

**KETUM (*MITRAGYNA SPECIOSA* KORTH.)
CONSUMPTION, LIPID PROFILE AND
ELECTROCARDIOGRAM (ECG)
ABNORMALITIES**

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**KETUM (*MITRAGYNA SPECIOSA* KORTH.)
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ELECTROCARDIOGRAM (ECG)
ABNORMALITIES**

by

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LIST OF ABBREVIATIONS

AHA	American Heart Association
AV	Atrioventricular
ALT	Alanine Transaminase
AST	Aspartate Transferase
ATS	Amphetamine-Type Stimulant
BMI	Body Mass Index
BPM	Beats Per Minute
CDDC	Compulsory Drug Detention Centre
CI	Confidence Interval
CYP3A4	Cytochrome P450 3A4
DDA	Dangerous Drugs Act
ECG	Electrocardiogram
FDA	Food and Drug Administration
G1	Growth 1 Phase
GC-MS	Gas Chromatography–Mass Spectrometry
GTC	Generalized Tonic-Clonic
HDL	High Density Lipoprotein
hERG	Human Ether-Ago-Go-Related Gen
HIV	Human Immunodeficiency Virus
HDL	High Density Lipoprotein
IC50	Half-Maximal Inhibitory Concentration
IPS	Institut Pengajian Siswazah
Kg	Kilogram
L	Liter
LA	Left Arm
LAD	Left Axis Deviation
LL	Left Leg
LDL	Low Density Lipoprotein
MDMA	Methylenedioxymethamphetamine
Mg	Microgram
M ²	Meter Square
Mg	Milligram
ml	Milliliter

MS	Millisecond
MMT	Methadone Maintenance Treatment
NADA	National Anti-Drugs Agency
NAS	Neonatal Abstinence Syndrome
NICU	Neonatal Intensive Care Unit
NPS	New Psychoactive Substance
OR	Odds Ratio
<i>p</i> -value	Probability Value
PWUD	People Who Use Drug
RA	Right Arm
RAD	Right Axis Deviation
RBBB	Right Bundle Branch Block
RL	Right Leg
RM	Ringgit Malaysia
RSR	Regular Sinus Rhythm
S	Synthesis
SD	Standard Deviation
SEAR	South-East Asia Region
SH-SY5Y	Thrice-Subcloned Cell Line
SPSS	Statistical Package for Social Sciences
SUD	Substance Used Disorder
THC	Tetrahydrocannabinol
UNODC	United Nations Office on Drugs and Crime
US	United States
USM	Universiti Sains Malaysia
WHO	World Health Organization

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(Meninjau Kesan Penggunaan Ketum Secara Kronik Ke Atas
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**PENGGUNAAN KETUM (*MITRAGYNA SPECIOSA* KORTH.), PROFIL
LIPID DAN KEABNORMALAN ELECTROKARDIOGRAM (ECG)**

ABSTRAK

Ketum (*Mitragyna speciosa* Korth.) sejenis tumbuhan perubatan tradisional di Asia Tenggara, telah digunakan di Malaysia selama beberapa dekad untuk sifat kuratif yang unik. Walaupun ketum mempunyai sifat terapeutik yang luas dan peningkatan dalam penggunaannya, profil keselamatan jangka panjang ketum, terutamanya risiko kardi toksik masih kurang dikaji dalam kalangan pengguna ketum tetap. Berdasarkan limitasi penyelidikan ini, kajian ini bertujuan untuk menilai kecelaruan elektrokardiogram (ECG) dan profil lipid diantara pengguna ketum tetap dan subjek kawalan yang sihat. Seramai 200 responden (n=100 pengguna ketum tetap dan n=100 subjek kawalan sihat) telah direkrut melalui persampelan mudah yang dijalankan di negeri Pulau Pinang, Utara Semenanjung Malaysia bagi kajian klinikal keratan-rentas ini. Semua responden dikehendaki menjalani penilaian ECG, dan sampel darah juga diambil untuk menilai ciri-ciri profil lipid responden. Kesemua responden adalah lelaki, majoriti berbangsa Melayu (97%, n=194/200) dan min umur sampel dalam kajian ini ialah 33 tahun (SD=6.7), manakala min tempoh pengambilan ketum untuk pengguna ketum adalah 6.4 tahun (SD=4.31). Min tekanan darah sistolik dan diastolik pengguna ketum adalah 132.9 (SD=17.3) dan 77.1 (SD=11.1), masing-masing. Dapatan kajian menunjukkan bahawa tiada perbezaan yang ketara dalam parameter ECG (blok jantung darjah 1, bradikardia sinus, penyongsangan T, sisihan paksi kanan,

sisihan paksi kiri, blok cawangan berkas kanan tidak lengkap, hipertrofi ventrikel kiri, dan *selang QTc yang berpanjangan*) di antara pengguna ketum tetap dan subjek kawalan sihat, kecuali takikardia sinus. Dapatan kajian juga menunjukkan bahawa tempoh penggunaan ketum (1-6 tahun berbanding >6 tahun) dan kuantiti harian penggunaan ketum (1-4 gelas berbanding >4 gelas) tidak berhubungkait dengan *selang QTc yang berpanjangan*. Walau bagaimanapun, mereka yang menggunakan ketum untuk tempoh masa yang lebih panjang (>6 tahun) dan kuantiti yang lebih tinggi (>4 gelas air ketum setiap hari) terdedah kepada *selang QTc pinggir*. Bagi profil lipid, pengguna ketum tetap mempunyai paras kolesterol dan lipoprotein ketumpatan rendah (LDL) yang jauh lebih rendah berbanding dengan subjek kawalan yang sihat. Manakala untuk trigliserida dan lipoprotein ketumpatan tinggi (HDL) di antara kedua-dua kumpulan berada dalam julat yang normal. Secara keseluruhan, kajian awal ini menunjukkan bahawa penggunaan air ketum secara tetap nampaknya tidak menyebabkan kecelaruan ECG yang ketara dan tidak mengakibatkan perubahan dalam profil lipid dalam kalangan pengguna ketum tetap. Oleh itu, kajian klinikal terkawal selanjutnya yang lebih tersusun dengan formulasi dan protokol dos yang lebih tepat amat diperlukan untuk mengesahkan penemuan ini, serta menyokong keberkesanan terapeutik ketum.

KETUM (*MITRAGYNA SPECIOSA* KORTH.) CONSUMPTION, LIPID PROFILE AND ELECTROCARDIOGRAM (ECG) ABNORMALITIES

ABSTRACT

Ketum (*Mitragyna speciosa* Korth.) a native medicinal plant of Southeast Asia, has been used in Malaysia for decades for its unique curative properties. Given its broad therapeutic properties and increasing utility, ketum's long-term safety profile, especially on its cardiotoxicity risk remains poorly investigated in regular ketum users. Given this research limitation, this study aims to evaluate the electrocardiogram (ECG) abnormalities and lipid profile between regular ketum users and healthy control subjects. A total of 200 respondents (n=100 regular ketum users and n=100 healthy control subjects) were recruited through convenience sampling from the northern peninsular state of Penang for this clinical, cross-sectional study. All were required to undergo an ECG evaluation, and blood samples were also drawn to characterize the respondent's lipid profile. All males, a majority were Malays (97%, n=194/200), and the samples mean age in this study was 33 years (SD=6.7), while ketum users mean duration of ketum use was 6.4 years (SD=4.31). Ketum users mean systolic and diastolic blood pressure rates were 132.9 beats per minute (SD=17.3) and 77.1 beats per minute (SD=11.1), respectively. Results indicate that there were no significant differences in the ECG parameters (1st degree heart block, sinus bradycardia, T inversion, right axis deviation, left axis deviation, incomplete right bundle branch block, left ventricular hypertrophy, and *prolonged QTc interval*) between regular

ketum users and the healthy control subjects, except for sinus tachycardia. Results also indicate that duration of ketum use (1-6 years versus >6 years) and daily quantity of ketum use (1-4 glasses versus >4 glasses) had no relationship with *prolonged QTc interval*. However, those who consumed ketum for a long-term period (>6 years) and at a higher quantity (>4 glasses of brewed ketum solution daily) were predisposed to *borderline QTc interval*. As for the lipid profile, regular ketum users had significantly lower total cholesterol and Low-Density Lipoprotein (LDL) levels than the healthy control subjects. While the triglyceride and High-Density Lipoprotein (HDL) levels between both groups were within the normal reference range. Taken together, this preliminary study indicates that regular ketum consumption in the form of a brewed solution in no circumstances cause significant ECG abnormalities, and alteration in the lipid profile of regular ketum users. Hence, further controlled-clinical studies with proper formulation and dosing protocols are crucially needed to confirm these findings, as well as to support ketum's therapeutic utility.

CHAPTER 1

INTRODUCTION

1.1 Introduction.

This is the first chapter of the thesis. A brief overview of the world drug abuse problem and Malaysian drug abuse problem, study problem statement, research questions and study objectives, as well as study implications are all clearly described in this chapter.

1.2 Brief Overview of the World Drug Abuse Problem

According to United Nations Office on Drugs and Crime (UNODC), approximately 275 million people (age between 15 to 64 years) have used drugs around the globe in 2020 (See Figure 1.1) (World Drug Report, 2021). Meanwhile, UNODC also estimated that out of this figure, 36.3 million people have experienced substance use disorder (SUD) in 2020 (See Figure 1.1) (World Drug Report, 2021).

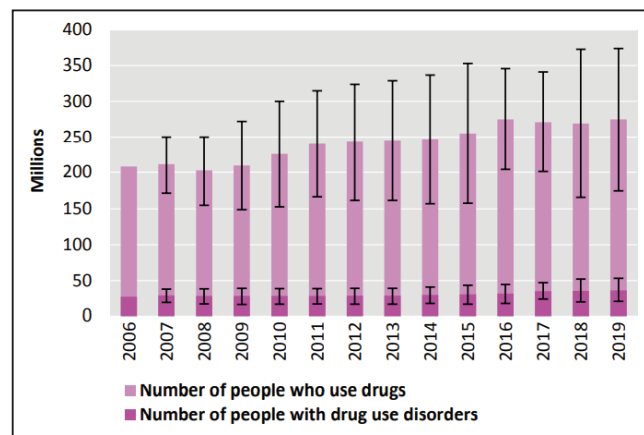


Figure 1.1, Global number of people who use drugs and people with drug use disorders (SUDs) from 2006 to 2019 (Source: UNODC, World Drug Report, 2021, p.21).

According to the Global Burden of Disease Study, deaths associated with drug use in 2019 is projected to be around 494,000 cases. Moreover, according to UNODC, approximately 18 million lives' have been lost to SUD. Notably, opioid use disorder has caused almost 88,000 deaths. The prevalence of drug use has also increased markedly from 0.6% in 2016 to 0.7% in 2019 (See Figure 1.2) (World Drug Report, 2021).

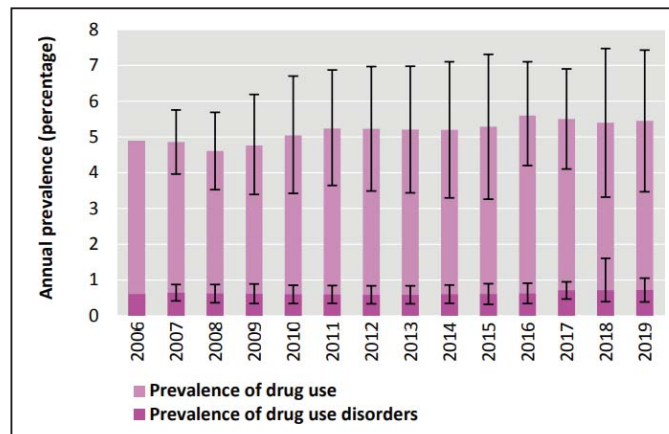


Figure 1.2, Global prevalence of drug use and prevalence of drug use disorder from 2006 to 2019 (Source: UNODC, World Drug Report, 2021, p.21).

Cannabis is the most widely used drug around the globe according to UNODC. In 2019, approximately 200 million people have used cannabis, in fact, cannabis consumption is reported to be prevalent especially among youngsters (age between 15 to 16 years) (World Drug Report, 2021). Besides cannabis use, opioid is the second most widely used substance around the globe, and about 62 million people are estimated to have used opioids in 2019. Notably, out of the 18 million deaths reported, 70% of the fatalities are contributed by opioid consumption. According to UNODC, a majority (70%) of people who use opioid are located in Asian countries (World Drug Report, 2021).

Apart from cannabis and opioid consumption, about 27 million people around the globe have also used amphetamine-type stimulant (ATS) both crystal methamphetamine and amphetamine. Crystalline methamphetamine is popularly used in Southeast Asia, given its proximity with the golden triangle. As for ecstasy, roughly 20 million people have used it in 2019 (World Drug Report, 2021). Furthermore, the emergence of new psychoactive substances (NPSs) has also seen a significant drop in 2019, probably due to the stringent law monitoring imposed by UN member states. NPS comprises of synthetic cannabinoid receptor agonists, synthetic cathinones, phenethylamines, piperazines, tryptamines, aminoindanes and NPS opioids. Besides chemically produced NPS, plant based NPS like kratom (*Mitragyna speciosa*), *Salvia divinorum* and *khat* (*Catha edulis*) popularity have also increased given its vast therapeutic properties and perceived benefits as a safe substitute to illicit narcotics.

In addition, the global prevalence of drug use among women is reported to be much lower than their male peers by UNODC (World Drug Report, 2020). Drugs that are commonly seized in bigger quantities by law enforcement agencies include cannabis and pharmaceutical opioids. Particularly, kratom seizures have been reported to have increased in Malaysia compared to other countries. In Asia, the amount of synthetic NPS seized has also increased from 38% (in 2009 to 2012) to 43% (in 2006 to 2019).

According to UNODC the consumption of illicit drugs is reported to cause various devastating health issues – such as drug use disorders, blood-borne diseases like HIV and hepatitis C, and mental health problems. Though, there is

pharmacotherapy for opioid use disorder, people who use ATS have no access to medicine-assisted treatment and continue to face various challenges while contemplating to access treatment. However, people who use ATS are often sent to compulsory drug detention centers (CDDCs) or jails, for rehabilitation in Southeast Asia.

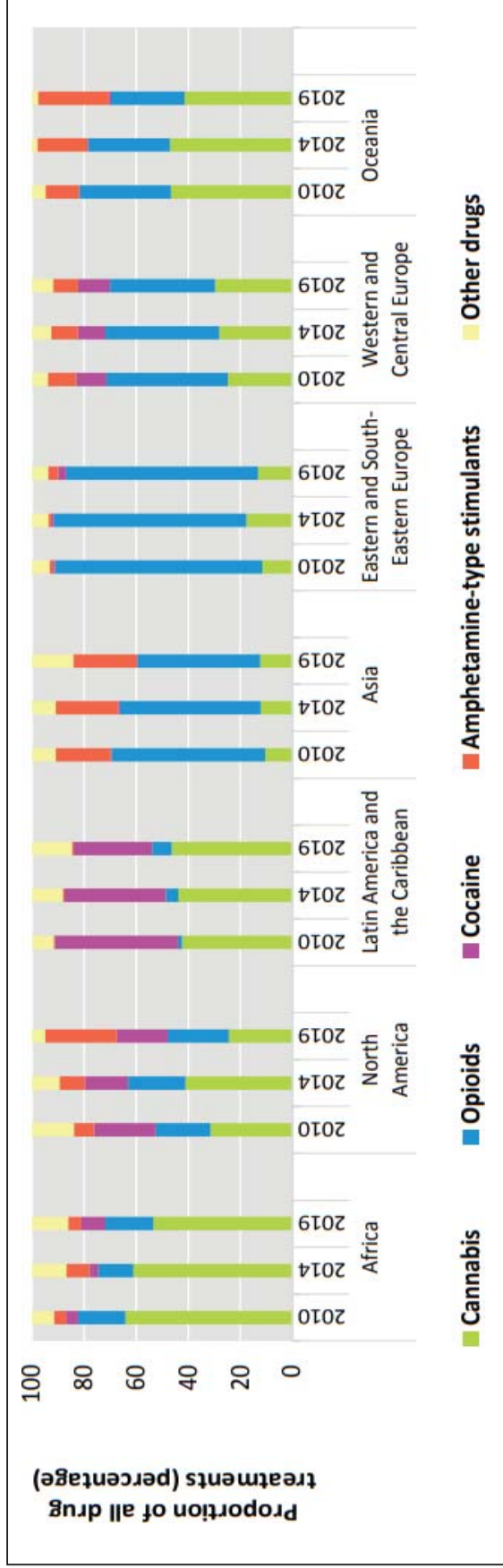


Figure 1.3, Trends in the primary drug of concern in people in treatment for drug use disorders, by region, for 2010, 2014 and 2019 (Source: UNODC, *World Drug Report, 2021, p.28*).

1.3 Drug Abuse Problem in Malaysia.

Malaysia began to experience major problems with illicit drugs, especially heroin use, as early as the 19th century when British was ruling in Malaya. To drive the economy, British had to employed labourers from India and Mainland China. Indians were positioned in rubber plantations, while the Chinese were deployed to work in the nascent tin mining industry. The migration process, also saw foreign workers introducing their opium and cannabis using behaviours to locals (Poh et al., 1981). Opium and cannabis consumption was not seen as a major problem among the foreign workers back then since opium was primarily used for improving work productivity and for its medicinal purposes. Given the sudden political unrest in Mainland China, the local Chinese intellectuals in Malaya pressed the British to ban opium use. To curb the opium misuse menace, the British finally passed the Drug Abuse Ordinance first, and then the Dangerous Drugs Act of 1952 replaced the former.

Since the drug abuse problem is seen as a security issue in Malaysia, the government then did not hesitate to adopt punitive measures to punish people convicted for drug trafficking offences (Scorzelli, 1986). Given its close proximity with the “*golden triangle*”, Malaysia continues to face major problems with the smuggling of illicit drugs. The number of people caught for drug abuse offences have increased significantly in the country over the years. Though opiate (heroin) still appeared popular in Malaysia, the use of ATSs has surpassed opiate popularity in recent years. Based on the National Drug Report, majority of people caught for drug abuse

offenses have a preference for ATS use than opioid (heroin) (National Drug Report, 2021).

In Malaysia, opioids like heroin and morphine continue to be the most often abused substances, while amphetamine-type stimulants (ATS) like ecstasy and methamphetamine have lately been identified as a developing issue in the country (Singh et al., 2013). Malaysia has a significant role in the world's drug trade and usage that occurs in Southeast Asian nations (UNODC, 2019). According to the government register, there were 234,000 people officially found to be using heroin in Malaysia in 2004 (Mazlan et al., 2006). The market for amphetamine-type stimulants (ATS) has grown significantly in the Asian region, raising serious concerns (Schottenfeld et al., 2008). Opiates were listed by NADA (7) as the primary substance that Malaysians commonly abused between 2009 and 2013, with 45% found to be abusing heroin. According to Degenhardt et al. (2010), ATS use is linked to a number of negative health outcomes, such as psychiatric issues, HIV infections, criminal behavior, and non-fatal overdose risk.

In a study conducted to determine the drug use and availability of drugs among university students by Chie et al., 2015, it was reported that heroin was rated as the most frequently used and easily obtainable substance. Since several Asian countries have become the primary hub for the production and trafficking of amphetamine-type stimulants (ATS),

64% of ATS seizures have taken place in Asian countries (UNODC, 2015). According to the United Nations Office on Drugs and Crime, Asia is home to more than half of the world's ATS users with around 3.9 million ecstasy users and 9.5 million methamphetamine users.

According to the National Anti-Drugs Agency (NADA), there was a modest decline in Malaysia's adult drug using population between 2016 and 2020. Methamphetamine is the second-most popular illicit substance in Malaysia after opiate-based heroin and morphine. The number of addicts found among adults whose age is 40 and above was a serious concern in 2016 because it showed an increase of 14.7% from the year before (Kanato et al., 2016). According to the World Drug Report of 2017, the use of opioids is associated with the greatest risk to one's health. The second most commonly abused drug was amphetamine, which is believed to be widely used in most of Asia and has an estimated of 35 million users. Although opiates are still the most popular drug choice in Malaysia, ATS use has grown significantly in recent years (National Drug Report, 2017). According to a study by Chooi et al. (2017) on the relationship between ATS usage and mental health, opiate users who reported initiating ATS at a younger age are more likely to suffer from severe cognitive impairments.

While heroin and ATS are widely used in Malaysia (Singh et al., 2013), at present it was found that people who use drugs (PWUDs) commonly use ketum (*Mitragyna speciosa* Korth.) to reduce their

dependence on the more expensive use of opioids like heroin (Vicknasingam et al., 2009). Besides that, NADA has named ketum as another class of drug which is gaining traction among PWUDs in the country (NADA, 2021). Ketum is frequently co-used with illegal substances for various reasons. A study from Thailand showed ketum users are prone to co-use ketum with illicit substances like opiates, methamphetamine, and cannabis (Talek et al., 2017).

Besides the Dangerous Drugs Act, Malaysia also has the Drug Dependents (Treatment and Rehabilitation) Act of 1983. This act allows law enforcement agencies to detain and confine people who use drugs (PWUDs) in compulsory drug detention centers (CDDCs) in the country. After having served a rehabilitation sentence in a control environment, PWUDs are also subjected to undergo community supervision program after their release from CDDCs. Currently, people who use opiate (heroin) are given access to methadone maintenance treatment (MMT) program in Malaysia. MMT was primarily introduced to curtail HIV spread among opiate injectors. MMT program is also now introduced to inmates in prisons and voluntary drug treatment programs. A few studies from Malaysia have shown that MMT program has many advantages and treatment providers have called the government to expand the program (Premila et al., 2012).

Despite the opiate use problem (heroin), ATS use has become a

major issue in Malaysia in the recent past. According to the National Anti-Drugs Agency (NADA), most of the detected PWUDs have ATS use history – this reflects opiate popularity has phased out. In the last few years, researchers have started to study ketum use among PWUDs in the country. Ketum also known as *Mitragyna speciosa* (Korth.) is an indigenous medicinal plant, native to Southeast Asia. More and more studies are beginning to describe ketum use among PWUDs. In Malaysia, ketum is used as an affordable and safe replacement to opiate (heroin) and ATS (Vicknasingam et al., 2010). Heroin and poly-drug users commonly consumed ketum to suppress withdrawal symptoms, reduce dependence on heroin and ATS, and to maintain sobriety (Vicknasingam et al., 2010). Since ketum is not regulated under the Dangerous Drugs Act of 1952 – the population size of ketum users in the country remains undetermined. However, at this moment, further research is needed to support ketum’s medicinal applicability for the management of pain and opioid use disorder.

KATEGORI DADAH	2018	2019	2020	PERBANDINGAN ANTARA TAHUN 2019 & 2020
ATS	84,439	91,684	83,698	-8.7%
OPIAT	41,337	43,578	39,599	-9.1%
GANJA	4,327	4,497	3,396	-24.5%
PIL PSIKOTROPIK	75	614	569	-7.3%
LAIN-LAIN	610	1,826	1,063	-41.8%
JUMLAH	130,788	142,199	128,325	-9.8%

Figure 1.4, Number of drug abuser and addicts according to drug category for 2018, 2019 and 2020 (*Source: NADA, 2020, p.22*).

1.4 Study Problem Statement

Mitragyna speciosa Korth. is locally known as Ketum in Malaysia, and kratom in Thailand and elsewhere. Ketum is an indigenous medicinal plant of Southeast Asia, and the species can be widely found in Malaysia, Thailand, and Indonesia (Adkins et al, 2011). Given its psychotropic properties, ketum is currently regulated in Malaysia under the Poisons Act of 1952. To date, though ketum is reported to have a myriad of health benefits, unfortunately its long-term safety profile remains poorly investigated in humans and warrants further study. Ketum is reported to have unique dose-dependent effects, both stimulant and opioid-like effects (Singh et al.,2017). *Mitragynine* as the most abundant alkaloid, and its potent metabolite *7-hydroxy-mitragynine* are currently regulated in many jurisdictions, though Thailand has recently legalized ketum consumption for its medicinal purposes. Though ketum is traditionally used in Malaysia for its vast therapeutic properties, however its long-term use is reported to cause dependence, withdrawal, and some unpleasant health effects particularly among regular users. Given that ketum's safety profile remains poorly investigated and it is widely used, there is an urgent need to understand and evaluate ketum's long-term health effects especially on cardiovascular functioning or electrocardiogram (ECG) abnormalities, and lipid profile in regular ketum users. This is because in the West, ketum consumption is reported to be associated with numerous health issues such as poisoning and mortalities, as well as alterations in biochemical parameters like lipid profile, while health authorities in Malaysia have never stop to caution the general public on ketum using risk. Similarly, given that ketum's consumption is also increasing and ketum's long-term health effects remains poorly documented, hence it is seen crucial that those proper controlled studies are conducted to investigate

ketum's side effects among regular users in traditional settings in Malaysia. The Malaysian government has consistently opposed drug abuse problem and aims to keep the drug abuse problem under control.

On the other hand, in Canada, Uruguay, and 21 U.S. jurisdictions (18 states, 2 territories, and the District of Columbia) as of January 2022, the laws of these nations have allowed cannabis to be cultivated, distributed and used recreationally (World Drug Report, 2022). Although cannabis usage is legal in US and Canada, these nations never stop to face issues with cannabis consumption. In US, by enabling the use of cannabis legally, cannabis usage among adults have increased but it does not seem to have increased among teenagers (Leung et al., 2018). In 2011, majority of the US public supported to legalize cannabis as they had three main supporting points which made them to support the use of cannabis legally. The first point is that cannabis usage is significantly less dangerous than the use of heroin, cocaine, and methamphetamine, as well as less detrimental than alcohol and tobacco use. The second is that African-American and Latino kids have unfairly been subjected to criminal consequences for cannabis use that are more harmful than the cannabis usage itself. The third point is that legalization is a better course of action than prohibition because it permits cannabis to be regulated in ways that protect public health, lowers the cost of enforcing criminal laws and the imprisonment of minority cannabis users, and generates taxes that can be used for social reasons (Head, 2019). Against this background, policymakers can learn how these countries successfully legalized cannabis even after having endured all sorts of challenges.

There have been numerous toxicity cases involving *mitragynine* poisoning. In a preliminary study, Lu et al. (2014) examined the cardiotoxicity of *mitragynine* using cardiomyocytes generated from human induced pluripotent stem cells. They discovered that *mitragynine* (10 mM) can induce arrhythmia. In this study, it was found that inhibiting the fast delayed rectifier potassium current (IKr) in human cardiomyocytes could lead to Torsade de Pointes (Lu et al., 2014). Torsades de pointes are a potentially fatal cardiac arrhythmia that is caused by drug-induced lengthening of the cardiac action potential, which is seen as a prolongation of the QT interval on an electrocardiogram (Shah, 2005). Following incidents of cardiorespiratory arrest caused by ketum consumption, case reports of ketum cardiotoxicity have been documented. According to Aggarwal et al. (2018), *mitragynine* is shown to be cardiotoxic or have calcium channel-blocking effects. There have been two occurrences of acute respiratory distress syndrome (ARDS) caused by the combined use of ketum with alcohol. Hypoxemic respiratory failure manifested in both cases (Chittrakarn et al., 2010; Pathak et al., 2014).

Given its widespread popularity, many researchers are studying ketum's medicinal applicability and its health risks from various dimensions. At present, ketum's safety profile, and its interactions with numerous medications have not been properly documented. This study aims to determine whether regular ketum consumption over a prolonged period can cause or lead to cardiovascular health problems or ECG abnormalities and elevation in lipid profile in regular ketum users. Findings from this preliminary study has many policy implications and can be used to guide clinicians and treatment providers to understand ketum's interaction with cardiovascular functioning, so that proper treatment guidelines can be developed to

help clinicians treat ketum users presenting with abnormal ECG readings and biochemical parameters such as lipid profile. Moreover, findings from this study can help researchers expand the scope of prospective studies to develop a better understanding on ketum. Last but not least, this preliminary study can be used as a guide to make more informed policy decision pertaining to ketum regulation in the country.

1.6 Study Hypothesis

Regular ketum consumption can result in cardiovascular health problems and lead to abnormal electrocardiogram (ECG) among regular ketum users in Malaysia.

1.5 Research Questions

The study's research questions are as follows.

1. What is the prevalence of electrocardiogram (ECG) abnormalities between regular ketum users and healthy controls in Malaysia?
2. What is the lipid profile between regular ketum users and healthy controls in Malaysia?
3. What are the risk factors for QT prolongation among regular ketum users in Malaysia?

1.6 Research Objectives

The study's research objectives are as follows.

1. To determine the prevalence of electrocardiogram (ECG) abnormalities between regular ketum users and healthy controls in Malaysia.
2. To evaluate the lipid profile between regular ketum users and healthy controls in Malaysia.
3. To identify the risk factors of QT prolongation among regular ketum users in Malaysia.

1.7 Scope of Study

People who self-reported to have used brewed ketum solution (or decoction) on a regular basis and reported to be healthy (without underlying medical and illicit drug use history) were recruited from various communities in the state of Penang, where ketum was reported to be prevalent. A comparison group comprising of people without ketum use history (control group) were also recruited for this clinical, cross-sectional study.

1.8 Significance of Study

To the best of my knowledge, this study has many advantages for relevant stakeholders. First, healthcare and treatment providers can rely on this study findings to gauge the safety profile of long-term ketum use, particularly in understanding ketum's effects on cardiovascular functioning and lipid profile in humans. Second, policymakers can rely on this study to make informed policy decisions – whether the government should toughen current laws to prevent ketum misuse and cultivation and *vice-versa*. Third, since there are many misconceptions around ketum use, thus, treatment providers and enforcement agencies can rely

on the study findings to warn or caution people on the side effects of long-term ketum use. Finally, this study can be used as a precedent to guide future studies and allow researchers to look at specific areas where further research might be needed to confirm or thoroughly study ketum's safety profile in humans. Since regulators such as the Food and Drug Administration (FDA) and the Expert Committee on Drug Dependence under the purview of the World Health Organization (WHO) is planning to regulate ketum and its active alkaloid (*mitragynine*), findings from this study can be used as a clinical proof to show that ketum consumption in traditional context is not associated with any known adverse health threat or issues.

1.9 Conclusion

The study problem statement, research objectives and study significance have been briefly delineated in this chapter. The next chapter is the literature review chapter.

CHAPTER
TWO
LITERATURE
REVIEW

2.1 Introduction

This chapter of the thesis will provide a brief overview of ketum use history in Southeast Asia, its traditional applicability, as well as its utility among people who use illicit drug. The pharmacological properties of ketum, its clinical manifestations in human subjects or users and neonatal withdrawal reports are also described in this literature review chapter.

2.2 Ketum use History in Southeast Asia.

Ketum is a plant from the Rubiaceae (coffee) family which is also known as *Mitragyna speciosa* Korth. (Hassan et al., 2012; Cinosi et al., 2015; Swogger & Walsh., 2017). This plant mainly grows in tropical areas like in Africa and in various parts of Southeast Asia (Adkins et al., 2011). In Malaysia, ketum is also known as *biak-biak* whereas in Thailand and elsewhere, it is often known as kratom (Ahmad & Aziz., 2012; Hassan et al., 2013). Ketum leaves are commonly used as a medicinal herb in Malaysia and Thailand (Hassan et al., 2012). Generally, ketum users in Malaysia will consume ketum in the form of a boiled decoction, though the leaves can also be chewed freshly or dried, turn into powder and ingested with tea/coffee (Singh et al., 2014). Tanguay (2011) reported that ketum's dried leaf can also be smoked with tobacco. Given its bitter taste,

ketum drinks are added with sweeteners (Tanguay, 2011). In Thailand, ketum is recreationally co-used with carbonated beverages or cough syrup that has the content of diphenhydramine. This combination is reported to provide a stronger euphoric effect (Tanguay, 2011; Hassan et al., 2013). According to Saingamet al (2013), the outcome of consuming fresh or dried ketum leaves have no differences as both gives the same effect to ketum users. Ketum is also said to be added with harmful substances such as mosquito coils or rat poison, or dead body ashes – as it is believed to provide better effects to users, however such occurrences have not been scientifically established and remained as a myth (Saingam et al., 2013).

Usually, regular ketum users will grow/plant their own ketum trees at their own surroundings so that they can consume it whenever they wish too. Ketum is currently regulated under the Poisons Act of 1952 in Malaysia. Ironically, planting ketum is not seen as an offence in Malaysia, however those caught for possessing and distributing ketum can be detained and slapped with a court fine or jail if they are convicted. Despite this fact, there are still people who are involved in illegal ketum distribution activities in their neighborhood (Singh et al., 2017). In Thailand, ketum consumption has been criminalized since 1943 (Tanguay., 2011). Recently, the Thai government has legalised ketum (kratom) strictly for its medicinal use. Ketum is easier to be obtained in Malaysia because it is sold at a more affordable price and can be obtain easily from illegal traders (Ramanathan & Mansor., 2014). Ketum users believed that ketum consumption is not harmful or dangerous and they often use it as a safe alternative to

illicit substances (Saingam et al., 2013).



Figure 2.1, Ketum leaves and trees (Source: Singh et al., 2017).

2.3 Traditional Use of Ketum.

In Southeast Asia, ketum is popularly known for its unique medicinal value and used for its vast medicinal applicability (Singh et al., 2017). In traditional setting, ketum is commonly used to treat diabetes, cough, fever, pain and hypertension (Ahmad & Aziz., 2012; Singh et al., 2017). Ketum is also used to cure or heal muscle strain/soreness, stomach pain and diarrhoea (Vicknasingam et al., 2010). Sometimes, ketum is also used to improve mood and for recreational purposes among the male populace. In Thailand, ketum is customarily used for religious purposes (Singh et al., 2017). Ketum consumption is reported to have many benefits; it is usually used to intensify endurance against hard labour and combat fatigue (Vicknasingam et al., 2010; Saingam et al., 2013). Regular users often developed a liking or penchant for using ketum after some time.

It is reported that regular ketum consumption can gradually induce or lead to dependence, craving and withdrawal symptoms in regular users (Singh et al., 2014).

A study conducted by Vicknasingam et al. (2010) reported that ketum consumption could also increase sexual performance, improve appetite, and improve work performance. Ketum leaves can also be used as a remedy to enhance blood flow in the body (Adkins et al., 2011; Ahmad & Aziz., 2012). At the same time, ketum usage is very popular among farmers and manual workers (Hassan et al., 2013). Apart from that, ketum is also consumed to decrease dependence on alcohol (Cinosi et al., 2015). Many other studies have also stated that the ketum plant has been used as a traditional medicine for treating many common health maladies in Southeast Asia (Chan et al., 2005; Assanangkornchai et al., 2007; Chittrakarn et al., 2010; Adkins et al., 2011; Hassan et al., 2013).

2.4 Ketum Use among People Who Use Drugs.

Especially in Southeast Asia, ketum is generally used as a safe substitute to opioid (morphine/heroin) (Tanguay., 2011). Despite the anecdotal account, ketum is also now used in the US among people suffering from opioid use disorder and mental health problems like anxiety and depression (Garcia-Romeu et al., 2020). A cross-sectional study from Malaysia reported that people who consume illicit drugs commonly ingest ketum as a replacement for their illicit drugs, since it is shown to reduce their dependence on drugs, suppress withdrawal and numb craving (Vicknasingam et al., 2010). On the other hand, in Thailand, ketum leaves are also used in drug rehabilitation programs to help wean off heroin users from heroin consumption (Suhaimi et al., 2016).

In western countries, people often use ketum (or kratom) to treat themselves from opiate withdrawal, chronic pain, and alcohol use disorder (Boyer et al., 2008). Furthermore, ketum can be obtained conveniently from the internet or

convenient stores and is often sold in various strains and assortments in the US (Boyer et al., 2008). Ketum consumption is also believed to produce both sedative and stimulant like effects, but their effects depends largely on the amount one uses (Hassan et al., 2013). Moreover, ketum has also been utilized effectively to overcome opioid withdrawal symptoms among out-of-treatment heroin users living in rural areas in Malaysia (Ahmad & Aziz., 2012).

2.5 Pharmacological Properties of Ketum.

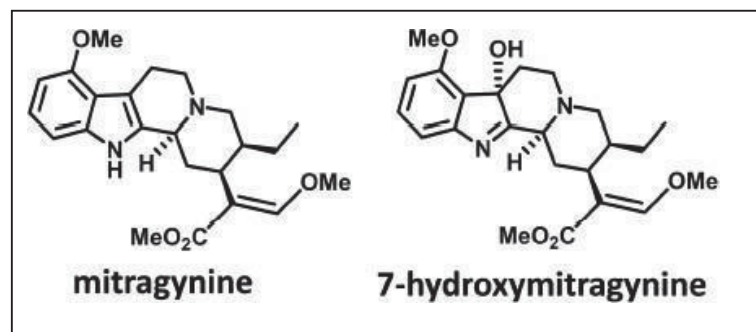


Figure 2.2, Kratom's main alkaloids. (Source: Kruegel et al., 2018).

To date, 25 alkaloids have been isolated and characterized in *Mitragyna speciosa* Korth. species. *Mitragynine* and *7-hydroxymitragynine* are the active compounds in ketum and both are reported to bind to opioid receptors with different affinity (Hassan et al., 2013; Warner et al., 2016). The principal active alkaloid *mitragynine* can range about 12-66% in ketum leaves, while *7-hydroxy-mitragynine* can only be detected in trace amount (about 2%) in ketum leaves (Philipp et al., 2009). Nevertheless, *mitragynine* concentration can vary from every plant or extracts and is generally influenced by different factors such as sun light content, water, leaves age, etc. (Takayama, 2004). There are also other types of alkaloids in ketum leaves such as *paynanthenine* (0.8%), *speciociliatine* (8.6%) and *speciogynine* (6.6%) (Takayama., 2004).

Mitragynine is reported to have analgesic properties at different doses (Kruegel et al., 2019). Hemby et al. (2018) found *7-hydroxy-mitragynine* can also produce analgesic effects which are 10 times more potent than