Adverse Events of Traditional Medicines and Herbal Products in the Thai Health Product Vigilance Center Database and the Ayurved Clinic of Applied Thai Traditional Medicine, Siriraj Hospital

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ABSTRACT

Objective: The aim of this study was to categorize adverse events (AEs) and symptoms related to traditional medicines (TMs) and herbal products (HPs) using the Thai Vigibase program (TVP).

Materials and Methods: TVP collected spontaneous AE reports including causality assessment of medical products in Thailand. For prospective data, Naranjo's algorithm (NJA) was used to determine the level of causality.

Results: There were a total of 1,133 AE case reports extracted from TVP and featured 1,229 TMs/HPs (310 TMs/HPs names) and 1,592 symptoms (204 symptom names). *Andrographis paniculata* was the product most frequently linked to AEs, with six cases of confirmed urticaria, 37 probable cases, and 24 possible causalities, 15 patients were given 23 TMs/HPs and this related to 33 AEs. The Ya Hom No.24 Tablets had the most reported AEs at 17.4% with only one causality, which was most probably linked to chest burning pain. There was also one case of herbal decoction relieving menopausal symptoms that was certainly related to chest fullness, feeling hot and cold, suffocation feeling, and sweating increase. Ayurved Siriraj Brand Ya Lom No.65 Pills, also reported one case that was linked to fatigue and drowsiness.

Conclusion: Reports from both data sources found a similar pattern in AE type and TMs/HPs. Naranjo's algorithm might be one of useful tools to help assess the causality between TMs/HPs and AEs. The results of this study serve as a good reference for causality between TMs/HPs and their AEs for all Thai traditional medicine practitioners.

Keywords: Traditional medicine; herbal product; adverse event; symptom name; and Naranjo's algorithm (Siriraj Med J 2023; 75: 377-391)

INTRODUCTION

Traditional medicines (TMs) and herbal products (HPs) are increasingly being used across the world. The Thai herbal industry grew from $US27 million in 2003 to $US300 million in 2014.[1,2] This acceleration of over 10% growth per year was the result of global exports of.[2] Although a great deal of research has been carried out to prove the benefits of TMs/HPs, adverse events (AEs) remain a concern. Minimal adverse effects of TMs/HPs have been recorded worldwide and systemically

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Received 24 February 2023 Revised 18 March 2023 Accepted 27 March 2023
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https://doi.org/10.33192/smj.v75i5.261512

categorized.[3-5] An understanding of AEs associated with TMs/HPs is essential for accurate prescriptions and to ensure user safety. Global organizations, such as the World Health Organization (WHO), have stored safety profile data of TMs/HPs use, including AE reports.[6] Regulatory authorities in many countries such as the Therapeutic Goods Administration (TGA) in Australia or even the China Food and Drug Administration (CFDA) in China, have tried to establish prospective surveillance in order to gain an understanding of the frequency, severity and causes of AEs involving TMs/HPs.[7-9] As a result of continuous data collection in studies from around the world, there is an abundance of results regarding herbal safety. For example, several studies have examined possible AEs linked to TMs/HPs through regulatory pharmacovigilance programs. A study of ADRs in Brazil[10], a prospective study with complementary medicine inpatients in Germany[11] and a study of AE using complementary and alternative medicine (CAM) products in Singapore[12] all looked at herbal drug ingredients.

In 1980, the Ministry of Public Health of Thailand began drug monitoring in hospitals with the founding of the Health Product Vigilance Center (HPVC), which in 1983 came under Thai Food and Drug Administration (Thai FDA). The Thai Vigibase Program (TVP) was created to collect AE reports of health products, including HPs from all over the country.[13] In Thailand, pharmacovigilance studies on the safety of herbal products have increased, especially of Traditional Thai medicine. A study conducted in 2000 at Lampang Hospital, in the north of Thailand reported hepatotoxic effects in Type 2 diabetes patients treated with *Tinospora crispa*.[14] Retrospective data from TVG between 2001-2012 described AEs, including hypersensitivity reactions to Andrographis products.[15] Studies looking at some specific TMs/HPs and serious AEs used the TVG which collects all AEs from health products, including TMs/HPs.[16,17] However, in this study, there was a plan to collect and analyze AE reports of HPs from two dimensions: retrospective data from database in Thailand and prospective visitors to Ayurved Clinic (AC) at Siriraj Hospital.

The Ayurved Clinic (AC) of Applied Thai Traditional Medicine under the Center of Applied Thai Traditional Medicine (CATTM), Faculty of Medicine Siriraj Hospital provides all types of traditional Thai treatments, including TMs/HPs to patients. Ingredients of TMs/HPs at the AC are not only known for their efficacy, but also manufactured following factory qualified standards or Good Manufacturing Practice (GMP) and the Pharmaceutical Inspection Co-operation Scheme (PICS). However, adverse effects caused by TMs/HPs need to be classified and incorporated with the national database of Thailand. Following a previous AE study, this report was designed to continuously and retrospectively collect AEs related to TMs/HPs.[16] This prospective collection of AEs at the AC provides a more complete picture of patient information compared to retrospective data of the former study. Therefore, the aim of this study was to describe characteristics of AEs using TVP and patients' data from AC.

MATERIALS AND METHODS

This study was approved by the Ethics Committee for Research in Humans via certificate of approval No. Si 410/2015, and ran at the Faculty of Medicine Siriraj Hospital between 2015 and 2017. There were two sets of data, including a retrospective part that looked at TVP data from the national database and a prospective part in which patients experienced AEs as a result of TMs/HPs at the AC.

Thai Vigibase Program (TVP)

Retrospective data was extracted from TVP, a database that collects spontaneous AE reports in the country. The reports were submitted either as an electronic form via an online reporting system or in paper format to the Health Product Vigilance Center (HPVC), Thai Food and Drug Administration (Thai FDA). The HPVC shares this data for use in pharmacovigilance studies. Each data point in the reports extracted characteristics of patients such as, names of products, terms and characteristics of AEs between January 2009 and July 2015.

Ayurved Clinic (AC)

A prospective study at the AC, Faculty of Medicine Siriraj Hospital was conducted between August 2015 and March 2016 and the prevalence of AEs in patients prescribed TMs/HPs was recorded. AEs were assessed by doctors who specialize in traditional Thai medicine and Western physicians, including follow-ups by telephone to record patients' sign and symptoms. The **World Health Organization's Adverse drug Reaction Terminology (WHO-ART)** was used to explain symptoms linked to AEs. **Naranjo's algorithm (NJA)** is a widely used tool among pharmacists to assess the ADRs of patients and the causality of adverse drug reactions through the answering of 10 questions.[18] Each question was answered and then categorized according to a scoring system divided into four levels of causality, including "Certain", "Probable", "Possible", and "Unlikely". The total score is shown as level of the causal relationship [9-13 points = certain, 5-8 points = probable, 1-4 point (s) = possible, or less than 1 point = unlikely/doubtful].[18,19]

Data analysis

Retrospective data from the TVP was imported into Microsoft Excel for data generation and preliminary analysis. The SPSS program was used for statistical analysis.[20] Descriptive statistics including mean, mode, and frequency were used to describe data in both retrospective and prospective studies.

RESULTS

Retrospective Results from Thai Vigibase Program and Prospective Results from Ayurved Clinic

Results from the TVP between January 2009 and July 2015 revealed, 1,131 patient reports, and a total of 1,229 products (310 product names) associated with 1,592 symptoms (204 symptom names). Some of the reports had just one product linked to one symptom, while some had one product linked to two or more symptoms. Some products also had contained more than one symptom associated to it.

According to data from the AC over the eight-month period from August 2015 to March 2016, 9,959 visitors were prescribed TMs/HPs. Of these, 15 visitors (0.15%) informed of an AE linked to clinical use of TMs/HPs use. Five of them had repeated AE after retaking the same products. There were 23 products (17 product names) linked to 33 symptoms (29 symptom names) and some of the reports were the same as in TVP or products that had more than one AE linked to it.

Fig 1 shows the characteristics of reports and patients in TVP and AC. The report characteristics include type, quality and seriousness. According to characteristics, data from the TVP and AC were presented as spontaneous in quality level 2 and non-serious events. All reports from AC were of the spontaneous type. No clinical trials have been performed using either sets of data. Referring to the seriousness of AEs, one "death" was associated to an AE in TVP. The most serious reported AE in TVP were "Initial or prolongation of hospitalization", which was similar to reports from AC where two serious AEs in this category were reported. According to patient characteristics from both sets of data, most of the patients were female and outpatient. All AE cases at the AC were outpatients. The age of TVP-patients mostly ranged from 46-60 whereas it was 61-75 at the AC.

Fig 2 shows the number, name and type of AE reported in products in TVP. The AE reports extracted 310 products, consisting of 64 known and 246 unknown ingredients, and 1,229 product reports. The 246 unknown ingredients may have been repeatedly reported by different events, so the exact total of unknown product names might be less than 246. The types of products included 27 single herbs and 37 herbal formulas. The single herb

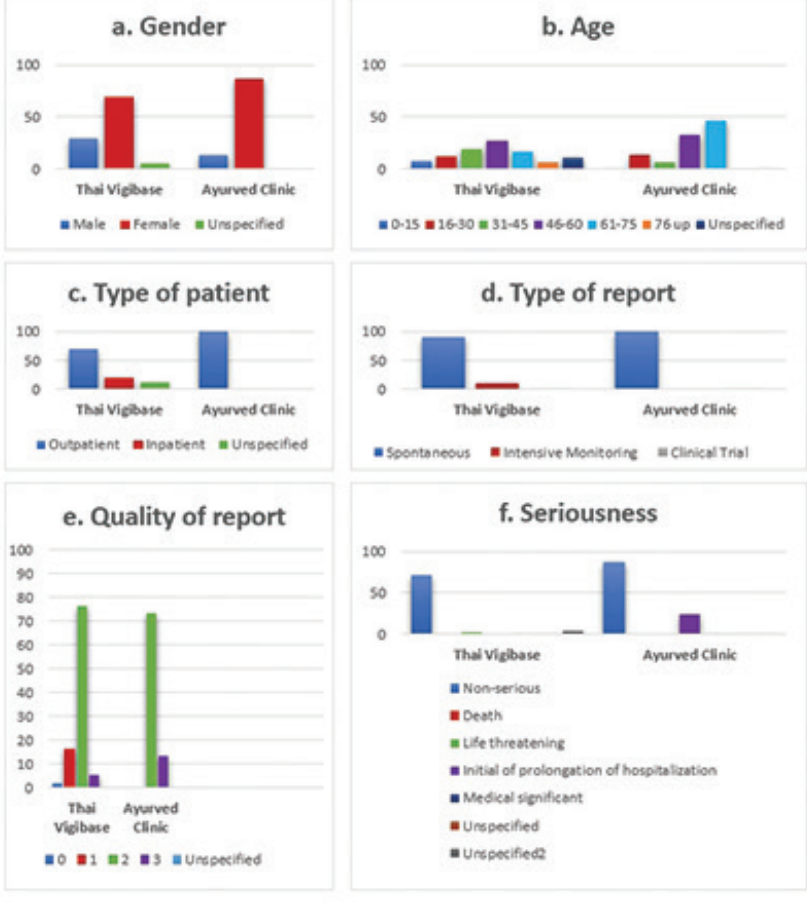

Fig 1. Report characteristics and patients from the Thai Vigibase Program between January 2009 and July 2015 and Ayurved Clinic between August 2015 and March 2016.

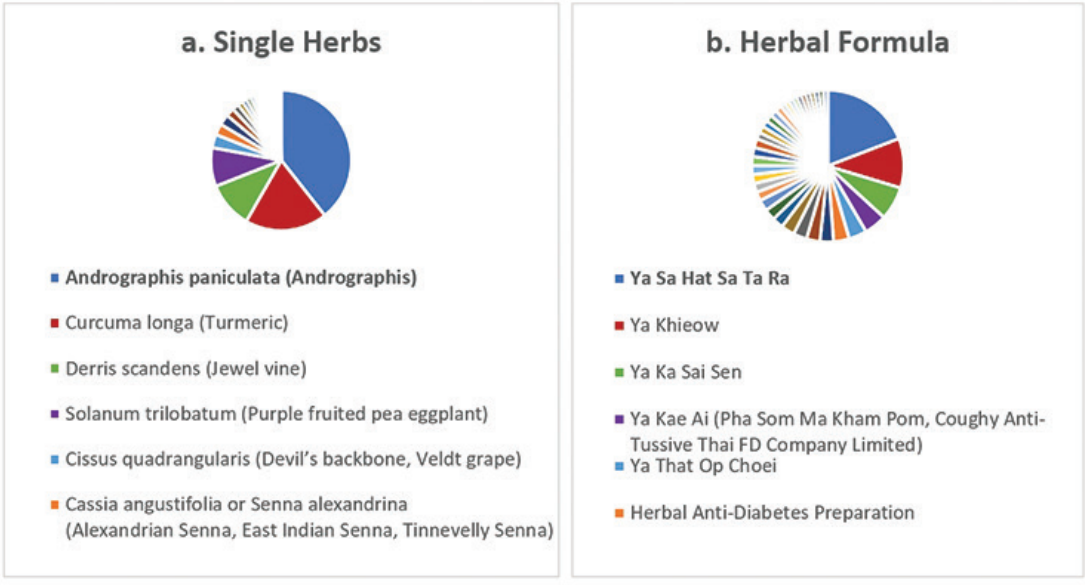

Fig 2. Products associated with adverse events from the Thai Vigibase Program between January 2009 and July 2015.

consisted of one HP while herbal formulas contained multiple single herbs. For the single herbs, the products were reported as scientific names, including their common names. The single herb product *"Andrographis paniculata"*, had the most AE associated with it. The top five on the chart mostly show four single herbs, and one herbal formula known as "Ya Sa Hat Sa Ta Ra". Although "Ya Sa Hat Sa Ta Ra" ranked fifth in the chart, it reported the most AEs among the herbal formula products. As seen in Table 2, the top 10 included 11 products in total. "Ya Ka Sai Sen" had and equal number of reports to *"Zingiber cassumunar"* in 10th place. The top 10 in the chart includes three herbal formulas "Ya Sa Hat Sa Ta Ra", "Ya Khieow", and "Ya Ka Sai Sen".

Table 1 shows the 11 products that had the most reported AEs, causalities, and symptom names. Each product had four levels of causalities, including an unspecified level. The four levels were; certain, probable, possible and unlikely. Each was calculated using Naranjo's algorithm assessment. The unspecified level included products that reported no causality. Most of the symptoms associated with these products fell in the probable level. In first place was *"Andrographis paniculata"*, which mostly led to urticaria. In second place was *"Curcuma longa"*, which mostly led to rash. However, for "Ya Sa Hat Sa Ta Ra", *"Cassia angustifolia* or *Senna alexandrina", "Momordica charantia"*, "Ya Ka Sai Sen", and "*Zingiber cassumunar*", there was no data at the certain level. Among all the data in the table, *"Andrographis paniculata"* was the only product to have an unspecified causality of two symptoms.

Fig 3 shows the name, type and the number of product reports from the AC. A total of 17 products reported 23 AEs. Of this, 17 TMs/HPs were single herbs and the rest herbal formulas. All products were named after the "Ayurved Siriraj Manufacturing Unit of Herbal Medicine and Products" so that reported AEs had a registered name even if there was no scientific name of a single herb. The mode of administration included pills, capsules, tablets and three different formulas of decoction. Almost all of the 17 products were herbal formula, except for "Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion", which was the only single herb causing AE. "Ayurved Siriraj Brand Ya Hom No.24 Tablets", a herbal formula was the product that reported the most AEs. In second place for AEs were three products, "Ayurved Siriraj Brand No.11 Antiflatulent Tablets", "Ayurved Siriraj Brand No.39 Antiflatulent Tablets" and "Ya Med Kae Nam Luang Sia, Ayurved Siriraj Brand". Most of the products were marked for internal-use except Ayurved Siriraj Brand Medicated Balm formula 1, which was meant for external use.

Table 2 shows the 17 products that had an AE associated with causalities and symptoms at the AC. "Ayurved Siriraj Brand Ya Hom No.24 tablets" had the most reported AEs. However, the "probable" category had the highest level of causalities in most products. Only two products reported a certain level of symptoms. "Herbal decoction relieving menopausal symptoms" was certainly related to chest fullness, feeling hot and cold, suffocation feeling, and sweating increase. "Ya Lom No.65 Pills, Ayurved Siriraj Brand" was also certainly related to drowsiness and fatigue.

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015.

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
1	*Andrographis paniculata* (Andrographis) 305 (24.81)	Certain	Urticaria (6), Pruritus (2), Angioedema (1), Fixed eruption (1), Macular rash (1), Oedema mouth (1), Papular rash (1), Rash (1), Rash maculo-papular (1)
		Probable	Urticaria (37), Rash maculo-papular (35), Angioedema (16), Pruritus (14), Rash (13), Oedema eyelid (12), Anaphylactic shock (11), Rash erythematous (11), Anaphylaxis (10), Face oedema (7), Itching (7), Dyspnoea (5), Nausea (5), Papular rash (5), Vomiting (5), Macular rash (4), Chest tightness (3), Chest fullness (2), Dizziness (2), Flatulence (2), Lips swelling non-specific (2), Oedema legs (2), Acute generalized exanthematous pustulosis (1), Anaphylactic reaction (1), Anaphylactoid reaction (1), Blisters (1), Bloating (1), Breath shortness (1), Chest discomfort (1), Coughing (1), Diarrhoea (1), Erythema (1), Eye discharge (1), Faintness (1), Fever (1), Gastro-intestinal disorder NOS* (1), Hearing impaired (1), Hepatic enzymes increased (1), Measly rash (1), Mouth ulceration (1), Muscle cramp (1), Oedema (1), Oedema generalized (1), Oedema genital (1), Oral mucosal eruption (1), Pain (1), Papulovesicular rash (1), Paralysis muscle local skeletal (1), Purpura allergic (1), Red eye (1), Skin flushed (1), Stevens Johnson Syndrome (1), Tongue disorder (1), Urticaria acute (1), Weariness (1)
		Possible	Urticaria (24), Rash (17), Rash maculo-papular (14), Angioedema (9), Rash erythematous (9), Face oedema (7), Oedema eyelid (7), Papular rash (6), Oedema mouth (5), Pruritus (5), Anaphylactic shock (2), Anaphylaxis (2), Dyspnoea (2), Itching (2), Macular rash (2), Nausea (2), Oedema (2), Stevens Johnson Syndrome (2), Vomiting (2), Anaesthesia mouth (1), Anaphylactic reaction (1), Arthritis rheumatioid aggravated (1), Burning sensation (1), Chest fullness (1), Chest tightness (1), Coughing (1), Dermatitis exfoliative aggravated (1), Diarrhoea (1), Dizziness (1), Eczema (1), Eosinophilia (1), Eye inflamed (1), Fever (1), Fixed eruption (1), Hepatitis (1), Inflammatory swelling (1), Morbilliform rash (1), Numbness oral (1), Oedema of extremities (1), Oedema peripheral (1), Pain (1), Palpitation (1), Skin vasculitis NOS* (1), Stomatitis (1), Sweating increased (1), Wheezing inspiratory (1)
		Unlikely	Constipation (1), Dizziness (1), Stool black (1)
		Unspecified	Rash (1), Urticaria (1)
2	*Curcuma longa* (Turmeric) 146 (11.88)	Certain	Burning sensation (1), Extrapyramidal disorder (1), Fixed eruption (1), Nausea (1), Rash maculo-papular (1), Vomiting (1), Weakness generalized (1)
		Probable	Rash maculo-papular (13), Urticaria (13), Rash (12), Pruritus (9), Angioedema (6), Dizziness (6), Itching (5), Nausea (5), Oedema legs (5), Dyspnoea (4), Palpitation (4), Face oedema (3), Headache (3), Oedema (3), Vomiting (3), Anaphylaxis (2), Chest tightness (2), Constipation (2), Diarrhoea (2), Macular rash (2),

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
			Mouth dry (2), Oedema eyelid (2), Rash erythematous (1), Abdominal pain (1), Anaphylactic shock (1), Breath shortness (1), Buccal mucosa ulceration (1), Burning sensation (1), Chest distress (1), Chest fullness (1), Coughing (1), Erythema (1), Faintness (1), Fixed eruption (1), Flatus (1), Fullness abdominal (1), Hearing impaired (1), Heat rash (1), Lip soreness (1), Mouth ulceration (1), Oedema mouth (1), Oedema peripheral (1), Oral mucosal eruption (1), Pain (1), Papular rash (1), Stevens Johnson Syndrome (1), Stomach upset (1), Tongue disorder (1), Weariness (1)
		Possible	Rash (10), Rash maculo-papular (6), Urticaria (6), Pruritus (3), Angioedema (2), Diarrhoea (2), Dyspnoea (2), Vomiting (2), Abdominal pain (1), Anaphylactic shock (1), Anorexia (1), Chest tightness (1), Constipation aggravated (1), Dizziness (1), Erythema multiforme (1), Fatigue (1), Flatulence (1), Headache (1), Itching (1), Lethargy (1), Macular rash (1), Mouth dry (1), Nausea (1), Oedema eyelid (1), Oral ulceration (1), Palpitation (1), Papulovesicular rash (1), Rash erythematous (1), Rash pustular (1), Stevens Johnson Syndrome (1), Throat dry (1)
		Unlikely	Allergic conjunctivitis (1), Dizziness (1), Hypoglycaemia (1), Oedema of extremities (1), Pruritus (1), Rash (1), Urticaria (1)
		Unspecified	-
3	*Derris scandens* (Jewel vine) 83 (6.75)	Certain	Angioedema (1), Anorexia (1), Burning sensation (1), Dizziness (1), Itching (1), Mouth dry (1), Nausea (1), Palpitation (1), Pruritus (1), Sleepiness (1), Throat dry (1)
		Probable	Rash (6), Urticaria (6), Angioedema (5), Palpitation (5), Face oedema (3), Itching (3), Urinary frequency (3), Vomiting (3), Diarrhoea (2), Dizziness (2), Macular rash (2), Nausea (2), Papular rash (2), Rash erythematous (2), Rash maculo-papular (2), Angioedema (1), Abdominal pain (1), Anaphylactic shock (1), Anaphylaxis (1), Bewilderment (1), Breathing difficult (1), Bruise (1), Convulsions (1), Bullous eruption (1), Debility (1), Eczema (1), Erythema multiforme (1), Eye irritation (1), Fixed eruption (1), Haemorrhage NOS* (1), Hypokalaemia (1), Mouth dry (1), Mouth ulceration (1), Numbness (1), Oedema mouth (1), Oedema of extremities (1), Oedema peripheral (1), Pruritus (1), Stools watery (1), Throat dry (1), Tiredness (1), Urinary retention (1)
		Possible	Angioedema (5), Urticaria (5), Itching (3), Abdominal pain (2), Dizziness (2), Rash (2), Anorexia (1), Bullous eruption (1), Chest tightness (1), Constipation (1), Convulsions (1), Diarrhoea (1), Erythema (1), Extremities hot feeling (1), Faecal abnormality NOS* (1), Headache (1), Insomnia (1), Mouth irritation (1), Muscle pain (1), Muscle rigidity (1), Oedema mouth (1), Papular rash (1), Rash erythematous (1), Throat irritation (1), Urinary frequency (1)
		Unlikely	Giddiness (1), Nausea (1), Vision blurred (1)
		Unspecified	-

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
4	*Solanum trilobatum* (Purple fruited pea eggplant) 69 (5.6)	Certain	Fixed eruption (1), Pruritus (1), Rash maculo-papular (1), Urticaria (1)
		Probable	Rash (9), Rash maculo-papular (7), Urticaria (6), Oedema eyelid (5), Pruritus (5), Angioedema (4), Chest fullness (3), Face oedema (3), Oedema mouth (3), Macular rash (2), Oedema (2), Rash erythematous (2), Stevens Johnson Syndrome (2), Anaesthesia local (1), Anaesthesia mouth (1), Anaesthesia tongue (1), Bronchospasm (1), Dermatitis exfoliative (1), Dizziness (1), Dyspepsia (1), Dyspnoea (1), Eye irritation (1), Flatulence (1), Gastro-intestinal disorders NOS* (1), Hot flushes (1), Joint pain (1), Lips dry (1), Lips swelling non-specific (1), Mouth dry (1), Mouth ulceration (1), Nausea (1), Palpitation (1), Papulovesicular rash (1), Rash bullous (1), Tiredness (1), Vomiting (1)
		Possible	Rash maculo-papular (5), Itching (2), Rash (2), Urticaria (2), Angioedema (1), Chest fullness (1), Diarrhoea (1), Face oedema (1), Gasping (1), Lips swelling non-specific (1), Oedema eyelid (1), Oral ulceration (1), Papular rash (1), Rash erythematous (1), Rash petechial (1)
		Unlikely	Lips swelling non-specific (1), Oedema (1), Pruritus (1), Rash erythematous (1)
		Unspecified	-
5	Ya Sa Hat Sa Ta Ra 40 (3.25)	Certain	-
		Probable	Abdominal pain (3), Diarrhoea (3), Throat dry (3), Flatulence (2), Mouth dry (2), Nausea (2), Pruritus (2), Anorexia (1), Bloating (1), Dizziness (1), Eczema (1), Hearing impaired (1), Peripheral oedema / Acute gout attack (1), Rash erythematous (1), Rash maculo-papular (1), Sleepiness (1), Stools loose (1), Tongue disorder (1), Urticaria (1), Vomiting (1)
		Possible	Abdominal pain (5), Anorexia (4), Diarrhoea (4), Dizziness (4), Mouth dry (4), Throat dry (4), Rash erythematous (3), Constipation (2), Pruritus (1), Rash (1), Urine discolouration (1), Urticaria (1), Vomiting (1), Weakness generalized (1)
		Unlikely	Abdominal pain (1)
		Unspecified	-
6	*Cissus quadrangularis* (Devil's backbone, Veldt grape) 24 (1.95)	Certain	Adult respiratory distress syndrome (1), Urticaria (1)
		Probable	Burning sensation (2), Dizziness (1), Dyspnoea (1), Headache (1), Lip soreness (1), Nausea (1), Pruritus (1), Rash erythematous (1), Rash maculo-papular (1)
		Possible	Chest tightness (2), Diarrhoea (2), Flatulence (2), Pruritus (2), Abdominal discomfort (1), Angioedema (1), Constipation aggravated (1), Dizziness (1), Nausea (1), Rash (1)
		Unlikely	-
		Unspecified	-
7	Ya Khieow 22 (1.79)	Certain	Anaphylaxis (1), Urticaria (1)
		Probable	Rash erythematous (2), Rash maculo-papular (2), Stevens Johnson Syndrome (2), Anaphylactic shock (1), Anaphylaxis (1), Burn (1), Erythema multiforme severe (1), Eye inflamed (1), Face oedema (1), Fever (1), Oedema eyelid (1), Pruritus (1), Rash (1)

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
		Possible	Rash maculo-papular (2), Urticaria (2), Urticaria acute (2), Angioedema (1), Bronchospasm (1), Eye pain (1), Face oedema (1), Oedema eyelid (1), Oedema mouth (1), Rash (1), Toxic epidermal necrolysis (1)
		Unlikely	Choking (1), Rash maculo-papular (1), Unconsciousness (1)
		Unspecified	-
8	*Cassia angustifolia* or *Senna alexandrina* (Alexandrian Senna, East Indian Senna, Tinnevelly Senna) 20 (1.63)	Certain	-
		Probable	Urticaria (3), Dizziness (2), Dyspnoea (2), Oedema mouth (2), Rash erythematous (2), Rash maculo-papular (2), Anaphylactic shock (1), Anaphylactoid reaction (1), Anaphylaxis (1), Angioedema (1), Coughing (1), Itching (1), Pruritus (1), Rash (1), Rash erythematous aggravated (1), Wheezing inspiratory (1)
		Possible	Erythema multiforme (1), Fixed eruption (1), Hepatitis (1), Rash erythematous (1), Urticaria (1)
		Unlikely	-
		Unspecified	-
9	*Momordica charantia* (Bitter melon, Bitter gourd) 19 (1.55)	Certain	-
		Probable	Urticaria (2), Angioedema (1), Anorexia (1), Dizziness (1), Flatulence (1), Nausea (1), Rash erythematous (1), Rash maculo-papular (1), Vomiting (1)
		Possible	Dizziness (2), Anaesthesia mouth (1), Anaesthesia tongue (1), Diarrhoea (1), Face oedema (1), Faintness (1), Headache (1), Hepatitis (1), Insomnia (1), Nausea (1), Oedema mouth (1), Palpitation (1), Pruritus (1), Rash (1), Rash erythematous (1), Rash maculo-papular (1), Throat dry (1)
		Unlikely	Flatulence (2), Abdominal pain (1), Paraesthesia (1), Rash erythematous (1), Sleepiness (1), Stools loose (1), Urine discolouration (1)
		Unspecified	-
10	Ya Ka Sai Sen 15 (1.22)	Certain	-
		Probable	Urticaria (2), Anaphylaxis (1), Bradycardia (1), Face oedema (1), Gastrointestinal tract bleeding NOS* (1), Macular rash (1), Nausea (1), Oedema eyelid (1), Papular rash (1), Rash erythematous (1), Rash maculo-papular (1), Stevens Johnson Syndrome (1), Vesiculobullous rash (1)
		Possible	Pruritus (2), Urticaria (2), Angioedema (1), Papular rash (1)
		Unlikely	-
		Unspecified	-
11	*Zingiber cassumunar* or *Zingiber montanum* (Phlai, Cassumunar ginger) 15 (1.22)	Certain	-
		Probable	Rash (3), Itching (2), Angioedema (1), Application site reaction (1), Bullous eruption (1), Burning sensation (1), Burning skin (1), Dermatitis contact (1), Eruption (1), Erythema (1), Macular rash (1), Pruritus (1), Rash bullous (1), Rash maculo-papular (1), Urticaria (1), Vesicular rash (1)
		Possible	Abdominal pain (1), Anorexia (1), Dermatitis contact (1), Rash erythematous (1)
		Unlikely	-
		Unspecified	-

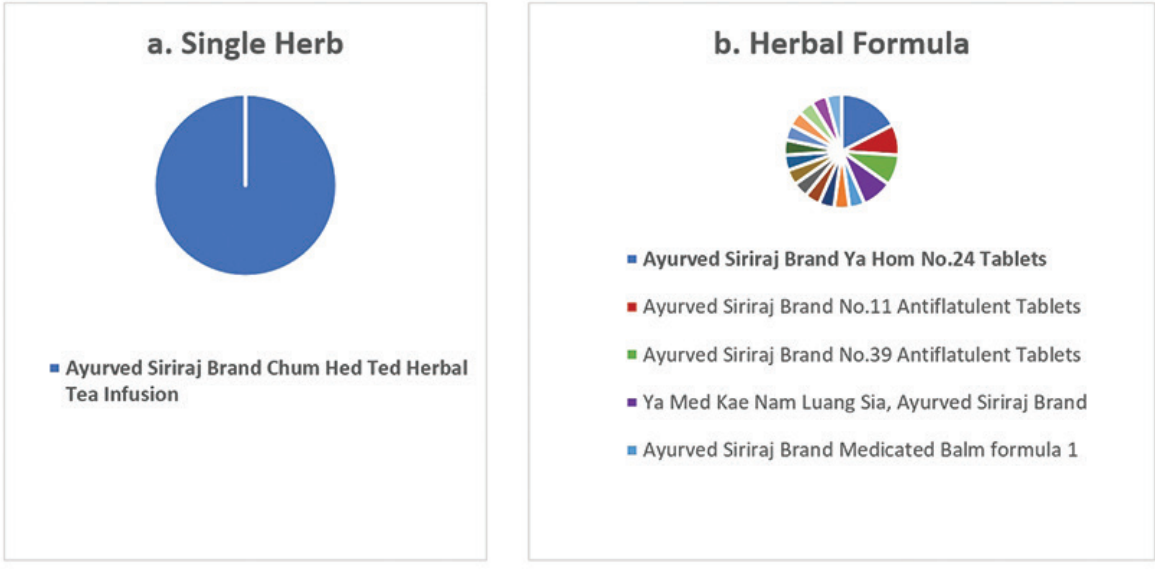

Fig 3. Products that reported adverse events at the Ayurved Clinic between August 2015 and March 2016.

TABLE 2. Products that reported level of causalities and symptom names at Ayurved Clinic between August 2015 and March 2016.

No.	Product report No. (%) [n=23]	Level of Causalities	Symptom Name (n) [n=51]
1	Ayurved Siriraj Brand Ya Hom No.24 Tablets 4 (17.4)	Certain	-
		Probable	Chest burning pain (1)
		Possible	Abdominal discomfort (1), Chest fullness (1), Debility (1), Dizziness (1), Feeling hot and cold (1), Headache (1), Pruritus (1), Sleeplessness (1), Suffocation feeling (1), Sweating increase (1), Urticaria (1)
		Unlikely	-
2	Ayurved Siriraj Brand No.11 Antiflatulent Tablets 2 (8.7)	Certain	-
		Probable	-
		Possible	Abdominal pain (1), Nausea (1), Large bowel obstruction (1)
		Unlikely	Leg cramps (1)
3	Ayurved Siriraj Brand No.39 Antiflatulent Tablets 2 (8.7)	Certain	-
		Probable	Chest burning pain (1)
		Possible	Burning mucosal (1), Nasal congestion (1), Throat dry (1)
		Unlikely	-
4	Ya Med Kae Nam Luang Sia, Ayurved Siriraj Brand 2 (8.7)	Certain	-
		Probable	Oedema eyelid (1), Oedema mouth (1), Urticaria (1)
		Possible	Face oedema (1), Oedema eyelid (1), Urticaria aggravated (1)
		Unlikely	-
5	Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion 1 (4.35)	Certain	-
		Probable	Dizziness (1)
		Possible	-
		Unlikely	-
6	Ayurved Siriraj Brand Medicated Balm formula 1 1 (4.35)	Certain	-
		Probable	Burning sensation (1), Itching (1)
		Possible	-
		Unlikely	-

TABLE 2. Products that reported level of causalities and symptom names at Ayurved Clinic between August 2015 and March 2016. (Continued)

No.	Product report No. (%) [n=23]	Level of Causalities	Symptom Name (n) [n=51]
7	Ayurved Siriraj Brand No.12 Pills 1 (4.35)	Certain Probable Possible Unlikely	- Abdominal pain (1), Nausea (1), Large bowel obstruction (1) - -
8	Ayurved Siriraj Brand No.30 Ya Satree Pills 1 (4.35)	Certain Probable Possible Unlikely	- - Face oedema (1), Oedema eyelid (1), Urticaria aggravated (1) -
9	Ayurved Siriraj Brand Ya Hom No.20 Tablets 1 (4.35)	Certain Probable Possible Unlikely	- Palpitation (1) - -
10	Ayurved Siriraj Brand Ya Hom No.47 Tablets 1 (4.35)	Certain Probable Possible Unlikely	- - Burning mucosal (1), Nasal congestion(1), Throat dry (1) -
11	Bantaoridsidwangthawan Pills, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- - Dizziness (1) -
12	Herbal decoction relieving joint pain or inflammation (fruit instead stem of khi ka daeng formula) 1 (4.35)	Certain Probable Possible Unlikely	- Abdominal discomfort (1) - -
13	Herbal decoction relieving menopausal symptoms 1 (4.35)	Certain Probable Possible Unlikely	Chest fullness (1), Feeling hot and cold (1), Suffocation feeling (1), Sweating increase (1) - - -
14	Herbal decoction relieving menopausal symptoms (Benjakool formula, remove Ha-rak ingredients) 1 (4.35)	Certain Probable Possible Unlikely	- Pruritus (1), Urticaria (1) - -
15	Ya Lom No.65 Pills, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	Drowsiness (1), Fatigue (1) - - -
16	Ya Sahatsatara Tablets, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- - Papulovesicular rash (1) -
17	Ya Sattakavata, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- Leg cramps (1) - -

DISCUSSION

This study examined AEs relating to TMs/HPs by looking at retrospective data in the TVP database over a seven-year period and prospective data from the AC over an eight-month period. In the TVP, some of the 1,133 patients had a poly-medicine regimen, so 1,229 and 1,732 symptoms were reported as seen in Table 1 and Table 2. Differences of AE relations were reported. Each report from both datasets used either a product or poly-medicine. Some reports showed a product with a symptom or more than one symptom while other reports showed more than a product with a symptom or more than a symptom.

As seen in data from TVP and AC data in Fig 1, most reports and patient characteristics were similar. As a result of establishing a routine for AE assessment in TMs/HPs among health professionals, there was not a clinical trial that reported on a data or intensive monitoring of TVP. Due to this reason, it would be beneficial to collect more AE data in a further study to learn about AEs linked to TMs/HPs. To improve patient safety standards, proactive collecting of AEs from clinical-trial studies at the AC should be promoted. Both sets of data were recorded at quality level two or three, which means it was mostly complete when compared to data from TVP. Even though the number of non-serious AEs was high in both datasets, there was one death in the TVP dataset and two cases of "initial or prolongation of hospitalization" at AC. No inpatient was reported at the AC because the clinic serves only outpatients. Also, patients over 45 in both datasets had more AEs reports.

As TVP-product data shows in Fig 2, TMs/HPs consist of drug such as "Thai Thip O-Soth Herbal Medicine" or food supplements such as the "Dietary Supplement Product (Sun Clara)" manufactured in Thailand. However, some products have their origin in Chinese traditional medicine or products such as "Jiu Jeng Pushen Jiao Nang" and "Yong Heng Herb Solution". Some of those products are also sold in other countries such as "Garcinia extract + Emblica extract plus several vitamins and amino acids (Ketosteril, Amiyu)" and "Pudina Satva (A Blend of Mint Oils)". These various forms have both internal and external use. This shows the variety in behaviors of use of TMs/HPs as either drugs or food supplements among Thais. The three single herbal products, *"Andrographis paniculata"*, *"Curcuma longa"*, and *"Derris scandens"*, are in the list of top three most frequently used products. Moreover, they are listed in the Thailand National List of Essential Medicines (Thailand NLEM) and observed under an intensive monitoring program by HPVC.[6] The wide use of the first of these products, *"Andrographis paniculata"*, is due to its properties of relieving sore throat, fever, cough and other inflammations, and it is a nationwide-reported herb in HPVC.[6] When comparing AE data from TVP to the former study, *Andrographis paniculata, Curcuma longa,* and *Derris scandens* still ranked in the top 10 during this study period. One possible explanation is that these products are known and popular among users and easily accessible over the counter via drugstores or convenient stores.

"Ya Sa Hat Sa Ta Ra", a popular drug used to relieve muscle pain had the most AEs reported among all herbal formulas. "Ya Sa Hat Sa Ta Ra" is manufactured by AC and has 21 single herbs.[23-25] The four main ingredients of "Ya Sa Hat Sa Ta Ra" are *"Piper nigrum, Piper retrofractum, Plumbago indica,* and *Acorus calamus"*, all of which have a hot tasted." In the Thai NLEM, "Ya Sa Hat Sa Ta Ra" is prescribed in the form of capsules, powder, tablets or pills. Its properties list the ability to expel wind which obstructs your muscles and causes pain.[22] A result that was different in this study from the former (6) was an increase in the number of AEs linked to *"Andrographis paniculata"* and *"Derris scandens"*. This could be due to awareness amongst users of the latest information about, *"Cissus quadrangularis, Centella asiatica,* and *Zingiber cassumunar"* having less AEs compared to the former 5.

According to symptoms of TVP-products in Table 1, *"Andrographis paniculata"* had the most AEs associated to it, leading mostly to urticaria in certain, probable and possible level of causalities. According to MEDSAFE – a New Zealand Medicines and Medical Devices Safety Authority[26], TGA and the WHO, *"Andrographis paniculate"* was reported as the leading cause of allergic reactions, including urticaria. A study from Thailand looking at *"Andrographis paniculata"* mostly reported cases of urticarial.[15] As seen in reports from many other countries, *"Andrographis paniculata"* should be carefully used. Due to its strongly cold taste in Thai traditional medicine, the body may rapidly respond by generating heat and express it out via the blood and skin through conditions such as urticaria and rash. According to traditional Thai pharmaceutical knowledge, the tastes of herbal medicine is divided into nine groups or three main groups.[27] On the other hand, AE reports linked to use of "Ya Sa Hat Sa Ta Ra" ranked fifth on the chart, but it was the highest rank among herbal formulas. AEs linked to "Ya Sa Hat Sa Ta Ra" were the mostly linked to the gastro-intestinal system, such as abdominal pain, diarrhoea, and throat dry. Moreover, the hot taste of "Ya Sa Hat Sa Ta Ra" can also disturb the internal body system, especially the gastrointestinal system.[22] However, there were no symptoms at the certain level of data in the first period.

There needs to be an increase in the number of reports collected to support a higher causality.

According to the 17 AC-products listed in Fig 3, most AEs were the result of herbal formulas and prescriptions that require use of more than one herb. Most of the data, 13 out of 17 product names to be precise, equally reported one symptom each, so the data shows a spread of AEs linked to each TM/HP. Among the 17 product names, "Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion" was the only a single herb that had AE reports. The top four products on the chart have a blended-hot tasted which can generate most of the symptoms linked to use of TM/HPs. "Ayurved Siriraj Brand Ya Hom No.24 Tablets" had the most reported AEs. The four main ingredients of this product included *"Nigella sativa, Coriandrum sativum, Aquilaria crassna,* and *Jasminum sambac"*. However, causality assessment of AEs of single herbs will lead to better conclusion of the result of an adverse event than herbal formulas with multiple compounds.

According to data from AC in Table 2, most of the 17 products had a hot taste or blended-hot taste that led to AEs. "Ayurved Siriraj Brand Ya Hom No.24 Tablets" is frequently used because of its various medicinal properties in stimulating blood circulation, but it also leads to a high number of AEs. In one case it related to chest burning pain. Even though the AE wasn't assessed as the highest causality (certain level), the reliability of the event was strong enough to elicit careful use of this product as supported by data from ADRs in Thailand NLEM regarding a burning gastrointestinal system.[22] The main ingredient, known as Benjakool, is one of the five hot tasting herbs which consists of *Piper longum, Piper sarmentosum, Piper wallicii, Plumbago indica,* and *Zingiber officinale*. Each of them was involved in causing AE symptoms as reported in the table. Similar to Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion, Thailand NLEM recorded how "Ya Chum Hed Ted", prescribed as a stimulant laxative could lead to abdominal pain or abdominal discomfort due to its effect on the contraction of the large intestine. However, in this report, only one case was probably linked to dizziness caused by the nine tastes of traditional Thai medicines. "Chum Hed Ted" has a nauseating taste and among the three patients prescribed herbal formulas, the first patient reported an AE from "Herbal decoction relieving joint pain or inflammation (fruit instead stem of Khi Ka Daeng formula)" which caused abdominal discomfort because the fruit of "Khi Ka Daeng" (*Gymnopetalum integrifolim*) stimulates the bowel system. Meanwhile, the second patient experienced "Herbal decoction relieving menopausal symptoms: Harak formula" which led to an AE relating to her *Imperata cylindica* allergy, which was one of the ingredients of the formula. Lastly, the third patient experienced an AE from "Herbal decoction relieving menopausal symptoms: Benjakool formula" which is made up of 32 crude drugs, including five hot tasting herbs as in "Ya Sa Hat Sa Ta Ra" and "Ayurved Siriraj Brand Ya Hom No.24 Tablets". According to AE results from the herbal formula, Benjakool would be an interesting choice for further pharmacovigilance. In Table 2, almost all of the reports were assessed as possible causality, so that more cases of AE could be gathered to improve our understanding.

TVP-products in Fig 2 and AC products in Fig 3 show AE data from both single herbs and herbal formulas from former study that only presented from single herbs.[6] There was an increase in AEs linked to herbal formulas in this study which had single herbs in both the TVP and AC. Following HPVC policy, promoting careers in health instead of reporting on AEs caused by TMs/HPs led to the increase in reports of herbal formulas in the period this study was conducted. However, across Thailand, single herbs still had more representation in TVP as they were heavily and extensively promoted in the health system for a long period of time. As a result of herbal formulas with many herbs, it was difficult to figure out which herb directly caused symptoms.

In Table 1 and Table 2, products and their causalities relating to symptoms are listed. What is certain that the highest level of causalities which were mostly in TVP rather than at AC. The reason for this is the abundance of data and reports that helped make a strong assessment of those products and their symptoms. The more AE reports that were analyzed, the more statistics there were on hand to study products and symptom causalities. Previous AE reports of the same symptoms resulting from the same product can support the decision of causality results. However, a lowe number of certain results in AC products proved data collection is just in the starting stages and more AE reports are required to ensure causality. With a total of 305 AE reports for *"Andrographis paniculata"*, it far outnumbered the 40 AE reports of "Ya Sa Hat Sa Ta Ra". Meanwhile, collection of AE reports of "Ya Sa Hat Sa Ta Ra" use just started in the first period which means the results are probably to a certain level.

NJA is a convenient tool that helps assess causality between AEs and TMs/HPs in AC. In order to group causality, the tool helped answer and calculate the score of questions. This conventional and scientific method helped interpret AE information relating to herbs. However,

many of the AEs lacked some basic information to answer questions 1, 6, 7, and 10 which caused an incomplete assessment of those reports. The first question was about AE reported for all collection but there was little evidence of it being recorded. Meanwhile, question six was about AEs treated by a placebo to compare symptoms of TMs/HPs, however, this process was not done at AC. Question number seven was about AEs that found a toxic amount of the drug in blood or other fluids but AC did not process these results before the patients were informed. Last but not least, question number 10 was not marked because the event ended before confirmation of any objective evidence. Even though there was no marked point on these four questions, some reports could be calculated to a certain level. NJA is a professional and international assessment tool, however, a proper tool is required for specific assessment of TMs/HPs in the future.

For herbal formulas or combinations of TVP and AC, it was difficult to identify individual herbs that most likely caused an AE. However, expertise in prescribing traditional Thai medicine is required to consider which herbal ingredients cause AE. Using herbs in the early stages of traditional Thai Medicine did not result in systemic records as national evidence. So, details of AEs from herbs were confirmed by experts' experience along with collection of more reports of the same product. For precise assessment, AEs related to a culpable herb, and research about each herb is needed.

Even though pharmacovigilance studies of herbs have been conducted worldwide, this study was designed to look at collected data of AEs at the AC. According to AEs from TVP, there was enough variety for interpretation. Most AE reports showed a high use of herbs and promotion of health careers paying attention to reports. Meanwhile regarding data collection at AC mostly had essential data because of systemically planning ensured patients received a case record form.

Despite the existing TVP reporting systems, the numbers do not represent the incidence of AEs related to TMs/HPs. There are many limitations of our spontaneous reporting system.[28] Regulatory authority programs were unable to capture all occurrences linked to TMs/HPs. The healthcare professionals and consumers' decision on reporting depended on many factors such as their awareness, incentive, as well as the convenience of reporting system. Another limitation was the causality assessment, which depends on expertise of health professionals and other contributing factors (comorbidity, concomitant drugs, and timing). Thus, data from reporting systems can only serve as a screening tool for generating a hypothesis. In spite of these challenges, AE data from TVP and prospective surveillance can provide insight into occurrences of AEs involving TMs/HPs. A well-established program is needed to collect information and systemically categorize association between TMs/HPs and AEs.[29] This program will help ensure the safe use of TMs/HPs. The government should create a policy urging the health professionals to report and collect more AEs. This will ensure the safety of each drug and help to promote product exports from Thailand.

CONCLUSION

The findings show AEs and level of causalities associated with TMs/HPs products in Thailand. More details of each AE symptom and its link to individual single herbs or herbal formula had been seen at the AC. These would help increase the awareness of possible AEs when use some specific TMs/HPs.

It is difficult to identify which herb in a formula may link to occurred AEs. We still need to collect more reports and study each type of herb in vitro, in vivo and in a clinical study.[30-34] Moreover, individual pharmacological studies of each herb serve as strong supporting evidence. The gathering of information of each herb could help clarify the real causality between their AE symptoms. NJA might be a potential tool in assessing the causality between AEs and TMs/HPs. Other specific tool for assessing AEs/ADRs in a single herb, herbal formula, or even combinations of herbs should also be studied.

In order to establish risk-benefit profiles of TMs/HPs, a further study and systemic analyses of the existing information, and intense prospective surveillance is needed. Updated information of the top products associated with AEs, would help promote cautious consumption and reduce AE symptoms in the future.

ACKNOWLEDGEMENTS

We are grateful for the help provided by the Health Product Vigilance Center, Technical & Planning Division, Thai Food and Drug Administration, Ministry of Public Health for retrospective data collection through the national system known as the, Thai Vigibase Program. Regarding the valuable assessment process, we thank the specialist team of Ms.Wimon Suwankesawong, Dr.Sareeya Wechwitan and Dr.Pakawadee Sriphiromya for making the best decisions and providing useful comments regarding the application of Naranjo's alogorithm to score adverse events at Ayurved Clinic. We are also thankful for cooperation in research between the Center of Applied Thai Traditional Medicine and Department of Pharmacology, Faculty of Medicine Siriraj Hospital. We would also like to thank lecturer Suwat Tangjitjaroen,

a traditional Thai medicine expert, and senile teachers at CATTM who provide advice and shared experiences about symptoms caused by traditional medicine. We are also thankful to Miss Phutsadee Pudchakan and Mrs.Panadda Swasdimongkol from the Adverse drug reaction center, Siriraj Hospital for advising the use of NJA to assess causality of AEs in complementary and traditional medicine. We also thank our Adverse Drug Reaction team for creating a routine for the greater unit in CATTM; Ms.Patthanin Sathiansri, Ms.Kalayaporn Termnark, Mrs.Panida Smith, Ms.Natchaya Ziangchin, Mr.Niismael Doloh, Ms.Viewwadee Boonleang, Mr.Pasin Pantuwanich and Mr.Patpanat Hutapaet. Lastly, we thank the Routine to Research unit, Faculty of Medicine Siriraj Hospital for funding this project.

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