigilansi dengan jumlah sampel yang lebih besar dan menggunakan desain

*kohort untuk mengetahui keamanan penggunaan obat herbal.*

## INTRODUCTION

The use of herbal medicine in Indonesia became widespread. People in Indonesia are more giving attention in using traditional medicine in a various form including herbal medicines. The Indonesian government realize that the use of traditional medicine should be integrated into the formal health care,<sup>1</sup> Brazil and India are two examples of countries which the use of traditional medicine also going increase<sup>2,3</sup>. In India, one of the methods of traditional medicine, which is Ayurveda has been included in the health care system.<sup>3</sup>

However, the use of herbal medicine should be closely monitored due to the potential of Adverse Drug Reaction (ADR). The potential ADRs that caused by herbal medicines were related to cardiotoxicity, hepatotoxicity and carcinogenic.<sup>4</sup> The safety of herbal medicine is not only related to the potential ADR, but also related to the poor of pharmacokinetic data to understand the potential herbal-drug interaction.<sup>2</sup>

The previous study in Africa, showed that only five countries which had regulatory status and quality control of herbal medicines. Most of the countries still needed the development of pharmacovigilance of herbal medicine. They only received very low number of herbal medicine reports.<sup>6</sup> The study of pharmacovigilance study in ayurveda medication in India showed that there was 1.14% patients experienced the ADRs and 25% of them are related with herbal formulations.<sup>3</sup> Previous study in Thailand, showed that Thai Traditional Medicine was contributed to the 0.001% of serious ADR. *Andrographis paniculata* was significantly related to the anaphylactic shock and green traditional medicine was significantly related to the Stevens-Johnson syndrome.<sup>7</sup> This study was aimed to understand the safety profile of herbal medicine used in Yogyakarta.

## METHODS

We used retrospective data of adult patients who were prescribed herbal medicine by the physicians in two Public Health Centers in Yogyakarta from January to October 2015. We searched for the patients identity in the medical records then we did the interview and gave questionnaire to the patients at their homes. The ADRs were identified by Naranjo algorithm.

This study has been approved by research ethic committee of Universitas Ahmad Dahlan, Yogyakarta.

## RESULTS

We identified 47 patients who got herbal medicine as prescribed in their treatment. Most of the patients were female 61.7%. The average of age in this population was 53.3. Most of the patients had a permanent job (65.9%) and their last education was senior high school (48.9%). Table 1 lists the demographic data of the patients.

Table 1 Patient Demographic Data

Patients' Demographic	Percentage (%)
Age (X ± SD)	53.4 ± 15.70
<b>Sex</b>	
Female	61.7
Male	38.3
<b>Occupation</b>	
Permanent Work	65.9
Not Work	34.1
<b>Last Education</b>	
Elementary	38.3
Senior High School	48.9
Academic	12.8

The number of patients experienced ADR and causality assessment results using Naranjo algorithm is shown in Table 2.

The benefit of Active alert village showed the development of Active alert village in Tridadi has caused improvement of community health

Table 2 ADR and Causality Assessments

ADR	Medication	Causality assesment	No of ADR events
Pruritus	Tensigard	Probable	4
		Possible	2
Pruritus	Niran	Possible	1
Pain	Calculusol	Probable	1
Nausea	Niran	Probable	1
Dizziness	Niran	Probable	1
Tachicardi	Tensigard	Probable	1
Diarrhea	Guazoma ulmifolia Lamk	Probable	3
	Murraya paniculata (L) Jack		
	Rheum officinale L		
	Sonchus arvensis L		
Diuresis	Apium graviolens L	Possible	1
	Orthosipons aristatus		
	Centella asiatica		

Tensigard is the most medication which caused pruritus. In this study, the patients reported that, when they stop to use tensigard, the pruritus was gone. Diarrhea was experienced by 3 patients prescribed with the herbal mix formulation. The probable category has bigger adverse events than possible category.

## DISCUSSION

According to the patient's characteristics, our study findings are in line with the previous in Hong Kong, which divided the age category into 45-64 years old and more than 64 showed that most of the patients who got herbal prescription were in the first category. Also female patients was the most patients using traditional Chinese medicine.<sup>8</sup>

Pruritus is the most ADR experienced by patients in this study, The previous study also reported that Tensigard can cause pruritus, nausea, dizziness, tachycardia and fatigue in around 70 patients.<sup>9</sup> The content of tensigard are Orthosipons aristatus extract and Apium graviolens leaves. The herbs had calcium antagonist and beta blocker effect, respectively.<sup>7</sup>

According to Aronson,<sup>10</sup> Apium graviolens L had pruritus as an ADR.

Diarrhea which experienced by 3 patients may caused by Rheum officinale L. This herb had laxative effect due to its content of tannin and anthraquinon.<sup>11</sup> The herbs of Guazoma ulmifolia Lamk, Murraya paniculata (L) Jack, Rheum officinale L and Sonchus arvensis L are used for anticholesterolemia.<sup>12-15</sup> The other herbs-mixed was used as antihypertension. Apium graviolens had hypotensive, negative inotropic and chronotropic effect. The flavonoid of apionin, luteolin and quercetin can cause vasodilator effect and inhibit muscarinic effect to decrease the blood pressure.<sup>9, 13, 16</sup>

The probable category has bigger adverse events than possible category. The previous study of pharmacovigilance for herbal products which was conducted in Brazil, also showed that the highest causality was probably for Senna alexandrina. The study was carried out for the herbal products in over-the-counter media. Only 5 among 100 subjects which reported the ADR.<sup>17</sup>

Some previous studies in other countries showed that the development of

pharmacovigilance for herbal remedies should be continued or being the concern for the countries. In South Korea, there were 9624 of adverse events reported during 11 years. Around 5.4% of them were related to the herbal medicines. The most frequent adverse events reported was liver problems.<sup>18</sup> In our study, it is difficult to identify the liver problems from retrospective data. Because there was no laboratory data examination in the medical record or patients did not recognize the symptoms of liver problems due to the lack of information. In Singapore, over 10 years, there were 627 cases of adverse events related to complementary alternative medicine. Again liver problem was the most organs with serious cases.<sup>19</sup>

Due to the limited development system of pharmacovigilance in many countries over the world, meaning while the use of herbal medicine is going increase and the people opinion that herbal medicine is safe, some suggestion need to be considered, like the introduction of pharmacovigilance in the curriculum of postgraduate, the mandatory regulation for herbal medicine ADR report, human resources development for being alert to the herbal-drug interaction.<sup>20</sup>

Our study has some limitations, we did not explore the preparation, storage and administration which is probably causes an ADR during the treatment. We also did not explore the possible herb-drug interaction which may increase or decrease the ADR of herbal medicines.

## CONCLUSION

Around 20% patients experienced ADR due to the herbal medicine prescription in complementary treatment. Thus, the study of pharmacovigilance is needed to be conducted in bigger sample size and cohort design to understand the safety profile of herbal medicine used.

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