

**MEASURING DEPENDENCE SEVERITY OF KETUM
(MITRAGYNA SPECIOSA) USE AMONG KETUM LEAF USERS
IN MALYSIA**

by

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TABLES OF CONTENTS

Acknowledgement.....	ii
Table of Contents.....	iii
List of Tables.....	xiii
List of Figures.....	xv
List of Abbreviation.....	xvii
Abstrak.....	xx
Abstract.....	xxii

CHAPTER 1 - INTRODUCTION

1.0 Introduction.....	1
1.1 Global Drug Abuse Situation.....	1
1.2 The Drug Abuse Problem in Malaysia.....	4
1.3 Ketum (<i>Mitragyna speciosa</i> , Korth).....	10
1.4 Ketum Studies in Humans.....	12
1.5 Statement of Problem.....	14
1.6 Research Questions.....	16
1.7 Study Objectives.....	16
1.8 Scope of Study.....	17
1.9 Significance of Study.....	17
1.10 Study Limitation.....	17
1.11 Conclusion.....	19

CHAPTER 2 - LITERATURE REVIEW

2.0 Introduction.....	21
2.1 History of <i>Mitragyna speciosa</i> or ‘ketum’ usage.....	21
2.2 Pharmacological Studies on <i>M.speciosa</i>	24
2.3 Ketum Use in Humans.....	31
2.3.1 Ketum Dependence in Human.....	31
2.3.2 Ketum Withdrawal in Human.....	32
2.3.3 Ketum Craving in Human.....	35
2.4 Law on Ketum Use in Malaysia.....	35
2.5 Types of Illegal Drugs and its Effects on Human.....	36
2.5.1 Opiate.....	36
2.5.2 Cocaine.....	38
2.5.3 Methamphetamine.....	39
2.5.4 Cannabis.....	41
2.5.5 Amphetamine.....	43
2.5.6 Ketamine.....	44
2.5.7 Codeine.....	46
2.5.8 Benzodiazepine.....	46
2.5.9 Ecstasy.....	48
2.6 Early Addiction Theories.....	49
2.7 Drug Addiction and Diagnosis of Drug Dependence.....	50
2.7.1 Stages of Addiction.....	52

2.7.2 Diagnostic and Statistical Manual of Mental Disorders-4 th Edition.....	53
2.8 Withdrawal Theories.....	55
2.8.1 Corticotropin-releasing factor (CRF).....	56
2.8.2 Reinstatement.....	58
2.8.3 Cognitive-Behavioural Model.....	59
2.8.4 Person-Situation Interaction Theory.....	60
2.8.5 Cognitive Appraisal Theory.....	60
2.8.6 Self-Efficacy and Outcome Expectations.....	61
2.9 Craving Theories.....	62
2.9.1 Craving and Loss of Control.....	63
2.9.2 Urges and Craving.....	63
2.9.3 Theories of Craving-Conditioning Based Models.....	64
2.9.3.1 Withdrawal Model.....	65
2.9.3.2 Compensatory Response Model.....	66
2.9.3.3 Opponent-Process Model.....	67
2.9.3.4 Incentive Conditioning Model.....	68
2.9.4 Allostasis and Neuroadaptation.....	68
2.9.5 Activation of Behaviour.....	70
2.9.5.1 Dopamine and the Ventral Tegmental Area (VTA).....	71
2.9.5.2 Amygdala.....	72
2.9.5.3 Prefrontal Cortex.....	72
2.9.5.4 Nucleus Accumbens.....	73

2.9.6 Incentive-Sensitisation Model.....	73
2.9.7 Unified Framework for Addiction Model.....	75
2.9.8 Model of Interoceptive Dysregulation.....	77
2.9.9 Pavlovian (or classical) Conditioning.....	80
2.9.10 Prime Theory.....	82
2.9.11 Motivation: Positive and Negative Reinforcement Mechanisms.	84
2.10 Drug Substitution Treatment.....	85
2.10.1 Methadone.....	86
2.10.2 Opioid Antagonists.....	88
2.10.3 Opioid Agonists.....	89
2.10.4 Buprenorphine.....	90
2.11 Detoxification.....	91
2.11.1 Post-Withdrawal Interventions.....	92
2.12 Social Functioning.....	93
2.13 Study Instruments.....	94
2.13.1 ASI.....	98
2.13.2 Leeds Dependence Questionnaire (LDQ).....	100
2.13.3 Marijuana Craving Questionnaire-Short Form (MCQ-SF).....	102
2.13.4 Marijuana Withdrawal Checklist (MWC).....	103
2.14 Conclusion.....	104

CHAPTER 3 - METHODOLOGY

3.0 Introduction.....	105
3.1 Study Location and Population.....	105
3.2 Research Design.....	107
3.3 Sampling and Data Collection.....	107
3.4 Study Incentive.....	110
3.5 Sample Size.....	110
3.6 Study Respondents.....	111
3.7 Study Inclusion Criteria.....	111
3.8 Study Exclusion Criteria.....	112
3.9 Urine Test.....	112
3.10 Research Instruments.....	113
3.10.1 Addiction Severity Index Fifth Edition.....	113
3.10.2 Leeds Dependence Questionnaire (LDQ).....	116
3.10.3 Marijuana Withdrawal Checklist (MWC).....	118
3.10.4 Marijuana Craving Questionnaire-Short Form (MCQ-SF).....	119
3.11 Scoring.....	120
3.11.1 Leeds Dependence Questionnaires.....	120
3.11.2 Marijuana Withdrawal Checklist.....	120
3.11.3 Marijuana Craving Questionnaire-Short Form.....	121
3.11.4 Addiction Severity Index.....	121
3.12 Training of Interviewer.....	121
3.13 Translation Procedure.....	122

3.14 Measures Adopted to Minimize Acquiescence Biasness.....	123
3.15 Pilot Test.....	123
3.16 Data Analysis.....	124
3.17 Chromatographic Analysis.....	125
3.18 Ethical Approval.....	126
3.19 Conclusion.....	127
CHAPTER 4 - RESULTS	
4.0 Introduction.....	128
4.1 Sample Size.....	128
4.2 Respondent’s Sociodemographic Characteristics.....	128
4.2.1 Gender and Age.....	129
4.2.2 Ethnicity.....	129
4.2.3 Marital status.....	129
4.2.4 Employment.....	129
4.2.5 Occupation.....	130
4.2.6 Education.....	130
4.2.7 Accommodation.....	130
4.4.8 Income.....	130
4.2.9 Family use.....	131
4.2.10 Sociodemographic Characteristics of Medium and Long-Term Ketum Users.....	133
4.2.11 Summary of Respondent’s Sociodemographic Characteristics.	134

4.3 Ketum Use History.....	134
4.3.1 Methods of Use.....	134
4.3.2 Former-Drug Users.....	134
4.3.3 Duration of Ketum Use.....	135
4.3.4 Age of First Ketum Use.....	135
4.3.5 Daily Frequency of Ketum Use.....	136
4.3.6 Daily Quantity of Ketum Use.....	136
4.3.7 Reasons for Using Ketum.....	137
4.4 Family Views and Cessation Effects.....	138
4.4.1 Family Use.....	138
4.4.2 Sexual Performance.....	139
4.4.3 Need to Use Ketum Daily.....	140
4.4.4 Appetite.....	140
4.4.5 Social Functioning.....	140
4.4.6 Ketum Addiction.....	140
4.4.7 Sleeping Problems.....	141
4.4.8 Nervousness.....	141
4.4.9 Desire.....	142
4.4.10 Treatment for Ketum Use Problems.....	142
4.4.11 Days Suffered from Withdrawal.....	142
4.4.12 Abstinence History.....	143
4.5 Ketum Dependence.....	144
4.5.1 Severity of Ketum Dependence.....	144

4.5.2 Variables Associated with Severe Dependence.....	145
4.5.3 Variables Associated with Dependence Severity.....	149
4.6 Ketum Withdrawal.....	151
4.6.1 Physical Withdrawal Symptoms.....	153
4.6.2 Common Physical Withdrawal Symptoms.....	155
4.6.3 Psychological Withdrawal Symptoms.....	156
4.6.4 Common Psychological Withdrawal Symptoms.....	158
4.6.5 Withdrawal Severity in Medium and Long-Term Ketum Users..	159
4.6.6 Variables Associated with Severe Withdrawal.....	160
4.6.7 Variables Associated with Ketum Withdrawal.....	163
4.6.8 Common Physical Symptoms with Withdrawal Severity.....	165
4.6.9 Common Psychological Symptoms Associated with Withdrawal Severity.....	167
4.7 Ketum Craving.....	170
4.7.1 Craving Intensity with other Variables.....	174
4.7.2 Variables Associated with High Craving for Ketum.....	176
4.8 Addiction Severity Index (ASI-5 th Edition).....	177
4.8.1 Medical Problem.....	177
4.8.2 Employment Problem.....	179
4.8.3 Alcohol/Drug Problem.....	181
4.8.4 Legal Problem.....	182
4.8.5 Family/Social Problem.....	183
4.8.6 Psychiatric Problem.....	184

4.8.7 Composite Scores.....	186
4.9 Conclusion.....	187
4.9.1 Socio-Demographic Characteristics.....	187
4.9.2 Ketum Use History.....	187
4.9.3 Ketum Dependence Severity.....	188
4.9.4 Ketum Withdrawal Severity.....	188
4.9.5 Ketum Craving.....	189
4.9.6 Addiction Severity Index.....	189
 CHAPTER 5 - DISCUSSION	
5.0 Introduction.....	190
5.1 Sociodemographic Characteristics of Study Respondents.....	191
5.2 Respondents Ketum Use History.....	195
5.3 Ketum Dependence.....	197
5.4 Ketum Withdrawal.....	205
5.5 Ketum Craving.....	215
5.6 Social Functioning.....	220
5.6.1 Medical Status.....	223
5.6.2 Employment Status.....	224
5.6.3 Alcohol and Drug Status.....	225
5.6.4 Legal Status.....	226
5.6.5 Family/Social Relationship Status.....	226
5.6.6 Psychiatric Status.....	227

5.7 Conclusion.....	228
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CHAPTER 6 - CONCLUSION

6.0 Introduction.....	230
-----------------------	-----

6.1 Summary of Results.....	230
-----------------------------	-----

6.2 Study Implication.....	232
----------------------------	-----

6.3 Study Limitation.....	233
---------------------------	-----

6.4 Suggestions for Future Studies.....	234
-----------------------------------------	-----

6.5 Conclusion.....	234
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REFERENCES.....	235
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APPENDICES

LIST OF TABLES

	Page
Table 2.1 Measurement Tools	95
Table 2.2 Leeds Dependence Questionnaire	101
Table 3.1 Study Locations	106
Table 3.2 Study Instruments	113
Table 3.3 Internal Consistency, Test-retest and Interclass Correlation Coefficient Reliability Scores	125
Table 3.4 Mitragynine Content	127
Table 4.1 Demographic Characteristics of ($n=293$) Respondents	132
Table 4.2 Sociodemographic Characteristics of Medium and Long-term Users	133
Table 4.3 Duration of Ketum Use	135
Table 4.4 Dependence Severity of Medium and Long-term Ketum Users	145
Table 4.5 Variables Associated with Severe Dependence	148
Table 4.6 Variables Associated with Dependence Severity	149
Table 4.7 Physical and Psychological Withdrawal Symptoms	152
Table 4.8 Medium and Long-term Ketum Users Withdrawal Severity	159
Table 4.9 Variables Associated with Severe Withdrawal	160

Table 4.10	Factors Associated with Ketum Withdrawal Severity	163
Table 4.11	Common Physical Symptoms with Withdrawal Severity	165
Table 4.12	Common Psychological Symptoms with Withdrawal Severity	167
Table 4.13	Intensity of Ketum Craving	170
Table 4.14	Medium and Long-term Users Ketum Craving Intensity	172
Table 4.15	Craving Intensity with Other Variables	173
Table 4.16	Variables Associated with High Ketum Craving	176
Table 4.17	Composite Scores for ($n=293$) Ketum Users	186
Table 5.1	A Comparison of the Sociodemographic Characteristics between Four Other Studies	194
Table 5.2	A Comparison between the Withdrawal Effects of Four Other Studies	212

LIST OF FIGURES

	Page
Figure 1.0 Annual Prevalence and Number of Illicit Drug Users at the Global Level, In the Late 1990s-2009/2010	2
Figure 1.1 HIV Cases by Risk Factors	7
Figure 1.2 Ketum (<i>Mitragyna speciosa</i>)	10
Figure 2.1 <i>Mitragyna speciosa</i> Trees	21
Figure 2.2 Chemical Structures of Mitragynine and 7-Hydroxymitragynine	25
Figure 3.1 A Sketch of the Targeted Study Areas	109
Figure 4.1 Daily Frequency of Ketum Use	136
Figure 4.2 Daily Quantity of Ketum Use	136
Figure 4.3 Reasons for Ketum Use	137
Figure 4.4 Family Views	138
Figure 4.5 Sleeping Problems	141
Figure 4.6 Days Suffered from Ketum Withdrawals	142
Figure 4.7 Ketum Dependence Severity	145
Figure 4.8 Physical Withdrawal Symptoms	154
Figure 4.9 Seven Common Physical Withdrawal Symptoms	155
Figure 4.10 Psychological Withdrawal Symptoms	157
Figure 4.11 Psychological Withdrawal Severity Symptoms	158
Figure 4.12 Ketum Withdrawal Severity	159
Figure 4.13 Ketum Craving	172
Figure 4.14 Lifetime Hospital Admission	177

Figure 4.15	Medical Problems in the Last 30-days	178
Figure 4.16	Interviewer Severity Rating	179
Figure 4.17	Work Patterns in the Last Three Years	179
Figure 4.18	Employment Problems	180
Figure 4.19	Last Abstained from Ketum Use	181
Figure 4.20	Duration of Abstinence from Ketum Use	181
Figure 4.21	Detained by Police	182
Figure 4.22	Involvement in Criminal Activity	182
Figure 4.23	Spending Time with Family and Friends	184
Figure 4.24	Reported Psychiatric Problems in the Last 30-Days	185
Figure 5.1	Reasons for Using Ketum	196

LIST OF ABBREVIATIONS

AADK	Agensi Anti Dadah Kebangsaan
ACTH	Adrenocorticotropic Hormone
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
APA	American Psychiatric Association
ASI	Addiction Severity Index
AST	Aspartate Aminotransferase
ATS	Amphetamine Type Stimulants
BNST	Bed Nucleus of Stria Terminalis
BUP	Buprenorphine
BZ	Benzodiazepine
C&C	Care and Cure
CeA	Central Nucleus of the Amygdala
CNS	Central Nervous System
CR	Conditioned Response
CRF	Corticotropin Releasing Factor
CS	Conditioned Stimuli
DA	Dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
HCT	Hematocrit
HCV	Hepatitis C Virus

HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Adrenal
ICD-10	International Classification of Diseases
IDUs	Injecting Drug Users
IM	Interim Methadone
LAAM	Levo-Alpha Acetyl Methadol
LDQ	Leeds Dependence Questionnaire
MCHC	Mean Corpuscular Hemoglobin Concentration
MCQ-SF	Marijuana Craving Questionnaire Short Form
MDMA	3, 4-methylenedioxy- <i>N</i> -methylamphetamine
METH/MA	Methamphetamine
MMT	Methadone Maintenance Treatment
mRNA	Messenger Ribonucleic Acid
MS	Mitragyna Speciosa
MSM	Male Who Have Sex with Males
MWC	Marijuana Withdrawal Checklist
NADA	National Anti-Drug Agency
NADI	National Drug Information System
NMDA	<i>N</i> -Methyl- <i>D</i> -aspartate
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSEP	Needle Syringe Exchange Program
OST	Opiate Substitution Treatment

PUSPEN	Pusat Pemulihan Penagihan Narkotik
RBC	Red Blood Cells
STI	Sexually Transmitted Disease
THC	Tetrahydrocannabinol
UN	United Nations
UNAIDS	United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Sessions On HIV and AIDS
UNODC	United Office on Drugs and Crime
US	Unconditioned Stimuli
USA	United States of America
VTA	Ventral Tegmental Area
WBC	White Blood Cells
WHO	World Health Organisation

Definition of terminology

<i>Dependence</i>	Implies use which is more problematic, compulsive, and difficult to stop despite adverse consequences.
<i>Withdrawal</i>	Is a clinical syndrome of unpleasant, sometimes dangerous, signs and symptoms developing after a period of substance use ends. Efforts to relieve withdrawal symptoms may lead to further drug use.
<i>Craving</i>	The subjective desire for the effects of a drug. A strong desire or sense of compulsion to take the substance.

**MENGUKUR KETERUKAN PERGANTUNGAN TERHADAP KETUM
(*MITRAGYNA SPECIOSA*) DI KALANGAN PENGGUNA DAUN KETUM
DI MALAYSIA**

ABSTRAK

Ketum atau *Mitragyna speciosa* merupakan sejenis tumbuhan psikotropik semulajadi yang selalu digunakan untuk nilai perubatannya. Kajian mengenai penggunaan ketum masih terhad, oleh itu penyelidikan lanjutan diperlukan untuk mengkaji risiko kesan penggunaan jangka panjang dalam manusia. Tujuan kajian adalah untuk menentukan ciri-ciri sosiodemografi, mengukur tahap keterukan pergantungan ketum, keterukan penarikan ketum, tahap gian terhadap ketum dan menilai fungsi sosial pengguna daun ketum. Sejumlah 293 pengguna ketum telah ditinjau dari tiga negeri di utara semenanjung Malaysia (Pulau Pinang, Kedah dan Perlis). Kajian keratan rentas menggunakan teknik persampelan bukan-kebarangkalian (purposif dan kuota) telah digunakan untuk mengumpul data. Empat instrumen kajian iaitu Leeds Dependence Questionnaire, Marijuana Withdrawal Checklist, Marijuana Craving Questionnaire-Short Form, dan Addiction Severity Index telah digunakan untuk mengukur tahap keterukan pergantungan terhadap ketum dikalangan pengguna daun ketum. Semua peserta adalah lelaki, majoriti berbangsa Melayu. Lapan-puluh lima peratus mempunyai pekerjaan, 46% adalah di antara umur 18-25 tahun, 41% sudah berkahwin, manakala tiga-perlima telah menamatkan 11 tahun (SPM) pendidikan. Tujuh-puluh sembilan peratus melaporkan bahawa mereka perlu menggunakan ketum setiap hari, 83% melaporkan ketum boleh menyebabkan ketagihan jika digunakan dengan kerap, 64% mengalami masalah susah tidur, 67% menjadi gementar, 72% tidak dapat mengawal keinginan terhadap ketum dan 90%

mempunyai fungsi sosial yang baik. Tiada perbezaan yang signifikan diantara pengguna ketum jangka sederhana dan jangka panjang dari aspek keterukan pergantungan terhadap ketum ($p>0.243$), keterukan penarikan terhadap ketum ($p>0.322$) dan tahap gian terhadap ketum ($p>0.777$). Lima-puluh lima peratus daripada sampel menunjukkan pergantungan terhadap ketum yang teruk, 33% menunjukkan keterukan penarikan terhadap ketum dan didapati 23% menunjukkan kegiatan yang tinggi terhadap ketum. Mereka yang minum ≥ 4 gelas ketum setiap hari (*setiap gelas bersamaan dengan 350ml jus ketum segar*) lebih cenderung melaporkan pergantungan terhadap ketum yang teruk (OR: 4.09; 95%CI: 2.32-7.24; $p = 0.001$), penarikan terhadap ketum yang teruk (OR: 3.31; 95%CI: 1.96-5.59; $p = 0.001$) dan gian tinggi terhadap ketum (OR: 2.47; 95%CI: 1.41-4.34; $p = 0.001$). Tambahan pula, tiada kesan ketara dalam fungsi sosial pengguna ketum jangka sederhana dan jangka panjang. Tidak terdapat perbezaan ketara diantara pengguna ketum jangka sederhana dan jangka panjang dalam keterukan pergantungan terhadap ketum dan fungsi sosial. Lebih banyak kajian khasnya kajian klinikal diperlukan untuk menunjukkan keselamatan penggunaan ketum dalam manusia.

**MEASURING DEPENDENCE SEVERITY OF KETUM (*MITRAGYNA
SPECIOSA*) USE AMONG KETUM LEAF USERS
IN MALAYSIA**

ABSTRACT

Ketum or *M.speciosa* is an indigenous psychotropic plant commonly used for its medicinal value. Studies on ketum use is still scarce, hence further research is needed to elucidate its prolonged use risk in humans. Study aim to determine the sociodemographic characteristics, measure ketum dependence severity, ketum withdrawal severity, ketum craving intensity and analyze the social functioning of ketum leaf users. A total of 293 ketum users were surveyed from three northern states of peninsular Malaysia (Penang, Kedah and Perlis). A cross-sectional study design using non-probability sampling techniques (purposive and quota) was used to collect data. Four study instruments specifically the Leeds Dependence Questionnaire, Marijuana Withdrawal Checklist, Marijuana Craving Questionnaire-Short Form, and Addiction Severity Index were used to measure ketum dependence severity among ketum leaf users. Respondents were all male, majority of Malay ethnicity. Eighty-five percent were employed, 46% were between the ages of 18-25 years, 41% were married, while three-fifths had completed eleven years (SPM) of education. Seventy-nine percent reported that they need to use ketum daily, 83% reported ketum can cause addiction if used regularly, 64% encountered sleeping problems, 67% became nervous, 72% were unable to control ketum desire and 90% had better social-functioning. There were no significant differences between medium and long-term ketum users in their ketum dependence severity ($p>0.243$), ketum withdrawal severity ($p>0.322$), and ketum craving intensity ($p>0.777$). Fifty-five

percent of the sample reported severe ketum dependence, 33% reported severe ketum withdrawal and 23% reported high ketum craving. Those who consumed ≥ 4 glasses of ketum daily (*each glass is equivalent to 350ml of fresh ketum juice*) were more likely to report severe ketum dependence (OR: 4.09; 95%CI: 2.32-7.24; $p = 0.001$), severe ketum withdrawal (OR: 3.31; 95%CI: 1.96-5.59; $p = 0.001$) and high ketum craving (OR: 2.47; 95CI%: 1.41-4.34; $p = 0.001$). In addition, there were no significant impairments in the social functioning of medium and long-term ketum users. There were no significant differences between medium and long-term ketum users in their ketum dependence severity and social functioning. More studies especially clinical studies are needed to show the safety of ketum use in human.

CHAPTER 1

INTRODUCTION

1.0 Introduction

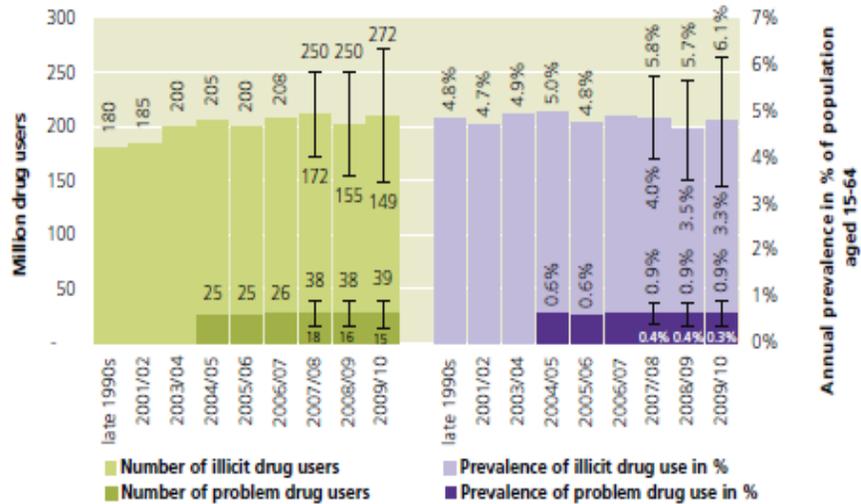
This chapter introduces the topic of thesis. The global drug problem and widespread ketum use practice is discussed in this chapter. In addition, the research questions and study objectives are also clearly elucidated in this chapter.

1.1 Global Drug Abuse Situation

The ¹United Nations Office on Drugs and Crime (UNODC) estimated that a total of 149 to 272 million people (3.3% to 6.1% of the world population between the age of 15-64 years) around the world have used illicit substances in 2009/2010 (UNODC, 2011). An additional 22 million people are estimated to have used illicit drugs in 2009/2010, compared to the previous year, as shown in Figure 1.0. The sharp increase in the number of illicit drug users globally, could be attributed to the widespread abuse of non-medical use of prescription drugs, and the uncontrolled availability of 'legal highs' (UNODC, 2011). On the contrary, the prevalence rate for problem drug use continued to remain stable from 2008 to 2010, despite a marginal increase in the global prevalence rate of illicit drug use (UNODC, 2011). UNODC estimated that there are approximately 15 to 39 million (0.9 to 3.3 of the world population between the age of 15-64 years) problem drug users worldwide, of which 15.9 million are forecasted to be injecting drug users (Mathers et al., 2008). It is interesting to note that the use of new synthetic psychotropic substances such as

¹ UNODC-United Nations Office on Drugs and Crime

‘legal highs’ (e.g. spice, krathom) is beginning to gain more prominence among substance users around the globe (UNODC, 2011; Vandrey et al., 2012).



Source: (UNODC, 2011).

Figure 1.0 Annual prevalence and number of illicit drug users at the global level in the late 1990’s to 2009/2010.

Cannabis is the most widely used and produced illicit drug around the world. UNODC estimated that approximately 125 to 203 million people have used cannabis at least once in 2009. ²Amphetamine-type-stimulant (ATS) is the second most extensively used illicit drug globally. It is estimated that about 13.7 to 15.64 million people aged between 15-64 years have used ATS drugs at least once in 2009 (UNODC, 2011). About 10,600 (26% increase compared to the previous year) ATS related clandestine manufacturing laboratories were eradicated in 2009 (UNODC, 2011). The third most commonly used illicit drugs are opiates. UNODC estimated that approximately 12 to 21 million people have used opiates globally in 2009, of which three-quarters were heroin users.

² ATS-Amphetamine Type Stimulants

The global opium poppy cultivation area in 2010 has increased marginally (195,700 hectares) compared to 2009 (185,900 hectares), and nearly two-thirds of the world opium is produced in Afghanistan. However, the global opium yields reduced significantly in 2010, mainly due to disease in opium poppy plants in Afghanistan (UNODC, 2011). In 2009, seizure for ATS type of drugs have surged significantly, compared to 2007. However the seizure for heroin/morphine remained stable in the last three years. Demand for opiate treatment in countries like Europe and Asia remained high, while treatment demand for ATS use continued to escalate in countries like Southeast Asia, North America and West and Central Europe (UNODC, 2011).

People who use illicit drugs by injection route are irreversibly exposed to multiple health problems, such as ³Human Immunodeficiency Virus (HIV). At present, globally 33.4 million people are living with HIV, and HIV transmission is reported to be high in women (UNAIDS, 2010). Two million deaths are reported per year, while 2.7 million new infections are reported yearly. Only about 40% knew about their HIV status. About 4.7 million people in Asia are infected with HIV, and nearly 10 million people are still waiting to receive treatment for HIV. The reference group to the UN on HIV and Injecting Drug Use, estimated that there were approximately 15.9 million (range 11-21 million) injecting drug users worldwide, and in fact, roughly 3.0 million (range 0.8-6.6 million) people who injected drugs might be HIV positive. UNODC estimated that in 2009, one out of five injecting drug users are HIV positive. The three countries with the highest prevalence of HIV and number of injectors were reported in China (12%), USA (16%) and Russia (37%), respectively (Mathers et al., 2008). The reference group also estimated that in

³ HIV-Human Immunodeficiency Virus

2007, there were about 3.4 to 4.9 million people who injected drugs in East and Southeast Asia, of which 313,000 to 1.2 million people are HIV positive (Mathers et al., 2008).

Injecting with a contaminated needle and syringe used by someone infected with hepatitis C (HCV), has been identified as the primary risk factor for ⁴HCV transmission during a drug injecting episode (Garfein et al., 1998). The prevalence of hepatitis C among injecting drug users at the global level is estimated to be at 50%, of which nearly 8.0 million IDUs are infected with hepatitis C (UNODC, 2011). Overdose is a leading cause of death among illicit drug users (Degenhardt et al., 2006). Of the 104,000 to 263,000 reported deaths per year are due to the use of illicit drugs, in fact, more than half of the mortality incidents are caused by overdose (UNODC, 2011).

1.2 The Drug Abuse Problem in Malaysia

Malaysia has been experiencing a serious drug abuse problem since the 1970s, and the increase in HIV spread in Malaysia stems from the illegal abuse of drugs. Between 1988 and 2006 more than 300,000 individuals, approximately 1% of the general population were registered as substance abusers in Malaysia, with heroin abuse accounting for 62.6% of those registered in Malaysia (⁵AADK, 2007). In fact, the actual number of illicit drug users in the country could be larger than the reported figures. In 2012 the Reference Group to the United Nations on HIV and Injecting Drug Use, estimated that there are approximately between 170,000 to 240,000 injecting drug users in Malaysia, and the prevalence rate of HIV among people who

⁴ HCV-Hepatitis C

⁵ AADK-Agensi Anti Dadah Kebangsaan

inject drugs in the country was 10.3%, while about 22% of the ⁶IDUs are living with HIV (Mathers et al., 2008; UNGASS, 2010). Between 4,135 to 6,538 drug users, were reported to be receiving opiate substitution treatment (OST) in the country in 2010 (Mathers et al., 2010).

2011 National Drug Report indicated that a total of 4,784 drug users are currently enrolled in 20 government drug rehabilitation centres nationwide (Pusat Pemulihan Penagihan Narkotik-PUSPEN), of which 126 are female drug users (AADK, 2011). At present, nearly 56,314 recovering drug users are enrolled in ⁷Therapeutic Community (TC) program under the supervision of National Anti Drug Agency. Since the inception of Cure and Care programme (C&C), about 528 drug users have voluntarily sought treatment from C&C clinics until the end of December 2011 (AADK, 2011).

The 2011 National Drug Report, reported that heroin (followed by ATS and cannabis) still remains the most popular and widely abused illicit drug in Malaysia (AADK, 2011). There has been a significant increase in the seizure for heroin base, heroin no.3, *syabu*, *yaba pills*, psychotropic pills and ketum juice in the country in 2011, compared to 2010 (AADK, 2011). Relapse rate among drug users in Malaysia is high, and can sometimes reach up to 70-90% (Reid et al., 2007). The 2011 National Drug Report also reported, that there have been a marked increase (17.99%) in the number of people arrested under the Dangerous Drug Act 1952 in 2011 (111,719), compared to 2010 (94,689) (AADK, 2011). Hence, forty-percent of the Malaysian prison population who were incarcerated in 2007 were held for drug-related offences (Amnesty International, 2011).

⁶ IDU-Injecting Drug Users

⁷ TC-Therapeutic Community

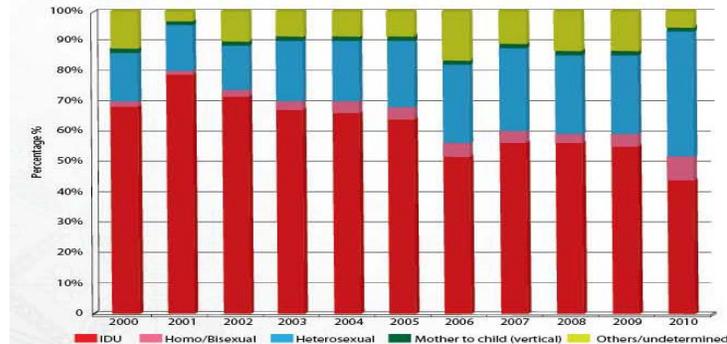
Almost ten thousand (9,776) illicit drug users were detected in 2011, of which (63% were new, and 37% ex-drug users) in the country. Notably, the number of illicit drug users detected in 2011 (9,776) have decreased markedly, compared to 2010 (23,642) (AADK, 2011). This significant decrease is primarily attributed to the establishment of the voluntary treatment based 'Care & Cure' clinics, scaling-up of ⁸methadone maintenance treatment (MMT) programmes, and the constant police crackdowns on drug peddlers and traffickers. The highest number of drug users in the country in 2011, were detected in Perak, Penang and Kuala Lumpur (AADK, 2011). Majority of the drug users in Malaysia were still in their adolescent age (range 19-34), in fact most had completed lower secondary education (nine years of education) (AADK, 2011).

The HIV transmission in Malaysia is predominantly driven by IDUs who are engaged in receptive drug injecting behaviours, as shown in Figure 1.1. Based on the 2010 Malaysian AIDS council report, the national HIV incidence rate in 2010 was 12.9 cases per 100,000 persons (Malaysian AIDS Council, 2010), and the prevalence of HIV infection among street drug users accessing ⁹Needle Syringe Exchange Programme (NSEP) in Malaysia, ranges from 25% to 45% (Kamarulzaman, 2009; Ministry of Health Malaysia, 2009). In fact, 73.7% of the reported HIV cases in Malaysia occurred among people who used drugs (Mesquita et al., 2008; UNGASS, 2008). The first HIV case in Malaysia was reported in 1986, since then the HIV pandemic continued to proliferate, prompting the government to adopt pragmatic harm reduction measures to curtail HIV spread among the IDU population. As of December 2009, a total of 87,710 (79,691 males, 8,091 females) HIV cases have been reported throughout the national HIV surveillance system (UNGASS, 2010).

⁸ MMT-Methadone Maintenance Treatment

⁹ NSEP-Needle Syringe Exchange Programme

The HIV epidemic is found to be largely concentrated in four ‘most-at-risk’ population with a prevalence of (>5%). The four most-at-risk population include; IDUs, female sex workers, men having sex with men (MSM), and transgender (UNGASS, 2010). Kelantan, Pahang, Kuala Lumpur and Johor reported to have the highest HIV incidence rates in Malaysia (Malaysian AIDS Council, 2010).



Source: Malaysian AIDS Council 2010.
 Figure 1.1 HIV Cases by Risk Factors.

A study conducted by Chawarski et al., (2006) among heroin dependents in Malaysia showed, HIV prevalence was significantly high among heroin users who reported lifetime drug injection history, lack of consistent condom use, and Malay ethnicity. This is true, since less than three-quarters (71.4%) of the HIV patients in Malaysia were Malays (Malaysian AIDS Council, 2010).

Similarly, in a recent local study conducted by Vicknasingam et al., (2008) showed that, IDUs preferred to inject drugs due to peer influence, decrease in heroin purity, shortage of heroin supply, and also to maximise euphoric effects. Nineteen IDUs in the study were injecting heroin with benzodiazepines. Findings from the study also showed, that IDUs frequently shared their injecting equipments (e.g. cookers, rinse water, syringes, etc), and reported injecting in groups. Among one of the earliest studies assessing the injection drug using behaviours of IDUs in Kelantan

in 1992, reported that out of the 210 recruited IDUs, 30% (62/210) were HIV positive, and half reported sharing other IDUs' injecting paraphernalia during the last time of their injection (Singh and Crofts, 1992). Moreover, a study conducted by Vicknasingam et al., (2009) among out-of-treatment drug users reported, 65% of the study participants ($n=522$) were HCV positive, and the HCV incidence rate was high in IDUs than non injecting drug users.

In addition, study conducted by Bachireddy et al., (2011) among HIV-infected male prisoners in Malaysia found, out of the 102 participants, 66% reported sharing needles, and 37% had unprotected sex in the last 30-days prior to their incarceration. During their pre-incarceration period (30-days), 77% reported injecting drugs, while 71% were injecting drugs daily. Findings from the study also showed, nearly 32% reported 1-10 episodes of sharing their needle or syringe, 13% reported 11-30 episodes, and 41% reported 31 or more episodes of engaging in risky drug injecting behaviours. Hence, approximately half (51%) of the participants believed that ¹⁰(OST) would be helpful, 54% believed that OST after release would prevent relapse, and 70% expressed interest in learning more about OST options.

In another study conducted by Vicknasingam et al., (2010) reported, ¹¹BUP IDUs in Malaysia remained at high risk of HIV transmission because of continued injection drug use, and sharing of injection equipments. BUP injection drug use during the past 30-days was reported by 97%, and 63% reported at least daily BUP injection drug use during the past 30-days. Of the 480 participants, almost a third was (27%) reported to be HIV positive. Findings from the study also showed,

¹⁰OST-Opiate Substitution Treatment

¹¹ BUP-Buprenorphine

lifetime sharing needles was reported by 82% ($n=225/276$), and current sharing was reported by 55% ($n=153/276$) of the participants.

IDUs who inject ATS type of drugs are also susceptible to HIV infection. A study conducted by Chawarski et al., (2012) found, out-of-treatment opiate injectors who used ATS are at elevated risk of HIV infection in Malaysia. Findings from the study showed, of the 732 opiate IDUs, 27.6% (194/704) were HIV positive. Two factors were found to be significantly associated with HIV infection in this sample; lifetime history of ATS use, and lifetime history of sharing injection equipment. It appears that opiate IDUs in Malaysia are engaging in high risk behaviours regardless of their HIV status, and the transition into ATS injection drug use could be due to the low purity of street heroin in Malaysia (Vicknasingam and Navaratnam, 2008), and the widespread availability of ATS drugs.

Out of the 11,194 registered drug cases in 2011, about 76.72% were using drugs via chase route, 14.09% smoked, 4.58% took drugs orally, 4.51% injected, and 0.10% drank drug solutions (AADK, 2011). Of the 11,194 drug users, 70.82% were abusing opiates, 14.82% ATS and 13.93% cannabis (AADK, 2011). Indeed, the seizure for processed ketum juices, and dried ketum leaves have increased substantially in the country. This reflects that ketum is probably used as a substitute for other illicit drugs, since findings from (Vicknasingam et al., 2010) showed ketum can be used as a narcotic substitute to reduce addiction to other drugs, as well as ameliorate opiate withdrawal symptoms. The 2011 National Drug Report showed, seizure for ketum have increased four-fold, compared to 2010 (22,790.92 liters). In 2011, 85,058.35 liters of processed ketum juice, and 2,784.21 kg of dried ketum leaves were seized by the enforcement agencies (AADK, 2011). This significant

increase in ketum seizure indicates that ketum is fast gaining more popularity due to its psychotropic like effects.

1.3 Ketum (*Mitragyna speciosa*, Korth)



Figure 1.2 Ketum Tree

Ketum or locally known as '*biak*', and in Thailand as '*krathom*' (*Mitragyna speciosa*, Korth) is an indigenous tropical plant of Southeast Asia, as shown in Figure 1.3. Ketum trees can be widely found in the northern states of Peninsular Malaysia, as well as, in the central and southern parts of Thailand. Village folks have used ketum leaves for decades traditionally for its medicinal value, and for its narcotic-like effects which resembles like *coca* and *opioids* (Shellard, 1989; Grewal, 1932). Ketum leaves have been used in Malaysia as an opium substitute when opium itself was unavailable or unaffordable, and was also used to suppress opiate withdrawal symptoms (Burkill, 1935; Burkill and Haniff, 1930; Jansen and Prast, 1988). According to (Kumarnsit et al., 2006) the leaves are the most effective part of the plant. Mitragynine is reported to be a central nervous system stimulant rather than a depressant. However its effects are 'dose-dependent' (Grewal, 1932a), it

induces stimulant effects at lower doses, and opiate effects at higher doses in humans (Babu et al., 2008). Wray (1907a) reported that kratom effects were similar to opium, with large doses leading to stupor, while a “slothful life” was a result of habitual use. Despite its narcotic-like effects, kratom leaves have been traditionally used by rural folks as a remedy to counteract fever, malaria, cough, hypertension, diarrhoea, to prolong sexual intercourse, and to treat opiate addiction (Assanangkornchai et al., 2007; Idayu et al., 2011). People in the northern states believed that kratom using practice is an intractable aspect of their socio-culture, and it is often used in the community during social gatherings.

Males commonly used kratom leaves to enhance their work productivity, while in Thailand the society does not accept female kratom addicts (Suwanlert, 1975). Kratom leaves can be chewed, smoked or brewed into herbal tea. Kratom users in Thailand like to chew kratom leaves, whereas in Malaysia kratom is commonly ingested as a solution. Kratom leaves produce greater effect when chewed (Grewal, 1932). Extracts from kratom leaves contain several active alkaloids. But the two alkaloids particularly, ¹²*Mitragynine* and ¹³*7-Hydroxymitragynine* is reported to have exceptional opiate-like properties, although its chemical structure is quite different from that of morphine. *Mitragynine* is a major constituent which accounts for two-thirds of the total alkaloids extracted from the young kratom leaves (Shellard, 1974). *Mitragynine* which is an opioid receptor agonist, exhibits antinociceptive actions in supraspinal opioid systems when orally administered in rodents (Matsumoto et al., 1996a), and its action is dominantly mediated by *mu* and *delta* receptors (Matsumoto et al., 1996a). *7-hydroxymitragynine* which is another minor constituent of *mitragyna speciosa* (Ponglux et al., 1994) is a novel opioid agonist

¹² *Mitragynine*

¹³ *7-Hydroxymitragynine*

(Matsumoto et al., 2005). This alkaloid is 13 times stronger than morphine, and 46 times stronger than mitragynine (Takayama et al., 2002). 7-hydroxymitragynine is reported to induce potent analgesic activity when orally administered (Matsumoto et al., 2004). The mitragynine content in ketum leaves may vary, depending on the geographic origin of trees and seasons (Shellard et al., 1974).

The “Thai Narcotic Book” written by Norakanphadung in (1966) reported that krathom was weaker than morphine with shorter effects, less harmful than *cocaine* and had a milder withdrawal syndrome than was seen with opiates. It was said to stimulate like *coca*, and have a depressive effect like opium and cannabis. Krathom leaves have been used in Thailand, to treat morphine addicts. Preclinical trials in humans, carried out by Smith, Kline and French Laboratories in the 1970’s, apparently revealed that ketum can induce some unacceptable acute effects (Raffauf, 1986). In a nutshell, it seems many Asians can tolerate krathom effects despite of its chronic administration (Jansen and Prast, 1988b).

1.4 Ketum Studies in Human

To date, numerous animal studies have been carried out to determine the pharmacological efficacy of *Mitragyna speciosa*, korth. Studies on opiate receptor bindings, anti-inflammatory activity, analgesic potency, neurogenic contraction of vas deferens, and anti-depressant efficacy of *Mitragyna speciosa* have shown to be of significant value. Similarly, toxicity and cognitive behavioural function studies conducted in animal models showed, *Mitragyna speciosa* can induce severe hepatotoxicity, mild nephrotoxicity, physical dependence and cognitive impairments when administered in high doses.

Previous studies on ketum use in humans were exploratory and descriptive in nature. In fact, they chiefly elucidated the demographic characteristics of ketum users, patterns of use, duration of use, and the prolonged withdrawal effects of ketum use (Suwanlert, 1975; Assanangkornchai et al., 2007; Vicknasingam et al., 2010; Ahmad and Aziz, 2012). Krathom was generally used in Thailand by middle age labourers, mainly to heighten their physical tolerance to hard work under the blazing sun, and to combat fatigue (Suwanlert, 1975). Suwanlert (1975) reported that krathom users eventually become dependent on krathom after using krathom for prolonged periods. Likewise, findings from a more recent study showed people in Thailand commonly used krathom to improve work efficiency, and to relieve fatigue (Assanangkornchai et al., 2007). People in Thailand often viewed krathom using practice as less harmful, than other illicit drugs. Hence, about 61% of the regular krathom users in Assanangkornchai et al., (2007) study, reported being dependent on krathom. Nevertheless, krathom was also reported to be used in Thailand in the past to treat morphine addicts (Suwanlert, 1975), and its use as an opiate suppressor was also mentioned by Jansen and Prast (1988a). In a more recent study conducted by (Vicknasingam et al., 2010) showed, ketum is getting more appeal among poly-drug users particularly in the northern states of Malaysia, where it is used to help reduce addiction to other illicit drugs, and to attenuate opiate withdrawal effects.

Ketum is also reported to be used in Europe and in United States as “legal highs”. Ketum or Krathom can be easily acquired via some internet sites without doctor’s prescription (Schmidt et al., 2011). Findings from a recent study showed, a 43-year old man in the United States who suffered from chronic pain reported to have used krathom to relieve opioid withdrawal, and to self-manage his chronic pain (Boyer et al., 2008). In another case from Germany, a 25-year old man was

diagnosed with “intrahepatic cholestasis” (*i.e. a medical condition caused by interruption in the excretion of bile—a digestive fluid that helps the body process fat*) after ingesting powdered kratom for two weeks (Kapp et al., 2011). While a 64-year old patient from United States was also rushed into an emergency room after he was found at home unconscious, and in seizures after using kratom tea (Nelsen et al., 2010). Another internet based survey conducted with representatives from 13 different countries, found a small proportion of the respondents in the United States (42 out of the 50 states) preferred to use miscellaneous drugs such as kratom with spice probably to augment euphoric effects (e.g. synthetic cannabinoids) (Vandrey et al., 2012).

Apart from drinking unadulterated ketum juice, there are more alarming issues concerning the increasing abuse of the ¹⁴4x100 cocktail in Thailand (Tanguay, 2011). The 4x100 cocktail is usually concocted with kratom, cough syrup/benzodiazepines, coca-cola and chilled with ice cubes. This adulterated concoction can lead to serious addiction problems. In fact, many ketum users in the northern states of peninsular Malaysia have begin to use the 4x100 ketum cocktail for a better high.

1.5 Statement of Problem

Ketum leaves have been used since decades for its innocuous medicinal properties, despite its reported narcotic effects. At present, there is a paucity of research on whether prolonged ketum use can lead to severe dependence, withdrawal, cause craving, and impair the social functioning of ketum users. The National Drug Information System (NADI) does not capture any epidemiological or behavioural information on ketum users. The only available source of information on

¹⁴ 4x100-Adulterated ketum cocktail

ketum in the country is on ketum seizures, which is documented in the National Drug Report. According to the National Drug Report, seizure for ketum has increased markedly in the last few years. In 2011, 83,466.12 litres of processed ketum juice and 1,626.65/kg of dried ketum leaves were confiscated (AADK, 2011). The seizure for both processed ketum juice and dried ketum leaves increased significantly in 2009 (5,139.61 litres/ 1,797.85 kg) and in 2010 (6,484.36 litres/ 1,637.55 kg) (AADK, 2008-2011). Nevertheless, more ketum users are diverting into anomalous ketum using practices, like mixing ketum with other illicit substances. Concocted use of ketum juice can cause ketum users to develop severe ketum dependence and withdrawal problems, and cause other adverse health problems to ketum users.

Suwanlert (1975), Assanangkornchai et al., (2007) and Vicknasingam et al., (2010) reported, that prolonged ketum use can cause dependence, and abrupt cessation from ketum use can lead to adverse withdrawal effects. Ahmad and Aziz, (2012) reported, 87% of respondents in their study, were unable to refrain from ketum use when they wanted. Similarly, nearly 78% of the respondents in (Vicknasingam et al., 2010) study reported that they were unable to quit from ketum use.

Previous studies on ketum use in humans were generally descriptive and exploratory. No objective measures were used to measure and assess the severity of ketum dependence, withdrawal, craving intensity, and the social functioning of ketum users. Studies conducted in Thailand and Malaysia only provided the context of ketum use among human subjects. The self-report of dependence and withdrawal were captured qualitatively. More quantitative studies are needed to show whether

prolonged ketum use can adversely lead to severe ketum dependence problem, and impair the social functioning of ketum users.

1.6 Research Questions

Based on the statement of problem, five research questions are posed in this study.

- a) What are the sociodemographic characteristics of ketum users in Malaysia?
- b) What is the severity of ketum dependence among ketum users in Malaysia?
- c) What is the severity of ketum withdrawal among ketum users in Malaysia?
- d) What is the intensity of ketum craving among ketum users in Malaysia?
- e) What are the social domains where ketum users' social functioning is affected?

1.7 Study Objectives

Five study objectives were constructed for this study, as listed below:

- a) To determine the sociodemographic characteristics of ketum users in Malaysia.
- b) To measure the severity of ketum dependence among ketum users in Malaysia.
- c) To measure the severity of ketum withdrawal among ketum users in Malaysia.
- d) To measure the intensity of ketum craving among ketum users in Malaysia.
- e) To analyze the social functioning (e.g. medical, employment, legal, family/social relationship, and psychiatric status) of ketum users in Malaysia.

1.8 Scope of Study

Information gathered through focus group discussions with several key informants, literature review and fieldwork observations showed that ketum is now gaining more widespread appeal among the local populace in the northern states of Peninsular Malaysia. Ketum use in these states (Penang, Kedah and Perlis) are rampant, thus these locations were selected for this study.

1.9 Significance of Study

To my knowledge, this study is first to provide some vital insights on the effects of ketum use in humans, especially in Malaysia. At this juncture, it is still unknown whether prolonged ketum use can lead to severe ketum addiction problems. In fact, future studies can rely on the findings of this study to build their investigations more methodologically. The instruments used in this study were adapted, and may be used as a diagnostic tool by general practitioners for measuring ketum dependence, withdrawal, craving and the social functioning of ketum users seeking treatment in clinical settings. Findings from this study can also fill some of the gaps in ketum literature, specifically in human subjects.

1.10 Study Limitation

This study has some limitations, thus results from this study should be interpreted with caution. First, the sample was non-randomly selected, and on that account our results cannot be generalized to all ketum users in the northern states or elsewhere, since the study was a cross-sectional survey study mainly designed to determine severity of ketum dependence in regular ketum users. It was not possible to use a probability sampling technique, because ketum users were scattered in small

numbers across the study locations, as well as, there was no sampling frame available for ketum users. The size of ketum population is still yet to be determined in Malaysia. Both purposive and chain referral sampling techniques were used to recruit respondents for this study. Traditionally, non-random sampling methods (e.g. chain referral and targeted sampling) have been used to sample hidden populations because sampling frames are unavailable for such populations (Watters & Biernacki, 1989). These proposed sampling methods are considered suitable because of its potential to generate a representative sample, and other advantages including, efficiency, cost effectiveness, increased safety for research staff, and has the potential to reach the most hidden segment of target populations (Johnston et al., 2008a).

Second, data in this study is based on self-reports, which may affect the validity of the findings, hence recall bias due to social desirability might also exist. In view of the retrospective nature of this study design, findings from this study might be subjected to inaccuracy, over-reporting or probably under-reporting. In order to overcome these limitations, all the interviews were carried out in places which were convenient for both the interviewer and interviewee. Respondents were assured that no 'personal identifiers' describing their whereabouts will be collected, and were also allowed to take their time in answering the questions.

Third, there was significant difficulty in recruiting ketum users for this study. Potential ketum users in some targeted study locations refused to cooperate with the researcher. Ketum users in these locations were unwilling to participate in the study, because they were afraid that their personal information would be disclosed to the police. Fourth, the researcher also encountered some difficulty in recruiting ketum

users who only used ketum. Many ketum users in some of the targeted study locations were using other illicit drugs, or were mixing their ketum drinks with other substances, thus making them unsuitable for the study.

1.11 Conclusion

The next chapter is the literature review chapter. Detailed explanation regarding the pharmacological effects of ketum use in humans and animal models, types of illegal drugs and their effects, drug dependence, withdrawal theories, craving theories, treatment modalities, and the different types of measurement instruments are discussed in the following chapter. There are six chapters altogether in this thesis and the summary of each chapter is shown below.

Chapter 1: In the first chapter, the global substance abuse problem, HIV prevalence in IDUs, the ketum and illicit drug abuse problem in Malaysia, problem statement, study objectives and study limitations are clearly elucidated.

Chapter 2: The second chapter covers the literature review. In this chapter, all the relevant and important literature relating to the study context is delineated.

Chapter 3: The third chapter is the methodology chapter. In this chapter, the type of study design, study instruments, inclusion and exclusion criteria, as well as the study locations and how the study was conducted are explained.

Chapter 4: The fourth chapter is the results chapter. In this chapter, all the significant differences between the study participants are analyzed and presented.

Chapter 5: The fifth chapter is the discussion chapter which discusses the findings of the current study, and the findings are compared with previous studies.

Chapter 6: The sixth chapter is the final chapter of the thesis. In this chapter all the findings are summarized. It also provides some recommendations on how to improve and conduct future studies related to ketum use in human subjects. This final chapter also addresses some of the current gaps in the existing studies on ketum use in humans.

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

In this chapter, various important literature on *Mitragyna speciosa*, pharmacological studies on *M.speciosa*, types of illicit drugs and their effects, the definition of drug dependence, withdrawal and craving, drug substitution treatment, detail description of study instruments used in this study, and recommended study tools for future studies are delineated and discussed.

2.1 History of *Mitragyna speciosa* or *ketum* usage



Figure 2.1 *Mitragyna speciosa* Trees.

Mitragyna speciosa Korth, as shown in Figure 2.1, which belongs to the *Rubiaceae* family, is a tropical plant of Southeast Asia. Ketum trees can be found widely in the northern states of Peninsular Malaysia and southern Thailand. Ketum trees usually grow in hot and wet climate. This indigenous plant is popularly known in Malaysia as ‘ketum’ or ‘biak’, and in Thailand as ‘krathom’. Krathom leaves have been used since olden times both in Thailand and Malaysia for its ‘opium-like’ and

'cocaine-like' effects (Grewal, 1932; Burkill, 1935) for increasing work productivity (Suwanlert, 1975). Ketum was reported to be a central nervous system stimulant rather than a depressant (Grewal, 1932a). Ketum leaves have been used since the colonial era by the natives of Malaya as an "opium-substitute", when opium supply was unavailable and unaffordable (Burkill, 1935). In Thailand krathom was used to wean morphine addicts off morphine addiction (Suwanlert, 1975). Moreover, krathom was reported to have the potential to suppress, as well as ameliorate opiate withdrawal symptoms (Burkill and Haniff, 1930; Vicknasingam et al., 2010).

Ridley in 1897 described that krathom leaves can be used as a cure for opium habit. After several decades Shellard (1974) claimed, that krathom does not have addictive properties like morphine, indeed it was weaker than morphine because it induces transient withdrawal effects, which is less harmful than cocaine (Norakanphadung, 1966). Krathom leaves were generally chewed to "calm the mind" (Suwanlert, 1975). Apparently many Asians are able to tolerate its effects, especially on daily basis (Jansen and Prast, 1988). The only disadvantage of ketum is, when it is used in large doses it induces stupor, while an indolent life is a result of frequent and prolonged indulgence in ketum use (Jansen and Prast, 1988). Those who get the habit of using it, find it as difficult to leave off '*biak*' use (Burkill, 1935).

Besides using it for its narcotic-like effects, ketum leaves were also traditionally used for its medicinal properties. Rural folk normally used ketum leaves to treat various health problems, such as diabetes, hypertension, fever, diarrhea, muscle strain, prolonging sexual intercourse, as a wound poultice, and to alleviate fatigue (Suwanlert, 1975; Reanmongkol et al., 2007). Hence, manual workers usually chew krathom leaves to improve their work productivity, or to boost their physical

endurance under the blazing sun (Suwanlert, 1975; Assanangkornchai et al., 2007). Krathom leaves can be chewed, as well as brewed into tea. Krathom users in Thailand prefer to chew krathom leaves, while in Malaysia ketum is usually consumed as a herbal tea. The former practice is quite rare in Malaysia, compared to Thailand. There are two types of krathom leaves, *red* and *green* veined leaf. The red veined species is reported to have stronger pharmacological activity, than the latter (Chittrakarn et al., 2008). It is an offence to use ketum in Malaysia and Thailand. However, people from both this geographical divide still continue to adamantly use ketum, despite its prohibition. Regular krathom users in Thailand believe that their krathom using practice does not disturb anyone, and krathom is better than other illicit substances (Assanangkornchai et al., 2007). Ahmad and Aziz (2012) reported that 99% of the ketum users in their study have not neglected their families, despite being a regular ketum user.

During the old days krathom was popular among the older age people who mainly used krathom for its medicinal effects. In fact, many young people are beginning to use ketum now, probably for its stimulant and euphoric like effects. If used excessively krathom may cause ‘psychological dependence’ (Win Pe, 1980). However, krathom withdrawal syndrome was reported to be milder than opiates (Jansen and Prast, 1988). Currently, krathom can be purchased from several internet sites as “legal-highs” or as herbal dietary supplements, where information on its adverse side-effects is scantily disclosed (Schmidt et al., 2010). On the other hand, processed ketum juice can also be easily acquired from unscrupulous ketum traders in the community for local consumption.

2.2 Pharmacological Studies on *M.speciosa*

The pioneers' researcher who worked with *M. speciosa* in 1897 was Ridley. In the early nineteen century, Wray (1907) described that krathom leaves can be smoked, chewed or consumed as an infusion with opium-like effects regardless of the method of administration. Since Field first isolated *mitragynine* in 1921, numerous investigations have been conducted to determine the pharmacological efficacy of *M.speciosa* use, specifically for its analgesic value. Up to now, over 25 alkaloids have been isolated from the leaves of *M.speciosa*, in fact the two principal components which have received overwhelming research interest in the last couple of years include *mitragynine* (major alkaloid of MS¹) and *7-hydroxymitragynine* (a minor constituent of MS). These two compounds are reported to have potent analgesic effects. The chemical structures of both the compounds are depicted in Figure 2.1. The other analogues of *M.speciosa* encompass *speciogynine*, *speciociliatine*, and *paynantheine* (Takayama, 2004). Mitragynine is an indole alkaloid which accounts for about 66.2% of the total alkaloid extracted from the young leaves of *M.speciosa* (Ponglux et al., 1994; Shellard, 1974). Mitragynine is an opioid receptor agonist (Watanabe et al., 1992; Tsuchiya et al., 2002).

Mitragynine was reported to be a central nervous system stimulant rather than a depressant (Grewal, 1932a). However the effects of *M.speciosa* are dose-dependent, it induces stimulant effects at lower doses, and opiate effects at higher doses (Suwanlert, 1975, Grewal, 1932). Notably, large doses escalate exploratory behaviour without the opiate “fear and rage” complex in cat (Jansen and Prast, 1988). Kumarnsit et al., (2007) reported that *M.speciosa* extract has ‘stimulatory effect’ on

¹ MS (*Mitragyna speciosa*).