COMPLEMENTARY AND ALTERNATIVE MEDICINE: PHARMACOVIGILANCE IN MALAYSIA AND PREDICTORS OF SERIOUS ADVERSE REACTIONS

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COMPLEMENTARY AND ALTERNATIVE MEDICINE: PHARMACOVIGILANCE IN MALAYSIA AND PREDICTORS OF SERIOUS ADVERSE REACTIONS

ABSTRACT

In Malaysia, Complementary and Alternative Medicine (CAM) products are readily available and increasingly used. Associated with their use were reports of serious adverse effects. The Centre for Adverse Drug Reaction (ADR) Monitoring, National Pharmaceutical Regulatory Agency (NPRA) through its spontaneous reporting system has received many reports of serious adverse events associated with the use of CAM products. Yet, we know little about factors associated with serious adverse reactions. The study aimed to describe the pattern of spontaneously reported adverse reactions associated with CAM products and identify risk factors associated with serious reactions. We reviewed and analysed all adverse reactions associated with CAM products (including health supplements) submitted to the NPRA between 2000 and 2014. Data analysed and described included patient demography, characteristics and descriptions of adverse reactions, suspected CAM products, severity and outcome of adverse effects. Adverse reactions were considered serious if the reactions led to death, hospitalisation or prolongation of hospitalisation, that were life-threatening, or that caused significant disability.

From 74,997 of all reports received by the Centre, 930 (1.2%) involved CAM products. Out of these, 242 (26%) were serious with 36 deaths. Most (78.1%) of the reports implicated unregistered products with 16.7% confirmed to contain adulterants which were mainly dexamethasone. Most of the adverse reaction reports involved Malay users (59.9%), followed by Chinese (32.3%) and they were all mostly adults between the ages of 19-60 (65.2%). Those who experienced adverse effects took CAM

products mainly for health maintenance and weight loss (61.2%) while the rest used CAM for chronic conditions such as diabetes mellitus, hypertension, stroke, and cancer. The top two most reported adverse events were related to skin and appendages disorders (18.4%) followed by liver and biliary system disorders (13.7%). Binary logistic regression analysis revealed that serious adverse effects were associated with the variables ethnicity, concurrent disease, concurrent drugs taken and use of CAM for a chronic illness. The odds of experiencing serious adverse effects increased if the respondents used CAM products for chronic illnesses compared to those who used CAM for health maintenance [odds ratio (OR) 1.99, 95% confidence interval (CI) 1.46-2.71], having concurrent disease [OR 1.53, CI 1.05-2.19] and taking concurrent drugs [OR 1.44, CI 1.03-2.02]. Compared to Malay, being of Indian race was associated with decreased odds of experiencing serious adverse effects [OR 0.09, CI 0.01–0.63]. Meanwhile the odds of having serious adverse effects among the race categorised as 'others' increased about 2.7 folds compared to Malay [OR 2.64, CI 1.36–5.13]. The findings of this study provide important information on adverse reactions associated with CAM and may help healthcare professionals and the public take necessary measures to ensure its safe use as some products can be life-threatening.

Keywords: herbal medicines; health supplements; adulteration; spontaneous reports; logistic regression.

UBAT KOMPLEMENTARI DAN ALTERNATIF: FARMAKOVIGILANS DI MALAYSIA DAN PREDIKTOR KESAN ADVERS SERIUS

ABSTRAK

Di Malaysia, produk perubatan komplementari dan alternatif (CAM) mudah diperolehi dan semakin digunakan. Kesan advers yang serius telah dilaporkan berikutan penggunaan CAM. Pusat Pemantauan Kesan Advers Ubat (ADR), Bahagian Regulatori Farmasi Negara (NPRA) melalui sistem pelaporan spontannya telah menerima banyak laporan advers serius berkaitan dari penggunaan produk CAM. Namun demikian, tidak banyak yang diketahui tentang faktor-faktor yang boleh dikaitkan dengan kesan advers serius. Kajian ini bertujuan untuk mengenalpasti corak kesan advers yang dikaitkan dengan produk-produk CAM seperti yang dilaporkan serta faktor risiko kesan advers serius. Semua kesan advers yang dikaitkan dengan produk CAM (termasuk suplemen kesihatan) yang dikemukakan kepada NPRA di antara tahun 2000 hingga 2014 telah dikaji dan dianalisa. Data yang dianalisa merangkumi demografi pesakit, ciri-ciri/huraian kesan advers, produk CAM yang disyaki, tahap serius kesan advers serta hasil kesan advers. Kesan advers dianggap serius jika tindak balas menyebabkan kematian, kemasukkan ke hospital atau pemanjangan jangkamasa hospitalisasi, mengancam nyawa, atau menyebabkan kecacatan ketara.

Dari jumlah 74,997 keseluruhan laporan yang diterima oleh Pusat ADR, 930 (1.2%) melibatkan produk CAM, dan 242 (26%) adalah ADR serius dengan 36 kematian. Kebanyakan (78.1%) daripada ADR yang dilaporkan membabitkan produk tidak berdaftar dengan 16.7% disahkan mengandungi bahan campur palsu terutamanya deksametason. Kebanyakan laporan kesan advers melibatkan pengguna Melayu (59.9%), diikuti dengan pengguna Cina (32.3%) dan majoriti adalah orang dewasa berumur diantara 19-60 tahun (65.2%). Sebahagian besar pengguna yang mengalami

kesan advers mengambil CAM produk untuk penjagaan kesihatan (61.2%) termasuk untuk penurunan berat badan manakala 38.8% yang selebihnya adalah untuk kegunaan bagi penyakit kronik seperti kencing manis, darah tinggi, strok dan kanser. Dua kesan advers tertinggi yang dilaporkan melibatkan sistem organ kulit (18.4%) diikuti dengan hati dan gangguan sistem biliari (13.7%). Analisis regresi logistik binari mendapati bahawa pemboleh ubah etnik, kewujudan serentak penyakit lain, pengambilan bersama dengan ubat-ubatan lain serta penggunaan produk CAM untuk penyakit kronik dikaitkan dengan kejadian kesan advers serius. Kemungkinan seseorang mengalami kesan advers serius meningkat jika produk CAM digunakan untuk merawat penyakit kronik berbanding untuk penjagaan kesihatan [nisbah kemungkinan (OR) 1.99, selang keyakinan (CI) 1.46-2.71], mempunyai penyakit lain serentak [OR 1.51, CI 1.04-2.19] dan mengambil serentak ubat-ubatan lain [OR 1.44, CI 1.03-2.02]. Berbanding dengan Melayu, kaum India dikaitkan dengan kurang risiko mengalami kesan advers serius [OR 0.09, CI 0.01-0.63]. Manakala itu, etnik kaum yang dikategorikan sebagai 'lain' dihubungkait dengan peningkatan hampir 2.7 kali ganda kemungkinan mengalami kesan advers serius berbanding kaum Melayu [OR 2.64, CI 1.36 – 5.13]. Hasil kajian ini memberi maklumat penting tentang ADR yang dikaitkan dengan produk CAM dan boleh membantu profesional penjagaan kesihatan dan orang ramai mengambil langkah-langkah yang perlu untuk memastikan penggunaannya yang selamat kerana sesetengah produk CAM boleh mengancam nyawa.

Kata Kunci: ubat-ubatan herba; suplemen kesihatan; campurpalsu; laporan spontan; regresi logistik.

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LIST OF SYMBOLS AND ABBREVIATIONS

ADR	:	Adverse drug reaction
ALP	:	*Alkaline phosphatase*
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
CAM	:	Complementary and alternative medicine
CHM	:	Chinese herbal medicine
DCA	:	Drug Control Authority
DRESS	:	Drug Reaction with Systemic Eosinophilia Syndrome
DRGD	:	Drug Registration Guidance Document
EICCAM	:	European Information Centre for Complementary and Alternative Medicine
FDA	:	Food and Drug Administration
INR	:	International Normalised Ratio
LFT	:	Liver Function Test
MADRAC	:	Malaysian Adverse Drug Reaction Advisory Committee
MHRA UK	:	Medicines Health Regulatory Agency, United Kingdom
MOH	:	Ministry of Health
MOPI	:	Malaysian Organisation of Pharmaceutical Industries
NCCIH	:	National Centre of Complementary and Integrative Medicine
NPRA	:	National Pharmaceutical Regulatory Agency
NSAIDs	:	Nonsteroidal Anti-inflammatory Drugs
PSD	:	Pharmaceutical Services Division
SOC	:	System-Organ-Class

TEN	:	Toxic Epidermal Necrolysis
TGA	:	Therapeutic Goods Australia
TM	:	Traditional medicine
UK	:	United Kingdom
UK MHRA	:	United Kingdom Medicines & Health Regulatory Agency
UMC	:	Uppsala Monitoring Centre
US	:	United States
US FDA	:	United States Food and Drug Administration
WHO	:	World Health Organization
WHO-UMC	:	World Health Organization-Uppsala Monitoring Centre

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CHAPTER 1: INTRODUCTION

Complementary and alternative medicine (CAM) is an important component of health service and has a long history of use in health maintenance and disease prevention and treatment, particularly for chronic diseases (WHO, 2013). The term Complementary medicine or alternative medicine is often used interchangeably with traditional medicine (TM), also known worldwide as 'natural' medicine, non-conventional medicine, or holistic medicine (Mandel, 2009). In Malaysia, for regulatory purposes, CAM is used synonymously with the term TM that also includes health supplements. The World Health Organization (WHO) 2014 statistics reported that in Europe, over 100 million people use CAM with one-fifth of Europeans being regular users (EICCAM, 2008) while in China, CAM accounts for approximately 40% of all health-care delivered (WHO, 2013). CAM is also widely used in Malaysia (Aziz & Tey, 2009; Mahmud et al., 2009; Johny et al., 2017) with an out-of-pocket spending of about USD85.8 (RM353) million in 2016, an increase of 33% from USD64.2 (RM264) million in 1997 (MOH, 2018). The Malaysian Organisation of Pharmaceutical Industries estimated total market size in 2009 for CAM products to be RM3 billion, in comparison to RM4.5 billion for prescription and over the counter medicine (MOPI, 2019).

CAM products are often perceived as being natural with the assumption that it is completely safe and harmless (WHO, 2004; Dunn et al., 2005; Johny et al., 2017), but the fact is, some CAM may cause direct and indirect harm to humans (Ernst, 2004; Myers & Cheras, 2004). Numerous adverse effects such as nephrotoxicity, hepatotoxicity, and allergic reactions have been attributed to CAM (Nelson & Perrone, 2000; Niggermann & Grüber, 2003). Some CAM substances have caused cancer and even death (Nortier et al., 2000; Pittler & Ernst, 2003).

Risks associated with CAM include use of poor quality, adulterated or counterfeit products, and exposure to misleading or unreliable information (Ernst, 2002; Ventola, 2010; WHO, 2013). The adulteration of CAM preparations is an illegal practice and nearly 30% of CAM products confiscated by the Malaysian Regulatory Authority were tested and found to contain controlled medicines (Pharmaceutical Services Division, 2015). Thus, the increasing popularity of CAM products with their associated safety issues worldwide and in Malaysia, reflects the need to increase CAM pharmacovigilance activities.

A major problem associated with the pharmacovigilance of CAM products is under reporting by health professionals and consumers. While healthcare professionals are required to report ADR, they often do not take reporting seriously, probably partly due to absence of penalty for failure to report (Tabali et al., 2012). Meanwhile, most patients are unwilling to tell their healthcare professionals about their use of CAM products, so any adverse reactions or impact on their clinical outcomes could not be associated with CAM (Strouss et al., 2014; Gan et al., 2015).

Even though CAM use is widespread in Malaysia, we know little about its safety, types of products involved, types of adverse reactions, the seriousness and factors associated with it. Thus, this study aimed to analyse and describe the pattern of adverse reactions associated with the use of CAM products and to identify factors associated with serious adverse reactions. It is crucial to examine all the reported cases especially serious reactions related to CAM products as they can be life threatening, and identify the causes whether they are due to the compounds or substances in the products or other issues such as adulteration with controlled medicines.

CHAPTER 2: LITERATURE REVIEW

2.1 Definitions of Complementary and Alternative Medicine (CAM)

The term "complementary medicine" means complements the standard medical practices; an add-on treatment to the conventional ones, while the term "alternative medicine" refers to the medical treatment to replace the standard practices. CAM has many definitions and various organisations have defined it differently. For example, the World Health Organization defined CAM as 'a broad set of healthcare practices that are not part of a country's own tradition and not integrated into dominant healthcare system' (WHO, 2013). The National Centre for Complementary and Integrative Health (NCCIH), US Department of Health and Human Services meanwhile uses the term "complementary health approaches" to discuss practices and products of non-mainstream origin (NCCIH, 2016). NCCIH classifies CAM into three main types:

a) Natural products such as herbal medicine and dietary supplements
b) Mind and body medicine, for example, meditation, yoga, and acupuncture
c) Manipulative and body-based practices which include spinal manipulation and massage therapy

For the purpose of our study, the term CAM covered the first category of the NCCIH's classification (i.e. natural products such as herbal medicine and dietary supplements).

In Malaysia, CAM or natural products namely TM and health supplements are regulated by the NPRA. TM is defined as any product used in the practice of indigenous medicine; in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, or parts thereof; in the unextracted or crude extract form; and homeopathic medicine (NPRA, 2019). TM most commonly used are

Malay TM, Chinese TM, Indian TM (Ayurvedic medicine) and homeopathy. Health supplements encompass any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body and may contain among other ingredients vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances (NPRA, 2019).

2.2 Use of CAM Products

CAM has maintained its popularity and since the 1990s its use has surged in many developed and developing countries (WHO, 2013). In East Asia countries such as Japan, South Korea and Malaysia, the prevalence of population visiting CAM practitioners was estimated to be more than 50%, which is higher than other developed countries such as United States of America and United Kingdom (Harris et al., 2012).

In the US, almost four out of ten adults used CAM products and the non-vitamin, non-mineral, natural products such as fish oil, glucosamine and Echinacea and these products constitute almost 20% of total consumption (Barnes et al., 2008). The estimated expenditure for spending on CAM products amounted to USD 14.8 billion which is nearly 44% of total spent on CAM out-of-pocket and equivalent to approximately one-third of total out-of-pocket spending on prescription drugs (Nahin et al., 2007).

Meanwhile, in Malaysia the use of CAM particularly biological-based therapies including herbal therapy, is widespread. Consumers commonly use CAM for treating health problems and general health maintenance (Mahmud et al., 2009) with most using CAM besides their conventional medicines (Farooqui et al., 2015). Another Malaysian study involving patients with cardiovascular risk factors also showed a high preference for combining therapies while 20-30% substituted their conventional medications with CAM (Kew et al., 2015). Respondents from the younger age group of 18-40 years,

those with a high educational level and those with high income preferred the combination of both conventional and CAM (Kew et al., 2015).

2.3 Factors associated with CAM use

Several studies have reported that CAM users are female, of middle age and have higher education (Eisenberg et al., 1998; Tindle et al., 2005; Bishop & Lewith, 2008). Similarly, a Malaysian study reported that herbal medicines users are female, married, with health problems and with higher income levels (Aziz & Tey, 2009). Female patients were also more likely to use more than one CAM therapies (Gan et al., 2015). A more recent study supported CAM use to be significantly associated with gender, level of education, employment status, and monthly income (Farooqui et al., 2015).

Use of CAM in patients with a chronic illness such as diabetes and life-threatening diseases such as cancer is also common (Edge et al., 2002; Yeh et al., 2002; Molassiotis et al., 2005; Ching et al., 2013; Gan et al., 2015; Farooqui et al., 2015). A study involving Type 2 Diabetes mellitus patients from a health clinic in Malaysia also showed that CAM use was high, with females almost twice more likely to use CAM than males (Ching et al., 2013). Biological therapy especially the herbs bitter gourd (Momordica charantia) and "Misai Kucing" (Orthosiphon Stamineus Benth) are most popular, with Malays being the most frequent users (Ching et al., 2013). The prevalence of CAM use in haematological cancers was also high with biological-based therapies particularly health supplements and folk or herb remedies being most common. The same study found that the most common reason reported for CAM use was to boost immunity with most patients felt CAM was effective (Gan et al., 2015). Relieve of pain and symptoms were also reasons for CAM use in cancer patients (Al-Naggar et al., 2013).

2.4 Safety of CAM products

Compared to conventional drug treatments little is known about the relative safety of CAM products (Ernst, 1998). Even though some CAM products have been shown to have clinical benefits, their pattern of side-effects is similar to that observed with the use of conventional medicine (Niggemann & Grüber, 2003).

Users of CAM products can experience allergic reactions, toxic reactions, adverse effects related to their desired pharmacological actions, possible mutagenic effects, drug interactions, drug contamination and mistaken plant identities (Ernst, 1998; Myers & Cheras, 2004). Hypersensitivity reactions varying from transient dermatitis to anaphylactic shock have been reported (Perharic et al, 1993; Mullins, 1998) and there is also significant evidence that herbal medicines can cause serious adverse reactions (Farah et al., 2000).

The critical intrinsic factor that may influence the safety of CAM preparations, particularly herbal medicine is misidentification of compounds. Complex botanical identification has led to this problem (Ernst, 1998; Myers & Cheras, 2004). As an example, a plant *Angelica polymorpha* (formerly known as *Angelica sinensis*) is also known as “dong quai”, “dong guai”, “danggui”, and “tang kuei” and this can be confusing.

The contamination of medicinal plants from sources such as chemicals, pesticide residues, microorganisms, heavy metals, aflatoxins and radioactive substances is an important extrinsic factor that can lead to toxicity and also contribute to the cause of adverse reactions (Corns, 2003; Myers & Cheras, 2004).

Safety of CAM products also depends on consistency of their composition and biological activities. However, this is difficult to achieve due to the failure to identify

marker compounds (Myers & Cheras, 2004). Also, the variables such as growing environment, genetic variation and insufficient information on CAM active ingredients pose obstacles to standardisation (Marcus & Grollman, 2002). This lack of standardisation hinders the ability to ensure a safe and optimal concentration of such compounds.

Risks associated with CAM products can also include the use of poor quality, adulterated or counterfeit products and exposure to misleading or unreliable information (WHO, 2013). A CAM preparation is considered being adulterated when conventional medicine is added to CAM substances (Marcus & Grollman, 2002; Myers & Cheras, 2004). Chinese herbal medicines are widely available and becoming more popular but they are often adulterated with one or even more conventional drugs (Yoe et al., 2001; Ernst, 2002; Sarker, 2014). The adulteration with substances such as phenylbutazone, phenytoin, glibenclamide and corticosteroids are associated with serious adverse reactions (Ernst, 2002).

2.5 Serious adverse reactions due to CAM products

Serious adverse reactions as defined by WHO refer to "unintended medical occurrences that can cause death, require inpatient hospitalisation or prolongation, persistent or significant disability and also life-threatening; which may occur at any doses of the pharmaceutical product" (WHO, 2002). Over the years, many CAM products or components related to CAM adverse reactions have been reported. The adverse reactions reported vary in severity from mild to lethal (Mullins, 1998; Niggemann & Grüber, 2003; Ventura et al., 2006). CAM products are reported to cause serious adverse effects involving the following organ disorders:

2.5.1 Skin Disorders

Several CAM products, often reported to cause hypersensitivity reactions, are shown in **Table 2-1**. The most frequent adverse reactions involving skin is contact dermatitis (Simpson et al., 2004; Ventura et al., 2006). Other cutaneous reactions reported are urticaria-angioedema, maculopapular eruptions, photosensitivity reactions and the more serious; Steven-Johnson syndrome (Niggemann & Grüber, 2003; Ventura et al., 2006).

Table 2-1: **List of CAM products associated with hypersensitivity reactions**

Components of CAM products associated with hypersensitivity reactions
• Compositae family (*Arnica montana, Inula helenium, chamomile, Echinaceae angustifolia*) • Cucurbitaceae (*Echalium elaterium*) • Ginkgo biloba • *Glycyrrhiza glabra* • *Hypericum perforatum* • *Ophiopogonis japonicas* • Orange oils (*Citrus bergamia*) • *Pfaffia paniculate* • *Polygala tenuifolia* • Propolis • *Psoralea corylifolia* • *Rhus toxicodendron* • Rutaceae family (*Citrus hystrix*) • Tea tree oil

Adapted from Ventura et al., (2006)

2.5.2 Liver System Disorders

CAM may contain toxic substances that can induce liver toxicity ranging from the transient elevation of liver enzymes to sudden liver failure, and many challenges are faced in making diagnosis (Haller et al., 2002). Kava, a natural herbal supplement recommended for anxiety and to boost sleep has been reported to cause liver failure (Pittler & Ernst, 2003). Another product, Hydroxycut® used for weight loss was reported to cause hepatotoxicity possibly due to the presence of potentially hepatotoxic

components such as *Garcinia cambogia* and *Camelia sinensis* (Stevens et al., 2005; Dara et al., 2008).

2.5.3 Urinary System Disorders

Nephropathy has also been associated with CAM, and Chinese herbal preparations being the most commonly implicated products (Cosyns et al., 1994; Depierreux et al., 1994; Ernst, 1998; Niggermann & Grüber, 2003). The substance implicated for the nephrotoxic event is aristolochic acid (Depierreux et al., 1994; Ernst, 1998; Nortier et al., 2000). Chinese-herb preparation, which contains *Aristolochia fangchi*, has been confirmed to cause urothelial carcinoma (Nortier et al., 2000). The cumulative dose of the herb is reported to be proportional to the risk of the patient suffering from its carcinogenic effect.

2.5.4 Cardiovascular Disorders

CAM preparations have been reported to cause cardiovascular disorders, not only among patients with cardiovascular diseases but also among consumers who only take CAM products as a supplement (Haller & Benowitz, 2000; Wood et al., 2003). For example, a dietary supplement used for weight loss containing a combination of ephedrine alkaloids, caffeine, and other ingredients caused ventricular arrhythmia, which resulted in cardiac arrest (Haller & Benowitz, 2000).

2.5.5 Central Nervous System Disorders

CAM has also been reported to cause serious central nervous system disorders such as stroke, transient ischaemic attack and seizure. A common example is a dietary supplement containing ephedra alkaloids which is also known as “Ma Huang” has been associated with severe cerebrovascular events (Haller & Benowitz, 2000).

2.6 Regulatory Control of CAM Products

Even though CAM has been widely used in medical practice, very few countries have developed a national CAM policy (Bodeker & Kronenberg, 2002). One of the goals of the WHO Medicine Strategy 2014-2023 (WHO, 2013) is to address the promotion of safe and effective use of CAM through regulation. This is an important key element of a national CAM policy apart from other elements such as the definition of CAM itself, consideration of intellectual property issues and strategies for achieving the policy objectives. There has been significant progress with a record of 69 Member States having developed a CAM policy and, 119 member states regulating herbal medicines in 2012. The majority of Member States had voiced difficulty in addressing regulatory issues such as the lack of appropriate mechanisms to control and regulate herbal products including advertising and health claims (WHO, 2013).

In Malaysia, CAM practice is regulated by the Traditional and Complementary Medicine Division, Ministry of Health Malaysia (MOH) while CAM products are required to be registered by the Drug Control Authority (DCA) under two separate product categories: TM and Health Supplements. Products in these two categories have been regulated since 1992 under the Control of Drugs and Cosmetics Regulations 1984 (revised 2006). The National Pharmaceutical Regulatory Agency (NPRA) is the Secretariat to DCA.

Regulatory control of CAM products is through (i) evaluation of the quality and safety of products and (ii) licensing of CAM providers or manufacturers. CAM products are not subjected to rigourous tests to prove its efficacy. Nevertheless, The DCA requires the responsible companies to provide evidence that the products are formulated with known safe ingredients and are manufactured according to the quality processes as stipulated under Good Manufacturing Practice. Pre-registration tests are routinely

conducted to detect adulterants in TM. As part of the post-market surveillance and enforcement activities, market sampling to test CAM products is conducted regularly. Besides, public health measure of adverse event reporting is in place to safeguard the public.

As a result of regulation and continuous safety monitoring, regulatory agencies worldwide including Malaysia have taken action to prohibit or limit the use of herbs with safety issues such as ephedra (US FDA, 2004), aristolochic acid (MHRA, 2001; NPCB, 2001; TGA, 2001) and kava (NPCB, 2001; MHRA, 2002) to protect consumers from harm.

2.7 Pharmacovigilance of CAM Products

The concept of pharmacovigilance is usually not well understood, either by health professionals, patients or the general population even though it is important for the safe use of drugs (WHO, 2006). WHO defines pharmacovigilance as "the science and activity relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" (WHO, 2002). The important purpose of pharmacovigilance is to improve patient care and safety with the use of medicines including CAM.

Pharmacovigilance involves the complex and vital relationship between a broad range of partners including the WHO Quality Assurance and Safety Medicine team, the Uppsala Monitoring Centre, the National Pharmacovigilance Centres, hospitals and academia, health professionals and patients (WHO, 2002). It has become crucial and inevitable to include CAM in pharmacovigilance systems due to their high consumption globally and identify the risks related to their use (Shetti et al., 2011). Many pharmacovigilance centres worldwide have incorporated monitoring the safety of CAM in their existing national pharmacovigilance systems (WHO 2006).

In Malaysia, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) was established under the Drug Control Authority (DCA) to perform the function of pharmacovigilance for drugs (including CAM) registered for use in Malaysia as well as provides advice to DCA on drug safety matters for further regulatory action. The Centre for ADR Monitoring as the secretariat to MADRAC actively promotes and manages all spontaneous ADR reports in Malaysia including performing initial causality assessment. They also disseminate information on drug safety matters to healthcare professionals and the general public.

2.8 Current Reporting System for ADR in Malaysia

ADR reporting was first initiated in Malaysia in 1987 and the Centre for ADR Monitoring was accepted as the 30th Member of the WHO Drug Safety Monitoring Programme in 1990. Malaysia implements a spontaneous ADR reporting system, a method which is widely used in pharmacovigilance (WHO, 2006) and is defined as "a system whereby case reports of adverse drug events are voluntarily submitted by healthcare professionals and pharmaceutical manufacturers to the national regulatory authority" The Malaysian DCA encourages health professionals to voluntarily submit ADR reports especially those that are serious, unexpected or unlabeled. However, it is compulsory for product registration holders which include licensed manufacturers, wholesalers or importers to report the incidence of any adverse reactions as per Section 28, Control of Drugs and Cosmetics Regulation 1984, Sales of Drugs Act 1952 - revised 1989 (NPRA, 2016).

MADRAC provides prepaid postage report forms to encourage reporting. Reports can also be submitted online. Reporters are required to provide information such as patient details, description of the ADR, suspected drug including CAM products, relevant investigations or laboratory data, relevant medical history and also details of

the reporter. However, the main hindrance to documenting the suspected ADR is due to reporters not providing crucial information such as the onset of ADR and concurrent drugs taken by patients.

The ADR reports received are subsequently entered into the NPRA pharmacovigilance database if there is adequate information regarding the name of suspected drug, suspected drug reaction and details about the reporter and patient. Suspected drug reactions are reported based on system-organ classes as specified by WHO-UMC (**Appendix A).** ADR reporting gives a significant impact on the safety issues of drugs, whereby recommendations on drug usage and policies can be made from all the data available in the database.

2.9 Definition and types of ADR

The World Health Organization-Uppsala Monitoring Centre defines an ADR as "a response which is noxious and unintended, which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function" (WHO, 2002). The occurrence of the adverse reaction is suspected to be caused by the drug (including CAM) or treatment, as being judged by the reporting healthcare professional.

ADR can be classified into five types; A, B, C, D and E. Also known as augmented ADR, type A reaction is more common than type B. The reaction is predictable from the pharmacological properties of the drug. An example is psychosis caused by "Ma Huang" that contains ephedrine (Doyle & Kargin, 1996). A Type B adverse reaction is idiosyncratic and occurs less frequently and it includes immunological reactions like maculopapular rashes due to ayurvedic preparation (Ajanal & Prasad, 2013). Type C are reactions with chronic effect and normally associated with long-term effect of drug therapies such as adaptive changes and withdrawal effects as can be evidenced by the

induction of iatrogenic hyperadrenocorticism occurring with chronic use of corticosteroids. Type D reactions, also termed as delayed ADR, are reactions that occur after prolonged exposure to a drug while type E reactions occur when drug treatment is terminated suddenly as in adrenocortical insufficiency after glucocorticoid termination (Bennet & Brown, 2008; Walker & Whittlesea, 2012).

2.10 Causality assessment of ADR

Causality assessment is a practical tool used to classify the relationship between the suspected drug and adverse reaction in the assessment of case reports (UMC, 2019). WHO-UMC causality assessment system is being used in Malaysia which is a standardised case causality assessment and it provides a better evaluation of the risk-benefit profile of drugs (Hoe et al., 2007; UMC, 2019). Similar causality assessment method is carried out to classify adverse reactions reported for CAM products. However, there are several limitations to the WHO-UMC system whereby (i) it cannot give an accurate quantitative measurement of relationship likelihood, (ii) unable to quantify the contribution of a drug to the development of an adverse event nor (iii) can it prove the connection between drug and event (Meyboom et al., 1997). To minimise the limitations on causality assessment, all possible causations and causal chain of events to the adverse effect need to be considered and evaluated in determining the most accurate relationship between the suspected drug and adverse reaction (Edwards, 2012). The causality categories with their assessment criteria are as listed in **Table 2-2.**

Table 2-2: WHO-UMC Causality Category

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with
Adapted from: The use of the WHO-UMC system for standardized case causality assessment (*the* Uppsala Monitoring Centre, 2012)

2.11 Issues related to causality assessment of CAM adverse reactions

Several issues that may affect causality assessment of adverse reactions reports are as follows:

2.11.1 Mixture of active compounds in CAM products

One plant alone may consist of a wide variety of substances that are difficult to identify, hence causing confusion on which component contributes to the adverse reaction reported. For example, tea tree oil consists of more than 100 components (Brophy et al., 1989). The complex mixtures of chemicals in plants might also enhance the risk of chemical interactions either causing additive, synergistic or antagonistic effects. This may potentiate the occurrence of adverse reactions.

2.11.2 Insufficient data in adverse drug reaction report

The incomplete details submitted in the ADR reporting form is one of the obstacles in assessing the causality of the reported adverse reaction. Most CAM consumers do not report their medical history or other medications they are taking and thus lead to an inaccurate conclusion of the suspected adverse reactions. There is not enough evidence to prove that the CAM is solely responsible for the adverse reaction.

2.11.3 Confounders

There are associated confounders that can trigger adverse reactions in CAM use. Concurrent conventional medication taken with CAM for example have been documented to result in interactions that can lead to the inactivation or enhancement of pharmacological activity of either one or both constituents. For example, St. John's wort used for patients with mild to moderate depression. When St. John's wort is taken with other drugs like cyclosporine, amitriptyline or indinavir, it reduces the serum concentrations of these drugs since it is the inducer of cytochrome P450 3A4 (CYP3A4) enzymes (Izzo & Ernst, 2001). As a result of this drug-herbal interaction, a number of heart transplant patients had experienced rejection when they took St John's wort concurrently with cyclosporine (Ruschitzka et al., 2000).

CAM remedies are often used to treat chronic diseases like diabetes, hypertension and even cancer. Some adverse reactions of CAM substances are similar to symptoms of the disease; therefore it is difficult to distinguish which one is causing the reaction; the disease or the remedy (Winslow & Kroll, 1998).

2.12 Under-reporting of ADR

Another problem associated with safe use of medicines including CAM, in general relates to inadequate reporting of ADR by health professionals and consumers. While physicians are obligated to report ADR, the reporting is often taken lightly since there is no penalty for not reporting (Tabali et al., 2012). Under-reporting of ADR by Malaysian physicians is also of concern and one Malaysian study showed that the predictors for under-reporting are associated with uncertainty in reporting the types of ADR, lack of awareness about the existence, function and purpose of reporting (Aziz et al., 2007).

Another issue with the use of CAM is that, not all patients are willing to tell their healthcare professionals what CAM products they are using, so any suspected adverse effect or impact on the medical care outcome cannot be linked to CAM used (Strouss et al., 2014; Gan et. al, 2015).

CHAPTER 3: AIM AND OBJECTIVES

The aim of the study was to describe the pattern of spontaneously reported adverse reactions associated with CAM products and identify risk factors associated with serious adverse reactions.

The specific objectives are:

i. To classify the categories of CAM products and their indication of use
ii. To classify the adverse effects associated with CAM products
iii. To identify factors associated with serious adverse reactions

CHAPTER 4: METHODS

4.1 Data collection

All spontaneous adverse reactions associated with CAM reported to NPRA from January 2000 and 31 December 2014 was identified from the MADRAC database. Based on the report numbers, original ADR reports were retrieved from the specific folders. A copy of the ADR reporting form is attached as **Appendix B**. Since many CAM products may contain up to 20 ingredients, only names of products were documented. CAM ingredients are ingredients used to formulate a certain CAM product. For registered CAM products, it is mandatory to list the CAM ingredients on its labels. Selected registered products with list of CAM ingredients are attached as **Appendix C.** All adverse reaction terms as described in the ADR reports were extracted. The term 'severe' is used in the data entry of MADRAC database. However, it is not synonymous with serious as the term 'severe' is used to describe the intensity of adverse events while seriousness is based on patient outcome of reactions that led to death, hospitalisation or prolongation of hospitalisation, life threatening, or that caused significant disability. The WHO-UMC guideline used by the Pharmacovigilance Centre to standardise case causality assessment with terms "certain," "probable," "possible," "unlikely" and, "unclassifiable" was recorded.

The inclusion and exclusion criteria were as follows:

Inclusion Criteria

i) Products with at least one CAM ingredient as the suspected agent
ii) Adverse effects which involve CAM that contains natural products and health supplements

Exclusion criteria:

i) Adverse reaction reports involving animals

ii) Adverse effects which involve mind and body medicine and manipulative and body-based practices

iii) Incomplete/duplicate reports

The relevant information from the reports was extracted using a standardised data collection form (**Appendix D**). Information retrieved were as follows:

- patient's age, sex, race
- description of adverse reactions
- WHO System Organ Classification of the adverse reactions
- extent (mild, moderate, severe) and outcome of the adverse reaction (s)
- details of the suspected CAM products and registration status
- concurrent drug and disease

4.2 Data analysis

Data were coded, entered and subjected to statistical analysis using Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago IL, USA). Descriptive statistics were used to describe the demographic characteristics of the patients, reporters, details of CAM products and the reports. The results were expressed as the number of reports (n) or as the percentage of the total number of reports (%). Data for continuous variables were reported as the mean ± standard deviation (SD).

To explore differences between groups which involve comparing percentages, Chi-Square (χ^2) test was used to examine the association of categorical variables with the outcome of ADR.

4.3 Model building for predicting factors associated with serious adverse reactions

Univariate logistic regression analysis was then performed to identify variables for inclusion into the model. Statistical significance at $p < 0.10$ level was used to determine the significance of variables for inclusion into the model (Bursac et al., 2008).

''Concurrent disease'' was regarded as dichotomous variables and coded 0 = ''No'' response and 1 = ''Yes'' response. Nominal scale variable with more than two levels (such as ethnicity) were entered as $k-1$ dummy variables. For the ethnic variable, Malays was treated as the reference group as they form the major race group compared to Chinese, Indian and other races. For ordered categorical data with more than two levels, the variable was entered as $k-1$ dummy variables with the lowest level used as the reference group. A multivariate logistic regression analysis was performed to predict serious adverse reactions with an initial model that included as independent variables all factors found to be significant ($p < 0.10$) from the univariate logistic regression analysis. The variable sex which was not significant in the univariate logistic regression analysis was forced into the multivariate logistic regression analysis to see whether it is a contributing factor considering many studies have shown that the gender female has been associated with high use of CAM (Tindle et al., 2005; Bishop & Lewith, 2008; Aziz & Tey, 2009; Kristoffersen et al.; 2014; Farooqui et al., 2015; Alwhaibi et al., 2016).

CHAPTER 5: RESULTS

5.1 Characteristics of the adverse reaction reports

Out of 74,997 reports available from the ADR database from 2000-2014, 930 reports with 1816 adverse events were related to CAM. The age of patients involved with the CAM adverse reactions ranged between three days and 94 years. The mean age of patients was 46.1± 37.1 years and the median age was 47 years. The majority (88%) was adults above 18 years. **Table 5-1** shows more than 50% of the reports involved female patients and Malays (59.9%).

Nearly half of the total reporters were pharmacists. Hospitals contributed the most in ADR reporting with 87% of the total reports, while the lowest source of ADR reports was from community pharmacies. Most of the adverse effects reported by hospital pharmacists were the result of patients' hospitalisation. Only 21.9% of CAM products involved were registered with the DCA.

Table 5-1: Characteristics of reporters, patients and registration status of CAM products

Variables	No. of reports (%) (n=930)
Sex	
Male	407 (43.8)
Female	523 (56.2)
Race	
Malay	557 (59.9)
Chinese	300 (32.3)
Indian	32 (3.4)
Others	41 (4.4)
***Age**	
Neonates (<1 month)	22 (2.4)
Infants (1- 12 months)	6 (0.6)
Children (1-12 years)	39 (4.2)
Adolescent (13-18 years)	25 (2.7)
Adults (>18 years)	606 (65.2)
Elderly (> 60 years)	213 (22.9)
***Types of reporter**	
Pharmacist	447 (48.1)
Doctor	350 (37.6)
Consumer	31 (3.3)
Pharmaceutical Industry	10 (1.1)
Unknown	80 (8.6)
Others	7 (0.8)
***Sources of ADR reports**	
Hospital	809 (87.0)
Institution under Ministry of Higher Education	17 (1.8)
Clinic	26 (2.8)
Community Pharmacy	8 (0.9)
Drug company	10 (1.1)
Others	38 (4.1)
Unknown	4 (0.4)
Product registration status	
Registered	204 (21.9)
Unregistered	726 (78.1)

*Missing data was not counted

5.2 Category of CAM products

Chinese traditional medicines were the most reported with almost half of total reports followed by Malay traditional medicines (**Table 5-2**). The number of adverse events was on average two per report for all categories of CAM products. In the reports received, Chinese traditional medicines were sometimes labeled as such without any

proper names and also implicated were herbs, ginseng products and mushroom "Lingzhi" also known as ganoderma or ganocelium. For the Malay traditional medicines, commonly suspected substances were "Maajun", "Jamu", and "Gamat" products. Fewer reports were received for health supplements (15.3%) and the adverse effects were commonly related to acai berry, bee products (such as propolis and royal jelly) and spirulina.

Table 5-2: Category of CAM products reported and adverse events

Category of CAM Products	Number of Reports (%)	*Number of Adverse Events (%)
Chinese Traditional Medicine	403 (43.3)	795 (43.8)
Malay Traditional Medicine	315 (33.9)	606 (33.4)
Health Supplements (e.g. spirulina, bee products)	144 (15.5)	278 (15.3)
Other Traditional Medicines (e.g. Ayurvedic medicine, Homeopathy)	68 (7.3)	137 (7.5)

***** A report may contain more than one adverse event

5.3 CAM products and indication of use

Majority (61.2%) reported use of CAM products for general health including weight loss while the remaining 38.8% were for use in chronic conditions such as diabetes mellitus, hypertension, stroke and cancer.

5.4 Adverse effects associated with CAM products

5.4.1 Adverse effects classified by WHO System-Organ Class (SOC)

From the 930 reports, a total of 1816 adverse events were documented involving 28 WHO system-organ classes (SOC). At least one adverse event was reported in each report with one reporting a maximum of 10 events. **Figure 5-1** lists the top 15 out of 28 SOC encompassing 96% of total reported adverse reactions. Skin and Appendages disorders were the most common adverse reactions to be associated with all categories of CAM products with 18.4% of the total number of adverse events. The second highest

involved the Liver and Biliary system which contributed 13.7% of total adverse effects reported followed by Gastrointestinal disorders (12.3%), Body as a whole-general disorders (11.8%) and Urinary System disorders (8.7%). Other SOC namely Endocrine system disorders, Central & Peripheral Nervous System disorders and Metabolic & Nutritional disorders constituted five percent each of total reports.

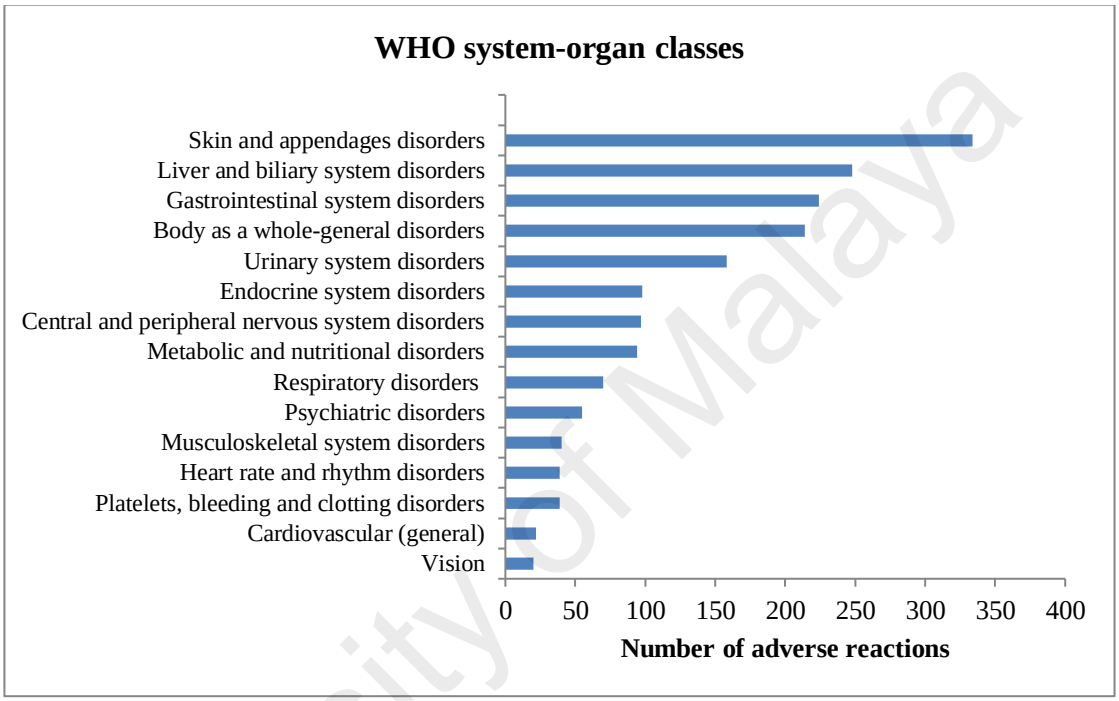

Figure 5-1: **Number of common adverse reactions by WHO system-organ class (2002-2014)**

5.4.2 Adverse effects according to category of CAM products

Figure 5-2 shows skin reactions were the most commonly reported for all categories of products; with health supplements being the most with nearly one-third of all reactions in its category closely followed by other traditional medicines. Chinese traditional medicines had the least problems with skin reactions with almost twice less compared to health supplements. Details of adverse events are as shown in **Table 5-3.**

Liver and biliary disorders in Malay traditional medicine users were high with 15.7% of total adverse events. Body as a whole-general disorder such as fever, generalised

weakness, peripheral oedema, fatigue, body ache, back pain was common adverse events generally occurring in consumers of Chinese traditional medicines (14.7%). Urinary system disorders were least problematic with Chinese traditional medicines and health supplements reporting only 7.3% and 7.9% of all adverse events in each category respectively as compared to the rest ranging from 10-12%.

Endocrine system disorders such as Cushing's syndrome, Addison's disease and Addisonian crisis, which is a medical emergency and potentially life-threatening situation was problematic with the use of Malay traditional medicine (8.1% of adverse events) as compared to Chinese traditional medicines (5.4%).

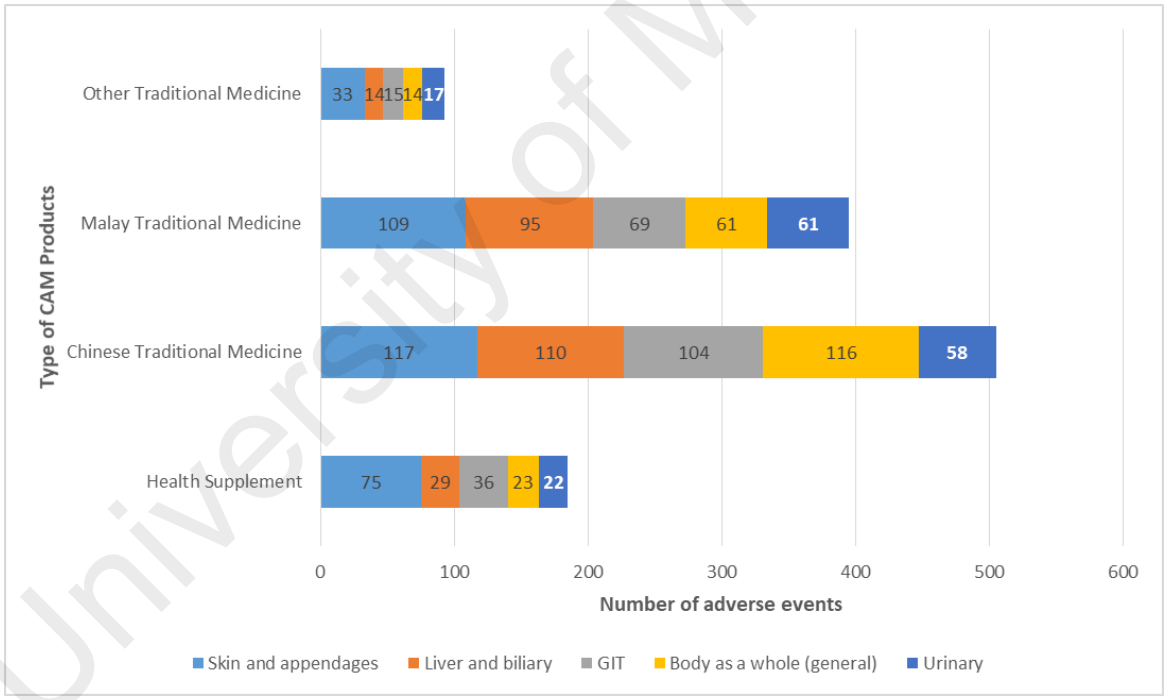

Figure 5-2: Top 5 adverse events reported according to CAM product categories

Table 5-3: **Most common types of adverse events reported to MADRAC**

WHO system-organ classes	Total number of adverse events (%)	Types of adverse events
Skin and appendages disorders	334 (18.4)	Rashes, itchiness, pruritis, erythema, urticaria, acne, striae, exfoliative dermatitis, dry skin, eczema, psoriasis aggravated, SJS, DRESS, abnormal pigmentation.
Liver and biliary system disorders	248 (13.7)	Acute hepatitis jaundice, increased hepatic enzymes, acute hepatic failure, increased ALT, increased ALP, increased AST, abnormal liver function tests, hepato-splenomegaly, cholecystitis, increased bilirubin.
Gastrointestinal system disorders	224 (12.3)	Vomiting, abdominal pain, diarrhoea, gastritis, acute pancreatitis, GI bleeding, nausea, epigastric pain not food-related, bloating, lips swelling non-specific, heartburn.
Body as a whole-general disorders	214 (11.8)	Fever, generalised weakness, peripheral oedema, fatigue, body ache, back pain.
Urinary system disorders	158 (8.7)	Acute renal failure, increased blood creatinine, legs oedema, urine discolouration, haematuria, interstitial nephritis, nephrotic syndrome, increased blood urea.
Endocrine system disorders	98 (5.4)	Cushing's syndrome, moon face, decreased cortisol, Addison's disease, Addisonian crisis,
Central and peripheral nervous system disorders	97 (5.3)	Headache, giddiness, numbness, dizziness, spasm, eye gaze upward, faintness, convulsions, epilepsy.
Metabolic and nutritional disorders	94 (5.2)	Weight gain, hypokalaemia, hypoglycaemia, hyperglycaemia, weight loss, metabolic acidosis, diabetic ketoacidosis, hyponatraemia, hyperkalaemia, diabetes mellitus.
Respiratory disorders	70 (3.8)	Shortness of breath, palpitation, sore throat, coughing, wheezes.
Psychiatric disorders	55 (3.0)	Lethargy, loss of appetite, increased appetite.
Heart rate and rhythm disorders	39 (2.1)	Bradycardia, tachycardia, others.
Platelets, bleeding and clotting disorders	39 (2.1)	Bruise, thrombocytopenia, coagulation disorder, purpura, increased INR, bleeding, menorrhagia.

5.5 Onset of adverse effects due to CAM

Only 653 (70%) of the reports provided data for onset of adverse effects. One third (30.5%) of the adverse event occurred within 3 days of consuming the CAM products

while 55 cases (8.4%) reported delayed reactions after one year. The longest delayed reaction was after 15 years. This was reported in a 61 year old male Malay patient who developed increased blood creatinine after consuming a product named "Nourish Blood Itch Removing" to treat his itchiness. Four other reports involved adverse events such as Cushing's syndrome, hepatitis and acute renal failure after 10 years of taking CAM products for joint and knee pains.

5.6 Extent and outcome of adverse effects

Table 5-4 shows the extent and outcomes of adverse effects associated with CAM products. Nearly half (40.4%) of the effects were severe. Thirty-six cases reported fatal outcomes either due to the adverse reaction or the CAM being a possible contributor. Almost half (46.1%) of the reports indicated that patients who suffered the reactions have not yet recovered at the time of reporting.

Table 5-4: **Extent and outcomes of adverse effects**

Variables	Number of reports (%)
Extent of adverse effects	
Mild	138 (14.8)
Moderate	385 (41.4)
Severe	376 (40.4)
Unknown	30 (3.2)
Outcomes of adverse effects	
Not yet recovered	429 (46.1)
Recovered without sequelae	277 (29.8)
Recovered with sequelae	13 (1.4)
Died-drug may be contributory	30 (3.2)
Died-due to adverse reaction	6 (0.6)
Died-unrelated to drug	3 (0.3)
Unknown	157 (16.9)
Missing data	15 (1.6)

5.7 Concurrent drug and disease

Slightly more than one third (36.9%) of the reports recorded other concurrent drug being taken with the CAM when the adverse event occurred. Only 27.2% of the cases

had reported existence of concurrent chronic diseases such as hypertension, diabetes mellitus or cardiovascular diseases that require prolonged continuous drug therapy.

5.8 Serious adverse reactions

From a total of 930 reports, 242 (26%) were serious adverse reactions with 36 deaths. Six died due to the adverse reactions as a result of taking the CAM while for the remaining 30 cases, the CAM used could be a "possible" contribution to the deaths. Half of the deaths were amongst Chinese consumers even though they constituted only 32.3% of the total reports. On the other hand deaths among Malay CAM users were relatively lower. **Table 5-5** shows the details of six reports of mortality attributed to the CAM products consumed. Three were Chinese and another three were Malays whilst females made up the four deaths. Four deaths were due to consumption of unregistered CAM products while another two were registered products containing health supplement spirulina and a Chinese traditional compound powder. The case with spirulina intake died due to acute liver failure. Another case who took the registered CAM for phlegm, fever, cough and cold, died from acidosis and septic shock. Two of the products namely "Figure up" and "Edoly" were tested positive for sibutramine and chlorpheniramine respectively.

Table 5-5: Adverse reaction reports of death attributed to CAM products

Gender	Race (Age in years)	Product Name	Product Registration Status	Indication	Adverse reaction
Female	Malay (Unknown)	Maajun Gamat Mengkudu Plus	Unregistered	General health	No information
Female	Malay (19)	Figure-up	Unregistered	Weight loss	Duodenal ulcer, Haemorrhage
Female	Chinese (57)	Shang Ke Huo Xue San	Unregistered	Hand bruising	Thrombotic thrombocytopenic purpura
Female	Chinese (18)	Spirulina	Registered	General health	Acute liver failure
Male	Malay (72)	Edoly Capsules	Unregistered	Psoriasis	General weakness, lethargy, dyspnoea, headache, chest pain, diarrhoea, adrenal crisis
Male	Chinese (less than 1 year)	Bo Ying compound powder	Registered	Phlegm, fever, cough, cold	Pneumoperitoneum, acidosis, septic shock

Thirty other reports of adverse effects associated with death were given causality grading of "possible". Details of the adverse effects are as in **Appendix (E)**

5.9 Adulteration of CAM products

A total of 155 of the reports had sample products which were tested and confirmed to contain controlled medicines. Most popular adulterants were dexamethasone, sibutramine, combination of chlorpheniramine and dexamethasone, phenylbutazone and chlorpheniramine. **Table 5-6** shows the common CAM products that were problematic. Details of the 155 products implicated are as in **Appendix F**. Description of common adulterated CAM products are as in **Appendix G.**

Table 5-6: Adverse reaction reports for common CAM products confirmed adulterated with controlled medicines

	Product	Indication	Registration Status	Adverse Reactions	Adulteration
1.	ABC Acaiberry products	To reduce weight	Unregistered	Weight loss, hepatitis, renal failure acute, dehydration, abdominal pain	Sibutramine
2.	Asam Urat Jaya Asli	Bone/joint/ ankle/knee pain	Unregistered	SJS, TEN, Dress Syndrome, hepatitis, macular rashes, mouth ulcers, nausea, vomiting, stomach ache, reddish stool, itchiness, LFT abnormal, generalised weakness	Phenylbutazone
3.	Edoly Capsule	Joint/knee pain/gout/ general health	Registered	Generalised weakness, joint pain, myalgia, haematemesis, gastrointestinal haemorrhage, chest pain, headache, abdominal pain, vomiting, dyspnoea, adrenal crisis, renal failure	Chlorpheniramine
4.	F.O.B	Backpain/ joint pain	Unregistered	Cushing's syndrome, acute renal failure, macular rashes, bruise, thrombocytopenia	Chlorpheniramine & Dexamethasone
5.	Figure Up	To reduce weight	Unregistered	Tremor, vomiting, duodenal ulcer haemorrhagic, seizure, renal failure, unexpected therapeutic benefit	Sibutramine
6.	Lami	To reduce weight	Unregistered	Palpitation, giddiness, chest pain dyspnoea, haematuria, thrombocytopenia, back discomfort, runny nose	Sibutramine
7.	Maajun Dua Istimewa products	Joint pain/ osteoarthritis	Unregistered	Cellulitis, pneumonia, Cushing's syndrome, face oedema, prolonged prothrombin time, rashes, 1st degree heart block, bradycardia, lethargy, pyrexia, dyspnoea, epistaxis, LFT abnormal, jaundice, hepatitis, acute liver failure, acute renal failure, appetite increased, weight gain, nausea, vomiting, loss of appetite, thrombocytosis, increased serum creatinine, chest pain, vomiting, headache	Dexamethasone
8	Pil Tupai Jantan products	Stamina/joint pain/improve sexual function	Unregistered	Hypotension, adrenal insufficiency, Cushing's syndrome, dyspnoea, mouth oedema, acute renal failure	Dexamethasone
9.	Seven Leave Ginseng products	Joint pain/ gout/general health	Unregistered	Movement disorder, pyrexia, muscle weakness, Cushing's syndrome, increased appetite, haematuria, rash ecchymotic, rash petechial, unexpected therapeutic benefit	Chlorpheniramine & Dexamethasone
10	Skyline Al Taqwa products	Joint pain/ Gout/energy/ appetite	Unregistered	Unexpected therapeutic Benefit, hypertension, moon face, cortisol decreased, weight increase	Dexamethasone; some with combination Chlorpheniramine & Dexamethasone

5.10 Causality grading assigned for CAM adverse reactions reports

The causality assigned by reporters and MADRAC is shown in **Table 5-7**. MADRAC was less likely to assign the causality "certain" and "probable" as compared to reporters.

Table 5-7: Causality of adverse reactions associated with CAM products assigned by reporters and MADRAC

Causality	Number of reports (%)	
	Causality assigned by reporter	Causality assigned by MADRAC
Certain	84 (9.0)	15 (1.6)
Probable	330 (35.5)	37 (4.0)
Possible	371 (39.9)	784 (84.3)
Unlikely	16 (1.7)	10 (1.1)
Unclassifiable	32 (3.4)	38 (4.1)

*Missing data was not counted
*Total reports of causality assessment by reporters = 833 reports
*Total reports of causality assessment by MADRAC = 884 reports

5.11 Predictors of serious adverse reactions

Preliminary univariate logistic regression analysis indicated serious adverse reactions was associated with age, race, concurrent disease, concurrent drug and indication of use. **Table 5-8** shows the results of a multiple logistic regression model predicting serious adverse reactions from the use of CAM products. The variables ethnic (Indian), ethnic (other races), concurrent disease, concomitant drug, and CAM use for chronic illness were statistically significant predictors of serious ADR associated with CAM use at $p < 0.05$. Compared to the Malays, the odds of a Chinese encountering serious adverse reactions from the use of CAM was not statistically significant. The odds ratio for the variable Ethnic (Indian) is less than 1. This indicates that the odds of an Indian experiencing serious adverse reactions were less compared to the Malays, all other factors being constant. The odds of a Malay encountering serious adverse reactions from the use of CAM products was 11.8 times higher than an Indian and 0.38 times

lower than the category of other races. Being ethnic of other races was associated with increased odds of experiencing serious adverse reactions compared to being Malays (2.6 times higher). The variable sex was not a significant predictor of serious adverse reactions.

The odds of someone with concurrent diseases or taking concomitant medications to experience serious adverse reactions are 1.51 and 1.44 times higher respectively all other factors being constant. The odds of a person taking CAM products for treating or alleviating chronic illness symptoms and then experiencing serious adverse reactions was almost doubled compared to a person not taking CAM for that purpose.

Table 5-8: **Predictors of serious adverse reactions in the multivariate logistic regression model**

Variables	Beta	S.E (beta)	Odds Ratio	95% CI
Sex (Male)	0.125	0.156	1.133	0.834 – 1.539
Ethnic (Chinese)	0.232	0.166	1.261	0.910 – 1.747
Ethnic (Indian)	-2.467	1.026	0.085	0.011 – 0.634
Ethnic (Others)	0.970	0.339	2.638	1.356 – 5.131
Concurrent disease (No)	-0.414	0.189	1.513	1.045 – 2.193
Concomitant drug (No)	-0.370	0.170	1.447	1.037 – 2.020
Chronic Illness Use (No)	-0.689	0.157	1.991	1.463 – 2.710

The reference category for the variable – Ethnic: (Malay), Concurrent disease: yes; Concurrent drug: yes; Chronic Illness Use: yes

Variable(s) entered on step 1: Sex, Race, Concurrent disease, Concurrent drug, Chronic Illness Use

CHAPTER 6: DISCUSSION

6.1 Summary of main findings

This study presents the analysis of CAM adverse reactions in Malaysia throughout a 15-year period extracted from the NPRA pharmacovigilance database, the implicated CAM products and the factors predicting serious adverse reactions. The CAM-related adverse reactions constituted about 1.2% of all ADR reports received from the year 2000 - 2014 and this percentage is comparable to the report in Sweden (Jacobsson et al., 2009), higher than the 0.5% of WHO figure (Farah et al., 2000) and lower than 3.8% figure from Singapore (Patel et al., 2012). Meanwhile, the Chinese National ADR Monitoring Center had much higher reports of 10-15% which correlates with the wide acceptance and extensive use of TCM by the Chinese people for treatment of chronic diseases and the organisational support for reporting of adverse reactions (Zhang et al., 2012).

A high number of these CAM adverse reactions were severe (40%) and serious (26%) and had been implicated in 36 fatal outcomes (3.9% from all CAM adverse reaction reports). Our figure of 26% serious reactions is comparable to published figures which ranged from 28% to 41% of total CAM reports received (Jacobsson et al., 2009; Kalaiselvan et al., 2015). For Malaysia, this high figure correlates with the intake of unregistered CAM products whereby they caused almost 70% of the suspected deaths. Products of dubious sources stand a high chance of containing unsafe substances even banned drugs such as sibutramine. Singapore reported similar scenario of the problem with adulteration where the majority of cases were also serious and 3.5% of suspected cases had the fatal outcome (Patel et al., 2012).

ADR involving skin and appendages disorders is top most (21.6%), followed by liver and biliary disorders (14.9%). This finding is in agreement with several other studies including information from the WHO adverse reaction database associated with the use of herbal medicines (Farah et al., 2000), Sweden (Jacobsson et al., 2009) and Italy (Vitalone et al., 2011). Thailand reported gastrointestinal disorders as the most common adverse event for CAM mainly from the intensive monitoring programme where selective CAM were monitored (Saokaew et al., 2011). Singapore had issues with CAM causing endocrine and central and peripheral nervous system disorders because of its high use of adulterated CAM products for sexual enhancement (Patel et al., 2012).

We reported more than half of the adverse event in female CAM users with high mortality and this correlates with the evidence that CAM users are females (Aziz & Tey, 2009; Mitha et al., 2013). Another study on the association between gender and predisposition of adverse reactions supported our findings that females are more prone to experience adverse reactions (Yusof & Gan, 2011).

Both reporters and MADRAC committee commonly rated "possible" for the relationship between the suspected CAM products and adverse reactions. However, there was a higher rating of "probable" (35.5% versus 4.0%) and "certain" (9.0% versus 1.6%) by reporters compared to causality assigned by MADRAC. This could probably be due to different personal clinical judgments and experiences by reporters. Causality assessment made by the MADRAC committee is based on consensus agreement by its expert panel using WHO-UMC guideline. The MADRAC committee also adhered to the critical criteria of positive rechallenge and dechallenge which needed to be fulfilled before the suspected CAM be implicated for causing the adverse reaction. Currently there are several ADR causality assessment tools available, each having its own

advantage and limitation which explains the variations in interpretations (Khan et al., 2016b).

The most common ADR reporters are pharmacists and doctors because it is their responsibility to report suspected ADR associated with any medications (NPRA, 2016). Our study shows pharmacists submitted the most CAM reports followed by doctors. We can attribute it to two main factors. One, pharmacists in Malaysia are trained in ADR reporting and as clinical pharmacists, they actively interview patient during ward admissions to obtain information on medication history including use of CAM. Two, reporting of ADR is also part of the required pharmacists' professional task. The sources of the reports were mostly from government hospitals, since 80% of the patients had experienced moderate to severe reactions from the use of CAM products requiring them to seek further medical management and even being hospitalised.

Concomitant use of other drugs with CAM makes it difficult to determine the causative agent of the adverse event. In this study, we found that cases that had concurrent disease or CAM taken with other conventional medicines had one and a half times more risk of developing serious reactions. Our findings are consistent with findings from other studies that show patients with multiple co-morbidities or medications appear to be at a higher risk for an ADR (Alhawassi et al., 2014) and increased risk for ADR-related hospitalisation (Angamo et al., 2016).

Our findings show that about 40% of the cases used CAM for managing chronic conditions such as arthritis, diabetes mellitus, hypertension, stroke and cancer. One third of cases that took CAM products for treating chronic illnesses developed serious reactions compared to those who took CAM products for general health maintenance. Treatment of acute and chronic pain was the single most reason consumers sought CAM products with 18% of the total reports. A review revealed that lack of effectiveness of

conventional therapy for treating arthritis is one major factor that influenced patients' decision of starting and persisting with CAM therapy (Khan et al., 2016a). Pain management is also an important health issue in the United States of America whereby the NCCIH reported that pain (back, neck, joint, arthritis) is the common complaint with 73% of people over 50 years old take CAM approach to reduce pain or treat painful conditions (NCCIH, 2011). This is in contrast with Singapore data, where nearly 50% had used CAM for sexual enhancement performance and very few to ease pain (Patel et al., 2012). Our data show a low use of CAM for sexual enhancement.

Amongst the Chinese Traditional Medicines, products containing Ginseng were most problematic while in the Malay traditional medicine group; "Jamu", "Maajun" and "Gamat" products were implicated. All of these products were mainly indicated for pain relief, general wellbeing and to increase vitality. Most were also found to be unregistered and had issues of adulteration with the corticosteroid dexamethasone either alone or in combination with an antihistamine or NSAID or paracetamol. In the "Jamu" cases, there were nearly twice as many severe reactions reported involving the liver and kidney organs as compared to the "Maajun" group while adulteration was three times more rampant with reported "Maajun" products. Two reports of severe skin reactions namely Steven Johnson syndrome and toxic epidermal necrolysis involving use of "Asam Urat Jaya", another unregistered "Jamu" product with a history of phenylbutazone adulteration widely circulated in East Malaysia (MADRAC, 2006) ended with fatality. Three reported cases of hepatitis, acute renal failure and cerebral haemorrhage had consumed unknown Chinese Traditional medicines and died.

"Gamat" products also posed as a health concern where 43 reports involving 12 products were found to cause adverse events with nearly half being renal disorders followed by liver and biliary disorders such as abnormal liver function test, jaundice and

hepatitis. In 2008, the DCA suspended and ordered market recall of two registered products containing the species "Gamat" also known as sea cucumber (Stichopus horrens). In Malaysia, "Gamat" is a local name for all species of the family Stichopodidae of which two groups; genus Stichopus and Thelenota are most popular (Kamarudin et al., 2010). Sea cucumbers (Phylum Echinodermata: Class Holothuroidea) with an estimated of 80 morphospecies are marine animals found in the seawaters of Malaysia and is popular due to their medicinal properties and commercial value. The products withdrawn from the market were "Gamat Emulsion" and "Gamatogen". The DCA made the decision due to 16 renal related adverse reactions reports of which 4 patients did not take any other medications apart from these "Gamat" products and had no concurrent disease that could have contributed to the adverse event (NPCB, 2009)

The 16 reports of sibutramine containing CAM products claimed for weight loss under several popular names such as "ABC Acaiberry", "Acaiberry Herba Pelangsing" and "Figure Up" caused adverse events such as giddiness, palpitations and acute renal failure. In one case bleeding ulcer caused death. Sibutramine, a centrally acting appetite suppressant withdrawn from the market worldwide including Malaysia in 2010 due to cardiovascular safety concerns such as increased risks of heart attacks and strokes (DCA, 2010), is still illegally available and has also been found added to registered CAM products. Between 2008 and 2015, seven CAM products registered in Malaysia were cancelled due to sibutramine adulteration (NPRA, 2016). Two other weight loss products reported were "P30" and "F.O.B.". Both are unregistered products and "P30" was confirmed to be adulterated with the scheduled medicine phentermine and "F.O.B" with triple combination of cyproheptadine, dexamethasone and niacinamide. The use of "F.O.B." resulted in serious adverse events such as thrombocytopenia, acute renal failure and Cushing's syndrome in four consumers with one death.

For the health supplement, spirulina had 22 adverse effects reports and bee derived products had 17 reports. Half of the reports for spirulina involved skin reactions with a quarter serious. One case died from liver failure while another two cases developed cirrhosis and abnormal liver function. For the bee products more than half involved propolis and adverse events ranged from skin reactions to liver and kidney complications.

The influx of unregistered CAM products in the Malaysian market is an ongoing and perpetuating problem and consumers face the consequence of harm from its use. In 2015 alone, an estimated RM34.1 million of unregistered products was seized from the market of which about a third with the value of RM10 million are CAM products. Seventy percent of such products tested was adulterated (PSD, 2015). As can be seen from this study, more than three quarters of CAM products implicated in the reports was unregistered with the Malaysian DCA. Out of the 930 reports, 155 (16.7%) of the CAM products used were confirmed to be adulterated by NPRA. Nearly three quarters of the adulterated CAM products implicated dexamethasone either alone or in combination with other controlled medicines.

The adulteration issue is not just confined to unregistered CAM products. In Malaysia, 54 registered CAM were cancelled between 2008-2016 due to adulteration with banned ingredients such as ephedra and sibutramine or controlled medicines such as antidiabetics, phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil and its analogues, antihistamines, corticosteroids and NSAID (PSD, 2018). Thus, it is possible that the adulterants were the cause to the adverse events rather than the substance in the CAM products itself. Due to this reason, CAM products have been reported to cause "false-positive" adverse reactions.

6.2 Limitations

There are several limitations of this study thus the results should be interpreted with caution. Since this is a retrospective study, several missing information such as indication of CAM products, medical and medication history as well as patient outcome could have affected data interpretation. Also, in many cases reporters did not specify the exact CAM product name or ingredients making it difficult to categorise them. Several products also may have different product names and contained various ingredients which create confusion whether the products are similar or not and it was difficult to determine which substance had caused the adverse effects.

Under reporting of ADR remain a major ongoing issue thus limiting the generalisability of the findings. In reality, many CAM consumers may not be vigilant or even unaware that the adverse effects they may experience, are associated with the CAM they are taking due to the misconception that CAM products are safe. Most doctors also rarely ask about the CAM use by their patients which compounds the situation.

Causality assigned by reporters and MADRAC show a big disparity especially in the decision to implicate the suspected product. More complete information and details particularly critical criteria such as drug positive rechallenge and dechallenge needs to be ascertained to assist in more definitive causality assignment so that preventive safety measures can be taken effectively by the DCA.

CHAPTER 7: CONCLUSION

Pharmacovigilance of CAM products is important as it helps to identify safety risks associated with its use and the current spontaneous reporting mechanism remains a useful monitoring tool. Under reporting of CAM adverse reaction is also an issue as of all ADR reports received, only slightly more than one percent was related to CAM products. More strategies need to be in place to increase reporting and empower consumer to self-report any problems related to CAM products, particularly because, CAM products can be bought through direct selling and online. With increased reporting and more data, ADR signal detection power of the current spontaneous reporting system may increase.

The most adverse reactions reported associated with CAM products use were skin and appendages disorders followed by liver and biliary system disorders. Thus, our study findings also demonstrated that the NPRA ADR database is an important source of information that can be used as part of the safety surveillance system of CAM products. However current mechanisms to track adverse effects of CAM products are inadequate and their toxicity may go unrecognised. Further studies are required to explore product specific adverse events possibly through intensive monitoring.

Substantial unregistered CAM products causing the adverse events create a worrying situation and more aggressive measures are needed to eradicate them from the market. Mass media platform is crucial to continuously engage consumers on the dangers of consuming unregistered CAM products. Risk communication particularly on serious adverse reactions or life-threatening situations associated with CAM should be done promptly to healthcare professionals and the public.

All reported cases of serious adverse reactions and deaths related to CAM use must be examined to identify the possible causative compounds, ingredients or contaminant. Regulations on CAM should be strictly implemented to prevent the common substances that caused serious or even moderate adverse reactions from being used in CAM products.

Predictors for serious adverse reaction would be helpful in prompt diagnosis and treatment of affected patients. Reason for taking the CAM products together with good history taking on concurrent medications and disease can help to prevent serious adverse events in people who consume or intend to consume CAM products. The decision to consume CAM products that have scientific evidence suggesting efficacy, but have concerns over safety of possible interaction with other medical therapies they are taking have to be balanced with risk benefit consideration.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

PUBLICATION:

1. Sameerah SAR, Zoriah A. Complementary and Alternative Medicine: Pharmacovigilance in Malaysia and Predictors of Serious Adverse Reactions. Journal of Clinical Pharmacy and Therapeutics (accepted)

PAPER PRESENTED:

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