

**PREVALANCE OF HEALTH SUPPLEMENT
PRODUCTS USE AND THEIR POTENTIAL
INTERACTIONS WITH DRUGS PRESCRIBED
FOR THE OUTPATIENT POPULATION OF
SARAWAK DISTRICT HOSPITAL**

LOO SHING CHYI

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FOR THE OUTPATIENT POPULATION OF
SARAWAK DISTRICT HOSPITAL**

by

LOO SHING CHYI

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LIST OF SYMBOLS

Z	Z statistic for a level of confidence.
P	Expected prevalence or proportion (in proportion of one).
d	Precision (in proportion of one).
n	Sample size.

LIST OF ABBREVIATIONS

HSP	Health Supplement Products
PM	Prescribed Medicines
PMHSPI	Prescribed Medicines Health Supplement Product Interaction
SDH	Sarawak District Hospital
HCP	Health Care Providers
USM	Universiti Sains Malaysia

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**PREVALENS PENGGUNAAN PRODUK SUPLEMEN KESIHATAN DAN
POTENSI INTERAKSI DENGAN UBAT PRESKRIPSI DALAM KALANGAN
POPULASI PESAKIT LUAR DI HOSPITAL DAERAH SARAWAK**

ABSTRAK

Penggunaan produk suplemen tambahan kesihatan (HSP) di Malaysia semakin meningkat kebelakangan ini. Namun demikian, kajian terhadap kelaziman penggunaan produk suplemen tambahan kesihatan dalam kalangan populasi Malaysia adalah terhad. Selain itu, kajian-kajian di Malaysia sebelum ini tidak menekankan kepada kelaziman penggunaan serentak ubat preskripsi dan produk suplemen kesihatan, serta amalan, persepsi, faktor penyumbang kepada penggunaan produk suplemen kesihatan dan potensi interaksi diantara produk suplemen kesihatan dan ubat preskripsi dalam kalangan populasi luar bandar di Sarawak. Kajian ini bertujuan untuk menilai kelaziman penggunaan produk suplemen kesihatan dan mengenal pasti amalan, persepsi, faktor yang mempengaruhi penggunaan produk tersebut, dan potensi interaksi di antara produk suplemen kesihatan dengan ubat preskripsi dalam kalangan pesakit yang mempunyai penyakit kronik di kawasan luar bandar di Sarawak, Malaysia. Kajian ini adalah satu kajian keratan rentas dengan pelbagai pusat yang dijalankan di Jabatan Farmasi Pesakit Luar di tujuh Hospital Daerah Awam di Sarawak. Satu borang pengumpulan data telah disediakan dan diuji secara rintis sebelum proses pengumpulan data dijalankan. Data telah dikumpul dari Jun sehingga Ogos 2018. Analisa secara regresi logistik binari telah digunakan bagi menilai hubungan antara data demografik sosial pesakit dan penggunaan produk suplemen kesihatan. Kajian ini telah berjaya mengumpul data daripada 350 pesakit.

Hanya 84 (24.0%) pesakit adalah pengguna aktif produk suplemen kesihatan dan 55 (65.5%) daripada mereka pernah menggunakan produk suplemen kesihatan secara serentak bersama ubat preskripsi. Kira-kira separuh (52.0%) daripada pengguna produk suplemen kesihatan aktif ($n = 84$) ini tidak pernah tanya dan mendapat nasihat dari pengamal perubatan berkenaan sebelum penggunaan produk suplemen kesihatan. Namun, kebanyakan pesakit bersetuju dengan keperluan untuk merujuk pengamal perubatan sebelum (82.0%) atau semasa (80.3%) penggunaan serentak produk suplemen kesihatan bersama ubat preskripsi. Pesakit dengan pendapatan isi rumah yang lebih tinggi ($> \text{RM } 2000$) didapati dengan ketara (nisbah kemungkinan = 4.23; $p < 0.001$) lebih berkemungkinan menggunakan produk suplemen kesihatan berbanding dengan pesakit berpendapatan isi rumah yang rendah ($\leq \text{RM } 830$). Selain itu, pesakit yang berpendapatan isi rumah lebih daripada RM 2000 dan mereka yang berpendapatan isi rumah antara RM 830 sehingga RM 2000 masing-masing didapati dengan ketara ($p < 0.001$) 9 kali dan 4 kali lebih cenderung menggunakan produk suplemen kesihatan secara serentak bersama ubat preskripsi, berbanding dengan pesakit berpendapatan isi rumah yang rendah. Sebanyak 84 interaksi di antara produk suplemen kesihatan dan ubat preskripsi adalah dikesan daripada 285 ubat preskripsi dari 84 orang pengguna aktif produk suplemen kesihatan. Cuma 40 orang pengguna aktif yang terlibat dalam potensi interaksi diantara produk suplemen kesihatan dan ubat preskripsi. Kadar potensi interaksi keseluruhan berdasarkan 285 ubat preskripsi dan 104 produk suplemen kesihatan yang digunakan oleh 84 orang pengguna produk suplemen kesihatan aktif adalah sebanyak 29.5%. Kadar ini dikira dengan menggunakan 84 potensi interaksi yang dijumpai dan dibahagikan oleh 285 jumlah ubat preskripsi yang digunakan. Kesimpulannya, penggunaan serentak produk suplemen kesihatan bersama ubat preskripsi adalah lazim dalam kalangan pesakit di

kawasan luar bandar Sarawak. Langkah- langkah drastik harus diambil untuk memupuk penggunaan produk suplemen tambahan kesihatan secara berkualiti dalam kalangan pesakit dari kawasan luar bandar Sarawak.

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ABSTRACT

Recently, the use of health supplement products is increasing among public in Malaysia. Nevertheless, there is limited research on the prevalence of health supplement products utilization among Malaysian population. Additionally, previous studies in Malaysia did not properly address the prevalence of concomitant use of prescribed medicines and health supplement products, as well as the practices, perceptions, factors which lead to the use of supplement products, and potential interaction between health supplement products and prescribed medicines among the rural population from Sarawak. This study aims to assess the prevalence of health supplement products consumption, and to identify practices, perception, factors affecting the use of such products, and potential interaction between health supplement products and prescribed medicines among patients with chronic diseases in rural area of Sarawak, Malaysia. This was a multicenters cross-sectional study conducted in outpatient pharmacy department of seven non-specialist government districts Hospitals in Sarawak. A data collection form was developed, and pilot tested prior to the data collection. Data was collected from June to August 2018. Binary logistic regression was used to assess the association between patients' social demographic characteristics and the consumption of supplement products. Upon completion of study, data was collected from 350 patients. Only 84 (24.0%) patients were active health supplement products users and 55 (65.5%) out of 84 of them ever

used supplement products concomitantly with prescribed medicines. Approximately half (52.0%) of the active HSP users (n = 84) never consult and get advise from health care providers before the use of supplement products. However, majority of them expressed agreement upon necessity to consult health care providers prior to (82.0%) or during the concomitant use of health supplement products with prescribed medicines (80.3%). Patients with higher monthly household incomes (> RM 2000) were significantly (odds ratio = 4.23; p < 0.001) more likely to use supplement products than the lower income group (\leq RM 830). Besides, those with household income more than RM 2000 and ranging from more than RM 830 to RM 2000 were found to be 9 times and 4 times significantly (p < 0.001) more tend to use health supplement products concomitantly with prescribed medicines as compared to the lower income group. A total of 84 potential interactions were identified from the total number of 285 prescribed medicines and 104 health supplement products among the 84 active health supplement users. Only 40 (47.6%) active HSP users were involved in the potential interaction rate found. The potential interaction rate calculated based on 84 potential interactions divide by 285 prescribed medicine was 29.5%. In conclusion, the concomitantly used of health supplements with prescribed medicines are prevalent among the patients. Tenacious efforts are required to instill quality use of health supplement products among the patients from rural area of Sarawak.

CHAPTER 1

INTRODUCTION

1.1 Prevalence and expenditure on health supplement products use

Notwithstanding the advancement in modern medicines and health technologies, the use of health supplement products (HSP) remains prevails particularly among patients with chronic diseases. According to the Dietary Supplement Health and Education Act of United States, the US Congress defined a HSP as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandular organs and metabolites. Dietary supplement can also be extracts or concentrates, and they can occur in many forms, such as tablets, capsules, soft gels, gel caps, liquids or powders (Siti *et al.*, 2009). As such, prescribed medicines health supplement products interactions (PMHSPI) caused by the concomitant use of HSP and prescribed medicines, had become a worrying issue among healthcare policy makers and practitioners due to potential severe health consequences.

Prevalence of HSP in United States, European and Asian countries range from 30% to 34%, as multivitamins was the most popular consumed supplement (Bailey *et al.*, 2011, Sichert-Hellert & Kersting, 2004, Yoon *et al.*, 2012, Mori *et al.*, 2011, Sien *et al.*, 2014). The expenditure recorded on HSP use in United States recorded USD 17.8 billion in year 1990 (Eisenberg *et al.*, 1993) and was increased to USD 36.7 billion in year 2014 (El Khoury, Ramadan & Zeeni, 2016). The use of HSP was found not only particularly among elderly persons who also consume

multiple prescription medications for multiple comorbid conditions, but as well as young's adults (Bailey et al., 2011, Sichert-Hellert & Kersting, 2004, Yoon et al., 2012, Mori et al., 2011, Yeo et al., 2014).

In Malaysia, HSP are gaining high level of public acceptance and popularity. According to the national morbidity and health survey done in 2003 and 2014, there was an increased on the use of HSP among adults in Malaysia. The prevalence of vitamins and mineral and food supplement consumption for year 2003 was 23.94% and 24.79% respectively. The prevalence was increased to 28.05% and 34.02% respectively in year 2014 (Aris et al., 2014). In additional, it was found that the five most commonly taken vitamin and mineral supplements were Vitamin C followed by multivitamins, calcium, vitamin B complex and folic acid; whereas top five most commonly taken food supplement were fish oil, royal jelly, spirulina, collagen and traditional herbs. Most of the Malaysian consumers were single supplement users, and the main indications of HSP was to improved their general well-being and act as an energy booster (Aris et al., 2014). Among the adolescence, the usage of vitamin and mineral supplements and food supplements was 54.1% and 40.2% respectively. The percentage of usage of HSP was found to be higher among younger adolescence (Sien et al., 2014).

On the other hand, according to a study by Siti et al. in year 2009, the used of pure herb for health maintenance among population in all states of Malaysia was as high as 29.6%, while vitamin and supplements was found to be 7.4% (Siti et al., 2009). The study also showed that the prevalence of Malaysian most commonly used herbs-based application/beauty/herb-based hygiene product for health problems was 23.6%, followed by herbs (17.1%) (Siti et al., 2009). A previous study also revealed

that among the aboriginal population of Sarawak, 91.2% of them were using biological-based therapies which was slightly higher than the national findings (Siti et al., 2009). In addition, a survey done in three primary care clinics in Kuching, Sarawak found that the prevalence of HSP use was 25% (Lee et al., 2007). Besides, in Malaysia, the expenditure of HSP was rapidly growing as well. For instance, the annual sales for HSP was increased from USD 385 million (RM 1 billion) in year 2000 to USD 1.29 billion (RM 4.5 billion) in year 2005 indicating an approximate 3.4 times increment within five years (Aziz & Tey, 2009).

1.2 Challenges to overcome issues related to prescribed medicines health supplement products interactions

Concomitant use of HSP with prescribed medicine without informing the health care provider could poses a high potential risk to prescribed medicines HSP interaction. Currently, there is a lacking information about pharmacokinetics, pharmacodynamics, efficacy, and safety of HSP. Scientific evaluation on HSP are limited. Evaluation such as randomized controlled trials was either not available, not demanded by consumers (patients) or health care practitioners, and some of the time not required by regulatory agencies (Tachjian, Maria & Jahangir, 2010). In Malaysia, such information were not mandatory for registration of a health supplement products. It depends on the level of claims of HSP. Only highest level of claims on disease risk reduction required scientific evidence from human intervention study, toxicology study and pharmacological study. Otherwise, for functional claims and general health claims, such information were not required for registration of HSP (Ministry of Health, 2016).

In additional, unethical marketing techniques give raise of tons of false advertisements about the safety and efficacy of the herbs spreading unfiltered to the general population (Tachjian, Maria & Jahangir, 2010, Morris & Avorn, 2003). This has eventually led HSP been promoted for treatment based on word-of-mouth traditions and beliefs that ignoring scientific evidence (Morris & Avorn, 2003). Evidence available for the safety of HSP was limited to case series and case study as clinical control trials to assign patients to experience adverse reactions was unethical (Fugh-Berman, 2000).

Unfortunately, death reports of adverse events and prescribed medicines HSP interactions were relatively low due to under-reporting. This was largely contributed by assumption on the HSP was safe and natural, and patients are reluctant to report an adverse effect from a self-medicated substance (Tachjian, Maria & Jahangir, 2010, Fugh-Berman, 2000). Under-reporting on the adverse reactions has cause significant loss of valuable safety data, which subsequently contribute to the lack of knowledge about prescribed medicines HSP interactions by the patients and health care providers. This could be extremely dangerous especially among vulnerable groups such as geriatric patients. This was supported by a study which revealed that 46% of the patients from geriatric clinic were taking supplements with anticoagulation properties. Most of the geriatric patients (73%) were also taking a prescription anticoagulant and were unaware of potential interactions (Tachjian, Maria & Jahangir, 2010). In spite of the widely use, potentially fatal prescribed medicines HSP interaction and unwillingness of disclosure, health care providers need to be aware of herb and supplement use by their patients, alerting patients on potential adverse reactions or interactions, and educate them about the proper use of HSP.

1.3 Problem statements

Despite extensive research on the prevalence and expenditure on HSP, previous studies conducted in Malaysia did not properly address the practice and perception of public towards the use of HSP, as well as the potential prescribed medicines HSP interactions. Ironically, such worry is also yet to be proactively addressed by healthcare professionals at the point of medical consultation and medication dispensing. Lack of knowledge on the type and pattern of concomitant use of HSP and prescription medicines by local patients is arguably to be the contributing factor that undermines the capability of healthcare professionals to address the problem of prescribed medicines HSP interaction.

Interactions and use of health supplements and other medications are rapidly and continually evolving. However, most of the studies did not disclosed or elaborate on the potential prescribed medicines and HSP interactions, even though the studies were investigating whether the patients were taking their HSP concomitantly with prescribed medicines. In addition, very little of the past studies included patients from Sarawak State of Malaysia. The previous studies was unable to bridge the gap in the literature and to provide practical implications for local healthcare professionals about the pattern of concomitant use of prescription medicines and health supplements. Besides, the risk of prescribed medicines and HSP interactions among patients with chronic diseases from the primary healthcare hospitals in rural area of Sarawak was not assessed in the previous studies.

This comes into our interest to find out more on the HSP use especially patients from district hospital which have chronic used of prescribed medicines in Sarawak. This was largely due to accessibility of public to the tertiary healthcare

services remain demanding in these areas, due to limited number of institutions and scattered distribution of population (Ismail, 2009). Hence, the district hospital plays a significant role in delivering quality healthcare services to the public in Sarawak.

Many studies have been conducted to assess factors influencing the use of HSP but there was variation in the study results. These variations are specific based on the study population, as different population would have different culture, lifestyle and believe. Therefore, there is a need to explore factors which would influence the utilization of HSP particularly among patients in rural areas of Sarawak, East Malaysia. The population in Sarawak is unique of its diverse native groups, for example, the Bidayuh, Iban and Melanau.

In order to fortified and address problems of prescribed medicines and HSP interaction, it is fundamental to identifying factors which influence the use of HSP, and also the practices and perception of the use of health supplements among the patients. This in return would raise the health care providers' concern on the issue and subsequently able to give better advice to the patients on the use of HSP (Ting *et al.*, 2009a).

Furthermore, it is essential to integrate and fortify the clinical and pharmacologic aspects of PM HSP interactions with available clinical interaction checkers. So that this information could help the physicians and pharmacists to measure the risk of interactions according to clinical effects and significance of the interactions. This information can enhance the current quality of the available clinical evidence and recommendations to handle the common potential interaction found among prescribed medicines and health supplement products consumed among the patients from district hospitals of Sarawak. Furthermore, this findings would help

the healthcare providers in providing better and clearer instructions when performing counselling for HSP interactions with prescribed medicines in the future.

1.4 Study objectives

1.4.1 Primary objective

To determine the prevalence of health supplement products (HSP) use and commonly used HSP and prescribed medicines among patients from outpatient pharmacy of Sarawak district hospitals.

1.4.2 Secondary objectives

1. To determine the prevalence of concomitant use of HSP with prescribed medicines and potential prescribed medicines HSP Interactions among patients among patients from outpatient pharmacy of Sarawak district hospitals.
2. To explore the practice and perception of patients from outpatient pharmacy of Sarawak district hospitals towards HSP.
3. To explore the association between social demographic characteristics of the patients with the use of HSP.
4. To explore the association between social demographic characteristics of the patients with the concomitant use of HSP and prescribed medicines.

CHAPTER 2

LITERATURE REVIEW

2.1 Traditional complementary alternative medicines

Definition and term of traditional and complementary medicine (TCM) is remain controversial issue in the world. TCM is known as different names such as traditional medicine, complementary and alternative medicine (CAM), complementary medicine, alternative medicine and unconventional medicine (Ministry of Health Malaysia, 2011). Traditional medicine is defined by the World Health Organization (WHO) as combination of the skills, knowledge and practices based on the indigenous theories, beliefs, and experiences from different cultures in the maintenance of health as well as diagnosis, treatment, improvement and prevention of physical and mental ailments (World Health Organization, 2001, World Health Organization, 2013).

In Malaysia, the term Traditional and Complementary Medicine (TCM) is used to address a practice of medicine that is other than the practice of medicine or dental practices employed by registered medical or dental practitioners (Ministry of Health Malaysia, 2011). According to the National Policy of Traditional & Complementary Medicine Malaysia, TCM is a form of health-related practice designed to prevent or treat illnesses and/or maintain the mental and physical well-being of patients. It comprised of traditional Malay medicine, Islamic medical practice, traditional Chinese medicine, traditional Indian medicine, homeopathy, and complementary therapies, and excludes medical or dental practices utilised by registered medical or dental practitioners (Ministry of Health Malaysia, 2011). The

diversified medical system reflects the heritage from diverse population of Malay, Chinese, Indian, and indigenous or aboriginals in Malaysia.

Recently, there is a concern on a part of TCM, which is refer as Health Supplement Products (HSP) particularly on the pattern of use and its potential interactions with prescribed medicines. TCM included other therapy which have less relevant and risk of interactions with prescribed medicines. For instance, a previous study done in Malaysia reveal that biological-based therapies were the main resource used for health problems (88.9%) and maintaining health (87.3%) in Malaysia (Siti *et al.*, 2009). Whereas, the whole TCM medical system which including acupuncture, Ayurveda, homeopathy, and traditional Chinese herb are shown to be the least use for health problems (1.9%) and maintaining health (1.5%) (Siti *et al.*, 2009). Similar finding was found in a study conducted by Than *et al.* in state of Terengganu Malaysia (Than *et al.*, 2019). Biologically based therapies are defined as the domain of biologically based practices including botanicals and animal-derived extracts, vitamins, minerals, amino acids, fatty acids, proteins, prebiotics and probiotics, whole diets, and functional foods (Siti *et al.*, 2009). It also included health supplements which are a subset of this domain.

2.2 Health supplement products

In Malaysia according to Control of Drug and Cosmetic Regulations 1984, drug here refer to medicine, and health supplement is classified under medicinal product as show below:

A “Product” as defined in the Control of Drug and Cosmetic Regulations 1984 in Malaysia (Legal Research Board, 2020):

- A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medical purpose;
- A drug to be used as an ingredient of a preparation for a medicinal purpose.

Medical purposes in the Control of Drug and Cosmetic Regulations 1984 in Malaysia were listed below (Legal Research Board, 2020):

- Alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
- Diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
- Contraception;
- Inducing anaesthesia;
- Maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function;
- Controlling body weight;
- General maintenance or promotion of health or wellbeing

Products could be further classified into four groups which is medicine, food-drug based, medical device based, and cosmetics according to the Drug Registration Guidance Documents (DRGD) issued by drug control authority in Malaysia. Medicine products was further sub classified into five categories which is new drug products (NDP), biologics, generic, health supplements, and natural products (Ministry of Health Malaysia, 2016).

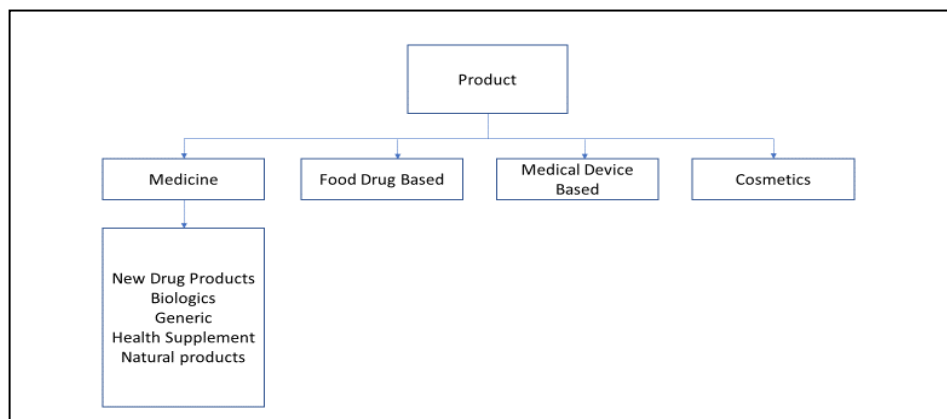


Figure 2.1 Products Classifications

2.3 Active pharmaceutical ingredients

Any manufacture pharmaceutical dosage form that contains substance or mixture of substances that possess pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. These substance or mixture of substance becomes an active ingredient of that pharmaceutical dosage form. (World Health Organization, 2012).

2.4 Products interactions

An interaction is defined as any modification caused by another exogenous chemical (medicine, herb or food) in the pharmacokinetics and pharmacodynamics of a medications in or on the body (Ismail, 2009, Hussain, 2011). This causes fluctuation of the pharmacological, toxicological or synergistic therapeutic effects of either component would complicate the dosing of long-term medications (Ismail, 2009, Hussain, 2011). Especially among modern medicine such as warfarin (anticoagulant) and phenytoin (antiepileptic) which is having narrow therapeutic

range, fluctuation of the concentration will likely cause toxicity or under dosage which lead to unintentional adverse event (Ismail, 2009).

Table 2.1 Prescribed Medicines Interaction Classification

Interaction Classification	Description
Major	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate	Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.
Minor	Minimally clinically significant. Minimize risk; assess risk and consider an alternative medicine, take steps to circumvent the interaction risk and/or institute a monitoring plan.
Unknown	No information available.

Adopted from Somogyi-Végh et al., 2019.

The classifications showed in table 2.1 are a general guideline. The relevance of a particular PM HSP interaction to a specific patient is difficult to determine by using this classification alone given the large number of variables that may apply.

2.5 Potential prescribed medicine and health supplement products interactions and the clinical implication

Due to high prevalence of concomitant use of HSP with prescribed medicines, an estimated 15 million adults are at risk for adverse interactions involving prescription medicines and herbs or vitamin supplements (Valli & Giardina, 2002). The prevalence of prescribed medicines and HSP interactions is extensive but exact prevalence was remained unknown. This was largely due to most of the studies reported was only the potential prescribed medicines and HSP interactions, as it was rather difficult to trace the association of an adverse event with the potential interaction retrospectively.

Despite of the uncertainty of the clinical significance of potential prescribed medicines and HSP interaction, it is important to bear in mind that any interaction has the potential to cause harm. Hence, reporting of any experienced adverse reaction resultant from HSP interactions is essential. According to a study conducted among dementia patients in Norway, it was found that the potential HSP and prescribed medicine interaction was as high as 11% (Risvoll *et al.*, 2017). In additional, 2 % of the elderly patients were potentially at risk of having major prescribed medicines and HSP interactions (Qato *et al.*, 2008), and 50% of these potential interactions were involved anticoagulant. Moreover, according to a systematic review, patients with chronic diseases and had education level lower than high school in Canada was 70% more likely to exhibits at least one potential interaction (Agbabiaka *et al.*, 2017). Most of the common interaction between HSP and prescribed medicines found globally with their clinical effect are summarized in Table 2.2.

The risk of prescribed medicines and HSP interactions increased with number of products consumed. It is found that the risk of interactions was 100% for consuming more than eight health supplement products (Ismail, 2009). The consequences could be devastating especially among medicines that have narrow therapeutic index or blood thinning effects. Ginkgo biloba is one of the examples of herb which frequently involved interaction. Case reports shows fatal seizures due to potential prescribed medicines and HSP interactions with ginkgo biloba as the results of inductions of the CYP 450 liver enzyme (Chavez, Jordan & Chavez, 2006, Kupiec & Raj, 2005). Ginkgo biloba increase metabolism of various antiepileptic medicines and lead to sub-therapeutics level of the antiepileptic medicines (Chavez, Jordan & Chavez, 2006, Kupiec & Raj, 2005). Additionally, ginkgo nuts contain a potent

neurotoxin, which is known to induce seizure activity (Kupiec & Raj, 2005). Gingko biloba also being interact with warfarin, aspirin or even ibuprofen which will increases bleeding tendency among patients (Ismail, 2009, Hussain, 2011, Chavez, Jordan & Chavez, 2006, Fugh- Berman, 2000, Brazier & Levine, 2003). There was a case report involved a 71-year-old male patient taking 40 mg of gingko biloba extract daily for over two years for the treatment of occasional dizziness (Chavez, Jordan & Chavez, 2006). The patient began taking ibuprofen 600 mg daily for osteoarthritis and four weeks after the regimen was begun, the patient suffered a cerebral haemorrhage, resulting in coma and death (Chavez, Jordan & Chavez, 2006). All of the interactions mention above were only tips of the iceberg, and it would bring catastrophic effects such as major organ failure and death if not being handled correctly by the healthcare professionals.

Currently, there are lack of study from Malaysia on the issue of PM HSP interaction. Most of the study found in Malaysia were focusing on specific group of patients which taking specific prescribed medicines such as anticoagulants. A previous survey involved 76 Malaysian patients in medical wards found a total of 16 (21%) patients co-ingested specified HSP with antiplatelet or anticoagulant therapy. A total of 8 (10.5%) patients were identified at risk of potential prescribed medicines and HSP interaction (Saw *et al.*, 2006b).

Table 2.2 Common Prescribed Medicines Health Supplement Products Interactions

HSP	Prescribed medicine	Clinical Effect	Interactions reported
Ginkgo (Ginkgo biloba)	Warfarin	Augmented effect	Potential increased INR and bleeding tendency, as possess blood thinning effect (Ismail, 2009, Hussain, 2011, Fugh-Berman, 2000, Brazier & Levine, 2003)
Danshen (Salvia miltiorrhiza),	Warfarin	Augmented effect	Potential increased INR and bleeding tendency, as possess blood thinning effect (Ismail, 2009, Hussain, 2011, Fugh-Berman, 2000, Brazier & Levine, 2003)
Dong quai or danggui (Angelica sinensis, syn A. polymorpha)	Warfarin	Augmented effect	Potential increased INR and bleeding tendency, as possess blood thinning effect (Ismail, 2009, Hussain, 2011, Fugh-Berman, 2000, Brazier & Levine, 2003)
Papaya (Carica papaya)	Warfarin	Augmented effect	Potential increased INR and bleeding tendency (Hussain, 2011)
Ginger (Zingibar officinale)	Warfarin	Augmented effect	Potential increased INR and bleeding tendency by increasing absorption of warfarin (Hussain, 2011)
Garlic (Allium sativum)	Warfarin Simvastatin Ibuprofen	Augmented effect Augmented effect Augmented effect	Potential increased INR and bleeding tendency, as possess blood thinning effect (Ismail, 2009, Hussain, 2011, Fugh-Berman, 2000, Brazier & Levine, 2003) Increased Simvastatin effect (Agbabiaka et al., 2017) Increased risk of bleeding (Agbabiaka et al., 2017)
Meadowsweet and black willow	Warfarin, Carbamazepine, Phenytoin	Augmented effect	Displacement of the drug from protein binding would cause sudden increased of the free drugs in serum concentration, affecting pharmacokinetics distribution of the medications thus increasing the adverse effects of these drugs (Ismail, 2009)

Table 2.2 Continued

HSP	Prescribed medicine	Clinical Effect	Interactions reported
St. John's Wort	Warfarin, Digoxin, Benzodiazepines, Tricyclic antidepressants, Verapamil, Statins	Inhibited effect	Induction of cytochrome P450 (CYP450) isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein, leading to decreased drug concentration (Ismail, 2009, Hussain, 2011)
Yohimbine (<i>Pausinystalia yohimbe</i>)	Tricyclic antidepressants	Augmented effect	Elevated effect of Hypertensive (Fugh-Berman, 2000)
Ginseng (<i>Panax spp</i>)	Warfarin	Inhibition effect	Potential Decreased INR (Fugh-Berman, 2000)
	Phenelzine	New effect	Headache and tremor, mania (Fugh-Berman, 2000)
	Alcohol	Inhibition effect	Increased clearance of Alcohol (Fugh-Berman, 2000)
Fish Oil	Warfarin	Augmented effect	Potential Increased INR (Gardiner, Phillips & Shaughnessy, 2008)
Vitamin E	Warfarin	Augmented effect	Potential Increased INR (Gardiner, Phillips & Shaughnessy, 2008)
Cranberry juice	Warfarin	Augmented effect	Potential Increased INR (Gardiner, Phillips & Shaughnessy, 2008)
Coenzyme Q10	Warfarin	Inhibition effect	Decreased the effect of warfarin (Chavez, Jordan & Chavez, 2006)
Echinacea	Simvastatin	Augmented effect	Increased drug level (Agbabiaka <i>et al.</i> , 2017)
	Lansoprazole	Augmented effect	Increased drug level (Agbabiaka <i>et al.</i> , 2017)
	Losartan	Augmented effect	Increased drug level (Agbabiaka <i>et al.</i> , 2017)
Flaxseed oil	Aspirin	Augmented effect	Affect blood pressure (Agbabiaka <i>et al.</i> , 2017)
Kava	Levodopa	Inhibition effect	Reduced the efficacy of levodopa with dopamine antagonist effect (Izzo & Ernst, 2009)

Clinical effect (Brazier & Levine, 2003) could be classified into “augmented effect” that refer to the presence of a prescribed medicine and HSP combination that

increases the effect of either therapy. “Inhibited effect” refer to the presence of a prescribed medicine and HSP combination that decreases the effect of either therapy. Meanwhile, “new effect” means combination of prescribed medicine and HSP that introduces a new effect not directly related to either therapy. Whereas, “no effect” refer to combination that does not alter the effect of either therapy. As for “conflicting evidence”, it refer to the presence of several studies of similar quality that reach different conclusions. Lastly, “no information” means there was no information on whether the interaction was augmented, inhibited, or caused a new effect.

2.6 Concomitant use of health supplement products with prescribed medicines

The consumption of health supplements in less than an hours before the consuming of prescribed medicines, or less than two hours after consuming prescribed medicines is considered as concomitant use of HSP and prescribed medicines. This classification was based on the general definition on empty stomach (United Kingdom National Health Service, 2018). There were three previous studies conducted in Malaysia which investigated concomitant use of prescription medicines and health supplements. The studies were limited to samples from single study centre namely Hospital Penang and public primary care clinic in Ipoh (Saw *et al.*, 2006a, Mahfudz & Chan, 2005), with specific disease such as hypertension (Mahfudz & Chan, 2005) or with specific type of medicines including anticoagulant (warfarin) and antiplatelet (aspirin) (Saw *et al.*, 2006b). Notably, all the studies were conducted more than a decade ago (Mahfudz & Chan, 2005, Saw *et al.*, 2006a), and there was no more recent study been conducted to address this issue.

A total of 21% among antiplatelet or anticoagulant medicines users were found to have concomitantly used HSP with prescribe medicine (co-ingested) (Saw *et al.*, 2006b). Meanwhile, 67.9% of multi-ethnic patients (Mahfudz & Chan, 2005, Saw *et al.*, 2006a) were found to have concomitantly used HSP together with their prescribed medicine. Among the hypertensive patient, majority (96%) were found to have used both HSP and prescribed medicine concomitantly (Mahfudz & Chan, 2005).

Considering the operational definition of concomitant use of HSP with prescribed medicines, most of the previous studies did not specified the timing for the ingestion. The timing could be ranged from no time gaps at all to 30 minutes as the definition of concomitant use of HSP and prescribed medicines. There was only one study done by Saw *et al.* 2006b which specifically used the term co-ingested, which implied that the patient consumed the prescribed medicines and HSP simultaneously without any time gap.

2.7 Prevalence of use or concomitant use of health supplement products (HSP) with prescribed medicines

Globally the prevalence of concomitant use of HSP with prescribed medicines were found to varied widely between 5.3% and 88.3% (Agbabiaka *et al.*, 2017). Majority of this findings were based on study conducted in United State of America (US) and United Kingdom (UK), and none of them were conducted in Asian country. Besides, most of the studies were focusing on concomitant use of HSP and prescribed medicines among older adults. Meanwhile, among adults in US, the prevalence of concomitant use of HSP with prescribed medicines were reported as 34.3% (Farina, Austin & Lieberman, 2014). Another systemic review reported that

10% to 64% of patients with proven or suspected cardiovascular diseases have concomitant use of HSP and prescribed medicines (Yong, Tan & Loh, 2014). Studies from various countries found that the prevalence in Israeli (49.5%) (Giveon *et al.*, 2004), South Africa (around 50%) (Singh, Raidoo & Harries, 2004), Scotland (39%), and Australia (around 20%) were varies in the issue of concomitant use of HSP with prescribed medicines (Armstrong *et al.*, 2011). A study found that among the adults in US who regularly take prescription medication, 18.4% have concomitant use of at least one herbal product or high-dose vitamin (Tangkiatkumjai *et al.*, 2013).

In Malaysia, the prevalence was found to be on par with the findings globally as the prevalence of concomitant use of HSP with prescribed medicines were ranging from 3.8% to 96% (Lee *et al.*, 2007, Saw *et al.*, 2006a, Saw *et al.*, 2006b, Mahfudz & Chan, 2005, Lim *et al.*, 2017, Ministry of Health Malaysia, 2002). These studies were mainly conducted in west Malaysia, and the population sampled were mainly population in the urban area. Noticeable 96% of the patients with hypertension in public primary care clinic in Ipoh concomitantly use prescribed medicines with HSP (Mahfudz & Chan, 2005). Whereas, 67.9% (Saw *et al.*, 2006a) patients from various wards and 21% (Saw *et al.*, 2006b) of patients whom took anticoagulant and antiplatelet in Penang Hospital found to use HSP with prescribed medicines concomitantly. A study from Selangor found that 56.1% of the patients were reported to concomitantly use HSP with their prescribed medicines (Lim *et al.*, 2017). The only study found in Sarawak state was conducted in the town area of Kuching in primary health care clinic in year 2004. The prevalence of concomitant use of HSP and prescribed medicines were found to be 37.8% (Lee *et al.*, 2007). All studies found were conducted in urban area such as state general hospital and health clinics. The prevalence among patients in district area of Sarawak Malaysia was not

assessed. Hence, this warrant study to explore prevalence of concomitant use of PM and HSP among patients in district area in the state of Sarawak.

2.8 Commonly used health supplement products among the patients and the concomitant prescribed medicines

The common health supplement products use reported in most study reviewed were classified into vitamins and mineral supplements such as multivitamins and individual vitamins or minerals. Besides, non-vitamin and mineral supplement mainly utilized were fish oil, coenzyme Q10, nopal, glucosamine, chondroitin, manzanilla, garlic, ginkgo biloba, Ling Zhi, ginseng, St John's wort, echinacea, saw palmetto, and evening primrose oil (Agbabiaka et al., 2017, Brazier & Levine, 2003, Izzo & Ernst, 2009, El Khoury, Ramadan & Zeeni, 2016, Bin & Kiat, 2011, Braun & Cohen, 2011, Yong, Tan & Loh, 2014). According to a study conducted by Siti et al. in Malaysia, the ten most commonly reported specific modalities used for health maintenance were topped by herbs (29.6%) and vitamin and supplement (7.4%), which is also classified as biologically based therapies as a type of traditional complementary alternative medicines use in Malaysia (Siti et al., 2009). Besides, a study done by Ching et al. in Selangor Malaysia among patients with hypertension and diabetes found that the HSP used were bitter ground, garlic, Misai Kuching, Ular Hempedu, basil leaf, and ginseng, which is in consistent with the findings found globally (Ching, Vasudevan, et al., 2013, Ching, Zakaria, et al., 2013). Similarly, a study by Hasan et al. in Seremban, Malaysia found that vitamins, herbal medicines, ginseng, America Ginseng, and Ling Zhi were commonly used among the outpatient department patients (Hasan et al., 2009). Meanwhile, a study conducted among patients admitted in Penang Hospital found that the commonly

used HSP were America ginseng, ginseng, Dong Quai, ginkgo, garlic, Mak Jun, and Tongkat Ali (Saw et al., 2006a). A study by Saw et al. which focusing on interactions between anticoagulant with HSP revealed that specific HSP possess blood thinning effect such as Panax Ginseng, garlic, ginkgo, chamomile, Dong Quai, Dan Shen, and ginger were used by patients with anticoagulant (Saw et al., 2006b).

Globally and locally, the common prescribed medicine taken by patients who consumed HSP were found to be cardiovascular agents, which including antihyperlipidemic agents, antihypertensive agents and anticoagulants (Agbabiaka et al., 2017, Brazier & Levine, 2003, Izzo & Ernst, 2009, Than et al., 2019). The anticoagulant use in Malaysia were found to be similar as reported globally which were aspirin and warfarin (Saw et al., 2006b). The commonly use antihypertensive reported were amlodipine, atenolol, furosemide, valsartan, metoprolol, and lisinopril (Qato et al., 2008), and most of it were commonly used locally (Than et al., 2019). As for antihyperlipidemic agents, statins group were most prominently found to be used among patients in overseas and locally in Malaysia. However, most of the studies in Malaysia were not listed down the specific prescribed medicines used by the patients.

2.9 Perception and practice towards the use of health supplement products

Previous studies from overseas and Malaysia revealed that general public perceived HSP as effective and relatively safe as compared to modern medicines. This could be due to the public perceived that supplements was not legitimate medicines which carry risks (Gardiner, Phillips & Shaughnessy, 2008) and they were generally not exposed to the potential side effects and interaction of HSP (Abuduli,

Ezat & Aljunid, 2011, Agbabiaka *et al.*, 2017, Gardiner, Phillips & Shaughnessy, 2008, Hussain, 2011, Ismail, 2009).

Furthermore, a systemic review by Agbabiaka *et al.* found that the HSP users perceived the healthcare providers as lacking knowledge on HSP. The HSP users viewed that the information about health supplements would not be useful and thus it is not necessary to consult or disclose such information to the healthcare providers (Agbabiaka *et al.*, 2017). Furthermore, as high as 76% of the HSP users perceived that HSP are good for their disease managements (Alshagga *et al.*, 2011). Nevertheless, more than 40% of the patients feel that taking herbal medicine along with prescription medication was more useful than taking either alone (Kuo *et al.*, 2004).

All these perceptions lead to major problems faced by healthcare providers which is the concomitant used of prescribed medicines with HSP among the patients without consult and informing their healthcare providers. This practice could lead to the risk of unsafe used of HSP as a study in Malaysia noted that there were medicinal products in the market which were not registered with Drug Control Authority (DCA) of Malaysia (Ting *et al.*, 2018). Despite the high rate of concomitant use of HSP together with prescribed medicines reported among the patients, large portion of them (61.5%-72%) did not disclose such information to their physicians (Eisenberg *et al.*, 1993, Wu *et al.*, 2014).

Moreover, this finding was also supported by the disclosure rate reported ranging from 12%-78% among older adults (Agbabiaka *et al.*, 2017). Among cardiovascular disease patients, it was reported that 35-92% of the general practitioner were unaware of the use of HSP among their patients (Grant *et al.*,

2012). These findings were further testified in a survey of 515 users of herbal remedies in the UK which found that 26% would consult their general practitioner for a serious adverse reaction associated with over the counter medicine but not for herbal medicines used. This was due to the patients were afraid of critics and not willing to unveil the use of HSP (Barnes *et al.*, 2002), and their perception mentioned earlier on. These have resulted in many unintended side effects and interactions between HSP and prescribe medicines (Eisenberg *et al.*, 1993).

In Malaysia, the disclosure rate was at the lower range recorded as 37.9%, 45.4%, and 21.1% respectively among chronic disease HSP users according to three different cross-sectional studies that conducted in Hospital Kuala Lumpur among asthmatic patients (Alshagga *et al.*, 2011), forty-five health clinics in Negeri Sembilan among diabetic patients, and Hospital Tuanku Ja'afar Seremban among chronic disease patients respectively (Baharom, Shamsul Azhar & Rotina, 2016). Additionally, it was found that up to 90% of the physician did not discuss about the use of HSP with their patients (Grant *et al.*, 2012, Alshagga *et al.*, 2011, Agbabiaka *et al.*, 2017, Hasan *et al.*, 2009). Time constrain during each patient visit was reported as one of the contributing factors (Agbabiaka *et al.*, 2017).

2.10 Association of social demographic characteristics of patients with the use of health supplement products

Various studies have been conducted to explore the factors associated with the use of HSP and the results were inconsistent. Generally factors that associated with the use of HSP were found to be and not limited to gender, age, ethnic, location (urban or rural), education level, body mass index (BMI), physical activity (uses of fitness facilities), smoking status, alcohol consumption status, medical history and

income (employment status/health insurance status) (Gardiner *et al.*, 2006, Aris *et al.*, 2014, Aziz & Tey, 2009, El Khoury, Ramadan & Zeeni, 2016, Marinac *et al.*, 2007, Tangkiatkumjai *et al.*, 2013, O'Brien *et al.*, 2017, Abdullah *et al.*, 2018, Alshagga *et al.*, 2011). The variation in the findings was due to different population, culture, and believed in the use of HSP among the patients. Hence this granted us to explore further on factors that would influence the use of HSP especially among district hospital patients in the state of Sarawak Malaysia.

2.11 Association of social demographic characteristics of patients with the concomitant use of health supplement products and prescribed medicines

There was a study conducted by Gardiner *et al.* which using 2002 National Interview Survey Data in the USA. After examined the patterns of use of HSP among adult's prescription medication users, factors associated with concomitant use of HSP and prescribed medicines included being female, being Hispanic or non-Hispanic, having more years of education, living in the Western Coast of United State, being a cigarette smoker or former smoker, having chronic conditions, and lacking medical insurance. Respondents older than 65 years, those who reported less use of a fitness centre, and those living in the Midwest or South of United State were less likely to use an HSP (Gardiner *et al.*, 2006).

Another study by Farina *et al.* revealed several demographic characteristics which were significantly associated with concomitant HSP and prescribed medicines use. Women were more likely than man to use HSP and prescribed medicines concomitantly. Older age (more than 60 years old) were more likely to concomitant use of HSP with prescription medicines as well. Those who have education level lower than college level were less likely to consumed HSP and prescribed medicines