

**A PRELIMINARY STUDY ON PAIN TOLERANCE
AND WITHDRAWAL SYMPTOMS AMONG ACTIVE
KETUM (*MITRAGYNA SPECIOSA*) USERS IN
MALAYSIA**

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UNIVERSITI SAINS MALAYSIA

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KETUM (*MITRAGYNA SPECIOSA*) USERS IN
MALAYSIA**

by

AZLAN BIN ABDUL RAHIM

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LIST OF SYMBOLS

%	Percentage
H_0	Null Hypothesis
H_1	Alternative Hypothesis
$^{\circ}\text{C}$	Degree of Celcius
kg	Kilogram
L	Litre
mg	milligram
ml	Mililitre
mmol	Milimoles
ng	Nanograms
$\text{kg}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$	Kilogram-force per square centimetre
Vd	Volume of Distribution

LIST OF ABBREVIATIONS

BAI	Beck Anxiety Inventory
BPI	Brief Pain Inventory
BPRS	Brief Psychiatric Rating Scale
BDI	Beck Depression Inventory
CANTAB	The Cambridge Neuropsychological Test Automated Battery
COWS	Clinical Opioid Withdrawal Scale
CPT	Cold Pressor Task
DDA	Dangerous Drugs Act
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
FNE	Free Nerve Endings
HDL	High-density Lipoprotein
ISAP	International Association for the Study of Pain
K	Ketum
LDL	Low-density Lipoprotein
L	Litre
MINI	Mini International Neuropsychiatric Interview
MRI	Brain Magnetic Resonance Imaging
NPS	New Psychoactive Substances
P	Placebo
PSQI	Pittsburgh Sleep Quality Index
PPT	Pressure Pain Threshold
TLFB	Timeline Follow Back
UNODC	United Nation Office on Drugs and Crime
US	United States
USM	Universiti Sains Malaysia
Vd	Volume of distribution
VAS	Visual Analog Scale

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**KAJIAN AWAL TOLERANSI KESAKITAN DAN SIMPTOM GEJALA
PENGUNDURAN DALAM KALANGAN PENGGUNA KETUM (*MITRAGYNA
SPECIOSA*) AKTIF DI MALAYSIA**

ABSTRAK

Kratom dikenali penduduk tempatan sebagai ketum atau biak (*Mitragyna speciosa*). Ketum adalah tanaman yang berasal dari Thailand, Malaysia, Indonesia, dan negara-negara Asia Tenggara. Daun ketum banyak digunakan di negara Barat dan Asia Tenggara sebagai herba (ubat tradisional) untuk rawatan alternatif sebagai ubat tahan sakit dan gangguan penggunaan opioid. Walau bagaimanapun, penggunaan ketum juga dikaitkan dengan masalah gejala tarikan. Oleh itu, untuk mengkaji kesan penggunaan ketum seperti yang dilaporkan dari penyelidikan lepas (toleransi kesakitan dan gejala pengunduran), satu kajian makmal melibatkan manusia telah dijalankan bersama 26 peserta lelaki di Pusat Sejahtera, Universiti Sains Malaysia (USM). Kajian ini bertujuan untuk mengenalpasti adanya gejala pengunduran menggunakan pengukuran klinikal yang disahkan, iaitu Skala Gejala Pengunduran Opiat Klinikal (COWS), setelah 12 jam tidak menggunakan ketum. Kedua, kajian ini bertujuan untuk mengetahui kesan ketum terhadap toleransi kesakitan dengan menggunakan eksperimen rendaman tangan dalam air sejuk. Hasil kajian menunjukkan bahawa tidak ada kaitan yang signifikan dalam penggunaan ketum dengan gejala penarikan dan toleransi kesakitan. Walau bagaimanapun, terdapat simptom gejala pengunduran ringan diperhatikan selepas 12 jam berhenti ketum seperti hidung berair, menguap, resah dan cemas. Kajian ini tidak melihat sebarang kesan signifikan penggunaan ketum terhadap toleransi kesakitan. Peserta yang mengambil ketum mempunyai toleransi kesakitan min (SD) sebanyak 40.95 (SD=39.33) saat sebelum mengambil (0 jam), dan

53.83 (SD=56.43) saat 1 jam selepas pengambilan [$t(19) = -1.81, p = 0.087$]. Walaupun penemuan itu tidak signifikan, kajian yang menangani batasan kajian semasa perlu dijalankan kerana trend perubahan dalam toleransi kesakitan selepas mengambil ketum nampaknya mencadangkan sifat analgesik yang berpotensi dalam daun ketum.

**A PRELIMINARY STUDY ON PAIN TOLERANCE AND WITHDRAWAL
SYMPTOMS AMONG ACTIVE KETUM (*MITRAGYNA SPECIOSA*) USERS
IN MALAYSIA**

ABSTRACT

Kratom is known locally as ketum or biak (*Mitragyna speciosa*) in Thailand, Malaysia, and Indonesia. Southeast Asian countries are home to the ketum plant. Ketum leaves are extensively used as an herbal supplement (traditional medicine) for self-treatment of medical conditions in the West and Southeast Asia, including pain and opioid use disorder (OUD). However, ketum consumption over a prolonged period was associated with withdrawal effects. Therefore, to systematically investigate the effects of ketum based on claims from previous research (pain tolerance and withdrawal symptoms), a human laboratory study was conducted with 26 male participants in Pusat Sejahtera, Universiti Sains Malaysia (USM). The study aimed to investigate withdrawal symptoms using a validated clinical measurement, the Clinical Opiate Withdrawal Scale (COWS), after 12 hours of ketum cessation. Secondly, the study investigated ketum effects on pain tolerance using the cold pressor task. Study findings suggested no significant association between ketum consumption with withdrawal symptoms and pain tolerance. However, mild withdrawal symptoms were observed during the 12 hours of ketum cessation such as runny nose, yawning, restlessness and anxiety. The study did not observe any significant effect of ketum consumption on pain tolerance. Participants who consumed ketum had a mean (SD) pain tolerance of 40.95 (SD=39.33) seconds before consuming (0 hour), and 53.83 (SD=56.43) seconds 1 hour after consumption [$t(19) = -1.81, p = 0.087$]. Though the findings were not significant, studies that address the limitations of the current study

should be conducted as the trend of change in pain tolerance after consuming ketum appears to suggest potential analgesic properties in ketum leaves.

CHAPTER 1

INTRODUCTION

1.1 Introduction

This chapter provides a brief overview of ketum plant, and its classification as a new psychoactive substance (NPS). Objectives, significance and the scope of study will be discussed.

1.2 Brief overview on ketum plant

Ketum is known locally as *ketum* or *biak* (*Mitragyna speciosa*). Thailand, Malaysia, Indonesia, and other Southeast Asian countries are home to the ketum plant. Ketum leaves are extensively used as a herbal supplement (traditional medicine) for self-treatment of medical conditions in the West and Southeast Asia, including pain and opioid use disorder (Prozialeck et al., 2019). The majority of ketum users use it because ketum appears to improve withdrawal effects from opiate addiction (Vicknasingam, et. al., 2010). Uncontrolled ketum consumption can cause physical withdrawal symptoms such as yawning, diarrhoea, runny nose, and muscle aches (Singh, Narayanan, & Vicknasingam, 2016).

There are various ways to ingest ketum. Ketum leaves can be chewed or served as drinks. Fresh leaves are boiled till the solution becomes greenish brown and then served as a drink (Vicknasingam et al., 2010). Ketum is traditionally used to treat muscle pain, coughing and diarrhoea (Suwanlert, 1975). Ketum users claim that ketum can increase their work capacity, become more active, reduce their dependence on other drugs, increase sex drive, and improve appetite (Vicknasingam et al., 2010).

Despite its traditional medicinal claims, ketum is also used to self-manage chronic pain and opioid withdrawal (Boyer et al., 2008).

Ketum leaves contain a variety of chemical compounds known as bioactive alkaloids (World Health Organization, 2021). The most widely known ketum compounds are *mitragynine* and *7 hydroxymitragynine*. (WHO, 2021). A previous study using the animal model reported that *mitragynine* binds to mu-opioid receptor (Tsuchiya, 2002). Additionally, Sabetghadam et al. (2010) also reported antinociceptive effects in ketum extract using animal model, and ketum users reported using ketum to manage pain (Vicknasingam, 2010). Many ketum users appeared to have had a previous substance use disorder or were seeking relief from chronic pain and did not want to use opioids (Vicknasingam, 2010). However, there have been a few cases where people who use ketum as a substitute for opioid medication have experienced severe kratom withdrawal symptoms (Muller et al, 2020; Galbis-Reig, 2019; Boyer 2008).

According to Singh et al. (2019), regular users frequently use ketum for coping (drinking ketum to forget about problems), enhancement (drinking ketum to feel better or be able to achieve tasks that would otherwise be impossible), and social reasons (drinking ketum to be sociable, to celebrate parties). According to surveys performed in the United States by Grundman et al. (2018), ketum has been used as a self-medication replacement for prescription and illegal opioids. Ketum addiction is on the rise due to its psychotropic effects, notably in northern Malaysia, Kedah and Perlis, where ketum trees grow naturally (Vicknasingam et al., 2010).

According to United Nation Office on Drugs and Crime (UNODC), ketum use gained popularity not only in Southeast Asia but also has been widespread in Northern America and Europe (World Drug Report, 2018). Between 2012 and 2017, 31 countries reported the discovery of ketum use. In North America, a range of products labelled as ketum has been sold, some of which may contain ketum in combination with other ingredients, often as unknown substances (World Drug Report, 2018).

1.3 Classification of ketum as new psychoactive substances (NPS)

The rapidly emerging number of new substances including ketum in the global market poses a significant threat to public health and a challenge to drug policy. Little is known about the negative health effects and social harms of new emerging substances, also labelled as new psychoactive substances (NPS) (UNODC, 2015). According to the UNODC, the term “new psychoactive substances (NPS)” is defined as “substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat”. Therefore, NPS refers to psychoactive substances that are not listed and not regulated by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances. (UNODC, 2019). Based on the UNODC, the substances classified as NPS can be divided into nine groups.

- i. Aminoindanes
- ii. Phencyclidine-type substances
- iii. Phenethylamines
- iv. Piperazines

- v. Plant-based substances
- vi. Synthetic cannabinoids
- vii. Synthetic cathinones
- viii. Tryptamines
- ix. Other substances

Ketum is classified under new plant-based NPS (UNODC, 2018) and is becoming increasingly popular in North America and Europe (UNODC, 2018). In the United States, ketum was not administered under the Controlled Substances Act; however, there are some state regulations or prohibitions against the possession and use of ketum in their territory. The Food and Drug Administration (FDA) has not approved ketum for any medical use (Drug Enforcement Administration, 2020)

In Malaysia, ketum is enacted under Section 30 (3) of the Poisons Act 1952 in 2003, which allows for a maximum sentence of four years in prison or a fine of RM10,000, or both, for the use of ketum leaves (Vicknasingam et al., 2010). The act also regulated the importation, possession, manufacture, compounding, storage, transportation, and selling of ketum (Law of Malaysia, 2006). Although the initiative from a legal point of view has designated ketum as a poison, the issue is still being discussed (Vicknasingam et al., 2010).

Ketum was the most common plant-based NPS seized between 2016 and 2018, however, the trend has changed in 2019 (World Drug Report, 2021). According to the World Drug Report, 222 tons of NPS were seized in 2019, with more than half were classified as plant-based NPS. From the total number of plant-based NPS seized, ketum was the second most common substance after the khat plant (World Drug

Report, 2021). Malaysia seized the most ketum, followed by Thailand (World Drug Report, 2021).

In Malaysia, a total of 27,976.5 kilograms ketum leaves were seized in 2019 that involved 3 states in the Northern and East Coast of Malaysia suggesting a high demand of ketum. The total amount of ketum leaves seized was worth RM1,023,315.00 (Malaysia National Border Control Agency, 2020), and the number of cases in the state, or place, seized is presented in Table 1.1.

Table 1. 1 Number of ketum leave seized in 3 States of Malaysia (Malaysia National Border Control Agency, 2020)

No	State	Value (RM)	Total of ketum leave seized (Kg)	Number of cases
1	Perlis	707,515.00	22,228.5	79
2	Kedah	140,000.00	2,188.0	1
3	Kelantan	175,800.00	3,560.0	13

1.4 Background of the study

Ketum has long been used in Southeast Asia to treat pain and opioid withdrawal (Suwanlert, 1975; Jansent & Prast, 1988; Vicknasingam et. al. 2010; Prozialeck et. al., 2012). People in the West are increasingly turning to ketum to manage pain from opioid medications like opioids and prescription pain relievers (Krauth, 2011; Ward et al., 2011). Aside from changes in consumption patterns among Southeast Asian ketum users, the use of ketums in Western countries, particularly the United States (US), has been shown to be increased. (Kruegel & Grundmann (2018).

There were several studies that examined the effect of ketum on pain management using animal models such as those conducted by Matsumoto et. al. (2004) and Sabetghadam et al. (2010). Both these studies evaluated the antinociceptive

activity of ketum using mice and rats. In human studies, studies by Coe et al. (2019), Viknasingam (2010), and Boyer et al. (2007) reported the use of ketum to manage opioid pain. However, an experimental study on the effectiveness of ketum as an analgesic has not yet been conducted. Therefore, in the current study, a validated experimental method was used to investigate the effect of ketum on pain tolerance by using a cold pressor task.

Studies documenting ketum withdrawal symptoms were mainly conducted with self-report measures (Galbis-Reig, 2019; Singh et al., 2018; Singh et al., 2014; Ahmad & Aziz, 2012; Vicknasingam et al., 2010; Assanangkornchai et. al., 2007; Suwanlert, 1975). The first study using a validated questionnaire to measure ketum dependence was conducted by Singh et al. (2014) in open-field settings, while Galbis-Reig (2019) was the first case study to observe ketum withdrawal symptoms using a validated clinical assessment in one patient. Studies on the psychological and physiological effects of ketum in humans reported mitragynine content and average consumption of ketum users, but ketum consumption findings were based on self-report (Singh et al. 2012, Vicknasingam et al. 2010).

Available studies thus far suggest that most ketum users experience withdrawal symptoms that can be classified as moderate to severe during ketum cessation (Galbis-Reig, 2019; Singh et al. 2012, Vicknasingam et al. 2010). As the current knowledge on ketum withdrawal symptoms were obtained from self-report methods and there is very limited data in assessment of ketum withdrawal using validated clinical assessments, the current study sought to fill the knowledge gap by systematically documenting the effects of ketum withdrawal using a validated measure for opioid withdrawal (Clinical Opioid withdrawal Scale) in a controlled setting. The current

study also aimed to determine the effects of ketum on pain tolerance using the cold pressor task.

1.5 Problem statement

In animal studies, it was discovered that mitragynine and 7-hydroxymitragynine cause withdrawal symptoms similar to opioid mechanisms in morphine withdrawal (Matsumoto et al., 2004). Based on existing ketum withdrawal studies conducted via self-reported measures (Viknasingam, 2010; Singh et al. 2014; Lydecker et al., 2017), Saingam et al (2014) developed the only valid measurement available to evaluate the severity of the ketum dependence. Even though the literature documenting various types of withdrawal symptoms experienced by ketum users, clinical observation on the severity of ketum withdrawal symptoms experienced by ketum user has not been done.

Although there is some research suggesting using kratom as an opioid substitute and pain reliever (Viknasingam et al., 2010; Boyer et al., 2008, Sabetghadam et al., 2010), these studies were not conducted in a laboratory and controlled setting among human ketum users.

1.6 Research questions

There are two research questions in this study:

- i. Do daily kratom users exhibit withdrawal symptoms, measured by COWS, 12 hours after kratom cessation?
- ii. Does kratom improve pain tolerance (longer hand immersion in cold water) compared to baseline?

1.7 Research objectives

There are two research objectives in this study.

- i. To investigate the presence of withdrawal symptoms using a validated clinical measurement, the Clinical Opiate Withdrawal Scale (COWS), after 12 hours of kratom cessation.
- ii. To determine the effects of kratom on pain tolerance by using the cold pressor task.

1.8 Research hypotheses

The research objective and research hypotheses are as follows:

Research objective 1

- i. H_0 : There are no significant withdrawal symptoms after 12 hours of kratom cessation among regular kratom users.
- ii. H_1 : There are significant withdrawal symptoms after 12 hours of cessation among regular kratom users.

Research objective 2:

- i. H_0 : There will be no significant increase in pain tolerance among the participants who consume kratom compared to the placebo.
- ii. H_1 : There will be a significant increase in pain tolerance among the participants who consume kratom compared to the placebo

1.9 Significance of the study

To my knowledge, this study is the first controlled human laboratory study to evaluate ketum effects on pain tolerance and withdrawal symptoms from ketum use. Previous studies were human field studies based on surveys and qualitative interviews that documented anecdotal responses from regular ketum users in the local community.

The significance of this study is that it provides preliminary objective data on pain tolerance and withdrawal symptoms from ketum. The data from this study can be used to further advance human trials that can potentially lead to medication development. Most studies on the effects of ketum were in the pre-clinical stage using animal models to study ketum effects from the aspect of psychochemistry. The pre-clinical study by Sabetghadam (2010) used the animal model to investigate the antinociceptive activity of ketum. Only one study was conducted clinically with humans, which was on the pharmacokinetics of ketum in the human body (Trakulsrichai et al., 2015). Furthermore, despite the fact that kratom has been reported to used in pain managment (Vicknasingam et al, 2010; Singh et al., 2014), there is no solid evidence to back up such claims, particularly in human trials. The current study directly tested the effects of kratom on pain tolerance and the severity of withdrawal symptoms experienced by participants during ketum use cessation.

Therefore, this study adds important knowledge to the understanding of ketum effects on humans. The current study uses established methods and tools to measure pain tolerance and withdrawal symptoms. As there are studies and research suggesting potential therapeutical benefits of ketum, systematic human studies on the effects of kratom such as the current study serves as an important stage in the development of ketum therapeutics.

1.10 Scope of the study

This study was conducted at Pusat Sejahtera, USM. All participants were recruited from the northern states of peninsular Malaysia (Penang, Kedah). Participants were also recruited based on data provided by the key informants.

This thesis is divided into six chapters, each of which explains a different topic starting from the introduction to the study conclusion.

Chapter 1: A basic review of the ketum plant, followed by the classification of ketum as a New Psychoactive Substance (NPS) according to the United Nation Office on Drugs and Crime (UNODC). The statistics of seized ketum in the illegal market is presented.

Chapter 2: An overview of studies relevant to ketum and its use is discussed. This chapter first discusses the ketum plant in terms of botanical description, history of use and its legal aspect, and public perception of ketum, the effect of ketum from the context of physiology and psychology, dependency, pain, and withdrawal. The research gap discussed in this chapter will be carefully analyzed to form research objectives and research hypotheses.

Chapter 3: Methods and instruments used in this study are described. There are nine sections, and the first three describe the study design, location of the study and study instruments. The next sections describe the sample size calculation, participant recruitment and the preparation of ketum and placebo drinks. The last two sections describe the randomization and blinding procedures.

Chapter 4: In this chapter, results of data analyses are presented. This chapter is divided into two main sections – the first section presents findings from the screening phase, and the second section presents findings from the experimental assessments.

Chapter 5: The findings of the study are discussed in this chapter. This chapter is divided into two parts. The first section is devoted to a discussion of the screening test results. The second section discusses the results of the experimental assessments.

Chapter 6: This chapter discusses the limitations of the study and suggestions for future research.

1.11 Operational definition

Pain tolerance

The maximum level of pain that one is willing to endure is referred to as pain tolerance. Tolerance varies greatly between individuals and is influenced by the medications they take (Kanner, 2009). In this study, pain tolerance was measured using the cold pressor task. Participant's pain tolerance was measured by the duration (seconds) of their hand immersed in the cold-water bath. The longer the duration of the hand immersion, the higher the pain tolerance.

Withdrawal symptoms

According to American Psychological Association (APA) (2022), substance withdrawal is defined as a syndrome that develops after the cessation of prolonged, heavy consumption of a substance. "*Symptoms vary by substance but generally include physiological, behavioural, and cognitive manifestations, such as nausea and vomiting, insomnia, mood alterations, and anxiety*" (APA Dictionary of Psychology,

2022). In this study the presence and severity of withdrawal symptoms were measured using the Clinical Opiate Withdrawal Scale (COWS).

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

In this chapter, an overview of studies relevant to ketum and its use will be discussed. This chapter first discusses the ketum plant in terms of botanical description, history of use and its legal aspect, and public perception of ketum. Then the discussion will continue with the effect of ketum from the context of physiology and psychology and ketum explanation in the perspective of pharmacology. The dependency and withdrawal of ketum will also be discussed before explaining the ketum relationship with pain and how pain is measured using several methods. The research gap discussed in this chapter will be carefully analysed to form research objectives and research hypotheses.

2.2 Ketum botanical description

Ketum (*Mitragyna Speciosa*) is a Rubiaceae species that grows in the tropics. Ketum is a natural plant that grows mostly in Thailand's central and southern regions and northern Malaysia and Indonesia. (Suwarnlert, 1975; Chan et al., 2005; Veltri & Grundmann, 2019). The ketum trees usually grow between 4 and 9 metres in height and 5 metres in width, and some trees can reach a height of up to 15 to 30 meters. The leaves are ovate-acuminate in shape with pointed tips and can grow to over 18 cm in length and 10 cm in width. (Hassan et al., 2013; Suwarnlert, 1975). The tree produces yellow flowers and grows in a globular cluster at the end of the branches. The trees thrive in swampy, rich soil with plenty of sunlight in wind-protected places (Hassan et al., 2013). Ketum is referred to as "biak-biak" or "ketum" in Malaysia, and "ketum," "kankum," or "kratoan" in Thailand (Adkins et al., 2011; Suwanlert, 1975).



Figure 2. 1 Ketum tree with flowers (Witworth, 2018)

2.3 History of ketum use

Since ketum trees are indigenous to Malaysia, Thailand, and Indonesia, the exact date when it was first utilised is unclear and undocumented; nonetheless, it may have been part of societal structures for hundreds of years (Suwanlert, 1975; Veltri & Grundmann, 2019). The usage of ketum was first documented in the scientific literature in 1983 when it was discovered that the Malay population utilised the ketum tree's leaves as a replacement for opium (Jansen & Prast, 1988; Veltri & Grundmann, 2019). Furthermore, ketum leaves are traditionally used for medicinal purposes in Southeast Asia (Singh, Narayanan & Vicknasingam, 2016) to treat diarrhoea, fever, diabetes and muscle pain (Hasan et al., 2013).

Besides the mentioned above, ketum leaves are also used as a wound poultice and manage withdrawal symptoms from opium and later heroin (Jansen & Prast; 1988, Veltri & Grundmann, 2019). In addition, ketum users claim that ketum could increase

their work capacity, help them become more energetic, reduce their dependency on other drugs, and increase sex drive and appetite (Vicknasingam et al., 2010).

Although ketum usage has a long history among villagers in rural Southeast Asia and is used as a treatment for various health concerns, men and women have different justifications for consuming it. In villages, women commonly use ketum leaves as a home medicine to cure common illnesses such as fever, cough, hypertension, and diabetes. It is also used as a poultice for wounds, a deworming agent, and an appetite suppressant (Assanangkornchai et al., 2007; Burkill, 1935; Burkill & Haniff, 1930; Lee, 1957; Saingam et al., 2012; Singh et al., 2017). Female users are ostracized, and female ketum users are fewer in local communities (Suwanlert, 1975; Veltri & Grundmann, 2019). Men, on the other hand, typically use ketum in the morning to improve job performance, reduce weariness from working in the hot sun, and as a drink during social gatherings (Singh et al., 2017).

Apart from being utilised as a medical treatment, ketum is frequently used in Thailand's villages for religious purposes (Saingam et al., 2013; Singh et al., 2017). Ketum has also taken on a role as a beneficial offering to a god or spirit in order to fulfil their wishes or vows (Saingam et al., 2013; Singh et al., 2017).

2.3.1 Traditional method to prepare ketum juice

There are several ways to consume ketum. Ketum leaves are usually consumed by chewing, smoking, brewing into a tea (Adkins et al., 2011) and mixed with coffee or carbonated beverages (Singh et al., 2017; Hassan et al., 2013). The ketum leaves are extensively used as a drink for ketum users in Malaysia, where they are picked from trees and washed carefully with water to remove any signs of dirt, then boiled with water for an average of four hours (Vicknasingam et al., 2010). The broth must be stirred every half hour while the ketum leaves are brewed to ensure the leaves do

not burn at the bottom of the pot, which will result in an unpleasant burnt taste. A newly brewed ketum leaf broth is a greenish-brown broth with a strong bitter flavour. The broth is then allowed to cool before being consumed. The cool, brewed ketum juice is then bottled and sold in tiny plastic bags (approximately 250 ml to 300 ml) for consumption (Vicknasingam et al., 2010; Singh et al., 2017). The packages are also frozen in ice to allow them to last for about 3 days (Singh et al., 2017).



Figure 2. 2 Ketum tree planted near the houses in rural areas

2.3.2 Reasons for ketum use historically, in Southeast Asia

Dated back to the early 1970s, research conducted by Suwernleart (1975) reported that ketum was used as traditional remedies for common illnesses and increase work ability in rural areas in Southeast Asian communities. The findings of the Suwanlert (1975) study are consistent with the findings by Ahmad and Aziz (2012). The study was conducted with 562 respondents, and the findings suggested more than one reason for using ketum among the respondents. Findings suggested that ketum was primarily used for stamina and endurance, social and recreational use, and enhancing sexual performance. Approximately one-third of the overall use of ketum is used for therapeutic purposes, including alleviating pain, diarrhoea, fever, and even diabetes and hypertension (Ahmad & Aziz, 2012).

Nowadays, new trends in ketum usage have emerged. Two new patterns have arisen among ketum consumers (Singh et al., 2017). Beginning with utilising ketum for homemade medicines to treat common illnesses, the pattern gradually evolved into a replacement for reducing illegal drug withdrawal symptoms. The ingredients to produce the ketum cocktail have evolved as well, from only ketum leaves to a combination of ketum and a range of other substances (Singh et al., 2017).

The emerging trend can be spotted from the study by Vicknasingam et al. (2010). According to the findings of a cross-sectional study performed in Malaysia, many illegal drug users in the country's northern regions utilised ketum as a cheap option to reduce their dependence on other illicit substances and suppress opiate withdrawal symptoms. A total of 136 active users participated in the study. They were recruited from the northern Malaysian states of Kedah and Penang, and selected from areas in which ketum usage was well-documented. The areas were identified based on previous research and information from key informants. During the recruiting phase, informants were either existing ketum users or officers from the National Anti-Drugs Agency. According to the findings, the majority of the participants (122/136) who were both short-term and long-term users of ketum used it to reduce their reliance on other illegal substances. Another reasonable explanation given by many users (114/136) was that ketum consumption helped to alleviate the symptoms of opiate withdrawal. Finally, 88/136 respondents said that the cost of ketum relative to heroin made a difference (Vicknasingam et al., 2010).

Apart from the changing trend in terms of using ketum, a few studies have reported that ketum use in urban communities among younger individuals in Malaysia and Thailand has become more dangerous (Singh et al., 2016). It has been reported

that ketum is used as a replacement for opioids and alcohol and provides a subjectively higher sense of euphoria (Singh et al., 2016; Tanguay, 2011; Tungtanuwat & Lawanprasert, 2010; Sing et al., 2017). The homemade ketum cocktail known as “*sii koon roi*” has grown popular among Thai teenagers and young adults. Cough syrup, drinks (such as Coca-Cola), and brewed ketum tea are commonly included in the mixture. Then, based on customer's preferences, substances including antidepressants, analgesics, and anxiolytics are also added (Tungtanuwat & Lawanprasert, 2010). Similar trends emerging in Malaysia have been identified with the same preparation method but with various mixed ingredients. The cocktail, known as “*koroi*” is the mixture of ketum juice with other ingredients such as Coca-cola and cough syrup. This trend is becoming increasingly popular among the community's young and older ketum users (Singh et al., 2017). However, because of their multidrug toxicity, cocktails including poly-drugs (anxiolytics or antidepressants) have the potential to be deadly (Tungtanuwat & Lawanprasert, 2010; Singh et al., 2017).

2.3.3 Ketum use from the social perspective

Ketum users are usually seen as hardworking individuals, but cannabis, alcohol, and cigarette users are stereotyped as lazy and reckless (Singh et al., 2017; Saingam et al., 2013). Because they are considered to be engaging in the habit for their own enjoyment, the viewpoint may be biased (Saingam et al., 2013). In Malaysia, a study observed that ketum users did not feel guilty about their ketum consumption because they deemed themselves as responsible members of their family. They were also seen as ordinary working people who contributed to society and the well-being of their families (Ahmad & Aziz, 2012; Singh et al., 2017). In comparison to morphine, opioid, or heroin addiction, the housewife of a husband who engages with ketum dependence in rural communities is not associated with serious stigma if the husband

still carries out the responsibility to support his family (Suwanlert, 1975; Veltri & Grundmann, 2019).

A few studies have discussed the effect of ketum on social functioning. There is no reported significant impairment in ketum users' social functioning caused by daily ketum use (Singh et al., 2015). Besides, ketum dependent users did not indicate that their daily ketum usage disturbed their social functioning or impaired it. Most ketum users in Southeast Asia are employed, married, and lived with their families (Assanangkornchai et al., 2006; Saingam et al., 2012; Singh et al., 2015; Singh et al., 2017). They also stated that since the beginning of their ketum use, none of them had experienced any serious health concerns (Singh et al., 2015). Singh et al. (2019) used the Drinking Motives Questionnaire (DMQ) to explore the motivation for consuming ketum with 116 regular ketum users. The original version of the Drinking Motives Questionnaire (DMQ) was adapted from Cooper et al. (1992). The instrument was then modified with the purpose to evaluate the motives and reason for ketum use by replacing the word "drinking" (alcohol) with "drinking ketum" and. It was then translated into the Malay language. The DMQ is a self-report questionnaire with 15 items. It is divided into three subscales: social (drinking ketum to be sociable, enjoying parties), coping (drinking ketum to forget about problems), and enhancement (drinking ketum to feel better or otherwise difficult to do things). The participants in this study were recruited via convenience sampling. According to the research, regular ketum users do so for a variety of reasons, including enhancement, coping, and social reasons. According to Singh et al. (2019), individuals who consumed ketum were most likely to engage with internal motives (coping or enhancement) rather than those who consumed ketum for external social motives.

Currently, the majority of studies have only been conducted with ketum users, and according to Singh et al. (2019), data was collected using retrospective and self-report methods. According to Singh et al. (2019), these studies' limitations lie in the nature of the data collecting approach, which might reflect some social desirability bias. Therefore, the pattern for social functioning seems to be positive.

2.2.3(a) The emergence of ketum consumption in the Western markets

Apart from changes in consumption patterns among ketum users in Southeast Asia, there has been an upsurge in ketum use in western nations, notably the United States (US). According to an anecdotal report, the pattern of ketum consumption has increased over the last decade (Veltri & Grundmann 2019). Ketum use in the United States began in the 1980s and 1990s when Southeast Asian migrants imported the plant to the country (Kruegel & Grundmann, 2017; Hennigfield et al., 2018; Veltri & Grundmann, 2019). Ketum was widely used in the US in the 2000s as an alternative treatment to improve mood and quality of life. Besides, ketum was also used as a supplement for individuals who have a problem with opioid dependence, either on prescription or illegal opioid consumption. Ketum is also used to reduce opioid pain during abstinence from using opioid. Overall, it is expected that several million individuals in the United States use ketum and purchase products from more than 100,000 ketum retailers, with a market value of 207 million USD in 2016 (Henningfield, Fant & Wang, 2018). Ketum has been sold online in herbs and tobacco stores. It is commonly sold as a herbal medication or a supplement to treat various ailments, including pain, mental health, and opiate withdrawal symptoms (Veltri & Grundmann, 2019).

Moreover, a survey conducted in the United States (US) found that 83.75 % of ketum users in the US felt an increase in energy after they used ketum. For risk

behaviors, ketum was always associated with consumer aggression of substances that could have a stimulant effect (Grundmann, 2017). Therefore, the study concluded that the impact of energy enhancement could stimulate risky behavior for ketum users. In addition, Grundmann (2017) reported that ketum was used to reduce pain. This indicates that ketum is a substance that influenced pain tolerance and known to have analgesic effects.

Smith & Lawson (2017) conducted a self-report survey among respondents who had a history of substance use disorder (SUD) in the US regarding the use of ketum products and the reasons for using them. A total of 500 people took part in the survey. According to the study's findings, 68.9% of respondents (344/500) said they had stopped or reduced their use of non-prescription opioids (NPO), and 64.1% (320/500) said they used ketum as a substitute. The study also found that 18% of ketum users chose ketum to reduce chronic pain. 34% (170/500) reported that ketum was readily available compared to NPOs. Moreover, 9.7% (48/500) of respondents preferred the effects of ketum use over NPO. Only 1.0% (5/500) of those who used ketum sought medical help. After consuming ketum, about 8% (40/500) of the respondents said they felt "hungover", and 8.7% said they felt "anxious". In comparison to NPO, ketum was found to induce fewer negative side effects by over 27.2% (136/500) of consumers. Finally, around 34% of respondents (170/500) stated they would try ketum again and that it was a helpful drug. However, ketum was not preferred compared to amphetamine, suboxone, and NPO (Smith & Lawson, 2017).

A comprehensive review conducted by Prozialeck (2016) highlighted the current scientific and legal conflict over ketum. Ketum was increasingly utilised for self-management of opiate withdrawal and pain (Prozialeck, 2016). Many in the

United States who use opioids for chronic pain seek alternatives that do not have the same negative effects or the risk for addiction that opioids do. However, there have been a growing number of complaints of negative side effects associated with the usage of ketum products. Ketum and its *mitragynine* components were classified as Schedule 1 prohibited drugs by the US Drug Enforcement Administration in August 2016, prompting a strong reaction from ketum supporters. After evaluating the literature, Prozialeck (2016) concluded that doctors should not prescribe ketum to their patients unless they had proven scientific evidence. The literature review suggested two main reasons why ketum consumption in the United States (US) has become popular. The first was the use of ketum as an opioid withdrawal replacement. Second was the use of ketum to alleviate chronic pain (Veltri & Grundmann, 2019; Smith & Lawson, 2017; Prozialeck, 2016). In contrast to the Southeast Asian pattern of obtaining ketum supplies, ketum customers in the United States order ketum from online stores that sell medical herbs. In comparison, both regions have a perspective of ketum use as herbal medicine or a traditional alternative rather than recreational use.

2.3.3.(b) Ketums and mental health

Substances with psychoactive properties are usually associated with psychiatric symptoms such as stimulants, hallucinogens, and euphoria. The World Health Organization (WHO) defines health as having a normal physical, mental, and social functioning free of illnesses or diseases (WHO, 2015), while substance abuse refers to the use of psychoactive substances (e.g. alcohol and drug abuse) that can harm an individual's mental and physical security (Vandendyck, 2015). WHO also reported that substance use disorder causes a 13% contribution to global health problems (WHO, 2015).

Swogger and Walsh (2018) conducted a systematic review comprising 13 studies on ketum use and mental health from a mental health viewpoint. The review focused on research published between January 1960 and July 2017. According to the review, ketum has the potential to be utilised as a risk reduction strategy, particularly as an opioid replacement in people who are addicted to opioids. The review also suggested that ketum was able to improve mood and relieve anxiety among ketum users. For most people, the negative effects of ketum-related mental health are mild withdrawal symptoms compared to those who use opioids. However, for several ketum users, withdrawal symptoms can be very uncomfortable. In conclusion, it appears that ketum use may have some mental health advantages that warrant further investigation. Even though ketum dependency can be a threat for some individuals, the ketum user's psychosocial and physiological dependence syndrome experience tends to be mild compared to opioid dependence (Swogger & Walsh, 2018).

Suicide behaviour is a set of behavior related to intentionally killing or hurting oneself such as planning a suicide, thinking of suicide, attempt to suicide and commit a suicide (Kittirattanapaiboon et al., 2014). There is a significant association between suicide and people who abuse alcohol and other substances (Kittirattanapaiboon et al., 2014; Harris & Barraclough, 1998). Suicide has been identified as the primary cause of premature mortality among those who misuse alcohol or tobacco (Kittirattanapaiboon et al., 2014; Harris & Barraclough, 1998). Suicide is also one of the major causes of death among people in underdeveloped nations (Nock et al, 2009; Kittirattanapaiboon et al., 2014). . In the 2008 Thailand National Mental Health Survey, a total of 17,140 participants reported that they had a history of illicit drug abuse over the past year (Kittirattanapaiboon et al., (2014). Their mental state was assessed using the Mini-International Neuropsychiatric Interview (MINI). Aspects of

current suicidal behaviour were included in the MINI evaluation (1 month before assessment). Mood episodes, anxiety disorders, psychotic disorders, and alcohol use disorders were also assessed throughout the study. The study also observed 537 subjects actively using illicit drugs, while 1,194 respondents were at risk of suicide. The respondents utilised the most frequent illegal substances, including ketum (59%) and methamphetamine (24%) in comparison to 16,603 Thais who do not utilise illegal drugs (Kittirattanapaiboon et al., 2014). Summaries from the overall results of this study suggest that ketum abuse may contribute to a potential cause of suicide.

For the time being, based on the findings of the aforementioned study, it can be stated that ketum use has both good and bad consequences. Therefore, more clinical studies on ketum consumption should be conducted to further examine the effects and benefits of ketum use.

2.4 Legal aspect and public perception of ketum

In Malaysia, ketum is placed under the Poisons Act 1952 because of its potential for abuse and was banned since 2003 (Vicknasingam et al., 2010). This Act is enacted to control the importation, possession, processing, selling and use of substances already specified in the Act (Singh, Narayan & Vicknasingam, 2016). Possession, import, and export of ketum have been prohibited in Thailand since 1943. (Assanongkorchai et al., 2007). Meanwhile, the Australian and Myanmar governments have designated ketum as a narcotic. In the United States, ketum is placed under the controlled substance Act Schedule 1 because of its negative impact (Grundmann et al., 2018).

A study was conducted by Singh et al. (2019) on public perceptions of ketum use in Malaysia involving 356 respondents. The participants consisted of 137 ketum users while 219 participants were not from among ketum users (137 ketum users and