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Original Article

Monitoring adverse drug reactions to Thai herbal remedies (Ya Satree) in Thailand: Observational study

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Abstract

Healthcare systems worldwide mainly require spontaneous reporting on identified adverse drug reactions (ADRs) to prevent future ADRs**.** This study aimed to investigate ADRs that may occur from the use of Ya satree and to determine unwanted incident information for selecting new drugs to be included in the National List of Essential Medicines in Thailand. A prospective study was conducted among patients from 13 government hospitals. The 1100 participants received Ya satree for 4 consecutive weeks. The data were collected by interviews and with a structured questionnaire. The results showed that 1044 cases were completely followed-up. 78 cases had progression of ADRs assessments. From Naranjo' Algorithm scores, 32 participants showed probable scores and had ADR symptoms such as dizziness and headache. 42 participants showed possible scores and had ADR symptoms such as increased appetite and dizziness. However, all ADRs were non-serious may be related to the use of Ya satree.

Keywords: monitoring, Adverse Drug Reaction **(**ADR**)**, Thai herbal remedies **(**Ya Satree**)**

1. Introduction

Being aware of the safety of medicines is crucial to the healthcare personnel who maintain all levels of patients. Healthcare systems worldwide rely largely upon spontaneous reporting to identify new, rare and serious adverse drug reactions and to evaluate drug risk factors for preventing future adverse drug reactions (ADRs) (Blenkinsopp, Wilkie, Wang, & Routledge, 2007). The ADR reports from healthcare providers and patients are necessary and important to get accurate information. Adverse drug reactions reported directly by the patient can be very useful for healthcare personnel and for public health systems (Dweik, Yaya, Stacey, & Kohen, 2016; Vaismoradi, Logan, Jordan, & Sletvold, 2019). Currently, policies promote the development of knowledge and the standardization of Thai traditional medicine and herbal medicines in order to make them safe and of as high a quality as possible, for use in the local healthcare system (Tangyuenyongwatana & Gritsanapan, 2015).

The World Health Organization (WHO) expected that approximately 80% of population in developing countries use herbal and traditional medicines as the primary method in healthcare (Ekor, 2014). Herbal and traditional medicine use has also been extensively adopted in many other countries (Fung & Linn, 2015; Wang & Zhang, 2017). The use of herbal remedies in traditional medicine is widespread in Thailand. Many Thai commonly used herbs have biological activities relevant for some types of disease prevention or treatment (Kanjanahattakij *et al.*, 2019). Thai Government plans to increase herbal medicines in the National List of Essential Medicines system in order to increase alternative medicine use for patients, and to promote herbal medicine in Thailand. Moreover, previous research has found that Thai herbs show efficacy in anticancer, anti-inflammation and antibacterial

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uses (Chunthorng-Orn, Panthong, & Itharat, 2012; Prajuabjinda, Panthong, & Itharat, 2012; Promraksa *et al.*, 2019; Tungsukruthai, Nootim, Worakunphanich, & Tabtong, 2018). However, little scientific data on the pharmacological properties have been reported and there is a lack of research information about ADRs of Thai herbal medicines, which should submitted to the Food and Drug Administration (FDA), Ministry of public health, in Thailand. A specific objective was to check whether the patients know how to proceed in the event of any adverse reactions and how to deal with ADRs.

Ya Satree is a traditional drug used for dysmenorrhea and irregular menstruation, and is produced by Thungsong Hospital, Nakhon Si Thammarat province, Thailand with the GMP standards for pharmaceutical production. The aims of this study were to investigate the drug adverse events that may occur from the use of a herbal medicine, the rate of ADR from the use of herbal medicines, and to bring unwanted incident information from the use of herbal medicines for selecting new drugs to be included in the National List of Essential Medicines. A specific objective was to check whether the patients know how to proceed in the event of any adverse reactions and how to deal with ADRs.

2. Materials and Methods

2.1 Sample and setting

A prospective study was conducted in May 2017 to 2019 among patients from 13 government hospitals in Thailand. The inclusion criteria were: female patients aged 18-50 years with maturity, unusual symptoms with menstruation such as primary dysmenorrhea, menstrual irregularities, and willing to participate in this research (targeting up to 1,100 cases). Trained interviewers introduced themselves and explained the purpose of this study to participants and performed follow-up after using herbal remedies for 4 weeks.

For practical reasons, we excluded participants who were unable to read and write or respond in the language of the interviewer and those with mental disabilities that might interfere with their ability to give verbal consent or understand the question asked. The data were collected via face to face interviews with a structured questionnaire. The questionnaire was divided into four 4 sections.

1) Demographic characteristics such as age, weight, type of patient, occupation, side effect history, patient history, type of medicine, signs and symptoms, the data of patients who had taken only Ya Satree or had combined it with other drugs (dosage of use).
2) The respondents answered questions concerning the details in reporting ADRs, including date on which started use of drug, date of follow-up, using medication according to prescribed treatment or not, other medication used during this herbal medicine, symptoms found after taking drug, satisfaction in choosing to use drugs in the future, and the appearance of adverse reactions in skin system, digestion, liver function, or other symptoms.
3) Adverse event tracking forms by medical personnel such as name of drug, dosage, date of starting drug use, date of stopping drug use, symptoms, severity, and reporter
4) Naranjo's algorithm was used to evaluate adverse reactions, assess the severity and rate the symptom relationship (Naranjo's algorithm scores: >9= certain, 5-8 = Probable, 1-4 Possible, and <1= unlikely)

Participants were provided an appointment card for the follow-up and a handbook to record the ADR by themselves. The researcher explained to the participants how to respond to any symptoms that occur while taking the medicine during the 1st week. In addition, the researcher called the participants to inquire about any ADRs, and if severe adverse reactions occurred the medication was immediately stopped and the patient was to see a doctor. In absence of ADRs signs, participants continued use of this medication, as prescribed by the doctor, until 4 weeks. Then, the participants saw the researcher and provided the medicine bottles in order to evaluate the ADRs and to confirm the medication intake by each participant. The list of herbs in Thai Herbal Remedies is shown in Table 1.

Table.1 List of herbs in Thai Herbal Remedies (Ya Satree)

Scientific name	Example
Curcuma longa L.	
Curcuma zedoaria (Christm.) Roscoe	
Zingiber officinale Roscoe	
Zingiber montanum Link ex Dietr.	
Curcuma comosa Roxb	
Cyperus rotundus L	
Piper nigrum L	
Tamarindus indica L.	
Sodium chloride	

2.2 Data analysis

The data were analyzed by descriptive statistics (percentages of variables). The study protocol was approved by the ethics committee of Thai Traditional Medicine and Alternative Medicine, Ministry of Public Health (approval number 0503.13/176). It was registered in the Thai Clinical Registration with identification number TCTR20191009003.

2.3 Thai Herbal Remedies (Ya Satree)

Indications of Ya Satree include use for the treatment of abdominal pain, vaginal discharge, or irregular menstruation. Dose and how to use: take 2 tablets (250 mg) 3 times a day after meals.

3. Results and Discussion

3.1 Participant demographics

Table 2 summarizes the participant demographics and answers in the questionnaire including age, weight, type of patient, occupation, history of drug allergy, history of allergies in the family, history of congenital disease, medication that is taken regularly, other medicine during this study period, do you take medication regularly, and use of other herbs together or not.

3.2 The ADR symptoms during using Ya satree

Then, the participants were asked more questions on what are the symptoms of your current condition, do you want to use this drug in the future, and do you have any unwanted symptoms while using this drug. The results showed that the symptoms of participants had improved for 81.42%, whereas worsening status was reported for only 0.67% of all participants, as shown in Figure 1.

Moreover, we also determined the satisfaction of participants, namely whether they want to use this drug in the future or not. The results showed that about 94% of all participants want to use this drug in the future, as shown in Figure 2.

In addition, we assessed any unwanted symptoms while using this drug, and the results showed that 40 (3.83%) of the participants had an unwanted symptom that might be associated with ADRs while using Ya satree (Figure 3).

From the assessment of ADRs, severity assessment, the herbal drug involvement according to the Naranjo' Algorithm scores and progression of ADRs assessments, the results showed a total of 78 adverse reactions, with these adverse reactions associated with herbal drugs. Non-serious cases may be related to the use of herbal medicines and in progression of adverse event there was recovery from all symptoms; (Possible score: 1-4) 42 participants including increased appetite, dizziness, drowsiness, headache, flatulence, constipation, dry mouth, dyspepsia, and nausea. Probable score (Probable score: 5-8) 32 participants with dizziness, headache, insomnia, nausea, or rash, as shown in Table 3.

Furthermore, in the participants who experienced ADRs, we discovered more in the history of using traditional medicine or other dietary supplements that were used while taking this medicine. However, most drug names were in English, so only few participants could provide competently information about the commonly used drugs such as Propranolol, Enapril, Mefenamic, fish oil, calcium, vitamin C, and coconut oil.

Table 2. Participant demographics

Factor	N = 1044	Percent (100%)
Age (years)		
<20	45	4.31
21-30	271	25.96
31-40	265	25.38
41-50	320	30.65
51-60	143	13.70
Weight (Kg)		
<40	15	1.44
41-50	245	23.47
51-60	411	39.37
61-70	233	22.31
71-80	80	7.66
>81	60	5.75
Type of patient		
Outpatient	1038	99.43
Inpatient	6	0.57
Occupation		
Farmer	213	20.40
Student	193	18.49
Employee	294	28.16
Government officer	113	10.82
Business	110	10.54
Housework	44	4.21
Not working	77	7.38
History of drug allergy		
Yes	938	89.85
No	106	10.15
History of allergies in the family		
Yes	992	95.02
No	52	4.98
History of congenital disease		
Yes	833	79.79
No	211	20.21
Medication that is taken regularly		
No	908	86.97
Yes	136	13.03
Other medicine during period		
No	928	88.89
Yes	116	11.11
Do you take medication regularly?		
Take medication regularly	751	71.94
Forget to take medicine sometimes	256	24.52
Forgot to take medicine often	31	2.97
Do not take medicine	6	0.57
Use other herbs together or not		
No	950	91.00
Yes	94	9.00

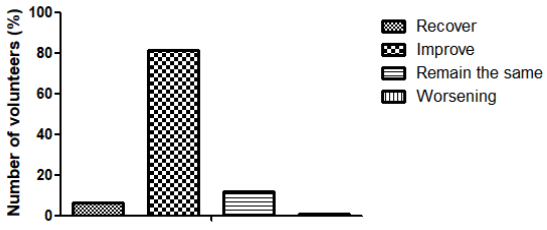

Figure 1. The symptoms of current condition of participants

Table 3. The Naranjo' Algorithm and progression of adverse event assessments

System	Symptom	Naranjo' Algorithm (10 scores)				Sum
		Definite >9	Probable 5-8	Possible 1-4	Doubtful <1	
Cardiovascular	Palpitation			1		1
Dermatologic	Chloasma			1		1
	Dry skin			1		1
	Rash		3	1	1	5
Gastrointestinal	Abdominal pain		1	1	1	3
	Aphthous ulcer			1		1
	Constipation		1	2		3
	Dry mouth			2		2
	Dyspepsia		1	2		3
	Flatulence		1	3		4
	Nausea		4	2		6
	Vomiting		1			1
Genitourinary	Breast pain			1		1
	Menstrual cramps			1		1
	Irregular menstruation			1		1
	Vaginal discharge		1	1	1	3
Metabolic	Increased appetite			9		9
	Weight gain			3		3
Nervous system	Dizziness		7	3		10
	Drowsiness			3		3
	Headache		6	3		9
	Insomnia		5		1	6
Other	Fatigue		1			1
Sum			32	42	4	78

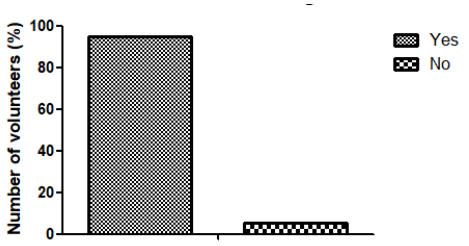

Figure 2. The satisfaction of using Ya Satree

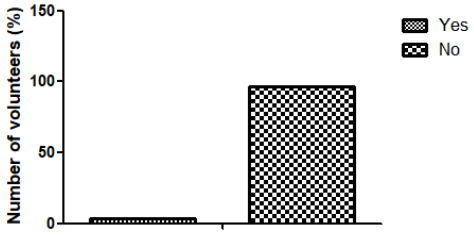

Figure 3. Unwanted symptoms while using this drug

4. Discussion

To our knowledge, this is the first observational study on the burden of adverse drug reactions (ADRs) in complementary and alternative medicine (CAM), when patients are treated with Ya Satree. Ya Satree is traditional drug used for dysmenorrhea and irregular menstruation, currently produced by Thungsong Hospital, Nakhon Si Thammarat province, Thailand, following GMP standards for pharmaceutical production. However, it has been speculated that CAM use may harmfully affect adherence to prescribed therapies (Krousel-Wood, Thomas, Muntner, & Morisky, 2004).

In this study, we found that the symptoms of participants had improved in 81.42% of the cases, whereas worsening was reported by only 0.67% of all participants (Figure 1). Based on medical records, in reactions by age group the symptoms were different. The age group of <30 years olds suffers from dysmenorrhea and back pain 1-2 days before menstruation period. In addition, for ages 31-50 years, most of the symptoms are irregular menstruation (excessive/ menorrhagia or hypomenorrhea), color of the menstrual blood is dark, with clotting, vaginal discharge, and melasma (chloasma). For age >50 years, most of the symptoms are excessive, skipping periods and melasma (Chloasma). In addition, most of them want to use this drug again in the future, as shown in Figure 2. Furthermore, we found that the participants had unwanted symptoms which might be associated with ADRs while using Ya Satree (Figure 3). Therefore, we assumed that these participants used other traditional medicine or dietary supplements while taking this medicine. From the data on the medication, the participants had non-serious ADRs which end after stopping use of the medication. In addition, the probable related ADRs with using herbs were headache, nausea, dizziness, constipation, insomnia, abdominal pain, and rash. However, it is not clear whether the herbs originated these ADRs or not.

Ya Satree has an astringent and slightly hot flavor. From the analysis of components of Ya Satree formulas, based on knowledge of Thai traditional Medicine theory, this drug can be divided into 3 groups as follows: first group have an astringent and slightly hot flavor such as *Zingiber montanum*

Link ex Dietr, Curcuma longa L, Curcuma zedoaria (Christm., Roscoe., and *Curcuma comosa Roxb* (40.20% of formula); second group have spicy taste such as *Zingiber officinale Roscoe, Cyperus rotundus L. and Piper nigrum L* (19.80% of formula); and the third group have a sour and salty taste such as *Tamarindus indica L*, and Sodium chloride (40% of formula). In Thai traditional Medicine Theory, the Thai traditional doctor uses astringent and hot flavored herbal medicines to expel blood or clot in the uterine cavity and to reduce flatulence and abdominal pain. Sour and salty flavor is used to clean and expel blood in uterus. In addition, previous studies found that mainly drug flavor of Ya Satree associated with unwanted symptoms and side effects as described below involved curcumin, *Curcuma Comosa Roxb, Zingiber officinale Roscoe and Piper nigrum L.*

As shown in Table 1, Ya Satree has many herbs in remedies which could result in ADRs and side effects to participants. Previous study found that seven subjects receiving 500–12,000 mg of curcumin and followed for 72 h experienced diarrhea, headache, and rash (Lao *et al.*, 2006). Moreover, subjects receiving 0.45 to 3.6 g/day curcumin for 4 months reported nausea and diarrhea and rise in serum alkaline phosphatase and lactate dehydrogenase (Sharma *et al.*, 2004). For *Curcuma Comosa Roxb*, previous research cautioned that it must be taken with monitoring for possible adverse effects, especially in the elderly as well as in persons with chronic diseases (Winuthayanon *et al.*, 2009).

Ginger (*Zingiber officinale Roscoe*), one herb in this type of medication, also is reported in ADRs. It is established that neither ginger nor its constituents have a role in the gastrointestinal adverse effects that are usually produced by the NSAIDs as a result of prostaglandin inhibition (Ali, Blunden, Tanira, & Nemmar, 2008). Furthermore, *Piper nigrum L.* also altered the pharmacokinetics of drug with a narrow therapeutic index which could lead to ADRs (Velpandian, Jasuja, Bhardwaj, Jaiswal, & Gupta, 2001). Interestingly, *Zingiber montanum Link ex Dietr. (Plai)* is reported for no adverse event of using Plai. Therefore, this suggested that the safety profile of Plai should be importantly highlighted (Chongmelaxme *et al.*, 2017).

Besides, among patients receiving Ya Satree, some patients used other medicine to treat the disease, including Propranolol, Enapril and Mefenamic. Side effects from using Propranolol include gastrointestinal disturbances, bradycardia, hypotension, bronchospasm, exertional dyspnea, hypoglycemia, dizziness, fatigue, and insomnia (Srinivasan, 2019). For Enapril, the side effects were hypotension, azotemia, cough, and fatigue which might be associated with participants who had ADRs as shown in Table 3 (Kostis *et al.*, 1996). In addition, Mefenamic acid 500 mg had evidence in ADRs for inducing migraine and moderate fever, however, not serious (Moll, Derry, Moore, & McQuay, 2011).

The dietary supplements that the patients consume with Ya Satree include collagen, vitamin C, fish oil, calcium, and coconut oil. All these dietary supplements could be involved in the ADRs in this study. For example, consumption of supplemental vitamin C leads to no significant adverse health effects to humans normally. However, some individuals with a history of kidney stone formation and who had iron overload should be careful on using vitamin C. Rarely, some persons experienced diarrhea or mild nausea. In addition, it is possible that simultaneously taking vitamin C with other drugs may contribute to adverse effects and that its inclusion in clinical laboratory tests has masked as diagnosis of a disease (Grosso *et al.*, 2013; Sestili, 1983).

Some of herbs in the drugs showed adverse effects. In contrast, we found that the symptoms of most participants have improved. The dosage of each herb was not more than in prior studies. Therefore, we assumed that the ADRs depend on the participants. Consequently, the prescription of female formulas in the case of abnormal menstruation patients. A doctor or traditional Thai physician who prescribes treatment should follow up with evaluation of the treatment and must have a detailed history of the ADRs occurring during the use of the drug, whether it is related to the symptoms before menstruation or not. If the patients experience severe adverse reactions, they must stop the drug use immediately.

Reporting of adverse effects is strongly helped even if the causality is not established, because any signs will let rapid regulatory actions to be taken. The analysis of reported adverse events is very important in monitoring the safety of Thai herbal medicine products and helps in the understanding of the benefits and jeopardies associated with the use of these products.

5. Conclusions

In conclusion, this study indicated that Ya Satree is effective for the treatment of abnormal menstruation, and the ADR observed were mild and non-serious. However, the physician should provide information about adverse drug reactions that may occur, to all patients. Further work to confirm the efficacy and safety of this drug type in randomized controlled trials is warranted in order to provide information supporting the applications in the health system in the future.

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