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# Signal detection for Thai traditional medicine: Examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk

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ABSTRACT

Herbal containing medicine consumption has increased while the awareness of adverse drug reaction (ADR) was less than conventional medicine. Early detection of unexpected numbers of ADRs from herbal medicines' reports which are abnormal from the whole database needs quantification. Disproportionality analysis has been performed for signal detection by using reporting odds ratio (ROR) as measurement. The impact of having medicine as exposures in each ADR should be measured by using reported population attributable risks (RPAR). This study aimed to quantify the contribution of Thai traditional medicine (TTM) to ADR reports and to assess the association between TTMs and serious adverse drug reactions. Data were retrieved from the adverse drug reaction surveillance database, Thai-Food and Drug Administration from 2002 to 2013. Crude and adjusted RORs for each drug–ADR pair and RPARs were computed. TTM contributed only 0.001% of all serious ADRs reported. Out of 4208 TTM-ADR pairs were examined, three had the statistically significant RORs, namely *Andrographis paniculata* and anaphylactic shock (ROR 2.32, 95% CI 1.03, 5.21); green traditional medicine and Stevens-Johnson syndrome (ROR 13.04, 95% CI 5.4–31.51) and *Derris scandens* Benth and angioedema (ROR 2.71, 95% CI 1.05–6.95). Their RPARs ranged from 0.05% to 0.16%. We conclude that TTMs need more intensive surveillance.



## 1. Introduction

The consumption of herbal medicine has been increasing worldwide. In the United States, more than 30 million adults spent money on complementary and alternative medicines while 7.2 million adults heavily spent money on complementary and alternative medicines (1385 USD) in 2007 (Davis and Weeks, 2012). In 2002, 22.3% of out-patients in a health centre in Sweden had used herbal medicine in the last six months (Al-Windi, 2004). Even though the consumption of herb containing products has been increasing, awareness of risk from adverse drug reaction is less. Less than half (46.6%) of herbal medicine users in Australia realized potential risk associated with herbal medicine (Zhang et al., 2008).

There have been several reports which falsify the belief that using herbal medicines is less harmful. In China, houttuynia injection for infectious disease reported 1232 cases of ADRs (Ji et al., 2009). In Japan Kampo (Japanese herbal used for abnormality of urogenital organ) has been reported to be associated with liver injury (Stickel and Schuppan, 2007). Many countries such as the United Kingdom, the Netherlands, New Zealand and including Thailand, conventional medicine safety information could be obtained from premarketing study, but not for herbal medicine. Therefore information on safety from population-based studies is generally lacking (Farah et al., 2000). Pharmacovigilance of herbal medicine has mostly been performed by the spontaneous reporting system (SRS).

The disproportionality analysis from SRS with statistical approach has been introduced. The analysis aimed to quantify the unexpected number of a drug–ADR pair compared to the expected derived from the whole database which is called a 'signal'. WHO defined signal as *"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously"* (The Uppsala Monitoring Centre, 2013a).

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Several measures can be applied in disproportionality analysis of signal detection, such as the reporting odds ratio (ROR), proportional reporting ratio and information component computed by Bayesian confidence propagation neural network (Kim et al., 2011). However there are advantages and limitations in each method. In Thailand, the Thai-Food and Drug Administration has implemented the reporting odds ratio (ROR) since 2005.

A signal detection tool using ROR as a measurement can be performed for early detection of association of ADRs and Thai traditional medicine (TTM) from a big dataset. However, there are many factors which induce ADRs associated with TTM such as multiple drugs used, age or underlying diseases. A ROR which is generated from the pharmacovigilance database should be adjusted for at least documented potential risk factors in ADR reports to represent the significant association before conducting further investigation.

Additionally the impact of each TTM on each ADR should be estimated. In conventional epidemiology, the population attributable fraction of a risk factor identified from multiple logistic regressions could be estimated (Stafford et al., 2008). In SRS database all the records available could be used instead. The calculated result is reported population attributable risk (RPAR) which indicates the proportion of a specific ADR in the whole dataset that could be avoided if the medicine is removed from use.

The objectives of this study were to quantify the contribution of TTM induced ADRs based on surveillance data and to assess the association between frequently used TTMs and serious ADRs.

## 2. Methods

### 2.1. Source of data

Although the national ADR surveillance system was initiated in 1984, TTMs-induced ADRs were not reported until after 2002. Our analysis was therefore based on reports received during 2002–2013. Herbal anatomic therapeutic chemical classification has been adapted for herbal medicines coding in the pharmacovigilance database. ADRs were coded following the WHO Adverse Drug Reaction Terminology which starts at the body organ level followed by the high level terms (grouping terms). These high level terms contain precise identification of ADRs, called preferred terms (The Uppsala Monitoring Centre, 2014), which were used in this analysis.

ADRs are identified as serious by the reporters following the WHO definition as follows: *"A serious ADR is any untoward medical occurrence at any dose which requires inpatient hospitalization, prolongation of existing hospitalization, is life-threatening, results in persistent or significant disability/incapacity or results in death"* (The Uppsala Monitoring Centre, 2013a). Each report may specify more than one suspected drug and more than one ADR. It is broken down into pairs of drug and ADR. Causality assessment of each drug–ADR pair is evaluated at the reporting health facilities using WHO causality assessment (The Uppsala Monitoring Centre, 2013b) or Naranjo's algorithm (Naranjo et al., 1981) or a local Thai algorithm developed by the Thai-FDA. Those pairs with "unlikely" level of causality were excluded from this analysis. For an ADR report to be eligible for this analysis, the report must contain information about the reporter, any one of the following patient characteristics (HN, patient code, name, age or sex), the ADR and at least one suspected drug.

### 2.2. Calculation of ROR

The records used for computation of ROR start from each year when the TTM was first reported. Each pair of eligible drug–ADR is used for tallying in the below 2-by-2 table. ROR and its 95% CI were then calculated using the following formula (van Puijenbroek et al., 2002a).

| | ADR of interest | All other ADRs |
|---|---|---|
| Herbal medicine of interest | a | b |
| All other drugs | c | d |

$$\text{Reporting Odds Ratio} = \frac{a/b}{c/d}$$

$$95\%\text{CI} = e^{\left[\ln(\text{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right]}$$

a: The number of reports with the interested ADR associated with the interested TTM.
b: The number of reports of other ADRs with the TTM of interest.
c: The number of reports of interested ADR with other drugs.*
d: The number of reports with other ADRs associated with other drugs.*
*Included all conventional and TTM reported.

For a drug to be classified as a potential cause of an ADR, the number of reports must be more than three as well as it having a significant ROR (van Puijenbroek et al., 2002a) with lower limit of 95% confident interval more than one. For each serious ADR, a scatter plot of ROR and the number of reports associated with any drug (conventional medicine and TTM) was done. The drugs with high ROR and/or causing a high number of ADRs are considered as having public health importance. Logistic regression is used to compute RORs adjusted for sex, age, underlying disease, history of allergy and number of drugs used.

### 2.3. RPAR calculation

The reported population attributable risk (RPAR) is calculated from the adjusted ROR using the following formula (Stafford et al., 2008).

$$RPAR = \frac{p({}_aROR - 1)}{{}_aROR} \times 100\%$$

where ${}_aROR$ is the adjusted reporting odds ratio and $p$ is the proportion of all study cases having the specific ADR.

All analyses were done using Epicalc package on R language and environment version 3.0.2.

## 3. Results

Between 2002 and 2013, there were 417,279 verified ADRs reported in the database and of these, 90,737 (21.7%) were serious. Table 1 presents the proportion of missing data of important variables in the national pharmacovigilance database during

**Table 1**
Proportion of missing data of important variables in SRS database.

| Variables | Missing data (%) |
|---|---|
| Gender | 0.3 |
| Age | 8.0 |
| Underlying diseases | 0.7 |
| History of allergy | 1.9 |
| Number of drugs use | 0[a] |

[a] It is mandatory to identify at least 1 drug in every ADRs reports.