SURVEYS ON THE USAGE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE, HERBAL PRODUCTS IN THE MARKET AND THE EFFECTS OF GINSENOSIDE RG1 ON MEDIAL PREFRONTAL CORTEX

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This work is dedicated to

My late father whose main concern was his children's education

My dear mother whose support has been eternal

and

The one without whom I would never begin, continue and finish this work, my love for ever, Dr. Sogand Zareisedehizadeh.

DECLARATION

I hereby declare that the thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in this thesis.

This thesis has also not been submitted for any degree in any university previously.

Mehdy Ghaeminia
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List of publications and conference presentations

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Summary

Usage of complementary and alternative medicine (CAM) is common worldwide. The most commonly used CAM practice is herbal medicine. Other common practices are acupuncture and its related practices, exercise based practices like qigong, tai chi and yoga and massage based practices like osteopathy and therapeutic massages. Similar to other parts of the world, the population of older adults in Singapore has shown a significant increase in recent years and it is predicted that it will rapidly increase further in next few decades. Since ageing is associated with higher risk of multiple chronic diseases, it is important to improve our knowledge and understanding about the health issues in older adults. One of the significant health conditions in this age group is their mental health and one of the possible players in their general health and mental health is the usage of CAM. Therefore, we performed this study to investigate the usage of CAM among older adults and its association with and effect on mental health using a multistep translational approach.

Hypothesizing a high prevalence of CAM usage among older adults and its association with a better neurocognitive performance, the baseline and four-year follow-up data from Singapore Longitudinal Ageing Study was analyzed to investigate the prevalence of the CAM usage and its associated factors. Among 4985 participants in baseline study who met the inclusion criteria, 2692 (54.0%) reported the usage of at least one type of CAM within the past 12 months. The usage of CAM was more common among younger female well-educated Chinese participants who lived in bigger houses and were suffering from one or two chronic medical conditions. Additionally, better physical and social activities and independency in cognitive and physical instrumental activities of daily living were associated with the higher

likelihood of using CAM. The most common types of CAM were herbal medicine (1720, 34.5%), qigong (749, 15.2%) and acupuncture (493, 10.0%) and the most commonly used medicinal herbs were evening primrose oil (245, 4.9%), ginseng (241, 4.9%) and ginkgo (222, 4.5%). The baseline neurocognitive assessment results were similar between the users of CAM and those who did not report its usage. However, after four years, CAM users and participants who reported using qigong showed a lower risk of developing cognitive decline. Besides indicating that CAM is an important and common player in the health of older adults, these results introduced qigong as a potential protective practice against the development of cognitive decline. The simplicity and affordability of qigong for older adults make it a promising cognitive protecting practice to be advised to older adults.

Since herbal medicine was the most commonly used CAM practice, a telephone interview based study was designed to improve our understanding about the usage of medicinal herbs among older adults and factors associated with their usage including neurocognitive factors. Contacting 198 older adults participating in the Jurong Ageing Study, we found that 134 (67.7%) had used herbal medicine within the past 12 months. Herbal medicine usage was again more common among younger female participants who lived in bigger houses. The top three commonly used herbs were American ginseng (*Panax quinquefolium*), wolfberry (*Lycium barbarum*) and Chinese ginseng (*Panax ginseng*) with 69, 39 and 36 users respectively. Three *Panax* species were found to be among the six most commonly used herbs (*P. quinquefolium, P. ginseng* and *P. notoginseng*). This finding shows the importance of this genus as a part of the health system of older adults. The usage of none of the medicinal herbs was associated with the baseline neurocognitive status of participants. We also found that the majority

(57.8%) of medicinal herbs users were using them for their general health improvement. Among those who used them for specific medical conditions, the usage for diseases based on traditional medicinal concepts was the most common reason for usage followed by neurological problems and musculoskeletal conditions.

Similar to reports from different countries, *Panax* species were the most common herbs used by participants in our study. Most of these herb users get these herbs from different shops over the counter and the information provided in their labels is the main source of information about each particular herbal product. Therefore, it is important to survey the products in the market containing these herbs to see how consistent their labels are with the local legislations. Therefore, all products containing the words "Panax" or "ginseng" found in five different shops in Singapore were surveyed. All the information provided in their labels was recorded and compared to local legislations. It was found that among 309 surveyed products, 188 were Chinese proprietary medicine, 85 were health supplements and 36 were food supplements. *P. ginseng* was the most common herbal ingredient followed by *P. notoginseng* and *P. quinquefolium.* The information provided in the labels of more than 96% of CPM products, 84% of HSs and 88% of FSs was consistent with respective legislations. The indications reported in the labels of these products were also studied showing that after health conditions based on traditional medical concepts, circulatory system disorders, pain and neurological conditions were the most common indications claimed in the labels of the products.

Considering the common usage of products containing *Panax* species for neurological purposes and the prevalent claim of being effective for neurological conditions, we chose one of the most abundant chemical constituents in major *Panax species*, ginsenoside Rg1 (a known neurostimulatory compound), for the next step of

the study. Considering the role of medial prefrontal cortex (mPFC) in decision making, cognition and behaviour, we hypothesized that ginsenoside Rg1 stimulates this brain locus. To investigate this hypothesis, three sets of experiments were performed. The first set of experiments revealed that three different doses of ginsenoside Rg1 (1, 3 and 10 mg/kg) suppressed the long-term potentiation in mPFC in response to electrical stimulation of ipsilateral intermediate and ventral hippocampus. In the second set of experiments, the systemic administration of all the three single doses and the accumulative doses of ginsenoside Rg1 showed a similar pattern of suppressing the spontaneous firing rate of half of the pyramidal cells in medial prefrontal cortex. In the third set of experiments, the expression of an immediate early gene, c-Fos, in medial prefrontal cortex was dose-dependently decreased in response to systemic administration of ginsenoside Rg1 (1, 3 or 10 mg/kg). All together, these three sets of experiments show the suppressing effect of ginsenoside Rg1 on medial prefrontal cortical neurons for the first time. This effect may explain the anxiolytic effects of ginsenoside Rg1, which indirectly improve learning and cognition.

In conclusion, a translational medical approach to the usage of complementary and alternative medicine was used in this study starting from getting information from community dwelling older adults about their trend of usage, continuing the survey focused on the usage of herbal medicine, collating information from available herbal products in the market and finally examining one of the possible mechanisms of neurological actions of one of the most abundant chemical constituents of the most commonly used herbal products. Such a study can open new windows to further research in the field of complementary and alternative medicine.

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Abbreviations

AC	After Christ Birth
AUC	Area Under the Curve
AVA	Agri-food and veterinary Authority
BD	Block Design
BDNF	Brain-Derived Neurotropic Factor
BPC	British Pharmacopeia Commission
CAM	Complementary and Alternative Medicine
CeLS	Center for Life Science
c-FOS	Cellular Finkel–Biskis–Jinkins Murine Osteosarcoma Oncogene Homologue
CI	Confidence Interval
cIADL	Cognitive Instrumental Activity of Daily Life
CMM	Crude Chinese Medicinal Material
COPD	Chronic Obstructive Pulmonary Disease
CPC	Chinese Pharmacopoeia Commission
CPM	Chinese Proprietary Medicines
DAPI	4’,6’-diamidino-2-phenylenindole dihydrochloride
DNA	Deoxyribonucleic Acid
ECAQ	Elderly Cognitive Assessment Questionnaire
FS	Food Supplement
GDS	Geriatric Depression Scale
GMP	Good Manufacturing Practice
GSL	General Sale List
HFS	High Frequency Stimulation
HP	Hippocampus
HS	Health supplement
HSA	Health Sciences Authority
IACUC	Institutional Animal Care and Use Committee
IADL	Instrumental Activity of Daily Life
ICV	Intracerebroventricular
IOC	Input Output Curve
IP	Intraperitoeneal
IRCH	International Regulatory Cooperation for Herbal Medicine

IV	Interavenous
JAS	Jurong Ageing Study
LLP	Long-Lasting Potentiation
LTP	Long-Term Potentiation
MMSE	Mini mental status examination
MOH	Ministry of Health
mPFC	Medial Prefrontal Cortex
NCCAM	National Center for Complementary and Alternative Medicine
NS	Normal Saline
NUS-IRB	National University of Singapore Institutional Review Board
OR	Odds Ratio
OTC	Over the Counter
PBS	Phosphate Buffer Saline
PET	Positron emission tomography
PFA	Paraformaldehyde
pIADL	Physical Instrumental Activity of Daily Life
PPD	Protopanaxadiol
PPT	Protopanaxatriol
RAVLT	Rey Auditory Verbal Learning Test
RNA	Ribonucleic Acid
SD	Sprague-Dawley
SLAS	Singapore Longitudinal Ageing Study
SPSS	Statistical Package for Social Sciences
TCM	Traditional Chinese Medicine
TTX	Tritone X
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

CHAPTER 1. Introduction

Medicine has been developed by observation and research for millennia. Since prehistoric times, humans have observed and studied nature to find ways to maintain and improve their health and fight the diseases threatening their well-being. Ancient tribal medical men learnt from nature and promoted the use of various dietary and topical remedies for diseases (e.g. fruits, linseed oil). Such knowledge passed through generations and became more organized into medical systems. It was around 1030 AC when Avicenna wrote the Canon of Medicine establishing the foundation for experimental and evidence based medicine for the first time (Chen et al., 2012). Through new advances in science in last few centuries, researchers have started to have the advantage of the microscopic approach to understand the molecular and structural bases behind diseases and bio-systems. Rapid advances in molecular research made scientific approaches at micro and nano levels, which were far from daily clinical practices (Kulikowski et al., 2009). The bridge connecting the research in basic science (micro level) to clinical practice (macro level) is called translational medicine (Satoh et al., 2012).

Translational medicine is a "feed-back-loop" with the aim of providing crucial information about the applicability of the methods and approaches in societal contexts and their success in improving human health (Sonntag, 2005). It is usually a journey from bed to bench to bed and beyond. Translational medicine starts from clinical observation of phenomena that attract attention from laboratory researchers. Laboratory researchers uncover molecular and cellular mechanisms, which can provide new approaches to clinical questions. Now it is the clinicians' role to apply those laboratory

findings and examine their applicability and efficacy in clinical trials and practices. The next step is to extend the clinical applications into diverse medical settings (Sachar, 2009). At each step, the feedback from clinics will go back to laboratories to improve the knowledge, deepen the understanding and optimize the applicability of new methods with respect to clinical settings.

In the current work, a translational approach was begun from clinical observation of the pattern of usage of complementary and alternative medicine (CAM) in the community and factors associated with it to find the most common CAM types and the trend of their usage. Then, the journey was pursued to bench side to understand the possible mechanisms of action and suggest the future path of research to make the findings more practical and improve health in the society.

1.1. Complementary and alternative medicine

Complementary and alternative medicine (CAM) is often defined as the range of health care approaches with a history of use or origins beyond mainstream (conventional) medicine. It can be used either for specific conditions or overall well-being. If CAM is used together with conventional medicine, it is referred as "complementary medicine" and if used in place of conventional medicine, it is called "alternative medicine". The combination of CAM with conventional medicine is termed as "integrative medicine", which is offered in many clinical settings in developed countries recently (NCCAM, 2013). Based on National Center for Complementary and Alternative Medicine (NCCAM) definitions, CAM can be categorized in two main subgroups, "natural products" and "mind and body approaches".

Natural products include a variety of products such as herbs, vitamins and minerals and probiotics, which are generally marketed as ready to use dietary supplements. Herbal medicine as the most commonly used type of CAM (Robinson et al., 2011) will be discussed in detail in section 1.2. Two closely related CAM practices are naturopathy and aromatherapy. Naturopathy aims to support the body in order to heal itself through the use of dietary and lifestyle changes together with other CAM modalities such as herbs, massage and joint manipulation (NCCAM, 2013). On the other hand, aromatherapy is concerned with physiological and pharmacological effects of essential oils introduced by means of inhalation, olfaction and dermal application (van der Watt et al., 2008).

Mind and body practices are very large and diverse groups of procedures or techniques administered or taught by a trained practitioner or teacher. They include acupuncture and moxibustion, massage therapy, meditation, movement therapies, relaxation techniques, spinal manipulation, osteopathic manipulation, tai chi, qigong, yoga, chiropractic, healing touch and hypnotherapy (NCCAM, 2013). In the following paragraphs, these CAM practices will be defined briefly.

Using specific anatomical points on the body to aim the treatment or health maintenance is the basis of some mind and body practices including acupuncture, moxibustion, acupressure and reflexology. Acupuncture is one of the most ancient healing modalities dating back to 6000 BCE. Although originated from China, it is practiced worldwide today (Zhang, 2008). In this practice, solid filiform needles are placed in specific points of the body to promote the health and treat the illnesses (Wang et al., 2013b). Acupuncture is closely carried out together with moxibustion, which involves the direct or indirect application of ignited mugwort (*Artemesia vulgaris*) on

acupuncture points or other specific parts of the body to facilitate healing (Xiong et al., 2013). Another related technique is acupressure, which is a deep and effective hands-on treatment for many conditions. It includes massage of acupuncture points or other specific areas, which is relaxing and provides support for general health and well-being (Suhrabi et al., 2014). Another close technique is reflexology, which has originated from Chinese and Indian traditional medicine. It is based on a belief that the whole human body is represented on the feet (mostly the soles) and the internal organs can be treated by pressing particular areas of the feet (Ernst, 2009).

In contrast to acupuncture and related practices that focus on specific points, there are other massage-based therapeutic approaches, which work with bigger body areas mainly focusing on the trunk. They include therapeutic massage, chiropractic, spinal manipulation and osteopathy. Therapeutic massage is defined as mechanical manipulation of body tissues with rhythmical pressure and stroking with purpose of promoting health and well-being (Weerapong et al., 2005). Chiropractic is a CAM approach that is involved in diagnosing and treating medical problems by adjustments made to spines and musculoskeletal system mainly by affecting the nervous system (Zhang, 2008). Spinal manipulation is a technique usually used as a part of chiropractic to achieve spinal adjustment by high velocity trusts with either a long or short lever-arm (Ernst et al., 2001). Furthermore, osteopathy has similar basics trying to face illnesses by manipulating mostly the spinal cord via vertebrae and other bones (Howell, 1999).

There are some techniques that aim to improve the body performance and general health based on utilizing internal energy and individual physical abilities such as meditation, yoga, movement therapies, tai chi and qigong. Meditation is defined as a

group of complex emotional and attentional regulatory training regimes developed for different aims including the cultivation of well-being and emotional balance (Lutz et al., 2008a). Relaxation techniques include deep breathing, guided imagery and progressive muscle relaxation, which are used to maintain body natural response. Movement therapies are a broad range of Eastern and Western movement-based approaches such as Feldenkrais method, Alexander technique, Pilates, etc. (NCCAM, 2013), which improve mind and body performance by sequences of movements and postures (Schmalzl et al., 2014). Tai chi, originated from China, is the mixture of deep breathing and relaxation with slow movement (Lee et al., 2012b). Similarly, qigong is a Chinese medical exercise, which combines static and dynamic physical exercises, breathing exercise and meditation (Lauche et al., 2013). Yoga, originated from Ayurveda, is an emotional harmonizing practice by the use of posture, isometric muscle contraction and breathing (Posadzki et al., 2009).

In addition to those mentioned practices, there are some other CAM practices that are mainly based on religious or supernatural beliefs with minimal or no scientific justification. Spirit medium healing is a religious based healing approach indigenous to various ancient societies in which some healers try to improve health and treat diseases based on guidance and connection to gods (Koss-Chioino, 2005). Healing touch is another supernatural healing strategy, which claims to heal through some exchange or channeling of supra-physical energy (Astin et al., 2000). Hypnotherapy is a kind of healer-patient therapeutic interaction during which the patient experiences suggested changes in sensation perception, thought or behavior using intense concentration and focus while being fully conscious (Beebe, 2014). Homeopathy can also be categorized in the supernatural therapeutic group. It is based on the premise that diseases can be

treated by substances that produce the same signs and symptoms in a healthy individual. The remedies are usually prepared by sequential dilution of the originally harmful substances with vigorous shaking of solutions between dilution sequences (Shang et al., 2005).

Finally, traditional medical systems can be considered as the most complete sets of CAM. These systems have been developed in different ancient societies over time and adapted by others during cultural and scientific exchanges. They usually include both "natural product therapy" and "mind and body approaches". For example, Traditional Chinese Medicine (TCM) is a defined medical system with more than 2500 years history, which has been used successfully to diagnose, treat, and prevent illness (Robinson et al., 2011). It includes both natural products and some mind and body practices such as acupuncture, tai chi and qigong. Natural products in TCM include both crude Chinese medicinal material (CMM) and Chinese Proprietary Medicines (CPM). The CMM includes any herbs, animals and minerals subject to simple process such as cutting and drying while CPMs are CMMs, which have been formulated into end products as capsules, tablets, powders and other dosage forms (Koh et al., 2000).

1.1.1. Global usage of complementary and alternative medicine

Many people around the world use CAM for their health maintenance or medical purposes. In a majority of developing countries, 70-95% of citizens use traditional and herbal medicines to address their primary health care needs and concerns (Robinson et al., 2011). In some developed nations, 70-90% of people have reported using traditional medicine under the title of "complementary", "alternative", or "nonconventional" medicines (Robinson et al., 2011) (Figure 1.1).

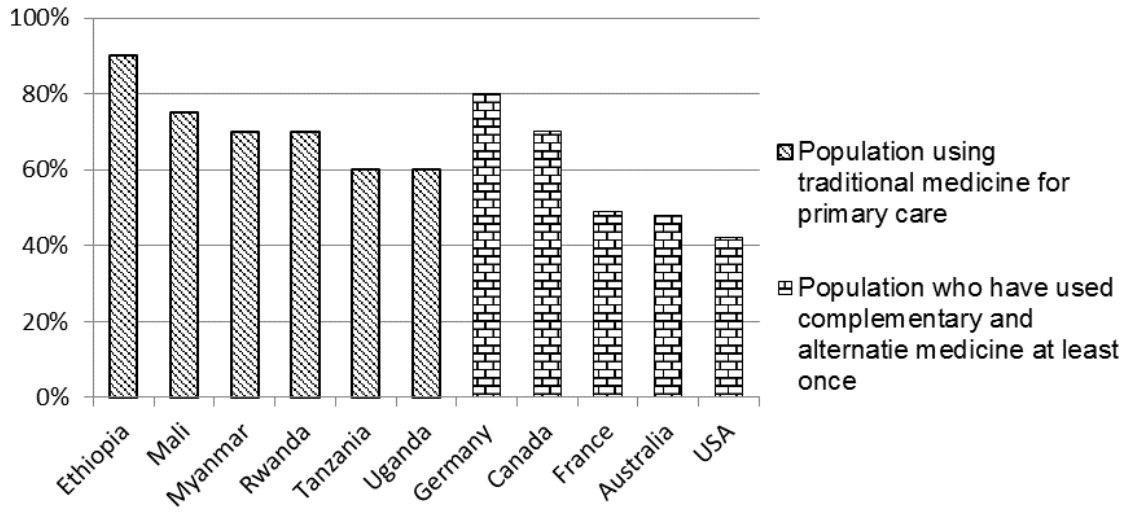

Figure 1.1. Global prevalence of CAM usage in selected developing and developed countries (adapted from Robinson et al., 2011).

The reports on the prevalence of CAM usage are very diverse in different countries. Based on the National Centre for Complementary and Alternative Medicine (NCCAM) reports, 38% of Americans use some forms of CAM. In an online survey performed in 2006, 46.2% of US adolescents had used dietary supplements excluding vitamins (Wilson et al., 2006). In some other western countries, reports show much less prevalence of usage. Ramsay et al. (2005) reported this prevalence in the UK as about 20%. In eastern countries, the usage of CAM is very common. In South Korea, the prevalence of CAM usage in general population was 75% in 2006 (Kang et al., 2012), which is comparable to studies on general population from Singapore where 76-86.5% of population uses some kinds of CAM (Koh et al., 2004; Lim et al., 2005). In Singapore, herbal medicine has been reported as the most commonly used CAM type used by 73.4% of general population of adults followed by non-herbal TCM (72.3%) and massage therapy (35.5%) (Koh et al., 2004). In a parallel study, 84.3% of pharmacists working in Singapore reported usage of some form of CAM. Among them, herbal medicine, non-herbal TCM and massage were the three most commonly used

forms among them with 72.0%, 56.8% and 35.3% popularity respectively (Koh et al., 2003). In another local study, the most common CAMs used by ambulatory patients with chronic diseases were TCM (37.8%), traditional dietary therapy (29.7%) and acupuncture (27.5%) (Lee et al., 2004b).

Furthermore, some special social or medical groups show more interest in the usage of CAM than the general population. For example, in a survey conducted in 2006, the usage rate of applicants for cosmetic medical interventions was more than twice the one of general American population (Heller et al., 2006), 78.5% of Korean "cancer patients" were using CAM in any form in 2004 (Kim et al., 2004a) while the prevalence of CAM usage in general population was 75% (Kang et al., 2012) and in the United Kingdom where the prevalence of CAM usage is about 20%, 26.9% of "patients starting warfarin" were taking some form of CAM (Ramsay et al., 2005).

This global high prevalence of usage makes a big and expanding market for CAM products and services such as traditional medicines. It is estimated that the growth rate of traditional medicine product sale in the last decade stands somewhere between 5-18% per annum (Robinson et al., 2011). Nowadays, CAM has a very big market all around the world, although it is not the same across different countries. In Brazil, herbal products form 7% of pharmaceutical industry and cost US$400 million per year (Auricchio et al., 2007). In China, traditional herbal preparations constitute 30-50% of the total medicines consumption. Its sales value in China was equal to US$14 billion in 2005 (Robinson et al., 2011). At the same time, Australians spent US$1.86 billion (Xue et al., 2007) and the Japanese spent over US$1 billion (Holtz, 2008) only on herbal medicines excluding animal or mineral products or other CAM services.

1.1.2. Reasons and purposes for usage of complementary and alternative medicine

There are complex and interrelated psychosocial and cultural factors impacting on the usage of CAM. These factors include dissatisfaction with conventional treatments, personal beliefs and preferences, and economic factors (Lee et al., 2004b). Some patients are not satisfied with their conventional treatments because of their efficacies, side effects, or costs. On the other hand, CAM and natural products are advertised to be safe with therapeutic potentials (Foroncewicz et al., 2011). Moreover, they seem to be cheaper because they are easily available over the counter without the need for prescription (Foroncewicz et al., 2011). Their availability is even increasing rapidly because there is less regulatory requirement for their safety and efficacy than requirements for conventional drugs and treatment protocols (Bardia et al., 2007). Moreover, some people prefer to have more control on their own treatment and find CAM more consonant with their personal values, religious and health philosophies (Lee et al., 2004b).

The purpose of using CAM varies in different societies and groups of people. For example, in Australia, general health improvement was reported as the most common reason (69.6%) for herbal medicine usage. However, some people use them to treat certain diseases such as colds, flu, cough, fever, skin conditions, and gastrointestinal conditions, sleep disorders, menopausal symptoms, urinary or bladder problems and anxiety or depression (Zhang et al., 2008a). In a study on Korean breast cancer patients, the main reasons of using CAM were to boost immune system (53.2%), promote health (46.8%) and prevent recurrence (37.7%) (Kang et al., 2012). In another study on Korean cancer patients, only 7% of them were using CAM for its anti-cancer effect and the

majority were using these products and practices as a nutritional support (19.1%) or to strengthen the body (17.8) (Kim et al., 2004a). Although the study designs are dissimilar, it can be concluded that general health improvement is the main purpose of using various CAM practices. However, some people use them to treat their illnesses especially when the conventional medicine is not easily affordable or its efficacy is suboptimal.

1.1.3. Risks associated with the usage of CAM

Some incorrect general beliefs may impair the proper usage of CAM products and can be considered as potential harms to users. For example, there are common misconceptions that "everything natural is good" or "no matter how consumed, if something comes from nature does not harm the consumer". In addition, people do not usually assume CAM products (e.g. the medicinal plants) as drugs although theoretically they are (Avello et al., 2010). Since herbal medicine are actual drugs with real effects, they are not free of adverse effects as well. There are several reports of different adverse effects of herbal products some of which very serious and dangerous. These adverse effects can be mild such as diarrhea or severe and life threatening such as bleeding tendency and organ failure. For example, bleeding tendency has been reported as a potential adverse effects of several herbs such as evening primrose oil (Wedig et al., 2008), *Serenoa repens* (Villanueva et al., 2009), *Angelica sinensis*, *Zingiber officinale* (ginger), *Panax ginseng*, *Panax notoginseng*, *Panax quinquefolium*, *Glycyrrhiza glabra* (licorice), etc. (Cordier et al., 2012). The other frequently reported serious adverse effect is hepatic injury which has been reported as a potential side effect of Rhubarb (*Rheum rhabarbarum*) (Wang et al., 2014c), *Cimicifuga racemosa* (Enbom et al., 2014), *Gynura segetum* (Zhou et al., 2014), *Tripterygium wilfordii* (Zhao et al.,

2014), etc. Renal toxicity is another life threatening side effect of some herbal products which has been reported from *Callilepis laureola* (Watson et al., 1979), *Dioscorea quinqueloba* (Kang et al., 2015), *Aristolochia indica* (Michl et al., 2013), etc.

Ordinary people can hardly believe that CAM may interfere with any conventional medicine they might use. These incorrect beliefs may increase the risk of inappropriate use of CAM products which can cause severe and dangerous interactions and side effects. For example in a study conducted in the UK, 26% of patients on warfarin were using CAM products among which 58% could interact with warfarin (Ramsay et al., 2005).

Therefore, all consumers, manufacturers, medical practitioners, policy makers, and anybody else involved in the usage of CAM have to improve their knowledge about risks and benefits of using these products in order to minimize the adverse effects of CAM use and improve the general health of society. Therefore, Singapore government has implemented several legislations to control the production, marketing and advertisement of CAM products (section 1.2.2).

1.1.4. Professional health practitioners interactions with patients using CAM

People generally hide their usage of complementary medicines from their physicians. It may be because of physician indifference or opposition toward CAM use, physicians' overemphasis on scientific evidence, or patients' anticipation of a negative response from the physicians (Kang et al., 2012; Tasaki et al., 2002). For instance, only 29.6% of Korean breast cancer patients who were using alternative medicines besides their conventional drugs had let their physicians know about it (Kang et al., 2012).

Another study in Korea showed a big gap of understanding between physicians and the cancer patients hiding their CAM usage from their health providers. Although 85% of cancer patients were using CAM because they thought that they are nontoxic, the oncologists estimated that only 24% of them are in favor of CAM because of their safety. In the same study, 86% of oncologists thought that their patients hide their CAM usage from them because they are afraid of discouragement or disapproval by the physicians while only 27% of patients were afraid of that and the most common (48%) reason for not disclosing this usage was that their physician never asked about it (Kim do et al., 2008). This problem is global and cross-cultural. In the UK, 92.2% of patients taking herbal medicine and warfarin together did not mention this usage to their conventional healthcare professionals (Smith et al., 2004). This proportion was 57.1% in Singapore (Goh et al., 2011). In other studies in Singapore, the reporting rate of concurrent usage of CAM and conventional medicine to physicians was only 16.3% in patients with chronic diseases (Lee et al., 2004b) and 30.4% in general population (Koh et al., 2004). This problem is not limited to the ordinary people and can also be seen among health care personnel. Among pharmacists participating in a survey in Singapore, 70.5% of those who used CAM and conventional medicine together did not consult a doctor about it (Koh et al., 2003).

Professional health care providers have easier access to available information sources about herbal products, scientific studies on them and their evidence-based indications, contraindications and adverse effects if any. On the other hand, ordinary people hardly use such information. Hence, lack of a sustained patient-physician relationship impairs the accessibility of the patients to this important knowledge and puts the CAM users at the risk of inappropriate treatment or adverse effects such as

herb-drug interactions (Bardia et al., 2007; Smith et al., 2004). In a survey conducted in the US, less than 10% of American athletes using health supplement gained their information from health professionals (Froiland et al., 2004). In Singapore, just 7% of athletes using supplements had consulted with a health professional and their major source of information was media such as television and magazines (25%) (Tian et al., 2010). Zhang et al. (2008) reported that more than half of herb users in Australia self-selected their medicines and only 27.4% had consulted with an herbalist and 8.2% with a medical practitioner (Zhang et al., 2008a). These reports emphasize that health professionals should consider the hidden usage of CAM by their patients to prevent adverse effects, drug-herb interactions or other risks of undisclosed usage of such products to their patients especially when dealing with high risk patients such as older patients and those under treatment with narrow therapeutic window drugs (e.g. warfarin and digoxin).

1.2. Herbal medicine

Herbal medicine is the most common CAM used worldwide in almost all reports (Chu et al., 2013; Posadzki et al., 2013a; Posadzki et al., 2013b; Robinson et al., 2011). Based on WHO definition, herbal medicine includes herbs, herbal materials, herbal preparations and finished herbal products that contain active ingredients from parts of plants. Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered. Herbal materials include, herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials. Herbal preparations are the basis for finished

herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials. Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. They may also contain excipients in addition to the active ingredients (Zhang, 2000).

Excipients are substances other than the active principal ingredients added intentionally to the medicinal formulations for different purposes such as improving the taste and dosage formula (Pifferi et al., 2003). In this study, substances like sweeteners, artificial colors, flavors, stabilizers, water, oils, resins, caramel, etc. were considered as excipients except those with specific traditional medical uses such as “dragon’s blood”, which is a resin with medical uses (Zhao, 2004).

Based on Chinese Materia Medica, some natural products with non-plant origins can also be considered as herbs such as those from animal origins and minerals (Bensky et al., 2004; Zhu, 1998). However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal (Zhang, 2000).

Since medicinal herbs are usually consumed orally, their chemical constituents deal with absorption, distribution, metabolism and excretion processes in the body. Therefore, the safety issues regarding their usage are more magnificent compared to other CAM practices. Many factors affect the risks and benefits of using natural

products. For example, dosing is usually difficult to measure because in traditional prescription it is not measured very accurately. In addition, active substances are not uniform even in well prepared commercially available products in the market (Avello et al., 2010).

One of important risks associated with usage of herbal medicine is the potential for interaction with other herbs, conventional drugs and food elements. These interactions can be due to two main mechanisms namely pharmacodynamics interaction and pharmacokinetic interaction. Pharmacodynamics interaction is modification of pharmacological effect of one chemical entity by another one without altering its concentration in the tissue fluid (by affecting the target molecule, competing in the receptor-ligand interaction, etc.) while pharmacokinetic interaction is based on changes in the concentration of a chemical entity in its site of action due to presence of another active chemical agent (by affecting absorption, distribution, metabolism or excretion). Such interactions are more important for drugs with narrow therapeutic range (small difference between minimum effective dose and maximum safe dose) and steep concentration-response curve (a small change in concentration causes a significant change in effect) such as antithrombotic, anti-arrhythmic, antiviral and antiepileptic drugs; lithium; and several antineoplastic and immunosuppressant drugs (Rang, 2012). There are several reports of potential interactions between conventional drugs, herbs or food elements as well as herbal medicine and other herbs (either used as another herbal medicine or used as a food item). Grape fruit which can be used either as herbal medicine or as a food can change the hepatic metabolism of many drugs such as important cardiovascular agents, CNS modulators, antiviral drugs, etc. (Bailey et al., 2004; Libersa et al., 2000; Rodriguez-Fragoso et al., 2011). Similar interactions through

altering hepatic or enteric metabolism have been reported from other citrus fruits like sour (Seville) orange, sweet orange and pomelo, pomegranate, grape, mango and cranberry affecting warfarin, antihypertensive and other drugs (Paine et al., 2007; Rodriguez-Fragoso et al., 2011). It is shown that *Evodia rutaecarpa* and herbal preparation Wu-Chu-Yu-Tang can dose-dependently decrease the theophylline concentration in blood (Jan et al., 2005). The interaction between digoxin and St. John's wort can also be dangerous (Dasgupta, 2008; Rang, 2012).

Different toxic and pathogenic materials may contaminate the herbal remedies. A group of pathogenic impurities are toxic botanicals such as *Spartium juncium, Aristolochia fangchi, Aristolochia manshuriensis, Teucrium* species and species containing tetrahydropalmatine or belladonna alkaloids. Microorganisms can grow and release microbial toxins in the herbal products and cause microbial poisoning. Usage of pesticides and fumigation agents can chemically contaminate the herbal products. Soil pollutions by radioactive material and toxic metals are another source of herbal pollution. Finally, there is always a risk of adulteration with synthetic pharmaceuticals and animal substances (Koh et al., 2000).

Another risk in using herbal preparations for treatment is unproven therapeutic indications. Although usage of many herbs has a long history and is documented in ancient medical books, the available scientific evidence is not enough in most cases. This lack of scientific proof is extended to undisclosed toxicities and potential interaction of the chemicals constituents of herbal preparations with each other and with concomitantly taken conventional drugs. Besides, incompatibilities with patient-related factors (e.g. age, sex, genetic background and the function of the organs responsible for metabolism and excretion of the chemicals in herbal preparations such as the liver or

kidneys) may cause adverse effect in susceptible consumers. It is difficult to standardize treatments because of lack of enough scientific literature for most of herbs. Finally, the concomitant usage of regular drugs with the herbal preparations without disclosure to medical practitioner increases the risk of herb-drug interaction and other adverse effects (Simaan, 2009).

Considering the great accessibility of medicinal plants and the misconceptions about their safety and efficacy, the lack of sufficient supervision and control on their production, sale and advertisement can encourage improper self-medication and may cause severe health issues (Avello et al., 2010).

1.2.1. Regulations for herbal medicine and other health products

Despite thousands years history of usage of medicinal herbs and most other CAM practices, the history of regulating their usage is short (Robinson et al., 2011). People and policy makers have various approaches to such products. It is reflected on the diverse terminology used to address them. They are sometimes referred as self-medications, faith-healing practices, home remedies, dietary supplements, health foods, functional foods, phytoprotectants, folk medicines, etc. (Adib, 2004; Robinson et al., 2011). Consequently, diverse legislations are used to regulate their marketing in different countries. Various legislative approaches for such products compared to conventional medicine include:

- Exemption from all regulatory requirements for herbal or traditional medicine
- Exemption from all regulatory requirements for herbal or traditional medicine concerning registration or marketing authorization

- Regulatory requirements similar to conventional medicine with certain types of evidence not required for herbal or traditional medicine
- Herbal or traditional medicine subject to all regulatory requirements
- Herbal or traditional medicine subject to all regulatory requirements concerning registration or marketing authorization (Zhang, 1998).

By increasing the worldwide prevalence of CAM usage, the importance of having proper regulation for their production and marketing has become more highlighted. Hence, from 1986 to 2007, the number of World Health Organization (WHO) members having some type of policy in place regarding regulation and registration of CAM products and services increased from 14 to 110 (Robinson et al., 2011).

The global need to have regulatory issues on the usage of alternative medicine, especially herbal medicine, led in the creation of the "international regulatory cooperation for herbal medicine (IRCH)" coordinated by WHO in 2006. The mission of IRCH is to protect and promote public health and safety through improved regulation of herbal medicines (Robinson et al., 2011). For this, IRCH has recommended the inclusion of proven traditional remedies into national drug policies and regulatory measurements. By integration of traditional medicines into national health care systems, development of technical guidelines and international standards will rationalize the use of traditional medicine and improve the dissemination of information on its various forms (Zhang, 1998). By 2009, twenty two countries including Singapore had joined IRCH (Robinson et al., 2011).

Having long history of usage and tradition of herbal medicine in Eastern countries such as Japan, China and Korea has made traditional medicine including herbal

medicine an important part of health care system in these countries (Cheung, 2011). Despite common roots and similarities in traditional medical care in these countries, the corresponding regulations and their legal processes are different (Cha et al., 2007; Sarfaraz, 2007).

In China, the Drug Administration Law is implemented, which says that traditional herbal preparations are generally considered "old drugs" and, except for new uses, are exempt from testing for efficacy or side effects. The Chinese Ministry of Public Health oversees the administration of new herbal products (Sarfaraz, 2007). On the other hand, in Japan, traditional medicine is regulated in the same way as conventional medicine and relevant laws are applied. The Ministry of Health, Labor and Welfare (MHLW) is responsible for writing the policies and developing the structure of the National Health Care Plan, and provides national oversight (MHLW, 2012). Traditional Japanese medicine, called kampo, is similar to and historically derived from Chinese medicine but includes traditional medicines from Japanese folklore as well. The Japanese herbal medicine industry establishes regulations to manufacture and control the quality of extract products in kampo medicine. These regulations comply with the Japanese government's Regulations for Manufacturing Control and Quality Control of Drugs (Sarfaraz, 2007). Recently, herbal products are specified as designated drugs by the Pharmaceutical and Food Safety Bureau to implicate a better control (MHLW, 2013). In Korea, current regulations on herbal medicine are legislated to improve quality control of imported herbal products, to require the use of real names in distribution of herbal medicine and use of standardized herbal medicine, to provide and improve the standards in decoction facilities outside clinics and traditional medical hospitals and to prohibit sale of herbal and other traditional medical products manufactured or packed

without national legislations (MOHW, 2014). Finally, Singapore Parliament passed the "TCM practitioners act" in 2000 to improve the standards of TCM services in Singapore. Since that time, some TCM services are allowed to be offered in hospitals (Lee, 2006). The TCM products are subject to several legislations which will be elaborated in section 1.2.2.

1.2.2. Singapore regulations for herbal medicine and other health products

Under Singapore legislations, herbal products are classified under the "complementary health products" category (HSA, 2012d). Health products are any substance, preparation or device represented for, likely to be taken for, or belonging to a category of products ordinarily intended for use by humans solely or principally for a health related purpose. These categories include conventional (Western) medicines, medical devices, complementary health products and cosmetic products. Complementary health products include "Chinese Proprietary Medicine", "Other Traditional and homeopathic Medicine" and "Health Supplement" (MOH, 2010).

Health products are legislated by Health Sciences Authority (HSA) under the "Medicines Act" and its regulations, the "Health Product Act" and its regulations, the "Poison Act" and its rules, the "Medicines (Advertisement and Sale) Act", the "Sale of Drugs Act", and the "Tobacco (Control of Advertisement and Sale) Act" (HSA, 2012d).

Under the Medicines Act, "medicinal product means any substance or article (not an instrument, apparatus or appliance) manufactured, sold, supplied, imported or exported or to be used as an ingredient in the preparation of a substance or article, to be administered to one or more human beings or animals for medicinal purposes". A medicinal purpose means treating or preventing diseases, diagnosing diseases or

determining the existence, degree or extent of a physiological condition, contraception, anesthesia, or preventing or interfering with the normal operation of a physiological function (MOH, 2008a).

HSA also governs the advertisement and labeling of the products. Under the Health Products Act, false or misleading advertisement can cause conviction to a fine not exceeding $20,000 or to imprisonment for a term not exceeding 12 months or both. An advertisement shall be taken as false or misleading if it falsely describes the health product or gives any false information concerning it, or it is likely to create an erroneous impression regarding the formulation, composition, design specification, quality, safety, efficacy or uses of the health product (Health product act, 2007).

Herbal products can be marketed as either health or food products and each of these have their own specific regulations. Therefore, categorization of a product into different health product categories or food supplements is at ultimate importance for assessment of a product. This process can sometimes be very challenging (Federici et al., 2005). The first step is to differentiate health products from food supplements. Under Singapore regulations, health products are under purview of Health Sciences Authorities (HSA) while Agri-Food and Veterinary Authority (AVA) regulates foods and supplements of food nature. In order to facilitate classification, HSA and AVA have developed a classification algorithm (Figure 1.2) (HSA, 2012a).

Health products will be further classified. Chinese proprietary medicines and health supplements are the major categories of health products besides conventional (western) medicine. In following sections, the regulations corresponding to Chinese proprietary medicines, health supplements and food supplements will be reviewed.

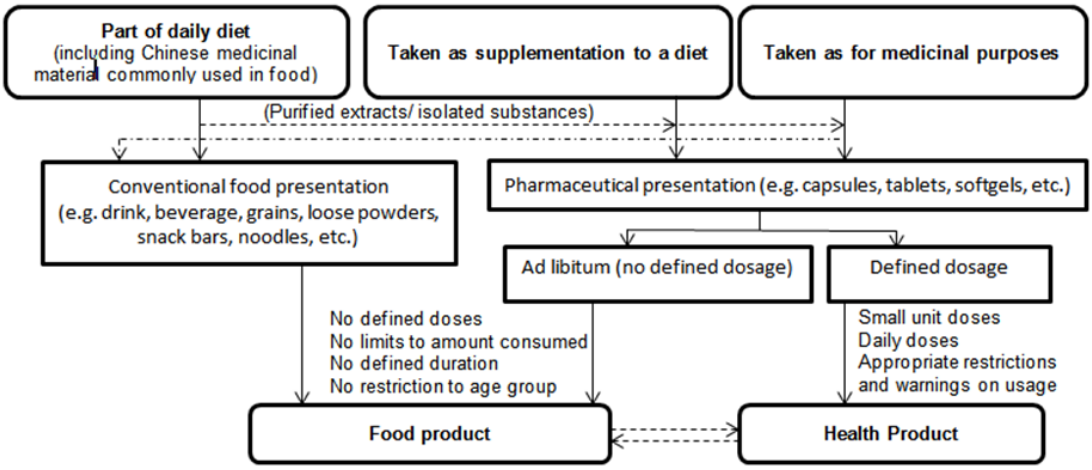

Figure 1.2. Classification tree for products in the food-health products interface (HSA, 2012a).

1.2.2.1. Chinese proprietary medicines

Under the Medicines Act, any medicinal product used for therapeutic purposes according to TCM methods can be a CPM. Such a product should be manufactured into a finished product and all its ingredients should be derived from plants, animals, or minerals. In addition, the product or all of its active ingredients should be described in current editions of any recognized Chinese Pharmacopoeia. These products shall not include any injectable medicinal product, any item specified in the poisons list in the Poison Act (MOH, 2008a, 2008b), or any chemically defined isolated constituents of plants, animals or minerals. Other prohibited ingredients include any synthetic drugs, more than certain amounts of toxic heavy metals (Arsenic 5 ppm, Copper 150 ppm, Lead 20 ppm, and Mercury 0.5 ppm) and microbial contamination, amygdalin, pangamic acid or its salts, danthron, suprofen or its salts, rhodamin, or any other substance except listed on the labels (MOH, 2008a).

Furthermore, labels should be in English and they have to have additional labels showing that they are categorized as CPM: "Allowed for sale as a Chinese Proprietary

Medicine based on information submitted to the Authority. Consumer discretion is advised. **根据向当局提呈的**资料允许作为中成药销售。谨慎选用。" (HSA, 2010; MOH, 2002). Other labeling requirements are listed in Table 1.1 (HSA, 2010).

Table 1.1. Labling requirement for CPM products (HSA, 2010)

No	Parameter	Inner label	Outer label	Package insert
1	Trade and brand name	Needed	Needed	Needed
2	Product name	Needed	Needed	Needed
3	Batch number	Needed	Needed	-
4	Expiry date	Needed	Needed	-
5	Names and quantities of ingredients	Needed	-	-
6	Importer's or wholesaler's name and address	-	Needed	Needed
7	Manufacturer's name and address	-	Needed	Needed
8	Assembler's name and address	-	Needed	-
9	Allowed for sale as CPM	-	Needed	-
10	Dosage	-	-	Needed
11	Indication	-	-	Needed
12	Contraindications	-	-	Needed
13	Side effects	-	-	Needed
14	The frequency and method of administration	-	-	Needed

Under Singapore legislations, CPM products should not make exaggerated therapeutic claims. They are also not allowed to make any claim directly or indirectly referring to any of 19 serious health conditions namely diabetes, hypertension, cancer, blindness, cataract, drug addiction, epilepsy or fits, paralysis, deafness, kidney diseases, leprosy, tuberculosis, menstrual disorders, sexual function, infertility, impotency, frigidity, insanity, conception and pregnancy (HSA, 2010; MOH, 2008a).

As CPM products contain natural ingredients with complex chemical constituents, it is very difficult to assess them in the same way as synthetic conventional

medicines containing known chemical substances that can be easily identified and assessed for purity or the presence of contaminants (MOH, 2002). To have a better control on quality of CPM products, all importers are required to submit documents showing safety of products for each batch imported. In addition, "Good Manufacturing Practice (GMP) Audit" program is implemented by HSA for local and international manufacturers (MOH, 2002).

1.2.2.2. Health supplements

Health supplement refers to a product which is used to supplement a diet, with benefits beyond those of normal nutrients, and/or to support or maintain the healthy function of the human body (HSA, 2012b). It includes "quasi-medicinal products" (including vitamins and nutritional preparations from natural sources), "traditional medicines" (other than CPM, Jamu, Ayurvedics, homeopatics), and "health foods" with vague and general medicinal claims. Health supplements contain vitamins, minerals, amino acids (either natural or synthetic) and/or substances derived from natural sources including non-human animals and botanical materials. They are presented in pharmaceutical dosage forms such as capsules, soft gels, tablets or liquids. Furthermore, health supplement cannot include any product as a sole item of a meal or diet or any injectable and sterile preparation (HSA, 2012b).

Health supplements should not contain any ingredient other than listed on the label, any human part or substances derived from human body, any substances listed in schedules of the Poison Act, any restricted substances more than certain limits (for example 30 mg Iron or 200 mg Potassium per unit dose), any prohibited substances (e.g. *Atropa belladona*, *Artemisia* species, *Aconitum napellus*, etc.), any active

substance which is a chemically-defined isolated constituent of plants, animals or minerals, any microbial contamination above certain limits (total aerobic microbial count limit is 10^5 per g or ml and yeast and mould limit is 500 per g or ml), or any substance that may adversely affect the health of consumer. Furthermore, the heavy metals (similar to CPM) and microbial loads should not exceed some specific levels (HSA, 2012b; Koh et al., 2000).

The labeling also should comply with certain regulations. For example, the information should be in English and clearly and legibly printed. The other labeling requirements for health supplements in Singapore are listed in Table 1.2.

Table 1.2. Labeling requirements for health supplements (HSA, 2012b)

No.	Basic supplemental facts and other required information
1	Name
2	Name and quantity of all active ingredients
3	Name of inactive ingredients (e.g. sweeteners, preservatives, colorants, etc.)
4	Recommended daily allowance and daily dosage
5	Instructions on proper usage
6	Pack size
7	Expiry date
8	Batch number
9	Name and address of manufacturer, packer and dealers
10	Mandatory precautionary label or statement where necessary

Furthermore, health supplements are not allowed to claim having any therapeutic effect for any specific medical condition. In addition, there should not be any direct or indirect reference to 19 prohibited diseases listed in "section 1.2.2.1". In addition, under HSA regulations, they are not supposed to imply to be effective in improvement of

performance in studies, making the consumer smarter, or improving IQ or memory; there should not be any direct or indirect suggestion for prevention, retarding or reversing the physiological changes associated with ageing; any implication that a product can induce sexual virility is prohibited; and any claims of having no adverse effects, being 100% safe or being safe because of being a natural product are banned (HSA, 2012b). Moreover there are 31 objectionable terms and claims which should not be found in their labels such as "no side effects", "guaranteed", "sensational relief", "effective", "boost/enhance immunity", "increase/improve memory", "anti-ageing", "longevity", "arousal", "libido", etc. (HSA, 2012b).

1.2.2.3. Food supplements

Under AVA regulations, all food products including food supplements (FS) should be packed properly and the basic information listed in Table 1.3 is expected to be declared in English on the labels (AVA, 2011).

Table 1.3. Labeling requirements for food supplements (AVA, 2011)

No.	Basic information needed
1	Name or description of product
2	Statement of ingredients
3	Declaration of foods and ingredients known to cause hypersensitivity
4	Declaration of net content in package
5	Name and address of local manufacturer or importer
6	Country of origin
	Additional information
7	Expiry date
8	Any sweetening agent added or sugar free foods
9	Special purpose foods
10	Low calorie, diabetic or infants' foods
11	Nutritional labeling

Furthermore, food products are not allowed to make any of prohibited claims including false or misleading statements, claims for therapeutic or prophylactic actions, and claim that health or improved physical conditions may be achieved by consuming any food or food supplement (AVA, 2011).

1.3. "Ginseng" and *Panax* species

One of the most worldwide popular herbal products that is marketed as either health or food products is "ginseng". In different countries from East to West it is one of the top highly used herbal products. It was the first ranked herbal and third ranked complementary health product used by Korean breast cancer patients (Kang et al., 2012). In another study in South Korea on cancer patients, "Korean red ginseng" was the most commonly used (35.6%) type of CAM (Kim et al., 2004a). In Singaporean polyclinic, patients on warfarin reported using "ginseng" as the most common TCM product sharing its rank with cordyceps and essence of chicken (Goh et al., 2011). Furthermore, among American university athletes, 89% consumed health supplements. Out of 26% of them who used herbal supplements, "ginseng" was the most popular ingredient (13%) (Froiland et al., 2004). In a similar study in Singapore, the prevalence of health supplement usage was 76.8% and "ginseng" stood at the second rank of herbal ingredients with 4.8% popularity (Tian et al., 2010). In Turkey, 16.5% of university students reported using non-vitamin non-mineral supplements where "ginseng" was second most popular one (36.4%) (Ayranci et al., 2005). Among American adolescents, "ginseng" was the second most popular herbal supplement with 17.4% use just after green tea with 21.5% (Wilson et al., 2006). This popularity has made "ginseng" the second highest selling herbal supplement in the United States (Jia et al., 2009a).

This wide global consumption has made its market one of the biggest herbal markets in the world. The total world export value of ginseng was reported over USD 350 million in 2010, which was predicted to increase to USD 400 million in 2012 (Smith et al., 2014). The next section will briefly review "ginseng" and other species in *Panax* genus.

The word "ginseng" comes from the Chinese term for *Panax ginseng,* Ren Sheng (human root). It is named because of its characteristic shape, which resembles the human body (Radad et al., 2006). "Ginseng" is a general name mostly referred loosely to several species of *Panax* genus (Jia et al., 2009a) including Chinese/Korean ginseng, American ginseng etc.

1.3.1. *Panax* species

Panax is a genus from Araliaceae family. The word "Panax" comes from Greek words "pan" (all) and "axos" (cure). This name was applied because of the wide range of therapeutic use of *Panax* species in TCM (Jia et al., 2009a). This genus consists of several species found in various regions across the world (Efloras; IPNI, 2012; "Plants database," 2012) (Table 1.4). In addition, there are some other plants from other families or genera (Table 1.5) that are sometimes referred as "ginseng" or "ginseng" alternatives. However, their botanical, chemical and pharmacological characteristics are different from *Panax* species.

Table 1.4. Species of *Panax* genus with their local names and geographical distributions (Bensky et al., 2004; Chan et al., 2011; Efloras; IPNI, 2012; Jia et al., 2009a; WHO, 2002)

No.	Scientific names	Common names	Geographical distribution
1	*Panax ginseng*, *Radix ginseng*	Panax schinseng Nees, Ren Shen, Chosen ninjin, ginseng, bang chui, Di Jing, Li Shen, Ren Xian, Shen Cao, Ginsengwurzel, hakusan, higeninjin, hongshen, hunseng, jenseng, jenshen, jinpi, kao-li-seng, Korean ginseng, minjin, nhan sam, ninjin, ninzin, niuhuan, Oriental ginseng, otane ninjin, san-pi, shanshen, sheng-sai-seng, t'ang-seng, tyosenninzin, yakuyo ninjin, yakuyo ninzin, yehshan-seng, yuan-seng, yuanshen, goryo insam	North East China and North Korea, Japan, and eastern Siberia
2	*Panax notoginseng*, *Radix notoginseng*, *Panax pseudoginseng var. notoginseng*	Sanqi, Sanchi, Tienqi, Tienchi, Jin Bu Huan, Pan long Qi, Sanshichi, samchil	China (Yunnan and Guangxi)
3	*Panax quinquefolium*, *Radix Panacis quiquefolii*	American ginseng, Xi Yang shen, seiyojin, seoyangsam, Quang Dong Ren Shen, Hua Qi Shen, Mei Zhuo Ren Shen, Xi Shen, Xi Yang Ren Shen, Yang Shen	North America, cultivated in North China
4	*Panax japonicus*	Japanese ginseng or Zhu Jie Shen	A big territory from North India to Japan
5	*Panax japonicus var. angustifolius*	Xia Ye Zhu Jie Shen	China (Guizhou, Sichuan, Yunnan), Bhutan, North East India, Nepal, North East Thailand
6	*Panax japonicus var. bipinnatifidus*	Ge Da Qi	China (Gansu, Hubei, Shaanxi, Sichuan, Xizang, Yunnan)
7	*Panax japonicus var. japonicas*	Zhu Jie Shen or Yuan Bian Zhong	East China, Japan, Korea and Vietnam
8	*Panax japonicus var. major*	Zhu Zi Shen, Zu Tzi Seng	South China, Nepal, Myanmar, Vietnam
9	*Panax vietnamensis*, *Panax stipuleanatus*	Ping Bian San Qi	China (Yunnan) and Vietnam
10	*Panax zingiberensis*	Jiang Zhuang San Qi	China (Yunnan)
11	*Panax pseudoginseng*	Jia Ren Shen	Nepal and eastern Himalayas

Table 1.5. List of the non-*Panax* species which are sometimes referred as "ginseng" (D'jang, 1999; Jia et al., 2009a)

No.	Scientific name	Common name
1	*Angelica sinensis*	Female ginseng, aka Dong Quai
2	*Eleutherococcus senticosus*	Siberian ginseng
3	*Eurycoma longifolia*	Malaysian ginseng, Tongkat Ali
4	*Gynostemma pentaphyllum*	Southern ginseng, aka Jiaogulan, five-leaf ginseng
5	*Lepidium meyenii*	Peruvian ginseng, aka Maca
6	*Oplopanax horridus*	Alaskan ginseng
7	*Pfaffia paniculata*	Brazilian ginseng
8	*Pseudostellaria heterophylla*	Prince ginseng
9	*Withania somnifera*	Indian ginseng, aka Ashwagandha

The following sections give an overview of the three most commonly used species among *Panax* genus (*P. ginseng, P. quinquefolium* and *P. notoginseng*) (Kim, 2012) and their chemical compositions.

1.3.1.1. *Panax ginseng*

Panax ginseng C.A Meyer (Araliaceae) or *Radix ginseng* is one of the most commonly used plant worldwide and is generally called “ginseng” (CPC, 2010) or Ren Sheng (Chang et al., 2000). Its other vernacular names are listed in Table 1.4. This plant grows in cool climates in Northern Hemisphere (Jia et al., 2009a) and the wild plant can be found in North East China, North Korea (Chang et al., 2000), Japan and East Siberia (WHO, 2002).

The leaves and roots can be consumed as herbal medicines, which taste sweet and bitter and are “warm” in nature (CPC, 2010). The most traditionally used preparation is the dried root (WHO, 2002). If preparation is from cultivated plants, it is called

Yuanshen or garden ginseng. Linxia Shanshen or Zihai is preparation derived from wild plants (CPC, 2010). In addition, based on the preparation process, it is subcategorized as white (raw) *P. ginseng* or red (steamed). *Radix ginseng rubra* (also known as red ginseng or Hongshen) is the steamed then dried root of cultivated *P. ginseng*, which is stronger and "warmer" in nature than white (raw) *P. ginseng* (Bensky et al., 2004; CPC, 2010). There are plenty of published reviews on *P. ginseng* (Chan, 2012; Choi, 2008; Jia et al., 2009a; Jia et al., 2009b; Lee et al., 2011c).

1.3.1.2. Medical usage and pharmacological activities of *P. ginseng*

Panax ginseng has been used at least for 5000 years. The first description of its medicinal use goes back to "Shen Nong Ben Cao Jing", the earliest Chinese pharmaceutical monograph written during the Qin and Han Dynasties (221 B.C.-220 A.C.) (Song et al., 2009). In Chinese Pharmacopoeia, a wide range of traditional usage has been reported for "Ren Shen" including reinforcing the vital energy, improving collapse and restoring normal pulse, promoting the production of body fluid, calming nerves, and benefitting spleen and lung (CPC, 2010). In addition, it has been used for many indications in folk medicine such as cough, fever, tuberculosis, rheumatism, vomiting of pregnancy, hypothermia, dyspnea and nervous disorders (WHO, 2002). The most reported neurologic actions for *P. ginseng* in TCM are tranquilizing the mind and replenishing wisdom (CPC, 2010) (anxiolytic and improving cognition, respectively). Based on the Chinese pharmacopeia, it is also indicated for vexation, fright palpitation, restlessness (CPC, 2010) (anxiety or hyperactivity) and mental confusion (CPC, 2010) (cognition problems or attention deficit). The traditional usage of steamed *P. ginseng* is quite different from the raw form. It is traditionally used for tendency to collapse, cool limbs, weak pulses, unusual bleeding, etc. (CPC, 2010).

Many scientists have tried to study pharmacological effects of Chinese ginseng. In a review by Colins (2011), papers published in "Chinese Medical Journal" between years 2000 and 2009 were evaluated and it was found that the most studied herb was *P. ginseng* (16.1% of publications on TCM) (Collins, 2011). The studied pharmacological activities of *P. ginseng* are presented in Table 1.6.

One of the most interesting properties of this herbal medicine is its adaptogenic effect (Kitts et al., 2000). Adaptogenic effect is a controversial concept referring to the capability of a substance to normalize body activities and reinforce systems affected by stress. It includes the protection against different environmental and emotional assualts (HMPC, 2008). *Panax ginseng* has known effects in enhancing tissue oxygen uptake (Bahrke et al., 2000), cellular glucose uptake (Wang et al., 1998) and corticosterone secretion (Kitts et al., 2000), concurrently with immuno-modulatory effects (Christensen, 2009; Ni et al., 2010; Yoo et al., 2012), which all can empower the body to tolerate environmental assaults.

1.3.1.3. *Panax notoginseng*

Panax notoginseng (Burk.) F.H. Chen is another famous species from the family Araliaceae. Its dried root (*Radix notoginseng)* is called Sanqi or Tianqi, which has a long history of traditional medical usage. The branch root is called "Jintiao" and the rhizome is known as "Jiankou" (CPC, 2010). Notoginseng is mainly produced in provinces of Yunnan and Guangxi of China (Chang et al., 2000). It tastes sweet and mildly bitter and is "warm" in nature (Bensky et al., 2004; CPC, 2010). A number of published reviews are available on *P. notoginseng* (Chen et al., 2008b; Ng, 2006; Zeng et al., 2012).

Table 1.6. Reported pharmacological activities of *P. ginseng*

Pharmacological effects		**Type of study**
Cardiovascular system	Treating chronic pulmonary heart disease	Clinical trials (Li et al., 2011a)
	Treating angina pectoris (better than nitrates)	Clinical trial (Jia et al., 2012)
	Improvement in ischemic and congestive heart diseases	Clinical trials (Lee et al., 2011c)
	Anti-hypertension	Clinical (Choi et al., 2011)
Alcoholism	Improving withdrawal symptoms	Clinical (Tomczyk et al., 2012)
Coagulation system	Increasing clotting time	Case report (Stanger et al., 2012)
Neurologic system	Improving cognition in 4 out of 6 studies	Clinical trials (Lee et al., 2011c)
	Improving signs of Alzheimer's disease	*In vivo* (Kurz et al., 2011)
	Improving cerebral blood flow after stroke	Clinical trials (Lee et al., 2011c)
Immune system	Anti-inflammation	*In vitro* and *in vivo* (Lee et al., 2011a)
		In vivo (animal) (Wang et al., 2011b)
		In vitro (Wang et al., 2011b)
	Immuno-modulation	Clinical (Vogler et al., 1999)
Cancer	Preventing gastric cancer	*In vitro* and animal (Won et al., 2011)
	Improving hepatocellular carcinoma	Clinical (Wu et al., 2009)
	Controlling growth and invasion of brain tumor and anti-angiogenesis	*In vitro* (Wang et al., 2011b)
Metabolism	Anti-hyperglycemic activity	*In vitro* and *in vivo* (Wang et al., 2011b)
	No convincing data on anti-hyperglycemic activity	Systematic reviews (Kim et al., 2011; Lee et al., 2011c)
	Anti-hyperlipidemic activity	*In vivo* (Cho et al., 2006)
	Anti-obesity activity	*In vitro* (de la Garza et al., 2011)
	Inhibiting liver enzymes	*In vitro* and *in vivo* (Choi et al., 2011)
Respiratory system	Improvement in chronic obstructive pulmonary disease (COPD) and respiratory infections	Clinical trials (Lee et al., 2011c)
Reproductive system	Improvement in erectile dysfunction and sexual satisfaction	Clinical trials (Ho et al., 2011; Jang et al., 2008)
General health	No effect on physical performance	Clinical trials (Lee et al., 2011c)

1.3.1.4. Medical usage and pharmacological activities of *P. notoginseng*

Panax notoginseng is traditionally used to improve blood circulation and remove blood clots, disperse swelling and relieve pain (CPC, 2010). This plant is also used for different kinds of heart disease and chest pain (Zhao, 2004). In addition, it is indicated for different bleeding related disorders such as hemoptysis, hematemesis, epistaxis, menorrhagia and spotting as well as chest pain, abdominal pain, and swelling and pain caused by injuries (CPC, 2010). Many studies have tried to evaluate its pharmacological effects and mechanisms of actions listed in Table 1.7.

Table 1.7. Reported pharmacological activities of *P. notoginseng*

Pharmacological effects		**Type of study**
Cardiovascular system	Anti-atherosclerosis	*In vivo* (Zeng et al., 2012)
	Treating myocardial ischemia	Animal (Shi et al., 2011)
Neurological effects	Facilitating improvement after ischemic stroke	Clinical (Chen et al., 2008b)
Pain	Alleviating pain caused by cervical disc degeneration	Clinical trials (Cui et al., 2010)
Immune system	Anti-inflammatory	*In vitro* (Spelman et al., 2011)
		In vivo (Zeng et al., 2012)

1.3.1.5. *Panax quinquefolium*

Panax quinquefolium L. or "American ginseng" is another species from the family Araliaceae (Zhao, 2004). Its dried root (*Radix Panacis quiquefolii)* is called Xi Yang Shen (Chang et al., 2000). It is originated from North America but it is successfully cultivated in North China. Similar to other *Panax* species, it tastes sweet and mildly bitter. On the other hand, in contrast to the other two major species, it is "cool" in nature (Bensky et al., 2004). There are some published reviews on *P. quinquefolium* (Qi et al., 2010, 2011; Vuksan et al., 2001).

1.3.1.6. Medicinal usage and pharmacological activities of *P. quinquefolium*

This plant is traditionally used for cough, hemoptysis, thirst, irritability and debility (Zhao, 2004). As it is "cool" in nature, it can be used for internal hotness and dryness as well as fatigue, wasting thirst (diabetes mellitus), and dry mouth and throat (Bensky et al., 2004). Its neurologic indication is vexation (CPC, 2010) (irritability and anxiety). There are recent reports on its pharmacological activities including effects on cardiovascular and central nervous system, anti-diabetic effects, anti-tumor activities and immunomodulatory properties (Shi et al., 2012b) as well as effects on post-menopausal syndrome (Shou et al., 2011) (Table 1.8).

Table 1.8. Reported pharmacological activities of *P. quinquefolium*

Pharmacological effects		**Type of study**
Cardiovascular system	No effect on ischemic and congestive heart diseases	Clinical trials (Lee et al., 2011c)
	Anti-ischemic, anti-hypertensive, anti-arrhythmic	*In vitro* (Qi et al., 2011)
Neurologic effects	Enhancing memory and anti-Alzheimer's diseases	*In vitro* (Qi et al., 2011)
	Anti-Parkinsonism	*In vitro* (Qi et al., 2011)
Cancer	Protecting against colon cancer	*In vitro* (Qi et al., 2011)
	Anticancer	*In vitro* (Qi et al., 2011)
Metabolism	Anti-diabetic effects in 4 out of 5 studies	Clinical trials (Lee et al., 2011c)
	Anti-diabetic	Clinical trial (Kasuli, 2011)
	Anti-obesity	*In vitro* (de la Garza et al., 2011)
Respiratory system	Relieving from acute respiratory infections and common cold	Clinical trials (Lee et al., 2011c)
Coagulation system	Reducing anti-coagulant effect of warfarin	Clinical trial (Shi et al., 2012b)
Gynecological disorders	Alleviating menopausal syndrome	Clinical trial (Shou et al., 2011)
General health	No effect on physical performance	Clinical trials (Lee et al., 2011c)

1.3.2. Chemical components of *Panax* species and their pharmacological effects

In 1854, the first chemical compound was extracted from *P. quinquefolium,* which was a saponin. Since then, many individual substances have been isolated from different *Panax* species (Kim, 2012) including more than 180 saponins (Christensen, 2009) and other chemical constituents such as polysaccharides, polyacetylenes, peptides and amino acids (Kim, 2012). The saponins from *Panax* species are generally called ginsenosides (Table 1.9).

1.3.2.1. Saponin components of *Panax* species (ginsenosides)

The major pharmacologically active ingredients of the *Panax* species are ginsenosides. With a few exceptions, they share a similar basic structure, which is a saturated 1,2-cyclopentanoperhydrophenanthrene steroid nucleus. Based on their skeleton of aglycones, they can be classified into two main groups namely dammarane-type and oleanane-type. The dammarane-type group consists mainly of three types classified according to their genuine aglycone moieties: protopanaxadiol (PPD), protopanaxatriol (PPT), and ocotillol, whereas ginsenosides of the oleanane-type are classified according to their aglycone oleanolic acid. Other types of ginsenosides isolated from ginseng species include panaxatriol-type and dammarenediol-type ginsenosides (Christensen, 2009). Most of the abundant ginsenosides belong to either the PPD or PPT groups (Figure 1.3). If two hydroxyl groups are attached to the back bone it will be categorized as protopanaxadiols while protopanaxatriols are ginsenosides with three hydroxyl groups attached to their backbone (Lu et al., 2009).

Table 1.9. Chemical constituents of *Panax* species

Type of compound	Class	Subclass	Approximate number of isolated members	Examples
Saponins	Dammarane -type	Protopanaxadiol	80	Ginsenosides I, Ginsenosides II, Ginsenosides III, F2, Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rg5, Rh1, Rh2, Rh3, Rk1, Rk2, Rs1, Rs2, Rs3, Rs4, Rs5, notoginsenosides (A, B, C, D, Fa, Fc, Fe, K, L and R4), quinquenosides (R1, Rs1, Rs2, I-V)
		Protopanaxatriol	65	Ginsenosides F1, F3, F4, F5 La, Re, Rf, Rg1, Rg2, Rg6, Rh4, Rh5, Rh6, Rh8, Rh9, Rk3, Rs6, Rs7 Notoginsenodsides (J, H, M, N, R1-3, R6, U) Quinquenosides L9
		Ocotillol-type	15	Vinaginsenoside R1, R2, R5, R6, R14
	Oleanane-type		10	Ginsenosides Ro, Roa, R15 vinaginsenoside R10, R11 pseudoginsenoside F11
	Modified ginsenosides		15	Ginsenoside Rh7 Notoginsenoside I, notoginsenoside G Quiquenoside IV Vinaginsenoside R3
Polysaccharides				Panasans A-E, poanaxans F-H, panaxan I-U, ginsenan PA and PB, L-arabinose, D-galactose, L-rhamnose, ginesan S-IA and S-IIA, quiquifolan A-C
Polyacetylenes				Trifolin, panasenoside, panaxynol, panaxydol, PQ-1-3,
Alcohols				Pansinsanol A & B, ginsenol, senecrassidiol
Peptides, amino acids, carbohydrates, vitamins, etc.				

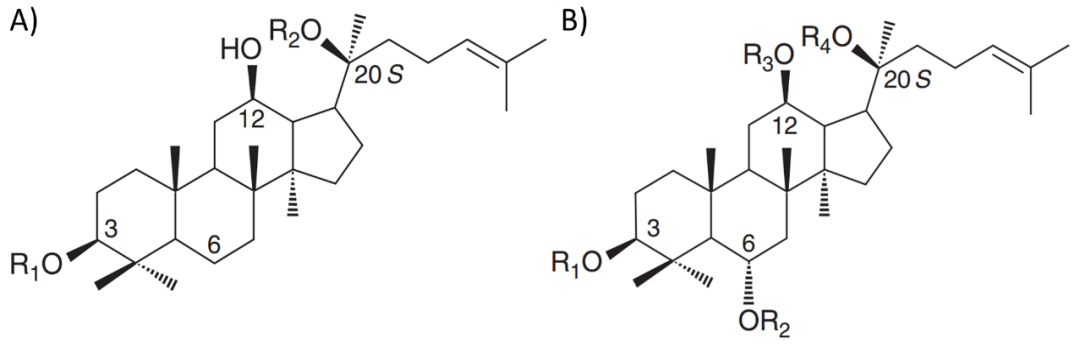

Figure 1.3. Basic structure of major ginsenosides. A) Protopanaxadiols; B) Protopanaxatriols. Adapted from (Christensen, 2009).

Differences in ginsenoside composition in various species of *Panax* genus lead to their different pharmacological properties (Kim, 2012). The next sections will briefly review most abundant ginsenosides.

1.3.2.1.1. Ginsenoside Rg1

Ginsenoside Rg1 is one of the most abundant saponins in major *Panax* species and the representative constituent of *P.* ginseng and *P. notoginseng*. The Rg1 content of *P. notoginseng* (~40 mg/g) is much higher than *P. ginseng* (~4 mg/g). It is also one of the most studied ginsenosides (Cheng et al., 2005; Collins, 2011; Lu et al., 2009; Wan et al., 2007).

Ginsenoside Rg1 has three hydroxyl groups and belongs to PPT category (Figure 1.3). The R_2 and R_4 substitutes are glucose and the other two are Hydrogen. After oral consumption, it undergoes two-step deglycosylation hydrolysis by gut bacteria. First step of deglycosylation produces ginsenoside Rh1 by through substitution of R_4 glucose by hydrogen or ginsenoside F by substitution of R_2 one. The hydrolysis of the other glucose group will produce 20(S) PPT (Hasegawa et al., 1996). Oxygenation is another major metabolic change occurring on orally taken Rg1 in the

gut resulting in the formation of mono-oxygenated Rg1 and mono-oxygenated PPT. All of these primary and secondary metabolites are measurable in blood, urine and feces with different abundances after oral consumption of ginsenoside Rg1 (Wang et al., 2014b).

Since the relative oral bioavailability of ginsenoside Rg1 is very low (2.5%) (Tan et al., 2013), other routs of administration have been considered by researchers. One of these alternative routes is intranasal administration. Intranasal administration of Rg1 leads in a higher concentration in blood and other tissues at each time point. Compared with intragastric administration, intranasal administration results in a shorter t_{max} (0.08 versus 1 h), a higher C_{max} (16.65 versus 11.29 μg/ml), and a higher area under the concentration-time curve (AUC) (592.91 versus 101.70 μgċh/ml) in the brain (Bai et al., 2012). Other alternative routes of administration are intraperitoneal (IP) and intravenous (IV). Although these methods of administration bypass the problem of low absorption of ginsenoside Rg1 from gastrointestinal tract to the blood, limited penetration into blood brain barrier causes very low brain concentrations after systemic administration. IP injection of Rg1 can cause maximum brain concentration in 30 minutes with rapid clearance in 4 hours. After 24 hours it is hardly detectable in brain. The maximum brain concentration is very low therefore the mechanism of action is most probably extra-cranial (Moore et al., 2011). Therefore, some researchers consider intracerebroventricaular (ICV) administration of ginsenoside Rg1 to study its direct effect on central nervous system (Wang et al., 2001b; Wang et al., 2009c; Xu et al., 2007).

Despite low bioavailability and limited body distribution of ginsenoside Rg1, many pharmacological effects have been reported for this compound. These pharmacological

effects include anti-cancer effects (Leung et al., 2006; Ma et al., 2006; Wang et al., 2009a), immunoregulatory effects (Cheng et al., 2005; Lee et al., 2004a), effects on cardiovascular conditions (Deng et al., 2009; Wang et al., 2010d; Zhu et al., 2009), hypoglycemic effects (Huang et al., 2010) and neurological effects (Table 1.10).

Table 1.10. Studied pharmacological activities of ginsenoside Rg1

Pharmacological activities		**Potential mechanisms**
Effect category	**Effect on**	
Neurology	Alzheimer's disease	Inhibiting amyloid beta induced cell apoptosis (Li et al., 2012a) via estrogen receptor-α and glucocorticoid dependent anti-protein nitrogen pathways (Wu et al., 2012b) and caspase-3 pathway (Wei et al., 2008), modifying the metabolism of amyloid protein precursor by affecting NF-^{k}B (Chen et al., 2012a), decreasing βamyloid synthesis via suppression of PPAR$^{\gamma}$-regulated activities (Chen et al., 2012b), improvement of spatial learning and memory with up-regulating NGF in basal forebrain (Wu et al., 2011), neuro-protective effect against hydrogen peroxide (Liu et al., 2011b), protecting against βamyloid cytotoxicity by inhibiting β-secretase activity (Wang et al., 2009b), anti-apoptotic by inhibiting JNK and caspase-3 (Chen et al., 2003a), inhibiting amyloid beta toxicity via acetylcholine esterase and choline amine transferase in hippocampus (Wang et al., 2001a)
	Memory	Protective effects on hippocampal nerves against electrical injury (Chen et al., 2011b), restoring learning deficit caused by morphine toxicity via NMDA signaling (Qi et al., 2009), improvement of signal transduction via NO synthesis and increasing acetylcholine and its receptor in CNS as well as anti-apoptotic effects (Cheng et al., 2005).
	Cognition	Increasing glutamate release (Liu et al., 2010)
	Dopaminergic neuroprotection	Up-regulation of Bcl-2, activation of Akt phosphorylation and inhibition of ERK1/2 phosphorylation (Ge et al., 2010)
	Parkinsonism	Dopaminergic neuroprotectionby inhibiting depressing nuclear transduction of P-ERK1/2 (Shi et al., 2009), or activating estrogen receptor (Xu et al., 2008), P38 signaling pathway (Wang et al., 2008a) or insulin like growth factor (Xu et al., 2009), inhibiting dopamine induced apoptosis (Chen et al., 2003b)
	Stroke	Decreasing hypoxic ischemic brain damage by inhibiting caspase-3 mechanism (Wang et al., 2010a) and regulation of hypoxia inducible factor-1α (Tang et al., 2011)
	Anti-depressant	Activating BDNF pathway and up-regulating hippocampal neurogenesis (Jiang et al., 2012)

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Cont. Table 1.10.

Cardiovascular system	Myocardial infarction	Angioneogenesis via hypoxia inducible factor-1 α (Wang et al., 2010d), myocardial protection by anti-oxidant activity and intracellular calcium homeostasis (Zhu et al., 2009)
	Coarctation of aorta	Inhibition of ventricular hypertrophy by inhibition of calcineurin and MAP kinase signaling pathways (Deng et al., 2009)
Metabolism	Hypoglycemic effect	Insulin-like activities on adipocytes causing glucose uptake (Huang et al., 2010)
Immune system	Immunoregulatory	Enhancing the proliferation of lymphocytes and production of IL-2, increasing cAMP and cGMP in lymphocytes (Cheng et al., 2005), enhancing CD4+ activity and Th1/Th2 differentiation (Lee et al., 2004a)
Blood forming system Angiogenesis	Increasing total white blood cell count	Promotion of myelopoiesis via cytokine regulation (Raghavendran et al., 2012)
	Red and white blood cell regeneration	Postponing hematopoietic stem cell senescence (Zhou et al., 2010)
	Anti-coagulant	By inhibiting platelet aggregation (Liu et al., 2006b) and inducing NO production (Xu et al., 1997)
Cancer	Increasing angiogenesis	Up-regulation of hypoxia-inducible factor-1α (Leung et al., 2011), regulating fibroblast growth factor receptor-1 (Cheung et al., 2011)
	Angiogenesis	Inhibiting TNF induced vascular smooth muscle proliferation (Gao et al., 2011; Ma et al., 2006) and vascular endothelial growth factor (Wang et al., 2011a) induction via PI3K/Akt pathway (Leung et al., 2006)
	Anti-proliferative effects	Cell cycle arrest and apoptosis more than other saponins from P. notoginseng (Wang et al., 2009a)
Hepatic system	Hepatocyte protection	Inhibiting lipid peroxidase activity (Deng et al., 1991)
Genitourinary system	Obstructive nephropathy	Inhibition of renal interstitial fibrosis (Xie et al., 2010b)
	Diabetic nephropathy	Anti-inflammatory effects such as reducing transforming growth factor β-1 (Ma et al., 2010b)
	Male sexual dysfunction	Maintaining testosterone level and nitric oxide mediated pathways (Wang et al., 2010c)
Dermatology	Premature ageing	Antagonizing the effect of UV on fibroblasts (Zhou et al., 2012), attenuating the G1 growth arrest in fibroblast induced by UV (Wang et al., 2011c)

Different scientists have tried to evaluate the effects of ginsenoside Rg1 on nervous system. Some of them study its protective function against different environmental insults such as hypoxic injury to brain after stroke (Tang et al., 2011; Wang et al., 2010a) or chemical and electrical injury (Chen et al., 2011b; Qi et al., 2009; Wu et al., 2012b). Some others suggest molecular pathways affected by ginsenoside Rg1 which are involved in neurological diseases or normal function such as the role of Rg1 on brain derived neurotrophic factor and its role in depression (Jiang et al., 2012), the effect of Rg1 on glutamate release to improve cognition (Liu et al., 2010) or enhancement of signal induction to improve memory (Cheng et al., 2005). Beside these molecular *in vitro* studies, animal based *in vivo* experiments would be useful to determine the neurological effects of ginsenoside Rg1 and the potential mechanisms involved. Some studies have reported positive effects of ginsenoside Rg1 on memory of different cognitively impaired animal models using Morris Water Maze (Li et al., 2011c; Li et al., 2012b; Qi et al., 2009; Wang et al., 2010b; Zhang et al., 2012b) or other neurobehavioral tests (Fang et al., 2012; Wang et al., 2010b; Wu et al., 2011; Yamaguchi et al., 1995). Some others used other neurobehavioral studies to verify the effects of ginsenoside Rg1 on depression (Carr et al., 2006; Cha et al., 2005; Jiang et al., 2012; Wu et al., 2012a). An alternative way of studying the neurological effects of Rg1 *in vivo* is via electrophysiological studies. *In vivo* electrophysiology evaluates the electrical charges in various brain regions and neurological pathways. Wang and his colleagues used perforant path-dentate gyrus excitability to suggest hippocampus as the main site of action for neurological effects of ginsenoside Rg1 (Wang et al., 2001b; Wang et al., 2009c). Qi et al. also focused on hippocampus and most specifically the CA1 stratum radiatum of the right hippocampal hemisphere in response to stimulation of the Schaffer collateral-commissural pathway (Qi et al., 2009). Other scientists also

focused on hippocampus in their electrophysiological studies to study the neurological effects of ginsenoside Rg1 (Mook-Jung et al., 2001; Xu et al., 2007). So far, almost all electrophysiological studies on ginsenoside Rg1 have been limited into the hippocampus.

Despite the long list of studies evaluating the pharmacological effects of ginsenoside Rg1, there are few reports on its toxicity study. Saw et al. studied the possible toxic effect for rg1 in HepG2-C8 cells observing no toxic effects *in vitro* (Saw et al., 2012). Park et al. also studied the toxicity of 4-weeks oral administration of combination of ginsenoside Rg1 and Rb1 in rats which revealed no toxic effect on any organ (Park et al., 2013). The only toxic effect of this ginsenoside was reported by Liu et al. who investigated the 48-hour exposure of rat embryo to different concentrations of ginsenoside Rg1. They observed several teratogenic effects in high concentrations of ginsenoside Rg1 (more than 30-50 μg/ml) (Liu et al., 2006a). Generally, ginsenoside Rg1 is a safe compound with more protective than toxic effects on different cell lines.

1.3.2.1.2. Ginsenoside Rb1

Another highly abundant saponin is ginsenoside Rb1, which can be found in all three major *Panax* species. Although ginsenoside Rb1 is the most abundant saponin in *P. quinquefolium* (~25 mg/g) and its representative chemical constituent, *P. notoginseng* is the major source of this molecule (~30 mg/g) (Cheng et al., 2005; Wan et al., 2007).

Table 1.11. Studied pharmacological activities of ginsenoside Rb1

Pharmacological activities		Potential mechanisms
Effect category	**Effect on**	
Neurology	Cognition	Regulating voltage gated calcium channels (Lin et al., 2012)
	Memory	Increasing cell survival in hippocampus (Liu et al., 2011a) and increasing acetylcholine and its receptor in CNS (Cheng et al., 2005)
	Alzheimer's disease	Protecting cells from Aβ injury functioning as an ROS scavenger (Xie et al., 2010a), decreasing Aβ(1-42)-induced neurotoxicity and tau hyperphosphorylation (Zhao et al., 2011)
	Stroke	Neuroprotective against ischemia by immunomodulatory effects affecting interleukins (Zhu et al., 2012) and regulation of BDNF and caspase-3 (Gao et al., 2010), inhibition of neuronal apoptosis (Yang et al., 2008)
	Depression	Increasing 5-HT level (Yamada et al., 2011) in brain by inhibiting MAO and activating TPH (Hao et al., 2011)
Cardiovascular system	Dilated cardiomyopathy	inhibition of HB-EGF (Lu et al., 2012)
	Hypertension	Vasodilation by activating NO via modulating the PI3K/Akt/eNOS pathway and l-arginine transport in endothelial cells (Pan et al., 2012)
	Myocardial infarction	Reduction of infarct size and plasma enzymes (Wang et al., 2008b)
	Endothelial dysfunction	Protecting endothelium from hemocystein induced dysfunction by increasing NO and via PI3K/Akt activation and PKC inhibition (Lan et al., 2011)
Metabolism	Adrenal hormone release	Increasing cell cycle rate in PC12 cells (Lee et al., 2010b)
	Hypoglycemic effect	Stimulation of glucose transport into insulin sensitive cells and promoting insulin signaling pathways (Shang et al., 2008)
Hepatic system	Hepatocyte protection	Inhibiting lipid peroxidase activity and scavengering effects (Deng et al., 1991)
Genitourinary system	Obstructive renal failure	Inhibition of interstitial fibrosis, tubular injury and collagen deposition as well as anti-oxidant effect (Xie et al., 2009b)
	Diabetic nephropathy	Inhibition of fibronectin expression due to hyperglycemia via the inhibition of MAPK-Akt signaling cascade
	Renal cell protection	Inhibition of ROS release induced by TGF-beta1 via suppression of p47phox expression (Xie et al., 2009a)
	Male sexual dysfunction	Maintaining testosterone level (Lian et al., 1998)

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Cont. Table 1.11.

Cancer	Skin cancer	Protection against UV induced apoptosis and induction of DNA repair (Cai et al., 2009)
	Anti-proliferative effects	Cell cycle arrest and apoptosis more than other saponins from *P. notoginseng* (Wang et al., 2009a)

Ginsenoside Rb1 belongs to the PPD group and has two disaccharide groups attached to its PPD backbone. The R_1 group is kojibiose and the R_2 group is isomaltose (Christensen, 2009). After oral consumption, some part of ginsenoside Rb1 will be deglycosided to ginsenoside Rh2 in acidic environment of stomach. The hydrolysis process continues by the gut intestine to produce ginsenosides Rd, F2, compound K and 20(S)PPD. The overall bioavailability of ginsenoside Rb1 is much less than ginsenoside Rg1 (1:10) (Takino, 1994).

Despite very low bioavailability, several pharmacological activities have been reported for ginsenoside Rb1. Some of these activities are the effect of secondary metabolites such as ginsenoside Rd or compound K. The reported pharmacological activities of ginsenoside Rb1 include neurologic effects (including neuroprotection and neurostimulation), anti-atherosclerosis, immunomodulatory effects, etc. Table 1.11 has summarized the studied pharmacological activities of ginsenoside Rb1.

1.3.2.1.3. Differences in saponin components of the three major *Panax* species

Although the majority of ginsenosides can be found in almost all *Panax* species, their compositions in different *Panax* species are not similar (Table 1.12). This causes different pharmacological properties and medicinal indications (Kim, 2012). In addition, ginsenoside composition can help differentiating the species from each other.

Table 1.12 shows a comparison between the three major *Panax* species based on their main saponin compositions.

Table 1.12. Comparison between the main saponins in three major *Panax* species

Chemical component	***P. ginseng***	***P. notoginseng***	***P. quinquefolium***
Protopanaxadiol	+	++++	++
Protopanaxatriol	++	++++	+
The most abundant saponins	Rg1, Rb1, Rb2	Rg1, Rb1, Rd	Rb1, Re, Rd
Octylotype saponins	+	-	++
Characteristic saponin	Rf	R1	F11
Rg1/Rb1	>1	>1	<0.4

+: presence, ++ significant presence, ++++ abundant presence, -: absence. Note that these signs are used for comparison purpose and it is not representing the exact quantity of the components.

One of the most important distinctive properties of these plants may be the Rg1/Rb1 ratio. Although Rg1 and Rb1 are among the most abundant saponins found in all three major species, their respective ratio is different in American "ginseng" compared to the other two major species. In other words, the Rg1/Rb1 ratio is less than 0.4 in American "ginseng" and more than 1 in *P. ginseng* and *P. notoginseng* (Christensen, 2009; Kim, 2012). In the available literature, Rg1 is reported as a strong neuro-stimulant while Rb1 has both neuro-stimulatory and neuro-inhibitory effects. Therefore, the lower Rg1/Rb1 ratio of *P. quinquefolium* compared to *P. ginseng* provides an explanation for the calming effect of "American ginseng" compared to the "Chinese ginseng" (Chen et al., 2008a). Based on Chinese material medica, Chinese "ginseng" is "warm" in nature (stimulatory) while American "ginseng" is "cool" (calming) (Bensky et al., 2004).

In addition to inter-species differences of the chemical profiles, processing of plants (such as steaming and drying) has a great impact on chemical and pharmacological

properties of the *Panax* species by structural transformation of some ginsenosides leading in altering the composition of extracts (Jia et al., 2009a; Smith et al., 2014; Toh et al., 2010). The traditional and most usual method of processing ginseng is steaming (Christensen, 2009). The alternative methods of plant processing include puffing (Yoon et al., 2010) and fermentation (Lim et al., 2010b). Table 1.13 shows some examples of changes in chemical composition of *P. ginseng* observed after processing. Such changes have been used to make *Panax ginseng* stronger and alter its pharmacological indications (CPC, 2010).

Table 1.13. Effects of some processing methods on selected saponins content of *P. ginseng* (Christensen, 2009; Lim et al., 2010b; Yoon et al., 2010)

Processing method	Effect
Steaming	Decrease in amount of Rb1, Rb2, Rg1, Rg2, Rc, Rd, Re
	Increase in amount of Rh1, Rh2, Rg5, Rg6, Rs 1-7, Rk1-3
	Release of malonyl group attached to Rb1, Rb2, Rc, Rd, etc.
Puffing dried root	Decrease in amount of Rg1, Rb1, Rb2, Rc, Re
	Increase in amount of Rg3
Fermentation[1]	Decrease in Rb1, Re, Rc
	Increase in Rb2, Rb3, Rd, , Rg1, Re

[1] Fermentation by a microbial mixture of Bacillus species including B. subtilis, B. licheniformis, B. senorensis and B. circulance for 15 days.

1.3.2.1. Non-saponin components of *Panax* species

Besides saponins, *Panax* species have other chemical components (Table 1.9) including polysaccharides, polyacetylenes, alcohols, vitamins, peptides, and amino-acids, which may play some role in their pharmacological activities. Although polysaccharides are more studied than other minor ingredients isolated from the *Panax*

species, the chemical structures of many of them have not been clearly elucidated, yet. It is known that acidic polysaccharides are more abundant in *P. ginseng* compared to the other two major species (Kim, 2012).

Some pharmacological effects of polysaccharides have been studied such as immunomodulatory and anti-cancer effects. For example, ginsan, an acidic polysaccharide, is shown to have immunostimulatory effects (Kitts et al., 2000; Wang et al., 2013c). In an animal experiment on influenza-A infection, polysaccharide fraction of *P. ginseng* improved the survival rate of animals comparable to the saponin fraction and total extract. Furthermore, polysaccharide fraction showed better anti-inflammatory effects on lung pathology (Yin et al., 2013). On the other hand, Fan et al. and Cai et al. reported anti-proliferative properties for composite polysaccharides from *Panax ginseng* (Cai et al., 2013; Fan et al., 2013). Rhamnogalacturonan I a polysaccharide backbone of petins from *Panax* species has aslo been studied as an inhibitor of cancer progression (Gao et al., 2013). Additionally, positive effects on diabetes and dyslipidemia have been reported for different polysaccharides from *P. ginseng* (Kwak et al., 2010; Niu et al., 2012; Wang et al., 2003)

1.3.3. Neurological effects of major *Panax* species and ginsenosides

Neurological effects are among most important pharmacological properties of *Panax* species. These herbs have been traditionally used for several neurological conditions reported in section 1.3.1 (CPC, 2010). Table 1.14 has summarized the studied neurological properties of three major species and more abundant saponins. Particularly, the memory improvement and mood stabilizing effects are often reported.

Table 1.14. Neurological effects of *Panax* species and selected constituents

Sample	Effect on	Type of study	Potential mechanisms
American ginseng	Cognition	Clinical (Chen et al., 2011a; Scholey et al., 2010) Review (Qi et al., 2011)	Increasing cell survival, extending neurite growth and inhibiting cell death (Qi et al., 2011), Inhibition of uptake of MPTP, suppression of oxidative stress, attenuation of MPP+induced apoptosis, potentiation of nerve growh factors, activation of IGF-1 receptor signaling pathway (Qi et al., 2011).
	Memory	Clinical (Chen et al., 2011a) Animal (Sloley et al., 1999; Wang et al., 2004) Review (Qi et al., 2011)	
	Parkinsonism	Review (Qi et al., 2011)	Increasing cell survival, extending neurite growth and inhibiting cell death (Qi et al., 2011), Inhibition of uptake of MPTP, suppression of oxidative stress, attenuation of MPP+induced apoptosis, potentiation of nerve growh factors, activation of IGF-1 receptor signaling pathway (Qi et al., 2011).
	Attention	Clinical (Lyon et al., 2001) Review (Rucklidge et al., 2009)	
	Mood and stress	Review (Qi et al., 2011)	
	Psychosis	Animal (Chatterjee et al., 2012)	
Crude *P. notoginseng*	Alzheimer's disease	Animal (Zhong et al., 2011) Cell line (Choi et al., 2010)	Increasing the level of 5-HT and norepinephrine, modulating Na and Ca channels, increasing nestin and brain-derived neurotrophic factor (Cui et al., 2011).
	Memory	Animal (Chuang et al., 2008; Hsieh et al., 2000; Zhou et al., 2007)	
	Depression	Animal (Xiang et al., 2011)	
Crude *P. ginseng*	Memory	Clinical (Kennedy et al., 2004; Neri et al., 1995; Reay et al., 2010; Tian et al., 2003; Wesnes et al., 2000) Animal (Hsieh et al., 2000; Lee et al., 2010a; Nishijo et al., 2004; Nishiyama et al., 1996; Nishiyama et al., 1994a, 1994b; Nishiyama et al., 1994c; Petkov et al., 2003; Petkov et al., 1993; Wang et al., 1995; Xie et al., 1996; Yun et al., 2007; Zhong et al., 2000) Review (Jesky et al., 2011; Ma et al., 1991; Perry et al., 2011; Petkov et al., 1992)	Enhancing the phosphatase activity of calcineurin affecting tau phosphorylation (Tu et al., 2009), antagonistic effects on morphine receptors to decrease morphine dependency (Seo et al., 2008), regulation of Ca current in neurons (Rhim et al., 2002), inhibiting nicotine induced DA surge in brain (Shim et al., 2000).
	Alzheimer's disease	Clinical (Heo et al., 2008; Lee et al., 2008b; Zhong et al., 2007) Animal (Cong et al., 2007; Wang et al., 2006) Review (Perry et al., 2011)	

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Cont. Table 1.14

Crude *P. ginseng*	Cognition	Clinical (Hartley et al., 2004; Kennedy et al., 2001, 2002; Scholey et al., 2002, 2004; Wesnes et al., 1997; Ziemba et al., 1999) Animal (Sanghavi et al., 2011)	Enhancing the phosphatase activity of calcineurin affecting tau phosphorylation (Tu et al., 2009), antagonistic effects on morphine receptors to decrease morphine dependency (Seo et al., 2008), regulation of Ca current in neurons (Rhim et al., 2002), inhibiting nicotine induced DA surge in brain (Shim et al., 2000).
	Attention	Clinical (Niederhofer, 2009)	
Ginsenoside Rg1	Memory	Cell line (Liu et al., 2010) Animal (Liu, 1996; Liu et al., 1996; Wang et al., 2010b) Review (Cheng et al., 2005; Perry et al., 2011)	Promoting neurotransmitter release via a protein kinase II-dependent signaling pathway.
	Alzheimer's disease	Cell line (Chen et al., 2006; Chen et al., 2012b; Shi et al., 2012a; Wang et al., 2009b) Animal (Fang et al., 2012; Li et al., 2011c; Shi et al., 2010)	
	Peripheral nerve regeneration	Animal (Ma et al., 2010a)	
	Inhibiting neurodegeneration	Review (Qi et al., 2011)	
	Schwann cell neurotropic activity	Cell line (Liang et al., 2010)	
	Anxiety	Animal (Cha et al., 2005)	
Ginsenoside Rh1 (an Rg1 metabolite)	Memory	Animal (Wang et al., 2009c)	Not reported.
Ginsenoside Rb1	Memory	Cell line (Liu et al., 2011a) animal (Salim et al., 1997; Wang et al., 2010b) review (Cheng et al., 2005; Perry et al., 2011)	Promoting neurotransmitter release via a cAMP-dependent protein kinase pathway (Qi et al., 2011), selective inhibition of voltage gated calcium channels (Lin et al., 2012), local anti-inflammatory effects in brain via different interleukins (Zhu et al., 2012), anti-oxidant effect against Aβ induced inflammation (Xie et al., 2010a), stimulating cell survival in hippocampus (Liu et al., 2011a).
	Alzheimer's disease	cell line (Zhao et al., 2011) animal (Lee et al., 2001; Wang et al., 2011d)	
	Depressant	Animal (Yamada et al., 2011)	Promoting neurotransmitter release via a cAMP-dependent protein kinase pathway (Qi et al., 2011), selective inhibition of voltage gated calcium channels (Lin et al., 2012), local anti-inflammatory effects in brain via different interleukins (Zhu et al., 2012), anti-oxidant effect against Aβ induced inflammation (Xie et al., 2010a), stimulating cell survival in hippocampus (Liu et al., 2011a).
	Neuroprotection	Review (Qi et al., 2011)	
	Schwann cell neurotropic activity	Cell line (Liang et al., 2010)	

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Cont. Table 1.14.

Compound K (an Rb1/Rd metabolite)	Depression	Animal (Yamada et al., 2011)	Suppression of NF-^{k}-B activation, pro-inflammatory cytokine, mitogen-activated protein kinase, reactive oxygen species, and mitogen-activated protein kinase, activation of peroxisome proliferator-activated receptor γ, increase of GLUT expression enhancement of PKA-dependent pathways Amelioration of insulin resistance through suppressions of endogenous glucose production and lipogenesis in the liver, and activated phosphorylation of AMPK in the HIT-T15 cells protective effects against beta-cell death, Inhibition of expression of Interferon-$^{\gamma}$, Induction of apoptosis by activation of caspase-8, suppression of nuclear factor-kappa B (NF-κB) pathways, and Janus activated kinase 1 (JAK1)-signal transducer and activator of transcription 3 (STAT3) signaling, suppressing matrix metalloproteinase-9 (MMP-9) expression and inhibitting basic fibroblast growth factor (bFGF)-induced angiogenesis (Wang et al., 2011b).
	Memory	cell line (Bae et al., 2010)	
Ginsenoside M1 (an Rb1 metabolite)	Alzheimer's disease	Animal (Tohda et al., 2004)	Not reported.
	Memory	cell line (Tohda et al., 2006)	
Ginsenoside Rb3	Depression	Animal (Xiang et al., 2011)	Neuroprotective effects by enhancing anti-oxiant abilities and lowering the amount of free radicals (Xu et al., 2005), inhibition of GABA exhaustion in nerves (Jiang et al., 2011), inhibiting NMDA-induced calcium influx and glutamate-induced cerebral damage (Cui et al., 2011), decreasing the affinity of glycine for hippocampal receptor and delaying receptor activation (Xu et al., 2005), increasing brain-derived neurotropic factor, controversial effects on dopaminergic and neurepinephric pathways (Cui et al., 2011), increasing cell viability, inhibiting LDH release, inhibition of apoptosis and MMP, increase in Bcl-2 protein expression(Zhu et al., 2010).
	Memory	Animal (Cui et al., 2011)	
	Stroke recovery	Animal (Cui et al., 2011)	

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Cont. Table 1.14.

Ginsenoside Re	Cognition	Animal (Liu et al., 2012b)	H2O2 and hydroxyl radical scavenging (Qi et al., 2011).
	Alzheimer's disease	Cell line (Chen et al., 2006)	
Ginsenoside Rd	Nerve apoptosis (prevention)	Animal (Li et al., 2010)	Anti-inflammatory response via P38 and JNK pathways (Yang et al., 2012), anti-Alzheimer's effects by enhancing the activity of protein phosphatase 2A on tau protein (Li et al., 2011b), neuroprotection against glutamate induced excitotoxocity by inhibiting Ca influx (Zhang et al., 2012a).
	Stroke recovery	Clinical (Liu et al., 2012a)	
	Inhibiting neurodegener-ation	Review (Qi et al., 2011)	
	Neuro-protection	Animal (Yokozawa et al., 2004)	
Ginsenoside Rg3	Alzheimer's disease	Cell line (Chen et al., 2006) Review (Perry et al., 2011)	Improvement of mitochondrial metabolism in nerves, decreasing mitochondrial permeability induced by Ca or H_2O_2 (Tian et al., 2009), neuro-protection by inhibiting voltage gated Na channels (Lee et al., 2008a), protecting neurons from NMDA induced neuronal death by antagonistic effects on NMDA receptor (Kim et al., 2004b).
	Inhibiting neurodegeneration	Review (Qi et al., 2011)	
	Memory	Animal (Bao et al., 2005)	
Ginsenoside Rg2	Memory	Animal (Ma et al., 1993; Zhang et al., 2008b)	Affects human nicotinic acetylcholine receptor (Sala et al., 2002).
pseudoginsenoside-F11	Memory	Animal (Li et al., 1999)	Neuronal excitatory effects by increasing the release of glutamate (Wang et al., 2011e), antagonistic effects to morphine induced memory-loss and analgesia (Li et al., 2000).
Combination Rg5/Rk1	Memory	Animal (Bao et al., 2005)	Not reported.
Ginsenoside Rh2	Memory	Animal (Yang et al., 2009b)	Not reported.
Non saponin fraction of "red ginseng"	Memory	Animal (Kurimoto et al., 2004)	Not reported.
Panaxynol (a polyacetylene from *P. ginseng*)	Memory	Animal (Yamazaki et al., 2001)	Not reported.
Polysaccharides	Memory	Animal (Liubimov et al., 1995)	Not reported.

1.4. The ageing world

Ageing is a global concern. Decreasing fertility rate and increasing life expectancy are increasing the average age in different parts of the world. It is predicted that by the year 2050 the global population of people older than 60 years old will be doubled (Lutz et al., 2008b). Singapore is also a rapidly ageing society. In 2000, 7.2% of population were older than 65. This proportion increased to 9.0% in 2010 (Wong, 2010) and it has been predicted that the population of older adults aged 65 or more in Singapore will be doubled by the year 2025 (Yap et al., 2011). On the other hand, ageing is associated with multiple chronic disorders leading in usage of multiple drugs (Willison et al., 2004). In addition, rate of chronic illness is also associated with higher usage of CAM (Feng et al., 2010).

Among age related disorders, mental disorders in elderly are of extreme importance. Although they are quite common in this age group (more than 30%), the patients can hardly have access to specialized mental health care and primary care physicians are more involved in their psychological care (Lyness et al., 1999). The most common mental health issues among older adults include depression, dementia, anxiety, etc. Moreover, these disorders have huge coincidence. In the following paragraphs, these mental disorders will be discussed more.

Cognitive decline is one of the most important mental health issues associated with ageing (Thies et al., 2013). The ultimate serious consequence of cognitive decline is dementia (American Psychiatric Association. et al., 2013). Dementia is a chronic progressive and incurable disorder with a significant psychosocial and economical cost for the affected patients, their families and the society. In 2010, the global prevalence of dementia was estimated as 35 million. Such a prevalence causes a global annual

financial burden of US$604 billion (Wimo et al., 2013). In Europe, 10.11 million people were suffering from dementia in 2008 and the total estimated cost of this problem to the European society was €177 billion (Wimo et al., 2011). Furthermore the risk of developing depression is higher in elderly patients with dementia (Samaras et al., 2013).

Depression is the most common mental disorder appearing in the elder affecting approximately 13% of older adult population worldwide (Samaras et al., 2013). Both the new incidence and the relapse of depression are common in this age group where the episodes of depression are prolonged and the periods of remission are shorten. In addition, the risk of resistance to the treatment is higher in older adults (Porzych et al., 2005). Not only depression is more prevalent among dementia patients (approximately 35%), but also depression can accelerate the progress of cognitive decline and interferes with neuropsychological testing of the patients (Samaras et al., 2013).

One of the most common symptoms accompanying the depressive disorders in the elderly patients is anxiety. Elderly patients with anxiety symptoms caused mainly by depression often complain of pain. Such patients usually suffer from lower self-esteem and the risk of suicidal thoughts and tendencies is higher (Porzych et al., 2005).

Considering the financial and psychological burden of mental health problems in older adults, it is important to investigate the factors associated with higher likelihood of developing such problems as well as potential protective factors. Clinical and epidemiologic investigations besides bench based studies provide valuable information regarding the risk factors and potential protective and curative treatments.

1.5. Laboratory animals as models for mental health

Since prehistoric times, human has considered animals and animal products as renewable natural resources to be used for food, clothing, transportation, recreation, sport and companionship (Bear et al., 2007). Similarly, usage of animal models in medical research has a history as long as the history of medicine. Throughout the history, the ethical and religious considerations and social prohibitions limited the experimental studies of human biology and pathology. In addition, sometimes it is not practical, economical or scientific to do the preliminary studies in human subjects. Therefore, most of our current basic knowledge of human biology, physiology, endocrinology and pharmacology has been derived from the studies using animals. In other words, animals have been used as "man models" for modeling human physiology and pathology to extrapolate the results from animal studies to understand human biology (Conn, 2008).

Alike other fields of medicine, development in neuroscience is indebted to the gift of animal studies. Most of what we know about the nervous system comes from experiments on animals. Neuroscience experiments are conducted using many different species ranging from snails to monkeys. However, more than half of the animals used for neuroscience research are inbred rodents (mice and rats) (Bear et al., 2007). Except the cerebral cortex which has had huge development in human, all mammals share even small details in their nervous system. This similarity in the brains of mammals makes it possible to study brain function and detailed neuronal connections in animals and then extrapolate the results to the human. Furthermore, the simplicity of rodents' brains compared to humans' (especially in cerebral cortical area) makes it easier to study and

understand the function and relationship of different parts of the brain by studying the rodent brain first (Watson et al., 2010).

In general, simpler nervous system, less ethical issues and more availability have made animal models an important research tool in neuroscience. For example, the possibility of genetic manipulation has provided suitable animal models for many human mutations and genetic variations responsible for neurological disorders (Donaldson et al., 2014). Techniques usually used for studying the brain includes thin sectioning of the brain and staining the brain sections, cell culture, hodology, molecular genetics, non-invasive imaging techniques, electrophysiology (Watson et al., 2010), behavioral studying methods and cognitive paradigms (Bear et al., 2007). In the next paragraphs, the most important techniques will be introduced briefly.

1.5.1. Sectioning the brain and staining the sections

Microscopic study requires very thinly sliced tissues. The brain is usually pretreated with chemical preservatives such as formaldehyde before sectioning. However, there are some techniques to cut the fresh or freshly frozen tissues. The sections are usually cut using a sophisticated machine named microtome (Watson et al., 2010). The sliced tissues can be used for further studies such as microscopy or staining just after slicing or preserved using cryoprotectant material to be used later (Watson et al., 1986). A proper cryoprotectant solution can preserve the morphology and peptide immunoreactivity of freely floating slices in -20° centigrade for further processing after more than 20 years (Hoffman et al., 2004).

Brain slices can be stained using routine methods like Nissle stain which is used for nuclei and ribonucleic acid (RNA) (Butskhrikidze et al., 2008) and luxul fast blue

method which stains myelin (Walker et al., 2014) or more sophisticated methods such as histochemical or immunohistochemical staining. They can be specific to particular proteins or some other biological molecules like deoxyribonucleic acid (DNA) and specific glycoproteins. One of most commonly used ones is 4',6'-diamidino-2-phenylenindole dihydrochloride (DAPI) forms fluorescent complex with DNA and can visualize the nuclei (Lee et al., 2012a). There are different proteins as target of immunohistochemical staining. One of these molecules is c-Fos.

Cellular Finkel–Biskis–Jinkins murine osteosarcoma oncogene homologue (c-Fos) is a cellular transcription factor (Milde-Langosch, 2005). C-Fos gene is one of the first identified immediate early genes. Immediate early genes are a class of genes which encode for a variety of cytoplasmic enzymes, secreted proteins and transcription factors. Their expression is low or undetectable in quiescent cells; but, they will be rapidly (in matter of minutes) transcribed in response to many extracellular signals. Their transcription is transient and independent of new protein synthesis leading in encoding a protein with a high turnover (Durchdewald et al., 2009; Healy et al., 2013; O'Donnell et al., 2012). So far, c-Fos have been identified to be involved in a variety of physiological and pathological activities including differentiation, proliferation, apoptosis and migration of different cell types including cancers, immune system, skin, bone and central nervous system (Durchdewald et al., 2009). Its expression in the central nervous system has been investigated in studies concerning anxiety, depression and other neurological disorders as well as pharmacological ones (Panhelainen et al., 2012; Verma et al., 2007). Mapping its expression in response to the administration of neuroactive drugs can provide information on brain region specificity for drug effects (Rajkumar et al., 2013).

1.5.2. Electrophysiology

Electrophysiology has been the gold standard in neuroscience investigation since the discovery of linkage between neuronal functions to electrical activity. Nowadays, electrophysiology is implicated in different scales of studies in neuroscience from molecular (single ion channel) to behavioral (hundreds of cells in neuronal networks) studies. Electrical charges in receptors, neurons or other regions in nervous system are transferred to sensitive amplifiers using metal, glass or silicon electrodes dedicated for optimal specific recordings (Merighi, 2011; Scanziani et al., 2009).

The electrophysiology techniques are categorized into three main groups based on where the electrode is placed in the neural specimen. In the extracellular recording experiment, the electrode is inserted just outside the neuron of interest. In the intracellular recording, it is placed inside the neuron of interest. The third category includes patch clamp techniques where the electrode is opposed to the neural membrane forming a tight seal with a patch of the membrane. All these techniques can be used for either *in vivo* or *in vitro* recording. However, most *in vivo* studies use extracellular recording (Carter et al., 2010).

Extracellular recording is based on changes in cell membrane potential during an action potential (a neuronal activity). This electrical change can be detected by the potential difference between a tip of electrode inserted close to cell membrane and a ground electrode placed in a distant extracellular position. During the neuronal rest, there is no difference in potential between these two electrodes. However, when an action potential arrives to the a nearby neuron, flow of the positive charges from the recording position toward the neuronal membrane causes a potential differences between the recording and ground electrodes. Similarly, when the action potential

passes by, the positive charges flow out from cell membrane toward the recording electrode and causes another change in the potential difference between the recording and ground electrodes. These changes in potential differences can be recorded and analyzed as a reflection of action potential (Carter et al., 2010; Bear et al., 2007).

The advantage of extracellular recording to intracellular or patch recording is that it does not need the precise and delicate electrode positioning inside the neuron. On the other hand, it is impossible to measure localized potentials using extracellular recording or minor potential changes, which are not big enough to produce an action potential (subthreshold potential changes). What we usually record from extracellular electrodes is the local field potential, the sum of all postsynaptic activity within a volume of neuronal tissue (Carter et al., 2010). In other words, it measures the sum of action potential in a group of neighboring neurons instead of a single one.

1.5.3. Behavioral studies

Humans are the only animals who can express their emotions, feelings, perception and knowledge by the use of words. The only way to understand the emotional perceptual and cognitive process of other animals is to observe their behavior. There are a variety of different batteries of tests that probe animals for clues about their mental status. Behavioral studies not only characterize the animal behavior but also identify and describe the genetic, biochemical and cellular correlates of each behavior. Therefore, behavioral techniques are usually applied in combination with systems and molecular techniques descried before (Carter et al., 2010).

1.6. Summary

Singapore is ageing. The increased prevalence of ageing indicates the importance of health concern of the elderly. Ageing is associated with higher risk of chronic disorders such as mental problem, higher usage of both conventional and complementary health remedies, and hence the higher risk of side effects and interactions. Therefore, it is very important to improve our understanding of usage of complementary and alternative medicine among older adults.

The most commonly used type of complementary and alternative medicine is herbal medicine. Usage of herbal medicine is associated with higher risk of herb-drug, herb-herb, and herb-food interactions compared to other complementary and alternative medicinal practices. Such risks are higher among older adults who are suffering from multiple chronic diseases and use poly-pharmacy. These facts show the importance of collating the information about trends of herbal medicine usage among older adults.

Panax ginseng, the most commonly used herb worldwide, is the prototype herb of *Panax* genus. This herb and other related herbs (commonly known as "ginseng") are commercially available in various forms from raw herb to fully processed pharmacological preparations. Since most of these preparations are sold over the counter without need to be prescribed, the information presented in their labels is the most precious source of knowledge for their users. Therefore, it is very important to investigate such products in the market and assess how much the information presented on their labels is consistent with local legislations and requirements.

Not only is "ginseng" the most commonly used and the best sold medicinal herb worldwide, but also it is one of the best-studied ones. Several pharmacological activities

have been studied in *Panax* species including anti-cancer, immunomodulatory, hypoglycemic, anti-hypertensive, analgesic effects as well as effects on reproductive, respiratory and neurologic systems. The neurologic functions of these herbs include promising effects for Parkinsonism, Alzheimer's disease, stroke and depression.

A few hundred active components have been isolated from *Panax* species. Among them, ginsenosides are the most abundant ones and the main contributors to their pharmacological activities. Ginsenoside Rg1 is one of the most abundant ginsenosides with reported neurological effects such as memory enhancing, anti-Parkinsonism, anti-depressant and neuroprotective activities. To the best of our knowledge, there is no study evaluating its effects on medial prefrontal cortex, an important brain region involved in data processing, decision making, working memory, anxiety and many other neurological functions.

Animal studies are important techniques in evaluating neuropharmacological properties of different substances such as natural products. Several methods have been applied in animal based neuroscience studies. It makes animal studies an excellent platform for bench work in a translational medical approach.

CHAPTER 2. Significance, hypotheses and objectives

Usage of complementary and alternative medicine is very common worldwide. Despite a long history of usage, there is a shortage in scientific approaches to the usage and efficacy of CAM practices. The translational medical approach is one of the best systematic approaches to biological research. This approach begins from clinical observations and continues the research to laboratory experiments. In this work, we follow the same path approaching the usage of CAM. The main hypotheses of this project are that the usage of CAM is common among older adults in Singapore and the usage of composite CAM or some of its specific types are associated with neurocognitive status of this age group. Therefore, we examine these main hypotheses in four continuous and interrelated steps. At the beginning, the information regarding usage of CAM and its subtypes by community dweller older adults is analyzed using a prospective cohort study. Then the usage of most commonly used CAM type, herbal medicine, by older adults in Singapore will be surveyed. The third step is to survey the various commercial products available in the local market containing the words "Panax" or "ginseng". Finally, some of the neurologic effects of one of the most abundant chemical constituents of *Panax* species will be studied using rats. The specific hypotheses and objectives of the work are presented below.

2.1. Usage of complementary and alternative medicine by older adults in Singapore

Similar to most other parts of the world, the population of older adults in Singapore is increasing in recent years (Lutz et al., 2008b; Wong, 2010). This fact emerges a need to have a better understanding of older adults and their health situation. Usage of CAM

plays an important role in health maintenance of older adults because of its potential effects on overall health and particularly their mental health (Landin et al., 2008).

The majority of older adults in Singapore are of Chinese ethnicity (Wong, 2010) and it is reported that CAM usage is more common among the Chinese population (Kennedy, 2005). Therefore, we hypothesize that CAM is commonly used among older adults in Singapore. Furthermore, there are several reports of positive neurocognitive effects of different CAM practices (Bai et al., 2013; Dos Santos-Neto et al., 2006; Gestuvo et al., 2012; Jung et al., 2013; Murray et al., 2004). Hence, we hypothesize that the usage of CAM is correlated with their mental health and its maintenance. The main objective of this part of the work is to evaluate the prevalence of usage of CAM and its main forms among older adults in Singapore and its associated factors including mental health. The second objective of this study is to assess the association of CAM usage with the development of cognitive decline in older adults after two years.

2.2. Usage of herbal medicine among older adults in Singapore

Herbal medicine is the most common type of CAM used worldwide as well as in Singapore (Robinson et al., 2011). Since medicinal herbs are mainly consumed orally, the risk of adverse effect and interaction with other herbs, conventional medicine and food is higher compared to other types of CAM such as acupuncture and qigong (Avello et al., 2010). Hence, it is important to improve our understanding on the trends of herbal medicine usage and factors associated with its usage in older adults. Additionally, there are reports of effectiveness of several herbs for neurocognitive improvement (Chang et al., 2008; CPC, 2010; Qi et al., 2011). Therefore, in the current work, we hypothesize that the usage of composite herbal medicine and the specific herbs among adults older

than 60 years old in Singapore is associated with specific demographic and health factors including neurocognitive status. The objectives of this part of the study are to collate the detailed information about the patterns of usage of herbal medicine among older adults in Singapore and to study factors (including neurocognitive assessment) associated with the usage of the most common herbs.

2.3. Survey of the products containing the words "Panax" or "ginseng" in their labels

Based on legislations in Singapore, health products other than Western medicines do not need premarketing approvals and licensing for their importation, manufacture and sales (MOH, 2008a). Hence, only dealers and sellers are responsible for the safety and quality of such health products (including herbal products) (HSA, 2012b; MOH, 2008a). To the best of our knowledge, all published studies on health products in the Singapore market have been focusing on adulterations and other prohibited and dangerous ingredients in such products (Koh et al., 2000; Yee et al., 2005) and there is no report evaluating their labeling information. Health and food products containing "ginseng" are well known and commonly used worldwide (Ayranci et al., 2005; Froiland et al., 2004; Kang et al., 2012; Smith et al., 2004). Most of these products are sold over the counter without any prescription. Hence, the information provided on their labels has an important impact on the selection of products by consumers. This information should be reliable, clear, and easy to understand by the ordinary people to avoid misunderstandings and inappropriate usage of such products. It is important to improve the knowledge and awareness of public as well as legislative bodies regarding the current situation of health products and level of compliance to local regulations. Accordingly, we hypothesize that the information provided on the labels of products

which have the words “Panax” and/or “ginseng” in their labels in the Singapore market is clear and comprehensive. The objectives of this part of the study are to collate and record information on the labels of the commercially available health and food products labeled with words “Panax” and/or “ginseng” in Singapore and to compare this information to the requirement provided by HSA and AVA.

2.4. The effect of ginsenoside Rg1 on medial prefrontal cortex

Ginsenoside Rg1 is one of the most abundant active compounds of most *Panax* species (Kim, 2012). There are several reports on neurological effects of this ginsenoside as a neurostimulatory and neuroprotective substance, which can enhance the memory and improve depression (Chen et al., 2008a; Huang et al., 2014). However, to the best of our knowledge, there is no report on its potential effects on medial prefrontal cortex. Medial prefrontal cortex is an important brain locus involved in working memory, cognition, decision making and anxiety (Farooq et al., 2013). Based on this, we hypothesize that ginsenoside Rg1 produces some of its neurological actions through increasing the activity of medial prefrontal cortex. To test this hypothesis, we use electrophysiological and histochemical approaches to study the effect of systemic administration of Rg1 on long-term potentiation in the hippocampal-medial prefrontal cortical pathway, the spontaneous firing rate of pyramidal cells in the medial prefrontal cortex and early gene transcription (c-Fos expression) of pyramidal cells in the medial prefrontal cortex.

CHAPTER 3. Usage of complementary and alternative medicine by older adults in Singapore

3.1. Introduction

With decreasing fertility and increasing life expectancy, the proportion of older adults in most countries is expanding (Lutz et al., 2008b). Ageing is associated with multiple chronic disorders and increased drug treatment (Willison et al., 2004). Rates of chronic illness are also associated with higher usage of CAM (Feng et al., 2010). In a study in Australia, 46.3% of diabetic patients were using some forms of CAM to treat their medical conditions or for general health purposes (Manya et al., 2012). This prevalence was 55% in another study in the US (Odegard et al., 2011). Additionally, 43.1% of British hypertensive patients reported usage of CAM (Gohar et al., 2008) while this proportion was 69.5% among Americans (Bell et al., 2006) and 39.1% among Nigerians (Amira et al., 2007).

Singapore is also an ageing country. The population proportion of Singaporeans and permanent residents more than 65 years old has been increased from 7.2% in 2000 to 9.0% in 2010 (Wong, 2010). Further increase in the population of older adults during the next few decades has been warned by population based studies (Yap et al., 2011). In older adults, both depression and cognitive impairment are common mental issues and the combination of these two conditions may aggravate each other (Guy G. Potter et al., 2007). Since psychological and mental status in this age group can be affected by CAM usage (Landin et al., 2008), the usage of CAM in older adults is becoming a global interest to research (McLaughlin et al., 2012).

There are reports of effectiveness of specific CAM forms (herbal medicine, qigong, acupuncture and relaxation) to improve the cognition in elderly using clinical trials and animal models (Bai et al., 2013; Dos Santos-Neto et al., 2006; Gestuvo et al., 2012; Jung et al., 2013; Murray et al., 2004; Oh et al., 2012). However, only few cross-sectional studies can be found reporting the prevalence of this usage in populations and its relationship with cognitive status. Besides, the existing reports usually have small sample sizes. A study in Canada reported that 38.3% of patients of a dementia clinic used some kind of alternative medicine (44/115) and usage of CAM was not correlated with their cognitive status (Hogan et al., 1996). Another study in Germany on 139 older adults revealed that those suffering from cognitive impairment used more CAM (47%) than healthy participants (18%) (Landin et al., 2008).

Similar to reports of CAM on the cognitive problems, the effectiveness of some CAM practices (e.g. acupuncture, qigong and herbal medicine) has been shown in depressive disorders (Tsang et al., 2002)(Dennis et al., 2013; Sarris et al., 2011). On the other hand, the association of CAM usage with depression is also under-studied. In a population-based study in England, usage of CAM was higher in participants (16 years or older) suffering from anxiety and/or depression (Hunt et al., 2010). A national survey in Australia on older adults (older than 50 years old) reported higher rate of consultation with CAM practitioners in those suffering from depression or anxiety (Yen et al., 2013).

One of the CAM practices which is common among older adults worldwide is qigong (Melchart et al., 1997). It is a Chinese medical exercise which combines static and dynamic physical exercises, breathing exercise and meditation (Lauche et al., 2013) Its simplicity and effectiveness in rehabilitation has made it more applicable than other

movement based therapies such as yoga and tai chi for older adults (Yost et al., 2013) who are at a higher risk of physical disabilities and are more susceptible to physical injuries. There are studies reporting positive cognitive effect for qigong in adult cancer (Oh et al., 2012) and middle-aged hypertensive patients (Lee et al., 2004c) as well as positive effects against pain, depression and anxiety in fibromyalgia syndrome patients (Creamer et al., 2000; Maddali Bongi et al., 2012). Since qigong is a combination of physical activity and meditation, it is difficult to study its effect using animal models. One way is to explain its positive cognitive effects using the known neurologic effects of physical exercise in animals. The hypothesized mechanisms for neuropsychological effects of qigong especially its anti-depressant effects include up-regulating monoamine neurotransmitters or reductions of adrenal glucocorticoid secretion by affecting amygdala. The other suggested mechanism of action is improving neurogenesis in the hippocampus by up-regulating brain-derived neurotropic factor (BDNF) or down-regulating cortisol (Tsang et al., 2008). Moreover, qigong as a moderate mindful physical activity can decrease the self-perceived functional limitation and increase the psychosocial resources, two factors suggested as psychological etiology of depression (Tsang et al., 2002). None of these theories can explain the neurocognitive effects of qigong properly. There is a shortage of enough evidence to support such theories and clinical observations and trials are needed to explain the effects.

Therefore, there is a shortage of observational reports on the usage of CAM and its individual types in older adults and their relationship with the neurocognitive status and prognosis. This fact emerges a need to have a better understanding of older adults and

their mental health situation considering the usage of CAM as an important player in the health maintenance of this age group.

3.2. Hypotheses and objectives

Considering the ethnic diversity of population of the older adults in Singapore where the majority are Chinese (Wong, 2010) and high prevalence of CAM usage among Chinese people (Kennedy, 2005), we hypothesize that usage of CAM is common among adults older than 60 years in Singapore. Additionally, since there are reports of positive neurocognitive effects of several CAM practices (Bai et al., 2013; Dos Santos-Neto et al., 2006; Gestuvo et al., 2012; Jung et al., 2013; Murray et al., 2004), we hypothesize that the usage of CAM in older adults is correlated with their mental health. To evaluate these hypotheses, the objectives of this part of the work are to assess the prevalence of usage of CAM and its main forms in a population-based sample of older adults in Singapore and its associated factors including mental health. The other objective of this study is to assess the association of CAM usage and its subtypes with the development of cognitive decline in older adults after four years.

3.3. Methods

The baseline data from Singapore Longitudinal Ageing Study I and II (SLAS) and 4-year follow-up data from SLAS I were used to evaluate the usage of CAM among Singaporean older adults. The details of data collection were as follows.

3.3.1. Participants

In SLAS, consecutive sampling method had been used to collect as many participants as possible. Baseline "SLAS I" was collated in 2003-2004 by a door-to-door census recruiting Singaporeans and Permanent Residents aged 60 and above. By visiting all the housing units in a selected territory in South West Singapore, all participants older than 60 were identified. From each housing unit, an older adult was invited to participate in the study. After four years, the participants were recalled to assess any change in their cognitive status. "SLAS II" was the continuation of new participant recruiting performed in 2007-2008. For this part of study the recruitment territory was extended to the South Central and South East Singapore. The older adults were voluntarily invited to participate in the study by giving informed consent. The study protocol was approved by the National University of Singapore Institutional Review Board (NUS-IRB).

3.3.2. The questionnaire

For all participants, a questionnaire was used to evaluate their demographic information (age, sex, race, educational level, etc.), physical, social and productive activities, instrumental daily activity, past medical history and drug history, any history of using CAM within the past 12 months, and depression and cognition status (Ng et al., 2004; Niti et al., 2008).

3.3.2.1. Usage of CAM

The participants were asked about any usage of various types of CAM including herbal medicine (considering specific herbs: "ginseng", "ginkgo", "evening primrose

oil", "garlic supplement", "lingzhi", "tianqi" and herbal tonics), acupuncture, acupressure and moxibustion, movement therapies such as Tai chi, Yoga, Qigong, etc., specific traditional medicines such as Jamu and Ayorvedic medicine, and other types of CAM including massage therapy, hypnotherapy, spirit medium healing, etc. Using any of these practices in past 12 month was considered as using CAM and was counted both as individual practice and as composite CAM practice. The collated information was recorded in a database for further analysis.

3.3.2.2. Physical, social and instrumental daily activity

Physical activity measurement was based on the frequency of involvement in any active sports, walking, swimming and regular exercise. For involvement in these activities, participant would be scored 2 (once a week or more), 1 (once a month to once a week) or 0 (less than once a month).

Social activity referred to how much the participant was involved in 16 social activities including hobbies, games, community work, religious activities, and daily activities such as shopping and cooking. For each activity, participant would score 2 (once a week or more), 1 (once a month to once a week) or 0 (less than once a month). The highest possible social activity score was 32 and the lowest possible score was 0 (Ng et al., 2008b).

The instrumental activity of daily life (IADL) was measured by level of independency in 7 daily activities including house work, grocery shopping, cooking, short travelling, managing money, taking medicine and using telephone. The first four items are considered as physical IADL and the last three items were considered as

cognitive IADL. Being unable to manage any of these items without help was considered as either physical or cognitive dependency in IADL (Ng et al., 2006).

3.3.2.3. Past medical history of chronic diseases

Past medical history of chronic diseases were evaluated based on self-reporting history of hypertension, hypercholesterolemia, diabetes mellitus, cerebrovascular accidents, cardiovascular problems (including heart attacks, atrial fibrillation, heart failure, etc.), ophthalmologic problems (including cataract and glaucoma), renal failure, pulmonary system problems (including asthma and chronic obstructive pulmonary disease, tuberculosis, etc.), chronic musculoskeletal problems (including arthritis, osteoporosis, hip fracture, etc.), neurological problems (including dementia, Alzheimer's diseases, Parkinsonism, depression, etc.), gastrointestinal issues (including dyspepsia, chronic reflux, chronic diarrhea or constipation, etc.), hyper/hypothyroidism and cancer. Participants were categorized based on the number of reporting chronic disorders into three groups namely having no history of chronic disorders, suffering from one or two chronic disorders and suffering from three of more chronic disorders. If a participant reported history of two similar interrelated disorders (such as both heart attack and heart failure or both osteoporosis and hip fracture), it was considered as a single chronic disease.

3.3.2.4. Neurocognitive assessment

The 30-itemed "Mini Mental State Exam (MMSE)" was used to evaluate cognitive status of the participants and 15-itemed "Geriatric Depression Scale (GDS-15)" was used for depression scoring. In addition, few other cognitive batteries were used to

further evaluate their cognitive performance including forward and backward digital span, 9-trial Rey auditory verbal learning test (RAVLT) and block design test.

The MMSE is one of the most common used screening test for cognitive status. It consists of 30 short answer questions to assess the orientation of the examinee to time and place, the short term memory (immediate recall) by memorizing three simple unrelated words and the long-term memory (delayed recall) by recalling the same list of word after some time gap, the attention by subtracting 7 from 100 for 5 times (till 65), the language by asking the name of familiar objects like pencil and watch, repeating a simple phrase read by the examiner, obeying simple tasks ordered by the examiners verbally and obeying a simple task written on a piece of paper as well as by the ability to make a complete sentence and finally the construction ability by recreating a simple construction drawn on a piece of paper. The maximum MMSE score is 30 and the minimum is 0. The higher MMSE score the less risk of dementia. Cutoff point for impression of cognitive impairment using MMSE test is 24 (Folstein et al., 1975; Rosselli et al., 2006). There are several reports on local validation and use of MMSE test in Singapore (Dong et al., 2012; Dong et al., 2013; Ng et al., 2007).

The geriatric depression scale is a 15 itemed yes/no question list, which evaluates the feeling of the examinee during past few weeks. By answering each question the examinee will be scored either 0 or 1. The higher the GDS score, the higher the risk of depression. The cutoff point for GDS to be considered as positive for depression is 5 (Li et al., 2012c; Lyness et al., 1997). This test has been validated and used locally (Lim et al., 2000; Nyunt et al., 2009).

The Rey auditory verbal learning test is designed to evaluate verbal memory in participants. It measures the short term and long-term memory by memorizing 15 one

or two syllabus simple words. To do that, 15 unrelated unrepeated simple words (list A) will be read to the examinee one by one (1 second each word). After that, the examinee is supposed to recall them. For each correct recalling, one point will be given to him. This learning process will be repeated for 5 times. After the 5^{th} trial, 15 other words (list B) will be read to the participant and he/she is asked to recall the new list (trial 6). After that, he/she will be asked to remember the first list of words (list A) without reading the list by the examinee (trial 7). Later, after 20-30 minutes gap, the participant is asked to recall the list (trial 8). Finally, a list of 50 shuffled words including list A, list B and 20 new words will be presented to the participant and he/she is supposed to recognize the words presented in the list A (trial 9). At each trial, the participant can use as much time as he/she wants to complete the trial by recalling the list. There are different measurements calculated based on scores gained for each trial. Trial 1 measures the immediate recall and trial 5 is the best learning experience. The sum of scores in trial 1 to 5 will be considered as total learning while the subtraction of score in trial 1 from that of trial 5 is called learning rate. The trials 6 and 7 assess proactive and retroactive interferences respectively. The trial 8 examines the delayed recall and trial 9 is named recognition measurement (Kreutzer et al., 2011; Poreh, 2006; Van der Elst et al., 2005).

The Block Design (BD) test requires the examinee to use three-dimensional blocks to construct a model from a two-dimensional stimulus card. Blocks consist of sides that are all white, all red, or diagonally half red and white. Performance is timed. Although bonus points are awarded for speed, the score is either all or none, that is, a score is awarded only if the model is correctly produced within the prescribed time limit. Successful completion of the BD test requires a host of cognitive abilities including

specific analytic and synthetic problem-solving strategies (Kreutzer et al., 2011; Poreh, 2006).

MMSE, RAVLT, forward and backward digit span, and block design tests were used for the follow-up cognitive assessment. Any change in the corresponding scores was calculated and used for further analysis. Accordingly, any decrease in 4-year follow-up MMSE score compared to baseline test for at least two points was considered cognitive decline (Feng et al., 2012). Declined in short memory (trial 1 in RAVLT) was assumed when any decrease compared to the baseline score was observed. Decline in total learning results in RAVLT was deliberated when the total learning score was decreased for at least 4 scores after four years. Comparing the 4-year follow-up score in RAVLT recognition to the baseline score, any decrease for at least 8% was defined as decline in recognition test. Decline in forward digit span was when the participant performance in follow-up test was at least 2 scores less than his performance in baseline test. This cutoff point for backward digit span was 1 score and for block design test was 2 scores.

3.3.3. Inclusion and exclusion criteria

The individuals with severe physical and mental disabilities limiting the completion of study were not recruited. All participants above 60 years old who were able to provide clear information about usage of CAM during baseline interview were included for this study. Any participants with incomplete MMSE or GDS tests or those with MMSE scores less than 18 were excluded from statistical analyses. For those participants participated in the four-year follow-up study, the minimum accepted

baseline MMSE was set as 24 in order to exclude those who were already suffering from cognitive impairment at the baseline.

3.3.4. Statistical analysis

Data from "SLAS I" was merged with "SLAS II" to obtain the final data pool. A participant was categorized as CAM user if he/she had reported any usage of at least one form of CAM within the last 12 months. The overall usage of composite CAM and its subtypes were analyzed among the participants. Then, the likelihood of using CAM in different demographic and sociophysical groups was analyzed using logistic regression models. At the same time the effect of neurocognitive assessment scores on the prevalence of CAM usage was studied. The "wald" value was used to compare the effect of each variable on this likelihood. Similar methods were used for major CAM practices to evaluate the association of demographic, life style and neurocognitive factors to the usage of common CAM practices. All statistical analyses were performed using SPSS-20 software (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA).

3.4. Results and discussion

3.4.1. Baseline data

From SLAS I and SLAS II, 2680 and 2305 participants were recruited respectively. A total of 4985 participants who were 60 years old and above was included. The mean age of participants was 66.3 years (range 60-98). The demographic information of included participants is presented in Table 3.1. Most of the participants were female, Chinese with primary or secondary school educational level.

In this study, the demographic data is not consistent with population distribution. For example, the majority of the studied participants were female (62.7%) while based on the Census of Singapore in 2010, 52.7% of Singaporeans older than 60 are female (Wong, 2010). Ethnic diversity is also a bit different from census results. In census 2010, 74.1% of Singapore population were Chinese, 13.4% were Malay, 9.2% were Indian, and 3.3% belonged to other ethnicities (Wong, 2010). However, in this study the percentages are 91.2%, 4.9%, 3.1% and 0.8% respectively.

Table 3.1. Demographic distribution of participants in the baseline study (n=4985)

Factor	**Number**	**Percentage (%)**
Gender		
Female	3124	62.7
Male	1861	37.3
Race		
Chinese	4546	91.2
Malay	243	4.9
Indian	157	3.1
Others	39	0.8
Educational level		
Nil	971	19.5
Primary or secondary	3410	68.6
Pre-university or university degree	592	11.9
Housing type		
1-2 room public apartment	892	17.9
3 room public apartment	1266	25.4
4-5 room public apartment, condominium or private landed housing	2819	56.6
Total	4985	100

3.4.1.1.1. Prevalence of the usage of CAM

Out of 4985 participants, 2692 (54.0%, 95% CI: 52.6% – 55.4%) reported using at least one type of CAM within the past 12 months (Table 3.2). The overall prevalence of the usage of CAM among older adults in this study showed slight increase compared to earlier local report on the same age group (44.6%) for which the participant were recruited in 2003-2004 (Feng et al., 2010). This minimal difference may be because of increasing usage rate. In addition, the sample size in this study is approximately 4.5 times bigger than that of Feng et al. (2010). A bigger sample size makes the present results more reliable. On the other hand, some other studies have reported higher prevalence in general population of Singapore (Koh et al., 2004; Koh et al., 2003; Lim et al., 2005). This discrepancy can be explained by differences in response rate of older adults compared to younger adults, different time of carrying out the studies, different CAM usage trends between these two age groups and also different sample sizes.

Herbal medicine (34.5%) was the most commonly used type of CAM followed by Qigong (15.2%) and Acupuncture (10.0%). This finding is in agreement with other studies reporting herbal medicine as the most common type of CAM (Robinson et al., 2011). In addition, Qigong and acupuncture are very common practices in Traditional Chinese Medicine, which are used worldwide (Melchart et al., 1997; Yang et al., 2002).

In this study, “primrose oil”, “ginseng” and “ginkgo” were the top three herbs used by 4.9%, 4.9% and 4.5% of Singaporean older adults respectively. The terminology used for data collation about usage of herbal medicine was based on the common names of herbs in folk medicine.

Table 3.2. Prevalence of different forms of CAM used by Singaporean older adults

CAM category	SLAS I		SLAS II		Total	
	No	%	No	%	No	%
Herbal medicine	1076	40.2	644	27.9	1720	34.5
Primrose oil	187	7.0	58	2.5	245	4.9
"Ginseng"	185	6.9	56	2.4	241	4.9
"Ginkgo"	171	6.4	51	2.2	222	4.5
Herbal tonics	189	7.1	15	0.7	204	4.1
"Lingzhi"	72	2.7	44	1.9	116	2.3
Garlic supplement	76	2.8	16	0.7	92	1.9
"Tianqi "	53	2.0	13	0.6	66	1.3
Qigong	569	21.6	180	7.9	749	15.2
Acupuncture	307	11.7	186	8.1	493	10.0
Massage	195	7.4	202	8.8	397	8.0
Tai chi	261	9.9	113	4.9	374	7.6
Reflexology	132	5.0	102	4.4	234	4.7
Ayurveda	0	0.0	37	1.6	37	1.6
Yoga	52	2.0	31	1.3	83	1.7
Meditation	0	0.0	34	1.5	34	1.5
Moxibustion	29	1.1	15	0.7	44	0.9
Jamu Malay medicine	17	0.6	21	0.9	38	0.8
Acupressure	26	1.0	12	0.5	38	0.8
Chiropractic	13	0.5	28	1.2	41	0.8
Osteopathy	32	1.2	0	0.0	32	1.2
Spirit medium healing	1	0.1	8	0.3	9	0.2
Homoeopathy	1	0.1	1	0.1	2	0.1
Aromatherapy	0	0.0	0	0.0	0	0.0
Hypnotherapy	0	0.0	0	0.0	0	0.0
Composite CAM use	1625	60.6	1067	46.3	2692	54.0%

Usage of folk names limits the accuracy of the collected data. For example, ginseng is mainly used for *Panax ginseng.* Although there are several species in *Panax* genus, "ginseng" is the common name loosely used for almost all of them in folk medicine (WHO, 2002). Therefore, it is difficult to know the prevalence of usage of each of those

species. Tianqi is the Chinese name for *P. notoginseng* (CPC, 2010) (section 1.3.1.3), which was reported being used by 1.3% of the participants (66 individuals) in this study. It was beyond the scope of this study to differentiate different species of common herbs. A more specific study focusing on herbal medicine can be helpful to improve our understanding about the prevalence of the usage of each herb.

3.4.1.2. The reason for using CAM

Among 2692 CAM users, 2301 mentioned their reason for usage. The majority (1738, 75.6%) were using CAM to maintain their health and only 11.6% (268 participants) were using it just for medical conditions. Two hundred and ninety five participants (12.8%) reported using CAM types for both reasons.

This finding was consistent with studies in other countries (Kang et al., 2012; Kim et al., 2004a; Zhang et al., 2008a). For example, in a study carried out in Australia, 69.6% of participants used CAM for general health improvement and not for any specific disorders (Zhang et al., 2008a).

3.4.1.3. Factors affecting the prevalence of usage of CAM

To study factors affecting usage of CAM, student t-test was used for continuous factors and chi square was used for categorical factors (Table 3.3). Using these unadjusted methods, we found that CAM users are younger Chinese female well-educated participants who live in bigger houses and are suffering from one or two chronic medical conditions. Such participants were more physically and socially active and less dependent in their physical and cognitive daily activities (pIADL and cIADL respectively).

Although there was no significant different between CAM users and non-users regarding their GDS, MMSE and forward digit span results, CAM users showed better performance in their other neurocognitive assessments including backward digit span, block design and different RAVLT measurements.

Table 3.3. Unadjusted association of demographic and neurocognitive factors to use of composite CAM

Factor	CAM usage		P value
	Yes	No	
Age	65.7 ± 7.2	67.0 ± 8.0	<0.001
Gender			<0.001
Female	1899 (60.8%)	1225 (39.2%)	
Male	793 (42.6%)	1068 (57.4%)	
Ethnicity			<0.001
Chinese	2539 (55.9%)	2007 (44.1%)	
Malay	91 (37.4%)	152 (62.6%)	
Indian	45 (28.7%)	112 (71.3%)	
Others	17 (43.6%)	22 (56.4%)	
Educational level			<0.001
Nil	453 (46.7%)	518 (53.3%)	
Primary or secondary	1858 (54.5%)	1552 (45.5%)	
Pre-university or university degree	376 (63.5%)	216 (36.5%)	
Housing type			<0.001
1-2 room public apartment	363 (40.7%)	529 (59.3%)	
3 room public apartment	661 (52.2%)	605 (47.8%)	
4-5 room public apartment or private or landed house	1665 (59.1%)	1154 (40.9%)	
History of chronic diseases			<0.001
No history	554 (50.0%)	554 (50.0%)	
History of one or two chronic diseases	1341 (56.9%)	1015 (43.1%)	
History of three or more chronic diseases	797 (52.4%)	724 (47.6%)	

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Cont. Table 3.3

Physical activity			<0.001
Once a month or less	141 (33.8%)	276 (66.2%)	
Once a month to once a week	982 (47.8%)	1073 (52.2%)	
Once a week or more	1548 (62.4%)	934 (37.6%)	
Social, productive and fitness activities	10.36 ± 4.38	8.13 ± 3.84	<0.001
Dependency in pIADL			<0.001
Yes	377 (48.4%)	402 (51.6%)	
No	2309 (55.0%)	1889 (45.0%)	
Dependency in cIADL			<0.001
Yes	45 (38.1%)	73 (61.9%)	
No	2641 (54.4%)	2218 (45.6%)	
GDS score	1.38 ± 2.31	1.33 ± 2.28	0.417
MMSE score	27.70 ± 2.48	27.34 ± 2.73	0.059
Forward Digit Span	11.49 ± 3.14	11.28 ± 3.43	0.137
Backward Digit Span	5.52 ± 2.32	5.22 ± 2.31	0.002
Block design	25.60 ± 10.30	23.76 ± 10.16	<0.001
RAVLT short memory	4.61 ± 2.00	4.32 ± 1.90	0.001
RAVLT total learning	43.32 ± 10.39	40.84 ± 10.68	<0.001
RAVLT total recognition percent	89.14 ± 10.69	86.79 ± 12.06	<0.001

To have a better understanding of association of different factors to the usage of CAM, a logistic regression model was built. Since neurocognitive assessments had high multicollinearity, only MMSE was included in logistic regression model building. MMSE was chosen because it was the only test available for all of the participants. All the other test were available for only a small proportion of the participants. Table 3.4 reports the results of logistic regression showing the association of different factors with the usage of CAM.

Among studied factors, gender had the highest impact on tendency to use CAM (wald = 119.4) where women were more than twice more likely to use CAM than men. This finding is consistent with other studies (Feng et al., 2010; Zhang et al., 2008a). The level of social, productive and fitness activity was the second most powerful predictor of usage of CAM (wald = 110.3). Social interactions can facilitate sharing information about CAM types and encourage the usage. In addition, the usage of CAM was significantly associated with the educational level. Similar results have been reported previously showing a better attitude of high educated people to use CAM (Seo et al., 2013; Willison et al., 2004; Zhang et al., 2008a).

Table 3.4. Adjusted association of demographic and neurocognitive factors to use of composite CAM

Factor	Odds ratio	95% CI	P value
Age	1.00	0.99 – 1.01	0.509
Female gender	2.14	1.87 – 2.45	<0.001
Ethnicity			<0.001
Chinese	1		
Malay	0.55	0.41 – 0.73	<0.001
Indian	0.33	0.23 – 0.49	<0.001
Others	0.44	0.22 – 0.90	0.024
Educational level			<0.001
Nil	1		
Primary or secondary	1.47	1.23 – 1.75	<0.001
Pre-university or university degree	1.96	1.50 – 2.56	<0.001
Housing type			<0.001
1-2 room public apartment	1		
3 room public apartment	1.45	1.21 – 1.75	<0.001
4-5 room public apartment or private or landed house	1.48	1.24 – 1.75	<0.001
History of chronic diseases			0.001
No history	1		
History of one or two chronic diseases	1.32	1.13 – 1.54	<0.001
History of three or more chronic diseases	1.35	1.13 – 1.60	0.001

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Cont. Table 3.4

Physical activity			<0.001
Once a month or less	1		
Once a month to once a week	1.66	1.30 – 2.10	<0.001
Once a week or more	2.52	1.99 – 3.20	<0.001
Social, cognitive and religious activity level	1.09	1.08 – 1.11	<0.001
Dependency in pIADL	1.11	0.92 – 1.33	0.287
Dependency in cIADL	0.69	0.45 – 1.06	0.089
GDS score	1.03	1.00 – 1.06	0.029
MMSE score	0.99	0.96 – 1.02	0.549

Having a better access to the sources of knowledge about CAM practices can increase the usage of CAM among people with high levels of education. It was observed that being Chinese is a good predictor of higher prevalence of CAM use. The stronger culture of traditional medicine among the Chinese (Kennedy, 2005) may explain the higher usage of CAM in this ethnic group. Housing type is a reflection of economic status. It is reported that better economic status is associated with higher usage of CAM (Molassiotis et al., 2005). Consistently, we found that participants living in bigger housing types use more CAM.

Consistent with previous reports (Feng et al., 2010), a higher prevalence of CAM usage was observed in participants suffering from medical conditions. Such participants may be looking for an alternative remedy for their chronic medical condition (Kim et al., 2013). Participants with better levels of physical activities were using more CAM. This association can be because of including some forms of movement and exercise in CAM such as “qigong”, “tai chi”, “yoga”, etc. which can be difficult to perform by those with limited abilities to manage their daily activities by themselves.

Although GDS had no association in unadjusted measurements, participants with higher GDS scores were more likely to use CAM in logistic regression model. It suggests that such older adults may use CAM to control their emotional instability. On the other hand, there was no significant correlation between CAM usage and MMSE score or physical or cognitive IADL. The association of cognition and usage of CAM is inconsistent in available literature. Some studies have reported higher usage of CAM in those suffering from cognitive disorders and depression (Hunt et al., 2010; Landin et al., 2008; Purohit et al., 2013) and some others could not find any association (Hogan et al., 1996). Differences in the study designs and definitions of CAM may explain such inconsistencies. The lack of association in our findings might be due to our exclusion criteria where all participants with severe mental and physical impairment were excluded. Furthermore, considering some reports on positive effects of CAM practices on cognitive status (Bai et al., 2013; Gestuvo et al., 2012; Jung et al., 2013), it can be hypothesized that some of participants with minimal and subclinical cognitive impairment use CAM to improve their condition. At the same time, some other participants with normal cognitive functions use CAM to prevent development of cognitive decline. Therefore, both groups of participants use CAM with similar prevalence. Such hypothesis should be examined in future by more sophisticated observational projects or longitudinal prospective studies.

In this study, age lost its association with the CAM use after controlling for other confounders. Although this finding was in contrast with a previous report (Feng et al., 2010), the lack of association was not unexpected. Ageing is associated with both limitation in physical abilities and increase in risk of suffering from multiple medical conditions. Limitation in physical abilities decreases the involvement in active CAM

types such as Qigong and Yoga. Suffering from medical problems increases the likelihood of using CAM to improve health. Therefore, although the pattern of CAM usage changes by age, the overall prevalence of CAM usage will not be changed significantly. For further confirmation of lack of correlation between age and prevalence of CAM use, participants were categorized in three age ranges to check any possible cluster effect of age on CAM usage, which failed to show any statistically significant effect (p=0.597).

3.4.1.4. Factors affecting the prevalence of usage of herbal medicine

Herbal medicine was the most common type of CAM used by our participants. It is also repeatedly reported as the most common CAM type in several studies (Asadi-Pooya et al., 2014; Barnes et al., 2008; Corey et al., 2014; Italia et al., 2014; Sait et al., 2014). Considering the risks associated with its usage and the general trend of hiding its usage from conventional health providers (section 1.1.3 and 1.1.4), it is important for medical practitioners to consider the possibility of their usage in their patients. Knowing the factors associated with higher usage of herbal medicine is helpful to find those who are more likely herbal medicine users and be prepared for possible risks. Table 3.5 shows the factors associated with higher usage of herbal medicine.

Table 3.5. Unadjusted association of demographic and neurocognitive factors to use of herbal medicine

Factor	Herbal medicine usage		p value
	Yes	No	
Age	65.4 ± 7.3	66.7 ± 7.7	<0.001
Gender			<0.001
Female	1231 (39.4%)	1891 (60.6%)	
Male	489 (26.3%)	1372 (73.7%)	
Ethnicity			<0.001
Chinese	1683 (37.0%)	2861 (63.0%)	
Malay	12 (4.9%)	231(95.1%)	
Indian	15 (9.6%)	142 (90.4%)	
Others	10 (25.6%)	29 (74.4%)	
Educational level			<0.001
Nil	260 (26.8%)	711 (73.2%)	
Primary or secondary	1206 (35.4%)	2202 (64.6%)	
Pre-university or university degree	250 (42.2%)	342 (57.8%)	
Housing type			<0.001
1-2 room public apartment	230 (25.8%)	662 (74.2%)	
3 room public apartment	430 (34.0%)	836 (66.0%)	
4-5 room public apartment or private or landed house	1057 (37.5%)	1760 (62.5%)	
History of chronic diseases			<0.001
No history	383 (34.6%)	724 (65.4%)	
History of one or two chronic diseases	878 (37.3%)	1478 (62.7%)	
History of three or more chronic diseases	459 (30.2%)	1061 (69.8%)	
Physical activity			<0.001
Once a month or less	104 (24.9%)	313 (75.1%)	
Once a month to once a week	617 (30.0%)	1438 (70.0%)	
Once a week or more	987 (39.8%)	1493 (60.2%)	
Social, productive and fitness activities	10.26 ± 4.42	8.84 ± 4.13	<0.001
Dependency in pIADL			0.002
Yes	231 (29.7%)	547 (70.3%)	
No	1485 (35.4%)	2712 (64.6%)	
Dependency in cIADL			0.014
Yes	28 (23.7%)	90 (76.3%)	
No	1688 (34.8%)	3169 (65.2%)	
GDS score	1.44 ± 2.38	1.31 ± 2.25	0.053
MMSE score	27.77 ± 2.45	27.41 ± 2.68	<0.001

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Cont. Table 3.5

Forward Digit Span	11.60 ± 3.13	11.28 ± 3.35	0.026
Backward Digit Span	2.75 ± 1.24	2.71 ± 1.27	0.536
Block design	25.61 ± 10.25	24.30 ± 10.26	0.017
RAVLT short memory	4.62 ± 2.01	4.40 ± 1.92	0.011
RAVLT total learning	43.50 ± 10.44	41.51 ± 10.62	<0.001
RAVLT total recognition percent	89.56 ± 10.30	87.29 ± 11.86	<0.001

Herbal medicine usage is more common among younger Chinese female highly educated participants who are more physically and socially active and stay in bigger houses. Having one or two chronic medical conditions would increase the likelihood of using herbal medicine while more medical conditions had the opposite effect. Using herbal medicine was less common among participants who were physically or cognitively dependent. The GDS score was slightly higher in medicinal herbs users while such participants had a better performance in almost all cognitive assessments (except backward digit span).

To adjust these associations with other potential variables, a logistic regression model was built using “enter” method. Similar to the model created for composite CAM usage, minor neurocognitive assessments were excluded from the model to improve its stability by removing multicollinearity (Table 3.6). Accordingly, age, history of chronic disorders, cognitive and physical IADL dependency, and MMSE score lost their association with the usage of herbal medicine and the effect of housing type became marginal. Since herbal medicine is the most common type of CAM, most discussion used for association of CAM with different factors is applicable to usage of herbal medicine, too. The trend of usage and associated factors were also almost the same in composite CAM usage and herbal medicine usage. The only differences were in the association of housing type and having positive history of chronic medical conditions.

Table 3.6. Adjusted association of demographic and neurocognitive factors to use of herbal medicine

Factor	Odds ratio	95% CI	P value
Age	0.99	0.98 – 1.00	0.235
Female gender	1.97	1.71 – 2.28	<0.001
Ethnicity			<0.001
Chinese	1		
Malay	0.92	0.51 – 0.166	<0.001
Indian	0.19	0.11 – 0.32	<0.001
Others	0.45	0.21 – 0.97	0.042
Educational level			<0.001
Nil	1		
Primary or secondary	1.62	1.34 – 1.96	<0.001
Pre-university or university degree	2.13	1.63 – 2.79	<0.001
Housing type			0.052
1-2 room public apartment	1		
3 room public apartment	1.28	1.05 – 1.57	0.016
4-5 room public apartment or private or landed house	1.14	0.95 – 1.38	0.155
History of chronic diseases			0.066
No history	1		
History of one or two chronic diseases	1.10	0.94 – 1.29	0.231
History of three or more chronic diseases	0.93	0.77- 1.11	0.418
Physical activity			<0.001
Once a month or less	1		
Once a month to once a week	1.35	1.04 – 1.75	0.022
Once a week or more	1.79	1.39 – 2.31	<0.001
Social, cognitive and religious activity level	1.04	1.02 – 1.06	<0.001
Dependency in pIADL	1.07	0.88 – 1.31	0.467
Dependency in cIADL	0.74	0.46 – 1.18	0.201
GDS score	1.04	1.01 – 1.07	0.009
MMSE score	0.99	0.96 – 1.02	0.592

Housing type which is a reflection of financial status and was positively associated with usage of CAM had marginal or no association with usage of herbal medicine. Since herbal medicine is sometimes believed to be a cheaper alternative to conventional drugs (Foroncewicz et al., 2011), it can be used more than other CAM types by older adults

with relative financial problems. This higher usage rate by people with financial problems can attenuate the overall positive association of financial status with usage of CAM. On the other hand, having positive history of chronic medical conditions had no association with usage of herbal medicine after taking into account other variables in the logistic regression model while it kept its association with CAM usage in the regression model. It can be because of pharmacological properties of medicinal herbs, which can be both protective and therapeutic. Therefore, both healthy participants and those affected by chronic medical conditions would use herbal medicine with similar prevalence. Considering the diversity of medicinal herbs used by participants, a more sophisticated and detailed study on herbal medicine can provide more comprehensive results.

3.4.1.5. Factors affecting usage of qigong

After herbal medicine, qigong was the most common CAM practice reported by our participants. Qigong users were mostly female Chinese older adults staying in larger houses and having better physical and social activities. Although qigong users were more independent in cognitive IADL, none of neurocognitive assessment scores was associated with the usage of qigong. Other demographic and life style factors were not associated with the usage of qigong, either (Table 3.7).

Creating a logistic regression model (enter method) we tried to adjust the association of these factor with qigong usage to other demographic, life style and neurocognitive factors. Similar to composite CAM and herbal medicine usage, minor neurocognitive tests were excluded to stabilize the model (Table 3.8).

Table 3.7. Unadjusted association of demographic and neurocognitive factors to use of qigong

Factor	Qigong usage		P value
	Yes	No	
Age	66.7 ± 6.7	66.2 ± 7.7	0.079
Gender			<0.001
Female	549 (17.8%)	2533 (82.2%)	
Male	200 (10.9%)	1630 (89.1%)	
Ethnicity			<0.001
Chinese	731 (16.3%)	3746 (83.7%)	
Malay	12 (5.0%)	228 (95.0%)	
Indian	3 (1.9%)	153 (98.1%)	
Others	3 (7.7%)	36 (92.3%)	
Educational level			0.177
Nil	143 (14.9%)	814 (85.1%)	
Primary or secondary	501 (14.9%)	2860 (85.1%)	
Pre-university or university degree	104 (17.9%)	478 (82.1%)	
Housing type			<0.001
1-2 room public apartment	69 (7.9%)	807 (92.1%)	
3 room public apartment	139 (11.1%)	1116 (88.9%)	
4-5 room public apartment or private or landed house	540 (19.5%)	2233 (80.5%)	
History of chronic diseases			0.199
No history	148 (13.6%)	942 (86.4%)	
History of one or two chronic diseases	359 (15.5%)	1955 (84.5%)	
History of three or more chronic diseases	242 (16.0%)	1266 (84.0%)	
Physical activity			<0.001
Once a month or less	3 (0.7%)	409 (99.3%)	
Once a month to once a week	152 (7.5%)	1875 (92.5%)	
Once a week or more	589 (24.1%)	1854 (75.9%)	
Social, productive and fitness activities	11.71 ± 4.37	8.91 ± 4.13	<0.001
Dependency in pIADL			0.403
Yes	114 (14.9%)	653 (85.1%)	
No	633 (15.3%)	3505 (84.7%)	
Dependency in cIADL			0.004
Yes	8 (6.8%)	109 (93.2%)	
No	739 (15.4%)	4049 (84.6%)	
GDS score	1.38 ± 2.14	1.35 ± 2.32	0.781
MMSE score	27.37 ± 2.66	27.56 ± 2.60	0.062

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Cont. Table 3.7

Forward Digit Span	11.10 ± 3.06	11.43 ± 3.33	0.086
Backward Digit Span	5.29 ± 2.25	5.39 ± 2.34	0.461
Block design	24.36 ± 9.23	24.80 ± 10.43	0.529
RAVLT short memory	4.56 ± 2.03	4.46 ± 1.95	0.418
RAVLT total learning	42.33 ± 10.85	42.14 ± 10.52	0.759
RAVLT total recognition percent	88.10 ± 11.03	88.01 ± 11.51	0.894

Despite composite CAM and herbal medicine usage, usage of qigong was more common among older participants and those suffering from more chronic medical conditions. It can be because of its simplicity that it can be used by even very old participants while younger participants can be involved in more energetic exercises such as yoga and tai chi. Therefore, some of younger participants who are trying to use exercise based remedies may be interested in those practices while the majority of older participants will try qigong.

Consistent with other types of CAM, usage of qigong was more common among female Chinese older adults and those who were more physically and socially active. The possible explanations for such associations have been presented in previous sections (sections 3.4.1.3 and 3.4.1.4). Since qigong is a physical exercise which is usually performed in groups, it is predictable that qigong users are more physically and socially active. Among neurocognitive tests, MMSE showed statistical association with usage of qigong. However, this statistical association was not much clinically significant. The mean MMSE score of qigong users (27.33 ± 2.66) was slightly less than that of non-users (27.56 ± 2.60), which does not look clinically relevant.

Table 3.8. Adjusted association of demographic and neurocognitive factors to use of qigong

Factor	Odds ratio	95% CI	P value
Age	1.03	1.01 – 1.04	<0.001
Female gender	1.67	1.36 – 2.04	<0.001
Ethnicity			<0.001
Chinese	1		
Malay	0.36	0.20 – 0.67	0.001
Indian	0.12	0.04 – 0.40	<0.001
Others	0.29	0.08 – 1.02	0.053
Educational level			0.485
Nil	1		
Primary or secondary	1.16	0.90 – 1.50	0.260
Pre-university or university degree	1.09	0.76 – 1.57	0.639
Housing type			<0.001
1-2 room public apartment	1		
3 room public apartment	1.27	0.92 – 1.75	0.150
4-5 room public apartment or private or landed house	2.09	1.56 – 2.79	<0.001
History of chronic diseases			0.027
No history	1		
History of one or two chronic diseases	1.10	0.88 – 1.38	0.390
History of three or more chronic diseases	1.38	1.07 – 1.78	0.013
Physical activity			<0.001
Once a month or less	1		
Once a month to once a week	9.47	2.98 – 30.06	<0.001
Once a week or more	31.42	9.98 – 98.85	<0.001
Social, cognitive and religious activity level	1.12	1.09 – 1.14	<0.001
Dependency in pIADL	1.05	0.81 – 1.35	0.740
Dependency in cIADL	0.34	0.15 – 0.73	0.006
GDS score	1.01	0.97 – 1.05	0.800
MMSE score	0.92	0.89 – 0.96	<0.001

3.4.1.6. Factors affecting usage of acupuncture

Acupuncture can be consider as the most globally adapted TCM practice (Melchart et al., 1997; Robinson et al., 2011; Yang et al., 2002). Availability and applicability to almost all groups of people has made it the second most common TCM practice in general population worldwide after herbal medicine (Mann, 1992; Xue et al., 2010; Yesilada, 2011). In our study, acupuncture was the third common CAM practice used by 10% of participants.

Among our participants, acupuncture users were female Chinese ones who lived in bigger houses and were suffering from more chronic medical conditions. They had better physical and social activities. The association of physical activity with acupuncture was small and complicated. Participants who did exercise rarely and those who did regularly were using acupuncture more than those who were moderately involved in physical activity. Such complicated association needs further investigation to be explained. The average GDS score of acupuncture users was higher than that of non-users. However, age, educational level, cognitive and physical IADL dependency and neurocognitive assessments rather than GDS were not associated with the usage of acupuncture (Table 3.9).

Table 3.9. Unadjusted association of demographic and neurocognitive factors to use of acupuncture

Factor	Acupuncture usage		P value
	Yes	No	
Age	65.9 ± 6.9	66.4 ± 7.6	0.145
Gender			<0.001
Female	359 (11.6%)	2730 (88.4%)	
Male	134 (7.3%)	1705 (92.7%)	
Ethnicity			<0.001
Chinese	484 (10.8%)	4007 (89.2%)	
Malay	3 (1.2%)	238 (98.8%)	
Indian	2 (1.3%)	955 (98.7%)	
Others	4 (10.3%)	35 (89.7%)	
Educational level			0.395
Nil	103 (10.7%)	860 (89.3%)	
Primary or secondary	324 (9.6%)	3044 (90.4%)	
Pre-university or university degree	65 (11.1%)	520 (88.9%)	
Housing type			0.001
1-2 room public apartment	59 (6.7%)	828 (93.3%)	
3 room public apartment	131 (10.4%)	1127 (89.6%)	
4-5 room public apartment or private or landed house	303 (10.9%)	2472 (89.1%)	
History of chronic diseases			0.002
No history	82 (7.5%)	1010 (92.5%)	
History of one or two chronic diseases	235 (10.1%)	2088 (89.9%)	
History of three or more chronic diseases	176 (11.6%)	1337 (88.4%)	
Physical activity			0.007
Once a month or less	39 (9.5%)	372 (90.5%)	
Once a month to once a week	174 (8.5%)	1871 (91.5%)	
Once a week or more	277 (11.3%)	2165 (88.7%)	
Social, productive and fitness activities	9.97 ± 4.15	9.26 ± 4.30	<0.001
Dependency in pIADL			0.181
Yes	85 (11.0%)	689 (89.0%)	
No	408 (9.8%)	3739 (90.2%)	

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Cont. Table 3.9

Dependency in cIADL			0.402
Yes	13 (11.0%)	105 (89.0%)	
No	480 (10.0%)	4323 (90.0%)	
GDS score	1.98 ± 2.89	1.29 ± 2.21	<0.001
MMSE score	27.48 ± 2.63	27.53 ± 2.61	0.690
Forward Digit Span	11.47 ± 3.24	11.38 ± 3.30	0.662
Backward Digit Span	5.34 ± 2.20	5.37 ± 2.33	0.836
Block design	25.08 ± 10.56	24.66 ± 10.24	0.615
RAVLT short memory	4.51 ± 1.88	4.47 ± 1.97	0.747
RAVLT total learning	43.00 ± 10.06	42.07 ± 10.62	0.209
RAVLT total recognition percent	88.42 ± 11.65	87.97 ± 11.41	0.578

Similar to other CAM practices, a logistic regression model was built for factors associated with the usage of acupuncture to adjust such associations with other variables (Table 3.10). After taking into account other studied factors, the association or lack of association in all variable was unchanged except for physical activity, which lost its minimal association.

Table 3.10. Adjusted association of demographic and neurocognitive factors to use of acupuncture

Factor	**Odds ratio**	**95% CI**	**P value**
Age	0.99	0.98 – 1.00	0.168
Female gender	1.58	1.26 – 1.99	<0.001
Ethnicity			<0.001
Chinese	1		
Malay	0.12	0.04 – 0.37	<0.001
Indian	0.11	0.03 – 0.45	0.002
Others	0.65	0.20 – 2.15	0.481

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Cont. Table 3.10

Educational level			0.527
Nil	1		
Primary or secondary	0.99	0.75 – 1.31	0.926
Pre-university or university degree	1.18	0.78 – 1.77	0.434
Housing type			0.023
1-2 room public apartment	1		
3 room public apartment	1.59	1.13 – 2.22	0.007
4-5 room public apartment or private or landed house	1.46	1.07 – 2.00	0.018
History of chronic diseases			<0.001
No history	1		
History of one or two chronic diseases	1.35	1.03 – 1.77	0.029
History of three or more chronic diseases	1.79	1.34 – 2.41	<0.001
Physical activity			0.284
Once a month or less	1		
Once a month to once a week	1.02	0.70 – 1.51	0.909
Once a week or more	1.20	0.82 – 1.76	0.340
Social, cognitive and religious activity level	1.03	1.00 – 1.01	0.021
Dependency in pIADL	1.14	0.86 – 1.52	0.364
Dependency in cIADL	0.98	0.52 – 1.85	0.949
GDS score	1.11	1.07 – 1.14	<0.001
MMSE score	0.99	0.94 – 1.03	0.596

Higher usage of acupuncture among female Chinese participants is similar to other CAM practices and has been discussed before. In addition, since it is one of basic and well-known TCM practices which does not need any specific training or knowledge from the users, educational level may have little or no effect on its prevalence of usage. On the other hand, ethnic beliefs may have the most important effect on the attitude toward this practice. Considering the several traditional therapeutic applications of acupuncture (Mann, 1992), it is understandable that being suffering from multiple

chronic disorders may increase the likelihood of using acupuncture (as well as other CAM practices) as an alternative remedy to conventional medical treatment (Kim et al., 2013). One of these chronic conditions can be depression. There are several reports of effectiveness of acupuncture in depression treatment (Dirmaier et al., 2012; Sniezek et al., 2013; Wu et al., 2012c). Therefore, it is explainable why participants with higher GDS scores tend more to use acupuncture. On the other hand, no association was observed between usage of acupuncture and cognitive tests. Although controversial in some cases, there are different reports of usage of acupuncture for different types of cognitive impairment (Avisar et al., 2012; Johnston et al., 2007; Lu et al., 2011). It can be suggested that not only those suffering from mild cognitive problems use acupuncture to improve their condition, but also the cognitively healthy participants use this method to prevent development of cognitive dysfunction. Therefore, both groups of participants use acupuncture and there is minimal difference in their usage.

Since acupuncture is applied by a trained practitioner and it does not need any special activity from the users, all participants with different levels of physical independency and in different ages can benefit from its usage. Therefore, we did not observe any association between acupuncture usage and age, physical or social activity or cognitive or physical IADL dependency.

3.4.2. Four-year follow-up data

Among 2680 adults older than 60 years old participating in baseline recruitment for SLAS I, 748 subjects participated in follow-up cognitive assessment. Among them, 709 participants had baseline MMSE scores greater than or equal to 24. Those with MMSE scores less that 24 were excluded because they were suffering from some degrees of

cognitive impairment at the baseline. By this way, the risk of cognitive decline was assessed in a cohort of normocognitive older adults. The demographic information of included participants is presented in Table 3.11.

During the follow-up visit, MMSE, RAVLT, block design and forward and backward digit span assessments were tested. The only test that was completed for all participants was MMSE. Other tests were conducted for only a small proportion of participants (16 – 91 persons). Additionally, since there were very few participants from minor ethnic groups all these groups were pooled together as non-Chinese for ease of analysis.

Table 3.11. Demographic distribution of participants in 4-year follow-up study

Factor	**Number**	**Percentage (%)**
Gender		
Female	430	60.6
Male	279	39.4
Race		
Chinese	679	95.8
Malay	11	1.6
Indian	13	1.8
Others	6	0.8
Educational level		
Nil	98	13.8
Primary or secondary	494	69.7
Pre-university or university degree	117	16.5
Housing type		
1-2 room public apartment	46	6.5
3 room public apartment	166	23.4
4-5 room public apartment or private or landed house	497	70.1
Total	709	100

3.4.2.1. Decline in MMSE score

Out of 709 participants, 95 (13.4.0%) developed decline in MMSE scores after four years. The association of demographic and psychological factors to development of cognitive decline in MMSE score is presented in Table 3.12.

Table 3.12. Unadjusted association of demographic and life style factors to the development of cognitive decline in MMSE score

Factor	Changes in MMSE score		P value
	Sustained	Declined	
Age	67.4 ± 5.5	70.4 ± 7.2	<0.001
Gender			0.259
Female	61 (14.2%)	369 (85.8%)	
Male	34 (12.2%)	245 (87.8%)	
Ethnicity			0.202
Chinese	590 (86.9%)	89 (13.1%)	
Others	24 (80.0%)	6 (20.0%)	
Educational level			<0.001
Nil	72 (73.5%)	26 (26.5%)	
Primary or secondary	435 (88.1%)	59 (11.9%)	
Pre-university or university degree	107 (91.5%)	10 (8.5%)	
Housing type			0.362
1-2 room public apartment	37 (80.4%)	9 (19.6%)	
3 room public apartment	142 (85.5%)	24 (14.5%)	
4-5 room public apartment or private or landed house	435 (87.5%)	62 (12.5%)	
History of chronic diseases			0.399
No history	134 (89.9%)	15 (10.1%)	
History of one or two chronic diseases	301 (85.5%)	51 (14.5%)	
History of three or more chronic diseases	179 (86.1%)	29 (13.9%)	
Physical activity			0.746
Once a month or less	85 (84.2%)	16 (15.8%)	
Once a month to once a week	66 (86.8%)	10 (13.2%)	
Once a week or more	461 (87.0%)	69 (13.0%)	
Social, productive and fitness activities	9.90 ± 4.37	9.28 ± 4.40	
Dependency in pIADL			0.040
Yes	110 (81.5%)	25 (18.5%)	
No	503 (87.8%)	70 (12.2%)	

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Cont. Table 3.12.

Dependency in cIADL			0.239
Yes	5 (71.4%)	2 (88.6%)	
No	608 (86.7%)	93 (13.3%)	
Baseline GDS score	1.54 ± 2.47	2.02 ± 2.79	0.085
Baseline MMSE score	28.02 ± 1.61	27.95 ± 1.91	0.739
Baseline Forward Digit Span	10.53 ± 2.79	9.29 ± 1.99	0.038
Baseline Backward Digit Span	5.38 ± 2.01	4.46 ± 1.82	0.036
Baseline Block design	22.81 ± 11.25	33.00 ± NA	NA
Baseline RAVLT short memory	4.49 ± 1.80	4.36 ± 2.75	0.770
Baseline RAVLT total learning	43.37 ± 9.34	40.23 ± 14.81	0.343
Baseline RAVLT total recognition percent	89.24 ± 10.99	88.70 ± 12.64	0.841

Development of cognitive decline in MMSE test was more common among older less educated participants who were dependent in their physical IADL and performed poorer in forward and backward digit span. Other variables had no association with development of cognitive decline in MMSE score. The association of age, educational level and IADL to the risk of developing cognitive decline is consistent with the available literature (Bennett et al., 2013; Fjell et al., 2014; Gold, 2012). Additionally, association of forward and backward digit span and none of other neurocognitive assessment tests suggest these simple tests to have positive predictive value for development of cognitive decline, which needs further investigation. To evaluate the positive predictive value of these tests, further investigation with larger sample sizes is necessary.

The association of the usage of composite CAM and specific CAM types with the development of cognitive decline was also studied (Table 3.13).

Table 3.13. Unadjusted association of CAM usage and its subtypes to the development of cognitive decline in MMSE score

CAM type		Cognitive decline		p value[1]	Odds ratio[2]	95% CI
		Yes	No			
Composite CAM use				0.002	0.52	0.34 – 0.80
	Yes	45 (10.3%)	390 (89.7%)			
	No	50 (18.2%)	224 (81.8%)			
Herbal medicine				0.404	0.90	0.54 – 1.51
	Yes	22 (12.6%)	152 (87.4%)			
	No	73 (13.8%)	456 (86.2)			
Ginseng				0.122	0.44	0.14 – 1.46
	Yes	3 (6.7%)	42 (93.3%)			
	No	92 (13.9%)	572 (86.1%)			
Ginkgo				0.578	0.97	0.40 – 2.35
	Yes	6 (13.0%)	40 (87.0%)			
	No	89 (13.4%)	574 (86.6%)			
Lingzi				0.084	-	-
	Yes	0 (0.0%)	17 (100.0%)			
	No	95 (13.7%)	596 (86.3%)			
Evening primrose oil				0.145	0.47	0.14 – 1.54
	Yes	3 (7.0%)	40 (93.0%)			
	No	92 (13.8%)	573 (86.2%)			
Garlic				0.520	0.75	0.17 – 3.32
	Yes	2 (10.5%)	17 (89.5%)			
	No	93 (13.5%)	596 (86.5%)			
Tianqi				0.209	2.19	0.58 – 8.25
	Yes	3 (25.0%)	9 (75.0%)			
	No	92 (13.2%)	605 (86.8%)			
Herbal tonics				0.127	0.38	0.09 – 1.60
	Yes	2 (5.7%)	33 (94.3%)			
	No	93 (13.8%)	580 (86.2%)			

To be continued on the next page

Cont. Table 3.13

Qigong				0.035	0.56	0.31 – 1.02
	Yes	14 (9.0%)	142 (91.0%)			
	No	81 (14.9%)	463 (85.1%)			
Acupuncture				0.313	0.79	0.39 – 1.58
	Yes	10 (11.2%)	79 (88.8%)			
	No	85 (13.9%)	528 (86.1%)			
Tai chi				0.477	1.07	0.54 – 2.11
	Yes	11 (14.3%)	66 (85.7%)			
	No	84 (13.5%)	540 (86.5%)			
Massage				0.322	0.73	0.31 – 1.76
	Yes	6 (10.5%)	51 (89.5%)			
	No	89 (13.8%)	555 (86.2%)			
Reflexology				0.123	0.37	0.09 – 1.58
	Yes	2 (5.7%)	33 (94.3%)			
	No	93 (14.0%)	573 (86.0%)			
Yoga				0.414	0.49	0.06 – 3.75
	Yes	1 (7.1%)	13 (92.9%)			
	No	94 (13.7%)	593 (86.3%)			
Others[3]				0.591	1.01	0.29 – 3.48
	Yes	3 (13.6%)	19 (86.4%)			
	No	91 (13.3%)	594 (86.7%)			

[1] p values were calculated using chi-square test;
[2] odds ratios were calculated using cross-table test;
[3] others includes acupressure, moxibustion, Jamu, Ayurveda, chiropractic, spirit medium healing, homeopathy, osteopathy, meditation, hypnotherapy and aromatherapy each of which has less than 10 users among included participants

The use of composite CAM and practicing qigong were negatively associated with developing cognitive decline. To evaluate the effect of other confounding factors on these associations, a set of sequential logistic regression models was used (Table 3.14). After finding composite CAM and qigong associated with the lower risk of developing cognitive decline in the unadjusted measurements (chi square in model 1), the first

logistic regression model was built to adjust their associations to the main confounders of developing cognitive decline, age and educational level (model 2). To develop the 2nd regression model (model 3), dependency in pIADL, the other statistically associated variable to the development of cognitive decline in unadjusted measurements, was added to the regression model. Due to high level of multicolinearity between neurocognitive tests and small proportion of participants with complete results, these tests were not included in the model. Then, gender, race, physical and social activities, dependency in cIADL and housing type were added to the regression model to build the model 4. Finally by adding baseline MMSE and GDS scores and self-report of any history of cardiovascular, metabolic or cerebrovascular disorders to the logistic regression model, the complete regression model (model 5) was developed. Some of our participants were using more than one CAM type. To evaluate whether the association of qigong with lower risk of developing cognitive decline is affected by concomitant other CAM types used, an additional regression model (model 6) was developed by adding the usage of other CAM types including particular herbs, acupuncture, tai chi, massage, etc. to the model 5 only for qigong usage. Since usage of any type of CAM had strong multicollinearity with usage of composite CAM, the last model was not applicable to usage of CAM.

Usage of CAM kept its significant association with sustained cognition throughout several steps of regression while qigong usage lost its association with sustained cognitive status after taking into account the effect of age and educational level. This borderline non-significant association was unchanged during subsequent steps of regression model building. This can be due to small sample size and is worth to be reevaluated in future studies. After removing the effect of other CAM types by adding

them to the regression model, the usage of qigong regained its statistically significant association with the lower risk of developing cognitive decline.

Table 3.14. Sequential logistic regression models of association between developing cognitive decline in MMSE score to CAM and qigong usage

Model[a]	CAM usage			Qigomg usage		
	P value	Odds' ratio	95% CI	P value	Odds' ratio	95% CI
1	0.002	0.52	0.34 – 0.80	0.035	0.56	0.31 – 1.02
2	0.013	0.57	0.36 – 0.89	0.058	0.56	0.30 – 1.02
3	0.013	0.57	0.36 – 0.89	0.062	0.56	0.30 – 1.03
4	0.013	0.55	0.34 – 0.88	0.063	0.54	0.28 – 1.03
5	0.013	0.55	0.34 – 0.88	0.059	0.53	0.28 – 1.02
6	NA	NA	NA	0.045	0.49	0.28 – 0.99

[a] Model 1: unadjusted values
Model 2: adjusted to age and educational level
Model 3: adjusted to age, educational level and pIADL dependency
Model 4: adjusted to age, educational level, pIADL dependency, gender, race, physical and social activities, cIADL dependency and housing type
Model 5: adjusted to age, educational level, pIADL dependency, gender, race, physical and social activities, cIADL dependency, housing type, baseline MMSE and GDS scores and self-reporting history of any cardiovascular, metabolic or cerebrovascular disorders
Model 5: adjusted to age, educational level, pIADL dependency, gender, race, physical and social activities, cIADL dependency, housing type, baseline MMSE and GDS scores, self-reporting history of any cardiovascular, metabolic or cerebrovascular disorders and usage of other CAM types.

In this study, for the first time we report the lower risk of developing cognitive decline in composite CAM and qigong users suggesting potential protective effects of CAM practices on mental status. Qigong as a combination of moderate physical exercises and meditation (Lauche et al., 2013) is easy to learn and practice for most older adults whose ability for more intense exercises like tai chi and yoga is limited (Yost et al., 2013). All physical, social and emotional benefits of qigong together can be involved in its protective effects against development of cognitive decline (Tsang et al., 2002; Tsang et al., 2008). Our results showed that none of the individual factors of

physical activity, social activity or baseline mood or cognitive status of participants had any association with final outcome of developing cognitive decline. Moreover, adjusting to these factors (physical and social activity and baseline neurocognitive assessment) caused no change in the association of qigong with lower risk of developing cognitive decline. Both together indicate that qigong as a whole has some effects more than the sum of its physical, social and psychological parts.

Such association was not observed between development of cognitive decline and other CAM practices close to qigong (yoga and tai chi). It can be due to more complexity of such practices which limits their usage to those who are physically fit enough to perform such intense physical activities. Since ageing is associated with a significant decrease in physical abilities, there are not enough tai chi and yoga users to have a reasonable sample size. In addition, physical activity is a major confounding bias for these CAM activities.

On the other hand, similar to other CAM practices, qigong usage was higher in more educated participants. This association caused some confounding effects on the lower risk of developing cognitive decline in qigong users because higher educational degrees have well-studied protective effects against cognitive decline. However, qigong kept its borderline association with lower risk of cognitive decline after adjusting for age and educational level. Furthermore, such an association with higher educational level can also be observed in other CAM practices which were not associated with lower risk of developing cognitive decline. After removing the confounding effect of concomitant usage of other CAM practices (model 5) qigong regained its significance association with lower risk of cognitive decline. It provides another evidence for a possible protective effect for qigong. Such effect needs further

investigation to be proved. Difficulties in designing animal models for qigong practice are major limitation for an evidence-based study. Therefore, longitudinal observational studies and clinical trials are the only available methods of investigation for future research.

In conclusion, although the association of qigong practice and sustained cognitive status was marginal and was partially affected by age and educational level, this result makes it a promising available exercise for elderly all around the world to maintain their cognitive function. Hence, it is important to encourage older adults to use qigong as a potential preventive method against cognitive decline. Additionally, it opens new ways of research to investigate the possible mechanisms of actions of qigong against development of cognitive decline.

3.4.2.2. Decline in other neurocognitive assessment tests

The follow-up data for neurocognitive assessment tests other than MMSE was available for a small proportion of participants. The number of participants with available data has been presented in Table 3.15.

The association of developing cognitive decline in any of these tests with different demographic and life style factors, usage of composite CAM and specific CAM practices and baseline neurocognitive assessment results was evaluated similar to what reported in section 3.4.2.1 for decline in MMSE scores.

Table 3.15. The number of participants participating in follow-up neurocognitive assessment for musing RAVLT, Digit Span and Block Design tests

Test	Sustained	Declined	Total
RAVLT			
Short memory	66	19	85
Total learning	70	15	85
Recognition percentage	68	15	83
Forward digit span	65	26	91
Backward digit span	58	29	87
Block design	10	6	16

Among RAVLT outputs, decline in short memory test (trial 1) was associated with dependency in physical IADL (OR = 6.13; CI 1.84 – 20.38; p = 0.004), usage of tai chi (OR = 4.917; CI 1.23 – 19.67; p = 0.030) and baseline short memory results (mean baseline short memory result equal to 5.63 ± 2.09 vs. 4.15 ± 1.81 for those who developed decline in short memory vs. those who sustained their short memory respectively, p = 0.003).

Developing cognitive decline in total learning test was more common among participants with better performance in baseline RAVLT short memory test (mean baseline short memory test equal to 5.53 ± 2.67 vs. 4.26 ± 1.72 for those who developed decline in short memory vs. those who sustained their short memory respectively, p = 0.021) and total learning result (mean baseline total learning result equal to 49.00 ± 12.19 vs. 41.56 ± 9.10 for those who developed decline in short memory vs. those who sustained their short memory respectively, p = 0.008).

Additionally, the risk of developing decline in recognition test (RAVLT trial 9) was higher in older participants (mean age 69.4 ± 4.5 for those who developed decline vs.

66.30 ± 4.17 for those who sustained their cognitive results in recognition test, p = 0.013) who were suffering from more chronic medical conditions (p = 0.013), performed worse in baseline total learning test (mean baseline total learning result equal to 37.93 ± 8.54 vs. 44.26 ± 10.03 for those who developed decline vs. those who sustained their results respectively, p = 0.026) and reported using ginkgo (OR = 8.25; CI 1.24 – 54.72; p = 0.039).

Developing decline in forward digit span test was associated with better performance in baseline forward digit span test (mean baseline forward digit span result equal to 12.54 ± 2.78 vs. 9.88 ± 2.35 for those who developed decline vs. those who sustained their results respectively, p < 0.001). In addition, usage of composite CAM (OR = 12.38; CI 2.70 – 56.71; p <0.001), herbal medicine (OR = 4.25; CI 1.62 – 11.15; p = 0.003) and ginseng (OR = 4.55; CI 1.66 – 12.46; p = 0.003) increased the risk of developing cognitive decline in forward digit span test.

Participants with better performance in baseline backward digit span (mean baseline backward digit span result equal to 6.48 ± 2.05 vs. 4.97 ± 1.74 for those who developed decline vs. those who sustained their performance respectively, p = 0.001) were more susceptible to develop decline in backward digit span test. However, usage of acupuncture (OR = 0.13; CI 0.02 – 1.03; p = 0.021) decreased the risk of developing cognitive decline in this test.

Since the sample sizes for these tests were very small the statistical analyses were not powerful enough to detect reliable associations. Further investigations using bigger study populations can be useful to investigate the clinical relevance of these neurocognitive assessments and the factors associated with developing decline in them.

3.5. Conclusion

The aim of this part of the study was to obtain detailed information about usage of complementary and alternative medicine among older adults in Singapore including the prevalence of usage, reasons for usage, forms of usage and factors associated with the usage. Among the associated factors, we focused on neurocognitive assessments and evaluated the changes in the neurocognitive performance of participants using four-year follow-up studies.

During two phases of participant recruitment, 4985 participants fitting to our inclusion criteria were recruited on whom the baseline study was performed. After four years, 709 of them participated in follow-up study where the neurocognitive assessment was repeated to investigate any decline in neurocognitive performance.

The analysis of baseline data revealed a high prevalence of CAM usage among older adults in Singapore (54%), which showed a significant increase compared to previous reports (Feng et al., 2010). Most of our participants were using CAM to improve their general health rather than for specific medical purposes. Consistent with available literature, demographic factors such as gender, ethnicity and educational level were the most important predictors of higher prevalence of using them (Kennedy, 2005; Kim et al., 2004a; Zhang et al., 2008a). Among various types of CAM, herbal medicines, qigong and acupuncture were used by more participants than other subtypes.

Usage of CAM and its subtypes had minimal association with cognitive and depressive status of participants. This lack of strong association could be because of the cross-sectional nature of this study. Clinical trials with prospective nature such as cohort studies may be more accurate in detecting any potential association.

After four years, 13.4% of included participants in follow-up study developed cognitive decline based on their MMSE scores. Besides well-known demographic factors, younger age and higher educational level, usage of composite CAM and qigong showed promising protective effects against development of cognitive decline. To the best of our knowledge, it is the first report of such protective effects in longitudinal observational studies. By repeating similar longitudinal studies in other settings and other countries, this association should be reexamined. If such association is observed in other studies, the next step can be large-scale randomized clinical trials to prove the protective effects. Although their association with lower risk of decline in MMSE score needs further investigation to be applied in clinical practice, this finding (if proved by other investigations) can be useful for both public and clinical practitioners to encourage older adults to use available, safe and easy CAM practices to promote their mental health and prevent cognitive impairment.

SLAS II is actually the continuation of participant recruitment for SLAS I. Instead of being two different survey, they are two phases of participant recruitment for the same study. The questionnaires used for these two phases are almost the same and the recruitment procedure is very similar. By merging these two, a bigger sample size is obtained. Furthermore, a bigger geographical territory in Singapore is covered by the merged study. Both these two factors can improve the validity of results. However, there are some difference in prevalence rate of usage of CAM and its subtypes between these two recruitment phases. Such difference can be due to changes in the trend of CAM usage by the time since there is a 4-year gap between two phases of the study. Participants of SLAS I were recruited from South West Singapore while the ones of SLAS II were from South Central and South East areas. In addition, participants in

SLAS I were different from those in SLAS II regarding their demographic information. Participants in SLAS I were younger, more physically and socially active and at a higher risk of depression and cognitive impairment compared to SLAS II participants. Proportion of participants who lived in bigger houses, had higher degrees of education and were from Chinese ethnicity were higher in SLAS I compared to SLAS II. These demographic differences can be due to different geographic territory where the participants were recruited from. Some of these differences were in favor of higher prevalence of CAM usage and some were in favor of lower prevalence. To avoid complicated discussion of the effect of differences in demographic factors on different CAM usage among participants in SLAS I and SLAS II, this data was removed from the thesis. However, merging two datasets can make a more homogenized study population which is more representative of older adults in Singapore.

Having a big sample size makes the baseline data a reliable source of information about the medical and cognitive health of older adults in Singapore where the society is ageing fast and geriatric problems can be the health issue of near future. Such information can be useful for clinical practitioners to keep in mind the possibility of usage of CAM by their patients in order to avoid any potential adverse effects and improve their mutual relationship with their patients. In addition, promising protective effects of composite CAM and qigong which are presented for the first time in a longitudinal observational study are very important for all sectors involved in the health maintenance of older adults.

The focus of this study was on the usage of CAM practices such as qigong. Therefore, participants with severe cognitive impairment or physical inabilities during baseline assessment were excluded to avoid the bias of limitation in practices and study

a normocognitive cohort of older adults. Furthermore, the hospitalized and other physically and mentally ill older adults were not included in this study. Such exclusion may affect the predictability of results for general population of older adults.

Having no information about the non-examiners is another limitation of the study. The data was collated in 2003-2008 and such information was not recorded. Therefore, it is impossible to compare different factors between respondents and non-respondents. Without such comparison it is difficult to generalize the results of the study to the whole population.

The other limitation of this study is the difference between demographic distribution of Singapore population and that of participants in the study. In this study 62.3% of participants are female while based on the latest Singapore census, 53.9% of above-60-year population are female (Wong, 2010). Additionally, among Singapore population older than 60, 83.3% are Chinese, 9.3% are Malay, 6.0% are Indian, and 1.4% belong to other ethnicities (Wong, 2010) while these proportions are 95.2%, 2.1%, 1.9% and 0.8% in our participants respectively.

Finally, the information about usage of CAM and its subtypes were collate as a part of a big questionnaire. Such method of data collating may affect the accuracy of data in some points. For example, the usage of herbal medicine was based on the most common local names of few herbs, which failed to clarify the exact species in most cases.

Further investigation can be directed to collate more focused data on usage of CAM and its types such as herbal medicine. It is important to improve the sampling method to have a study sample more consistent with the local population distribution.

Additionally, better encouragement of participant to participate in follow-up studies can provide valuable information about the changes in the physical and mental health of different cohort groups.

CHAPTER 4. Usage of herbal medicine among older adults in Singapore

4.1. Introduction

Herbal medicine is the most commonly used CAM practice all around the world from western to eastern countries and in different diseases and age groups (Asadi-Pooya et al., 2014; Barnes et al., 2008; Corey et al., 2014; Italia et al., 2014; Robinson et al., 2011; Sait et al., 2014). The first part of our study also revealed that 34.5% of older adults in Singapore use one or more herbs for their medical ailments or general health, which makes herbal medicine the most commonly CAM practice used by this age group in Singapore (section 3.4.1.1.1).

Despite its common usage, herbal medicine can be considered as the most dangerous CAM practice because of the higher risk of side effects, herb-drug or herb-herb interaction and inappropriate dosage (Corey et al., 2014; Yang et al., 2009a). Additionally, there is always the risk of contamination with other herbs and toxic material such as pesticides and soil pollutions (Awodele et al., 2013; Koh et al., 2000; Kong et al., 2014). Such health risks might be even more in older adults who are at high risk of being suffering from multiple chronic disorders and organ failure (Frohlich et al., 2014; Willison et al., 2004).

Relative high prevalence of usage, promising therapeutic effects and risks associated with its usage make herbal medicine an important topic for geriatric research. There are several reports on promising effects of different herbs on neuropsychological disorders such as depression, anxiety, cognitive dysfunction, etc. in different age groups

(Dos Santos-Neto et al., 2006; Sarris et al., 2011). However there is a shortage of population based observational studies assessing the prevalence of herbal medicine usage among older adults and its association with their neurocognitive status. Therefore this part of study was conducted to deepen our understanding about usage of herbal medicine among older adults in Singapore and factors associated to it.

4.2. Hypothesis and objectives

Since herbal medicine is the most common CAM practice in different reports (Robinson et al., 2011) and there are some herbs with known positive effects on neurocognitive status (Chang et al., 2008; CPC, 2010; Qi et al., 2011), we hypothesize that the usage of herbal medicine among older adults in Singapore is common and the usage of specific herbs are associated with demographic and health factors including the neurocognitive status of users. Therefore, the objectives of this part of study are to collate the information on usage of any medicinal herb in past 12 months by a population of older adults in Singapore and factors associated with their usage.

4.3. Methods

The participants were from the Jurong Ageing Study (JAS) who had given written consent to be recontacted if needed. The demographic data and neurocognitive assessment from JAS was merged with collated information about usage of herbal medicine obtained from follow-up telephone interview to evaluate the factors associated with the usage of composite herbal medicine and specific herbs.

4.3.1. Participants

JAS is an ongoing population based study started in 2011 in Jurong territory (South West area) of Singapore inviting older adults aged 60 years or more to participate by door to door census. The sampling was based on consecutive method to recruit as many participants as possible. Visiting each house, the older adults are recognized and invited to participate in the study. From each housing unit, only one resident older than 60 is invited to participate in the study, if there are more. The older adults are voluntarily invited to participate in the study by signing an informed consent. All study parts are approved by NUS Institutional Review Board (NUS-IRB).

4.3.2. Main questionnaire

The detailed demographic information is collated based on self-reporting using a questionnaire. The questionnaire includes several multiple choice questions to collect the details of personal information, date of birth, educational level, etc., which are completed by trained interviewers.

4.3.3. Physical and social, cognitive and religious activities

Physical activity assessment is based on participants' self-reporting of involvement in active sports and physical activities such as swimming, intense walking or other sports. Accordingly, participants would score 2 for involvement in activities more than once a week, 1 for once a month to once a week or 0 for less than once a month. The similar scoring was used for social, cognitive and religious activities. Then, the scores from social, cognitive and religious activities was summed to make a single variable named social, cognitive and religious activity, which ranged from 0 to 6.

4.3.4. Neurocognitive assessment

Trained interviewers examined the neurocognitive status of participants using 30-itemed MMSE, 15-itemed GDS, 10-itemed Elderly Cognitive Assessment Questionnaire (ECAQ) and 20-itemed geriatric anxiety inventory (GAI). The first two have been described before (section 3.3.2.4).

Geriatric anxiety inventory is a list of 20 agree/disagree questions introduced by Pachana in 2007. In this list, the self-assessment of stress feelings and perceptions about daily life is used to measure the susceptibility to anxiety disorders (appendix 4). The cutoff point for detection of general anxiety disorders is 11 (Pachana et al., 2007).

Elderly Cognitive Assessment Questionnaire is a locally developed short cognitive assessment questionnaire derived from MMSE and Geriatric Mental State Schedule tests introduced by Kua and Ko in 1992. This short 10-itemed test has three sets of short answered questions assessing the memory, orientation and information and memory recall (Kua et al., 1992; Lim et al., 2003).

4.3.5. Telephone interview

Those participants who had agreed to be recontacted if needed were chosen to be called via provided phone number to collate detailed information regarding usage of herbal medicine. At the beginning, the information on a verbal informed consent form (Appendix 1) was read to them by a trained interviewer who was able to fluently speak in English and Chinese (Mandarin) to get their permission to participate in this part of study. If agreed, a multiple choice detailed questionnaire was used to collate the information about usage of any herb in last 12 months (Appendix 2). There were

specific questions about the herbs used in SLAS I and II to know the exact type of herb used, preparation type, duration of usage, frequency of usage, source of information about the usage, reason of usage (including specific health issue if applicable) and satisfaction from usage. For herbs not included in SLAS studies, the same information was collated and recorded in a blank paper.

4.3.6. Inclusion and exclusion criteria

Any participant who had agreed to be re-contacted was chosen for telephone interview. After that, all contacted participants who gave verbal permission to be involved in this part of study were included. Any participant who could not be reached by telephone (after three attempts) or could not speak on phone because of cognitive or hearing issues or those who could not complete the phone interview because of being too much busy (after three attempts) was excluded.

4.3.7. Statistical analysis

All collated information about usage of herbs was entered into a predesigned database, which was later merged with demographic and neurocognitive assessment data to evaluate the usage of herbs. To study the herbs, any herb with at least 20 users was included in the study to evaluate the trend of usage and factors affecting the usage of each herb.

The associations were assessed using chi square, student t-test and regression models where applicable. All the statistical analyses were performed using SPSS-21 software (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA). The detailed statistical analyses were similar to those presented in section 3.3.4.

4.4. Results and discussion

The Jurong Ageing Study is an ongoing project (Still recruiting). Among recruited participants, 209 were contacted for the telephone interview. Eleven participants were excluded because of disagreeing to participate in the telephone interview (10) or hearing problems limiting the communication on the phone (1). Therefore the response rate was 198/209 (94.7%). The mean age of included participants was 68.2 ± 5.9 years. The demographic information of participants is presented in Table 4.1.

Table 4.1. Demographic distribution of participants in telephone interview

Factor	Number	Percentage (%)
Gender		
Male	51	25.8
Female	147	74.2
Race		
Chinese	193	97.5
Malay	1	0.5
Indian	4	2.0
Educational level		
Nil	43	21.7
Primary or secondary	136	68.7
Pre-university or university	19	9.6
Usage of herbal medicine in past 12 months	134	67.7%

The usage of herbal medicine was much higher than what reported before. In this study 134 participants (67.7%, 95% CI: 61.2% - 74.2%) reported usage of one or more herbs. This proportion was 34.5% in first part of the study based on the SLAS data. A possible explanation for this difference is changes in the trend of usage by the time. SLAS data was collated in 2003 to 2008 (2003 – 2004 for SLAS I and 2007 – 2008 for

SLAS II) while the data used for this part of the study was collected in 2013-2014. Usage of herbal medicine was 40.2% in SLAS I and 27.9% in SLAS II ($p < 0.001$). Since the usage of herbal medicine was statistically decreased from 2003 – 2004 to 2007 – 2008, it is unlikely to be three folds more only after 6 years. The other possibility for such a huge change is the differences in the method of data collection. The usage of herbal medicine in SLAS was collected as a small part of a big questionnaire while the data collection for telephone interview was focused on the usage of herbal medicine. It means that during telephone interview, the only information collated was the trend of the usage of herbal medicine. It makes it more possible to gather accurate information about usage of herbs.

To prove that the differences in method of data collection are responsible for the different results from SLAS and telephone interview, we considered the information about usage of herbal medicine collated during baseline interview in JAS. In JAS main questionnaire, there is a section asking about any usage of supplement usage including herbal medicine similar to the same part in SLAS questionnaire. Figure 4.1 shows the distribution of supplement usage based on the baseline data from JAS in comparison to usage of herbal medicine in the same participants based on telephone interview.

Based on data collected by JAS, only 10.1% of participants reported using some form herbal medicine (67.7% in the same participants based on telephone interviews). This difference in the results emphasizes the importance of focused and well-designed questionnaires to produce reliable accurate results.

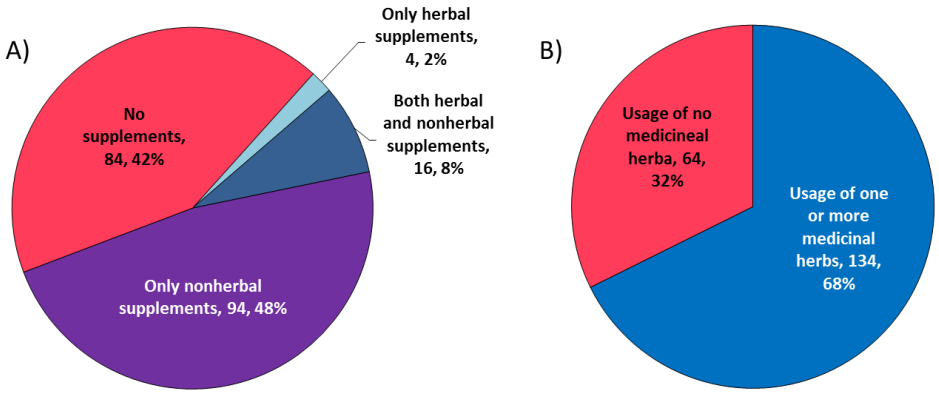

Figure 4.1. Comparison between the results of baseline interviews in JAS and telephone interviews regarding the usage of herbal medicine among same participants. Only 10.1% of participants reported using any herb in baseline JAS interviews (A) while 67.7% of them were using some kinds of herbs reported to telephone interviews.

A total of 44 medicinal herbs were reported to be used by participants (Table 4.2). The scientific name of each herb was obtained from various sources (Blumenthal et al., 2000; BPC, 2013; CPC, 2010). Some participants were using more than one herb concurrently. Therefore, the number of herb users is less than the sum of users of individual herbs.

Table 4.2. Herbs reported by participants in telephone interview

No.	Common name	Scientific name	Number of users	Rank
1	American ginseng	*Panax quinquefolium*	69	1
2	Wolfberry	*Lycium barbarum*	39	2
3	Chinese ginseng	*Panax ginseng*	36	3
4	*Codonopsis*	*Codonopsis pilosula*	30	4
5	Red date	*Ziziphus jujube*	25	5
6	Notoginseng / tianqi	*Panax notoginseng*	24	6
7	Lingzhi	*Ganoderma lucidum*	24	6
8	Chinese Yam	*Dioscorea opposite*	17	8
9	Ginkgo	*Ginkgo biloba*	12	9
10	Angelica (Dangqui)	*Angelica sinensis*	10	10
11	Lotus seeds	*Nelumbo nucifera*	9	11
12	Bei Qi or Huang qi	*Astragalus onobrychis*	9	11

To be continued on the next page

Cont. Table 4.2

13	Astragali	*Astragalus propinquus*	8	13
14	Cordyceps	*Cordyceps sinensis renamed now to Ophiocordyceps sinensis*	7	14
15	Longan	*Dimocarpus longan*	7	14
16	Primrose oil	*Oenotera biennis*	6	16
17	Polygonati (Huang Jing)	*Polygonatum kingianum*	6	16
18	Poria	*Wolfiporia extensa*	5	18
19	Dropberry (Yu Zhu)	*Polygonatum multiflorum* or *P. odorati*	5	18
20	Chrysanthemum	*Chrysanthemum indicum*	5	18
21	Gorgon Euryale	*Euryale ferox*	4	21
22	Barley	*Hordeum vulgare*	4	21
23	Luo Han guo	*Siraitia grosvenorii*	4	21
24	Eucommia (Duzhong)	*Eucommia ulmoides*	4	21
25	Garlic	*Allium sativum*	3	25
26	Honey date	*Phoenix dactylifera*	2	26
27	Licorice	*Glycyrrhiza glabra*	2	26
28	Lily	*Lilium pumilum* and other species of *Lilium* genus	2	26
29	White fungus	*Tremella fuciformis*	2	26
30	Cassia	*Cinnamomum verum*	2	26
31	Chuan xiong	*Ligusticum wallichii*	2	26
32	Mulberry	*Morus alba* and other *morus* species	1	32
33	Shou wu	*Fallopia multiflora*	1	32
34	Tian ma	*Gastrodia elata*	1	32
35	Black bean	*Phaseolus vulgaris*	1	32
36	Cranberry	*Vaccinium erythrocarpum*	1	32
37	Baizhu	*Atractylodes macrocephala*	1	32
38	Di huang	*Rehmannia glutinosa*	1	32
39	Bai Shao	*Paeoniae alba*	1	32
40	Ginger	*Zingiber officinale*	1	32
41	Soya bean	*Glycine max*	1	32
42	Haw chorn	*Crataegus pinnatifida*	1	32
43	Shi Hu	*Dendrobium nobile*	1	32
44	Pear	*Pyrus* species	1	32

Consistent with other reports (Ali-Shtayeh et al., 2011; Quan et al., 2008; Tangkiatkumjai et al., 2013), the main source of information about the herbal products was recommendations from family and friends (75, 66.4%) followed by self-study (34, 30.1%), consultation with TCM practitioners (21, 18.6%) and advertisements on media (19, 16.8%)[1]. None of our participants reported consulting with conventional (western) practitioners about the usage of herbal medicine. Considering the better access of conventional clinical practitioners to the scientific sources of information, they can be one of the best sources of reliable information. Furthermore, since clinical practitioners are responsible for prescription of conventional drugs and there is a risk of drug-herb interaction for undisclosed herbs used, it is very important to improve the physician-patient communication about the usage of herbal medicine (section 1.1.4)

In addition to changes in the prevalence of overall usage of herbal medicine in this study compared to what observed in SLAS data (chapter 3), the prevalence of usage of each herb was also different from what found in SLAS data analysis (**Table 3.2**). These different prevalence rates can be due to the changes in the trend of usage which can be under influence of commercial advertisement in media and advices from friends and family members (main sources of information about usage of herbal medicine based on reports by the participants). Furthermore, the methods of data collection about usage of herbal medicine were different between SLAS and our telephone interview. In SLAS,

[1] A total of 113 participants reported their source of information about the herbs they used. Since some of the participants reported different sources of information for different herbs they were using concurrently, the sum of percentages is more than 100.

the data were collected based on questions about seven selected herbs (**Table 3.2**) while, in the current study, any history of usage of any herb in last 12 months were collected and documents. This way of data collection provides more freedom in reporting usage of herbal medicine to our participants in telephone interview and makes the results more reliable and comprehensive.

Among participants who reported their reason for using herbal medicine, majority (67, 57.8%) used these products for general health improvement. Thirty one (26.7%) used it for medical purposes and 18 (15.5%) used some herbs for medical purposes and some other herbs for general health improvement. Among medical purposes reported by our participants, using herbs for health conditions based on TCM concepts was the most common purpose (38 participants) followed by neurological and musculoskeletal problems (22 and 10 participants respectively).

4.4.1. Factors associated with usage of composite herbal medicine

To evaluate factors associated with usage of herbal medicine, chi square test and student t-test were used for categorical and continuous factor respectively. Among factors, only age, gender and housing type had statistically significant association with usage of herbal medicine. Usage of herbal medicine was more common among younger female participants who lived in bigger houses (Table 4.3).

Table 4.3. Unadjusted association of demographic and neurocognitive factors with the usage of herbal medicine.

Factor	Herbal medicine usage		P value
	Yes	No	
Age	67.4 ± 5.6	69.8 ± 6.4	0.008
Gender			<0.001
Female	112 (76.2%)	35 (23.8%)	
Male	22 (43.1%)	29 (56.9%)	
Ethnicity			0.193
Chinese	132 (68.4%)	61 (31.6%)	
others	2 (40.0%)	3 (60.0%)	
Educational level			0.839
Nil	29 (67.4%)	14 (32.6%)	
Primary or secondary	91 (66.9%)	45 (33.1%)	
Pre-university or university degree	14 (73.7%)	5 (26.3%)	
Housing type			0.034
1-2 room public apartment	1 (20.0%)	4 (80%)	
3 room public apartment	23 (60.5%)	15 (39.5%)	
4-5 room public apartment or private or landed house	109 (70.8%)	45 (29.2%)	
History of chronic diseases			0.210
No history	18(64.3%)	10 (35.7%)	
History of one or two chronic diseases	61 (62.9%)	36 (37.1%)	
History of three or more chronic diseases	55 (75.3%)	18 (24.7%)	
Physical activity			0.766
Once a month or less	93 (66.0%)	48 (34.0%)	
Once a month to once a week	7 (77.8%)	2 (22.2%)	
Once a week or more	24 (66.7%)	12 (33.3%)	
Social, cognitive and religious activity level	3.5 ± 1.7	3.6 ± 1.6	0.693
GDS score	0.96 ± 1.13	1.03 ± 1.46	0.688
GAI score	0.75 ± 1.68	0.61 ± 1.82	0.583
MMSE score	28.65 ± 1.73	28.75 ± 2.10	0.727
ECAQ score	9.61 ± 0.75	9.57 ± 0.64	0.711

Then a logistic regression model was built to adjust the association of these variables with usage of herbal medicine to other demographic factors. Using the enter method to include all demographic factors, the Negelkerke R square was 0.281. After taking into account all factors together, age and housing type lost their association with the usage of herbal medicine and the only factor with statistically significant association was female gender (Table 4.4). Higher usage of herbal medicine in women compared to men is consistent with available literature (Eardley et al., 2012; Hughes et al., 2013; Picking et al., 2011).

None of neurocognitive assessment tests (GDS, MMSE, ECAQ and GAI) was significantly associated with usage of herbal medicine either in unadjusted measurements or adjusted ones. The lack of statistically significant associations in this study can be due to small sample size.

Table 4.4. Logistic regression model for association of demographic and neurocognitive factors with the usage of herbal medicine

Factor	Odds ratio	95% CI	P value
Age	0.95	0.88 – 1.03	0.199
Female gender	5.91	2.54 – 13.79	<0.001
Ethnicity			
Chinese	1		
Malay	NA	NA	
Indian	0.20	0.02 – 2.38	0.204
Educational level			0.956
Nil	1		
Primary or secondary	0.93	0.32 – 2.72	0.897
Pre-university or university degree	1.12	0.22 – 5.58	0.892
Housing type			0.132
1-2 room public apartment	1		
3 room public apartment	5.13	0.42 – 62.14	0.199
4-5 room public apartment or private or landed house	8.72	0.79 – 96.98	0.078
History of chronic diseases			0.285
No history	1		
History of one or two chronic diseases	0.84	0.28 – 2.49	0.751
History of three or more chronic diseases	1.64	0.51 – 5.33	0.407
Physical activity			0.393
Once a month or less	1		
Once a month to once a week	4.17	0.45 – 38.47	0.208
Once a week or more	0.97	0.37 – 2.55	0.958
Social, cognitive and religious activity level	0.98	0.79 – 1.23	0.888
GDS score	0.93	0.68 – 1.27	0.629
GAI score	1.04	0.81 – 1.34	0.751
MMSE score	0.87	0.68 – 1.12	0.281
ECAQ	1.36	0.71 – 2.59	0.355

4.4.2. Usage of American ginseng and factors associated with it

American ginseng (*P. quinquefolium*) was the most commonly used herbal medicine reported by 69 (35.2%) participants. As mentioned in section 1.3.1.5, this plant is one of *Panax* species with well-studied pharmacological activities. In our study, most "American ginseng" users used this herb once a month to once a week (23, 33.3%) as herbal soup with chicken or pork (31, 44.9%) (Figure 4.2).

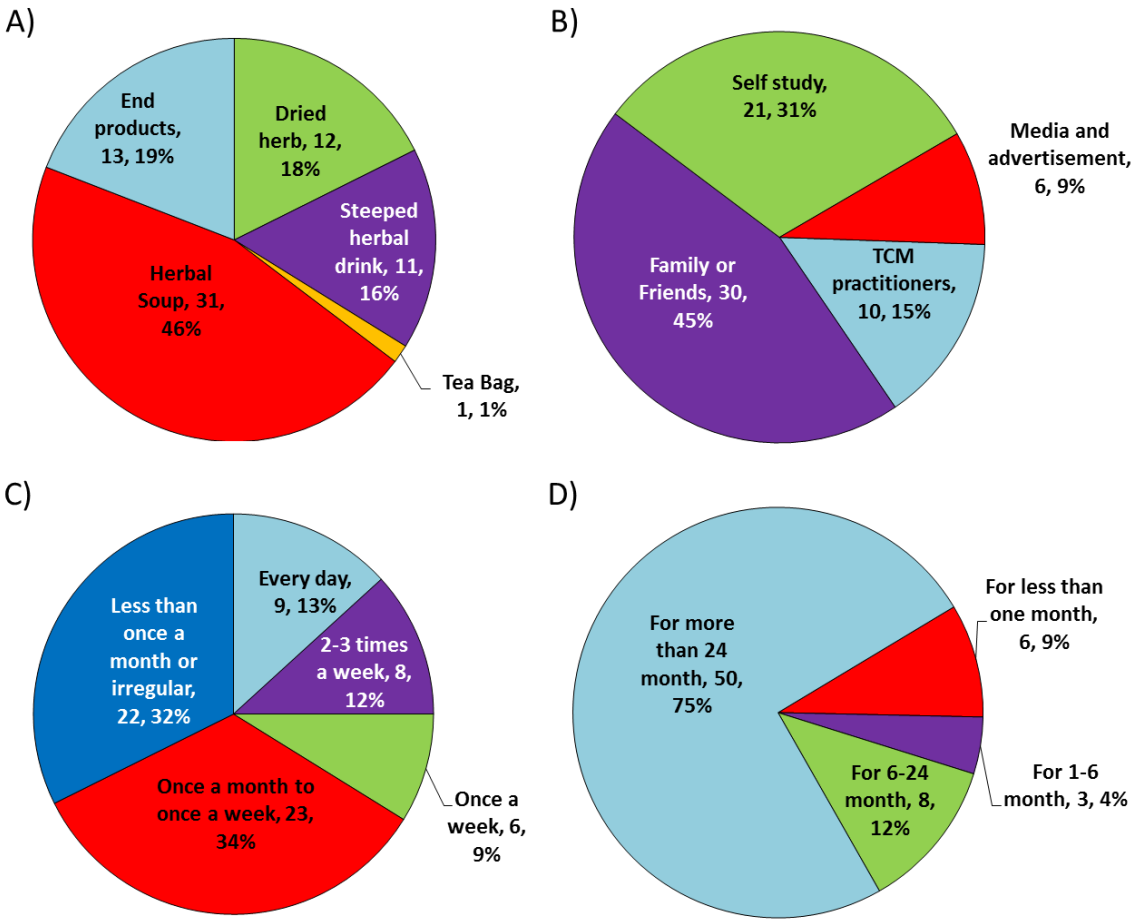

Figure 4.2. Details of usage of American ginseng by participants in telephone interview: A) the percentage of different forms of American ginseng used by participants, B) the different sources of information about the usage of American ginseng reported by participants, C) the frequency of usage of American giseng reported by participants, D) the duration of usage of American ginseng.

The main source of information about usage of American ginseng reported by participants was an unreliable source, family and friend. None of participants had consulted with a western medical practitioner regarding the usage of this herb and only 15% had discussed with TCM practitioners.

Most participants used American ginseng for general health improvement (Table 4.5). Among those who reported using it for specific medical purposes, majority used it for conditions determined in traditional medicine context. Since the theories and concepts in traditional medicine are different from those in conventional medicine, it may be difficult to categorize and explain them based on conventional scientific knowledge. Besides, five participants used it for neurological conditions. *Panax quinquefolium* is a known neuomodulator with memory enhancing, anti-Alzheimer and anti-Parkinsonism effects (Qi et al., 2011). A participant reported using it for musculoskeletal problems and another reported using it for urinary disorders. Usage of American ginseng for urinary problems is consistent with available literature. It has been used to improve *Candida albicans* urogenital infestation (Trammell et al., 2012). Furthermore, *P. quinquefolium* extract has proved renal protective effects via anti-oxidant activities or other mechanisms (Kim et al., 2007; Park et al., 2010). However, to the best of our knowledge, there is no published evidence for its effects on musculoskeletal issues. There is only a beverage containing American ginseng and many other ingredients patented to be used for soft tissue inflammation (Martin et al., 2005). Although, report of using this herb for musculoskeletal problems by a single participant may not have a great scientific value, such anecdotal report can open new windows for further investigations. Generally, 76.8% of American ginseng users were satisfied from its effects.

Table 4.5. Reasons for usage of American ginseng reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		48	73.8
Specific medical purposes	Disorders based on TCM[1] concepts	10	15.5
	Neurologic conditions	5	7.7
	Musculoskeletal problems	1	1.5
	Urological problems	1	1.5

[1] TCM: Traditional Chinese Medicine

American ginseng was used almost uniformly by different groups of study participants. Using unadjusted measurement, it was found that usage of American ginseng was higher in younger female participants and none of other demographic, life style or neurocognitive factors showed statistically significant association (Table 4.6).

To assess if association of age and gender with usage of American ginseng can be affected by other demographic, life style and neurocognitive factors, a logistic regression model was built. After taking into account these factors, the effect of age was disappeared and the effect of female gender became marginal (Table 4.7).

This lack of association of usage of American ginseng with different demographic factors together with high prevalence of its usage among older adults emphasizes the common uniform usage of this medicinal herb by the population. American ginseng is an important part of complementary and alternative medicine usage of older adults in Singapore.

Table 4.6. Unadjusted association of demographic and neurocognitive factors to use of American ginseng

Factor	Herbal medicine usage		P value
	Yes	No	
Age	66.7 ± 5.3	69.0 ± 6.1	0.010
Gender			0.001
Female	61 (41.5%)	86 (58.5%)	
Male	8 (16.3%)	41 (83.7%)	
Ethnicity			0.691
Chinese	68 (35.6%)	123 (64.4%)	
Others	1 (20.0%)	4 (80%)	
Educational level			0.808
Nil	13 (31.0%)	29 (69.0%)	
Primary or secondary	49 (36.3%)	86 (63.7%)	
Pre-university or university degree	7 (36.8%)	12 (63.2%)	
Housing type			0.205
1-2 room public apartment	1 (20.0%)	4 (80.0%)	
3 room public apartment	9 (24.3%)	28 (75.7%)	
4-5 room public apartment or private or landed house	59 (38.6%)	94 (61.4%)	
History of chronic diseases			0.388
No history	9 (32.1%)	19 (67.9%)	
History of one or two chronic diseases	38 (40.0%)	57 (60.0%)	
History of three or more chronic diseases	22 (30.1%)	51 (69.9%)	
Physical activity			0.800
Once a month or less	11 (30.6%)	25 (69.4%)	
Once a month to once a week	3 (33.3%)	6 (66.7%)	
Once a week or more	51 (36.4%)	89 (63.6%)	
Social, cognitive and religious activity level	3.5 ± 1.8	3.5 ± 1.7	0.952
GDS score	0.87 ± 1.1	1.03 ± 1.30	0.383
GAI score	0.55 ± 1.4	0.78 ± 1.9	0.378
MMSE score	28.74 ± 1.72	28.63 ± 1.94	0.100
ECAQ score	9.62 ± 0.73	9.59 ± 0.71	0.738

Table 4.7. Adjusted association of demographic and neurocognitive data with usage of American ginseng

Factor	Odds ratio	95% CI	P value
Age	0.94	0.87 – 1.01	0.078
Female gender	2.76	1.08 – 7.11	0.035
Ethnicity			
Chinese	1		
Malay	NA	NA	NA
Indian	0.60	0.05 – 6.91	0.678
Educational level			0.948
Nil	1		
Primary or secondary	1.17	0.45 – 3.07	0.743
Pre-university or university degree	1.15	0.28 – 4.80	0.846
Housing type			0.268
1-2 room public apartment	1		
3 room public apartment	0.74	0.06 – 8.93	0.811
4-5 room public apartment or private or landed house	1.59	0.15 – 16.90	0.700
History of chronic diseases			0.676
No history	1		
History of one or two chronic diseases	1.14	0.42 – 3.15	0.796
History of three or more chronic diseases	0.82	0.28 – 2.40	0.713
Physical activity			0.722
Once a month or less	1		
Once a month to once a week	1.57	0.28 – 8.96	0.611
Once a week or more	1.44	0.58 – 3.58	0.435
Social, cognitive and religious activity level	1.00	0.81 – 1.24	0.975
GDS score	0.95	0.68 – 1.33	0.770
GAI score	0.91	0.70 – 1.20	0.507
MMSE score	0.98	0.78 – 1.23	0.858
ECAQ	0.85	0.45 – 1.58	0.600

4.4.3. Usage of wolfberry and factors associated with it

Wolfberry was the second most commonly used medicinal herb reported by participants in telephone interview (39, 19.9%). It is the fruit of *Lycium barbarum* (Gouqizi 寧夏枸杞), a small red berry full of anti-oxidants, amino acids and trace minerals. It has been used traditionally as an immunomodulator and anti-ageing agent and to prevent cancer (CPC, 2010; Watson et al., 2008). Based on Chinese Pharmacopoeia, its action is to nourish liver and kidney and replenish essence to improve vision and its indications are pain in lower back and knees, dizziness and tinnitus, seminal emission, blood deficiency, blurred vision, etc. (CPC, 2010).

Among participants in telephone interviews, most wolfberry users used it as a part of herbal soups for general health improvements and 69.2% of users were satisfied of its effects. Figure 4.3 and Table 4.8 show the details of usage of wolfberry.

Similar to American ginseng, the main source of information about usage of wolfberry is the unreliable information from family members and friends. Participants reported various trends of usage but most of them were using it for more than two years. Most participants used wolfberry for general health improvement. Among those who used it for specific medical purposes, usage for disorders based on TCM context was the most common purpose followed by using for neurologic and ophthalmologic conditions.

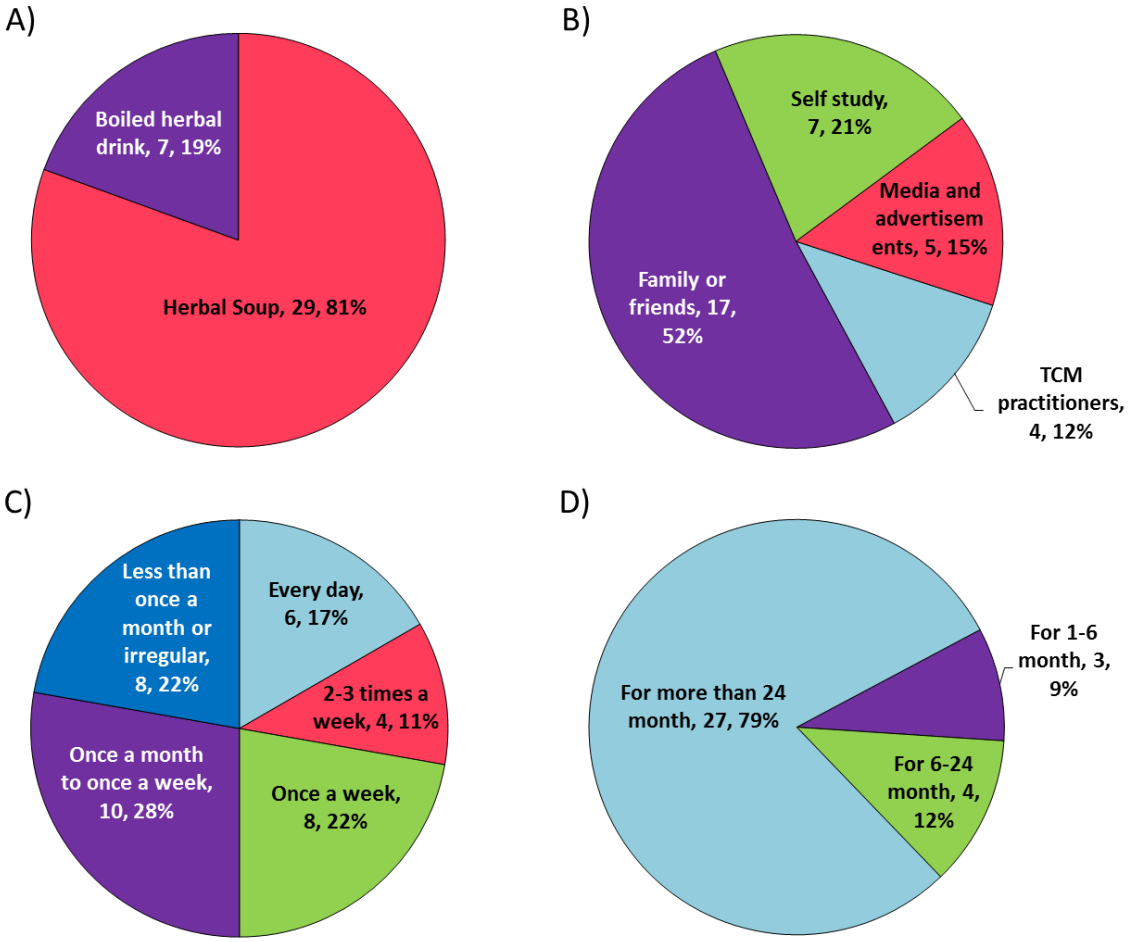

Figure 4.3. Details of usage of wolfberry by participants in telephone interview: A) the percentage of different forms of usage of wolfberry by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of wolfberry reported by participants, D) the duration of usage.

Table 4.8. Reasons for usage of wolfberry reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		20	54.1
Specific medical purposes	Disorders based on TCM[1] concepts	8	21.6
	Neurologic conditions	3	8.1
	Ophthalmologic conditions	3	8.1
	Musculoskeletal problems	2	5.4
	Dermatologic disorders	1	2.7

[1] TCM: Traditional Chinese Medicine

Using wolfberry for neurological and ophthalmologic conditions is consistent with availabnle literature. *L. barbarum* has well-studied anti-stroke, anti-Alzheimer's and neuroprotective effects (Chang et al., 2008; Ho et al., 2010; Wang et al., 2014a). Its positive effects on glaucoma and protection of retinal ganglia cells are also reported (Chan et al., 2007). Additionally, its high carotenoid content has made it a known herbal remedy for ophthalmologic problems (Watson et al., 2008), which is consistent with its traditional usage to improve vision and cure blurred vision (CPC, 2010). Two of our participants used this herb for musculoskeletal problems. Although it has been traditionally used for low back pain and knee pain (CPC, 2010), there is a shortage of available scientific literature supporting its musculoskeletal effects. On the other hand, Amagase and colleagues reported that 2-week treatment by wolfberry had no effect on the musculoskeletal problems of their participants (Amagase et al., 2008). Usage of this herb for dermatologic issues is also consistent with reports showing its anti-oxidant and anti-apoptotic effects leading in dermal protection as well as protective effects against ultra violet light induced cell proliferation in fibroblasts (Wang et al., 2011c; Zhao et al., 2005).

The next step in analyzing the usage of wolfberry was to study factors associated with its usage. Table 4.9 reports the factors associated with the usage of wolfberry. As can be seen, none of demographic or neurocognitive tests was significantly associated with the usage of wolfberry. Small sample size can be the cause of this lack of associations. Further studies with bigger sample sizes are recommended to improve our understanding of factors associated with its usage. Additionally, clinical trials or prospective follow-up observational studies may help to establish its possible pharmacological effects.

Table 4.9. Association of demographic and neurocognitive factors to use of wolfberry

Factor	Wolfberry usage		P value
	Yes	No	
Age	67.3 ± 5.0	68.4 ± 6.1	0.310
Gender			0.075
Female	33 (22.6%)	113 (77.4%)	
Male	6 (12.0%)	44 (88.0%)	
Ethnicity			0.529
Chinese	39 (20.4%)	152 (79.6%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.761
Nil	8 (19.5%)	33 (80.5%)	
Primary or secondary	26 (19.1%)	110 (80.9%)	
Pre-university or university degree	5 (26.3%)	14 (73.7%)	
Housing type			0.518
1-2 room public apartment	0 (0.0%)	5 (100%)	
3 room public apartment	7 (19.4%)	29 (80.6%)	
4-5 room public apartment or private or landed house	32 (20.8%)	122 (79.2%)	
History of chronic diseases			0.200
No history	9 (32.1%)	19 (66.9%)	
History of one or two chronic diseases	16 (16.8%)	79 (83.2%)	
History of three or more chronic diseases	14 (19.2%)	59 (80.8%)	
Physical activity			0.535
Once a month or less	6 (16.7%)	30 (83.3%)	
Once a month to once a week	3 (33.3%)	6 (66.7%)	
Once a week or more	28 (20.0%)	112 (80.0%)	
Social, cognitive and religious activity level	3.6 ± 1.7	3.5 ± 1.7	0.731
GDS score	1.21 ± 1.54	0.92 ± 1.15	0.280
GAI score	0.92 ± 1.99	0.65 ± 1.66	0.378
MMSE score	28.72 ± 1.64	28.67 ± 1.92	0.878
ECAQ score	9.54 ± 0.89	9.63 ± 0.65	0.478

4.4.4. Usage of Chinese/Korean ginseng and factors associated with it

Panax ginseng was the third most commonly used herb. People reported using it as white/raw Chinese, red/steamed Chinese or red Korean ginseng. Figure 4.4 shows the distribution of usage of these three types.

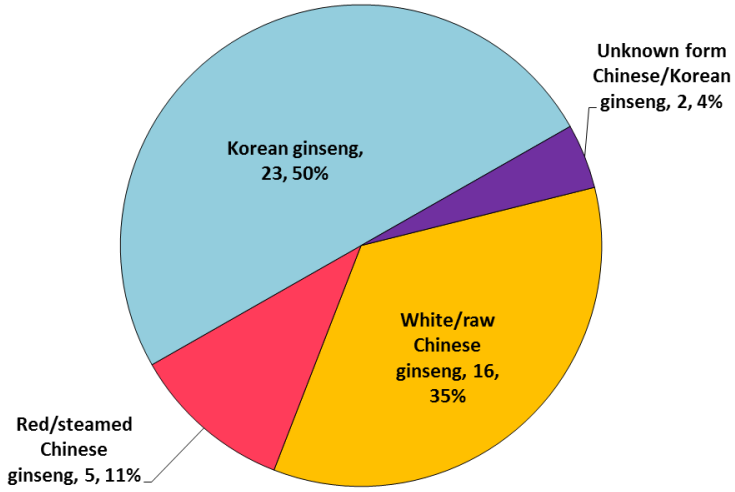

Figure 4.4. Distribution of usage of different types of *P. ginseng* reported by participants in telephone interview

Most Chinese ginseng users reported using this herb as an ingredient of herbal soups followed by commercially available end products containing *P. ginseng*. The trend of source of information was similar to what was observed among American ginseng and wolfberry users. Nobody got information from western practitioners and main source of information was word of mouth from family and friends (Figure 4.5). Among participants who reported their level of satisfaction from the usage of *P. ginseng*, 84.4% (27/32) mentioned that they are satisfied from its usage.

Among Chinese ginseng users who mentioned their reason for usage of this herb, 76.6% were using it for general health improvement. The remaining 8 participants were

using this herb for neurological, TCM based, cardiovascular, musculoskeletal or reproductive conditions (Table 4.10).

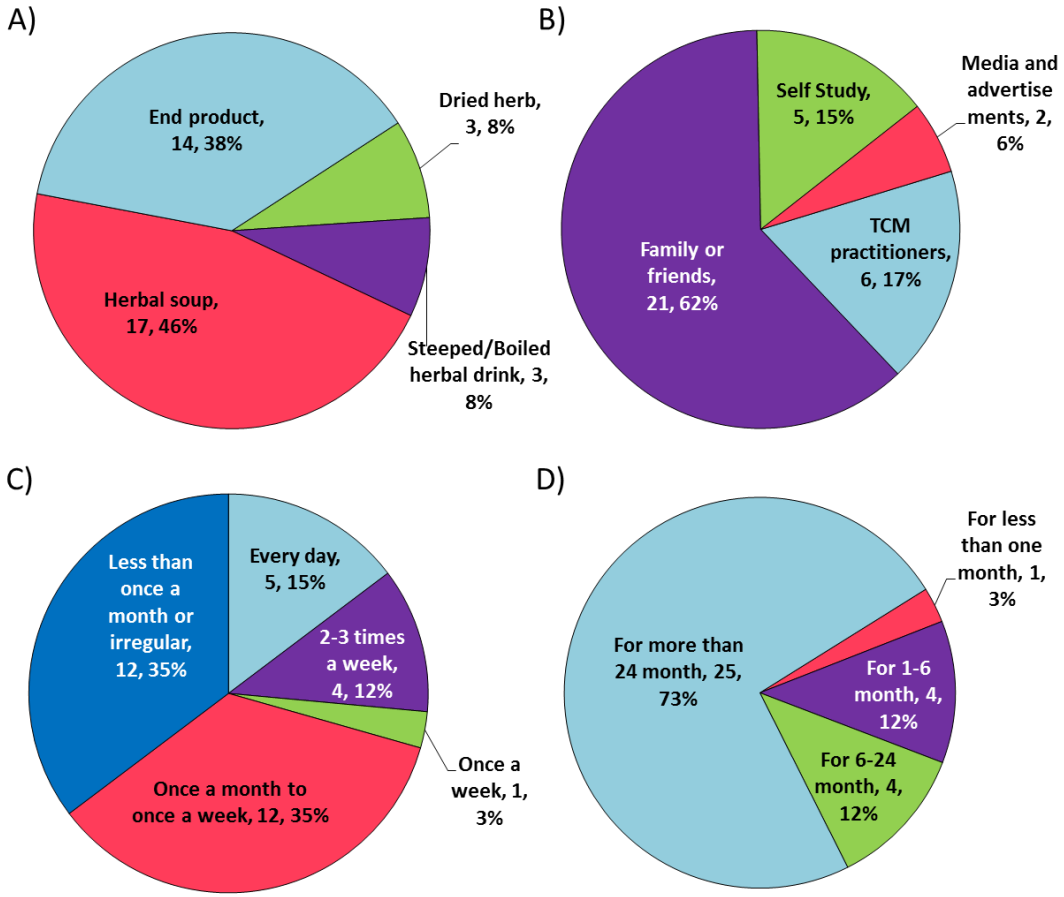

Figure 4.5. Details of usage of *P. ginseng* by participants in telephone interview: A) the percentage of different forms of usage of *P. ginseng* by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of *P. ginseng* reported by participants, D) the duration of usage.

The available literature on the effectiveness of *P. ginseng* for these medical condition has been reviewed briefly in section 1.3.1.2. There are several reports of the possible neurological effects of Chinese ginseng from memory enhancing to prevention and treatment of stroke and other effects (Cheon et al., 2013; Geng et al., 2010; Lee et al., 2013; Lee et al., 2011b). Therefore, it is not unexpected to have neurological conditions as the top of the list of medical purposes for usage of *P. ginseng*. In addition,

beneficial cardiovascular properties of this herb have been investigated extensively (Jia et al., 2012; Zheng et al., 2012). Although the number of publications reporting musculoskeletal properties of Chinese ginseng is limited, it has been shown to be an effective treatment for myalgia in some cases (Kim et al., 2014a; Kim et al., 2014b). Such effects have been reported for both ginsenoside and non-ginsenoside components of this *P. ginseng* (Kim et al., 2014a; Wang et al., 2013a). Chinese ginseng has been also tried in treatment of some reproductive issues such as erectile dysfunction. However the effect is still controversial (Ho et al., 2011; Jang et al., 2008; Moyad et al., 2012).

Table 4.10. Reasons for usage of *P. ginseng* reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		26	76.6
Specific medical purposes	Neurological conditions	3	8.8
	Disorders based on TCM[1] concepts	2	5.9
	Cardiovascular disorders	1	2.9
	Musculoskeletal problems	1	2.9
	Reproductive system disorders	1	2.9

[1] TCM: Traditional Chinese Medicine

To investigate the demographic, life style and neurocognitive predictors of usage of Chinese ginseng, the association of these factors to its usage was studied using chi square and student t-test (Table 4.11). None of the studied factors showed any statistically significant association. This lack of association can be because of small sample size. Although the positive cognitive effects of *P. ginseng* has been shown previously, the lack of association of its usage with neurocognitive performances can be due to usage of this herb for both treatment of mild cognitive impairment by subclinical patients and prevention of decline by cognitively normal participants.

Table 4.11. Association of demographic and neurocognitive factors to use of *P. ginseng*

Factor	Chinese ginseng usage		P value
	Yes	No	
Age	67.1 ± 5.8	68.4 ± 6.0	0.235
Gender			0.248
Female	29 (19.7%)	118 (80.3%)	
Male	7 (14.0%)	43 (86.0%)	
Ethnicity			0.564
Chinese	36 (18.8%)	156 (81.2%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.326
Nil	11 (26.2%)	31 (73.8%)	
Primary or secondary	22 (16.2%)	114 (83.8%)	
Pre-university or university degree	3 (15.8%)	16 (84.2%)	
Housing type			0.462
1-2 room public apartment	1 (20.0%)	4 (80.0%)	
3 room public apartment	4 (10.8%)	33 (89.2%)	
4-5 room public apartment or private or landed house	30 (19.5%)	124 (80.5%)	
History of chronic diseases			0.576
No history	5 (17.9%)	23 (82.1%)	
History of one or two chronic diseases	15 (15.6%)	81 (84.4%)	
History of three or more chronic diseases	16 (21.9%)	57 (78.1%)	
Physical activity			0.801
Once a month or less	6 (16.7%)	30 (83.3%)	
Once a month to once a week	1 (11.1%)	8 (88.9%)	
Once a week or more	27 (19.1%)	114 (80.9%)	
Social, cognitive and religious activity level	3.4 ± 1.8	3.6 ± 1.7	0.620
GDS score	0.83 ± 0.91	1.00 ± 1.30	0.466
GAI score	0.67 ± 1.76	0.71 ± 1.72	0.897
MMSE score	28.74 ± 1.61	28.66 ± 1.91	0.818
ECAQ score	9.64 ± 0.59	9.59 ± 0.74	0.732

4.4.5. Usage of *Codonopsis* and factors associated with it

Codonopsis Radix (Dangshen) is the dried root of *Codonopsis pilosula* which is natural (neither warm nor cold) and tastes sweet. Based on Chinese Pharmacopoeia, its action is to fortify the spleen and replenish lung, nourish blood and engender fluid. In addition, it has been traditionally used for fatigue, cough, dyspnea, qi and blood deficiency, palpitation, shortness of breath, etc. (CPC, 2010). Its pharmacological effects have been studied in stimulating the immune system, affecting neuroendocrine system, enhancing memory and preventing stress induced peptic ulcer (Bensky et al., 2004; Zhu, 1998).

Thirty participants in this study reported using *Codonopsis* within the past 12 months. Among participants who shared their level of satisfaction, 84.0% (21/25) were satisfied of its effects. Figure 4.6 and Table 4.12 show the details of usage of *Codonopsis*. This herb was mainly used as a part of herbal soup and most of its users were using it for several years. Similar to other herbs, family and friends had the highest impact in choosing *Codonopsis* as a medicinal herb by our participants.

Most *C. pilosula* users used this herb for general health improvement (74.1%). Among seven participants who used it for specific medical purposes, only one was using it for any condition other than those based on TCM concepts. This only conventional medical purpose of use was ophthalmologic conditions. This particular participant was using *Codonopsis* in combination with wolfberry, extractum astragali and red date to prepare chicken soup. As mentioned in section 4.4.3, *L. barbarum* is a known ophthalmologic remedy. Therefore, the usage of this combination was most probably for ophthalmologic properties of wolfberry not that of *Codonopsis*.

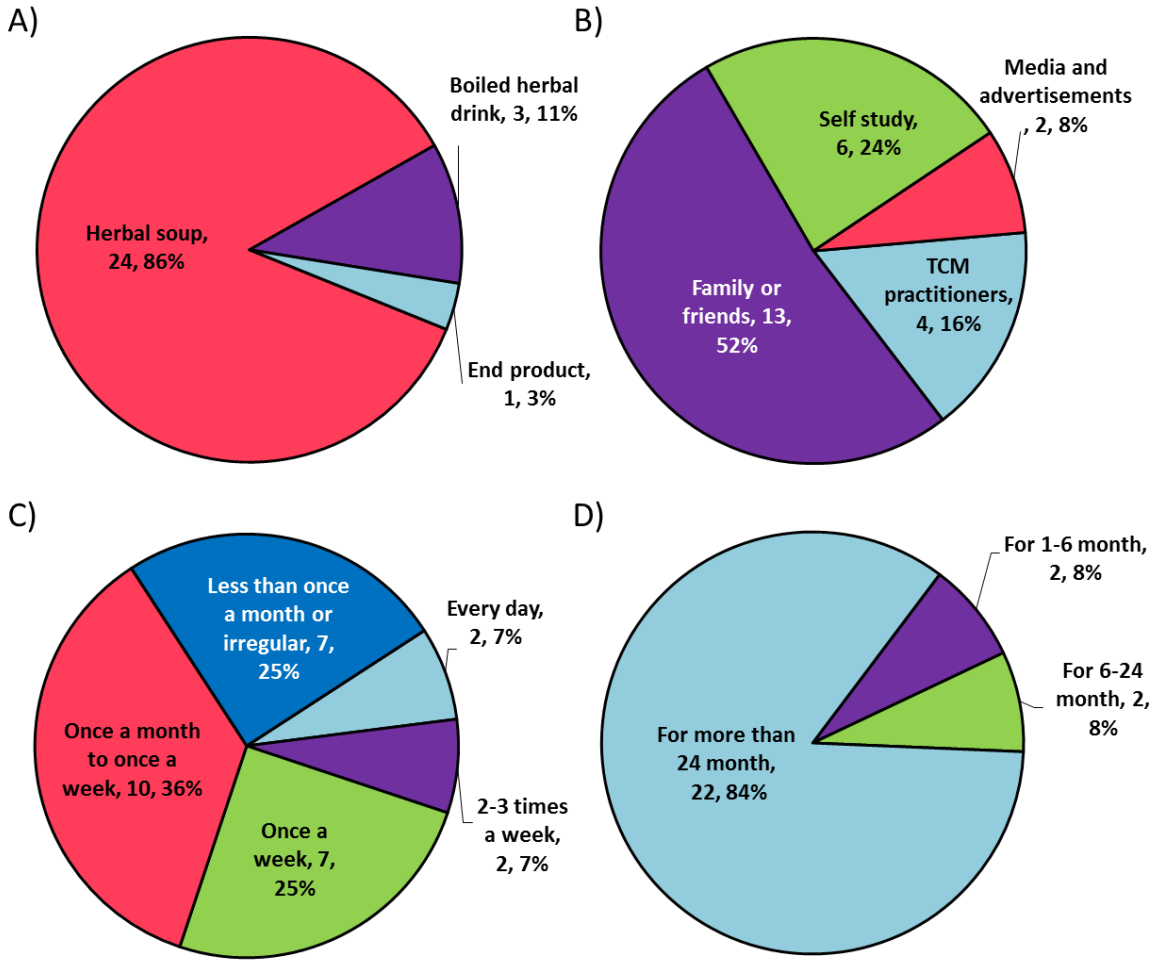

Figure 4.6. Details of usage of *Codonopsis* by participants in telephone interview: A) the percentage of different forms of usage of *Codonopsis* by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of *Codonopsis* reported by participants, D) the duration of usage.

Table 4.12. Reasons for usage of *Codonopsis* reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		20	74.1
Specific medical purposes	Disorders based on TCM[1] concepts	6	22.2
	Ophthalmologic problems	1	3.7

[1] TCM: Traditional Chinese Medicine

Usage of *Codonopsis* was more common among female participants in telephone interview. Age had a marginal effects in a way that the users were slightly younger than nonusers. Other demographic, life style and neurocognitive factors were not associated with the usage of this herb (Table 4.13).

To study whether the association of gender and age with *Codonopsis* usage is affected by other factors, a logistic regression model was built by the enter method. The Negelkerke R square for this model was 0.186 (Table 4.14). After taking into account all the studied variables, age lost its marginal association and the association of gender with the *Codonopsis* usage became marginal. Most probably, the lack of significant association is because of the small sample size, which can be improved by further bigger studies. To the best of our knowledge, there is no population based survey reporting factors affecting the prevalence of the usage of *Codonopsis* to compare the current results with.

Table 4.13. Unadjusted association of demographic and neurocognitive assessment factors to the usage of *Codonopsis*

Factor	*Codonopsis* usage		P value
	Yes	No	
Age	66.4 ± 4.3	68.5 ± 6.1	0.071
Gender			0.023
Female	27 (18.5%)	119 (81.5%)	
Male	3 (6.0%)	47 (94.0%)	
Ethnicity			0.629
Chinese	30 (15.7%)	161 (84.3%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.823
Nil	5 (12.2%)	36 (87.8%)	
Primary or secondary	22 (16.2%)	114 (83.8%)	
Pre-university or university degree	3 (15.8%)	16 (84.2%)	
Housing type			0.590
1-2 room public apartment	0 (0.0%)	5 (100%)	
3 room public apartment	5 (13.9%)	31 (86.1%)	
4-5 room public apartment or private or landed house	25 (16.2%)	129 (83.8%)	
History of chronic diseases			0.107
No history	8 (28.6%)	20 (71.4%)	
History of one or two chronic diseases	12 (12.6%)	83 (87.4%)	
History of three or more chronic diseases	10 (13.7%)	63 (86.3%)	
Physical activity			0.159
Once a month or less	3 (8.3%)	33 (91.7%)	
Once a month to once a week	3 (33.3%)	6 (66.7%)	
Once a week or more	24 (17.1%)	116 (82.9%)	
Social, cognitive and religious activity level	3.6 ± 1.7	3.5 ± 1.7	0.731
GDS score	0.93 ± 1.14	0.98 ± 1.26	0.844
GAI score	1.03 ± 1.87	0.64 ± 1.70	0.258
MMSE score	28.67 ± 1.52	28.68 ± 1.92	0.965
ECAQ score	9.73 ± 0.45	9.59 ± 0.74	0.300

Table 4.14. Adjusted association of demographic and neurocognitive factors to the usage of *Codonopsis*

Factor	Odds ratio	95% CI	P value
Age	0.97	0.87 – 1.07	0.503
Female gender	4.24	0.95 – 18.84	0.058
Ethnicity			
Chinese	NA	NA	NA
Malay	NA	NA	NA
Indian	NA	NA	NA
Educational level			0.962
Nil	1		
Primary or secondary	1.18	0.32 – 4.33	0.805
Pre-university or university degree	1.27	0.20 – 8.20	0.799
Housing type			0.917
1-2 room public apartment	1		
3 room public apartment	NA	NA	NA
4-5 room public apartment or private or landed house	NA	NA	NA
History of chronic diseases			0.261
No history	1		
History of one or two chronic diseases	0.38	0.11 – 1.25	0.112
History of three or more chronic diseases	0.42	0.12 – 1.46	0.174
Physical activity			0.155
Once a month or less	1		
Once a month to once a week	8.05	0.96 – 67.81	0.055
Once a week or more	2.29	0.58 – 9.07	0.239
Social, cognitive and religious activity level	0.97	0.74 – 1.28	0.845
GDS score	0.953	0.65 – 1.40	0.806
GAI score	1.24	0.95 – 1.62	0.115
MMSE score	0.91	0.67 – 1.24	0.532
ECAQ	1.41	0.52 – 3.84	0.499

4.4.6. Usage of red date and factors associated with it

Red date (Dazao or Chinese date) is a common herb used all around the world. It is the dried ripe fruit of *Ziziphus jujube* and is warm in nature and tastes sweet (CPC, 2010). Based on the Chinese Pharmacopoeia, red date can tonify (make stronger) the middle energizer and qi, nourish blood and tranquilize the mind. It has been traditionally used for reduced food intake caused by spleen deficiency, (improper digestion), lack of strength, sloppy stool and hysteria in women (CPC, 2010). These neurological effects have been investigated scientifically as well (Dey, 2013; Han et al., 2009; Jiang et al., 2007; Yeung et al., 2012). It has been used in TCM practice to treat asthma, hepatitis, diarrhea, dysuria, insomnia and joint pain (Watson et al., 2008). Its effects on asthma and joint pain can be partly due to its anti-inflammatory effects (Al-Reza et al., 2010; Goyal et al., 2011; Yu et al., 2012).

Usage of this herb was reported by 25 participants in the survey. Most of them used red date as a part of chicken or pork soup (21, 87%). Similar to other herbs, information from family and friends had the highest impact on the usage of this herb (Figure 4.7).

Most red date users reported using this herb for general health improvement. Among those using for specific medical conditions, the majority was usage for disorders based on TCM concepts (Table 4.15). Usage of this herb by a participant for neurologic conditions was consistent with its traditional action of tranquilizing the mind (CPC, 2010) and its indication to treat insomnia (Watson et al., 2008). Another participant used it for musculoskeletal problems. As mentioned before, Chinese date has been used traditionally for joint pain. The participant using this for ophthalmologic conditions was the one reported in section 4.4.5 who was using wolfberry, *Codonopsis* and red date to prepare his herbal chicken soup. As mentioned before, the herb affecting

his ophthalmologic condition was wolfberry. Among those who mentioned their level of satisfaction from its effects, the satisfaction rate was 76.2% (16/21).

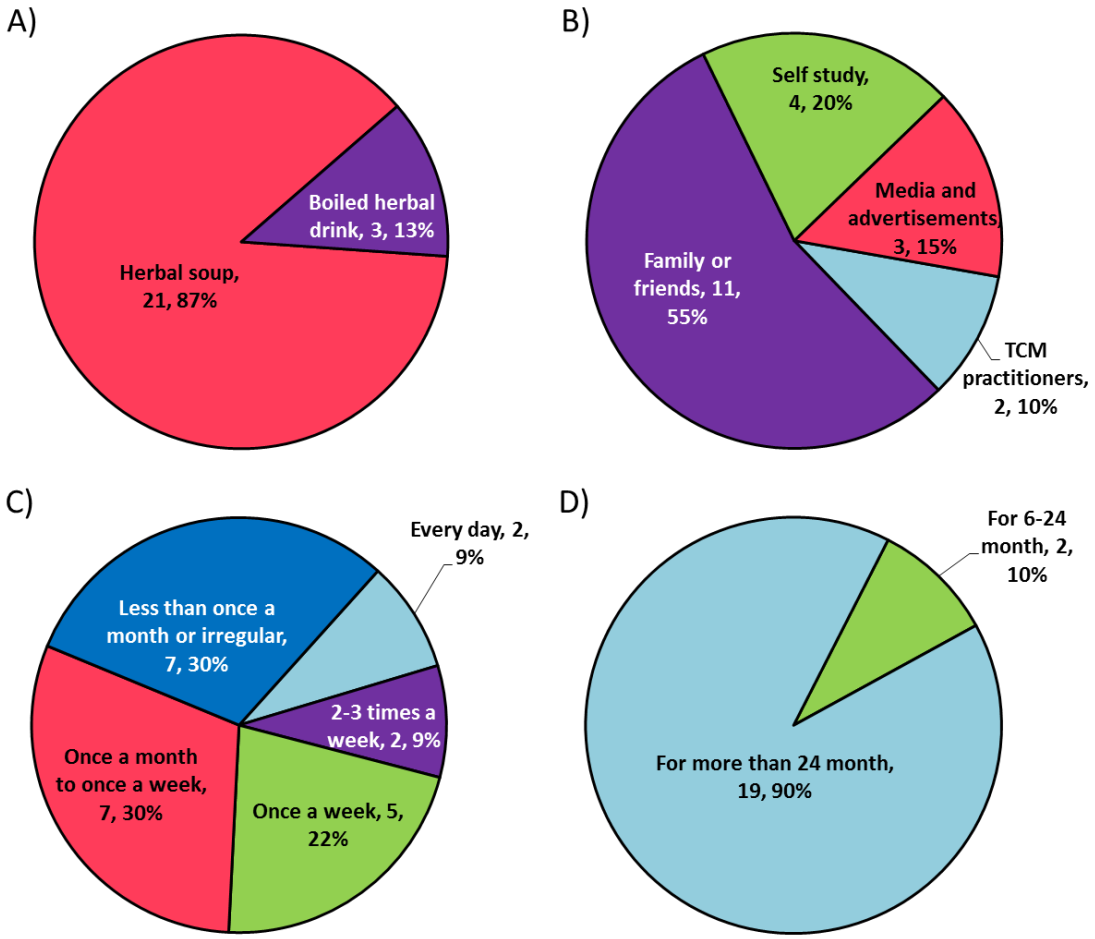

Figure 4.7. Details of usage of red date by participants in telephone interview: A) the percentage of different forms of usage of red date by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of red date reported by participants, D) the duration of usage.

Table 4.15. Reasons for usage of red date reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		16	72.7
Specific medical purposes[1]	Disorders based on TCM concepts[2]	4	18.2
	Neurological disorders	1	4.5
	Ophthalmologic problems	1	4.5
	Musculoskeletal problems	1	4.5

[1] one of the participants reported using ginkgo for both cardiovascular and metabolic disorders. Therefore, the sum of reasons for usage is more than the sum of users.
[2] TCM: Traditional Chinese Medicine

To study the factors associated with the usage of red date, chi square and student t-test were used for the categorical and continuous variables respectively. As presented in Table 4.16, none of the studied factors was associated with the usage of this medicinal herb. As mentioned before, the lack of found association can be due to the small sample size, which should be addressed in further bigger studies. So far, there is no available publication on factors associated with its usage to compare the data with.

Table 4.16. Association of demographic and neurocognitive assessment factors with the usage of red date

Factor	Red date usage		P value
	Yes	No	
Age	67.4 ± 5.1	68.3 ± 6.0	0.469
Gender			0.389
Male	6 (12.0%)	44 (88.0%)	
Female	19 (13.0%)	127 (87.0%)	
Ethnicity			0.699
Chinese	25 (13.1%)	166 (86.9%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.569
Nil	8 (19.5%)	33 (80.5%)	
Primary or secondary	15 (11.0%)	121 (89.0%)	
Pre-university or university degree	2 (10.5%)	17 (89.5%)	
Housing type			0.499
1-2 room public apartment	0 (0.0%)	5 (100%)	
3 room public apartment	7 (19.4%)	29 (80.6%)	
4-5 room public apartment or private or landed house	18 (11.7%)	136 (88.3%)	
History of chronic diseases			0.273
No history	4 (14.3%)	24 (85.7%)	
History of one or two chronic diseases	8 (8.4%)	87 (91.6%)	
History of three or more chronic diseases	13 (17.8%)	60 (82.2%)	
Physical activity			0.309
Once a month or less	2 (5.6%)	34 (94.4%)	
Once a month to once a week	2 (22.2%)	7 (77.8%)	
Once a week or more	17 (12.1%)	123 (87.9%)	
Social, cognitive and religious activity level	3.48 ± 1.47	3.54 ± 1.74	0.867
GDS score	1.08 ± 1.64	0.96 ± 1.18	0.723
GAI score	0.75 ± 1.96	0.70 ± 1.70	0.890
MMSE score	28.33 ± 1.90	28.73 ± 1.86	0.331
ECAQ score	9.54 ± 1.06	9.62 ± 0.64	0.612

4.4.7. Usage of notoginseng and factors associated with it

Notoginseng is another species from *Panax genus,* which was the sixth most commonly used herb by the participants in the telephone interviews with 24 users. This herb was introduced in the section 1.3.1.3. Figure 4.8 demonstrates the detailed information about the usage of notoginseng by participants in the study.

Despite other medicinal herbs discussed before, users of notoginseng usually took it as end product preparations such as tablets or capsules. Additionally, one participants used this herb topically. It was the only topical herbal medicine reported by our participants.

Most notoginseng users were using it for specific medical conditions. It was unique for *P. notoginseng* since the main purpose of usage for all other herbs was to improve the general health. Among reported medical purposes, disorders based on TCM concepts were the most common reason for usage followed by neurological and musculoskeletal problems (Table 4.17).

P. notoginseng is a known herbal remedy for prevention and treatment of cerebrovascular accident and its subsequent cognition impairment (Chuang et al., 2008; Gao et al., 2012; He et al., 2011; Zheng et al., 2008). There are also studies investigating its effect on other kinds of cognitive decline such as Alzheimer's disease (Choi et al., 2010; Hsieh et al., 2000; Zhong et al., 2011). The usage of this herb for musculoskeletal problems by 3 participants is consistent with its traditional indication for trauma management, which has been recently studied scientifically as well (CPC, 2010; Ng et al., 2008a; Peng et al., 2010). In addition to its usage for blood promoting to treat cardiovascular disorders for centuries (CPC, 2010; Han et al., 2013; Wang et al., 2012;

Zhang et al., 2011), the positive effects of using *P. notoginseng* on prevention and treatment of cardiovascular and cerebrovascular accidents can be due to its hypoglycemic effects as well. There are reports on usage of this medicinal herb as a hypoglycemic and anti-obesity remedy (Kim et al., 2009; Uzayisenga et al., 2014; Yang et al., 2010). It has also shown promising effects against hypertension in recent studies (Baek et al., 2009; Pan et al., 2012). Therefore, the usage of this herb for different medical purposes reported by our participants is consistent with available literature. Twenty out of 22 participants who explained their level of satisfaction about the usage of notoginseng were satisfied of its usage (90.9%).

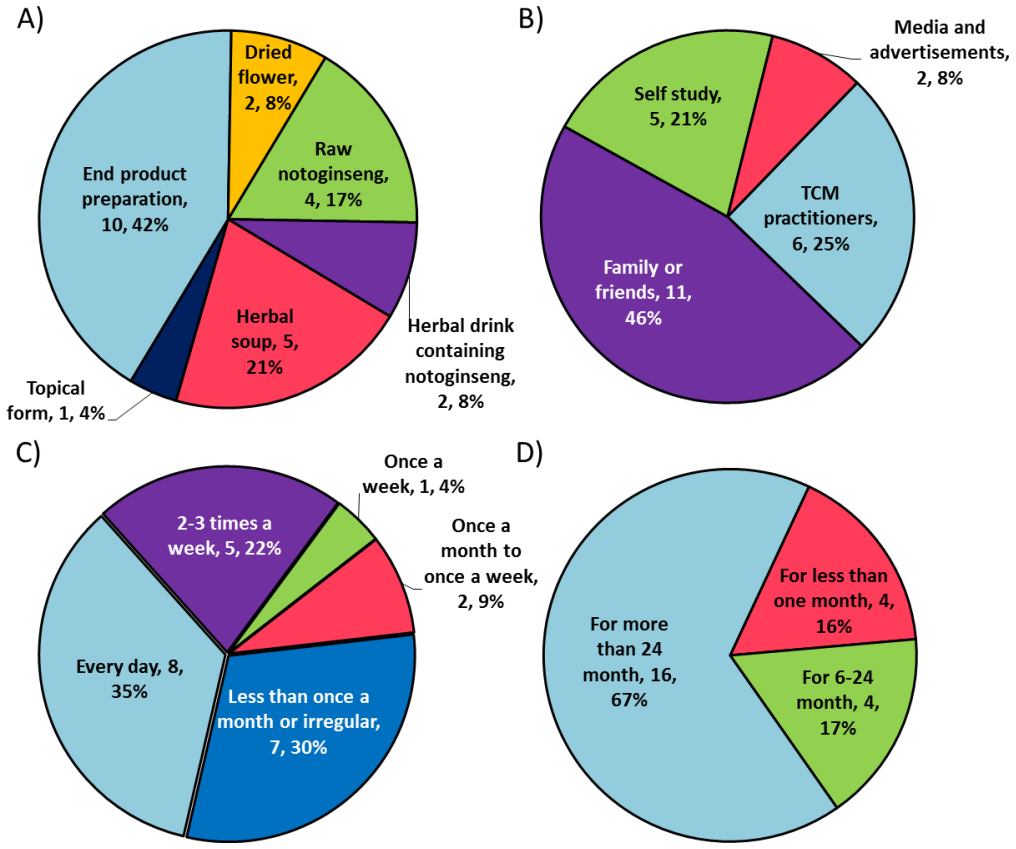

Figure 4.8. Details of usage of notoginseng by participants in telephone interview: A) the percentage of different forms of usage of notoginseng by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of notoginseng reported by participants, D) the duration of usage.

Table 4.17. Reasons for usage of notoginseng reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		9	37.5
Specific medical purposes	Disorders based on TCM[1] concepts	6	25.0
	Neurological disorders	3	12.5
	Musculoskeletal problems	3	12.5
	Cardiovascular diseases	2	8.3
	Metabolic disorders	1	4.2

[1] TCM: Traditional Chinese Medicine

To study the factors associated with usage of notoginseng, unadjusted methods were used, which is presented in Table 4.18. None of the studies factors showed statistically significant association with the usage of notoginseng. In this study, only 24 participants reported using *P. notoginseng* and their purposes of usage were diverse. Therefore, it is not expected to observe any statistically significant association. Larger studies can help to improve the understanding about factors associated with its usage.

Table 4.18. Association of demographic and neurocognitive assessment factors to the usage of notoginseng

Factor	Notoginseng usage		P value
	Yes	No	
Age	67.1 ± 6.1	68.3 ± 5.9	0.357
Gender			0.092
Female	21 (14.3%)	126 (85.7%)	
Male	3 (6.0%)	47 (94.0%)	
Ethnicity			0.701
Chinese	24 (12.5%)	168 (87.5%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.229
Nil	6 (14.3%)	36 (85.7%)	
Primary or secondary	18 (13.2%)	118 (86.8%)	
Pre-university or university degree	0 (0.0%)	19 (100%)	
Housing type			0.655
1-2 room public apartment	0 (0.0%)	5 (100%)	
3 room public apartment	4 (10.8%)	33 (89.2%)	
4-5 room public apartment or private or landed house	20 (13.0%)	134 (87.0%)	
History of chronic diseases			0.069
No history	2 (7.1%)	26 (92.9%)	
History of one or two chronic diseases	17 (17.7%)	79 (82.3%)	
History of three or more chronic diseases	5 (6.8%)	68 (93.2%)	
Physical activity			0.700
Once a month or less	3 (8.3%)	33 (91.7%)	
Once a month to once a week	1 (11.1%)	8 (88.9%)	
Once a week or more	19 (13.5%)	122 (86.5%)	
Social, cognitive and religious activity level	3.7 ± 1.6	3.5 ± 1.7	0.744
GDS score	0.79 ± 0.78	0.99 ± 1.29	0.454
GAI score	0.54 ± 1.44	0.72 ± 1.76	0.631
MMSE score	28.22 ± 2.09	28.74 ± 1.83	0.208
ECAQ score	9.42 ± 1.14	9.63 ± 0.63	0.382

4.4.8. Usage of lingzhi and factors associated with it

Lingzhi (Reishi) is the dried sporophore of *Ganoderma lucidum,* which is a mushroom endemic to East Asia. Its nature is natural (neither warm nor cold) and its taste is sweet. Lingzhi has been traditionally used to tonify qi and tranquilize the mind, suppress cough and relieve panting. Based on Chinese Pharmacopoeia, its indications are disquietude heart spirit, insomnia and palpitation, cough and panting, shortness of breath and lack of appetite (CPC, 2010).

Among participants in our study, this herb was the sixth most commonly used medicinal herb sharing its rank with notoginseng with 24 users. Figure 4.9 and Table 4.19 show the details of its usage. Similar to *P. notoginseng* and despite other herbs studied in this survey, users of *G. lucidum* were usually using it as an ingredient of health supplement end products. However, similar to other herbs, the main source of information about its usage was family and friends recommendation.

Most of lingzhi users used this herb for general health improvement and 5 participants who reported using it for specific medical conditions reported using it for respiratory, neurologic, musculoskeletal, cardiovascular and reproductive disorders.

Usage of *G. lucidum* for respiratory problems is consistent with its traditional uses (CPC, 2010). Furthermore, its therapeutic effects on asthma and bronchitis have been studied recently where its immune modulatory effects can be an important player (Batra et al., 2013; Jan et al., 2011; Kelly-Pieper et al., 2009). One participant used it for neurological conditions, which is consistent with its traditional usage for insomnia (CPC, 2010). Although the number of studies on this herb is limited, there are reports showing its positive effect as a tranquilizer to treat insomnia (Batra et al., 2013).

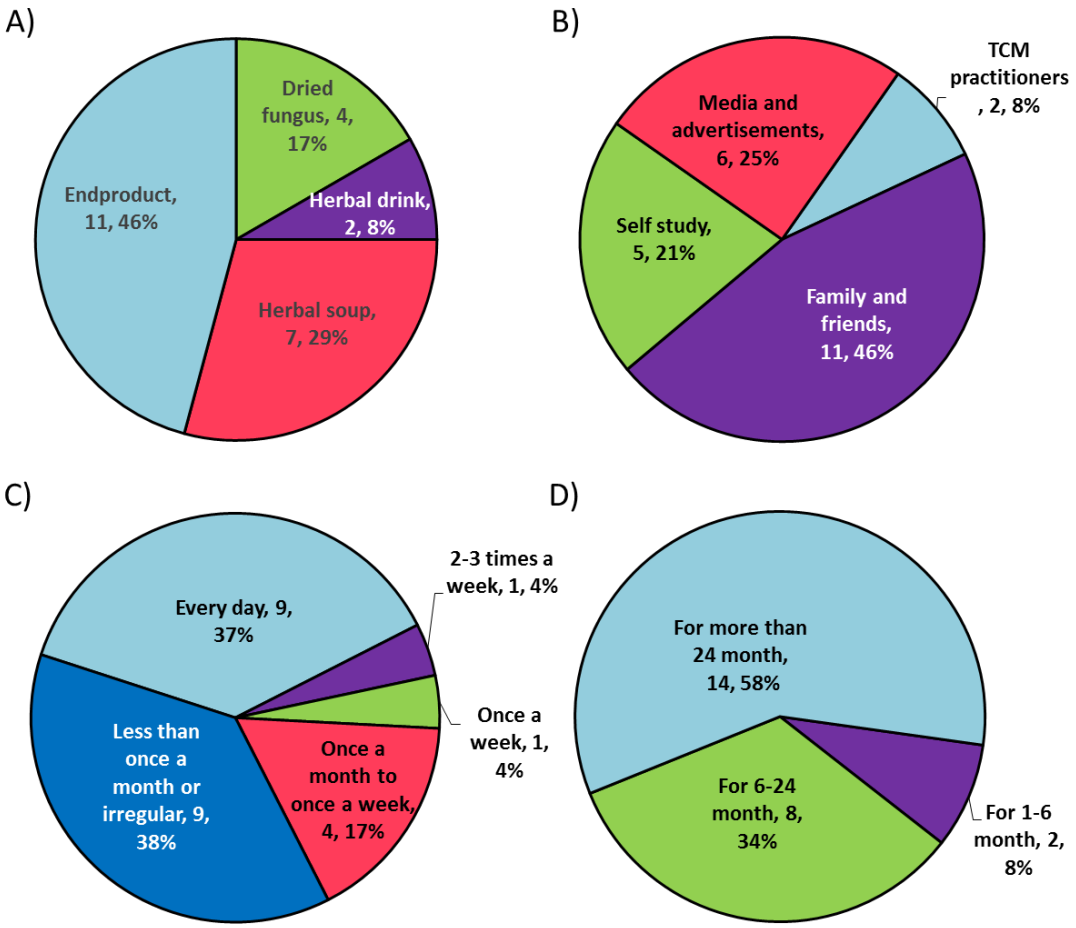

Figure 4.9. Details of usage of lingzhi by participants in telephone interview: A) the percentage of different forms of usage of lingzhi by participants, B) the different sources of information about its usage reported by participants, C) the frequency of usage of lingzhi reported by participants, D) its duration of usage.

Table 4.19. Reasons for usage of lingzhi reported by participants in telephone interviews

Reasons for usage	Description	Number of reports	Percent
General health improvement		19	79.2
Specific medical purposes	Respiratory problems	2	8.3
	Neurological disorders	1	4.2
	Musculoskeletal problems	1	4.2
	Cardiovascular diseases	1	4.2
	Reproductive system problems	1	4.2

[1]TCM: Traditional Chinese Medicine
[2] One of the participants reported using lingzhi for both cardiovascular and respiratory problems. Therefore, the sum of reasons for usage is more than the sum of users.

Although there is no traditional musculoskeletal indication for lingzhi to support its usage by a participant for this reason, its analgesic and immunomodulatory effects (Lam et al., 2008; Li et al., 2007; Xi Bao et al., 2006) can suggest it as an alternative or complementary treatment for rheumatoid arthritis and similar disorders. Usage of this herb by a participant for cardiovascular problems is also consistent with both the traditional and scientific literature suggesting its benefits in the management of cardiovascular problems from palpitation to myocardial ischemia (Chu et al., 2012; CPC, 2010; Lasukova et al., 2008). One of the participants used a health supplement containing lingzhi and steamed Korean ginseng for his reproductive problem. To the best of our knowledge there is neither traditional nor new literature reporting any reproductive pharmacological benefits for lingzhi. On the other hand, *P. ginseng* has established beneficial effects for sexual dysfunction (Choi et al., 2013; Leung et al., 2013). Therefore, it can be concluded that, the ingredient in the product which was effective for sexual problem was Korean ginseng and not lingzhi. The satisfaction rate for usage of lingzhi among participants was 58.3% (14/24).

To study factors associated with usage of lingzhi, demographic, life style and mental assessment factors were studied individually using student t-test and chi square whichever applicable. None of the studied factors showed any statistically significant association with the use of lingzhi, which can be because of the small sample size (Table 4.20)

Table 4.20. Association of demographic and neurocognitive assessment factors with the usage of lingzhi

Factor	Lingzhi usage		P value
	Yes	No	
Age	67.3 ± 3.6	68.3 ± 6.2	0.283
Gender			0.593
Male	6 (12.0%)	44 (88.0%)	
Female	18 (12.2%)	129 (87.8%)	
Ethnicity			0.701
Chinese	24 (12.5%)	168 (87.5%)	
Others	0 (0.0%)	5 (100%)	
Educational level			0.880
Nil	5 (11.9%)	37 (88.1%)	
Primary or secondary	16 (11.8%)	120 (88.2%)	
Pre-university or university degree	3 (15.8%)	16 (84.2%)	
Housing type			0.655
1-2 room public apartment	0 (0.0%)	5 (100%)	
3 room public apartment	4 (10.8%)	33 (89.2%)	
4-5 room public apartment or private or landed house	20 (13.0%)	134 (87.0%)	
History of chronic diseases			0.426
No history	5 (17.9%)	23 (82.1%)	
History of one or two chronic diseases	9 (9.4%)	87 (90.6%)	
History of three or more chronic diseases	10 (13.7%)	63 (86.3%)	
Physical activity			0.567
Once a month or less	4 (11.1%)	32 (88.9%)	
Once a month to once a week	2 (22.2%)	7 (77.8%)	
Once a week or more	15 (10.6%)	126 (89.4%)	
Social, cognitive and religious activity level	3.9 ± 1.9	3.5 ± 1.7	0.371
GDS score	0.96 ± 0.96	0.97 ± 1.27	0.962
GAI score	1.04 ± 1.81	0.65 ± 1.71	0.302
MMSE score	28.83 ± 1.47	28.65 ± 1.91	0.661
ECAQ score	9.67 ± 0.57	9.59 ± 0.73	0.636

4.5. Conclusion

The main aim of this study was to collate detailed information about the usage of herbal medicine among older adults in Singapore. For this, 209 older adults participating in Jurong Ageing Study were invited to participate in a follow-up interview on phone. Among them, 198 agreed to participate and shared the information about their usage of medicinal herb in past 12 months, if any. The prevalence of usage of medicinal herbs was 67.7%, which was about twice the prevalence of medicinal herbs among SLAS participants. This significant increase could hardly be explained by the changes in the usage during the time. The best explanation could be the differences in study design and having a focused questionnaire for getting information about herbal medicine usage by telephone interviews.

The top three common herbs used by participants were American ginseng, wolfberry and Chinese ginseng respectively. It was worth to note that three species from *Panax* genus were among the top six herbs used by our participants, namely *P. quinquefolium* (American ginseng), *P. ginseng* (Chinese ginseng) and *P. notoginseng* (notoginseng). It shows that *Panax* genus can be considered as the most commonly used group of medicinal herbs in this age group. This observation is consistent with other reports showing high prevalence of these herbs in different societies (Ayranci et al., 2005; Froiland et al., 2004; Kim et al., 2004a; Tian et al., 2010).

Most of our participants used to get the information about the usage of herbal medicine from family and friends. A small proportion obtained such information from TCM practitioners and nobody had consulted with a western practitioner regarding their use. It shows a huge gap of communication between health practitioners and older adults regarding the usage of herbal medicine, which is not only very commonly used

but also potentially a risk for herb-drug interaction and other dangerous adverse effects. Such a lack of proper communication has been reported by many other studies from different countries since several years ago (Asadi-Pooya et al., 2014; Koh et al., 2003; Smith et al., 2004) but the situation seems to be unchanged.

General health improvement was the most common reason for usage of medicinal herbs. Among those who were using herbal medicine for specific medical purposes, health conditions based on TCM concepts was the most common purpose of usage followed by neurological conditions and musculoskeletal ones. It demonstrate the importance of investigating the usage of herbal medicine for neurological conditions in older adults, which is one of the most important health issues in this age group.

Usage of herbal medicine was more common among younger female participants and those who lived in bigger houses in unadjusted measurements. However, after building a logistic regression model to consider the effect of other factors on these associations, only female gender kept its association. Such higher usage of herbal medicine by women has been reported before (Eardley et al., 2012; Hughes et al., 2013; Picking et al., 2011).

The detailed information about usage of seven herb with more than 20 user was analyzed. Most of these herbs were used as a part of food preparations (usually herbal chicken or pork soup) except notoginseng and lingzhi, which were used as end product health supplements. The medical purposes for using these herbs were also compared to available literature, which showed almost complete consistency.

The number of interviewed participants in this study is limited. This has led in the small number of users for each herb making it difficult to statistically evaluate the

correlation of using each herb to different factors. Additionally, although the detailed information on the usage of each herb (duration, frequency, etc.) was recorded, the number of participants in subgroups of herbal usage was very few. This fact made the statistical analysis of the association of duration and frequency of using each herb to different studied factors invalid. Recruiting more participants and continuation of the telephone interview can be helpful in preparing a better picture of their usage.

The demographic information of non-respondent to the original study was not recorded. Having no data on non-respondents, makes it impossible to calculate the response rate and compare the respondents to the non-respondents. Such comparison is essential for generalization of the findings and validation of the results. Since the project is ongoing, this limitation has been reported to its principle investigator hoping to solve the problem for the rest of the study.

The other limitation of the study was the ethnic distribution of participants. In this study, 97.5% of participants were Chinese, 2% were Indian and 0.5% were Malay. However, based on the latest national census, among Singapore population older than 60, 83.3% are Chinese, 9.3% are Malay, 6.0% are Indian, and 1.4% belong to other ethnicities (Wong, 2010). This difference in ethnic proportions can negatively affect the generalizability of the results.

Considering the high prevalence of herbal medicine as the most common complementary and alternative medicine with the highest risk of adverse effects and interactions, it is very important to improve our understanding of the trends of usage and factors associated with it. Such information can be useful for medical practitioners to improve their communication with their patients specially when dealing with high risk patients such as older adults. Simultaneously, policy makers, government bodies

and media producers should work together to improve the public knowledge and understanding about benefits and risks of using herbal medicine and to encourage the public to expand their communication with their health providers.

CHAPTER 5. Survey of the products containing the words "Panax" or "ginseng" in their label

5.1. Introduction

In Singapore, health supplements are not subjected to premarket approvals and licensing for their importation, manufacture, and sales (MOH, 2008a). The onus of responsibility for the safety and quality of health supplements rests with dealers and sellers (HSA, 2012b; MOH, 2008a). They must ensure that their product comply with the safety and quality requirements (HSA, 2012b). To the best of our knowledge, there are few available publications on their reliability and safety. Most studies done as a post-marketing surveillance have been focusing on adulterations, heavy metals, or poisonous ingredients in CPM products (Koh et al., 2000; Yee et al., 2005).

Health products containing "ginseng" are among the best sold herbal products worldwide (Ayranci et al., 2005; Froiland et al., 2004; Kang et al., 2012; Smith et al., 2004). Since most of these products are sold as general sale list medicines (GSL) or over the counter (OTC), the consumers may choose them based on their labeling while purchasing from retail shops. Therefore, the information provided in the labels is the most available source of information and plays a key role in the product selection and consumption by ordinary users. This information has to be reliable, clear, and understandable for the consumers to avoid misunderstandings and inappropriate usage of the products. Having realistic information from the labels of such products in Singapore market is important in improving public awareness and knowledge regarding their usage.

5.2. Hypotheses and objectives

We hypothesize that the information on labels of food and health products which are labeled with words “Panax” and/or “ginseng” and are available in Singapore market is clear and comprehensive. The objectives of this part of the study are to collate information of commercially available health and food products labeled with words “Panax” and/or “ginseng” in Singapore and to check if the product labels provide all information recommended by local legislations such as name, brand, expiry date, manufacturer, batch number, ingredients, dosage, indications and side effects.

5.3. Methods

During several visits to five different shops in Singapore, the information on all products having the words “Panax” and/or “ginseng” in their labels were collated and documented. The recorded information included names, brands, manufacturers, batch numbers, expiry dates, descriptions, actions and indications, dosage, contraindications, side effects, cautions, prices and any other available information. The shops visited for this purpose were “Sinchong Meheco”, “Unity Pharmacy, NTUC Healthcare Hougang mall Branch”, “Guardian Health and Beauty Lot 1 Shopper’s Mall Branch”, “GNC Lot 1 Shopper’s Mall Branch”, and “Fairprice 24 hours, HDB Clementi Branch”. They actually consist of a wide range of shopping places providing OTC health products that may be chosen by ordinary people from general branched shopping centers (fairprice NTUC) to health product shops (Guardian, GNC, Unity Pharmacy) to specific TCM halls (Sinchong Meheco).

Inclusion criteria were having the word “Panax” and/or “ginseng” on the packaging and being available in any of the shops mentioned above at the time of data collation.

The products were categorized into CPM, HS, or FS based on information provided by HSA website (the list of CPM products) (HSA, 2012c), the CPM labels on the products (MOH, 2002), or guidelines provided by HSA and AVA (HSA, 2012a, 2012b). After that, the ingredients listed on each product were studied to know the number of ingredients listed and the nature of them according to herbal, animal or other origins. The claimed indications of each product were compared to HSA legislations to find any incompliance with regulations. Other information available on the labels including recommended daily dosage, side effects, contraindications, cautions and interactions were also evaluated.

5.4. Results and discussion

The information on the package of products sold at five locations which were labeled with the words "Panax" or "ginseng" was documented (Table 5.1). In this study, the labeling information of 342 products was recorded in a database. The products with same name and brand were counted separately only if the ingredients, dosage forms, and/or usage information on packages were not the same. In the cases of different package sizes but same dose strength, ingredients and labeling, products were considered as repeated and only one of them was used for the study. Based on the mentioned criteria, 32 duplicate products and one which had no information in English on the labeling were excluded. The 309 included products were categorized in three groups (namely CPM, HS, and FS) based on HSA and AVA regulations (HSA, 2012a) (section 1.2.2).

Table 5.1. Number of products collated from each location

Location	Number of collated products
Sinchong Meheco	270
Unity Pharmacy, NTUC Healthcare Hougang Mall Branch	20
Guardian Health and Beauty Lot 1 Shopper's Mall Branch	18
GNC Lot 1 Shopper's Mall Branch	4
Fairprice 24 hours, HDB Clementi Branch	30
Total number of products	342[1]

[1] Including 32 repeated (duplicate) products and a product with no information (except the name) in English. The other 309 products were included in analysis.

Thirty six products which were not in the "end product preparation" form were categorized as food supplements including seasonings and ready-to-use herbal soups (HSA, 2012a). The remaining 273 products which were in end product preparation forms such as tablets, capsules, granules, powders, liniments, oral liquids, etc. were categorized into Chinese proprietary medicines or health supplements. A product was considered as Chinese proprietary medicine if it was listed in CPM list provided by HSA (HSA, 2012c) or it had the specific CPM label provided by HSA on its package (Figure 5.1). Among the collated products, 188 fulfilled the CPM criteria and the remaining 85 products were categorized as health supplements.

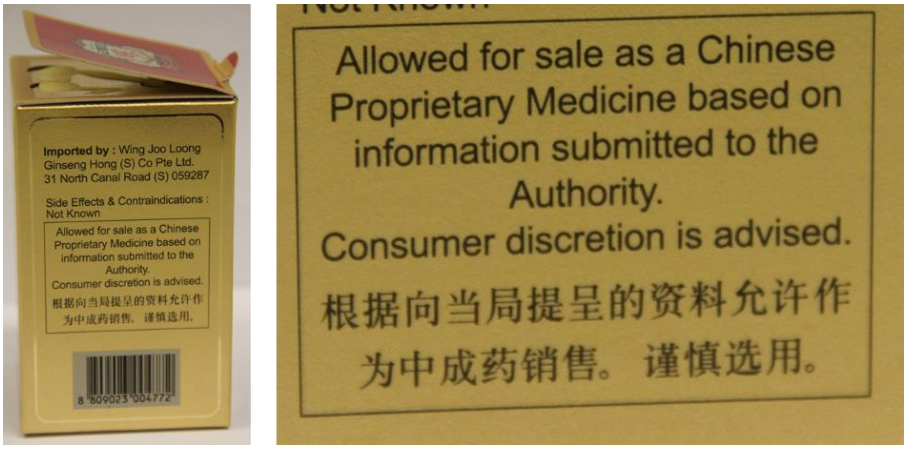

Figure 5.1. The CPM label on a surveyed product.

5.4.1. Products composition

As different plant species have different medicinal properties, it is very important to know the composition of each product. Hence, the products were further categorized based on the labeled composition of the *Panax* species or other herbs from other families referred as "ginseng" (Table 1.4 and Table 1.5 in section 0). Four species from *Panax* genus, namely *P. ginseng*, *P. quinquefolium*, *P. notoginseng* and *P. pseudoginseng*, and two species from other genera (*E. senticosus* and *G. pentaphyllum*) were found listed on product labels as ingredients. Figure 5.2 shows the number of collated products which listed each of these species in their ingredient lists.

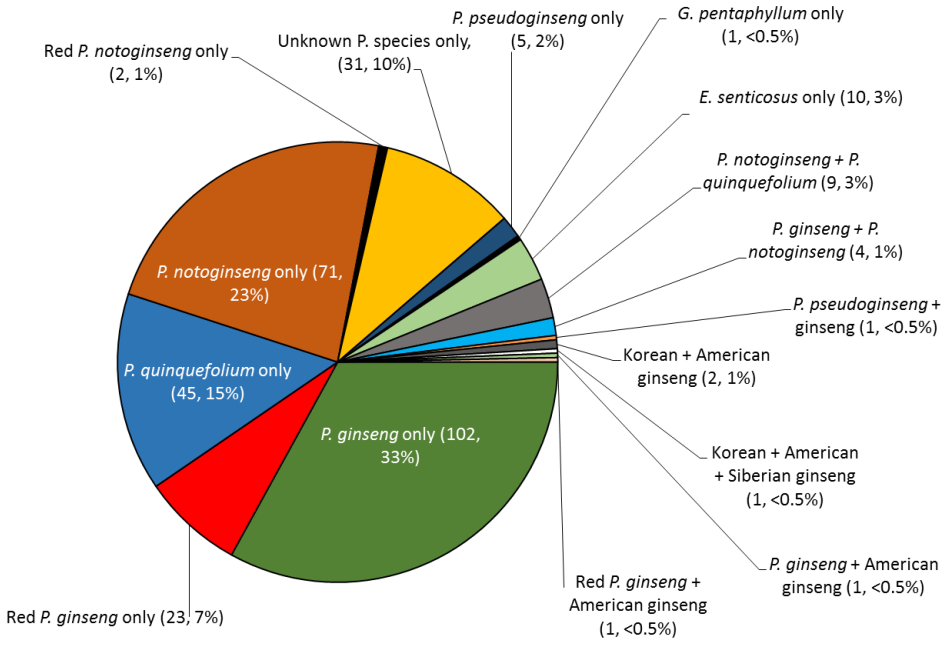

Figure 5.2. Presence of four *Panax* species (*P. ginseng*, *P. notoginseng*, *P. quinquefolium* and *P. pseudoginseng*), *E. senticosus* and *G. pentaphyllum* in the ingredient lists of products collated for this study.

The majority of the products (125, 40%) contained *P. ginseng*. this species was named in different ways on products including *P. ginseng* (16, 5%), *Radix ginseng* (74,

24%), “Chinese ginseng” (1, <1%), and “Korean ginseng” (34, 11%). All of these names were considered as *P. ginseng*. The next most common species was *P. notoginseng* (73, 24%), followed by *P. quinquefolium* (45, 15%). Eleven products had *Eleutherococcus senticosus* (Siberian “ginseng”) listed as one of their ingredients. Another product (“7 Leaf Ginseng Natural Health Tea”) contained *Gynostemma pentaphyllum,* which is sometimes called as “five-leaf ginseng” (D'jang, 1999) but not “seven”-leaf ginseng (please see section 0, Table 1.5). Since they satisfied our inclusion criteria, they were included in this study and categorized as “no *Panax*” group.

A discrepancy between the name of the product and the herbs listed in the ingredient list was observed in five products. They had the word “pseudoginseng” in their name but “notoginseng” in their ingredient list. These two species are considered different in some plant databases (Efloras; IPNI, 2012) and the same in some others such as Chinese pharmacopeia and plants database website (CPC, 2010; "Plants database," 2012). Although we had considered *P. pseudoginseng* as a separate species in this survey, in such cases of inconsistency between the name of product and the list of ingredients, the categorization was based on the ingredients list.

Eighteen products contained two species of *Panax* genus or other species which were referred as “ginseng” and one product had a combination of “Korean ginseng”, “American ginseng” and “Siberian ginseng” (*E. senticosus*) in its ingredients list.

It was found that, for 32 products, the ingredient was mentioned only as “ginseng” including a product which had listed *P. pseudoginseng* and “ginseng” in its ingredient list. The word “ginseng” is sometimes loosely used to refer to different species (section 1.3). When it was not clear which specific species the products contained, they were separately categorized as “unknown *Panax* species”.

A product, “Yunnan Baiyao Capsules”, did not have the word “ginseng” or “Panax” on its package. Therefore, although it is a very famous product containing *P. notoginseng* with a protected formula, it was not included in our study. Another product, “Muscle relaxing Herbal Analgesic Oil”, had the word “Tian Qi” (San qi) on its labeling and no “Panax” or “ginseng”. This word refers to *P. notoginseng* in Chinese (CPC, 2010; Zhu, 1998). As it did not satisfy the inclusion criteria, it was not also included in this study. This shows that although most products have reported their *Panax* ingredients properly, there is still some room for improvement especially for few incomplete or misleading ingredient lists.

5.4.2. Basic product label information

The labeling requirements for CPM, HS and FS have already been presented in Section 1.2.2 (Table 1.1, Table 1.2 and Table 1.3). The basic information on the labels of collated products was compared to respective requirements and their compliance was evaluated. Table 5.2 summarizes the percentage of each group of products providing the relevant information.

Considering the information which has to be present in the outer label of products (section 1.2.2), more than 96% of the CPM products, more than 84% of the health supplements, and more than 88% of the food supplements comply with the respective regulations. These results are consistent with a much smaller study in UK showing that 87% of 68 products containing herbal ingredients had provided the basic information on their package or in the leaflets based on the local legislations (Raynor et al., 2011).

It should be considered that the labeling requirements are applicable to the outer label, inner label and package insert. As some products are sealed, it is impossible to

have access to the inner label and package insert without opening the packages. For this study, all information has been based on whatever was available without damaging the packages.

Table 5.2. List of required information on product labels and the number of products in different groups which provided the relevant information

Information	Number of products with the relevant information			
	CPM	HS	FS	Total
Name	188(100%)	85(100%)	36(100%)	309(100%)
Brand	187(99.5%)	81(95.3%)	30(83.3%)	298(96.4%)
Batch number	182(96.8%)	72(84.7%)	17(47.2%)	281(90.9%)
Manufacturer	182(96.8%)	79(92.9%)	36(100%)	297(96.1%)
Expiry date	183(97.3%)	73(85.9%)	32(88.9%)	288(93.2%)
Name of ingredients	187(99.5%)	76(89.4%)	35(97.2%)	298(96.4%)
Recommended daily dosage	176 (96.2%)	51 (69.9%)	NA	227 (88.7%)
Indications	178(94.7%)	53(62.4%)	6(16.6%)	237(76.7%)
Side effects	1(0.5%)	3(3.5%)	0(0%)	4(1.3%)
Contraindications	91(48.4%)	12(14.1%)	3(8.3%)	103(33.3%)
Cautions	37(19.7%)	9(10.6%)	0(0%)	46(14.9%)
Interactions	38(20.2%)	0(0%)	1(1.2%)	39(12.6%)
Total	188	85	36	309

5.4.2.1. Name, brand, batch number, manufacturer information and expiry date

As presented in Table 5.2, all collated products had their name on their packages and most of them (96.5%) had mentioned their brand. Although all of the labeling information has to be in English (MOH, 2008a), labels of twelve products were mostly in Korean. Therefore, the information on their packages was not understandable by the

majority of consumers in Singapore. Indeed, this fact could affect their marketing as well.

About 10% of the products (28) had not reported their batch numbers in their labels. Batch number is a very important piece of information, which helps researchers and others track production series. Information on manufacturer was reported in 96.1% of the collated products (297).

Expiry date was generally present and was found to be missing in 5 CPMs (2.6%), 12 health supplements (14%) and 4 food supplements (11.1%). It is an important piece of information especially for health and food supplement which are consumed for health or medical purposes. Since using expired products can be harmful, it is essential to report the expiry date.

Absence of the basic information such as a proper name in English, batch number and expiry date makes the products difficult to track and susceptible to be harmful. It also increases the risk of misuse and potential adverse effects.

5.4.2.2. Ingredients

Among 309 collated products, 298 had listed their ingredients (Table 5.2). These ingredients could be herbal ingredients, animal originated ingredients, minerals or vitamins, or excipients. Figure 5.3 shows the number of listed ingredients on the products. The majority of products reported consisting of 5-10 ingredients in their labels. The maximum number of listed ingredient was 64 belonging to a product named "American Wisconsin Ginseng Root Tea" from Prince of Peace® brand. This CPM product listed 49 herbs, 12 ingredients with animal or mineral origins, and 3 excipients.

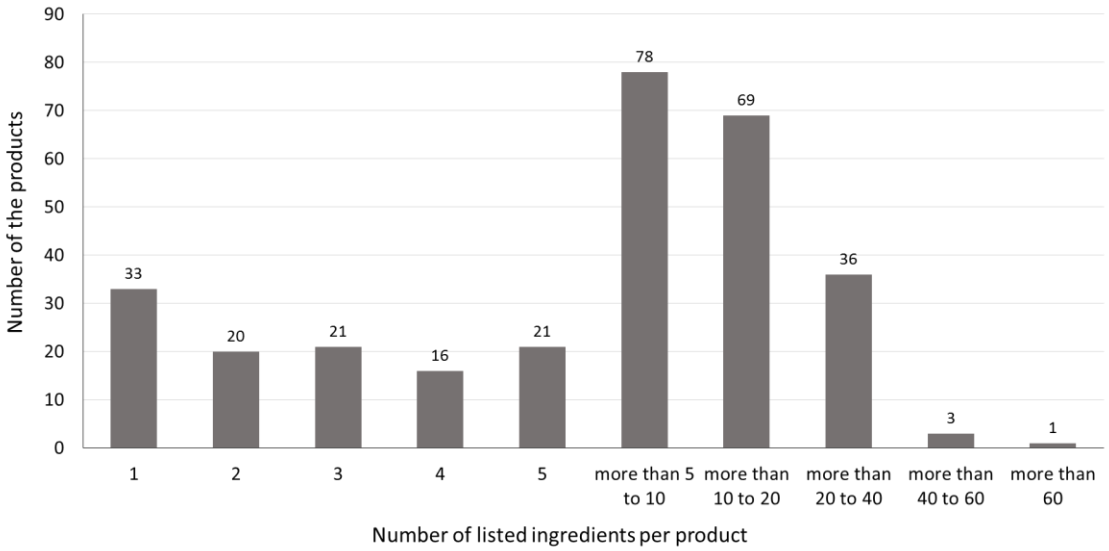

Figure 5.3. Number of listed ingredients on the collated products

It should be kept in mind that in TCM, herb is a common word not only used for plants but also including animal products (Chang et al., 2000). Table 5.3 shows the animal originated ingredients listed in labels of collated products and the definition of each ingredient. The definitions were obtained from various sources (Bensky et al., 2004; Clark et al., 1971; CPC, 2010; Wilson et al., 2005; Wu, 2005; Zhao, 2004).

The number of listed ingredients excluding excipients is presented in Figure 5.4. It includes herbal or animal originated ingredients, minerals and vitamins. Processed herbal products such as “Fujiflavon” (a soy bean extract) or “caffeine” were counted in this group.

Table 5.3. List of animal originated ingredients listed on the collated products

Ingredient	Remarks
Agkistrodan / A. japonicae	Snake
Arisaema cum bile	Arisaematis (herbal) + bile of oxen
Beeswax	Bees wax
Bombyx batryticatus	Stiff silk worm
Bombyx masculus	Male silk worm
Calculus bovis	The gall stones of Oxen
Carapax et Plastrum Testudinis	The shell of *Chinemys reevesii* (a turtle)
Carapax trionycis	Water turtle shell
Cauda cervi	The tail of deer
Colla Corii asini	The skin of donkey
Colla Cornus cervi	The skin of horn of deer
Concha Haliotidis	Sea snail shell
Concha Ostreae	Oyster shell
Cornu Bubali	The horn of buffalo
Cornu Cervi degelatinatum / Cornu Cervi pantotrichum	Deer horn
Cornu Cervi parvum	Proximal part of horns of deer
Cornu Saigae tataricae	The horn of Saiga (an animal similar to horse)
Dens draconis	Fossilized teeth
Eupolyphaga seu steleophaga	Dried female beetle
Foetus Cervi	Deer fetus
Formica fusca	Ant
Gecko	Lizard

To be continued on the next page

Cont. Table 5.3

Hirudo	Leech, Blood sucking worm
Honey	Honey
Ligamentium Cervi	The tail of deer
Lumbricus	Earth worm
Mel (feng mi)	Honey
Moschus	Dried pungent secretion of a deer
Ootecha mantidis	Egg case of praying mantis (praying bug)
Os draconis	the skeleton fossil of prehistoric mammals like hipparion (ancient horse), rhinoceros, deer, oxen, etc.
Os Sepia	Cuttlefish skeleton
Penis Canitis	The reproductive organs of male dogs
Penis Cervi	The reproductive organs of male deer
Penis Otariae	The reproductive organs of male seals
Periostracum Serpentis	The skin of snake
Pheretima	Earthworm
Propolis	A part of beehive
Pullus Cum Osse Nigro	Chicken egg
Royal jelly	The oral secretion of worker bees used as the diet of queen bee
Scolopendra	Centipede
Scorpio	Scorpion
Sheng yu	Fish
Snake gall	Bile of snakes
Testis et Penis Bovis	The reproductive organs of male oxen
Testis et Penis Canis	The reproductive organs of male dogs
Young deer	Young deer
Zaocys	Snake

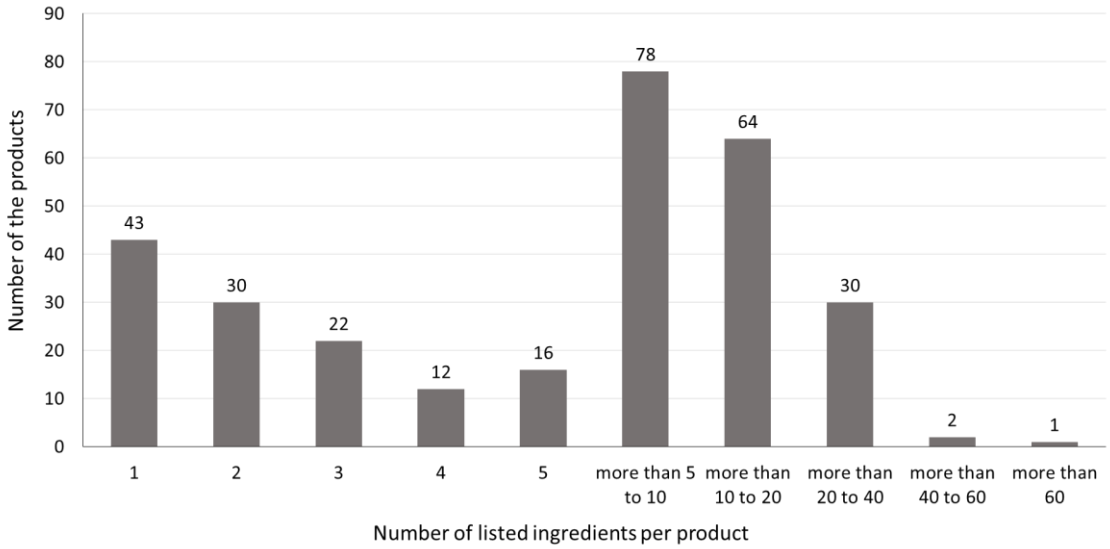

Figure 5.4. Number of herbal and animal originated ingredients, minerals and vitamins listed on collated products

In Traditional Chinese Medicine, fungi are often considered as plants (Bensky et al., 2004; Chang et al., 2000; Zhu, 1998). Based on this, all ingredients with plant or fungal origin (such as *Poria, Glossy ganoderma, Astragalus membranaceus, Cordyceps*, etc.) were also categorized as herbal ingredients. Two products had reported "Massa Fermentata" as one of their ingredients. As "Massa Fermentata" is actually made from 6 different herbal material including *Polygonum hydropiper* (or *P. flaccidum), Artemisia annua, Xanthium sibiricum, Semen Armeniacae* (Xing Ren), *Semen Phaseoli* (Chi Xiao Dou) and wheat (Chang et al., 2000; Hijikata, 2006), it was counted as 6 ingredients. By excluding excipients, ingredients with animal origin, vitamins, minerals and processed herbal ingredients (such as oils), Figure 5.5 shows the number of herbal ingredients listed on collated products.

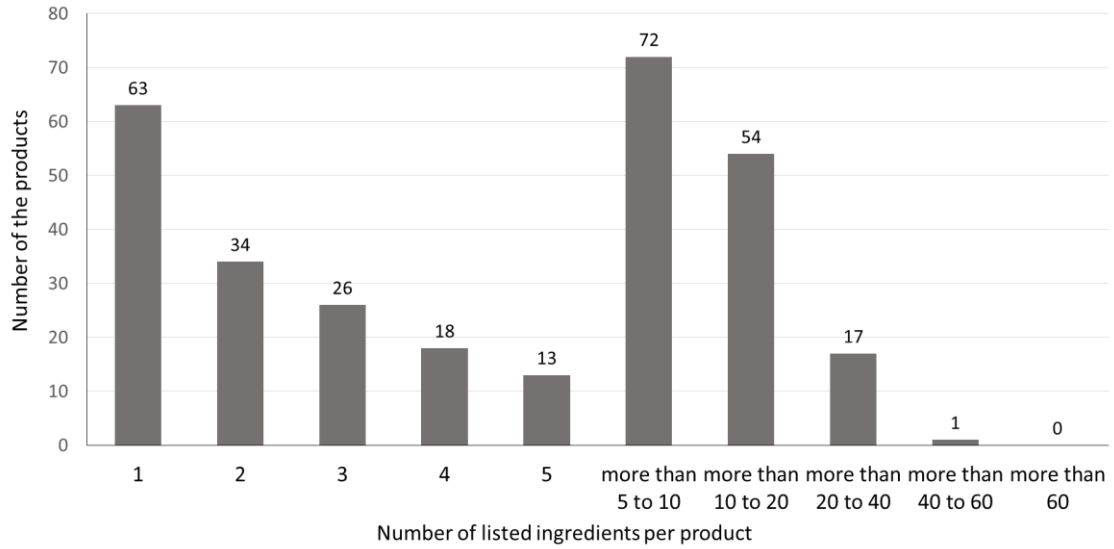

Figure 5.5. Number of listed herbal ingredients on the collated products (note that none of the products have more than 60 herbal ingredients).

Having one single ingredient decreases the risk of potential herb-herb interactions. In this study, there were 43 products with one single listed ingredient, among which 36 were in CPM category, 5 were HS and 2 products were categorized as FS. Figure 5.6 shows the herbal ingredient of 41 single ingredient CPM and Health supplements.

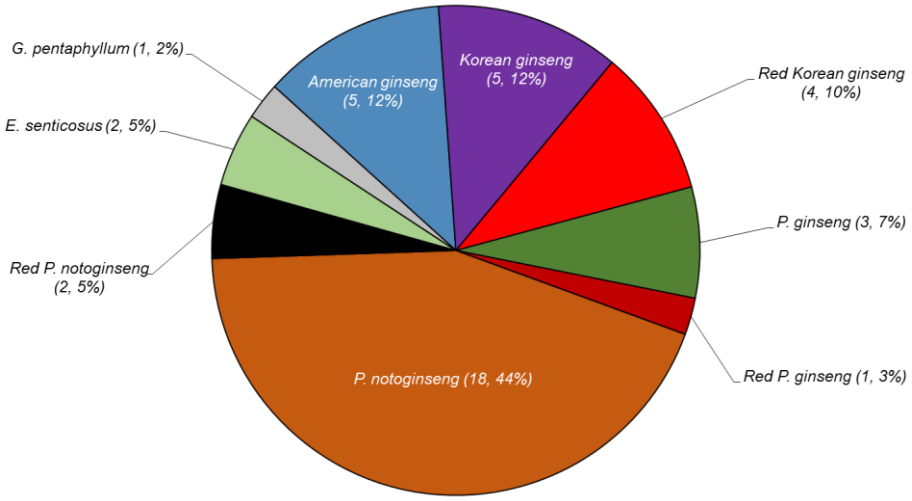

Figure 5.6. Presence of four Panax species (*P. ginseng, P. notoginseng, P. quinquefolium* and *P. pseudoginseng*), *E. senticosus* and *G. pentaphyllum* in health supplements and CPM products with single listed ingredient.

Majority of single ingredient products contained *P. notoginseng* (20, 48.8%) followed by *P. ginseng* (13, 31.7%). Having one single ingredient lowers the risk of herb-herb and herb-drug interactions and ease the chemical analysis of the products for any research or legal purposes.

5.4.2.3. Dosage forms and recommended daily dosages

The majority of health products collated for this study were in solid oral dosage forms (200, 73%) and the most common solid oral forms were capsules followed by tablets (Table 5.4). One of the CPM products, named Yunnan Baiyao Tincture, could be used both orally and topically. Thus, it was counted twice, both as liniment and as oral liquid.

Table 5.4. Distribution of dosage forms among the health products (CPM and Health Supplements)

Dosage form		CPM	Health Supplements	Health products with single listed ingredients
Category	**Form**			
Oral solid	Capsules	85	16	13
	Tablet, Caplet or Pill	40	19	8
	Powder	31	1	9
	Granule	4	0	0
	Slice	0	2	0
	Softgel	0	2	0
Oral liquid	Oral liquid	18	24	4
	Tea	3	9	5
	Sachet	2	0	2
Topical	Liniment	6	6	0
	Plaster	0	6	0
Total		189*	85	41

* There is a CPM product which can be used either orally or topically.

Dosage forms such as capsules and tablets facilitate proper dosing as they are convenient for consumption. On the other hand, powders and granules may cause some difficulties regarding the measurement of dosage. Among the collected products, 36 were in powder or small granular forms and their dosages were within the range of 1.5-6 grams per dose. Such dosing method can be very difficult to measure and may increase the risk of over-dosage or insufficient treatment. Providing spoons is a way to tackle this problem for powders and granules. Among 18 unsealed products in powder or granule forms, no one had provided any measuring tool. Since being provided in pharmaceutical presentations (dosage form) is one of the criteria used to differentiate health products from FSs (HSA, 2012a), food supplements were excluded from this part of study.

More than 96% of oral CPMs had mentioned their recommended daily dosage while such information was stated in the labels of less than 70% of the health supplements. Under Singapore regulations, recommended daily dosage, which is required for CPMs and Health Supplements, is not applicable to Food supplements and the topical health products. Therefore, food supplements were excluded from this analysis.

5.4.2.4. Indications:

About 95% of CPM products had stated the indications of usage clearly. This proportion was 50% for health supplement and less than 14% for food supplements. Table 5.5 gives an overview of indications listed by products collated in this study. Eleven health supplements and one food supplement had mentioned their indications indirectly. It means that after explaining the traditional usage of some herbs, they had

mentioned that the product contains those specific herbs. In other words, they explained the traditional or pharmacological uses of some of the herbal ingredients rather than stating the direct indications for the whole product.

A total of 636 indications were reported in all products. They are categorized in different groups in Table 5.5. Since traditional medicine is based on some theories and concepts (such as five element theory, qi concept, yin-yang theory) which are different from conventional medicine (Chen, 2004; Kefu, 2007), the indications were first categorized as based on traditional medicine or conventional medicine. Most products had claimed to be effective for some traditionally defined health problems such as improving yin-yang balance, nourishing different Zang-Fu organ systems, enhancing Qi, etc. These conditions are included under "suitable for traditionally defined diseases or general health" in this study.

Stated indications which were based on conventional medicine were categorized based on a list adapted from international classification of diseases version 10 (ICD-10) (WHO, 2010). Based on this categorization, improvement in circulatory system followed by analgesic effects was the most common reported conventional indications. The effect on "mental and behavioral disease and diseases of the nervous system" was the next most common indication stated by a total of 59 products.

One of the most important issues in stating the indications was mixing the traditional and conventional medical approaches to diseases. In TCM approach, besides the differences in the main concepts and theories, the body-organ system (Zang-Fu) is different from conventional medicine (Yuen et al., 2012). In other words, although there are some similar words such as "spleen", "kidney", "heart", "lung", "blood", etc. in both systems, the anatomical and physiological meanings of them in TCM may not be

the same (Chen, 2004; Kefu, 2007). In our study, regulation of blood circulation (categorized in circulatory system) was a very common claim in labels of products (52 products out of 311), which can have different meanings in traditional and conventional medicines. Consequently, the mixture of traditional and western approaches on the label of a product can cause significant misunderstanding and confusion especially for consumers who are not familiar with these two medical systems and the differences in their approaches.

Table 5.5. Indications listed on the product labels

Indication	Number of products			
	CPM	**HS**	**FS**	**Total**
Suitable for traditionally defined diseases or general health	152	42	4	198
Affecting the circulatory system	63	13	2	78
Analgesia	50	12	0	62
Affecting mental and behavioral condition and the nervous system	49	8	2	59
Suitable for diseases of musculoskeletal system and connective tissue	39	17	0	56
Affecting blood, blood forming organs & immune mechanisms	43	8	2	53
Affecting the digestive system	28	2	0	30
Affecting the genitourinary system	24	3	0	27
Affecting the skin and subcutaneous tissue	17	5	0	22
Affecting endocrine, nutritional and metabolism	18	3	0	21
Affecting the respiratory system	9	1	0	10
Affecting pregnancy, childbirth and the puerperium	6	2	0	8
Against certain infections or parasitic infestations	5	1	0	6
Affecting the eye and adnexa	4	1	0	5
Anti-neoplasm	0	1	0	1
Total	507	119	10	636

5.4.2.4.1. Nineteen prohibited claims

Based on Singapore legislations, CPM or HS should not make any claims regarding the 19 prohibited serious health conditions (sections 1.2.2.1 and 1.2.2.2). In this study, 23 products were found to make direct or indirect referral to the mentioned conditions.

Among them, two products had claimed to be effective for wasting and thirsting syndrome, which is a TCM definition for diabetes (Xiao Ke) (Tao et al., 2007). There was a claim regarding anti-cancer effect. It was written on a plaster used for contusion and musculoskeletal pain that the product has "antioncotic" effects. Such a claim can be seriously misleading and confusing for consumers. Few products had claimed to be effective on kidney diseases. Those products which had pure traditional approach to kidney (Chen, 2004) were not considered to have prohibited claims. Because, as mentioned before, the traditional approach to kidney is different from conventional one and HSA guidelines are based on conventional approaches. There was a CPM product claiming to be effective on "symptoms of pitting edema in the limbs and face, heaviness in the knees and abnormal urination due to kidney deficiency". This claim was clearly indicating the conventional renal deficiency and was considered as a prohibited claim. There were 18 products claiming to have therapeutic effects on menstrual problems including 16 claims to regulate menstruation, 9 claims to treat leucorrhea and 6 claims to subside dysmenorrhea. Finally, one of the health supplements had claimed to improve "libido in men".

This result shows the importance of post-marketing surveillances by HSA. Based on HSA regulations, products which make any of these 19 claims will be recalled from sales by authorities.

5.4.2.4.2. Regulations specific to health supplements regarding their indications of use

The actions and indications listed on 86 health supplements collated for this study were compared to Singapore regulations. As mentioned in section 1.2.2.2, any claim of therapeutic effects on any medical condition is prohibited for health supplements. Additionally they are not allowed to imply to be have any memory enhancing, anti-ageing or sensual enhancing effects, etc.

Among studied products, six had claimed therapeutic effects against specific medical conditions including rheumatism and arthritis, eczema, tinea and seborrhea capitis. Four products had claimed to improve memory or brain performance. Five products had referred to some anti-ageing effects and two products had referred to sexual function and relationship. Finally, two products had claimed to be safe or to have been safely used.

Furthermore, among 31 objectionable terms and claims listed by HSA (HSA, 2012b), the word “guaranteed” was found in two products, the word “effective” was found in one, the word “anti-ageing” in the labels of three HSs and “longevity” in two others. In addition, the phrase “boost immunity” was claimed by one and “enhance immunity” by two. Finally, “libido” was found in one of labels.

5.4.2.4.3. Regulation specific to food supplements governed by AVA

Based on AVA regulations, none of food products is supposed to have any therapeutic or other medical claims (AVA, 2011). There were three food supplements making claims to be effective for special health conditions. Two of them had claimed

improvement of blood circulation, immunity and body resistance and it was written in the label of a spice containing "ginseng" (the species was not specified) that the product can "enhance the memory and help relieve stress". Although there are reports on memory enhancing and anxiolytic effects of *Panax* species (Jesky et al., 2011; Perry et al., 2011; Qi et al., 2011), such claims from a food supplement is not acceptable.

5.4.2.5. Side effects, contraindications, cautions, and interactions:

Information on the side effects, contraindications, and interactions (if any) should be presented on the labels of all CPM and HS products, based on Health Products Act (MOH, 2008a).

Among 188 CPMs studied, 137 products (72.9%) had reported that "there is not any known side effect" or "side effects are not known". On the other hand, three (1.6%) had claimed to be "free of side effects". Only one product had reported a potential side effect, which was impairment of yin and blood by long-term usage of the product. The rest of products (47, 25%) had not mentioned side effects at all. Moreover, among 85 health supplements, the majority (78, 91.8%) had not indicated any side effect, three (3.5%) had reported potential side effects including "transient flushing due to nicotinic acid ingredient" and "allergic reactions", and 4 products (4.7%) had mentioned that "the side effects are not known". Although the side effects of many natural products are not reported yet, it is important to state this uncertainty in the labels of products. Such statements may work as an alarm to consumers especially those with specific health conditions to be more cautious about any potential adverse effects.

Some contraindications were reported in the labels of 48.1% of CPM products and 14% of health supplement as well as 8.3% of food supplements (Table 5.6). Only three

CPMs had claimed to have no contraindication and the majority of products (51.1%) had not mentioned contraindications at all. In the labels of 21.7% of CPM products and 2.3% of health supplements contraindications were mentioned as "unknown", which may be the best form of reporting when there is no available data.

Table 5.6. List of contraindications reported in the labels of surveyed products

No.	Contraindication	Frequency
1	Pregnancy, planning for pregnancy or lactation	77
2	Cold, influenza, flu, common cold, fever or pyrexia	18
3	Allergy, asthma or hypersensitivity to ingredients	10
4	Liver dysfunction	8
5	Kidney dysfunction	7
6	TCM conditions such as yin deficiency, excess and heat syndrome, etc.	4
7	Heart problems, heart attack or hypertension	4
8	Childhood	2
9	Acute bleeding	2
10	Diarrhea	2
11	Others (during menstrual period, sturdy[1] patients, diabetes mellitus or nose pharyngalgia)	4

[1] muscular and fit! It is mentioned on one of products that "sturdy" (muscular) patients should avoid using the product.

The precautions were also reported for 19.6% of CPM products and 10.5% of health supplements. Table 5.7 shows the precautions reported by the studied products. The most common precaution reported by products was pregnancy or planning for it.

The possibility of any food-drug interactions was reported by 38 CPM products (20.1%) and one (1.2%) health supplement. The most common reported interactions were with specific types of food such as raw, sour, or cold foods (20 products), pungent or spicy foods (18 products), fried, greasy, or oily foods (10 products), sea foods (3 products), broad bean, sugary foods and salt (2 products each), and peanut and irritant foods (one product each). Two products had mentioned possible interactions with

alcohol and cigarette while six products had listed conventional drugs or traditional herbs as possible interactions. The conventional drug reported for possible interaction was warfarin and the medicinal herbs, which were stated for potential interactions were *Rhizome et radix veratri*, *Fructose gleditsiae, Faeces trogopterori* and radish.

Table 5.7. List of cautions reported on the labels of Chinese proprietary medicines and health supplements

No.	Caution	Number of products
1	Pregnancy, nursing or planning for pregnancy	23
2	Childhood	11
3	Allergy, hypersensitivity or asthma	4
4	Hypertension	4
5	Taking other medications	3
6	Elderly	3
7	Kidney problems	3
8	Before surgery	2
9	Long-term usage	2
10	Gastrointestinal problems	2
11	Menstrual problems	2
12	Others including skin problems, bleeding tendency, weakness, common cold, liver problem	6

In general, it was stated in the labels of most products that the side effects, contraindications, or interactions are not known. Such statement is acceptable since there is not enough evidence of safety or toxicity for most natural products and traditional medical formulas. However, claims to have no side effect, contraindication, cautions or interactions need more attention. It is worth considering that people generally hide their usage of complementary medicines to their physicians (Kang et al., 2012; Tasaki et al., 2002). This lack of communication can cause major problems such as severe drug-herb interactions (Smith et al., 2004) especially when the potential side

effects are not reported in product labels, the main source of information for OTC products.

These results highlighted a much better product labeling situation in Singapore market compared to few similar reports from other countries, although there is still room for improvement. In a similar but much smaller study done in the UK, among 7 products containing *P. ginseng*, only one precaution was stated and none of them had reported any side effects or contraindications (Raynor et al., 2011). In another study in Brazil, 8 products containing "ginseng" were evaluated regarding their pharmacological claims. The authors found no homogeneity among products in their indications, adverse effects or interactions. In addition, the claims were not supported enough by available scientific data (Auricchio et al., 2007).

5.4.3. Misleading claims and information on the labels of the products

The products were also evaluated for misleading claims in their labels. Although such claims were not against any regulatory guidelines provided by HSA and AVA and they cannot be considered as illegal, it is possible that such claims cause misunderstanding and inappropriate usage. Here, some of misleading claims found in collated product labels are presented.

One product had claimed that it can help subside the "stabbing pain in the anterior pectoral region" caused by "coronary heart diseases and angina pectoris". In TCM, stabbing pain in chest is one of the symptoms associated with heart problems (Kefu, 2007) while coronary heart diseases rarely present with stabbing pain based on conventional medicine (Nabel et al., 2012). Furthermore, a product in plaster form claimed to "cure rheumatism". Rheumatoid arthritis is a chronic almost non-curable

inflammatory disease (McInnes et al., 2011). There are similar misleading and exaggerated claims such as “controlling body cells from being abnormal”; “regulation of the endocrine system”; “relieve from jaundice and other inflammation diseases”; being “effective for all types of constipation”, “effective for all kinds of inflammation, carbuncles and anonymous swelling boil”, “a safe and reliable remedy for the treatment of all skin diseases”, or “all kinds of skin pruritus”; or to treat “different kinds of hemorrhagic symptoms” or “gynecological diseases”. As everybody knows, each of these groups of diseases consists of many different disorders and it is hard to believe that one particular product can cure or be effective on all of them.

Moreover, there were some other claims found on the labels that could mislead consumers. For example, “acceptability [is] tested by world class sports players”, “[the product is] used by professional sportsmen”, “film stars, singers, and models use [this product]” or “certain groups of people have a special need for [this particular product] including business men, office workers, the older adults, athletes and sportsmen”, etc. Even though this kind of claims is not prohibited by HSA, having misleading information on products would be dangerous for consumers who are unable to test the reliability of claims. Such claims and information can lead in wrong usage of products by consumers. It is always better to provide scientific reference if a product wants to make a specific claim.

5.4.4. Price

Among the collated products in our study, the most expensive one was a health supplement called “Il Hwa Korean Honeyed Ginseng” which costed S$338 for a box and the cheapest one was a spice (FS), named Nature`s Cool JiaJia Herbal Tea-Less

Sugar, costing just S$0.70. Because of differences in package sizes, the raw prices printed on the packages is not representative of their cost per day. Hence, the prices were normalized based on the package sizes and daily recommended doses. Furthermore, the topical products and those without recommended daily dosages were excluded from this normalization. For food supplements, the cost per day was considered as the cost per suggested serving unit.

Based on this, the maximum cost per day was S$45.60 belonging to a CPM and the lowest one was S$0.24 for another CPM. The average cost per day was S$2.75 for CPM users, S$2.99 for HS users and S$3.53 for FS users. Table 5.8 shows the top ten expensive products after normalization to the package size. These results suggest that products containing "bird's nest" or "cordyceps" are more expensive than others. In other words, the *Panax* species have less effect on the final price of the product rather than its other ingredients.

Table 5.8. List of the top ten most expensive products after normalization to daily dosage

Rank	Type	Brand	Name	Daily price (S$)	Unit price (S$)
1	CPM	Ferragold	Essence of Bird`s Nest Ginseng & Cordyceps	45.60	22.80
2	HS	Ferragold	Shen Yu Jing with Cordyceps, Wild Ginseng & Radix Astragali	41.60	20.80
3	CPM	Mei Hua	Buyao Jing with Duzhong Cordyceps Baji	20.00	20.00
4	CPM	Mei Hua	Cordyceps Essence with American Ginseng	20.00	20.00
5	Food	E-Health	Essence of Chicken with Ginseng and Cordyceps	20.00	20.00
6	Food	Huiji	Huiji® Fish Essence with American Ginseng, Cordyceps & Radix Astragali	18.00	18.00
7	CPM	Shan Cheng Brand	Jing Zhi Wu Ji Ren Shen Bai Feng Wan	12.00	6.00
8	Food	Mei Hua	Bird`s Nest with American Ginseng	8.33	50.00
9	CPM	Mei Hua Brand	Bai Feng Wan Paoshen Chongcao (American Ginseng with Cordyceps pills)	7.80	46.80
10	Food	Brand`s®	Bird`s Nest with American Ginseng & Rock Sugar	7.80	46.80

Among the products with single ingredients, the highest price per product was S$176 for “Korean Red Ginseng Extract” from Korea Ginseng Corp.® followed by S$110 for “Radix Panacis Quinquefolii (D2470)” from Sanjiu Enterprise Group®. After normalizing to the package size, the most expensive product was still “Korean Red Ginseng Extract” costing S$5.33 per day followed by “Steamed Tienchi Tablets” from Camellia Brand costing S$3.2 daily.

Price is one of the most important factors affecting the marketing of a product (Foroncewicz et al., 2011). Furthermore, there is a general belief that cheap products are not as good as expensive ones. In a study in the US, the information stated on the labels of the products were compared to the available literature. The label information was consistent with textbooks in only 43% of herbal products. They also found that the price per recommended daily dose was a significant predictor of consistency (Garrard et al., 2003). It can be a sign of good manufacture practice, which makes the products not only more reliable but also more expensive. However, this statement can hardly be generalized to most products.

5.4.5. Typographical and grammatical errors

The found typographical and grammatical errors were categorized into two types. The minor grammatical and spelling mistakes could hardly cause misunderstanding or promote improper usage of products. They just showed lack of good manufacture practice. On the other hand, significant errors could be misleading and confusing. They could also cause dangerous adverse effects by improper usage especially in less educated and more susceptible consumers like older adults.

Minor mistakes were found in a large number of products (93, 49.2% of CPMs, 31, 36.0% of health supplements and 19, 52.8% of food supplements). For example “nad” instead of “and”, “palce” instead of “place”, “founction” instead of “function” or “prperation” instead of “preparation”, or grammatical errors such as “original” instead of “originally”, “relief” instead of “relieves”, “temperate” instead of “temperature” or “out of reached” instead of “out of reach”.

Significant and potentially dangerous errors were found in fewer product labels. A mistake was found in the ingredient list of a product where “Radix Panax Rehmanniae” was listed as one of ingredients. *Rehmannia glutinosa* is a traditionally used plant belonging to *Scrophulariaceae* family (Zhang et al., 2008c), which is not related to *Panax* family. Since different herbs have different pharmacological actions and dissimilar adverse effects and potential interactions, it is very important to state the correct name of herbal ingredients. As mentioned in section 5.4.2.4.1, a plaster used for contusion, had claimed to be “antioncotic”. If it is a typographical error (which seems to be), it can be extremely misleading and dangerous. In another product, “calcium lactas” and “zinci gluconas” were reported in ingredient list. “Zinci glucanas” is the Latin word for “zinc gluconate” but the Latin word for calcium gluconate is “calcii gluconas”.

It is very important to provide clear and understandable information on the labels of products. These labels should be free of major spelling and grammatical errors, even though minor mistakes can be ignored. In addition, the presence of typographical and grammatical errors indicates the lack of enough care and attention to details needed to produce a good quality product.

5.5. Conclusion

The aim of this part of study was to collate and evaluate the information provided on the labels of 309 products containing the word “Panax” or “ginseng” in the Singapore market. With regards to local legislations, more than 96% of CPM products, more than 84% of health supplements, and more than 88% of food supplements comply with respective basic requirements. The only exception was the information on recommended daily dosage. Only about 69.9% of the oral health supplements provided such information on their labels. On the other hand, almost 10% of CPM products, about 30% of HS and 10% of FS had made some kind of claims, which is not recommended by regulations.

Such products are among the most used supplements and herb based CAM products in the world and also in Singapore, studying them can give us a general information about the whole herb products in the market. The results of this study showed that although about half of products had minor errors in their labels, the overall information provided on packages was clear and understandable in most of products. Few products had more significant errors in their labeling, which could mislead the consumers. In addition, the public and health professionals can play an important part in reporting to the authorities any products with prohibited claims. At the same time, HSA and AVA will continue monitoring the market to help manufacturers provide more comprehensive information on their products and to improve safety and quality of products.

In this work, five shops providing herbal products were visited to collect the selected products. There may be some other products in the market which were not present in these five shops. Such products were not included in this study. Another

limitation of this work is that, the information provided in inner label and package insert of sealed products were not recorded because it was out of scope and budget of the project to purchase all available products. The other limitation of the work was the time and budget limitation to evaluate the different claims of the products regarding their ingredients, indications and toxicity. Such studies can provide a better understanding of the reliability of information provided in the label of available herbal products in the market.

Finally, since labels of OTC products have important effect on their public use, it is important to increase the public awareness about the importance of accuracy of the information provided on the labels of products in a way that they can wisely choose the products they use and prevent the inappropriate usage of a health product.

CHAPTER 6. The effects of ginsenoside Rg1 on medial prefrontal cortex

6.1. Introduction

As mentioned in the section 1.3.2.1.1 ginsenoside Rg1 is a known neurostimulatory saponin and one of the most abundant chemical constituents of *Panax* species, the most commonly used group of medicinal herbs among older adults in Singapore (CHAPTER 4). Its pharmacological effects on different systems and diseases have been studied including the cardiovascular, metabolic, immune, genitourinary and neurologic systems and premature ageing, abnormal blood lipid profile, cancer, Parkinsonism and Alzheimer's disease (Chang et al., 2000). Among them, its effects on the neurological system and neurocognitive disorders might be more important and interesting because of the high global burden of these diseases on the societies and the lack of proper curative and preventive treatments for most of them (Murray, 2013).

Several studies have tried to explain the mechanisms of neurological actions of ginsenoside Rg1. Some researchers focused on its anti-inflammatory effects, which can protect neurons against environmental assaults (Chen et al., 2011b; Liu et al., 2011b; Tang et al., 2011). Others suggested some molecular pathways to be affected by Rg1 such as caspase-3 (Wei et al., 2008), NF-κB (Chen et al., 2012a) and ERK1/2 (Ge et al., 2010; Shi et al., 2009) pathways. In addition, there are a few *in vivo* electrophysiological studies available reporting its effects on neuronal and synaptic activities. Among them, Wang and Xu reported that Rg1 can stimulate the "perforant

path-dentate gyrus" pathway in the rat hippocampus (Wang et al., 2001b; Wang et al., 2009c; Xu et al., 2007).

Medial prefrontal cortex is a bilateral brain structure, which receives neuronal projections from various parts of the brain (Groenewegen et al., 1997). It has had the highest development during the evolution and is the main brain region differentiating humans from other animals (Wallis, 2012). This important brain region integrates complex information from different brain regions (cortex, hippocampus, brainstem, etc.) to maintain and modulate the emotion, cognition and reward processing (Lim et al., 2010a). In addition, decision making and integrating emotions with specific memories (working memory and fear memory) are performed in prefrontal cortex affected by direct projection from hippocampus (Farooq et al., 2013).

The neurological activity of medial prefrontal cortex can be studied *in vivo* using electrophysiological analysis (section 1.5.2). This can be either by studying the spontaneous firing rate of medial prefrontal cortical neurons or by analyzing the neuronal projections from other brain regions such as the hippocampus (Farooq et al., 2013).

Furthermore, histochemical studies can also be used to evaluate the function of this brain region (Verma et al., 2007). In 1988, Halazonetis introduced the evaluation of expression of c-Fos as a potential histochemical indicator for analyzing cellular activity (Halazonetis et al., 1988). As mentioned in section 1.5.1, c-Fos is an immediate-early gene up-regulated rapidly and transiently upon stimulation of different cells (Durchdewald et al., 2009). This protein is involved in the transcription process (producing mRNA based on dsDNA sequences) and can be found in various activated cell lines including cancer, immune system, skin, bone and central nervous system

(Halazonetis et al., 1988; Kilberg et al., 2012). The expression of c-Fos in the central nervous system can be used to study the brain region specificity of drug effects (Rajkumar et al., 2013). It means that the brain regions which show significantly lower/higher c-Fos expression after administration of a drug compared to before it are considered as potential regions of effect of that drug.

To the best of our knowledge, all neurological studies on Rg1 have been focused on hippocampus and no published report is available on its effect on prefrontal cortex. Since medial prefrontal cortex in functionally linked to this brain region and receives direct projections from it, a question remains whether medial prefrontal cortex is also affected by ginsenoside Rg1 and if affected, whether this effect can be studied by routine electrophysiological and histochemical methods. Accordingly, the purpose of this chapter is to evaluate the effect of systemic administration of ginsenoside Rg1 on electrophysiological and histochemical characteristics of medial prefrontal cortex including evoked field potential in hippocampal-prefrontal cortical pathway, spontaneous firing rate of neurons in medial prefrontal cortex and c-Fos expression of neurons in this brain region. The results of this study may explain some potential mechanisms of neurological actions of ginsenoside Rg1. It should open new windows to the study of natural products and may suggest new areas for research on the treatment of neurological disorders such as anxiety, cognitive impairment and depression.

6.2. Hypotheses and objectives

As there are several reports of neurostimulatory effects of ginsenoside Rg1 (Chen et al., 2008a; Wang et al., 2001b; Wang et al., 2009c; Xu et al., 2007), we hypothesize that systemic administration of ginsenoside Rg1 increases the neuronal activity of

medial prefrontal cortex. Therefore, the objective of this part of study was to evaluate the effect of systemic administration of ginsenoside Rg1 on medial prefrontal cortex using three animal based methods including two electrophysiological methods and one histochemical method. Starting with the study of the effect of ginsenoside administration on long-lasting potentiation and long-term potentiation in hippocampal-medial prefrontal cortical pathway, we evaluate whether there is any effect on direct neuronal projection from hippocampus to medial prefrontal cortex. After that another electrophysiological and a histochemical method are utilized to assess if the potential site of effect is the medial prefrontal cortex. These methods include measuring the spontaneous firing rate of pyramidal cells in medial prefrontal cortex and expression of c-Fos in these cells.

6.3. Material and methods

6.3.1. The effect of systemic administration of ginsenoside Rg1 on hippocampal-prefrontal cortical pathway

6.3.1.1. Animals

Male Sprague-Dawley (SD) rats weighing 200 – 300 g were requested form InVivos to be delivered to the vivarium in Center for Life Science (CeLS). They were acclimatized in pairs there in room temperature (22 – 23 °C) with 12hr cycles of day/night light (07:00 – 19:00) with free access to food and water for at least 48 hours before transporting to the experimental lab. All animal procedures were approved by institutional animal care and use committee (IACUC) of the National University of

Singapore (protocol number 007-11) and were conducted in accordance with International Guiding Principles for Animal Research (Howard-Jones, 1985).

6.3.1.2. Chemicals

Chloral hydrate powder from Sigma Aldrich (Germany) was dissolved in sterile normal saline from B Braun (Malaysia) to prepare 7% w/v solution. 95% pure Ginsenoside Rg1 from Nature Standard (Shanghai, China) was dissolved in sterile normal saline to prepare stock solution of 25 mg/ml. The solubility of Rg1 in saline was facilitated by the room temperature sonication using a Branson 1510 sonicator (Mexico). The required preparations of 1, 3 or 10 mg/ml were obtained by diluting this stock solution (kept in 4° C refrigerator) with sterile saline when needed.

A solution of 0.9% w/v sodium chloride and 4% w/v paraformaldehyde (PFA) in phosphate buffer was used for animal perfusion. The 0.9% w/v sodium chloride was prepared by dissolving 18 g NaCl (Schedelco, Malaysia) in 2 liters of distilled water. Phosphate buffer was prepared by adding 23.005 g Na_2PO_4 (Merck, Germany) and 5.93 g $NaH_2PO_4.2H_2O$ (Merck, Germany) to 1500 ml distilled water and mixing it using a magnetic stirrer for 30 minutes in room temperature. Then, it was transferred to a fume hood and 80 g PFA (Sigma Aldrich, Germany) powder was added to it. By heating it to 125°C and stirring it with magnetic stirrer under fume hood for more than 2 hours, a clear solution was prepared. It was followed by filtration under negative pressure using a Cole Palmer (Korea) vacuum. The final volume was adjusted to 2 liters by adding the appropriate amount of distilled water. The 15% and 30% w/v sucrose in phosphate buffer saline (PBS) were prepared by adding 30 g and 60 g sucrose (Fisher Chemicals, UK) to 200 ml 10% PBS (1st Base, Singapore), respectively.

Ethanol 100% from Merck (Germany) was used to prepare 95% and 70% solutions by adding distilled water. Cresyl violet 0.1% in acetic acid was from Sigma Aldrich (Germany) and xylene was purchased from QReC (Thailand). The Surgipath micromount mounting medium (IL, USA) was used to fix the slides.

6.3.1.3. Animal preparation and surgery

All electrophysiology experiments were started between 8 – 9 am and only one animal was used each day. A rat weighing 280 – 380 g was transferred from vivarium to electrophysiology room in a proper cage or transport box. The rat was kept in the electrophysiology room for 30 minutes to acclimatize to the room environment. Then, it was weighed using a rat weighing boat and a Cole Palmer (Korea) weighing machine. After that 400 mg/kg chloral hydrate (Flecknell, 2009) was injected intraperitoneally (IP) as the loading dose.

The animal was transferred back to its cage or box and left for 5 to 10 minutes waiting for induction of anesthesia. Once the animal was knocked down, its scalp fur was shaved using an Andis (USA) electronic shaver and it was mounted in a stereotaxic frame (Leica Biosystems, Germany). The head was fixed using ear bars and the incisors holders. The body temperature was maintained at 36.5 ± 0.5°C using a Harvard Apparatus (USA) thermal blanket with rectal thermometer. Then, the tail vein was cannulated using a GA22 BD Insyte angiocatheter (USA) for maintaining anesthesia and drug administration. The anesthesia was maintained by intravenous (IV) administration of 0.10 – 0.25 ml from chloral hydrate 7% w/v solution every 30 minutes since 1 hour after loading dose till the completion of the experiment.

A sagittal incision in the scalp exposed the skull. Any minor bleeding was stopped using an aluminum sulfate based hemostatic chalk (Clubman Pinaud, USA) and the area was cleaned using cotton swabs (Smith and Nephew, Singapore). Once the animal was stable and the bleeding was controlled, trephine burr holes were drilled bilaterally above the medial prefrontal cortex and ventral hippocampus (Figure 6.1) according to the atlas of The Rat Brain in Stereotaxic Coordinates (Paxinos et al., 2007) using a Marathon driller (Korea). The coordinates used for the ventral hippocampus were 6.3 mm posterior and 5.5 mm medial/lateral to the bregma and the coordinates used for the medial prefrontal cortex were 3.3 mm anterior and 0.8 mm medial/lateral to the bregma.

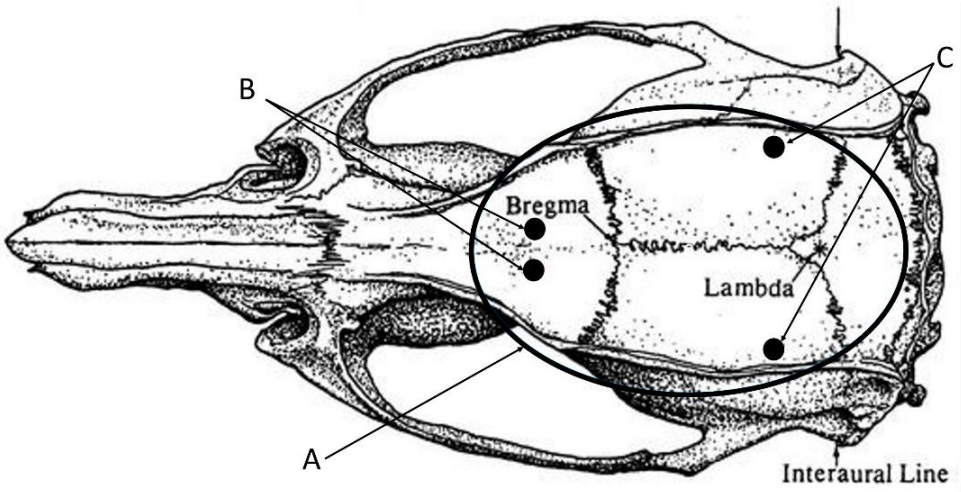

Figure 6.1. Schematic picture of the skull of rat adapted from (Paxinos et al., 2007). The oval (A) shows the exposed area during surgery, the black dots show the place used for drilling holes aiming medial prefrontal cortex (B) and ventral hippocampus (C). The distance between interaural line and bregma is aproximately 9 mm and the coordinates used for medial prefrontal cortex is +3.3 AP, +/-0.8 ML and the one for ventral hippocampus is -6.3 AP and +/-5.5 ML.

6.3.1.4. Electrophysiology

A concentric bipolar Nickle-Chromium stimulating electrode (SNE-100, Kopf Instruments, Tujunga, CA, USA) (250 μm outer diameter and 50 mm shaft and 500 μm tip separation) was placed in the right CA1/subiculum region of the ventral hippocampus (AP: -6.3 mm, ML: 5.5 mm, DV: 3.5 mm). A monopolar extracellular stainless steel recording electrode (SNE-300, Kopf Instruments, Tujunga, CA, USA) (100 μm diameter, 250 μm recording tip length and 50 mm shaft) was lowered to the ipsilateral infralimbic area of medial prefrontal cortex (AP: 3.3 mm, ML: 0.8 mm, DV: 4.2 mm) according to the atlas of The Rat Brain in Stereotaxic Coordinates (Paxinos et al., 2007) (Figure 6.2).

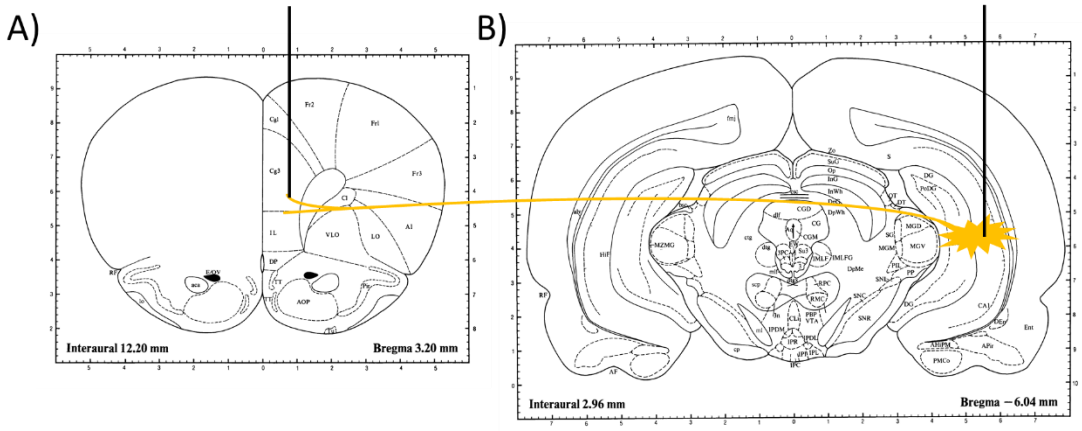

Figure 6.2. Schematic representation of the position of the recording electrode in the infralimbic region of medial prefrontal cortex (A) and the stimulating electrode in the CA1/subiculum region of ventral hippocampus (B). Adapted from The Rat Brain in Stereotaxic Coordinates (Paxinos et al., 2007). A schematic projection from ventral hippocampus to the infralimbic region is drawn.

It is known that electrical stimulation of the CA1/subicular region at a frequency of 0.01 – 0.1 Hz (50 – 500 μs duration) evokes a characteristic monosynaptic negative-going field potential with the peak latency of 18 – 24 ms (Lim et al., 2010a). By stimulating every 15 seconds with 300 mA current and 50 μs duration, the depth of

recording and stimulating electrodes (4.2 – 4.7 mm and 3.5 – 7.2 mm from skull surface respectively) were adjusted to maximize the amplitude of the negative going field excitatory postsynaptic potential (Figure 6.3). Once electrode placement was complete, a 30 minutes period was allowed for signal stability with electrical stimulation every 30 seconds.

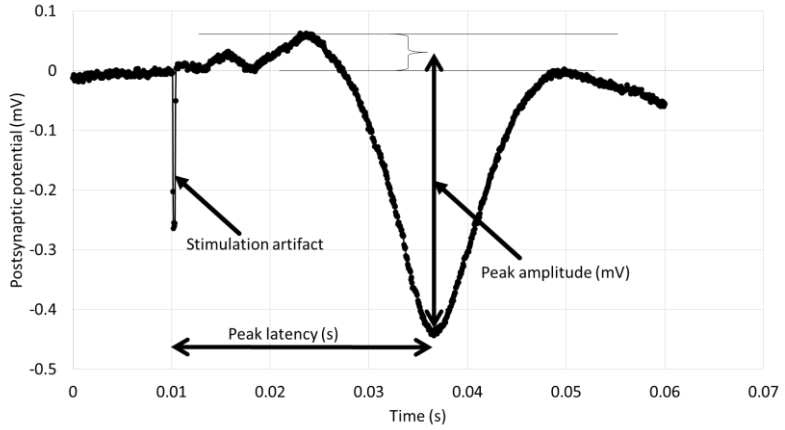

Figure 6.3. A representative prefrontal cortical postsynaptic potential elicited by single pulse stimulation of the CA1/subicular region in ventral hippocampus. Stimulation of this area evokes a characteristic negative-going field potential with the peak latency of 18-24 ms. The peak amplitude is also shown in the image.

Once the signal was stable, the input-output characterization of each rat was established. To do so, starting from 100 mA stimulation, the stimulation intensity was increased every 3 minutes (6 signals) 50 mA each time to reach the maximum of 450 mA stimulation. Then the input-output curve (IOC) was generated for each rat by averaging the amplitude of the negative-going field excitatory postsynaptic potential for each stimulation intensity (Figure 6.4).

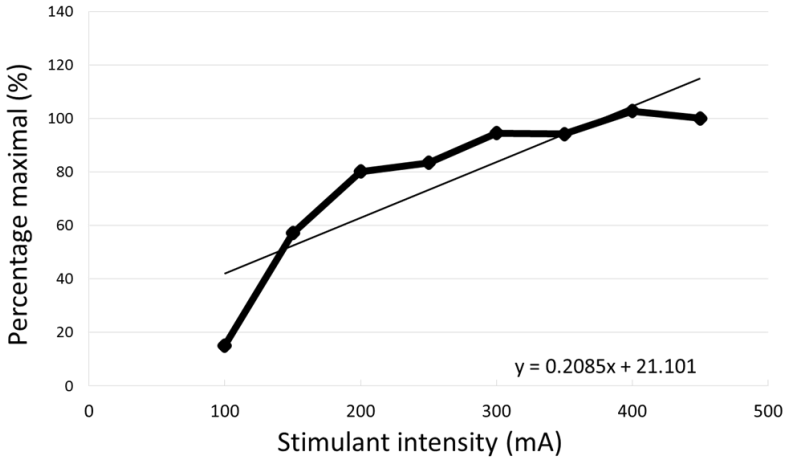

Figure 6.4. A representative input-output curve showing the increase in signal amplitude in infralimbic region of medial prefrontal cortex by increase in stimulation intensity in ventral hippocampus.

The stimulus intensity which produced approximately 60% maximal response was chosen for the test stimuli. The test was performed using a 4-step protocol (Figure 6.5). First, the baseline recording was performed with chosen signal intensity by stimulating every 30 s with stimulation duration of 50 μs to record 60 signals (30 minutes). After that, 1 ml/kg from the drug of choice (either normal saline or ginsenoside Rg1 concentrations of 1, 3 or 10 mg/ml) was slowly infused intravenously (over 15 s). The signal recording was continued for another 60 signals (30 minutes). After that, high frequency stimulation (HFS) was introduced to produce long-term potentiation (LTP). For this, the same intensity stimuli were applied with higher frequency (250 Hz) for 5 minutes. After that, the recording was continued with stimuli every 30 s similar to baseline recording for 90 minutes (180 Signals).

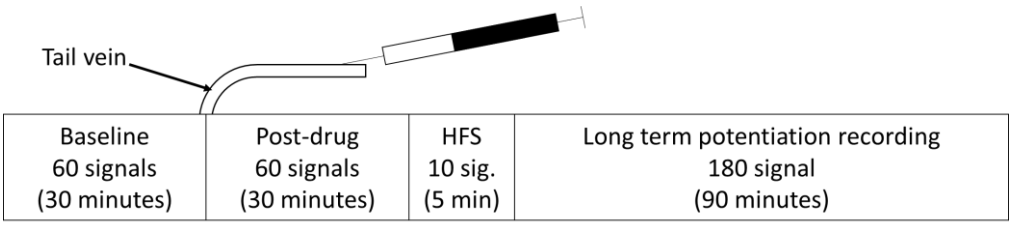

Figure 6.5. Schematic representation of experimental sequence used for evoked field potential study of ventral hippocampal medial prefrontal cortical pathway

Electrical stimulation of hippocampus was presented using a square pulse stimulator (S8800, Grass Instrument Co., Astromed, USA) and stimulus isolator (PSIU6, Grass Instrument Co., Astromed, USA). Field potentials were amplified using 2400 A extracellular preamplifier current pump (Dagan Corporation) and filtered by bandpass from 30 Hz to 3 kHz. Data collection and stimulus parameters were controlled using the Signal software (Version 5, Cambridge Electronic Design), running on a PC with a digitizing laboratory interface (Micro 1401 mk II, Cambridge Electronic Design).

6.3.1.5. Histological verification of stimulation and recording sites

At the end of each experiment, the rats were perfused transcardially with 300 ml normal saline followed by 400 ml 4% PFA in 0.1 M phosphate buffer. To do that, the rat would receive a dose of chloral hydrate to induce deep anesthesia. The depth of anesthesia was measured by the loss of pinch reflex. Then, the rat was mounted supine on a platform in the animal surgery fume hood. By a transverse incision in mid thoracic to mid abdominal area, the xiphoid process was exposed and pulled up to open up the rib cage by scissors. Then, the heart was completely exposed by carefully removing the pericardial tissue. While the heart was beating, a needle was inserted into the cardiac apex guided slowly toward aorta and normal saline was infused in. After few seconds,

the left ventricular wall was pale and right atrium was bulged. Cutting the right atrium caused a flush of blood out. The perfusion with saline was continued till there was no obvious blood stain dripping out from the heart. After that, the infusion system was shifted to PFA. Once PFA perfusion began, the rat would start shaking due to muscular fasciculation. By continuing the PFA perfusion, the rat became stiffed, which indicated a proper PFA perfusion. Then, the rat was decapitated by a guillotine, the scalp was completely removed and the skull was opened from sagittal suture. Brains were harvested and further fixed in 4% PFA for 2 – 7 days followed by 15% Sucrose in phosphate buffered saline (1×PBS) for 4 – 10 days and 30% Sucrose in 1×PBS for another 4 – 10 days. After that, the brains were cut in 45 μm thick slices using a rotary microtome (Leica CM 3050, Germany) and attached to poly-L-lysine coated glass slides (Superfrost Ultra Plus, Thermoscientific, Germany). The glass slides were left in room temperature for 48 hours to be dried and kept in 4° C refrigerator for staining.

The slides were cresyl violet stained by transferring them from 10 baths using the sequence presented in Table 6.1. Once completed, the slices were covered by mounting media and thin glass coverslip (CellPath, UK). Then, the covered slides were kept in room temperature for 24 hours to be dried and fixed with nail polish.

A light microscope (BX5, Olympus, Japan) and a digital camera (Olympus DP 71, Japan) were used to see the electrode tracks in the tissue. Only animals with proper tracking were included in data analysis.

6.3.1.6. Analyses and statistics:

Postsynaptic potential amplitude is expressed as a percentage of the mean amplitude recording during baseline. All results are given as mean ± SEM. All

statistical analyses were performed using SPSS-21 software (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA). Statistical tests were applied with a two-tailed significance criterion of $p<0.05$. The one-way ANOVA test was performed to compare different groups.

Table 6.1. Sequence of solvents used for cresyl violet staining

Bath number	Component	Temperature	Duration (minutes)
1	Ethanol 95% (20%) + Chloroform (80%)	Room temperature	10 minutes
2	Ethanol 95%	Room temperature	2 minutes
3	Ethanol 70%	Room temperature	2 minutes
4	Distilled water	Room temperature	<0.1[1]
5	Cresyl violet 0.1% in acetic acid	37° C	60
6	Distilled water	Room temperature	<0.1[1]
7	Ethanol 70%	Room temperature	1 minute
8	Ethanol 95%	Room temperature	1 minute
9	Ethanol 100%	Room temperature	1 minute
10	Xylene	Room temperature	2 minutes

[1] Dipped and rinsed.

6.3.2. The effect of systemic administration of ginsenoside Rg1 on the spontaneous firing rate of pyramidal cells in medial prefrontal cortex

6.3.2.1. Animals

Male Sprague-Dawley (SD) rats weighing 200 – 300 g were requested form InVivos to be delivered to the vivarium in Center for Life Science (CeLS). They were acclimatized in pairs there in room temperature with 12-hour cycles of day/night light

with free access to food and water for at least 48 hours before transporting to experimental lab.

6.3.2.2. Chemicals

The pontamine sky blue (2% w/v) in 2M NaCl was prepared by dissolving pontamine sky blue (Alfa Aesar, Germany) and NaCl (Schedelco, Malaysia) in distilled water.

6.3.2.3. Animal preparation and surgery

A completely similar protocol as mentioned in section 6.3.1.3 was used to prepare the animal for single unit recording. The only difference was that in this set of experiments, only burr holes were drilled on medial prefrontal cortical area at AP: 3.3 mm and ML: 0.8 mm (Figure 6.1). The hippocampal area was not drilled.

6.3.2.4. Electrophysiology

To produce glass microelectrodes, Starbore glass capillaries (Radnoti, USA) (150 μm inner diameter) were pulled using a micropipette puller (Narishige Instruments, PE-21, Japan) with no magnetic pull force at 56.0% heating capacity to produce microtubes with head outer diameters of <10 μm and 15 mm long slopes. The tubes were filled with 2% pontamine sky blue dye in 2M NaCl and kept for stability in room temperature for 30 minutes before the start of experiments. The impedance of electrodes was ranging from 28 to 38 MΩ. All microelectrodes were prepared on the day of each experiment. They were subsequently fixed in a microdrive assembly (Inchworm Microdrive System 8200, EXFO, Mississauga, Ontario, Canada) and lowered into the

brain using Scientifica (UK) electrode micromover. This machine can push down the electrode in micrometer steps during the actual signal recording. On reaching the prelimbic area, the electrode was lowered at a very low speed (approximately 10 μm/min) to ensure detection of the slow firing pyramidal cells in the medial prefrontal cortex.

Pyramidal cells in the medial prefrontal cortex have spontaneous firing, which can be differentiated from other electrical charges in the area by its specific biphasic shape, its voltage (0.5-5 mV), low frequency (0.1-4 Hz) and long duration (greater than 1.2 ms) (Puig et al., 2005; Rolls et al., 2003). The electrode was pushed in slowly from 3 to 7.2 mm deep from skull surface to seek for a proper spike (Figure 6.6). Once the signal was found, it was left for a period of stabilization for 15 – 30 minutes.

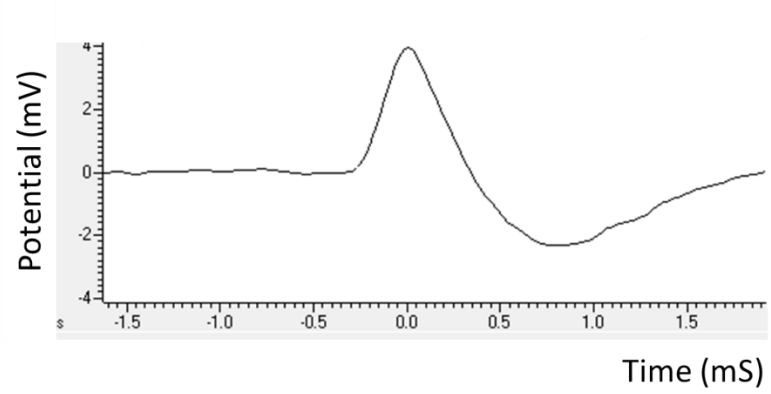

Figure 6.6. A representative prefrontal cortical pyramidal cell spontaneous spike. The characteristic bipolar signal with 0.5 to 5 mV amplitude, 1.5-3 ms length and low frequency rate can differentiate it from other spikes in the region (mostly from interneurons) with higher frequencies and distinguishable shapes.

If the signal stayed stable the recording was performed using single or accumulative doses administration of ginsenoside Rg1. In single dose experiments, after 3 minutes of baseline recording, 1 ml/kg sterile normal saline was infused. Three minutes later, 1 ml/kg from proper ginsenoside Rg1 solution (1, 3 or 10 mg/ml) was infused. The

recording was continued for 21 minutes. In accumulative doses protocol, after 3 minutes baseline, 100 µlit sterile saline was infused followed by 4 sets of infusion of 100 µlit from 12.5, 12.5, 25 and 50 mg/kg×mlit ginsenoside Rg1 respectively. The recording was continued for another 12 minutes. In both experiments a maintenance dose of anesthesia was administered 10 minutes before the start of recording and after a 27-minute complete recording, the last maintenance dose of chloral hydrate was infused to avoid both the early effect of chloral hydrate infusion on firing rate and the incomplete recording because of shallow anesthesia. The protocols of signal recording are summarized in Figure 6.7.

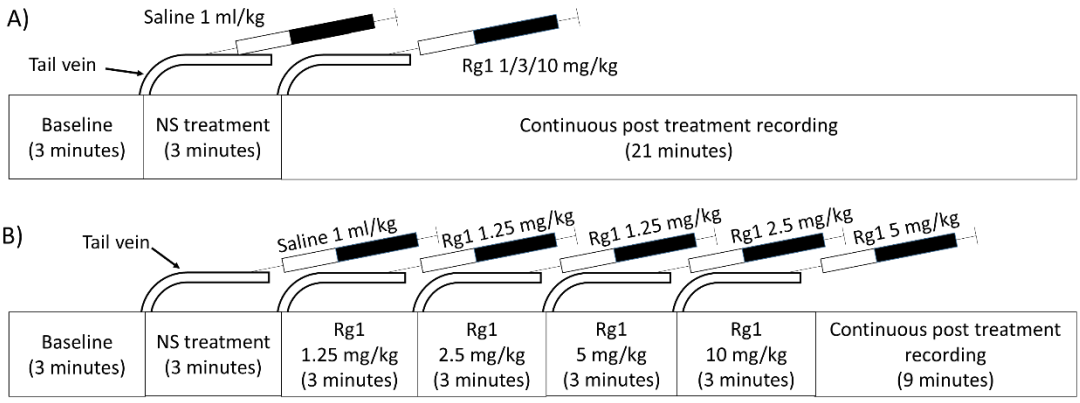

Figure 6.7. Experimental protocol for single unit recording of spontaneous firing rate of pyramidal cells in medial prefrontal cortex: (A) shows the single dose study of either 1, 3 or 10 mg/kg and (B) shows the accumulative study of 1.25, 2.5, 5 and 10 mg/kg. The orange lines represent the cannula in the tail vein.

The electrical charge of spontaneous firing of pyramidal cells in the medial prefrontal cortical region was acquired, amplified 100 times and band pass filtered to the range of 100-2000 Hz using ELC-03XS amplifier (npi Electronics, Tamm, Germany). The signal was filtered via a Humbug (Quest scientific, Vancouver, Canada) to remove 50-60 Hz noise, digitalized using Power 1401 MK2 interface (CED, Cambridge, UK) and viewed real time with Spike 2.7 software (CED, Cambridge, UK).

Later, the spikes were sorted to remove artefacts using the offline forced clustering and principal component analysis module of the Spike 2.7 software.

6.3.2.5. Histological verification of stimulation and recording sites

At the end of each experiment, the animal was transferred to the fume hood for perfusion as mentioned in section 6.3.1.5. Then, the brain harvesting, slicing and staining were performed accordingly. Only animals with proper tracking were included in the data analysis.

6.3.3. The effect of systemic administration of ginsenoside Rg1 on c-Fos expression in medial prefrontal cortical area

6.3.3.1. Animals

Male Sprague-Dawley (SD) rats weighing 200 – 300 g were requested form InVivos to be delivered to the vivarium in Center for Life Science (CeLS). They were acclimatized in pairs there in room temperature with 12-hour cycles of day/night light and free access to food and water for at least 48 hours before transporting to experimental lab.

6.3.3.2. Chemicals

Cryoprotectant solution (Watson et al., 1986) was prepared by mixing 500 ml 0.1 M phosphate buffer, pH 7.2 (50% v/v) including 1.59 g $NaH_2PO_4.H_2O$ (Merck, Germany), 5.47 g Na_2HPO_4 (Merck, Germany) and 9 g NaCl (Scheldelco, Malaysia) in 500 ml distilled water; 300 g sucrose from Fisherman (UK) (30% w/v), 300 ml ethylene glycol (30% v/v, from Sigma Aldrich, Germany) with final volume adjusted

to 1000 ml with distilled water. Triton X-100 (TTX) was purchased from Science Lab (USA) and mixed with PBS (1st BASE, Singapore) to prepare 0.3% v/v washing solution. Goat serum was obtained from Millipore, Germany. Primary antibody used in this experiment was rabbit anti-c-Fos antibody from Santa Cruz Biotechnology, CA, USA. The secondary antibody was Alexa Flour 555 goat anti-rabbit IgG (USA). Prolong Gold Anti-fade with DAPI (Alexa Flour, USA) was used as mounting media as well as dye to stain the nuclei.

6.3.3.3. Animal handling

Each day, 2 rats were transferred from vivarium to experimental room at 8 am. After leaving animals there for acclimatization for 30 minutes, an animal was weighed and received 1ml/kg either normal saline or ginsenoside Rg1 solution (1, 3 or 10 mg/ml) IP. After another 30 minutes, the other animal was injected by proper saline or ginsenoside Rg1 as well. After injections, the rats were transferred back to their cages and left in room temperature for 2 hours before transcardial perfusion and brain harvesting as explained in section 6.3.1.5.

6.3.3.4. Tissue preparation

The harvested brains were sequentially fixed in PFA and Sucrose as mentioned in section 6.3.1.5. Once fixed properly, the prefrontal cortical areas were serially sectioned using the rotary microtome in 45 μm thick slices. The sections with approximately 300 μm distances were collected and transferred and freely floated into the well plates containing cryoprotectant anti-freeze solution (Hoffman et al., 2004; Watson et al., 1986). The well plates were kept in -20° C to be preserved for staining.

To stain the preserved slices, the cryoprotectant solution content of well plates was replaced by PBS on the day of experiment. After that, the slices were washed by the washing mixture (0.3% v/v TTX in 1XPBS) for 4 rounds (5 minutes each). Then, the slices were incubated in the blocking solution (5% v/v goat serum in washing mixture) for 1 hour in the room temperature followed by being incubated overnight in 4° C in the primary antibody (rabbit anti-c-Fos antibody) titrated as 1:600 v/v in blocking solution.

On the day after, the slices were washed by the washing mixture for 4 times (5 minutes each) and transferred to the dark afterward. In the dark, they were incubated in room temperature in secondary antibody (555 goat anti-rabbit IgG) titrated as 1:200 v/v in blocking solution for an hour. The rest of experiment was continued in the dark. After an hour incubation, the slices were washed for 4 times (5 minutes each) with the washing mixture and mounted on the slides. The excess liquid was dabbed from the slide and the slices were covered by Prolong Gold Anti-fade with DAPI mounting media and cover-slipped. After 24 hours drying in the room temperature and fixation with the nail polish, the slides were studied under microscope or kept in -20° C for further investigation. Figure 6.8 schematically shows the process of slice staining for c-Fos expression.

Under fluorescent enabled light microscope (BX50, Olympus, Japan), medial prefrontal cortex was evaluated. Using a 10× object lens, two photos were taken from each side of each slice, one from prelimbic area and the other from infralimbic area. The prelimbic photos were approximately from 200 μm to 1100 μm lateral to the midline and 2300 μm to 2900 μm ventral to the dural surface. The infralimbic photos

were approximately from 200 μm to 1100 μm lateral to the midline and 3300 μm to 3900 μm ventral to the dural surface Figure 6.9.

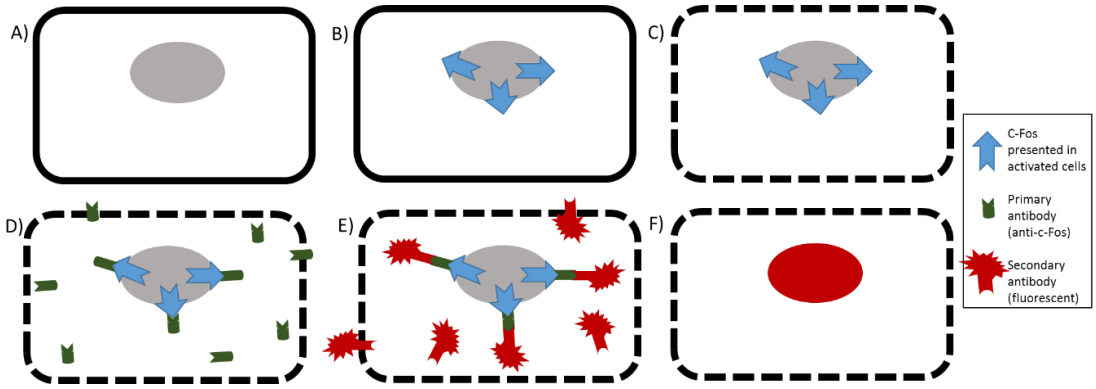

Figure 6.8. Schematic presentation of c-Fos activation and staining. The inactivated cells (A) will express c-Fos in their nuclei upon external stimulations (B). By treating these cells using washing mixture, the cell wall permeability will be increased (C) to allow transportation of proteins such as antibodies. By exposing cells to anti-c-Fos antibodies, the antibodies will attach to the c-Fos expressed in the cells (D). Now, the fluorescent secondary antibodies can attach to anti-c-Fos antibodies (E) and label the c-Fos expressing cells (F).

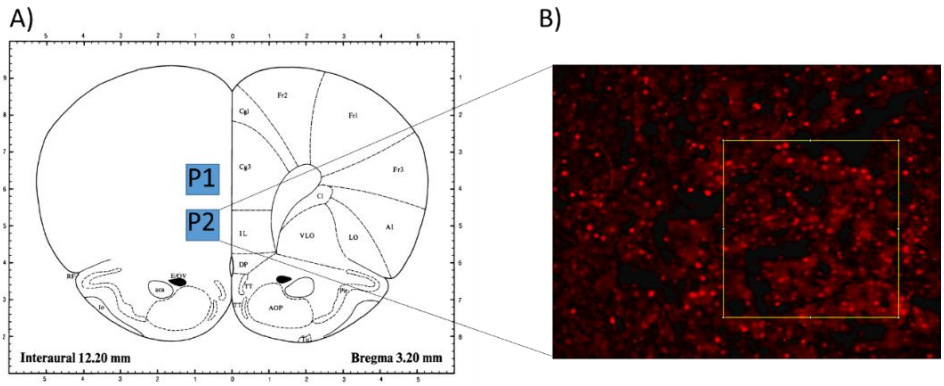

Figure 6.9. Schematic presentation of the positions of pictures taken from prelimbic (P1) and infralimbic (P2) areas (A) adapted from The Rat Brain in Stereotaxic Coordinates (Paxinos et al., 2007) and a representative picture taken from infralimbic area (B). The yellow box shows the 400 μm × 400 μm square in which the number of cells were counted.

6.3.3.5. Analyses and statistics

Using ImageJ software, a 400 μm × 400 μm square was drawn in each photo and the number of c-Fos positive cells in the square was counted for each area (Figure 6.9). The photo-taking and cell-counting were performed blinded to the animal treatment using numerical slide coding. The statistical analysis was performed using SPSS-21 software (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA). Statistical tests were applied with a two-tailed significance criterion of $p<0.05$. The one-way ANOVA test was performed to compare the different groups.

6.4. Results and discussion

6.4.1. The effect of systemic administration of ginsenoside Rg1 on hippocampal-prefrontal cortical pathway

Twenty five rats were included for the analysis based on the histological verification of the electrode position including 5 animals receiving normal saline, 7 animals receiving 1 mg/kg ginsenoside Rg1, 6 animals receiving 3 mg/kg ginsenoside Rg1 and 7 animals receiving 10 mg/kg ginsenoside Rg1.

Neither negative control (Normal Saline) nor any dose of ginsenoside Rg1 could induce long-lasting potentiation, a gradual increase in the amplitude of field-evoked potential, during 30 minutes post injection recording (Figure 6.10). On the other hand, high frequency stimulation (HFS) induced long-term potentiation (LTP) in all experimental groups manifested by the sudden increase in the amplitude of the negative going wave lasting for more than 30 minutes ($F_{30, 630} = 29.125$, $p<0.001$).

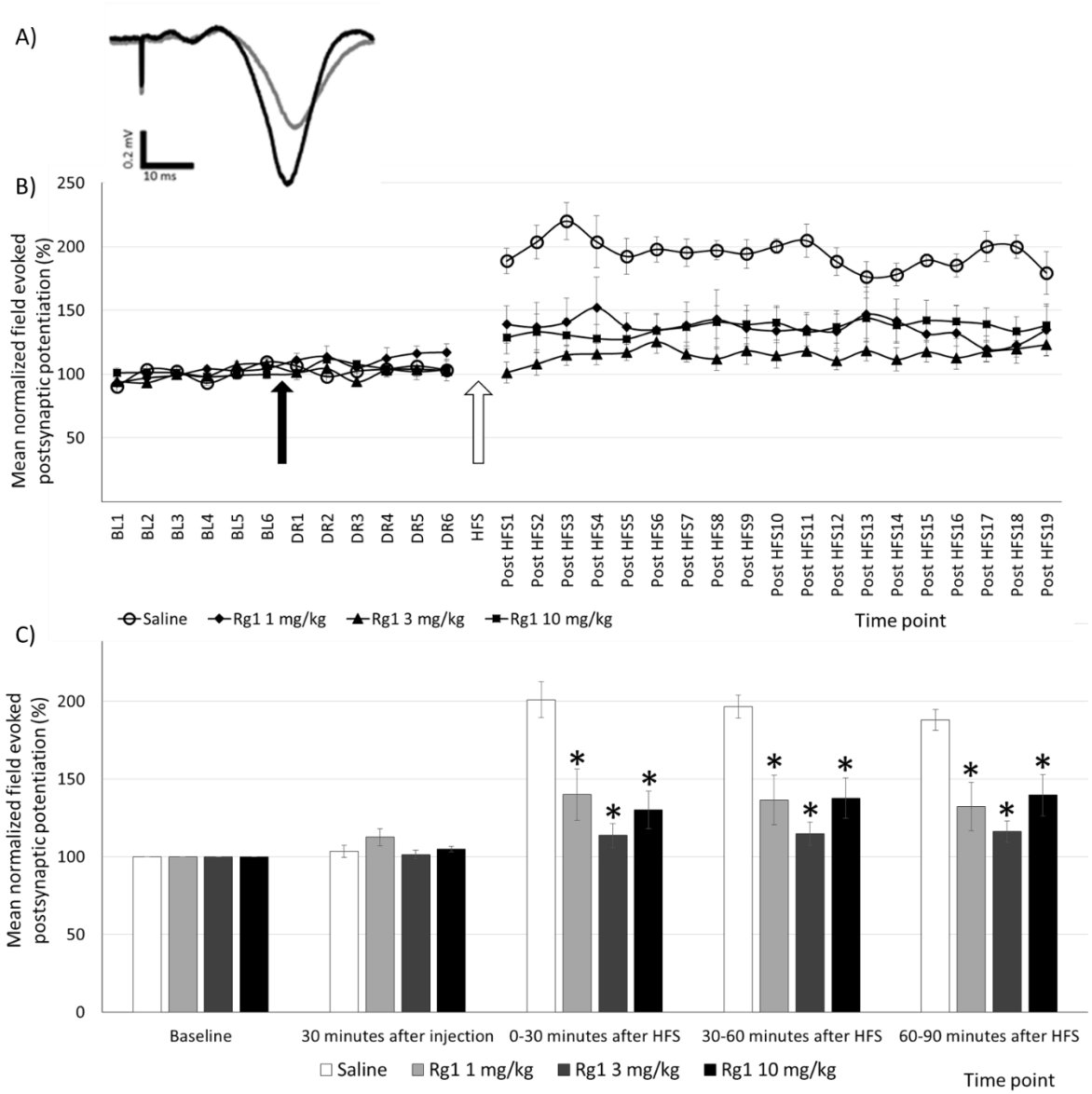

Figure 6.10. Long-term potentiation in hippocampal prefrontal cortical pathway. (A): A representative increase in amplitude of post-synaptic potential. By increase in the amplitude, the latency will be shorter. (B): Average LTP observed in four experimental groups. Each point is the average of normalized potentiation in 5 minutes in animals of the group. Error bars represent the standard error of mean. After drug injections (black arrow) there is no change in baseline field-evoked potential. While after HFS (white arrow), long-term potentiation was observed in all groups. However, the potential was significantly suppressed by ginsenoside Rg1. (C): The average of every 30 minutes shows a significant increase in the potentiation after HFS which is suppressed by ginsenoside injection. Error bars represent the SEM and * represents p value <0.05 compared to normal saline group. Abbreviations: BL: baseline, DR: drug treatment, HFS: high frequency stimulation

However, in rats receiving any dose of ginsenoside Rg1 (1, 3, or 10 mg/kg), the long-term potential was suppressed ($F_{3, 21} = 5.747$, $p = 0.005$). By averaging every 30 minutes, the effects of HFS and ginsenoside treatment was recalculated. Again, ginsenoside Rg1 treatment could significantly attenuate long-term potentiation in hippocampal-medial prefrontal cortical pathway ($F_{3, 21} = 6.026$, $p = 0.004$). Using post-hoc analysis, all three doses were significantly different from saline treatment ($p<0.005$). However, there was no statistically significant difference between different doses of ginsenoside Rg1. The lack of observed dose-dependent response can be due to the small sample size.

Ginsenoside Rg1 is generally known as a neurostimulatory substance responsible for the "warm" nature of *Panax ginseng.* on the other hand, *Panax quinquefolium* (American ginseng), which consists of more ginsenoside Rb1 than Rg1 (ginsenoside Rg1 is the third most abundant chemical constituent in *P. quinquefolium* after Rb1 and Re) (Chen et al., 2008a) is considered as "cold" in the nature. Here is the first report of neuroinhibitory effect of ginsenoside Rg1.

Suppression of hippocampal medial prefrontal cortical pathway can be by suppression of either the origin of pathway (hippocampus) or the end of it (the medial prefrontal cortex). There are several reports of stimulatory effects of this chemical constituent on hippocampus (Wang et al., 2001b; Xu et al., 2007) while to the best of our knowledge there is no report on its effect on medial prefrontal cortex. The rest of this study is focused on its effect on this brain region.

6.4.2. The effect of systemic administration of ginsenoside Rg1 on the spontaneous firing rate of pyramidal cells in medial prefrontal cortex

Among animals used for this study, 58 animals were included in the final analysis. The most common cause of exclusion from the study was unstable anesthesia, either dying or waking up during recording, which led in abortion of the study. Among the included animals, 18 were used for accumulative doses studies and the rest were used for single dose studies including 12 rats for 1 mg/kg, 20 rats for 3 mg/kg and 8 rats for 10 mg/kg ginsenoside Rg1 experiments. The mean baseline firing rate of included spikes were 0.77, 1.85, 1.43 and 1.76 Hz for 1 mg/kg, 3 mg/kg, 10 mg/kg and accumulative doses respectively.

In different groups, half of animals showed decrease in the firing rate of pyramidal cells in medial prefrontal cortex. Figure 6.11 shows the proportion of different responses in different treatment groups.

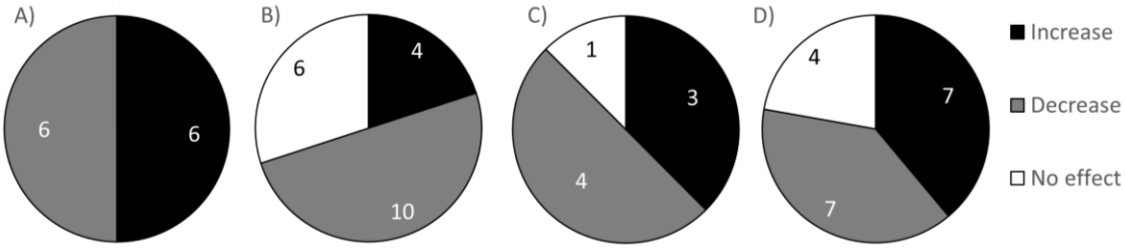

Figure 6.11. Proportion of changes in spontaneous firing rate of pyramidal cells in medial prefrontal cortex in response to treatment with different doses of ginsenoside Rg1: 1 mg/kg (A), 3 mg/kg (B), 10 mg/kg (C) and accumulative doses of 1.25, 2.5, 5 and 10 mg/kg (D).

The animals were grouped based on the response of recorded spike into the increase group, decrease group and no effect group for statistical analyses. In the increase group there were 6 animals receiving 1 mg/kg, 4 animals receiving 3 mg/kg and 3 animals

receiving 10 mg/kg ginsenoside Rg1. The observed increase in all the treatment groups was statistically significant ($F_{8,\ 80}$ = 6.846, p < 0.001). There was no statistically significant difference between different dosage groups ($F_{2,\ 10}$ = 3.680, p = 0.063) the only minor difference was between 3 and 10 mg/kg groups in 4th 3-minute period after ginsenoside Rg1 infusion (Figure 6.12).

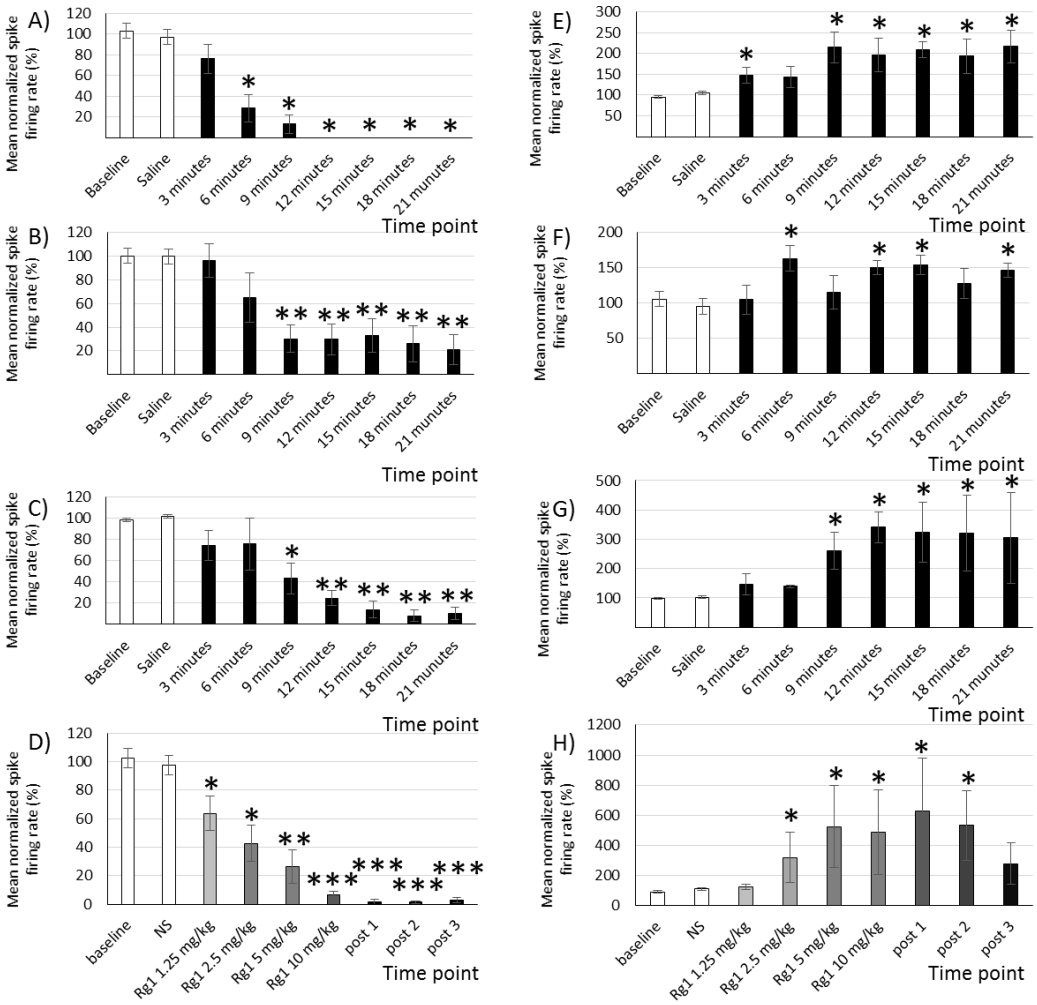

Figure 6.12. Average normalized spike firing rate in different treatment groups. At the left side graphs report spikes showing decrease in firing rate in response to 1mg/kg (A), 3 mg/kg (B), 10 mg/kg (C) or accumulative doses (D) of ginsenoside Rg1 infusion. At the right side graphs report spikes showing increase in firing rate in response to 1 mg/kg (E), 3 mg/kg (F), 10 mg/kg (G), or accumulative doses (H) of ginsenoside Rg1 infusion. Error bars represent the SEM, * represents p value <0.05, ** represents p values <0.01 and * represents p values <0.001.**

Totally, spikes from 20 animals receiving single dose of Rg1 showed a decrease in firing rate including 6 rats from 1 mg/kg group, 10 rats from 3 mg/kg group and 4 rats from 10 mg/kg group. The observed decrease in different groups was statistically significant ($F_{8, 136} = 23.646$, $p < 0.001$). There was also a significant difference between groups ($F_{2, 17} = 4.389$, $p = 0.029$). The difference was mainly between 1 and 3 mg/kg groups. In 3 and 10 mg/kg groups few spikes showed no response to infusion of Rg1 ($F_{8, 40} = 1.888$, $p = 0.090$) and there was no difference between treatment groups ($F_{1, 5} = 1.168$, $p = 0.329$). In animals receiving accumulative doses of ginsenoside Rg1, the same three patterns of response were observed. Generally, minor statistically significant difference was observed between different treatment groups receiving 1, 3 or 10 mg/kg ginsenoside Rg1. This lack of dose-dependent response could be due to small sample size.

In addition, in both decreasing and increasing groups, the changes in the spike firing rate were irreversible. In other words, the firing rate of the spike never changed back to the baseline value. It can be due to our short recording time. Since the anesthesia drug used for this set of experiments was chloral hydrate which needs maintenance doses every 30 – 40 minutes and has immediate short effect on firing rate, the recording period was limited to anesthesia safe window (10 – 40 minutes after the last maintenance dose). Longer recording times can be achieved by recording in the awake animals or anesthetized animals with long-lasting agent such as urethane (Flecknell, 2009; Kohn, 1997).

This set of data suggests that there might be different populations of pyramidal cells in medial prefrontal cortex with different response patterns to ginsenoside Rg1 or the same population of cells is producing different responses. The presence of different

populations of neurons in medial prefrontal cortex have been proposed in different animals although nobody has reported any differences in their morphological characteristics. Gabbott and Rolls described three populations of neurons located in the medial prefrontal cortical area of macaque brain, which show distinct activity patterns during asleep and awake periods (Gabbott et al., 2013; Rolls et al., 2003). Similar differences in neuronal activity was reported for the populations of cells in the rat medial prefrontal cortex during working memory tasks (Bai et al., 2012; Hyman et al., 2010), in response to stressful conditions (Jackson et al., 2006) or amphetamine administration (Gulley et al., 2010) or in mouse medial prefrontal cortex during spontaneous oscillation (Ruiz-Mejias et al., 2011). These functional differences can be due to diverse receptor expression. Using rat brain slices *in vitro*, Moore and colleagues showed that by dopamine administration, pyramidal neurons in medial prefrontal cortex with predominant D1 receptors will be severely suppressed while those mainly expressing D2 receptors will be significantly activated (Moore et al., 2011). These differences in characteristics of different populations of pyramidal cells in medial prefrontal cortex have been suggested to be involved in the tolerance and adaptive responses, which are important in the behavioral modification by the time (Jackson et al., 2006).

To evaluate the possibility that these are different populations of cells which respond differently to ginsenoside Rg1, burst analysis in bigger sample sizes can be useful (Farooq et al., 2013; Zhang et al., 2010) to mathematically evaluate the characteristics of groups of spikes with specific patterns of response to the ginsenoside Rg1. If no difference is found in burst analysis, the different patterns of response can be explained by lateral inhibition effect of groups of cells. It means that once a group

of cells are affected by ginsenoside Rg1, the neighboring cells try to compensate the effect by changing their behavior. Therefore, at any time point, there are populations of cells showing direct response to the external stimulus (ginsenoside Rg1 in this case) and some other populations showing the reverse response.

6.4.3. The effect of systemic administration of ginsenoside Rg1 on c-Fos expression in medial prefrontal cortical area

Twenty four animals were grouped into 4 treatment groups randomly. The control group received 1 ml/kg from sterile normal saline and ginsenoside Rg1 groups received 1 ml/kg from either 1, 3 or 10 mg/ml ginsenoside Rg1 solutions (IP) 2 hours before perfusion and harvesting the brains. From each animal, 12 brain slices from frontal lobe were collected for staining (Figure 6.13).

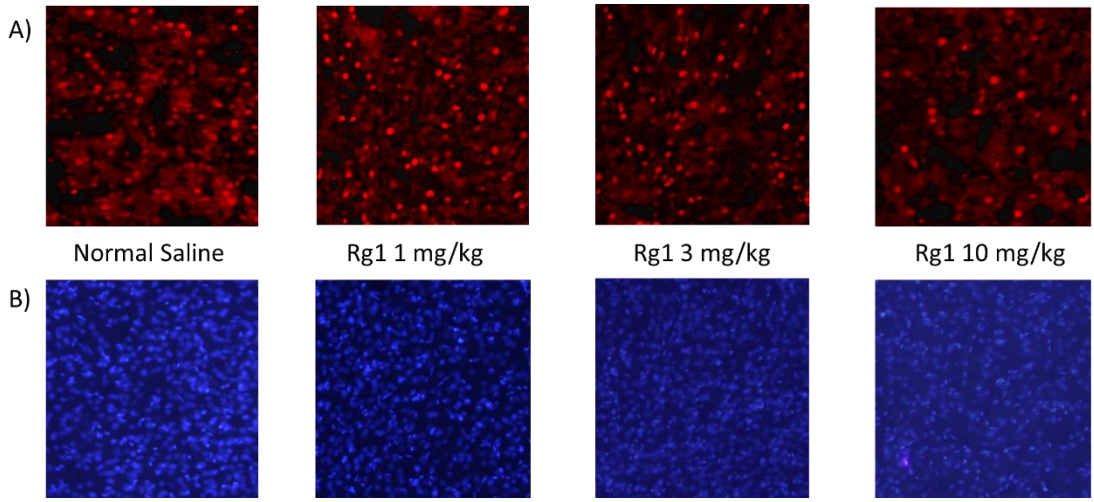

Figure 6.13. Representative slides from infralimbic area of medial prefrontal cortex of animals receiving saline (NS) or ginsenoside treatments. The first row shows the c-Fos fluorescent stains (A) and the second row shows the DAPI stains from the same region (B). Consider that although the number of c-Fos positive cells is significantly different in different treatment groups, the number of nuclei stained by DAPI seems equal.

Ginsenoside Rg1 treatment significantly decreased the number of c-Fos positive cells in medial prefrontal cortex (one-way ANOVA, $F_{3, 326} = 87.791$, $p < 0.001$). This effect was observed in both prelimbic (one-way ANOVA, $F_{3, 326} = 48.887$, $p < 0.001$) and infralimbic (one-way ANOVA, $F_{3, 326} = 40.384$, $p < 0.001$) areas. Additionally, the decreasing effect of ginsenoside Rg1 was dose-dependent in prelimbic ($y = -23.45 x + 192.63$, $R^2 = 0.8659$), infralimbic ($y = -22.29 x + 185.35$, $R^2 = 0.9645$) and pooled prelimbic and infralimbic ($y = -22.915 x + 189.04$, $R^2 = 0.9382$) areas (Figure 6.14).

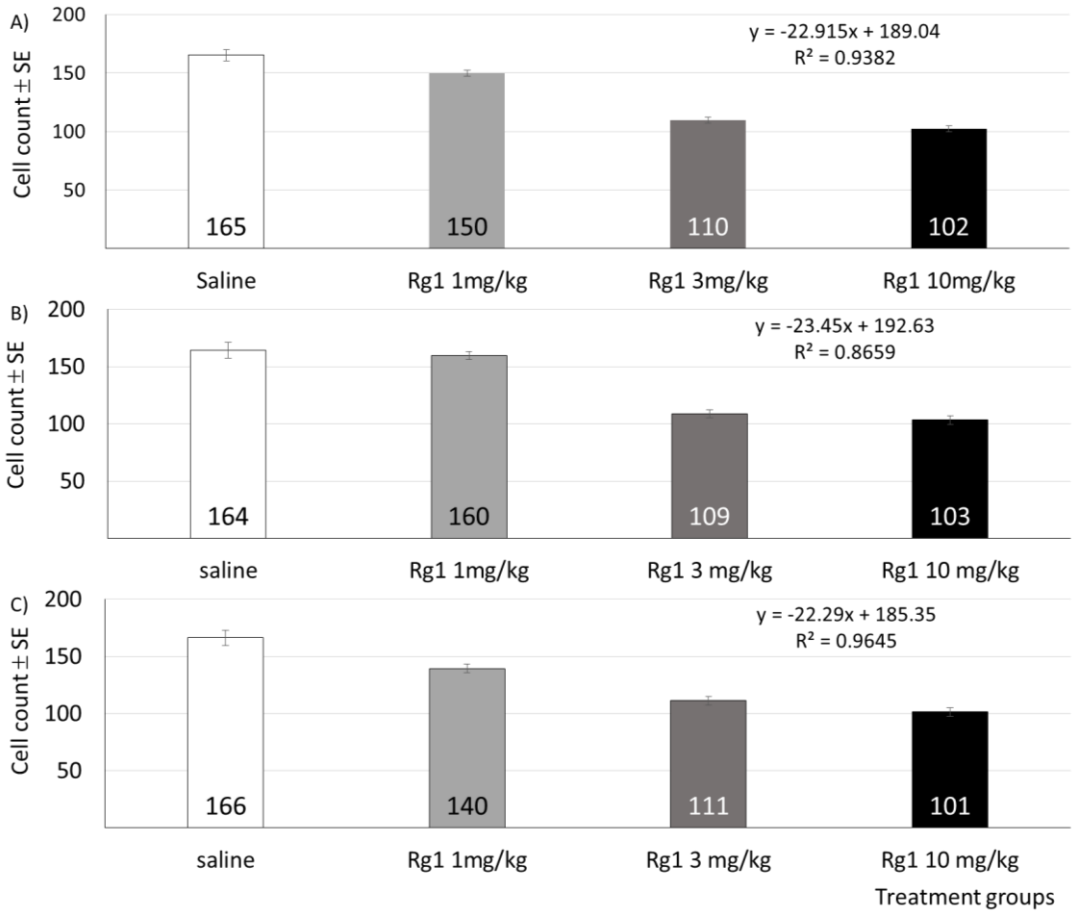

Figure 6.14. Average count of c-Fos positive cells in different treatment groups (n = 6 animals in each group) in medial prefrontal cortex (A), prelimbic area (B) and infralimbic area (C). Error bars represent the SEM.

Since c-Fos staining was performed on free floating slices, it was impossible to differentiate the right and left sides of brain. All electrophysiological studies were

performed on the right medial prefrontal cortical nuclei while the immunohistochemistry was measured as the sum of right and left sides. The next step is to perform the staining on fixed slices attached to microscopic slides to examine any difference in c-Fos expression between right and left medial prefrontal cortical nuclei, which is not feasible with the current technologies.

It is known that the number of c-Fos positive cells in medial prefrontal cortex (either prelimbic or infralimbic) has a diurnal rhythm with the highest peak in the evening (6pm) and the lowest peak in the morning (10 am) (Baltazar et al., 2013). To avoid the intereference of this natural rhythm to our results, all experiments were started at a particular time (8-8:30 am). Additionally, stress and handling have significant effects on c-Fos expression in medial prefrontal area (Adamec et al., 2012; Panhelainen et al., 2012). To avoid such effect, extreme care in animal handling was performed and all animals were solely handled by a single person (the author).

c-Fos expression in the medial prefrontal cortex is increased by stress (Panhelainen et al., 2012; Silva et al., 2012) and has been used as a marker of anxiety, which shows immediate response to herbal and non-herbal anxiolytic agents (Shoji et al., 2013; Wislowska-Stanek et al., 2008). The changes in c-Fos expression in medial prefrontal cortex has also been shown to be associated with memory and cognition changes in different studies. Methamphetamine exposure could impair the memory and increase the c-Fos expression in medial prefrontal cortex simultaneously (Chiu et al., 2014). Furthermore, N-acetylcysteine, an anti-hallucinogenic agent, has been shown to decrease the c-Fos expression in the medial prefrontal cortex (Lee et al., 2014). Therefore, it can be suggested that ginsenoside Rg1 as a natural inhibitor of medial prefrontal cortex (our results) and stimulator of hippocampus (Mook-Jung et al., 2001;

Wang et al., 2001b; Xu et al., 2007) may help to improve cognition by decreasing anxiety via affecting medial prefrontal cortex.

The dose-dependent decrease in number of c-Fos positive cells in combination to electrophysiological studies is consistent in indicating that the medial prefrontal cortex is mainly suppressed by ginsenoside Rg1. The lack of observed dose-dependent trends in electrophysiological studies may be due to small sample size or the nature of those procedures, which is less quantitative than the immunohistochemical analyses of cell activity such as c-Fos staining.

6.5. Conclusion

The main aim of this chapter was to investigate the effect of systemic administration of ginsenoside Rg1 on the medial prefrontal cortex. Three investigating methods were chosen including electrophysiological investigation of LTP induction in direct projection from hippocampus to medial prefrontal cortex and spontaneous neuronal firing of pyramidal cells in medial prefrontal cortex as well as histochemical study of cell activities in medial prefrontal cortex.

The first set of experiments studied the effects of intravenous administration of ginsenoside Rg1 on synapse plasticity of hippocampal-medial prefrontal cortical (HP-mPFC) pathway using long-lasting potentiation (LLP) and long-term potentiation (LTP) in this pathway. We observed that not only ginsenoside Rg1 failed to induce LLP in the HP-mPFC pathway, but also it attenuated the LTP induced by high frequency electrical stimulation. Similar effects were observed in all three doses used in the experiment (1, 3 or 10 mg/kg).

To the best of our knowledge, it is the first report of the effect of ginsenoside Rg1 on hippocampal-medial prefrontal cortical pathway, which suggests neuroinhibitory effects. Since this method studies the projection form hippocampus to the medial prefrontal cortex, the suppression of the pathway may not specifically show whether the origin of the pathway (hippocampus) or the end point (medial prefrontal cortex) is affected. Neuroinhibitory effects of ginsenoside Rg1 seem to be in contrast with previously published data showing neurostimulatory effects of this natural product (Qi et al., 2009; Wang et al., 2001b; Xu et al., 2007). Nevertheless, it should be kept in mind that almost all these researchers have been studying the effects of Rg1 administration on afferent pathways to the hippocampus while we investigated an efferent pathway originating from hippocampus toward medial prefrontal cortex. In the other words, although ginsenoside Rg1 is known to increase the hippocampal reaction to pathways originating from other brain nuclei, it suppresses the response of medial prefrontal cortex to stimulations from hippocampus. Such reaction can be due to a stronger suppressing effect of ginsenoside Rg1 on medial prefrontal cortex, which can modify its stimulatory effects on hippocampus. Therefore, it suggests that medial prefrontal cortex is one of the primary brain nuclei affected by this natural product. Therefore, the investigation of the effect of ginsenoside Rg1 on the spontaneous neuronal activity of medial prefrontal cortex and the histochemical analysis of neuronal activity affected by its administration could be helpful. The next two experimental sets attempted to investigate the effect of ginsenoside Rg1 on the medial prefrontal cortical cells.

In the second set of experiments, we studied the *in vivo* effect of intravenous administration of ginsenoside Rg1 on the spontaneous firing rate of medial prefrontal

cortical neurons. Using either single dose of 1, 3 or 10 mg/kg or accumulative doses of 1.25, 2.5, 5 and 10 mg/kg of ginsenoside Rg1 significantly decreased the frequency of spontaneous firing of almost half (50%) of the medial prefrontal cortical pyramidal cells. This result is in agreement with the findings of the previous set of experiments showing the attenuation of LTP induction in HP-mPFC pathway. Therefore, this finding suggests the neuroinhibitory effects of ginsenoside Rg1 by affecting the medial prefrontal cortex. However, the molecular mechanism of the effect remains elusive. Future pharmacological studies using antagonists are needed to figure out possible mechanisms. These studies can focus on drug, which might suppress the effect of Rg1 on medial prefrontal cortex. One possible drug of choice is antalarmin, a blocker of corticotropin-releasing factor (Webster et al., 1996). Corticotropin-releasing factor is an endogenous hormone, which is involved in stress response. Its receptors have been found in medial prefrontal cortex (Seidel et al., 2011). It is known that administration of this hormone can induce similar effects in medial prefrontal cortex as what we observed from administration of ginsenoside Rg1 (Farooq et al., 2013). Therefore, corticotropin-releasing factor and its antagonist antalarmin can be considered to investigate the mechanism of action for the suppressing effect of Rg1 on medial prefrontal cortex.

The third set of experiment was to investigate the effect of ginsenoside Rg1 on the cell activity in the medial prefrontal cortex using histological techniques. The brains of rats were harvested 2 hours after intraperitoneal administration of either normal saline (as control) or ginsenoside Rg1 (1, 3 or 10 mg/kg). The numbers of c-Fos expressing cells in medial prefrontal cortex were compared across different treatment groups. Rg1 dose-dependently decreased the number of these cells in the treated animals compared

to control group. Consistent with previous findings, it showed that ginsenoside Rg1 can suppress the medial prefrontal cortical neurological activity. Presenting dose-dependent suppression is the most significant finding of this set of studies. However, the underlying mechanisms for the suppressing effect of Rg1 on medial prefrontal cortex remains unclear. Since the effect of Rg1 on the number of c-Fos expressing cells is dose-dependent, this method may serve better than the electrophysiology based ones to investigate the mechanism of action of Rg1 such as antagonistic studies. The effect of systemic administration of ginsenoside Rg1 on the other molecular changes related to c-Fos expression such as formation of c-Fos—c-Jun heterodimer and activator protein 1 (AP-1) can be evaluated as the future work.

In summary, these findings demonstrated for the first time that ginsenoside Rg1 suppresses the medial prefrontal cortical activity using three different methods. Considering the available literature on neurostimulatory effects of this natural product on other brain regions especially hippocampus, the results presented in this report can open new windows to understanding the neurological activities of ginsenoside Rg1. However, the biomolecular mechanisms behind the effect of Rg1 on medial prefrontal cortex remains elusive, which should be addressed by future research using mechanistic studies such as antagonistic approaches. Based on the present report, histochemical analysis is a better experimental method compared to the electrophysiological analyses for future studies.

As people use natural products orally, we only studied the systemic administration of the ginsenoside Rg1 and the local administration (ICV) was not evaluated here. Furthermore, the effects of its metabolites (ginsenosides Rh1, F, PPT) and the effects of ginsenoside Rg1 on other brain regions were beyond the scope of this study. Finally,

correlating our results with other methods of study including behavioral studies should be considered in future work.

CHAPTER 7. Conclusion

The overarching aim of this study was to evaluate the usage of CAM with specific focus on neurological effects. First, we began with getting information about the usage of CAM from community dwelling older adults and its association with their neurocognitive status. Then, we surveyed on the usage of herbal medicine in the same age group. Collating information about available CAM products in the market was the third step. Finally, we moved to bench work by investigating the effect of an active component of *Panax ginseng*, ginsenoside Rg1, on the neuronal activity of medial prefrontal cortex, an important brain region involved in cognition, memory, decision making and other advanced neurological functions.

In the first part of the study, the data from Singapore Longitudinal Ageing Study (SLAS I and II) was analyzed. A high prevalence of CAM usage among older adults in Singapore (53.4%) was found. This prevalence showed an increase compared to a previous reports from the same age group in Singapore (Feng et al., 2010). The most commonly used CAM practices were herbal medicine, qigong and acupuncture. The top three medicinal herbs used by participants were evening primrose oil, ginseng and ginkgo. Similar to available literature (Feng et al., 2010; Zhang et al., 2008a), CAM usage was more common among more educated Chinese female participants who were suffering from one or two chronic disorders and had better physical and social activities. On the other hand, age was not a significant factor in the prevalence of usage of CAM in contrast to other reports (Feng et al., 2010). Ageing is associated with both limitation in physical abilities (which decreases the usage of some forms of CAM) and increase in risk of suffering from multiple medical conditions (which increases the usage of CAM). Therefore, although the pattern of CAM usage changes by age, the overall

prevalence of CAM usage will not be changed significantly. Contrary to our predictions, CAM usage was not associated with cognitive or depressive status of participants. It is reported in clinical trials that CAM practices can improve both cognitive and depressive situations (Dennis et al., 2013; Dos Santos-Neto et al., 2006; Murray et al., 2004; Sarris et al., 2011). Since this study was a cross-sectional population based observational study, it could not differentiate those who use CAM to improve their cognitive and depressive situation from those whose cognition and mood is normal because of using CAM.

To evaluate the association of cognitive decline with the usage of CAM, the data from 4-year follow-up of "SLAS I" was analyzed, which showed lower risk of developing cognitive decline among CAM users and qigong practitioners. Consistent with the available data showing their effects in improving cognitive status (Lee et al., 2004c; Oh et al., 2012), our data suggest a positive protective role for these practices against cognitive decline for the first time as a longitudinal observational study. However, the effect of qigong was marginal. There is a need for more investigation in other well-designed longitudinal observations and randomized clinical trials to prove their role as promising preventive factors against cognitive decline in older adults.

Since herbal medicine was the most commonly used CAM practice among participants in SLAS, the second part of the study was performed to collate more information about the usage of herbal medicine and factors associated with it. Re-contacting 209 participants in Jurong Ageing Study to perform detailed telephone interview, we observed that the real prevalence of usage of herbal medicine is much higher than what was reported previously. Based on the results of telephone interviews, 67.7% of older adults used one or more medicinal herbs, which was about twice

prevalent than SLAS results. This difference was not explainable by changes in the prevalence by time and was more due to a better and more accurate method of data collection. It shows the importance of using focused questionnaires in observational studies. The most commonly used herb was American ginseng followed by wolfberry and Chinese/Korean ginseng. Usage of herbal medicine was more common among younger female participants and no association was observed between most demographic and neurocognitive factors and usage of individual herbs. This lack of association could be due to small sample sizes. Three of top six common herbs belonged to *Panax genus* family, an important group of medicinal herbs, which are loosely named as "ginseng". It was also observed that medicinal herbs are mainly used more for general health improvement rather than specific medical conditions. Among those who used medicinal herbs for medical conditions, the majority were using medicinal herbs for diseases and health conditioned defined based on traditional Chinese medicine followed by neurological conditions and musculoskeletal problems. The main source of information about the usage of medicinal herbs was by word of the mouth from family and friends. None of the participants had consulted a western (conventional) health practitioner to get knowledge about usage of medicinal herbs. It emphasizes the importance of improving physician-patient communication about the usage of herbal medicine to prevent the adverse effects of improper usage of herbs, which may lead in drug-herb and herb-herb interactions and other dangerous adverse effects. For such an observational study, the sample size was not big enough to detect any association of usage of individual herbs with studied factors including neurocognitive status. Therefore, by increasing the sample size in future studies, more significant results can be observed.

To improve our understanding of usage of medicinal herbs, the third part of the study was conducted to investigate the herbal products in the local market. Since three of six most commonly used herbs reported by participants in telephone interview belonged to *Panax genus* family, it was decided to survey herbal products in market, which have the words "Panax" or "ginseng" in their labels. For this part of study, 309 products were collected from the market and the information provided in their labels was analyzed. These products are sold over the counter without any need for prescription. Consumers have access to them in the market and chose them mainly based on the information provided in their labels. Therefore, such information plays an important role in the public education and has a significant effect on their consumption. Comparing the information provided in the product labels with the local legislations, it was found that required information was provided by more than 84% of products in different categories, which was comparable to a similar study in the UK on 68 products containing "ginseng" (Raynor et al., 2011). Additionally, there were some prohibited claims of efficacy and safety, which could mislead the users. Reviewing the indications claimed by products, it was found that being effective for the traditionally defined diseases and general health is the most common claim on products followed by affecting circulatory system and having analgesic effects. Being effective for mental and behavioral conditions and the nervous systems was the fourth most commonly claimed indication. To prove or reject any claim of effectiveness, a complete set of translational research is needed to be conducted from *in vitro* studies to *in vivo* animal work to clinical trials, which is beyond the time limitations of a PhD project.

The fourth part of the study was to investigate the effect of ginsenoside Rg1 on the medial prefrontal cortex. Ginsenoside Rg1 is one of the most abundant chemical

constituents of different *Panax* species. Studies had reported its positive effects on memory and cognition by stimulating hippocampus (Qi et al., 2009; Wang et al., 2001b; Wang et al., 2009c; Xu et al., 2007). To the best of our knowledge, there is no report on its effects on medial prefrontal cortex, an important brain region involved in memory, cognition, stress and decision making (Groenewegen et al., 1997; Lim et al., 2010a). Three sets of *in vivo* and *ex vivo* studies were performed to investigate its effect on this brain region. Firstly, the effect of systemic administration of ginsenoside Rg1 (1, 3 or 10 mg/kg) on the induction of long-lasting potentiation and long-term potentiation in hippocampal-medial prefrontal cortical pathway was investigated. None of the three tested doses could induce long-lasting potentiation in this pathway. Moreover, ginsenoside Rg1 treatment in all the three doses attenuated the high frequency electrical stimulation induced long-term potentiation. It is the first report of neuroinhibitory effects of ginsenoside Rg1. Since there are several reports of its stimulatory effects on hippocampus, our results of inhibiting hippocampal-medial prefrontal cortical pathway could suggest inhibition of medial prefrontal cortex by this ginsenoside. The second set of experiments assessed the effects of systemic administration of ginsenoside Rg1 on spontaneous firing rate of neuronal spikes in medial prefrontal cortex. Both single dose (1, 3 or 10 mg/kg) and accumulative doses (1.25, 2.5, 5 and 10 mg/kg) of this natural product could suppress almost half of the recorded neurons and had stimulating effects or no effects on the other half. This finding suggested that ginsenoside Rg1 has suppressing effects on some neuronal populations in medial prefrontal cortex, which is in favor of the previous findings in the same study showing attenuation of long-term potentiation in hippocampal-medial prefrontal cortical pathway. Small sample size and recording one single neuronal spike from each animal were the main limitations of this electrophysiological method in investigating

the neurological effects of ginsenoside Rg1. The third set of experiment was complementary to investigate the effect of ginsenoside Rg1 on medial prefrontal cortex where the effect of its systemic administration on the number of c-Fos positive cells in this cortical region was observed. Using immunohistochemical staining, it was shown that ginsenoside Rg1 dose-dependently decreases the number of c-Fos positive cells in medial prefrontal cortex, which is a reliable indicator of its inhibitory effects. The all three sets of experiments gave a general overview of inhibitory effects of ginsenoside Rg1 on medial prefrontal cortex. This is the first report of its effect on medial prefrontal cortex and the first report of its inhibitory effects. Such inhibition can improve learning and cognition by decreasing the stress and anxiety. However, the molecular mechanism of action needs further studies. Antagonistic studies can be suggested as potential paths for future investigations. Additionally, the behavioral effects of suppression of medial prefrontal cortex by ginsenoside Rg1 can shed more light on the neurological effects of this natural product. Additionally, since ginsenoside Rg1 has low bioavailability and will be metabolized to secondary ginsenosides (Rh1, F and finally PPT) and it has limited permeability through brain blood barrier (Cheng et al., 2005; Christensen, 2009), the possibility of affecting medial prefrontal cortex via other metabolites should be considered for future research.

In summary, a translational medical approach to the usage of CAM was performed in this work by obtaining the information from community dwelling population and available products in the market and evaluating some neurological effects of a commercially available natural product. A high prevalence of usage of CAM and its main subtype, herbal medicine, was observed among older adults in Singapore. Surveying the herbal products in the local market, we found that some of them have

improper information provided in their labels, an important source of information for most users. The high prevalence of usage and lack of reliability in sources of information should be considered by medical practitioners dealing with older adults who are more susceptible to the possible harms and risks of usage of CAM. The real effects and indications of the natural products need scientific assessment using different methods of translational medical approaches from *in vitro* studies to clinical trials.

Our results highlight the important role of CAM practices (such as qigong) and products (such as herbal products containing “ginseng”) in the health maintenance of modern society and provide evidence for their potential protective and therapeutic neurocognitive effects. Considering the lack of proper communication between users of CAM and health providers, this work as a translational research improves the realistic understanding about CAM among the scientists, care providers and the public. Moreover, it helps maximize the benefits of its usage to the society and minimize potential risks. Further scientific evaluation of CAM facilitates its better integration into the conventional medical systems by providing reliable information about its safety, efficacy and the mechanism of action. Both the public and health systems will finally benefit from such integration.

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Appendix 1: English and Chinese consent form for telephone-based interviews and participant particulars form

Telephone script for the study of usage of medicinal herbs in older adults in Singapore

Good morning / afternoon.

I am ..... (the name of interviewer) calling from national university of Singapore. May I speak to Mr/Ms ..... or his/her care giver?

I am calling you today because you / your care recipient have participated in a research study "The association between diet and health status in Asian elderly study" conducted in Jurong Point and you / your care recipient have agreed to be re-contacted for further questions. Today, I would like to ask you some questions about using of medicinal herbs over the telephone (or by your care recipient). This will take approximately 15-30 minutes of your time. You are not obligated to participate in this study and can withdraw from the study by stopping me any time. All information obtained from you will be kept confidential and nobody will be used it at any time against you. If you prefer, I can call you later / another day.

Shall I continue? Do you have any questions? Do you think you would like to take part in this research?

1. **(Subject / caregiver gives verbal agreement):**

Thank you for your verbal agreement and I will proceed with this telephone interview. Also, we will use part of your data that have been collected from the diet and health study and need your verbal permission for us to do so. Do you agree?

Before I start asking questions on your / your care recipient's medicinal herbs usage, may I just check some information to confirm your / your care recipient's identity?

You / Your care recipient are / is Mr. /Ms. .....

<Administer Questionnaire>

<End of questionnaire administration>

(Before ending the call, provide the subject / care-giver with the contact name and number of both the research team and NUS-IRB (independent opinion) for any further questions about the study.)

Should you have any further questions about the study, please call the below numbers.

Tel: 6516 3264 Assoc. Professor Tan Chay Hoon (Principle Investigator of Research project)

Tel: 6516 1234 Mr. Chan Tuck Wai (NUS Institutional Review Board, NUS-IRB)

2. **If subject / caregiver decline / refuse participation**, thank the person for his/her time and politely end call.

Follow-up interview on usage of medicinal herbs

SUBJECT'S PARTICULARS:

Subject name: <Pre-entered from 10-517 study>

Subject number: <Pre-entered from 10-517 study>

Questionnaire number: <Pre-entered>

Date of Birth (dd/mm/yyyy):

Age:

Gender:

- ○ **Male**
- ○ **Female**

Race:

- ○ **Chinese**
- ○ **Malay**
- ○ **Indian**
- ○ **Others**

Subject has verbally *agreed / not agreed for the research team to use part of his / her research data collected from the diet and health study (NUS-IRB Ref Code 10-517) to be linked to this follow-up interview for medicinal herbs users study.

** please circle.*

Name of interviewer: ..... ***Date of interview:*** ..... ***Signature:*** .....

新加坡老年人在药草使用方面的研究的电话面谈稿

上午/下午好。

我是.....（面试者的名字）来自新加坡国立大学。我可以跟..... 先生/女士或他/她的照顾者讲话吗？

我打电话给您是因为您/您的护理接收者参与了在裕廊坊进行的“亚洲老年人饮食与健康状况的关联”的研究。您/您的护理接收者已经同意被重新联系作此研究的进一步调查研究。今天，我只想通过电话问您/您的护理接收者一些药草使用的问题。这会用到您大约 15-30 分钟的时间。您参与这项研究并不是义务性的，可以随时中断我退出研究。从您获得的所有信息将被保密，没有人会在任何时候用它对您不利。如果您不方便，我可以过后/改天再打电话给您。

我可以继续吗？您有任何疑问吗？您愿意参与这项研究吗？

1. **（研究对象/照顾者给予 口头同意）：**

感谢您给予口头同意，那我就开始电话访谈。我们也会使用从饮食与健康状况研究项目取得的您的部分研究数据，需要您的口头同意。您同意吗？

在我开始问您/您的护理接收者的药草使用方面的问题前，我可以先确认您/您的护理接收者的身份？

您/您的护理接收者是.....先生/女士

（开始问卷调查）

（结束问卷调查）

（结束电话之前，提供研究对象/照顾者研究小组和新加坡国立大学机构审查委员会 NUS-IRB 的联络人和联络电话，以便他们有其他疑问时使用）

您如果有任何关于此研究的疑问，请打以下电话。

研究小组首席研究员陈晴云副教授，电话：65163264

新加坡国立大学机构审查委员会 NUS-IRB？？（Mr. Chan Tuck Wai）先生，电话： 65161234

2. **（如果研究对象/照顾者拒绝参与，感谢对方，礼貌地挂断电话。）**

感谢您的时间。再见！

研究对象的个人资料:

研究对象名字：（根据 10-517 研究预先输入）

研究对象编码：（根据 10-517 研究预先输入）

问卷编码：(预先输入)

出生日期 （年/月/日）：

年龄:

性别:

- ○ 男
- ○ 女

种族:

- ○ 华人
- ○ 马来人
- ○ 印度人
- ○ 其他

研究对象已口头*同意/不同意 研究组使用从饮食与健康状况研究项目（NUS-IRB Ref Code 10-517）取得的部分研究数据为此药用植物使用者后续面谈研究所用。

**请画圈*

面试者姓名：..... 面试日期：..... 签名：.....

Appendix 2: English and Chinese questionnaire for telephone-based interviews

Usage of medicinal herbs

1. Have you been using any of these herbs in the last one year?

☐ Ginseng (Chinese / Korean/American)
- ☐ Ren shen / white ginseng **(please proceed to page 3)**
- ☐ Hong Shen / Red ginseng **(please proceed to page 3)**
- ☐ Korean ginseng **(please proceed to page 3)**
- ☐ American ginseng (pao shen / hua qi shen / xi yang shen) **(please proceed to page 5)**
- ☐ Others (please specify): .....**(please proceed to the last page)**

☐ Notoginseng / San qi / Tian qi **(please proceed to page 7)**

☐ Garlic **(please proceed to page 9)**

☐ Ginkgo **(please proceed to page 11)**

☐ Primrose oil **(please proceed to page 13)**

☐ Lingzhi **(please proceed to page 15)**

☐ Herbal tonics (please specify): .....**(please proceed to the last page)**

Ginseng usage

Ren Shen, 人参

2. Which form of ginseng product do you use?
- ☐ Dried herb
- ☐ Boiled herbal drink
- ☐ Steeped herbal drink
- ☐ Tea bags
- ☐ Herbal soup
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

3. How often do you use this herb/ product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

4. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

5. Who recommended you to use this herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

6. What is the reason you use herb/product for?
- ☐ Medical purposes **(please proceed to question 7)**
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

7. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

- ☐ Health problems in Traditional Chinese Medicine context (please specify):
  .....
  .....
  .....
- ☐ Others (please specify):
  .....
  .....
  .....
  .....

8. Are you satisfied with the usage of this product for improvement in your medical condition?
- ○ Yes
- ○ No

American ginseng usage

xi yang shen, 西洋参, 花旗参

9. Which form of American ginseng product do you use?
- ☐ Dried herb
- ☐ boiled herbal drink
- ☐ steeped herbal drink
- ☐ tea bags
- ☐ herbal soup
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

10. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

11. How long have you been using this herb/ product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

12. Who recommended you to use this herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

13. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 14**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

14. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

- ☐ Health problems in Traditional Chinese Medicine context (please specify):
  .....
  .....
  .....

  Others (please specify):
  .....
  .....
  .....
  .....

15. Are you satisfied with the usage of American ginseng for improvement in your medical condition?
- ○ Yes
- ○ No

Notoginseng usage

田七, 三七

16. Which form of notoginseng product do you use?
- ☐ Raw notoginseng
- ☐ Steamed herb
- ☐ Herbal drinks containing notoginseng
- ☐ Herbal soup
- ☐ Topical form
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please mention): .....

17. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

18. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

19. Who recommended you to use this herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

20. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 21**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

21. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

- ☐ Health problems in Traditional Chinese Medicine context (please specify):
  .....
  .....
  .....

  Others (please specify):
  .....
  .....
  .....
  .....

22. Are you satisfied with the usage of notoginseng for improvement in your medical condition?
- ○ Yes
- ○ No

Garlic usage

蒜

23. Which form of garlic product do you use?
- ☐ Fresh garlic cloves
- ☐ Dried garlic cloves
- ☐ herbal soup
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

24. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

25. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

26. Who recommended you to use herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

27. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 28**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

28. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

☐ Health problems in Traditional Chinese Medicine context (please specify):

.....

.....

.....

Others (please specify):

.....

.....

.....

.....

29. Are you satisfied with the usage of this product for improvement in your medical condition?
- ○ Yes
- ○ No

Ginkgo usage

银杏，白果

30. Which form of ginkgo product do you use?
- ☐ Dried/powdered leaves /leaf extracts
- ☐ Ginkgo nuts
- ☐ herbal drink
- ☐ herbal soup
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

31. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

32. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

33. Who recommended you to use herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

34. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 35**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

35. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

☐ Health problems in Traditional Chinese Medicine context (please specify):

.....

.....

.....

Others (please specify):

.....

.....

.....

.....

36. Are you satisfied with the usage of this herb for improvement in your medical condition?
- ○ Yes
- ○ No

Primrose oil usage

月见草油

37. Which form of primrose oil product do you use?
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

38. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

39. Who recommended you to use herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

40. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

41. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 42**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

42. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

- ☐ Health problems in Traditional Chinese Medicine context (please specify):
  .....
  .....
  .....

  Others (please specify):
  .....
  .....
  .....
  .....

43. Are you satisfied with the usage of this product for improvement in your medical condition?
- ○ Yes
- ○ No

Lingzhi usage

灵芝, reishi

44. Which form of lingzhi product do you use?
- ☐ Dried fungus (herb)
- ☐ herbal drink
- ☐ herbal soup
- ☐ End product preparation
  - ☐ Chinese Proprietary Medicine (CPM)
  - ☐ Health supplements
- ☐ Others (please specify): .....

45. How often do you use this herb/product?
- ○ Every day
- ○ 2-3 times a week
- ○ Once a week
- ○ Once a month to once a week
- ○ Less than once a month

46. How long have you been using this herb/product?
- ○ Less than one month
- ○ One month to 6 months
- ○ 6 months to 2 years
- ○ More than 2 years

47. Who recommended you to use herb/product?
- ☐ Western health practitioners
- ☐ TCM practitioners
- ☐ Friends
- ☐ Family members
- ☐ No one in particular
  - ☐ Self-prescription based on personal knowledge
  - ☐ Getting information from media (such as advertisements)
- ☐ Others (please specify): .....

48. What is the reason you use herb/product for?
- ☐ Medical purposes (**please proceed to question 49**)
- ☐ General health improvement
  - ☐ As a tonic
  - ☐ To improve/boost the immunity
  - ☐ Others (please specify): .....

49. If you are using this herb/product for medical purposes, for which medical condition(s) do you use it?

Neurological disorders:
- ☐ Memory loss
- ☐ Depression
- ☐ Anxiety
- ☐ Psychosis
- ☐ Parkinsonism
- ☐ Stroke
- ☐ Vertigo/dizziness
- ☐ Tinnitus
- ☐ Pain (please specify): .....
- ☐ Others (please specify): .....

Cardiovascular/hematologic problems:
- ☐ Hypertension
- ☐ Heart diseases
- ☐ Atherosclerosis
- ☐ Peripheral vascular diseases
- ☐ Coagulopathies
- ☐ Immunity problems
- ☐ Others (please specify): .....

Gastrointestinal problems
- ☐ Indigestion
- ☐ Parasitic infestation
- ☐ Gastrointestinal infections
- ☐ Others (please specify): .....

Ophthalmologic problems
- ☐ Glaucoma
- ☐ Retinal detachment and other retinal diseases
- ☐ Other eye problems (please specify): .....

Metabolic disorders:
- ☐ Hyperglycemia/diabetes
- ☐ Dyslipidemia (cholesterol, TG problems)
- ☐ Obesity
- ☐ Others (please specify): .....

Respiratory disorders
- ☐ Cough
- ☐ Common cold
- ☐ Rhinitis
- ☐ Asthma
- ☐ Bronchitis
- ☐ Pneumonia
- ☐ Others (please specify): .....

Musculoskeletal problems:
- ☐ Osteoporosis
- ☐ Arthritis (including rheumatoid arthritis)
- ☐ Musculoskeletal injury
- ☐ Muscular pain
- ☐ Others (please specify): .....

Reproductive system problems:
- ☐ Menopausal syndrome
- ☐ Menstrual problems
- ☐ Breast problems
- ☐ Male reproductive problems (e.g. impotence)
- ☐ Prostate problems
- ☐ Others (please specify): .....

Dermatologic problems:
- ☐ Acne
- ☐ Eczema
- ☐ Psoriasis
- ☐ Itchiness
- ☐ Fungal infection
- ☐ Others (please specify): .....

Other health conditions:
- ☐ Cancer (please specify): .....
- ☐ Edema
- ☐ Bacterial infection (please specify): .....
- ☐ Withdrawal syndrome (please specify): .....

☐ Health problems in Traditional Chinese Medicine context (please specify):

.....

.....

☐ Others (please specify):

.....

.....

50. Are you satisfied with the usage of this herb for improvement in your medical condition?
- ○ Yes
- ○ No

51. Thank you for participating in this survey. Do you permit us to re-contact you later if any clarification is needed?
- ○ Yes
- ○ No

药用植物的使用

1. 你是否在过去的一年中一直使用以下所列的任何一种草药?

□ 人参（中国/韩国/美国）
- □ 人参/白人参 （**请到第 3 页**）
- □ 红参 （**请到第 3 页**）
- □ 韩国人参 （**请到第 3 页**）
- □ 美国人参（泡参/花旗参/西洋参）（**请到第 5 页**）
- □ 其他（请注明）:…… （**请到最后一页**）

□ 三七/田七 （**请到第 7 页**）
□ 蒜（**请到第 9 页**）
□ 银杏（**请到第 11 页**）
□ 月见草油（**请到第 13 页**）
□ 灵芝（**请到第 15 页**）
□ 中草药补品 （请注明）：……（**请到最后一页**）

人参的使用

2. 您使用哪种形式的人参产品
□ 干药草
□ 煮凉茶饮料
□ 冲泡药草饮料
□ 茶包
□ 药材汤
□ 成品制剂
  □ 中国成药
  □ 健康补充剂
□ 其他（请注明）：

3. 您多常使用本草药/产品？
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

4. 你使用这个草药/产品有多长时间了？
○ 不到 1 个月
○ 1 个月~6 个月
○ 6 个月至 2 年
○ 2 年以上

5. 谁推荐你使用这个草药/产品？
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
  □ 基于个人知识的自我处方
  □ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

6. 您使用本草药/产品的原因是什么？
○ 医疗用途（**请到问题 7**）
○ 改善健康状况
  ○ 作为补品
  ○ 改善/增强免疫力
  ○ 其他（请注明）：.....

7. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而使用这个产品？

神经系统疾病：
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题：
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题：
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题：
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱：
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题：
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题：
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如习痿）
□ 前列腺问题其他（请注明）：.....

皮肤问题：
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 痕痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况：
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
.....
.....
.....
.....

8. 您是否满意使用人参对您的病情的改善？
○ 是
○ 不

西洋参的使用

9. 您使用哪种形式的人参产品
□ 干药草
□ 煮凉茶饮料
□ 冲泡药草饮料
□ 茶包
□ 药材汤
□ 成品制剂
  □ 中国成药
  □ 健康补充剂
□ 其他（请注明）: .....

10. 您多常使用本草药/产品?
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

11. 你使用这个产品有多长时间了?
○ 不到 1 个月
○ 1 个月～6 个月
○ 6 个月至 2 年
○ 2 年以上

12. 谁推荐你使用这个草药/产品?
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
  □ 基于个人知识的自我处方
  □ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

13. 您使用本草药/产品的原因是什么?
○ 医疗用途（**请到第问题 14**）
○ 改善健康状况
  ○ 作为补品
  ○ 改善/增强免疫力
  ○ 其他（请注明）：.....

14. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个产品?

神经系统疾病:
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题:
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题:
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题:
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱:
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题:
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题:
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如阳痿）
□ 前列腺问题其他（请注明）：.....

皮肤问题:
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 瘙痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况:
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的促康问题（请注明）：
.....
.....
.....

其他（请注明）：
.....
.....
.....
.....

15. **您是否满意使用西洋参对您的病情的改善?**
○ **是**
○ **不**

三七的使用

16. 您使用哪种形式的三七产品
- □ 生三七
- □ 熟三七
- □ 含三七的草本饮料
- □ 药材汤
- □ 外用形式
- □ 成品制剂
  - □ 中国成药
  - □ 健康补充剂
- □ 其他（请注明）：.....

17. 您多常使用本草药/产品?
- ○ 每天
- ○ 每周 2-3 次
- ○ 一周一次
- ○ 每月一次到每周一次
- ○ 每月少于一次

18. 你使用这个草药/产品有多长时间了?
- ○ 不到 1 个月
- ○ 1 个月~6 个月
- ○ 6 个月至 2 年
- ○ 2 年以上

19. 谁推荐你使用这个草药/产品?
- □ 西医
- □ 中医
- □ 朋友
- □ 家人
- □ 没有特定的人
  - □ 基于个人知识的自我处方
  - □ 从媒体获取信息（如广告）
- □ 其他（请注明）：.....

20. 您使用本草药/产品的原因是什么?
- ○ 医疗用途（**请到问题 21**）
- ○ 改善健康状况
  - ○ 作为补品
  - ○ 改善/增强免疫力
  - ○ 其他（请注明）：.....

21. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个草药/产品?

神经系统疾病:
- □ 记忆力衰退
- □ 抑郁症
- □ 焦虑症
- □ 精神病
- □ 帕金森病
- □ 中风
- □ 晕眩/头晕
- □ 耳鸣
- □ 疼痛（请注明）：.....
- □ 其他（请注明）：.....

心血管/血液问题:
- □ 高血压
- □ 心脏病
- □ 动脉弱样硬化
- □ 外周血管疾病
- □ 凝血障碍
- □ 免疫问题
- □ 其他（请注明）：.....

胃肠道问题:
- □ 消化不良
- □ 寄生虫感染
- □ 胃肠道感染
- □ 其他（请注明）：.....

眼科问题:
- □ 青光眼
- □ 视网膜脱离等眼底疾病
- □ 其他眼睛疾病（请注明）：.....

代谢紊乱:
- □ 高血糖/糖尿病
- □ 性高血脂（胆固醇，甘油三酯的问题）
- □ 肥胖
- □ 其他（请注明）：.....

呼吸系统疾病
- □ 咳嗽
- □ 普通感冒
- □ 鼻炎
- □ 哮喘
- □ 支气管炎
- □ 肺炎
- □ 其他（请注明）：.....

肌肉与骨骼的问题:
- □ 骨质疏松
- □ 关节炎（包括类风湿关节炎）
- □ 肌肉骨骼损伤
- □ 肌肉疼痛
- □ 其他（请注明）：.....

生殖系统问题:
- □ 更年期综合症
- □ 月经问题
- □ 乳房问题
- □ 男性生殖问题（如勃痿）
- □ 前列腺问题其他（请注明）：.....

皮肤问题:
- □ 痤疮
- □ 湿疹
- □ 牛皮癣
- □ 痕痒
- □ 真菌感染
- □ 其他（请注明）：.....

其他健康状况:
- □ 癌症（请注明）：.....
- □ 水肿
- □ 细菌感染（请注明）：.....
- □ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
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.....

22. **您是否**满意使用人参对您的病情的改善?
- ○ **是**
- ○ **不**

蒜的使用

23. 您使用哪种形式的蒜产品
□ 新鲜蒜瓣
□ 干蒜
□ 药材汤
□ 外用形式
□ 成品制剂
  □ 中国成药
  □ 健康补充剂
□ 其他（请注明）：.....

24. 您多常使用本草药/产品？
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

25. 你使用这个草药/产品有多长时间了？
○ 不到 1 个月
○ 1 个月～6 个月
○ 6 个月至 2 年
○ 2 年以上

26. 谁推荐你使用这个草药/产品？
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
  □ 基于个人知识的自我处方
  □ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

27. 您使用本草药/产品的原因是什么？
□ 医疗用途（**请到问题 28**）
□ 改善健康状况
  □ 作为补品
  □ 改善/增强免疫力
  □ 其他（请注明）：.....

28. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个草药/产品？

神经系统疾病:
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题:
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题:
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题:
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱:
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题:
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题:
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如妇瘘）
□ 前列腺问题其他（请注明）：.....

皮肤问题:
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 瘙痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况:
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
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.....
.....
.....

29. **您是否**满意使用人参对您的病情的改善？
○ **是**
○ **不**

银杏的使用

30. 您使用哪种形式的银杏产品
□ 干/粉状叶/叶提取物
□ 银杏果仁
□ 草本饮料
□ 药材汤
□ 成品制剂
  □ 中国成药
  □ 健康补充剂
□ 其他（请注明）：.....

31. 您多常使用本草药/产品?
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

32. 你使用这个草药/产品有多长时间了?
○ 不到 1 个月
○ 1 个月—6 个月
○ 6 个月至 2 年
○ 2 年以上

33. 谁推荐你使用这个草药/产品?
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
  □ 基于个人知识的自我处方
  □ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

34. 您使用本草药/产品的原因是什么?
□ 医疗用途（**请到第问题 35**）
□ 改善健康状况
  □ 作为补品
  □ 改善/增强免疫力
  □ 其他（请注明）：.....

35. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个草药/产品?

神经系统疾病:
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题:
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题:
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题:
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱:
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题:
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题:
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如习癆）
□ 前列腺问题其他（请注明）：.....

皮肤问题:
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 痕痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况:
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
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.....
.....
.....

36. **您是否**满意使用人参对您的病情的改善?
○ **是**
○ **不**

月见草油的使用

37. 您使用哪种形式的月见草油产品
□ 成品制剂
□ 中国成药
□ 健康补充剂
□ 其他（请注明）：.....

38. 您多常使用本草药/产品?
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

39. 你使用这个草药/产品有多长时间了?
○ 不到 1 个月
○ 1 个月~6 个月
○ 6 个月至 2 年
○ 2 年以上

40. 谁推荐你使用这个草药/产品?
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
□ 基于个人知识的自我处方
□ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

41. 您使用本草药/产品的原因是什么?
□ 医疗用途（**请到第问题 35**）
□ 改善健康状况
□ 作为补品
□ 改善/增强免疫力
□ 其他（请注明）：.....

42. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个草药/产品?

神经系统疾病:
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题:
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题:
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题:
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱:
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题:
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题:
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如勃起）
□ 前列腺问题其他（请注明）：.....

皮肤问题:
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 瘙痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况:
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
.....
.....
.....
.....

43. **您是否**满意使用人参对您的病情的改善?
○ 是
不

灵芝的使用

44. 您使用哪种形式的灵芝产品
□ 干灵芝
□ 草本饮料
□ 药材汤
□ 成品制剂
  □ 中国成药
  □ 健康补充剂
□ 其他（请注明）：.....

45. 您多常使用本草药/产品？
○ 每天
○ 每周 2-3 次
○ 一周一次
○ 每月一次到每周一次
○ 每月少于一次

46. 你使用这个草药/产品有多长时间了？
○ 不到 1 个月
○ 1 个月～6 个月
○ 6 个月至 2 年
○ 2 年以上

47. 谁推荐你使用这个草药/产品？
□ 西医
□ 中医
□ 朋友
□ 家人
□ 没有特定的人
  □ 基于个人知识的自我处方
  □ 从媒体获取信息（如广告）
□ 其他（请注明）：.....

48. 您使用本草药/产品的原因是什么？
□ 医疗用途（**请到第问题 49**）
□ 改善健康状况
  □ 作为补品
  □ 改善/增强免疫力
  □ 其他（请注明）：.....

49. 如果你因医疗用途而使用它，那么你是因什么病情 （医疗症状）而**使用**这个草药/产品？

神经系统疾病:
□ 记忆力衰退
□ 抑郁症
□ 焦虑症
□ 精神病
□ 帕金森病
□ 中风
□ 晕眩/头晕
□ 耳鸣
□ 疼痛（请注明）：.....
□ 其他（请注明）：.....

心血管/血液问题:
□ 高血压
□ 心脏病
□ 动脉粥样硬化
□ 外周血管疾病
□ 凝血障碍
□ 免疫问题
□ 其他（请注明）：.....

胃肠道问题:
□ 消化不良
□ 寄生虫感染
□ 胃肠道感染
□ 其他（请注明）：.....

眼科问题:
□ 青光眼
□ 视网膜脱离等眼底疾病
□ 其他眼睛疾病（请注明）：.....

代谢紊乱:
□ 高血糖/糖尿病
□ 性高血脂（胆固醇，甘油三酯的问题）
□ 肥胖
□ 其他（请注明）：.....

呼吸系统疾病
□ 咳嗽
□ 普通感冒
□ 鼻炎
□ 哮喘
□ 支气管炎
□ 肺炎
□ 其他（请注明）：.....

肌肉与骨骼的问题:
□ 骨质疏松
□ 关节炎（包括类风湿关节炎）
□ 肌肉骨骼损伤
□ 肌肉疼痛
□ 其他（请注明）：.....

生殖系统问题:
□ 更年期综合症
□ 月经问题
□ 乳房问题
□ 男性生殖问题（如勃痿）
□ 前列腺问题其他（请注明）：.....

皮肤问题:
□ 痤疮
□ 湿疹
□ 牛皮癣
□ 瘙痒
□ 真菌感染
□ 其他（请注明）：.....

其他健康状况:
□ 癌症（请注明）：.....
□ 水肿
□ 细菌感染（请注明）：.....
□ 戒断综合征（请注明）：.....

□ 在中国传统医学背景下的健康问题（请注明）：
.....
.....
.....

□ 其他（请注明）：
.....
.....
.....
.....

50. **您是否**满意使用人参对您的病情的改善？
○ **是**
○ **不**