A STUDY ON THE PROFILE OF KETUM PREPARATION USING COLOUR TEST AND GC-MS

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A STUDY ON THE PROFILE OF KETUM PREPARATION USING COLOUR TEST AND GC-MS

by

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SYMBOLS

µ	Micro
℃	Degree Celsius
%	Percent

LIST OF ABBREVIATIONS

mL	Mililitre
min	Minutes
sec	Seconds
M	Molar concentration
GC-MS	Gas chromatography-mass spectrometry
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
UNODC	United Nations Office on Drugs and Crime
DEA	Drug enforcement administration
NIH	National library of medicine
SWGDRUG	Scientific Working Group for the Analysis of Seized Drugs
Amu	Atomic mass units

KAJIAN KE ATAS PROFIL PENYEDIAAN KETUM MENGGUNAKAN UJIAN WARNA DAN GC-MS

ABSTRAK

Mitragyna speciosa, atau lebih dikenali sebagai ketum di Malaysia, sering disalahguna sebagai dadah herba. Selalunya, ketum dijual sebagai daun, minuman, kapsul di pasaran dan juga di dalam talian internet, dan juga tersedia di sekitar kawasan pedalaman di negara Asia Tenggara sebagai ubat tradisional, terutamanya di Malaysia dan Thailand. Ketum amat popular dalam kalangan pekerja lelaki di Malaysia dan Thailand. Sejak beberapa dekad yang lalu, daun ketum telah digunakan oleh orang tempatan oleh kerana kesannya seperti candu dan mempunyai keupayaan perangsang seperti kokain untuk meningkatkan tenaga dan melawan keletihan. Mitragynine, alkaloid daripada daun ketum bertanggungjawab untuk kesan perangsang dan ini menyebabkan minuman ketum menjadi pilihan dadah yang disalahgunakan yang semakin meningkat bilangannya. Namun, adakah tidak diketahui sama sekali sama ada bahan lain juga diadukkan ke dalam minuman ketuan yang boleh diperolehi di pasaran. Kajian ini dijalankan untuk menentukan sebatian aktif dalam campuran minuman ketum dan untuk mengkaji trend "koktel" ketum pada masa kini. Dalam kajian ini, semua minuman ketum diperolehi dalam bentuk minuman sahaja. Ujian warna presumptif ke atas sampel ketum telah berjaya dilakukan menggunakan reagen Van Urk dan 70 sampel telah memberi perubahan warna merah, 4 sampel memberi perubahan warna merah jambu gelap dan satu sample menunjukkan keputusan negatif. Penyediaan standard minuman ketum berjaya dilakukan dengan merebus 10 helai daun ketum dalam bikar di atas alat pemanasan. Selain itu, proses pengekstrakan mitragynine daripada semua 75 sampel telah berjaya dilakukan menggunakan kaedah

pengekstrakan cecair-cecair. Kemudian, ekstrak kloroform telah dianalisa menggunakan kromatografi gas-spektrometri-spektrum jisim (GC-MS). Kromatogram yang terhasil dan laluan pemecahan yang mungkin dikesan oleh GC-MS telah dibincangkan. Daripada 75 sampel, hanya satu sampel tidak menunjukkan puncak mitragynine dan majoriti menunjukkan kromatogram ringkas dengan adanya hanya beberapa puncak dalam kromatogram termasuk kafein (RT=5.137) dan mitragynine (RT=18.839). Sampel 49 menunjukkan kromatogram yang paling kompleks dengan kehadiran puncak MDMA. Seterusnya, trend campuran minuman ketum di Malaysia turut dikaji. Penemuan kami menunjukkan bahawa kebanyakan minuman ketum adalah teh ketum, tanpa sebarang bahan asing. Namun, beberapa sampel adalah dalam bentuk koktel, dan ini boleh menyebabkan kesan kesihatan yang serius. Oleh itu, pemantauan adalah penting, mungkin melalui penyeledikan pemprofilan yang lebih kerap untuk memperoleh maklumat yang berguna untuk perisikan forensik dan membuat keputusan oleh pihak berkuasa yang berkenaan.

Kata kunci: *Mitragyna speciosa*, ketum, “koktel”, mitragynine, reagen Van Urk, kafein, MDMA.

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ABSTRACT

Mitragyna speciosa, or known as ketum in Malaysia, is always misused as herbal drug of abuse. Typically, ketum is sold as their raw leaves, drinks or campsules in the street as well as incense online and also available at markets in more rural areas in Southeast Asia as traditional medicine, especially in Malaysia and Thailand. Ketum is very popular among men workers in Malaysia and Thailand. Many decades ago, ketum leaves have been used by natives due to its opium-like effect and cocaine-like stimulant ability to increase energy and combat fatigue. Mitragynine, an alkaloid from ketum leaves is responsible for these mentioned effects and this makes ketum drinks to become the emerging drug of abuse. However, it is unknown at all whether or not other ingredients were added in the ketum drinks available in the market.This present study was done to determine active compounds in the ketum drinks mixtures and to study the recent trend of ketum "cocktails". In this study, all ketum drinks were obtained in the form of drinks. Presumptive colour test on ketum samples was successfully conducted using Van Urk reagent and 70 samples gave pink colour change, 4 samples gave dark pink colour change and one showed negative screening results. The preparation of ketum drink standard was successfully done by boiling 10 ketum leaves in a beaker on a hotplate. Besides, the extraction process of mitragynine from all 75 samples were successfully performed using liquid-liquid extraction method. Afterwards, the chloroform extracts were subjected to gas chromatography-mass spectrometry (GC-MS) analysis. The resulting chromatograms and possible fragmentation pathways detected by GC-MS were discussed extensively. Out of 75

samples, only one sample did not exhibit mitragynine peak and majority showed simple chromatograms with only several peaks present in the chromatogram which include caffeine (RT=5.137) and mitragynine (RT=18.839). Sample 49 showed the most complex chromatograms with the presence of a MDMA peak. The trend of ketum drink mixtures in Malaysia was also studied. The findings showed that most of the ketum preparation were merely ketum drinks, without addition of any adulterants. A few samples were, however, in the form of cocktails, and these can cause serious health effects. It is therefore important that the monitoring of the streect drugs are conducted, perhaps via a more frequent drung profiling study to obtain information which could be useful for forensic intelligence as decision making for the respective authorities.

Keywords: *Mitragyna speciosa*, ketum, “cocktails”, mitragynine, Van Urk reagent, caffeine, MDMA.

CHAPTER 1

INTRODUCTION

1.1 Background of study

Ketum, or kratom becomes a subject in forensic science and forensic laboratory analysis for many years. The main reason of its "popularity" is the secondary metabolites present in this plant, particularly the compounds in the forms of various alkaloids. Among them, mitragynine and 7-hydroxymitragynine are the two main psychoactive alkaloids of interests which are potentially being abused and thus making ketum to become the centre of discussion on its control. Although ketum plant is not control at the international but some countries have put Ketum plant under national control such as Singapore under Misuse Drug Act 2019, Malaysia under Poisons Act 1952, while mitragynine is a controlled substance in Poisons Standard. In Thailand, Ketum was once on Thailand's prohibited list of plants for use in in their narcotic Act, but the Thai House of Representatives has passed a bill to remove the kratom plant from its narcotics list to allow for regulated sale and consumption of kratom.

In Malaysia, any activity related to possessing, selling, using, transporting, processing, importing or exporting ketum is prohibited. Although this is clear under the Act, ketum has been traditionally used in selected areas and associated issues of ketum use and abuse were reported from time to time especially on the frequent seizure of ketum leaves and its preparation. The situation becomes more complex when ketum and its preparation are transformed into new preparation, traded by drug dealers and traffickers together with other controlled substances. The users could be the single drug used of ketum addition as well as other more dangerous poly-drug abusers seeking stimulating, sedative and euphoria effects.

When ketum and its liquid preparations or processed materials were seized by the law enforcement agencies, analysis have to be conducted to establish if the materials contain mitragynine, the psychotropic substance listed under the First and the Third Schedule of Poisons Act 1952. The selling of ketum leaves and its preparation is an offence, where upon conviction, will result with a penalty of RM10,000 or jail sentence of four years or both.

1.2 Ketum use and abuse

The scientific name of ketum is *Mitragyna speciosa* (Korth). It belongs to the Rubiaceae family, i.e. a family of flower plants or the coffee family. It grows well in tropical and subtropical areas and are commonly a native tree commonly available in Malaysia, Thailand, Indonesia, the Philippines and Papua New Guinea.

Mitragyna speciosa is called differently in different countries using the local language. In Thailand, it is known as Kratom or Kakuam, meanwhile it is called as ketum (Biak) in Malaysia, and Neithum in Laos (Charoenratana et al., 2021). In Myanmar, it is known as beinsa or bein-sa-ywat. In Indonesia, the common name is kedamba, purik or kayu sepat while in the Philippines, it is called mambog, lugub or polapuport (Jelsma 2021).

Traditionally, due to its naturally occurring properties, its leaves are usually chewed, or prepared as a tea but they are seldom being smoked (Ratard 2019). An earlier UNODC study on ketum eaters in Thailand by Suwanlert (1975) showed that 90% of the ketum are used by chewing the fresh leaf or grinding the dried leaves. Upon consumption, the users would then drink some warm water or hot coffee. It was reported that after five to ten minutes upon consumption, the user will feel happy, strong and active (Suwanlert 1975).

In Malaysia, the ketum leaves are believed to have been used traditionally to increase energy for labour work, and used traditionally to treat backache, flu, cough, worms, diabetics and hypertension (Hasan 2014). Local community utilises it as herbal drinks for both the stimulant and sedative effects. As demand increased and more desired properties are sought after, ketum preparation becomes famous where the leaves are boiled to create a ketum drink, which is typically sold to consumers in small packets in Malaysia. Ketum's popularity rocketed due to its easy accessibility and extremely low cost than other controlled substances. According to information from the media and law enforcement authorities, fresh and powdered leaves for making drinks are available for 4 ringgit (RM) (about 1 US dollar) and RM 25 per kilogram, respectively, while small packet drinks are sold for RM 1 (Chan, Pakiam & Rahim, 2005).

Over the years, more varieties of ketum mixtures have been created mainly by Southeast Asians, including mixing with other psychoactive compounds such as "4x100" – a mixture of boiled ketum leaves, cola soft drink and codeine- or diphenhydramine, and other drugs which were once well known in Thailand. Fatal cases have been reported as a result of consumption of the mixtures (Tungtananuwat & Lawanprasert, 2010). The cocktails of 4x100 were reported to have been popularly consumed by young Thai militants to make them "*more bold, fearless, and controllable*" (DEA, 2019; Drug Enforcement Administration) especially when there was political tension with Muslim communities between the central government and the southern regions. The changing trend of ketum use was also seen to be as "a substitute" for alcohol among people (Singh et al., 2017).

It is of great concern despite the possibility of ketum having "*bona fede"* traditional use and licit agriculture practice, there have been numerous reports in recent

years of its abuse of ketum and its preparation as a cheaper substitute for opiates or stimulants (Mallow 2020). The easy availability of ketum plants and its “modifiable” preparation with various additives worsens the scenario. Deviating from its original use, ketum has been viewed as “legal high” in the western countries distributed via online shops (Cinosi et al., 2015) and as “botanical”, “herbal” or “alternative” medical supplements in the headshops in the United States (Demick et al., 2020). Also, some users misused kratom by combining it with other drugs to achieve a "legal high" (Sharma and McCurdy, 2020). Online retailers sold a variety of herbal products containing kratom powder, one of which is depicted in Figure 1.1.

Figure 1.1 Herbal products available online. Adapted from My Kratom Club, 2022.

It was also reported previously that the herbal mixture known as "Krypton," which is said to contain kratom leaves, has become a very famous herbal mixture (EMCDDA, 2010; European Monitoring Centre for Drugs and Drug Addiction). In fact, the products marketed as Krypton contained no ketum but caffeine and synthetic O-desmethyltramadol, an active metabolite of tramadol. For their psychoactive effects,

kratom products have more recently been marketed as "incense," but the concentrations of the active substances mitragynine and 7-hydroxymitragynine in these products vary depending on the plant variety, the environment, and the time of harvest (Ratard 2019). Kronstrand et al. (2011) reported that the addition of the O-desmethyltramadol to powdered leaves made from Kratom contributed to the unanimity of the nine fatal cases.

Additionally, according to a recent report, a series of K2 (synthetic cannabinoids) products did not contain any recognized cannabinoid but did contain mitragynine as a psychoactive compound (Logan et al., 2012).

The above examples provide a quick snapshot on the emergence and trends of ketum use and abuse. This “distorted” emerging trend has attracted a lot of attention on the regulation of the sales and use on one side in countries where ketum are not controlled, and the deterrence of its illegal sales and abuse on the other side.

1.3 Problem statement

It was estimated that, in Kedah state alone, about 700- 900 people were arrested every year between 2012-2016 as a result of ketum offence, leading to the seizure of more than 26,000 kilogrammes of ketum leaves and about 60,000 liters of ketum preparation involving about 3,400 prosecutions in the five year periods (Khalil, Ahmad, & Abdullah, 2020). As the users are looking for cheaper substitutes for drugs of abuse, especially during the post-covid-19 era and under the current difficult economy situation, the cases involving illegal selling and distribution of ketum and its preparation is expected to remain high. Also, due to the continuous evolvement of mixture in ketum drinks, especially when the syndicates use some preferred formulation such as 4x100 or follow some international trend of product blending, it

is all unknown to us on the actual contain of so-called ketum preparation in hand, which can be present in various forms of liquid drinks available in the dark market. Except for the targeted analytes of interest, the complete compilation of information on all possible compounds present might not be required by routine forensic analysis. It is important that profiling on the compounds available in ketum drinks are to be conducted from time to time, where the information serve as useful lead for preventive actions as well as to become resources for information sharing and strategic planning. Therefore, this study was conducted to provide a qualitative study on the compounds present in ketum drink mixtures.

1.4 General objective and Specific objectives

The general objective of this study is to study the possible compunds present in ketum drinks samples using colour test and GC-MS. To achive the general objective, a few specific objectives were set as follows:

(i) To familiarise with standard operating procedures for ketum standard and ketum preparation extraction.

(ii) To investigate the suitability of chemical spot test on ketum preparation bearing different colour.

(iii) To study the resulting chromatograms and possible fragmentation patterns of compounds detected by GC-MS.

(iv) To study the trend of ketum drink mixtures in Malaysia.

1.5 Scope of study

This project aims to perform a qualitative analysis on the possible compounds present in ketum drinks. All samples used were in the form of ketum drinks. Ketum leaves, capsules or ground-ketum materials were not included. GC-MS instrument is

used for compound separation and analyte determination, upon liquid-liquid extraction, without derivatisation.

1.6 Significance of study

The result of this provides a quick snapshot on the possible formulation of ketum drinks. Besides establishing the presence or absence of any regulated substances, the patterns of ketum drink preparation can provide forensic intelligence and scientific information on the trend of ketum drink mixtures in Malaysia which could be useful for strategic decision-making by lawmakers in Malaysia or for any precautionary actions.

CHAPTER 2

LITERATURE REVIEW

2.1 Mitragyna-the source of mitragynine

This section provides an in-depth review of the species of Mitragyna. The genus Mitragyna belongs to the family of Rubiaceae and was reported to have consist of about 10 species (Shellard & Phillipson, 1964). Early literature have reported that among others, *Mitragyna hirsuta* Havil, *Mitragyna tubulosa* Havil, *Mitragyna javanica* Koord and Valebon, *Mitragyna parvifolia* (Roxb.) Korth, *Mitragyna rotundifolia* (Roxb.) O. Kuntze, and *Mitragyna speciosa* Korth were designated as early as 1963 (Hepper & Kew, 1963). Shellard, Houghton and Resha (1978) reported this genus of plants thrives in swampy terrain, on riverbanks, and in frequently wet environments. A few plants of this genus have been reported to be used for many purposes such as for treating fever and reduce muscular pain (Shellard and Phillipson, 1964). Other Mitragyna species are used in traditional medicine, but only *Mitragyna speciosa* possess stimulant, sedative, psychoactive effects (EMCDDA, 2021), which is due to its active ingredients, mainly by the indole-alkaloid Mitragynine (see Section 2.3).

Mitragyna speciosa Korth was also reported to become the substitute for opium as reported by Burkill and Hanif (1930). This could probably due to its similar properties of compounds in the plant to that of opium on human body. The leaves of *Mitragyna javanica*, also known as *Mitragyna parvifolia*, are used as a substitute for kratom when it is not readily available (EMCDDA, 2021). Also, the leaves of *Mitragyna speciosa* have been considered an alternative treatment for opium addiction (Hooper 1907).

The anatomy of leaves of *Mitragyna rotundfolia* was described by Shellard and Shadan (1964) while detailed anatomy description for *Mitragyna speciosa Korth*

including its macroscopic features as in Figure 2.1 and microscopic features as in Figure 2.2 has also been studied by Shellard and Lees (1965). The flowers and fruits of *Mitragyna speciosa Korth* was also described by Shellard and Walker (1969).

In forensic analysis, such as in cannabis, careful forensic characterisation at macroscopic and microscopic level for its botanical features has been established for defensible examination (Hauber 1992). Therefore, in case of careful anatomy is needed for forensic characterization, the work by Shellard and Lees (1965) and Shellard and Walker (1969) become important reference materials.

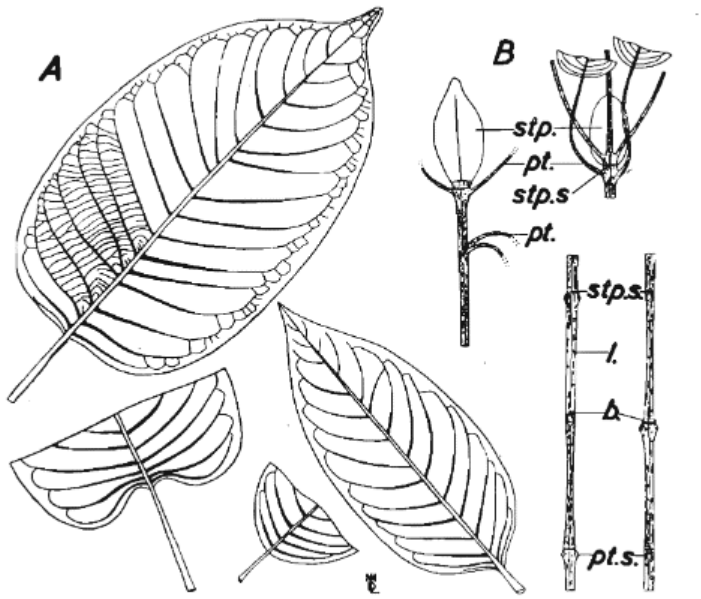

Figure 2. 1 Mitragyna speciosa. A: Leaves, B: Young stems, b:bud, I:lenticel, pt.:petiole, pt.s: scar of petiole; stp.:stipule, stp.s: scar of stipule. Adapted from Shellard and Lees, 1965.

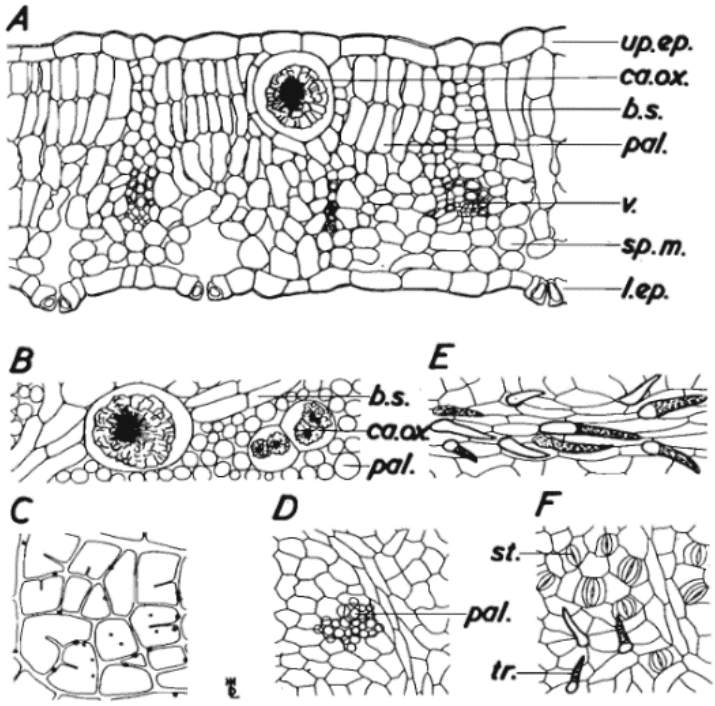

Figure 2. 2 *Mitragyna speciosa*. A:Leaf, lamina Leaf, lamina, transverse section, X 300 - B. Leaf, palisade layer, surface view X 300 - C. Leaf, vein-islets, X 30 - D. Leaf, upper epidermis, surface view, X 135 - E. Leaf, lower epidermis over vein, surface view, X 135 - F. Leaf, lower epi- dermis, surface view, X 135 The " represents cluster crystals of calcium oxalate, b. s., bundle-sheath; ca. ox., calcium oxalate; I. ep., lower epidermis; pal., palisade; sfi. m., spongy mesophyll; st., stoma; tr., tri- chome; up. ep., upper epidermis; u., vein. Adapted from: Shellard and Lees, 1965.

The leaves *of Mitragyna speciosa* Korth (Figure 2.2) were reported to have contained many alkaloids, among others, mitragynine, mitravesine, rhynchophylline, stupilatine (Shellard and Phillipson, 1964), corynantheide, isomitraphylline, speciogynine, speciofoline (Beckett et al., 1965), mitraphylline, speciophylline, speciophylline, (Beckett et al., 1966), speciogynine, paynantheine, speciociliatine (Beckett et al., 1966).

Figure 2. 3 *Mitragyna speciosa* Korth leaves. Adapted from Freepik company, 2022.

Literature search indicated that Hooper first isolated an alkaloid in 1907, and Field soon followed in 1921, naming the compound as mitragynine. Moreover, Shellard, Houghton and Resha (1978) found that among the alkaloids, mitragynine and paynantheine were dominant in the mature plant of *Mitragyna speciosa* Korth from Thailand.

According to Grundmann (2017), *Mitragyna speciosa Korth*'s alkaloid has pharmacological properties that may help with pain relief. It is estimated that over 40 structurally related alkaloids, numerous flavonoids, terpenoid saponins, polyphenols, and different glycosides are among the phytochemicals that have been isolated to date from the various parts of the plant. Nonetheless, many of them have not been carefully characterized on their pharmacological and toxicological properties, except for mitragynine.

2.2 Nomenclature

For the purpose of discussion, it is important to define the nomenclature of the scientific name and the common lane of the species of interest. In this study, the term “Kratom” commonly used in the scientific reports is used interchangeably with “ketum” which is a more common term used in Malaysia setting.

The name Kratom, believed to have been used in Thailand is generally refering to the plant with the scientific name *Mitragyna speciosa* Korth. Note that when using the scientific names, they are often written in italic or underlined as they are Latin names. In brief, the scientific name of a plant has a genus name followed by a specific epithe, therefore, in this case, “*Mitragyna*” is genus in botany naming classification while “*speciosa*” is refering to the particular species. In the case where a third name such as “Korth” appear in the name which is not italicized, it can refer to the name of the person who has first described the plant.

Mitragyna speciosa is a tree native to Malaysia, Myanmar, Thailand and other Southeast Asian countries. Kratom belongs to the same plant family as the coffee tree and is also indigenous to muddy areas of Africa (Shellard 1989). Korthals, a Dutch botanist, gave the genus its name Mitragyna because the plant's leaves and stigmas resemble the shape of an a bishop’s mitre (EMCDDA 2010). Other names for kratom include ketum, biak-biak, kakuam, ithang, thom, sepat, and kutum (Ahmad et al., 2022). Kratom, like coffee, contains numerous alkaloids, some of which are active in the central nervous system (CNS) and can cause a variety of physiological and behavioral effects (Raffa et al., 2015).

2.3 Origin of kratom use

Few decades ago, Kratom has been used by natives of Thailand and other parts of Southeast Asia as kratom has been viewed as an unordinary plant due to its double functions as a sedative and stimulant (Babu et al., 2008). In Malaysia, kratom is locally known as ketum, which is readily accessible in the northern states of Kedah, Perlis, Perak and Kelantan in the Peninsular of Malaysia that share a common border with Thailand. Besides various types of unreported traditional use, it is commonly sold as drinks and teas (Chan, Pakiam & Rahim, 2005) and it is believe that the herbal drinks has been traditionally used before for decades before it was turned to be a substance of abuse as seen today.

The wide spread use or abuse of kratom can be traced back to the historically used which was associated with working-class men in Thailand (Suwanlert 1975). It is worth noting that its usage by women was deemed rare (Suwanlert 1975). Kratom has also been used for medicinal and social benefits and to manage painful demands of physical labour (Aziz 2014; Swogger et al., 2015). Furthermore, some people list kratom use as a substitute for drugs on which they had become dependent (Aziz 2014). Additionally, southern people in rural areas used kratom as a mild narcotic (Assanangkornchai et al., 2007).

According to Singh et al. (2014), most kratom users share the belief that consuming kratom can improve work performance compared to using illicit stimulant drugs, which is more costly to low income users who might not afford for other options. In contrast to opioid users, kratom users were perceived as "*diligent*" and "*hardworking*" despite the fact that they were dependent, and many experienced mild withdrawal symptoms upon discontinuation of use. Regular kratom users were reported as having "increased calm" and "increased tolerance for work" (Aziz 2014). In addition

to its analgesic, anti-inflammatory, local anesthetic, hypoglycemic, anti-diarrheal, and antimalarial properties, kratom is also said to improve circulation, relieve muscle pain, and prolong sexual activity (Leon et al., 2009; Harizal et al., 2010). Also, ketum leaves can improve alertness, work capacity, sociability, and occasionally increased sexual desire (Houghton & Shellard, 2006).

For several decades, kratom was used by manual labourers in Thailand and Malaysia to increase productivity and for its euphoric effect at low doses. The users were reported to chew the leaves to gain more energy, to ease sore muscles and to work stronger (DEA, 2019; Drug Enforcement Administration). It was reported that regular and dependent users of kratom will chew the leaves three to ten times daily. Probably due to its availability, kratom was utilised by native Thais and people in Southeast Asia as a substitute to opium and conventional medicines (DEA, 2019). Vicknasingam et al. (2010) found that users in northern Malaysia relied on ketum for these purposes because it was affordable and widely available. In fact, the observation of opioid-like effects at larger doses, as well as its usage to alleviate pain and opium addiction was reported as early as the nineteenth century (Shellard 1989).

Besides the ability to increase endurance to physical strength for laborous work, the active compound was found to have analgesic properties (Shellard 1988), act as a stimulant, produce sedative effects, and the property of being a potent opioid agonist, and produces effects similar to morphine (Vicknasingam et al., 2010). It is significant to note that the indole alkaloids in kratom differ from their opioid counterparts both structurally and pharmacodynamically, producing effects that are slightly similar but not exactly the same. To distinguish them from morphine, semisynthetic opioids, and endogenous ligands, these compounds have been given the name "atypical opioids" (Raffa et al., 2018).

Suwanlert (1975) reported there are a few modes of ingesting kratom including chewing fresh ketum leaves. Fresh and dried ketum leaves were mainly used to prepare a decoction by brewing the leaves and consuming them as a drink. The effects in this form have mainly been defined as analgesic, calming, anti-diarrheal, antipyretic, and anti-diabetic. Chewing, smoking, and usual decoction are all traditional methods of kratom administration (Singh, Narayanan & Vicknasingam, 2016). Smoking dried leaves is much less common, though it has been reported on a few occasions in Malaysia and is said to have a calming effect (Hassan et al., 2013). If the plant is plentiful, ketum users can preserve the leaves in dry form because the effects are the same in both fresh and dried forms (Saingam et al., 2013). Furthermore, ketum has been reported to be utilized as an aphrodisiac (Vicknasingam et al., 2010).

The current mode of ketum abuse is mainly in the form of solution made from boiled ketum leaves. To match the flavour of young adults and new users, energy drink, sweet beverages, such as Coca Cola and Fanta with boiled ketum tea to mask its bitterness (Suwanlert 1975). Singh et al. (2017) reported the process of making ketum juice is not as hard as making other illicit drugs. Usually, each packet or plactics of ketum drinks (consists of 250 and 300 ml) is sold around RM5 in Malaysia in the year before 2014 (Singh et al., 2014).

In recent years, kratom has become more well-known in for its euphoric effects and is being promoted as a safe herbal product that can produce a "legal" high (Swogger et al., 2015) and as a substitute to other drugs (Warner et al., 2016). Also, Warner, Kaufman and Grudmann (2016) reported that ketum leaves were also made into capsules, gums, powders, and pills. An internet search, Figure 2.4, shows that ketum was also blended into powder and package as capsules, often labelled as botanical extracts, herbal products, and natural preparation or food supplements that appears to

be deemed “safe”. Nonetheless, its authenticity, safety and ingredients are at all unknown given that their production quality assurance is in doubt, and especially in clandestine drug laboratories, many synthetic compounds can be added as well, and certainly, these products warrant extensive research and profiling work.

Figure 2. 4 An internet image on ketum capsules. Adapted from Kures Apothecary, 2022.

2.4 Chemical properties of the main alkaloids in kratom

As mentioned earlier, there were about 40 alkaloid compounds from the kratom plants which have been isolated. To date, Mitragynine and 7-hydroxymitragynine, which are both unique to *Mitragyna speciosa*, are the main psychoactive substances in Kratom leaves that attract main attention (EMCDDA, 2019; European Monitoring Centre for Drugs and Drug Addiction).

Chemical properties of mitragynine (Figure 2.5) was described by Beckett et al (1965) in detailed.

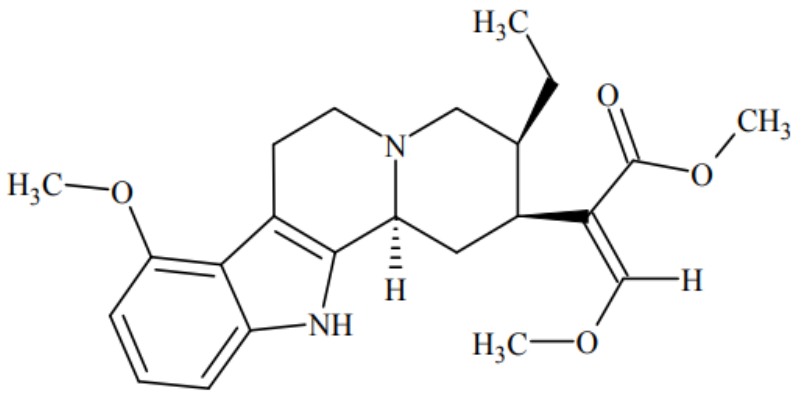

Figure 2. 5 Chemical structure of Mitragynine. Adapted from SWGDRUG, 2013.

In terms of solubility, mitragynine was found to be soluble in ether, ethanol, acetone and chloroform, but was only slightly soluble in light petroleum. It is insoluble in sodium hydroxide. The Mitragynine's IUPAC name is methyl (16E, 20b)-9, 17-dimethoxycoryn-16-en-16-carboxylate. Molecular weight of the base of mitragynine is determined to be 398 amu.

Mitragynine produces a deep blue colour when mitragynine was combined with hydrochloric acid and vanillin (Beckett et al., 1965). Note that in the study of plant materials and their extracts for secondary metabolites, several reagents could be used as indicator for possible presence of a particular type of alkaloids and have been used in many application in the detection of alkoloids in plants. The chemical formula of mitragynine is $C_{23}H_{30}N_2O_4$ (SWGDRUG, 2013). In the laboratory, pure mitragynine forms white, amorphous crystals that melts at 102-106 °C.

In the salt form, the melting point of mitragynine hydrochloric acid is 243 °C (EMCDDA, 2021). Note that mitragynine was first isolated in 1921 and its chemical structure was fully elucidated in 1964 (EMCDDA, 2021).

In general, mitragynine is classified under indole group of alkaloids, i.e. a class of alkaloids containing a structural moiety of indole. Note that indoles are molecules whose core chemical structure is the fusion of a benzene (left) and pyrrole (right) ring (Zapata et al., 2021), Figure 2.6.

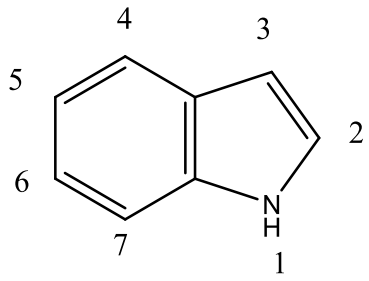

Figure 2. 6 Chemical structure of indole.

Mitragynine posseses the methoxyl group at the indole's position 4 and appears to be analogue to the 4-substituted indole psychedelics such as psilocybin and lysergic acid amide (Emboden 1979). It is important to note that other than mitragynine, 7-hydroxymitragynine is found to be unique in kratom plant. The structure of 7-hydroxymitragynine is shown in Figure 2.7 (Kruegel et al., 2019). Note that the difference from mitragynine is at position 1 (i.e. N in 7-hydroxymitragynine compare to NH in mitragynine) an OH group was attached to and at position 3 where the indole structure of 7-hydroxymitragynine.

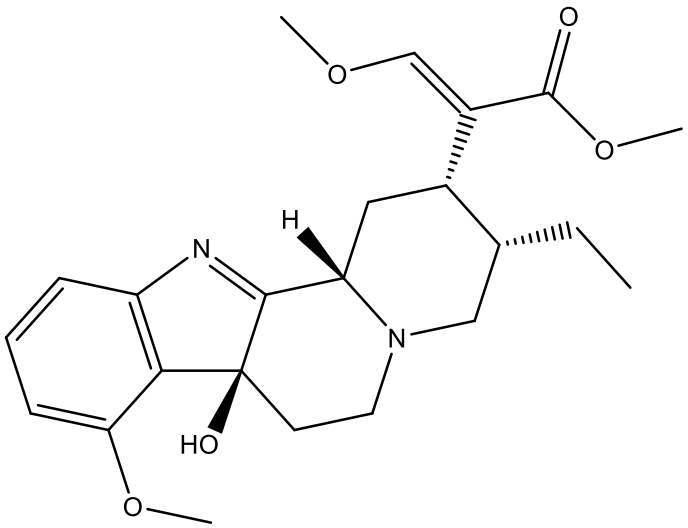

Figure 2. 7 Chemical structure of 7-hydroxymitragynine.

The presence of 7-hydroxymitragynine could be a part of the plants secondary metabolites. Kruegel et al. (2019) found that metabolic transformations of mitragynine could produce 7-hydroxymitragynine. *In vitro,* it was found to be 10 times more potent that mitragynine at mu-opioid receptor (MOR) (Kruegel et. al., 2019).

When kratom leaves are boiled, it is likely that most water extractable alkaloids, including mitragynine and 7-hydroxymitragynine, as well as other compounds that could have the similar effects are all present in the solution. By taking the preparation, the user therefore will receive the effects of all the compounds that present the effects, and certainly, this could be a concern to possible intoxication of its careless use, which is further discussed in the following section.

2.5 The Health Concerns

According to Babu, McCurdy and Boyer (2008), kratom has a stimulant effect at low doses, but an opioid effect is more prominent at higher doses. Houghton and Shellard (2006) reported that within 10 minutes of ingesting a few grams of dried ketum leaves, euphoria and energizing effects can be felt and these effects last for one to one

and a half hours. Ketum is also associated with side effects and high addictive liabilities (Hassan et al., 2013).

Kratom consumption can lead to addiction. According to Mallow (2020), it was reported that when a person consumed ketum drinks, it will negatively affect the nervous system and leads to ketum addiction. Patients had a low-addiction reaction after withdrawing from *Mitragyna Speciosa*, according to observations from the Clinical Opiate Withdrawal Score (COWS) (Sablahan & Gautam, 2020). A recent study from Malaysia found that more than half (55%) of regular users of ketum experienced extreme dependence (Singh, Narayanan & Vicknasingam, 2016).

Some clinical observations such as anorexia, weight loss, insomnia, dry mouth, frequent urination, and constipation were side effects of prolonged kratom use. Jansen and Prast (1988) reported that chronic ketum users may result in darker complexion, eventhough the user stay indoors. Furthermore, ketum is also associated with withdrawal symptoms. For instance, Boyer et al. (2008) had reported that a patient managed opioid withdrawal with kratom purchased from internet vendors when hydromorphone was unavailable. In order to improve alertness even more, the patient tried co-administration of 100 mg modafinil with kratom. He had a generalized tonic-clonic seizure that lasted 5 minutes to 20 minutes after ingestion. The researchers identified no contaminants or adulterants and confirmed the identity of the plant matter he ingested as kratom.

Singh et al. (2014) also reported common psychological withdrawal symptoms including restlessness, tension, anger, sadness, and nervousness and they also found that consistent kratom use is linked to drug dependence, the onset of withdrawal symptoms, and craving. Besides, wet nose, aggressive behavior, emotional instability, sore muscles and bones, and other withdrawal syndrome symptoms were also observed (DEA, 2019).

Also, Smid et al. (2018) studied two cases of pregnant women with kratom dependence and conclude that pregnant women who stop using kratom may experience opioid-like withdrawal symptoms. A recent study involving 293 regular Malaysian users of kratom was conducted and according to the findings, dependence symptoms developed at high rates and grew worse with prolonged use (Singh, Muller, & Vicknasingam, 2014).

Chronic opioid users have also used kratom to treat their withdrawal symptoms from opioids (DEA, 2019). Additionally, several cases of kratom psychosis were seen, where kratom addicts displayed psychotic symptoms like confusion, delusion, and hallucinations. Nelsen et al. (2010) reported a 64-year-old man was intubated for seizure activity thirty minutes after ingesting a kratom/Datura tea for chronic pain and mitragynine was detected in his urine. Sheleg and Collins (2011) speculate that high doses of the substance may suppress thyroid function because one case of severe hypothyroidism was reported in a 44-year-old patient in conjunction with "kratom addiction".

Moreover, Kronstrand et al. (2011) reported nine human deaths over the course of a year were attributed to the powdered mixture "Krypton" in a case series from Sweden. 'Krypton' is a herbal mixture containing kratom leaves as well as O-desmethyltramadol as an artificial additive (Arndt et al., 2011). Furthermore, Neerman, Frost and Deking (2013) reported a case of a 17-year-old boy who misused kratom died possibly because of kratom intoxication. According to Food and Drug Agency (FDA) in 2017, the majority of kratom-related deaths appear to have been caused by adulterated products (other drugs mixed with kratom). Besides, 660 calls reporting kratom exposure were received by poison control centers between 2010 to 2015 and the number of calls per year multiplied tenfold (National Poison Data System (NPDS), 2015).

According to the 2003 National Household Survey of Substance Users, 221,600 Americans (0.5% of the adult population) reported using kratom within 30 days of the survey. The southern region had the highest usage rate (128,200 users, or 2.2% of the adult population). In the United States, the number of kratom-related exposures has rocketed tenfold from 26 cases in 2010 to 263 cases in 2015 (Anwar et al., 2015).

It was observed previously that many shops sell kratom on the online platform, indicating that there was a high demand for this product. A quick internet search also found a website containing the title "*Where to Buy Kratom Online – Best Kratom Vendor Review*" (https://www.kratomnews.org/where-to-buy-kratom-online/) on September 2022. Various information on Kratom, including its use, opinion, as well as related news and publication were available, however, a search on legal status in the United States was not available on the website at the time of access (6 September 2022).

Due to its negative effects on humans, kratom and its main psychotropic constituent, mitragynine, are now regarded as a global health concern (Hassan et al., 2013).

2.6 The degree of Ketum Situation in Malaysia

The quick internet search limited to Malaysia revealed multiple cases on the seizure of ketum leaves by custom officers indicating the cross-border activities of ketum smuggling. Rationally, this phenomena should be dealt with more serius and effective measures if the degree of problem is serious.

Figure 2.8 shows the data from 2015 to 2019 on the quantity (in kilogram) of kratum leaves seized by the border control agency (AKSEM) based on four states having shared border with Thai.

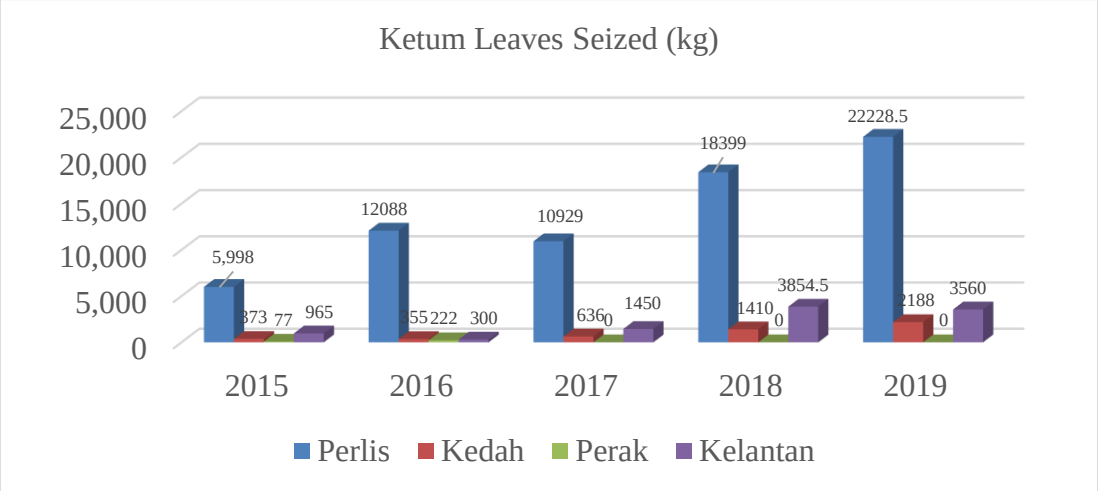

Figure 2. 8 Quantity of Ketum leaves (in kg) seized by boarder control agency in Malaysia according to states (Note: Data available only from 2015 – 2019)

In general, there was an increasing trend by looking at the quantity of kratom leaves seized as shown in Figure 2.9. Note that the data exclude ketum drinks which were also seized by the authority.

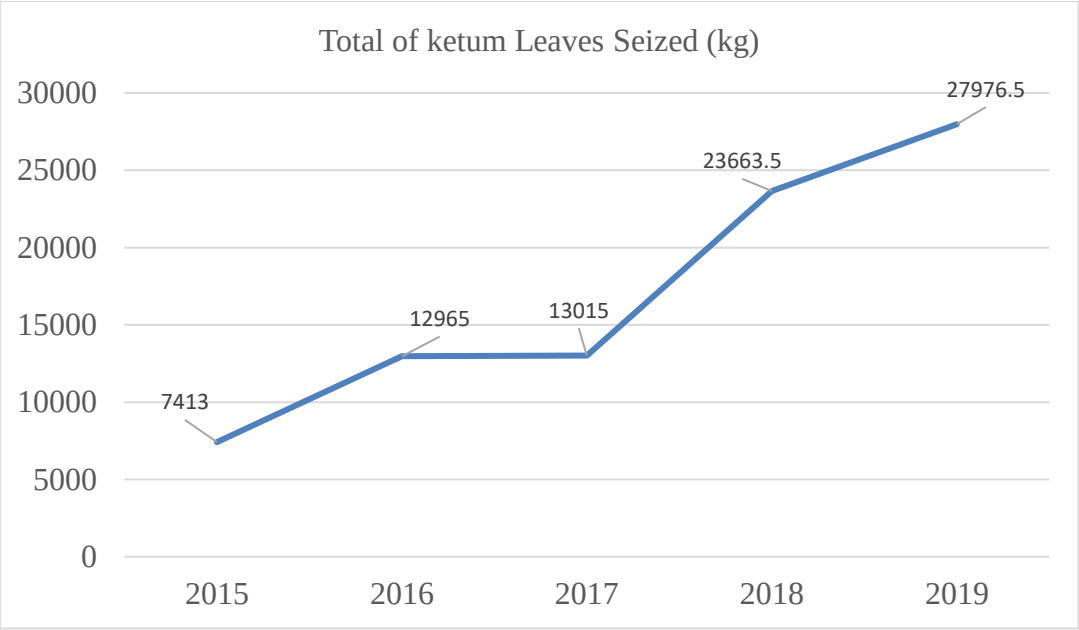

Figure 2. 9 Total quantity of Ketum leaves (in kg) seized by boarder control agency in Malaysia (Note: Data were processed from the raw data obtained from data.gov.my, 2022)

The most recent data was not available but a quick internet search using ketum as keyword on local newspapers indicate that multiple news were reported about large seizure of ketum leaves and its preparation. For instance, the local main stream newspaper, Berita Harian had reported a case of smuggling an amount of 1.35 tonnes of kratom leaves to South Malaysia in May 2022 (Zuliaty Zulkiffli, 2022).

Another case was reported by Berita Harian involving a quantity of 3.2 tonnes of ketum leaves was seized by Malaysian Maritime Enforcement Agency in February 2022 (Aizat Sharif 2022). In addition, Utusan Malaysia reported one case involving male suspects who were arrested for manufacturing ketum drinks in their house in January 2022 (Kamal Abas, 2022). Another case involving a man who sold 676 ketum concoctions in plastics were reported by Berita Harian ("Lelaki ditahan bersama 676 bungkus air ketum," 2022). In June this year, Utusan Malaysia also reported a case of two male suspects were arrested for smuggling ketum to South Malaysia (Othman Yahaya 2022). A media coverage on the phenomena of Ketum epidemic was also covered by Astro Awani, a local media (Sheikh Yahya 2020) where among others, the issues and factors relating to widespread of ketum drinks were discussed.

The quick snapshot above could give some ideas on the prevalence of ketum smuggling and could therefore associate to its degree of abuse. This also implies that there is a huge demand for Ketum especially in Malaysia, Thailand and possibly other Southeast Asia countries, probably due to its traditional use, deemed safe as traditional medicine preparation or possibly due to its nature as a cheaper options of drug of abuse, especially when the affordability for opioids could have been significantly affected by the lost of income or jobs especially in the post-pandemic era. Certainly, this warrants further investigation, perhaps with better and more comprehensive data collection by the respective authorities.