NEUROCOGNITIVE FUNCTIONING IN KETUM (*MITRAGYNA SPECIOSA* KORTH) LEAF USERS IN NORTHERN PARTS OF PENINSULAR MALAYSIA

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UNIVERSITI SAINS MALAYSIA

2012

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by

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Thesis submitted in fulfillment of the requirements for the degree of

Master of Science

July 2012

ACKNOWLEDGMENT

Firstly I would like to express my sincere gratitude to my principal supervisor Associate Professor Dr B.Vicknasingam, and co-supervisors Professor Emeritus Dato Visweswaran Navaratnam and Professor Sharif Mahsufi Mansor for their direction, assistance, and guidance. Their encouragements and support is appreciated.

I also wish to thank Professor Suresh Narayanan for his assistance in understanding the tools used to analyse my research data. My sincere thanks also go to Associate Professor Dr Marek Chawarski from Yale University School of Medicine for his immense knowledge and insightful comments.

Special thanks should be given to Mr. Firdaus Ramli from the Centre for Drug Research, Universiti Sains Malaysia for his help with the coordination of the study participants and conducting the interviews. I also wish to acknowledge the help of my colleagues at Centre for Drug Research especially Mr Darshan Sing and Dr Zohre Shamandi and outreach workers from AIDS Action and Research Group (AARG) especially Mr Mohamad Firdaus. I wish to thank all my friends for their support and encouragement especially Ms Cindy Hung.

I would also like to acknowledge the Ministry of Science, Technology, and Innovation (MOSTI) for providing research grant for the current study.

Lastly, I am very thankful to my family for supporting and encouraging me throughout all study in Universiti Sains Malaysia.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficiency Hyperactivity Disorder
AIDS	Acquired Immune Deficiency Syndrome
ATS	Amphetamine Type Stimulants
ALT	Alanine Transaminase
BQSS	Boston Qualitative Scoring System
BVFD	Benton Visual Form Discrimination
CB1	Cannabinoid Receptor Type 1
CNS	Central Nervous System
DOS	Department of Statistics
DSM-IV	Diagnostic and Statistical Manual, fourth edition
FMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Amino Butyric Acid
HIV	Human Immunodeficiency Virus
HRP	Harm Reduction Program
IQ	*Intelligence Quotient*
INCB	*International Narcotics Control Board*
LDH	*Lactate dehydrogenase*
MDMA	3,4-methylenedioxymethamphetamine
MMT	Methadone Maintenance Therapy
NGO	Non Government Organization
NMDA	N-Methyl-D-aspartic acid
NSEP	Needle Syringe Exchange Program
PASW	Predictive Analytic Software

RCFT	Rey Complex Figure Test and Recognition Trial
ROCF	Rey-Osterrieth Complex Figure Test
RPM	Ravens Progressive Matrices Test
THC	Tetrahydrocannabinol
UNAIDS	United Nations AIDS Program
UNODC	United Nations Office on Drugs and Crime
USM	University Sains Malaysia
VTA	Ventral Tegmental Area
WAIS	*Wechsler Adult Intelligence Scale*
WHO	World Health Organization

FUNGSI NEUROKOGNITIF DALAM PENGGUNA DAUN KETUM (*MITRAGYNA SPECIOSA* KORTH) DI BAHAGIAN UTARA SEMENANJUNG MALAYSIA

ABSTRAK

Penyalahgunaan Ketum (*Mitragyna speciosa* Korth) telah meningkat sejak kebelakangan ini di Malaysia. Banyak kajian farmakologi berkenaan kesan ketum ke atas haiwan telah dijalankan. Namun kajian corak pengunaan ketum ke atas fungsi neuropsikologi manusia adalah terhad.

Untuk mengukur fungsi neurokognitif pengguna daun ketum di bahagian utara semenanjung Malaysia dan membandingkan dengan subjek sihat yang tidak menggunakan dadah (kumpulan kawalan) serta dengan penagih heroin. Membandingkan fungsi neurokognitif pengguna daun ketum jangka pendek dan jangka panjang.

Kajian keratan lintang telah dijalankan di tiga negeri yang terletak di bahagian utara semenanjung Malaysia, menggunakan kaedah persampelan bertujuan dan persampelan rujukan rantaian, di mana sebanyak 116 peserta (41 penagih heroin, 43 pengguna daun ketum aktif, dan 32 peserta yang bebas dari penyalahgunaan dadah) terlibat dalam kajian ini. Lima kajian neuropsikologi bukan lisan (Digit Span Test, Block Design Test, Ravens Progressive Matrices Test, Benton Visual Form Discrimination Test, and Rey-Osterrieth Complex Figure Test) telah diuji ke atas semua peserta.

Semua peserta adalah lelaki yang berumur antara 18-65 tahun. Peserta heroin berpendidikan rendah, bujang, menganggur dengan berpendapatan rendah berbanding dengan dua kumpulan yang lain. Hasil kajian menunjukkan bahawa pengguna daun ketum menunjukkan prestasi yang kurang dalam kebolehan persepsi visuospatial yang diukur dengan ujian ROCF berbanding kumpulan pengguna heroin. Perbezaan signifikan juga telah dikesan diantara kumpulan pengguna heroin dan kumpulan kawalan dalam aspek tumpuan menggunakan ukuran ujian "Digit Forward". Perbandingan pengguna daun ketum jangka pendek dan panjang menunjukan bahawa pengguna daun ketum jangka panjang tidak menunjukkan masalah di bahagian hujah analogi, fungsi eksekutif, dan memori visual.

Walaupun tiada bukti kukuh kemerosotan dalam fungsi neurokognitif pengguna daun ketum dalam kajian ini, tetapi kajian menunjukkan bahawa terdapat kemerosotan dalam keupayaan persepsi visuospatial yang akan menjejaskan pelbagai tugasan harian seperti membaca, menulis, mengira dan memandu. Kesimpulan tidak dapat dibuat untuk mengaitkan bahawa kemerosotan yang berlaku pada pengguna daun ketum adalah akibat langsung dari penggunaan daun tersebut. Kemungkinan kemerosotan tersebut telah berlaku sebelum mereka mula menggunakan daun ketum. Oleh itu, disyorkan supaya kajian prospektif bersama dengan kajian teknik pengimejan otak dilaksanakan untuk membuktikan bahawa daun ketum tidak atau mempunyai kesan minima terhadap fungsi kognitif manusia.

NEUROCOGNITIVE FUNCTIONING IN KETUM (*MITRAGYNA SPECIOSA* KORTH) LEAF USERS IN NORTHERN PARTS OF PENINSULAR MALAYSIA

ABSTRACT

Abuse of ketum (*Mitragyna speciosa* Korth) has increased recently in Malaysia. While there are extensive pharmacological studies of ketum effects on animals, human studies on patterns of neuropsychological function of ketum leaf users are limited.

To measure the neurocognitive function of ketum users in the northern parts of peninsular Malaysia and compare it with that of healthy non-drug users (control group) and heroin dependents, also to compare the neurocognitive function of long term and short term ketum users.

A cross sectional study conducted in three northern states of peninsular Malaysia using purposive sampling and chain referral methods and total of 116 participants (41 heroin dependents, 43 active ketum users, and 32 non drug users) were included. Five non verbal neuropsychological tests (Digit Span test, Block Design test, Ravens Progressive Matrices test, Benton Visual Form Discrimination test, and Rey-Osterrieth Complex Figure Test) were administered in all participants.

All participants were males aged 18-65 years. Heroin participants were less educated, single, and more unemployed with lower income levels than the other two groups. Results showed a significantly poorer performance by ketum users on visuospatial perception ability measured by ROCF test compared to the heroin group.

Significant difference was also found between heroin and control group on attention measured by digits forward test. Comparing long-term and short-term ketum users revealed that domains of analogical reasoning, executive functioning, and visual memory are not impaired in long-term ketum users.

Despite no evidence of substantial impairment in neurocognitive function among ketum users in this study, there was a significant impairment in their visuospatial perception ability which affects many daily tasks such as reading, writing, arithmetic, and driving. There is no definite conclusion that the impairment in ketum users is a direct result of their ketum use. There is a possibility that these impairments were present in the users even before the initiation of their addiction. Further prospective studies together with brain imaging techniques are recommended to prove no or minimal effects of ketum use on human cognitive function.

CHAPTER 1

INTRODUCTION

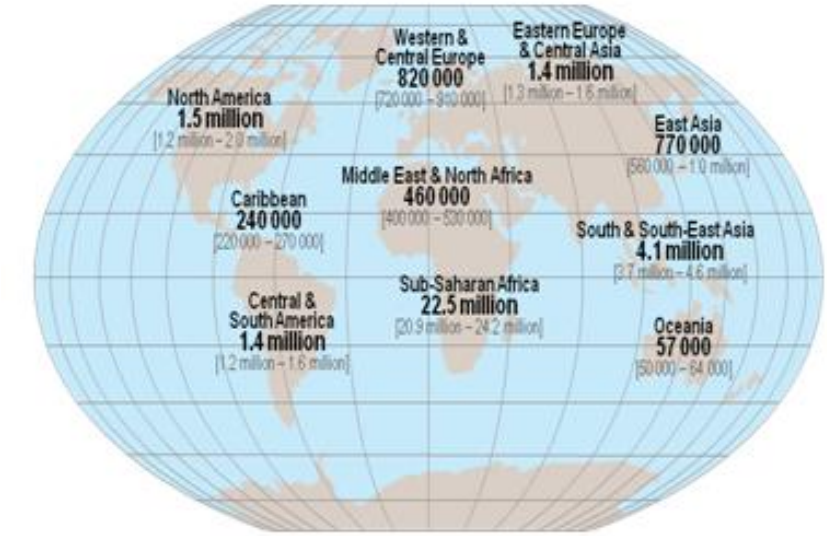
1.1 Drug Abuse in the World

It is estimated that in 2009, 3.3% to 6.1% of the world's aged 15-64 population (149 to 272 million people in the world), used some kind of substances in the past year (United Nations Office of Drugs and Crime [UNODC], 2011). Estimations also show that in the same year, half of this population were current drug users who used drugs at least once in the previous month. Cannabis is reported to be the most widely used illicit drug followed by amphetamine-type stimulants (ATS) and opioids including opium and heroin. Trends of heroin use in almost all areas of the world are mostly stable or downward while use of synthetic and prescription drugs is reported to be increasing (UNODC, 2011).

According to WHO, 148 countries reported injecting drug use of which 120 of them reported HIV infection amongst this population (World Health Organization [WHO], 2011). In 2009, there were an estimated 33.3 million people (31.4 million – 35.3 million) living with HIV (Figure 1.1), 2.6 million new HIV infections, and 1.8 million AIDS-related deaths (United Nations program on HIV/AIDS [UNAIDS], 2010). Over 7000 new HIV infections a day reported in 2009 and about 6000 were in adults aged 15 years and older, of whom almost 51% were among women and about 41% were among young (15-24 years) people (UNAIDS, 2010).

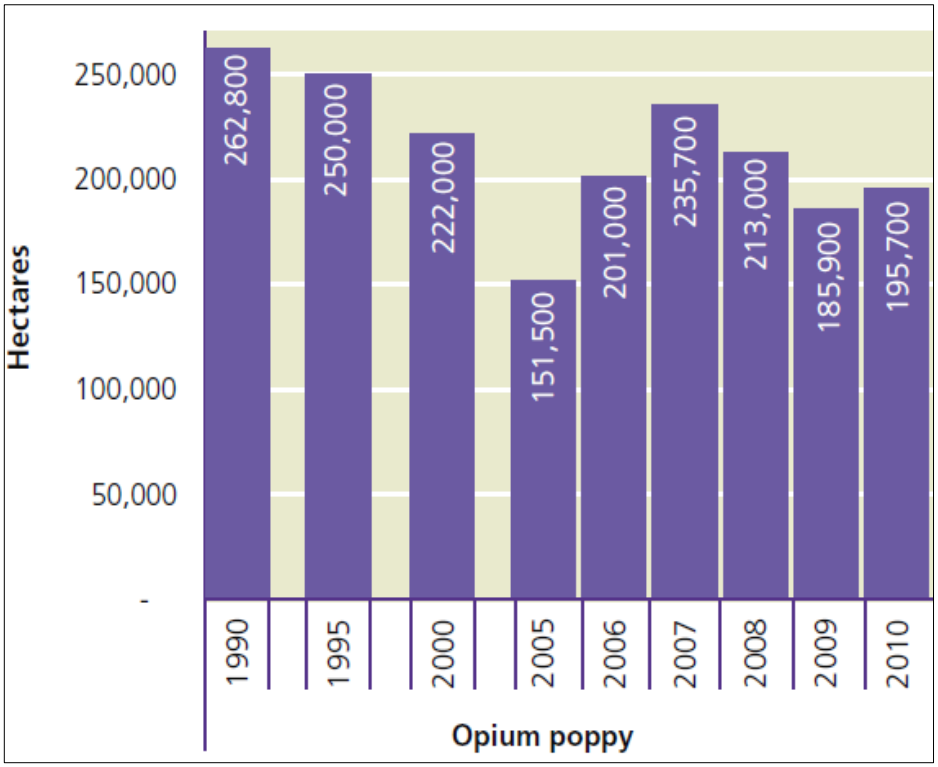
According to the World Drug Report 2011, 11 to 21 million people within the age range of 15-64 are injecting drugs. Approximately 17.9% of drug users who

inject their drugs (2.8 million people) are HIV positive. This shows that one fifth of injecting drug users are living with HIV. It is also estimated that about half (45.2 % - 55.3%) of the injecting drug users are infected by hepatitis C virus (UNODC, 2011). Also 104,000 to 263,000 deaths per year is estimated to be related or associated with drug use and more than half are because of overdose (UNODC, 2011).



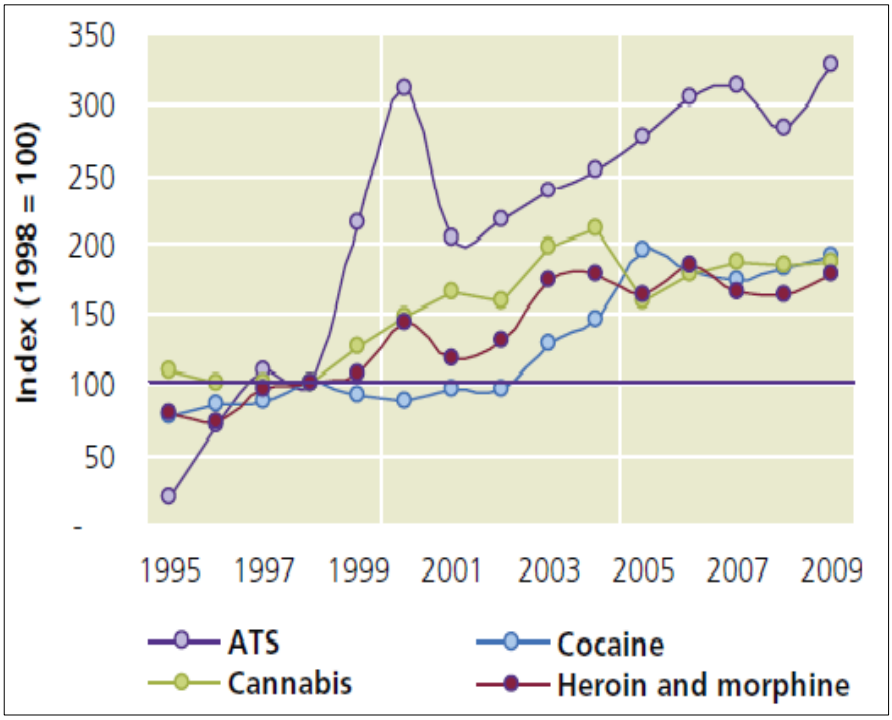
Source. (UNAIDS, 2010)
Figure 1.1. Adults and children estimated to be living with HIV in the world

Although there was a steady decrease in the global cultivation of opium poppy from 2007 (235,700 ha) to 2009 (185,900 ha), global opium cultivation has increased slightly from 185,900 ha in 2009 to 195,700 ha in 2010 (Figure 1.2). The major of opium which is cultivated in Afghanistan remained stable and the global increasing trend is mainly due to cultivation in Myanmar with an increase of 20%. However, opium production in the world has been reduced from 7,853 in 2009 to 4,860 in 2010 due to the disease of poppy plants in Afghanistan (UNODC, 2011).



Source: (UNODC, 2011)
Figure 1.2. Global opium poppy cultivation (ha), 1990-2010

It was reported in the World Drug Report 2010 that drug use is shifting towards new drugs and new markets. The report indicated that compared to the developing countries where drug use is increasing, in the developed countries drug use has stabilized. It is also reported that abuse of amphetamine-type stimulants (ATS) and prescription drugs are growing all over the world (UNODC, 2010). Figure 1.3 shows long-term trends in the volume of seizures for all major drug types according to the World Drug Report 2011 published by UNODC.



Source. (UNODC, 2011)
Figure 1.3. Trends in the volume of seizures, by main drug categories

1.2 Drug Abuse Definition

Drug abuse is the habitual use of any chemical substance to alter the state of the person's body or mind for non medical purposes. There are various systems for classifying drugs, for instance by origin (those that come from plants, such as the opiates), by therapeutic effects, by the site of drug action (which parts of the body physical changes due to the drug are appeared, for example by this classification alcohol is a depressant and cocaine is a stimulant drug), by chemical structure, by mechanism of action or by street name (Maisto, Galizio, & Connors, 2010).

1.3 Drug Abuse in Malaysia

Heroin epidemic in Malaysia began in the late 1970 and is present until today (Chawarski, Mazlan, & Schottenfeld, 2006). There are nearly 12- 21 million people who used opiates in the world and from this total 75% used heroin. The key consumption markets for opiates are Europe and Asia. In 2009, heroin was the principal drug used in countries including China, Malaysia, Myanmar, Singapore, and Vietnam (UNODC, 2011).

According to the Malaysian department of statistics (DOS) online services total population of Malaysia is about **28,607,000.** In Malaysia from 1988 to 1998, 162,750 drug addicts were identified and 88,527 of them were recognized as first time users. This means that approximately 0.73% of Malaysia's population were drug addicts at that time (Karofi, 2005). In 2006 the total number of drug users recorded by the AADK (Agensi Antidadah Kebangsaan) was 300,241 people, about 1.1% of Malaysia's population.

According to the last report of the International Narcotics Control Board (INCB), which was released in 2009, the most commonly abused drug in Malaysia is heroin. Based on this report about 61 percent of drug users in the country abuse heroin and 120,000 of them inject their drugs (International Narcotics Control Board [INCB], 2009).

Abuse of some drugs increased in 2011 compared to the same period in the previous year. This is evident from the drugs that are seized by Malaysian enforcement agencies (Royal Malaysia police, Royal Malaysian Customs and the Ministry of Health Malaysia). Some of these drugs are listed as: raw opium,

methamphetamine, ecstasy tablet, heroin, and ketum (AADK, 2011). Detailed information is presented in Table 1.1.

Table 1.1

Type of drugs used in Malaysia in 2011 (January-October) and 2010

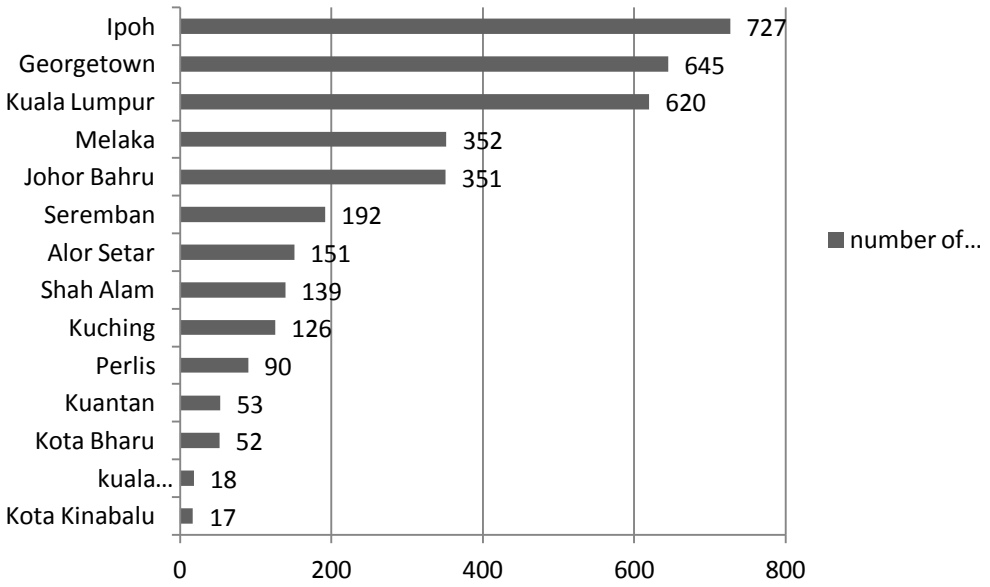
Drugs	**2011**	**2010**	**Index**
Heroin base (kg)	254.45	30.54	↑
Heroin No.3 (kg)	390.65	216.01	↑
Heroin No.4 (kg)	30.6	30.584	↑
Marijuana (kg)	984	1006.13	↓
Raw opium (kg)	0.74	0.01	↑
Cook opium (kg)	0.12	4.36	↓
Cocaine (kg)	1.76	20.57	↓
Methamphetamine (kg)	992.18	788.1	↑
Ecstasy powder (kg)	26.45	100.86	↓
Ecstasy tablet (N)	96205	37088	↑
Yaba tablet (N)	250534	84649	↑
Psychotropic tablet (N)	374329	264486	↑
Eramin 5 (N)	1079403	2012177	↓
Ketamine (kg)	184.27	263.92	↓
Codeine (liter)	2295.22	27185.39	↓
Ketum (liter)	85058.35	6484.36	↑
Ketum (kg)	2784.21	1637.55	↑

Source. (AADK, 2011)

Figure 1.4 describes the number of addicts detected in all state capitals in Malaysia during January-October 2011. Numbers are low because following harm reduction (HR) approaches that are being implemented in Malaysia, most of the drug

users attended in the Needle and Syringe Exchange Program (NSEP) and Methadone Maintenance Therapy (MMT) program and not many drug users were arrested since then (NSEP was introduced in 2006 and MMT was introduced in 2005 in Malaysia). Georgetown (capital of Penang state) is amongst the states which have high numbers (645) of newly detected addicts (AADK, 2011).

It should be mentioned that in addition to the synthetic drugs being abused in Malaysia, there are also natural substances that are being abused. One of these substances is *Mitragyna speciosa* Korth (ketum) which is more prevalent in the rural areas especially in the northern states of peninsular Malaysia and based on the last AADK report (January- October 2011) its abuse increased in 2011 compared to the same period previous year.



Source. (AADK, 2011)

Figure 1.4. Drug distribution in all state capitals for January-October 2011

1.4 Ketum

Ketum “biak” is a regional name for *Mitragyna speciosa* Korth in Malaysia (Figure 1.5). In Thailand it is usually called kratom. *Mitragyna speciosa* is a psycho-stimulant plant belongs to the Rubiaceae family and Mitragyna genus, in the same family as coffee tree. It is found natively in Southeast Asia and is cultivated especially in central and southern parts of Thailand and northern parts of peninsular Malaysia. It is a tropical and non-seasonal plant which is sensitive to drought and cold (Harizal, Mansor, Hasnan, Tharakan, & Abdullah, 2010).

Ketum leaves were traditionally used to alleviate diarrhoea, fever, cough, diabetes, and pain. They were also used for their stimulant effect to enhance workers energy and also for their opium like effects as a substitute for opioids (Chan, Pakiam, & Rahim, 2005; Jansen & Prast, 1988; Suwanlert, 1975).

Figure1.5. Ketum leaves and trees

Earliest pharmacological studies of *Mitragyna speciosa* were done in 1932 and ketum was reported as a treatment for opium withdrawal symptoms (Jansen & Prast, 1988). Later investigations revealed morphine-like antinociceptive activity of Mitragynine alkaloids through the opioid receptors (Matsumoto et al., 1996). Mitragynine is the major constituent of *Mitragyna speciosa* (Kumarnsit, Keawpradub, & Nuankaew, 2006) and acts in animals' gastrointestinal system through the opioid receptors (Tsuchiya et al., 2002; Watanabe, Yano, Horie, & Yamamoto, 1997). The minor component of *Mitragyna speciosa*, 7-Hydroxymitragynine, showed almost 13 times higher potency than morphine in animal studies (Matsumoto et al., 2004). This component develops tolerance and withdrawal signs through similar opioid mechanisms for morphine (Matsumoto et al., 2005). The most potent opioid agonistic effect is found in MGM-9 which produces more antinociceptive effects and less adverse effects than morphine (Matsumoto et al., 2008).

In animal behavioral studies, methanol and alkaloid extracts of *Mitragyna speciosa* leaves had no significant effect on pentobarbital-induced sleep or in locomotor activity in mice and rats (Moklas et al., 2008; Reanmongkol, Keawpradub, & Sawangjaroen, 2007).

In a recent behavioral study, object placement task which is a valid animal model for assessing object recognition in mice, was administered to evaluate the effect of mitragynine on this cognitive function and results showed significant impairments in the performance of mice (Apryani, Hidayat, Moklas, Fakurazi, & Idayu, 2010).

1.5 Ketum Studies in Human

There are limited studies about ketum use in human. Existing studies are upon the self reports of participants about using ketum. In a study conducted in Thailand in 2007, it has been shown that Thai ketum users use ketum primarily to increase their work capacity. In another study performed in Malaysia, it has been shown that the majority of ketum users use it because it reduces addiction to other drugs, helps to improve withdrawal effects from opiate addiction and it is more affordable relative to heroin (Vicknasingam, Narayanan, Beng, & Mansor, 2010b). However, these were self-reports by ketum users and no objective measures were used to measure these effects.

There are some studies which were done in United States, UK, and Germany including a case report of 43 years old male who used ketum to self-manage the chronic pain and opioid withdrawal in US (Boyer, Babu, Adkins, McCurdy, & Halpern, 2008), a case of young man with intra-hepatic cholestasis following abuse of powdered ketum (Kapp, Maurer, Auwärter, Winkelmann, & Hermanns-Clausen, 2011), and a 44 years male with inpatient detoxification after ketum dependence (McWhirter & Morris, 2010). Another study is a study upon internet postings about ketum which shows a remarkable increase in the number of ketum users who use ketum to modulate opioid withdrawal symptoms in the United States (Boyer, Babu, Macalino, & Compton, 2007).

1.6 Statement of Problem

Chronic use of opiates such as heroin and morphine leads to cognitive impairments (Cipolli & Galliani, 1987; Guerra, Solé, Camí, & Tobeña, 1987; Hauser, Houdi, Turbek, Elde, & Lii, 2000; Spain & Newsom, 1991; Yin et al., 2006). It has been shown that abuse of heroin which is one of the most commonly abused drugs is linked to poorer performance on attention and memory tasks (Guerra et al., 1987). It is suggested that opiates affect structures of the brain that are related to memory and learning such as hippocampus and it has been shown that chronic exposure to morphine reduces the viability of fetal mouse hippocampus neurons significantly and dose dependently (Svensson, Bucht, Hallberg, & Nyberg, 2008). In addition opiates elicit apoptosis in human neurons via opioid receptor mechanism (Hu, Sheng, Lokensgard, & Peterson, 2002).

In animal studies it has been determined that Mitragynine and two other components of *Mitragyna speciosa* (7-Hydroxymitragynine and MGM-9) develop tolerance and withdrawal signs through similar opioid mechanisms to morphine (Matsumoto et al., 2004; Matsumoto et al., 2005; Matsumoto et al., 2008; Tsuchiya et al., 2002; Watanabe et al., 1997).

Ketum abuse has increased in recent years in Malaysia based on national drug reports by AADK. Despite of many studies about the effects of *Mitragyna speciosa* and its components in animals, human studies about ketum is scarce. Existing few human studies are descriptive studies outside a treatment setting. In the most recent study performed in northern parts of Peninsular Malaysia, users reported that they found ketum as an affordable way to reduce their addiction to opioids and it also eases the withdrawal symptoms for them. Although the majority of ketum users

reported difficulty in withdrawing from ketum, ketum withdrawal symptoms were less irritating than those from other drugs they used before (Vicknasingam, et al., 2010b). There are no studies about ketum possible effects on the cognitive functioning in human. Hence a study on the neurocognitive function of ketum use in human will help identify if ketum use is safe and can be potentially used in treatment programs for drug users.

1.7 Research Questions

Based on the statement of problem this study will attempt to answer two questions below:

a) What are the neurocognitive effects of ketum use in humans?

b) What are the differences in neurocognitive functioning between ketum users and heroin users?

1.8 Study Objectives

a) To measure the neurocognitive function of ketum users in the northern parts of peninsular Malaysia
b) To compare the neurocognitive function of ketum users and healthy non-drug users.
c) To compare the neurocognitive function of ketum users and heroin users
d) To compare the neurocognitive function of long term and short term ketum users

1.9 Scope of Study

The northern states of peninsular Malaysia consist of four states (Perlis, Kedah, Penang and Perak). Based on the data provided by key informants, there are more ketum users in the states of Kedah, Perlis and Penang. For this reason this study was carried out in the states of Kedah, Perlis, and Penang.

1.10 Significance of Study

This study is the first known study about the neurocognitive functioning of ketum use in humans and will provide the neurocognitive profile with the emphasis on attention, visual memory, visuoperceptual abilities, visuoconstructional abilities, and executive functioning in ketum users and this will be compared with heroin users, and healthy non-addicts. It is hoped that this study will present insights about possible neurocognitive impairments related to ketum use.

In addition, this study will also provide data on the neurocognitive function of heroin users in the country since there has been no known study to measure this in Malaysia. While, there are some studies about neurocognitive functioning in opiate users in other countries, it is clear that this function depends on many factors, like the type and the amount of drug, the stage when the participants were evaluated, and the cultural and regional factors.

1.11 Study Limitations

Recruitment limitations: non-random sampling technique is limitation of the study. As the study was conducted in the community it was not possible to use probability sampling techniques. However, purposive sampling technique used together with chain referral sampling technique ensured that participants were representative across the three groups of samples.

Another limitation is that it was difficult to recruit only heroin users as most heroin users in the country are poly drug users. Therefore the results of the heroin group may not reflect the effect of heroin on their neurocognitive function.

Interviewing and testing limitation: Obtaining some of the information was based on the self report and data derived from this source is always biased by the impaired memory or even in healthy people due to recall bias. To ensure this limitation we used a Timeline Follow back (TLFB) method to obtain information regarding their drug use. Secondly, to perform the tests the environment requires being silent and well lightened with no or less distractions while in this study the interviews were done in small rooms or even outreach shelters for drug users and the researchers in some sites were unable to eliminated the distracting factors such as noise. During the study the researchers tried to minimize the effects of intoxication or withdrawal in heroin group participants while performing the tests. However, this is not possible to differentiate the participants who are between two ranges with varied degrees of concentration.

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

In this chapter related and important literature in this study will be discussed. The terms and definitions used in this study, structural concepts, statistical facts, and relevant studies will all be included in this chapter.

2.1 Drug Abuse

The origin of the word drug is from a French word "drogue" which means "a dry substance" as dried herbs were widely used to prepare most of the pharmaceuticals at that time (Abadinsky, 2010). According to the World Health Organization (WHO) report published in 1981, drug is defined in the broadcast sense as "any chemical entity or mixture of entities, other than those required for the maintenance of normal health (like food), the administration of which alters biological function and possibly structure". Some experts today prefer to use substance abuse instead of the term drug abuse as there is no distinctive definition for the term drug.

Table 2.1 shows the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) definition of substance dependence.

Table 2.1

DSM-IV Diagnostic Criteria for Substance Dependence

Substance Dependence:

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12 month period:

1. Tolerance, as defined by either of the following:
   (a) Need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) Markedly diminished effect with continued use of the same amount of the substance

2. Withdrawal , as manifested by either of the following:
   (a) The characteristic withdrawal syndrome for the substance
   (b) The same (closely related) substance is taken to relieve or avoid withdrawal symptoms

3. The substance is often taken in larger amounts or over a longer period than was intended

4. A persistent desire or unsuccessful efforts to cut down or control substance use

5. A great deal of time is spent in activities necessary to obtain the substance(e.g., visiting multiple doctors or driving long distances), to use the substance(e.g., chain-smocking), or to recover from its effects

6. Important social, occupational, or recreational activities given up or reduced because of substance use

7. Continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem that is likely to be caused by or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine –induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Specify if:

With physiological dependence: evidence of tolerance or withdrawal (that is, either item [1] or [2] is present).

Source. Diagnostic and statistical manual of mental disorders, fourth edition, 1994

2.2 History of Ketum Use

The local name for the leaves of the tropical plant *Mitragyna speciosa* Korth in Malaysia is ketum or biak. *Mitragyna speciosa* Korth is a medicinal plant native to Southeast Asia especially grown in central and southern parts of Thailand and northern states of peninsular Malaysia. In southern Thailand these leaves are usually called krathom (Chan et al., 2005).

Use of ketum as a substitute for opiates in Malaysia was published for the first time in 1836 by Low and again mentioned in 1895 by Holmes who described ketum as *Mitragyna speciosa* (Jansen & Prast, 1988). In 1907, opium like effects of ketum apart from of its method of administration was described by Wray and it was stated that using large amounts of ketum products lead to stupor in users. In 1921, Field isolated Mitragynine alkaloid from *Mitragyna speciosa* in the University of Edinburgh. In 1930 Burkill stated the use of ketum in treatment of fever and as a wound poultice. He also recorded it as a suppressor for opiate withdrawal symptoms (Jansen & Prast, 1988).

First serious pharmacological studies were performed on animals at the University of Cambridge by Grewal in 1932 (Grewal, 1932b) and in this report it was mentioned that Mitragynine is a central nervous system stimulant which resembles cocaine in effect and has been widely consumed in Thailand by farmers to enhance their work effectiveness. In his report ketum addicts were described as being thin, unhealthy with dry skin and dark lips (Grewal, 1932a).

The first case of ketum addiction in human was reported by Thuan in 1957 and the effects again mentioned as “like cocaine”. This case was a chronic male ketum

user with withdrawal symptoms who stated that ketum habit caused no changes on his physical or mental condition (Jansen & Prast, 1988).

In Thai narcotic book it was mentioned that ketum is weaker than morphine, less damaging than cocaine and causes milder withdrawal symptoms than opiates. It has both coca like stimulant and opiate and cannabis like depressive effects simultaneously. In this book medical uses of ketum in treating addicts in Thailand have been described (Jansen & Prast, 1988).

By applying new analytic techniques in 1972 mitragynine was found to be comparable with codeine in animal studies in analgesic and cough suppressant effects with much less side effects than codeine. Great doses of mitragynine in cats had stimulating consequences which were different from what opiates caused. It was also found that mitragynine is much more active orally than subcutaneously suggesting that its metabolites might be the active analgesic (Jansen & Prast, 1988; Macko, Weisbach, & Douglas, 1972).

Ketum also has been used by local healers for treatment of medical problems such as diarrhea, diabetes mellitus, and also for improving blood circulation. Addictive nature of ketum, its withdrawal symptoms and its side effects of long-term use were reported in 1975 in Thailand (Suwanlert, 1975).

Two types of ketum plant, one with red and another one with green veins in the leaves exist in Thailand and it is thought that the red vein variety plant has more biological activities (Chittrakarn, Sawangjaroen, Prasettho, Janchawee, & Keawpradub, 2008).

In recent years there has been an increase in the number of drug addicts who use ketum as their main drug of abuse. Compared to other drugs which are strictly controlled accessing ketum is easier and it is also more affordable because of its easy availability and significantly lower prices (Chan et al., 2005).

2.3 Legal Aspects of Ketum Use

In Thailand planting, possession, import and export of ketum are illegal since 1943 (Assanangkornchai, Muekthong, Sam-angsri, & Pattanasattayawong, 2007). While in Malaysia ketum use was only banned since 2003. In Malaysia planting of the tree is not an offence but as Mitragynine (the major component of ketum) was listed in the first and third schedule of the poisons act 1952, possession and selling any ketum preparations containing Mitragynine carries a fine of RM 10,000 (US$1 = 3 RM), a four year jail sentence or both (Chan et al., 2005).

Ketum detection in different types of its products (drinks, powdered or macerated leaves) can be made only by identifying the presence of Mitragynine by specific gas chromatography methods (Chan et al., 2005).

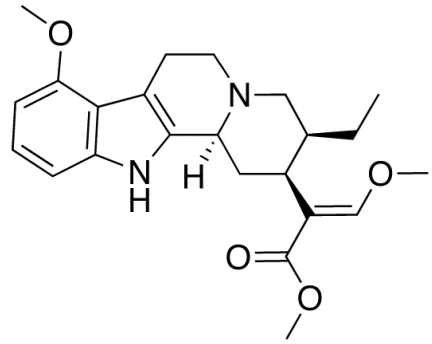
Although ketum use is illegal or controlled in some countries including Malaysia, Thailand, Myanmar, south Korea, Australia, new Zealand, Finland, Germany, Romania, and Denmark, its use in most of other countries in the world is uncontrolled and ketum can be purchased online (Chittrakarn et al., 2008; Erowid, 2004).

2.4 Pharmacological Studies

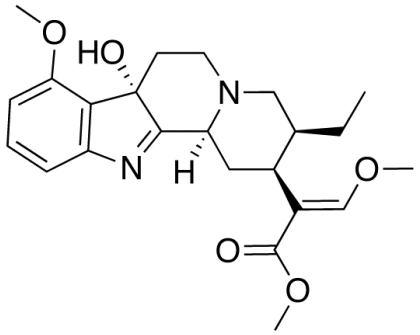
The earliest formal pharmacological studies were carried out in 1932 and the cocaine like stimulant effect of mitragynine was identified (Grewal, 1932b). In 1960 applying new analytic methods, several indole alkaloids were isolated from ketum leaves and in 1978 Shellard et al, isolated more than twenty alkaloids of *Mitragyna speciosa* Korth (Jansen & Prast, 1988; Takayama, 2004).

Mitragynine found to be the major component with about 66% of basic extract of *Mitragyna speciosa* Korth (Figure 2.1). 7-Hydroxymitragynine is the minor constituent (2%) of *Mitragyna speciosa* with higher opioid receptor binding affinity than mitragynine and has long been used in traditional Thai medicine for its opiate-like effect (Takayama, 2004; Takayama et al., 2002).

Mitragynine was found to be an opioid receptor agonist that inhibits the electrically stimulated contraction in guinea-pig ileum and gastric acid secretion in rats (Tsuchiya et al., 2002; Watanabe et al., 1997; Yamamoto et al., 1999). Mitragynine also showed morphine-like antinociceptive activity in in-vitro and in-vivo experiments through supraspinal μ and δ opioid receptors (Matsumoto et al., 1996; Thongpradichote et al., 1998; Tohda et al., 1997). Later studies showed that analgesic activity of methanol and alkaloid extracts of ketum is partly related to opioid receptors in supraspinal opioid system (Reanmongkol et al., 2007). Mitragynine inhibits the pain transduction in guinea pigs vas deferens by blocking the calcium channels while opioid receptors are not involved in this process (Matsumoto et al., 2005b).



Mitragynine



7-hydroxymitragynine

Figure 2.1. Chemical structures of mitragynine and 7-hydroxymitragynine
Source. (Matsumoto et al., 2004)

Mitragynine pseudoindoxyl (a derivative compound of mitragynine) was much more potent opioid agonist than morphine but had less antinociceptive effect comparing with morphine (Takayama, et al., 2002; Yamamoto, et al., 1999).

The most potent opioid agonistic effect is found in MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate] which produces more antinociceptive effects and less adverse effects than morphine (Matsumoto et al., 2008).

7-hydroxymitragynine has opioid agonistic effect through μ, δ, and κ opioid receptors but receptor-binding analyzes showed higher affinity of this constituent for μ opioid receptors than other types of opioid receptors. 7-hydroxymitragynine exhibits higher antinociceptive effect than that of morphine, especially with oral administrations (Matsumoto et al., 2004; Takayama et al., 2002). 7-

hydroxymitragynine develops tolerance and withdrawal signs through similar opioid mechanisms for morphine (Matsumoto et al., 2005a).

Administration of *Mitragyna speciosa* aqueous and alkaloid extract induces antidepressant effect maybe through serotonin or noradrenalin neurotransmitters and also reduces the ethanol withdrawal symptoms in mice. These results in animal studies suggest that mitragynine could have a role in managing the depressive disorders (Idayu et al., 2011; Kumarnsit, Keawpradub, & Nuankaew, 2007a; Kumarnist, Vongvatcharanon, Keawpradub, & Intasaro, 2007b).

Acute and chronic administration of certain doses of *Mitragyna speciosa* alkaloid extract significantly decline voluntary food and water consumption in rats. Gaining body weight is considerably suppressed by chronic administration of alkaloid extracts. These results confirm the imipramine like anorectic effect of *Mitragyna speciosa* extract without making any clear tolerance (Kumarnsit et al., 2006).

Inhibitory effects of *Mitragyna speciosa* extract on food and water intake have different underline mechanisms. Rather than opioid related mechanism that is thought to mediate the food intake inhibition effect of *Mitragyna speciosa* extract, as water intake is inhibited by activation of adrenergic and serotonergic systems, it is suggested that *Mitragyna speciosa* extract may act on these central systems to induce its water intake suppression effect. All together it is proposed that food intake suppressing effect of *Mitragyna speciosa* extract indirectly reduces the blood glucose level (Kumarnsit et al., 2006).

Ketum has been used by traditional healers to treat diarrhea and some gastrointestinal infections (Chittrakarn et al., 2008). Ketum methanolic extract had been used to treat castor oil induced diarrhea in rats and results were compared with the effects of loperamide (a μ opioid receptor agonist) as a standard anti-diarrheal drug and controls. Ketum methanolic extract reduced the severity of diarrhea, intestinal transit and fecal weight. The anti-diarrheal effect of ketum methanolic extract was same as that of loperamide but this effect was not antagonized by naloxone (Chittrakarn et al., 2008).

In fourteen days of acute toxicity evaluation no mortality or toxicity symptoms happened in rats given the toxic level of *Mitragyna speciosa* extract. Minimal changes in respiratory and nervous system were happened which were rapidly reversed. Single dose oral administration of *Mitragyna speciosa* extract in rats caused no significant changes in body weight, food and water consumption, absolute organ weight, hematological parameters and hippocampal neurons. However, significant increase in blood pressure, increased levels of ALT, LDH, cholesterol, urea, and creatinine in biochemistry assessments and abnormal liver cell morphology were observed (Harizal et al., 2010).

Ketum has been used traditionally by workers to manage the muscle pain and strain. *Mitragyna speciosa* methanol extracts reduced muscle contractions by a greater effect on neuromuscular junction than on the skeletal muscle or somatic nerve (Chittrakarn et al., 2010).

In animal behavioral studies, methanol and alkaloid extracts of *Mitragyna speciosa* leaves had no significant effect on pentobarbital-induced sleep or in locomotor activity in mice and rats (Moklas et al., 2008; Reanmongkol et al., 2007).

In a recent behavioral study, object placement task which is a valid animal model for assessing object recognition in mice, was administered to evaluate the effect of mitragynine on this cognitive function and results showed significant impairments in the performance of mice (Apryani et al., 2010)

2.5 Ketum Studies in Human

In a study conducted in Thailand in 1975 by Suwanlert, thirty ketum users who had been using ketum for more than five years were studied. Most dominant aspect of ketum addiction in this group was strong desire to do manual work. The leaves were chewed freshly or taken as powder by majority (90 %) of ketum users and salt was added to prevent constipation. They chewed ketum leaves three to ten times a day and reported that stimulant effects began in five to ten minutes. It was reported by almost all of the users that they had become addicted to ketum (Suwanlert, 1975). Several side effects were reported by ketum users including mouth dryness, anorexia, weight loss, and constipation. In long term ketum users, typical withdrawal symptoms like violent behavior, rhinorrhea, body aching and jerky movements were reported (Jansen & Prast, 1988; Suwanlert, 1975).

In another study in Thailand in 2007, 149 regularly ketum users who had been using ketum daily for more than five years, 168 irregular users (less than once a week in social circumstances or for medical purposes), and 116 nonusers participated and patterns and consequences of ketum use was studied in them. Most of the ketum users participated in the study (90.22%) mentioned that they worked harder and longer, felt happier and had a better mood following the consumption of ketum and only 4-14% of them reported negative effects. Among the negative effects