KRATOM USE, PSYCHIATRIC COMORBIDITY AND THE PSYCHOSOCIAL CORRELATES AMONG FELDA SETTLERS IN NORTHERN PENINSULAR MALAYSIA

DR AL-ZILAL ABDUL WAHID

FACULTY OF MEDICINE

UNIVERSITY OF MALAYA

KUALA LUMPUR

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DR AL-ZILAL ABDUL WAHID

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KUALA LUMPUR

2018

This is to certify that the candidate, Dr Al-Zilal Abdul Wahid carried out this research project, and to the best of my knowledge, this dissertation is entirely his work.

……..

Associate Prof Dr. Rusdi Bin Abdul Rashid

Consultant Psychiatrist

Department of Psychological Medicine

Faculty of Medicine

University of Malaya.

This is to certify that the candidate, Dr Al-Zilal Abdul Wahid carried out this research project, and to the best of my knowledge, this dissertation is entirely his work.

……..

Associate Prof Aili Hanim bt Hashim

Consultant psychiatrist, Consultant Child and Adolescent Psychiatrist,

Department of Psychological Medicine

Faculty of Medicine

University of Malaya

This is to certify that the candidate, Dr Al-Zilal Abdul Wahid carried out this research project, and to the best of my knowledge, this dissertation is entirely his work.

……..

Dr Omar bin Ali

Consultant psychiatrist

Head of Department of Psychiatry and Mental Health

Hospital Sultanah Bahiyah

Alor Setar.

UNIVERSITY OF MALAYA
ORIGINAL LITERARY WORK DECLARATION

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ABSTRACT

Kratom use, psychiatric comorbidity and the psychosocial correlates among FELDA settlers in Northern Peninsular Malaysia

Introduction:

Kratom (Mitragyna Speciosa, Korth) is an indigenous plant of South East Asia, particularly in Malaysia, Thailand, and Indonesia. For centuries people use Kratom as a traditional remedy to treat various ailments. Its inclusion into the New Psychoactive Substance (NPS) and extensive availability have brought about concerns regarding its current use, and potential harm. Despite the rising concerns, the prevalence of its use among rural settlers, its sociodemographic factors as well as the impact on mental illness of regular-users and quality of life is scarce.

Objectives:

The study aims at finding the prevalence of Kratom use among the rural settlers in a Felda settlement, located in the northern region of Malaysia. Its associating factors, as well as any psychiatric co-morbidities, is examined to ascertain the effects of Kratom use among the respondents.

Method:

The study recruited participants on a voluntary basis. The study chose the largest Felda settlement in Perlis. Its residents all originate from Perlis and have stayed at the site for generations. The study obtained the sociodemographic data, and trained individuals assessed all the respondents using the MINI, ASSIST-M, WHOQoL-Bref questionnaires.

Results:

The study recruited a total sample of 144 participants. The Kratom users were determine using the MINI, the ASSIST-M and the WHOQoL-BREF-Malay Version questionaire. The prevalence of Kratom use was 24.3% (n=35) among the participants. The univariate analysis found statistically significant association ($p<0.01$) between the Kratom user and age, gender, marital status, education level, employment status, general illness, history of illicit substance use, the presence of family members abusing illicit substance, smoking and opioid dependency. The multiple logistic regression analysis identified a significant association between Kratom users with history of drug, and tobacco use. The participants with moderate and high tobacco use and past and present other substance usage are likely to be a Kratom-user.

In the assessment of their quality of life, Kratom-users reported feeling physically healthier than the non-users. However, though close to 70% are employed, their average income is less than two thousand ringgits per month. Moreover, among the Kratom-users, almost all are smokers, smoking an average of 20 sticks per day (IQR=10) and they started smoking at a mean age of 15.4 years (SD=3.35).

Conclusion:

The study found a high prevalence of Kratom-use among the rural settlers. The study identified a robust association of Kratom use with tobacco and opioid usage. The participants with moderate and high tobacco use plus past and present other substance use are likely to be a Kratom-user. The study concludes the severity of the problem is chronic and worrying. The report should serve as a precursor for further researches in this area as well as possible health policy-making.

ABSTRAK

Penggunaan Kratom, penyakit psikiatri dan hubungan psikososial di kalangan peneroka FELDA di Utara Semenanjung Malaysia

Pengenalan:

Kratom (Mitragyna Speciosa, Korth) merupakan sejenis tumbuhan asli di Asia Tenggara, terutamanya Malaysia, Thailand dan Indonesia. Kratom telah digunakan sebagai ubat tradisional untuk merawat penyakit sejak abad yang lalu. Kemasukannya ke dalam Bahan Psikoaktif Baru (NPS) telah membawa kebimbangan mengenai tahap penggunaan semasa, seta potensi ianya membawa bahaya. Walaupun kebimbangan yang semakin meningkat, kelaziman kegunaan Kratom di kalangan peneroka luar bandar, faktor sosio-demografik , kesannya terhadap penyakit mental dan kualiti hidup masih belum ditentukan.

Objektif:

Kajian ini bertujuan untuk mengkaji tahap kepenggunaan Kratom di kalangan peneroka luar bandar dalam penempatan Felda yang terletak di wilayah utara Malaysia. Faktor-faktor berkaitan kepenggunaan, serta penyakit-penyakit psikiatri juga akan diperiksa dan akhirnya mengkaji kesan penggunaan Kratom ke arah kualiti hidup di kalangan peneroka.

Kaedah:

Peserta yang direkrut dalam kajian ini semuanya secara sukarela. Penempatan terbesar Felda di Perlis dipilih sebagai tapak kajian kerana sifat penduduknya yang berasal dari Perlis dan telah tinggal di sana selama beberapa generasi. Data sosiodemografi

diperoleh, dan semua responden dinilai oleh individu yang terlatih dengan menggunakan soal selidik MINI, ASSIST-M, dan WHOQoL-Bref.

Keputusan:

Jumlah sampel yang diambil untuk kajian ini adalah 144 peserta. Pengguna Kratom ditentukan menggunakan soalan ASSIST-M no.1 item J (Kratom). Kadar kepenggunaan Kratom adalah 24.3% (n = 35) di kalangan peneroka luar bandar di Felda Chuping. Analisis univariat mendapati persefahaman statistik yang signifikan ($p < 0.01$) diantara pengguna Kratom dan umur, jantina, status perkahwinan, tahap pendidikan, status pekerjaan, penyakit umum, sejarah penggunaan dadah, kehadiran ahli keluarga menyalahgunakan dadah, merokok dan kebergantungan kepada dadah jenis opioid . Analisis regresi logistik berganda mendapati persefahaman statistik yang signifikan bagi sejarah penggunaan dadah serta penggunaan tembakau yang sederhana dan tinggi. Pengguna Kratom juga didapati memiliki skor min yang lebih tinggi untuk domain kesihatan fizikal bagi soal selidik WHOQOL-BREF. Pengunaan Kratom juga didapati berkait rapat dengan Perkara J (Penyalahgunaan Bahan dan Ketergantungan) dari soal selidik MINI. Penggunaan tembakau dan opioid juga sangat berkaitan dengan penggunaan Kratom berdasarkan skor ASSIST-M.

Kesimpulan:

Kajian ini mendapati bahawa kadar kepenggunaan Kratom di kalangan peneroka luar bandar di utara Malaysia adalah tinggi, dan sejajar dengan negara-negara jiran. Pelbagai faktor didapati memainkan peranan penting dalam penggunaannya yang berleluasa. Walau bagaimanapun, tumpuan haruslah diberikan kepada mereka yang mempunyai sejarah penggunaan dadah dan perokok. Masalah penggunaan Kratom adalah membimbangkan dan kajian ini boleh menjadi pemangkin untuk penyelidikan akan datang seterusnya membantu untuk melakar dasar dan polisi di masa hadapan.

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LIST OF ABBREVIATIONS

ASSIST-M	The Alcohol, Smoking and Substance Involvement Screening Test-Malay
MINI	Mini International Neuropsychiatric Interview
DSM	Diagnostic and Statistical Manual
WHOQOL	World Health Organization Quality Of Life
NPS	New Psychoactive Substance/ Novel Psychoactive Substance
MS	Mitragyna Speciosa
CI	Confidence Interval
OR	Odds Ratio

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1 INTRODUCTION

Since time immemorial, humans use various methods to alter the state of their mind and consciousness or try to dwell into the unconscious (MacRae, 1998; Müller, Carey, Huston, & De Souza Silva, 2007; Müller, Pum, Schumann, & Huston, 2010). The most natural and widespread methods used include using substances in the form of alcohol, or plant derivatives (MacRae, 1998; Müller et al., 2007; Müller et al., 2010). Ever since then, in the various culture and traditions, the use of substances has continued (Aragon-Poce et al., 2002; Brownstein, 1993). History indicates the use of opium begun as early as 5000 BC by the Sumerians, and by 3500 BC the Egyptians started brewing alcohol (Aragon-Poce et al., 2002; Macht, 1915).

The (United Nations Office on Drugs and Crime, 2016) are among many organizations who have raised caution on the new and emerging group of illicit substances, coined the 'New Psychoactive Substances' or NPS. Intriguingly, the NPS era began with people looking for a less complicated, and less stigmatizing as well as a cheaper alternative to the traditional illicit drugs. Interestingly, these new psychoactive substances, are not covered by the existing system of drug regulations and prohibitions yet poses risks to persons who abuse it (Mdege, Meader, Lloyd, Parrott, & McCambridge, 2017; United Nations Office on Drugs and Crime, 2016; University New South Wales & NDARC, 2016).

Among the NPS are a wide range of products, from natural plant-originated substances to synthetic compounds (J.B Zawilska, 2015; J.B. Zawilska & Andrzejczak, 2015). Many of these substances are for recreational use (Reuter & Pardo, 2017). Similar to the original illicit drugs, which cover the largest segment of illicit drugs sold

and used, the new psychoactive substances have raised concerns (Reuter & Pardo, 2017).

Among the New Psychoactive Substances (NPS) that have been making headlines includes Kratom (Pizarro-Osilla, 2017; Pompei, 2016). Mytragyna Speciosa (MS) or commonly referred to as Kratom is a native plant of South East Asia and is a member of the Rubiaceae family (Feng, Battulga, Han, Chung, & Li, 2017; Singh, Narayanan, & Vicknasingam, 2016). Kratom is an active agent of opioid receptor agonists, and has diverse physiological and behavioral effects contributing to its increasing popularity (K. M. Babu, McCurdy, & Boyer, 2008; Henningfield, Fant, & Wang, 2017).

However, there is a clash between the traditional use of Kratom and the emergence of data highlighting its abuse potential. In Malaysia, Kratom is popular and is used among the rural population (Adkins, Boyer, & McCurdy, 2011; Hassan et al., 2013), as a type of traditional treatment for ailments as well as in social activities (Cinosi et al., 2015; Singh, Müller, & Vicknasingam, 2014). In the western countries, Kratom is marketed as a "legal high" and is easily obtained in different forms, through the Internet. Reports on the mortality and toxicity associated with Kratom use in the West are increasing. The documents have brought about controversy with regards to its safety and legal implications. There have been attempts to identify the psychological and cognitive effects of chronic use of Kratom. There is a gap in the understanding the effects of Kratom to human and how it is related to a particular psychiatric illness.

The present study is to investigate the association between Kratom use and psychiatric comorbidities, as well as if there any associated factors. The findings may help the relevant authorities or groups comprehend the complex nature of the problem and find ways to tackle the issue, particularly in Malaysia where Kratom is abundant.

2 LITERATURE REVIEW

2.1 THE RELEVANCE OF SUBSTANCE USE

Tobacco, alcohol, and illegal drugs remain as significant contributors to preventable morbidity and mortality across the globe (S. A. SAMHSA, Mental Health Services Administration 2010). Research has continuously focus and scrutinized drug use and its impact on human behaviours (Hammersley, 2011; Rowley et al., 2017; Thomas, Pollard, & Grabenauer, 2013; Tomlinson, Brown, & Hoaken, 2016). The reason for the course of action is that illicit drug usage presents a substantial problem to many communities. Many individuals using substance exhibit worrying behaviours. Their conducts include behaving irresponsibly, putting themselves or others at risk, and they frequently come to the attention of the legal system (Condon & Smith, 2003; DeLisi, Angton, Behnken, & Kusow, 2015; Hammersley, 2011; Pihl & Peterson, 1995). The relationship between drug use and aggressive behavior presents an ongoing and a serious concern. Equally worrying is the presence of major psychiatric disorders in the substance using individuals with very few of the individuals seeking treatment (Pettinati, O'Brien, & Dundon, 2015; Quello, Brady, & Sonne, 2005; Strain, 2002). Data suggests close to a third of individuals with a mood disorder have a co-occurrence of substance use (Pettinati et al., 2015; Quello et al., 2005; Strain, 2002). A tragic association between substance and the psychiatric disorders is suicide (Quello et al., 2005).

(Tomlinson et al., 2016) defined 'drug' as any recreational substance which people ingest either through oral consumption, injection, insufflation, inhalation or as a suppository. The goal of the intake is to produce a personally enjoyable physiological and perceptual effect. Problematic drug use is often characterized by dependency and the use of hard drugs such as opiates, cocaine or amphetamines (Hammersley, 2011;

Hawkins, Catalano, & Miller, 1992; Kraus et al., 2003). Drug-using behavior is a denounced conduct and prosecuted by law in many countries, yet it remains prevalent. The (WHO, 2002b) estimated that 2.1% of the burden of disease in the European countries with very low mortality and 1.6% of all European countries in the year 2000 were attributable to illegal drug use.

The substance use field is fast and continuously changing. Despite the risk of being toxic upon single or chronic consumption, new drugs or products continuously appear and make their way into the drug-taking communities (Hagen et al., 2009; Karila, Megarbane, Cottencin, & Lejoyeux, 2015). People are continually looking for ingredients to use and sell. The makers of these drugs develop new chemicals to replace those that are banned, which means that the chemical structures of the drugs are constantly changing to try to stay ahead of the law (Baumeister, Tojo, & Tracy, 2015; Coppola & Mondola, 2012). Thus, there is the endless emergence of alternative and new products (Thomas et al., 2013). Since the 1920s, synthetic recreational drugs have been present in several forms (Coppola & Mondola, 2012; Hill & Thomas, 2011). There is often the advent of the 'newer' more advanced and synthetically enhanced substances in the global market (Hassan et al., 2017; Pan et al., 2013; Schifano, Orsolini, Papanti, & Corkery, 2015).

The continuous need to seek 'excitement' and with something 'more exciting' has resulted in the evolution of the novel psychoactive substances (NPS) (K. Babu, Boyer, Hernon, & Brush, 2005; Nelson, Bryant, & Aks, 2014). These NPS are also known as "legal highs," across the world (Mdege et al., 2017; Nelson et al., 2014; J.B Zawilska, 2015; J.B. Zawilska & Andrzejczak, 2015). Accordingly, many communities have had to handle the growing drug industry and global market of designer drugs (Duff, 2005; Macleod et al., 2004; Nelson et al., 2014; Thomas et al., 2013). There are

constantly new preparations that appear into drug-taking communities either as something to transform the 'mental state,' pharmaceutical and even dietary supplements/ nutraceuticals (Nelson et al., 2014; Thomas et al., 2013).

The production of these NPS is thought to have begun as early as 1929 and has continued until the present times (O'Hagan & Smith, 2017). Humans create these new substances by altering the chemical structures of the active ingredients found in the traditional drugs (O'Hagan & Smith, 2017). The modification of these substances alter slightly the chemicals derived from other known drugs of abuse (Nelson et al., 2014). The NPS are pharmacological similarities of compounds forbidden in the current drug laws of many countries. The compounds include the amphetamines and cannabis, and are now readily obtainable from online dealers or in so-called 'head shops'(Baumeister et al., 2015). The products are sold as designer drugs, dietary products, or food supplements (O'Hagan & Smith, 2017; Thomas et al., 2013). Based on the spectrum of their actions on cognitive processes, mood, and behavior, "legal highs" can be classified into four basis categories: amphetamine- and ecstasy-like stimulants, synthetic cannabinoids (SCs), hallucinogenic/dissociative, and opioid-like compounds (Z) (J.B. Zawilska, 2011).

The continuing emergence and availability of these alternative forms and formulations continues to cause considerable public concern. The use of recreational substance among young people is widespread and associated with numerous psychological and social harm (Duff, 2005; Macleod et al., 2004). Additionally, the number of users are increasing in a worrying proportion (Condon & Smith, 2003). The products are easily available. People distribute these substances on a personal level, and in the recent times, these substances are readily available on the internet via online shops (O'Hagan & Smith, 2017; Thomas et al., 2013). Manufacturers and consumers

alike often claim that their products are legal or do not contain compounds that have been specifically banned (Thomas et al., 2013). In reality, these "legal highs" or novel psychoactive substances mimic the psychoactive effects of the original illicit drugs of abuse (J.B Zawilska, 2015; J.B. Zawilska & Andrzejczak, 2015).

Kratom is considered one of the NPS and its increasing and continued use is worrying. Kratom is most commonly used for the hallucinogenic effects but may also be used less commonly for management of opioid withdrawal (Nelson et al., 2014). It is as well much cheaper and widely available in the northern states of Malaysia (Ahmad & Aziz, 2012; Hassan et al., 2013). Kratom is primarily known for its use among rural folks doing laborious work, to help them reduce their fatigue, promote work desire, and enhance their physical tolerance to debilitating work (Hassan et al., 2013; Singh, Müller, Vicknasingam, & Mansor, 2015; Singh et al., 2016). The consumption of Kratom in the United States has grown drastically over the last decade boosted by its diverse consumptions, comparable to its use in Southeast Asia (Brown, Lund, & Murch, 2017). However, unlike its usage in Southeast Asia, there are growing concerns over the safety of using Kratom. Many emerging facts suggesting Mitragyna Speciosa is addictive, with a potential to be misused, and has led to adverse reactions including death (Brown et al., 2017; Henningfield et al., 2017; Warner, Kaufman, & Grundmann, 2016).

2.2 PSYCHOSTIMULANT PLANTS

For centuries, humans have found valuable medicinal properties in certain plants (Kingston, 2010; Naman, Leber, & Gerwick, 2017; Newman & Cragg, 2012). These plants have been a valued source of many therapeutic agents, until the present times. Simultaneously, humans pursue natural products newer psychoactive substances. History revealed as long as human record keeping dates back, humans consume psychoactive plant preparations. Over 200 years ago, a young pharmacist's apprentice obtained morphine from opium by cutting poppy seed pods. That was the earliest pharmacologically active pure compound from a plant (Li & Vederas, 2009).

The history showed, humans continue to use plant-derived materials as an adjunct to treat diseases and as a performance enhancer (Hassan et al., 2013; Prozialeck, 2016). By the 1990s, more than 80% of drugs were either natural products or analogs inspired by plants (Li & Vederas, 2009). With regards to anxiolytic and stimulating properties, history suggests the evolution was due to human's innovation to obtain substances to achieve a euphoric or numbing effect (Brownstein, 1993; Naman et al., 2017). Psychoactive substances are pursed continuously to induce and maintain a desired mental state, and for some individual to arouse a different mental state (Gilani, 2015; Hassan et al., 2017; Soussan, Andersson, & Kjellgren, 2017).

Humans have continued their attempts to locate and determine which molecules in the plant structures are useful materials to the society (Naman et al., 2017). Up to 70% of all drugs on the market today have an origin or inspiration from Nature (Naman et al., 2017; Newman & Cragg, 2012).

Society often referred to the plant-derived materials as "herbal" or "botanical" remedies, and as they are natural products, many communities are more acceptable to its usage (Newman & Cragg, 2012; Prozialeck, Jivan, & Andurkar, 2012). The first written

records on the therapeutic purposes of plants dating back to 2600 BC (Borchardt, 2002; Cragg & Newman, 2013). The report suggested the existence of a refined medicinal system in Mesopotamia, encompassing about 1000 plant-derived medicines (Borchardt, 2002; Cragg & Newman, 2013). From then on, the Chinese Materia Medica, the Indian Ayurvedic, the Greeks and Roman system received the credit to the expansion of the use of herbal drugs in the ancient Western world (Borchardt, 2002; Cragg & Newman, 2013).

Humans utilized the plant-derived materials in a variety of ways driven by the individuals' needs and the global market (Rosenbaum, Carreiro, & Babu, 2012; R. J. Sullivan & Hagen, 2002). Many continue to use the herbal remedies as alternatives to or in conjunction with mainstream medical care (Atanasov et al., 2015; Barnes, Bloom, & Nahin, 2008; Harris & Rees, 2000). Several groups of people and numerous industries use the derived ingredients as materials for beauty products, or in ways to handle stresses, for pain relief as well as in methods to alter states of awareness (Barnes et al., 2008; Harris & Rees, 2000). Consumers of these herbal remedies are particularly in economically disadvantaged countries where access to modern medicine remains insufficiently inexpensive and excess to proper medical care is problematic (Li & Vederas, 2009). Moreover, the many herbal remedies have yet to establish its reliability in controlled clinical trials despite its vast popularity and usage.

A few natural plants are known for its psychostimulant effect, thus, why its continued and popular usage (Apryani, Hidayat, Moklas, Fakurazi, & Idayu, 2010; Favrod-Coune & Broers, 2010; Scholey, Kennedy, & Wesnes, 2011). For centuries(Prozialeck et al., 2012; M.T. Swogger et al., 2015), Mitragyna Speciosa (MS) is one of the psychostimulant plants used as an herbal remedy (Reanmongkol, Keawpradub, & Sawangjaroen, 2007; Singh et al., 2014; Ulbricht et al., 2013). While in

countries such as Somalia, Yemen, Kenya and Ethiopia, the Khat plant (Celastraceae edulis; Catha edulis) is well accepted and readily consumed (Favrod-Coune & Broers, 2010).

The Mitragyna Speciosa (MS) is a plant from the Rubiaceae, or the coffee family (Cinosi et al., 2015; M.T. Swogger & Walsh, 2017; Takayama, 2004). The leaves of MS is commonly known as Kratom (Takayama et al., 2002). In Thailand, Papua New Guinea and Peninsular Malaysia the Rubiaceae is a tropical and home-grown plant commonly found in the swamps (Ahmad & Aziz, 2012; Chan, Pakiam, & Rahim, 2007).

Kratom has received increasing public attention in recent years. For many years, the product is thought to be a safe and legal psychoactive product (Ward, Rosenbaum, Hernon, McCurdy, & Boyer, 2011; Warner et al., 2016). The leaves from the MS have been customarily used as medicinal and stimulant properties to treat chronic pain (Boyer, Babu, Adkins, McCurdy, & Halpern, 2008; Boyer, Babu, Macalino, & Compton, 2007; McWhirter & Morris, 2010). In other instances, MS helps improves mood and relieves pain (Prozialeck et al., 2012; M.T. Swogger & Walsh, 2017; P. Tanguay, 2011). Users chew the raw leaves of the plant, or smoked the leaves when dry or boil them (Ahmad & Aziz, 2012; Singh et al., 2016; P. Tanguay, 2011). The Kratom is served as a tea, or smoked or vaporized (Singh et al., 2016; P. Tanguay, 2011). Users are mainly laborers and blue-collar workers (Jansen & Prast, 1988; Suwanlert, 1975).

Since the early 1970's reports emerged stating the leaves of MS has stimulating effects (Jansen & Prast, 1988; Rosenbaum et al., 2012; Suwanlert, 1975). Unknowingly, its use progressively and subtly shifted from folks' remedy to that of an opioid accessory, thus opening its traditional use to an abuse potential (Hassan et al., 2013). In Thailand, Kratom is chewed or brewed in tea and is regarded as being relatively

harmless (Cinosi et al., 2015). (Jansen & Prast, 1988) summarized MS a drug with a highly unusual but well-documented history of both a depressant and a stimulant. It is not surprising that in recent years the use of Kratom has expanded (M.T. Swogger & Walsh, 2017).

2.3 PHARMACOLOGY OF KRATOM

Kratom has maintained its popularity as a recreational drug, throughout the world (Warner et al., 2016) raising concerns about its misuse and abuse (Boyer et al., 2008). In parts of Malaysia and Thailand, Kratom remains its widespread acceptance as a *folk remedy* among the rural population (Adkins et al., 2011; Hassan et al., 2013). The problem with the community's perception of Kratom is that people see it as a more 'natural use' as a plant preparation and many believe it to be less associated with addiction and health problems (Hassan et al., 2013).

Since the early 1960's, numerous scientists have performed studies to identify the chemical constituents of Mytragyna Speciosa (MS). The leaves are known as "Kratom" in Thailand, while in Malaysia, they are known as 'ketum' or 'biak' (Ahmad & Aziz, 2012). The investigations reveal the MS has psychoactive properties and opioid-like activity (Chan et al., 2007; Vicknasingam, Narayanan, Beng, & Mansor, 2010). The opioid-like effects are encountered when higher doses are taken (Thongpradichote et al., 1998). Kratom acts on opioid receptors, with a stimulant effect at low doses and a sedative effect at higher doses (Macdonald & Nacapew, 2013; Ulbricht et al., 2013).

Investigations revealed the tropical plant Mitragyna speciose, has Mitragynine and 7-hydroxymitragynine as its active compounds (Adkins et al., 2011; Takayama, 2004; Takayama, Aimi, & Sakai, 2000). Other analyses show the presence of 20 active compounds alkaloids namely Mitragynine and its analogs such as speciogynine, speciociliatine, paynanthine among others (Adkins et al., 2011; Takayama, 2004;

Takayama et al., 2000). These agents produce a wide variety of pharmacologic effects (Adkins et al., 2011; Takayama, 2004; Takayama et al., 2000). Both the mentioned alkaloids produce dose-dependent narcotic effects, stimulant effects at lower doses and sedative-like effects at higher doses (Smith & Lawson, 2017).

Additionally, a newer and more potent alkaloid, 7-hydroxymitragynine or 7-HMG was also isolated from the plant and since then has been investigated for its properties (Kikura-Hanajiri et al., 2009; Takayama et al., 2002). The 7-HMG has a 13-fold higher potency than Mitragynine, and 46 times more potent than morphine in its nociceptive/analgesic ability, opening further its future potential use as a novel pain-relieving agent (Matsumoto et al., 2004). (K. M. Babu et al., 2008) concluded the two alkaloids in Kratom: mitragynine and alkaloid 7-hydroxyminitragynine, act as agonists to supraspinal mu- and delta-opioid receptors and produce effects similar to morphine. Remarkably, (Matsumoto et al., 2004) reported Kratom had more than ten times higher potency than morphine.

The presence of various alkaloids points towards a complex mechanism of action towards various receptors in human and animal studies. Among the receptors involved includes opioid receptors namely μ- δ, and κ-opioid receptors (Hassan et al., 2013; M.T. Swogger et al., 2015; Yamamoto et al., 1999). Reports suggest Mytraginine produces a stimulating effect for its users at lower doses (Macdonald & Nacapew, 2013; Ulbricht et al., 2013). Kratom used in low to moderate doses generate a mild stimulant effect enabling workers to rid their fatigue (Assanangkornchai, Muekthong, Sam-Angsri, & Pattanasattayawong, 2007; Suwanlert, 1975). Not surprisingly users focused on the perceived advantages of Kratom use, e.g. the increased work endurance and pain reduction (M.T. Swogger et al., 2015; P. Tanguay, 2011), rather than its harmful effects (Assanangkornchai, Muekthong, et al., 2007; Rosenbaum et al., 2012).

At higher doses, however, Mitragynine and other alkaloids act as a partial agonist to opioid receptors and in turn creates the anti-nociceptive effect similar to morphine and other opioids (K. M. Babu et al., 2008; Kruegel et al., 2016). Besides related opioid receptors, derivatives of Mytragyna Speciosa are implicated with different central nervous system receptors including alpha-2 adrenergic receptors, adenosine A2areceptors, dopamine D2 receptors, and the serotonin receptors 5-HT2C and 5-HT7 (Boyer et al., 2008).

Thus, Kratom has dual properties within a differential diagnosis for several presentations, e.g. sympathomimetic, opioid, and opioid withdrawal (Nelson et al., 2014). Therefore, explains the increasing use of Kratom for the self-management of pain and withdrawal from opioid drugs (K. M. Babu et al., 2008; M.T. Swogger et al., 2015; Ward et al., 2011). The Kratom administration itself is associated with modest abstinence symptoms (K. M. Babu et al., 2008).

In a study to investigate the effect of MS on anxiety, alertness, and cognitive functioning, (Moklas et al., 2013) found in the rats studied, *Mitragyna speciosa* used in low dosages minimally impair alertness and cognitive functioning. When used in low dosages *Mitragyna speciosa* is an excellent antianxiety agent. The effects are however lost in higher doses, with impairment of cognitive and motor performance. In (Hassan et al., 2013)'s review paper stated tolerance develop during prolonged use, and users were escalating doses to maintain the desired effects. Thus, the matter shows the possible aversive side effects of Kratom usage and the possibility of its the consumption towards health risk.

2.4 KRATOM USE: PAST, CURRENT, REGIONAL and WORLDWIDE

Kratom is also known as Biak or Ketum in Malaysia, and as Thom, Kakuam and Ithang in Thailand (Adkins et al., 2011; Feng et al., 2017). The plant has been widely used throughout Southeast Asian countries as a herbal drug for decades, as early as late 1800 (Nelson et al., 2014).

As previously mentioned, humans have consumed Kratom for centuries in particularly in South-East Asia as a treatment for ailments (Boyer et al., 2008; Hassan et al., 2013; Matsumoto et al., 2004). Traditionally dwellers in Thailand and Malaysia use Kratom to alleviate musculoskeletal pain and to increase energy, appetite, sexual desire (Boyer et al., 2008; Brown et al., 2017; Vicknasingam et al., 2010). Additionally, Kratom is used as a dietary supplement (Boyer et al., 2007). The leaves were traditionally used to treat intestinal infections, muscle pain, even to reduce coughing and aid for diarrhea (Suwanlert, 1975; Vicknasingam et al., 2010).

Additionally, among workers, (Suwanlert, 1975) reported MS is mainly used by laborers who work long hours in the sun. Its stimulant effect helped the workers to rid their fatigue and sustain their stamina and increase productivity. The news often reported claims of Kratom used as affordable, readily available and had no severe side effects despite prolonged use (Chan et al., 2007; Vicknasingam et al., 2010).

Concerns emerged with the increasing number of users taking Kratom to reduce intake of the more expensive opiates and as an alternative to other opioid-replacement medications. Additionally, investigations show users develop euphoric or pleasure effect (Chan et al., 2007; Hassan et al., 2013; Vicknasingam et al., 2010). (Suwanlert, 1975) proved Kratom users could become addicted.

In the 1900's, (Burkill & Haniff, 1930) reported native Malayans using the Kratom leaves as an opium substitute during times when opium was unavailable or unaffordable. The observation was similarly reported by (Grewal, 1932). (Grewal, 1932) found Mitragynine as a central nervous system stimulant rather than a depressant. The findings clarified the popularity of Kratom's use in Thailand. Many users reported benefits using Kratom such as it helped increase work productivity and tolerance to the hot weather (Prozialeck et al., 2012; Suwanlert, 1975). From then on, many more reports emerged reporting worrying usage of Kratom (Macdonald & Nacapew, 2013; McWhirter & Morris, 2010; Nelsen, Lapoint, Hodgman, & Aldous, 2010; M.T. Swogger et al., 2015; Tungtananuwat & Lawanprasert, 2010).

Additionally, MS helps alleviates opioid withdrawal symptoms (Prozialeck, 2016) and users often develop a euphoric or pleasurable effect (Prozialeck, 2016). (Chan et al., 2007) reported the traditional healers use Kratom extensively such as to wean addicts off heroin addiction, to deworm, to cure diarrhea, and even to treat diabetes. Kratom has a quick time of onset and duration effect for about an hour plus is dose-dependent (Nelson et al., 2014).

The Malaysia government has banned Kratom use, but it is still used mainly in the Northern states for its therapeutic value and socioeconomic reasons (Singh et al., 2015). In 2003, the Malaysian government listed MS in the Poison Act, 1952 (Ministry of Health Malaysia, 1952). Under this Act, anyone found to possess or sell MS leaves or other MS preparations such as drinks and teas containing Mitragynine may be fined a maximum penalty of RM 10,000 (USD 3300), a four-year jail sentence or both (Ministry of Health Malaysia, 1952).

In Malaysia, the use of Kratom is mainly in the form of tea or juice made by boiling the Kratom leaves (Singh et al., 2014). The MS teas are available in the villages and are inexpensive (Ahmad & Aziz, 2012). (Ahmad & Aziz, 2012) reported the Kratom juice is readily available from local coffee shops, and users drink it daily. (Chan et al., 2007) discovered in early 2004's, stalls selling Kratom drinks and teas mushroomed in several towns in the Northern states attracting youths to the concoctions. Interestingly, (Ahmad & Aziz, 2012) found close to 90% of the respondents were unable to stop using MS when they wanted, indicating the possibility of dependence. The same study reported a very high percentage (99%) asserted that they did not neglect their family while using MS. The observation is present despite the fact that close to 80% of the respondents reported having undesirable effects when stopping MS use.

2.5 CONCERNS REGARDING KRATOM

As discussed earlier, the leaves of the MS contain some active alkaloids that produce narcotic-like actions when smoked, chewed, or drunk as a suspension (Nelson et al., 2014; Prozialeck et al., 2012; M.T. Swogger et al., 2015). The concerns regarding MS use is that its long-term use is associated with the development of misuse, abuse, dependence and addiction (Hassan et al., 2013). The literature searched showed regardless of the method of administration, due to its opium-like effects, and the users consumed kratom when opium was unavailable or unaffordable (Hassan et al., 2017; P. Tanguay, 2011; Tungtananuwat & Lawanprasert, 2010). It is indeed worrying, (M.T. Swogger & Walsh, 2017) stated that kratom appears to mild relative to those of opioids; however, the withdrawal is highly uncomfortable and maintaining abstinence is difficult.

(Suwanlert, 1975) had raised concerns about the Kratom users becoming addicted to MS. (Suwanlert, 1975) stated the dependence could undoubtedly occur in the long-term users. Kratom withdrawal is indistinguishable from opioid withdrawal and it present as symptomatology identical to the opioid withdrawal. Hostility, aggression, excessive tearing, inability to work, aching of muscles and bones and the jerky movement of limbs are the examples of its typical withdrawal symptoms (Chan et al., 2007; Nelson et al., 2014). (Hassan et al., 2013) suggested the withdrawal symptoms reported implied an addiction potential. The first case of addiction to MS was reported in 1957, and a case series of addiction was subsequently published in 1975 (Suwanlert, 1975). Additionally, (Suwanlert, 1975) found long-term Kratom addicts having difficulties with appetite, weight, and sleep. Reports suggest the long-term use of Kratom is linked with tolerance, withdrawal symptoms, anorexia, psychosis, insomnia, and poor concentration (McWhirter & Morris, 2010; Vicknasingam et al., 2010).

The concerns are further added with more reports. The usage of adulterated cocktails of Kratom and combining it with other substances, particularly in urban areas by younger population, has been associated with its euphoric effects (Singh et al., 2015). In recent years, the younger people in Bangkok and the South of Thailand have utilized Kratom in a cocktail called '4x100' which includes Kratom tea, Coca-Cola, cough syrup and ice cubes (Macdonald & Nacapew, 2013; Tungtananuwat & Lawanprasert, 2010). Users were all young people who had to drink the 4x100 in hidden settings due to fears of arrest by law enforcement (Tungtananuwat & Lawanprasert, 2010). In these instances, the conservative elders discriminate the users because of the psychoactive properties as found in the cocktail additives.

(Singh et al., 2015) investigating 293 regular Kratom consumers reported the similar development of dependence occurring at a high rate and the symptoms worsened with prolonging used. (Singh et al., 2015) reported withdrawal symptoms commonly felt among the users were restlessness, tension, anger, sadness, and nervousness. Similar to (Ahmad & Aziz, 2012), (Singh et al., 2015) regular users who consumed ≥3 glasses Kratom per day, had higher probabilities of developing severe Kratom dependence, withdrawal symptoms, and the inability to control Kratom their craving. In (Singh et al., 2015)'s study, all respondents were dependent on Kratom, yet they believed Kratom is not as harmful as the other available drugs, such as methamphetamine or heroin. The respondents emphasized they use Kratom to improve their work performance. Interestingly, the study found the Malay village community do not discriminate Kratom users as they accept the practice as an inherent aspect of their ancestral traditions.

Other scientists have reported deaths associated with, but not directly attributable to Kratom use (Domingo et al., 2017; Hassan et al., 2013; Holler, 2011). (Kronstrand, Roman, Thelander, & Eriksson, 2011) reported a particular form of Kratom, named "Krypton," caused severe presentation and resulted in nine cases of fatality. The complexity in the chemistry and pharmacological effects, coupled with the possibility of polysubstance use and adulteration processes, poses a threat to the Kratom users and may place them in potentially life-threatening consequences (Corazza et al., 2013). Additionally, (Nelsen et al., 2010) reported a case of a 64-year-old male presenting to emergency with seizure following Kratom consumption. The patient had used Kratom as a form of tea.

2.6 KRATOM AND ITS USE AS A 'LEGAL HIGH'

The term 'legal high' is mainly used to describe New Psychoactive Substances (NPS). Among the NPS are a wide range of products, from natural plant-originated substances to synthetic compounds (J.B Zawilska, 2015; J.B. Zawilska & Andrzejczak, 2015). In the recent years, the new range of new mostly synthetic substances which often mimic many of the effects of the "traditional" drugs have become popular (Pompei, 2016; Schmidt, Sharma, Schifano, & Feinmann, 2011). Equally concerning is that it can be purchased both online and from high street retailers (O'Hagan & Smith, 2017; Pompei, 2016). The recreational use of these novel psychotropic "herbal highs" are seen as legal alternatives to conventional controlled drugs (O'Hagan & Smith, 2017; Pompei, 2016).

Kratom is currently one of the most popular NPS available in the market and is now available worldwide (Boyer et al., 2008; Cinosi et al., 2015; Gilani, 2015; Prozialeck et al., 2012; Schmidt et al., 2011). Both the purified Mytraginine or other product containing a blend of substances are increasingly available on a worldwide scale via the Internet (Boyer et al., 2008; Cinosi et al., 2015; Gilani, 2015; Prozialeck et al., 2012; Schmidt et al., 2011). (Schmidt et al., 2011) reported various categories of mixed products resulting in a hallucinogen-stimulant combination (to mimic ecstasy), or stimulant-sedative combinations (to mimic opiates), among many. The products were reasonably affordable but little product information provided to consumers. Thus, the safety information was scarce and of the quality of the products questionable.

Recently, Kratom has made its way to Europe and the United States and is currently among the most commonly used NPS (K. Babu et al., 2005; K. M. Babu et al., 2008; Boyer et al., 2008). It was inevitable that Kratom will eventually find its way across the world. By the 1990s, aided by the increasing migration of people from SE

Asia to Europe and the United States (US), Kratom consumption as a natural remedy commenced outside of SE Asia (Henningfield et al., 2017). Its spread and increase usage is facilitated by dissemination of information and marketing on the internet (Henningfield et al., 2017; Pizarro-Osilla, 2017; Pompei, 2016).

An online study by (EMCDDA, 2012) noted 44% of the online shops investigated, provided Kratom as one of their 'legal highs.' The widespread use of Kratom is aided by its cheap cost, and it remains easily available (Boyer et al., 2008; Prozialeck et al., 2012; Vicknasingam et al., 2010). Added to the fact that Kratom is marketed for chronic pain to self-manage opioid withdrawal (K. M. Babu et al., 2008; Henningfield et al., 2017). By the early 2000s, Kratom was increasingly used in the US as a natural remedy to improve mood and quality of life (Chien, Odonkor, & Amorapanth, 2017; Henningfield et al., 2017). In Europe and the US, Kratom is found either as in its pure preparation (Cornara et al., 2013; Forrester, 2013) or as a herbal ingredient of 'legal' or 'herbal high' preparations. These concoctions are distributed under various names such as Krypton, K2, or Spice (Lindigkeit et al., 2009; Seely, Lapoint, Moran, & Fattore, 2012; Uchiyama, Kikura-Hanajiri, Ogata, & Goda, 2010).

There is currently a worldwide scarcity of studies depicting the actual prevalence of NPS use particularly Kratom. Among countries in Europe, a similar picture is seen. A recent study in 2011 by EMCDDA also showed that Kratom was the most widely available product and 20% of online shops ships Kratom to European Countries (Cinosi et al., 2015). Kratom is currently depicted as the safe herbal dietary supplement capable of inducing a 'legal high' (Swogger et al., 2015), and as a cheaper and economical substitute for other sedative or stimulating drugs (Warner et al., 2016). A recent study by (Schmidt et al., 2011) noted an increase in global popularity of Kratom evidenced by the emergence of more international works of literatures and online websites selling

Kratom and its products. Most studies to date had been in the form of online surveys or directed mainly at a specific group of users. This, in turn, creates a gap between actual use of NPS in the population, and perceived use of the illicit substances among a specific targeted population. A study done in 2012 showed that 65.8% of nightclub visitors in the UK used NPS. However only 8% of youth in EU had experience with NPS (Wood, Greene, & Dargan, 2010).

Thailand has been in the forefront of Kratom studies for many years as Kratom is said to be the most popular illicit substance used (Assanangkornchai, Muekthong, et al., 2007; Hassan et al., 2013; Wonguppa & Kanato, 2017). Since early 2000's, the use of Kratom has been included in their national survey, and they are able to gauge the trend of Kratom use in Thailand. The Thailand National Household Survey 2011 found that the estimated rates of past-year and past-30-day Kratom use were 8.37 and 5.98 per 1000 population, and the highest rate of Kratom use was in the southern part of Thailand with 8.6% of adults being lifetime Kratom users (Administrative Committee of Substance Abuse Academic Network, 2012).

Their latest survey in 2012 noted that 1,233,176 persons had experienced using Kratom in their lifetime (Administrative Committee of Substance Abuse Academic Network, 2012). A study in 2008 portrayed an almost similar albeit higher prevalence of Kratom use among the adult population in the southern region, at 9.29% (Assanangkornchai, Muekthong, et al., 2007; Hassan et al., 2013; Wonguppa & Kanato, 2017). It is important to note that in these surveys, under-reporting of substance use needs to be taken into consideration. The current legal status, local culture/norms, as well as how the substances are perceived by the population at the time of survey plays a vital role in determining the level of response, and how it affects the outcome of the studies.

In Malaysia, the use of Kratom in northern areas mainly bordering Thailand is widely reported (Ahmad & Aziz, 2012; Vicknasingam, Narayanan, Beng, & Mansor, 2010). However, its actual prevalence is unknown. (Chan et al., 2007) hypothesized the growing trend was among drug addicts who were unable to get their regular supply of opiods and marijuana.

Studies done in the past had used the snowball-sampling method in a particular area to achieve the desired number of samples. Using such methods may cause a perceived bias as the sample taken was not representing the population as a whole. A study conducted by (Vicknasingam et al., 2010) reported only one female respondent out of 136 participants who agreed to be interviewed for the study. The author concluded there might be under-reporting of Kratom use among female users and the reluctance of female users to participate in similar studies.

As of 2016, there are an estimated 35.7 million people around the world who are currently abusing amphetamine-type stimulants (United Nations Office on Drugs and Crime, 2016). The (EMCDDA, 2012) in 2008 and 2011 conducted an online survey and found that Kratom was among the most widely supplied NPS in the market, placing in the top three together with Khat and S. Divinorum. At present, there is no systemic data on the prevalence of Kratom use in Malaysia (Cinosi et al., 2015; United Nations Office on Drugs and Crime, 2016).

The use and effects of MS are still widely debated. Users still believe in the stimulant effects of MS, despite the lack of evidence. While authorities, relevant and concerned parties and groups deem the consumption of Kratom will lead to the abuse of other drugs and ill-health.

2.7 KRATOM AND PSYCHIATRIC ILLNESS

As the review revealed, Mytraginine is the major psychoactive alkaloid compound of the plant Kratom (Adkins et al., 2011; Takayama, 2004; Takayama et al., 2000; Yusoff et al., 2016). In Southeast Asia, Kratom is widely still used as a recreational drug and recognized for its medicinal values (Singh et al., 2016; P. Tanguay, 2011). While in the Western countries its use is increasing as a pure compound or a component of 'herbal high' preparations (Yusoff et al., 2016). In recent years, many individuals, or groups state the legal highs are the compounds that are legal to sell, possess and use (EMCDDA, 2012; J.B. Zawilska, 2011). These legal highs" mimic psychoactive effects of illicit drugs of abuse (O'Hagan & Smith, 2017; Pompei, 2016; Yusoff et al., 2016).

What is the relationship between Kratom use and mental health? Are there potential benefits as claimed by its users or risks? (Smith & Lawson, 2017) stated it is difficult how to characterize notions of kratom dependence verses kratom utility. In an investigation regarding Kratom affect, (M.T. Swogger et al., 2015) stated much of the data on Kratom use in humans is informal and anecdotal. Reports among Kratom users in Southeast Asia is positive. They feel Kratom have an energizing effect on them (Chan et al., 2007; Singh et al., 2014; P. Tanguay, 2011; Vicknasingam et al., 2010). Thus, it is not unexpected; many Kratom users state them using Kratom does not constitute to 'drug use or abuse.' (Singh et al., 2016) investigating 293 regular Kratom user reported a calming effect at higher doses. The positive mood was likewise found in the study by (Ahmad & Aziz, 2012). In a quarter of the 530 respondents reported feeling euphoric, relax, or contentment resulting in them experiencing increased energy and alertness. Interestingly, the study by (Singh et al., 2016) found the regular consumers did not experience significant impairments in their social functioning. Consequently, the individuals are not stigmatized or discriminated users (P. Tanguay, 2011).

However, (Singh et al., 2016) postulated the regular and prolonged Kratom use is linked to dependency on MS. Intriguingly, almost all of the respondents were aware that Kratom might be addictive and can cause dependence. It is not surprising why researchers warn about the risk of potential abuse of Kratom (Smith & Lawson, 2017; Yusoff et al., 2016). The findings corresponded to research showing Kratom in small or moderate doses can produce mild stimulant effects while higher doses, generate opioid-like effects (Adkins et al., 2011; Macdonald & Nacapew, 2013; Thongpradichote et al., 1998; Ulbricht et al., 2013).

(Suwanlert, 1975) was the first person who reported withdrawal symptoms, in five cases of manual workers using Kratom as a relaxant and for their mood. The Kratom resulted in them having a pleasant mood. However, psychiatric problems arose after prolonged usage.

The trend of increasing reports of psychiatric problems associated with Kratom usage continues. Researchers were worried as reports of Kratom emerging as a substance of abuse is on an upward trend. In recent years, many more reports have emerged. (Assanangkornchai, Pattanasattayawong, Samangsri, & Mukthong, 2007) Conducting a large-scale study over three years and investigating substance use among high-school students in Southern Thailand, found Kratom and cannabis were the most commonly used illicit substances. The study concluded Kratom usage was on the rise by both boys and girls in 2003 and 2004, assisted by the general perception of Kratom as a folk medicine in Thailand and is readily available. The continued and increasing trend of Kratom use is worrying. (Assanangkornchai, Pattanasattayawong, et al., 2007) hypothesized the Kratom preparations abused by these high school students at a similar rate to them using cannabis.

In a cross-sectional survey of 136 active users conducted in the northern states of Kedah and Penang, (Vicknasingam et al., 2010) found the subjects use Kratom to manage the illicit substance withdrawal symptoms and to reduce their intake of the more expensive opiates. The trend was explicitly noted amongst the younger subjects, who were already using other substances. The findings of the study differed from the studies done in Thailand which noted people use Kratom primarily to increase physical endurance for sustained work. (Vicknasingam et al., 2010) as well reported three-quarters of the subjects surveyed, reported having difficulties diminishing from using Kratom. Thus, indicating the possibility of dependency.

(Hassan et al., 2013) related in 562 respondents using studying Kratom for social and recreational needs, found more than three-quarter of the respondents were not able to stop using MS. Conversely, (Singh et al., 2014) in the cross-sectional survey of 293 regular Kratom users raised concerns about the drug-dependency and possibility of the impact of withdrawal symptoms. However, none of the responders thought they were dependent on the produce. (Singh et al., 2014)'s study raised the possibility of regular Kratom use and its association with the drug dependency. In the study, close to three-quarters of the subjects reported physiological and psychological withdrawal symptoms, while almost all experienced moderate to severe withdrawal effects after Kratom cessation. Subjects who consumed more than 3 glasses of Kratom daily were more likely to report severe withdrawal symptoms during their cessation. (Singh et al., 2014) concluded all the respondents surveyed were dependent on Kratom. Similarly, other studies conducted in Malaysia and Thailand have reported about the problem of the withdrawal symptoms associated with Kratom use in (Singh et al., 2014)'s study. The literature review showed the users were aware of Kratom dependency. However, due to the little symptomatology felt, most have no insight to their addiction while expressing difficulty to abstain.

The review highlights the changing trends of Kratom usage as seen in studies such as (Assanangkornchai, Muekthong, et al., 2007), (Assanangkornchai, Pattanasattayawong, et al., 2007) and (Singh et al., 2014). While users before focused on the perceived advantages of Kratom concerning its aid with increased work endurance, and as herbal medication, Kratom is progressively recognized for its harmful effects. (Trakulsrichai et al., 2013) reviewing data from the Ramathibodi Toxic Surveillance System from 2005-2009, identified more withdrawal cases and Kratom poisoning. Likewise, (Trakulsrichai et al., 2013) reported a quarter of the cases identified reported physiological and psychological withdrawal symptoms. The common withdrawal symptoms were myalgia, insomnia, fatigue and chest discomfort. The psychological withdrawal symptoms comprise restlessness, tension, anger, and depression have been reported (Pizarro-Osilla, 2017). Interestingly in the 78 cases of Kratom exposure, there were 40 cases of Kratom poisoning.

The literature review showed the possible medical life-threatening and psychological symptoms associated with Kratom usage. Outside South-East Asia, worrying reports concerning the use of Kratom has appeared. Consumers use Kratom primarily for the self-treatment of pain, mood disorders, and withdrawal symptoms, and its popularity is on the rise (Anwar, Law, & Schier, 2016; Grundmann, 2017; Warner et al., 2016). Its popularity is driven by the associated beneficial effects of Kratom, including pain relief, improved mood and energy, relaxation, pleasant somatic sensations, resulting in the increased socialization of the individuals (Grundmann, 2017; Hassan et al., 2013; Smith & Lawson, 2017).

While its users speak volume about its goodness, there is increasing reports about its misuse, abuse and medical emergency. These many reports have caused increasing

concerns regarding its consumption. (Forrester, 2013) using data from the Texas Poison Center noted there were no reports regarding Kratom exposure before 2013. From then on reports the range from medical complication following Kratom use alone or involving other additional substances, intentional misuse or abuse, an adverse reaction, a therapeutic error and intentional use. There were as well several toxic exposures recurring referral to the health facilities.

Similarly, (Anwar et al., 2016) using the National Poison Data System found the U.S. poison centers received 660 calls concerning reported exposure to Kratom. While more than half of the calls were related to single Kratom use, the rest were of Kratom in combination with other substances. The majority of the calls concerned were mild disability thus recurring no treatment. In about 50% were moderate to major severity and required treatment. The complaints ranged from tachycardia (n = 165, 25.0%), agitation or irritability (157, 23.8%), drowsiness (128, 19.4%), nausea (97, 14.7%), and hypertension (77, 11.7%). There was, unfortunately, one reported death, in a person who was exposed to the medications paroxetine (an antidepressant) and lamotrigine (an anticonvulsant and mood stabilizer) in addition to Kratom.

Interestingly, (Grundmann, 2017) from an online anonymous cross-sectional survey among close to 8000 responders, found more users reported beneficial effects of Kratom: decreased pain (85.01%), increased energy (83.75%), and feeling less depressive (80.00%). The responders reportedly use Kratom primarily for self-reported treatment of acute and chronic pain as well as for mood conditions such as anxiety and depression. Besides the perceived beneficial effects, some respondents reported adverse effects. In 51 users (0.65%) the negative or adverse effects required outpatient treatment or hospitalization. Despite the low incidence of adverse side-effects, the symptoms were similar to opioid withdrawals (Henningfield et al., 2017). (Grundmann, 2017) concluded users perceived beneficial effect using lower amounts. However, most of the

side-effects were dose-dependent, and its use is associated with risk of increased frequency of dosing posing a possibility of abuse and dependency (Anwar et al., 2016; Cinosi et al., 2015; Grundmann, 2017).

The review of literature seemed to conclude Kratom appears beneficial to all its users, and they are oblivious to the psychiatric and medical concerns. In the medical field, its efficacy and adverse effects are mixed. The medical data seemed to state there are pros and cons of kratom use.

3 AIMS AND OBJECTIVE

This study aims to assess the prevalence of Kratom use among rural settlers in Northern Malaysia, as well as its psychiatric co-morbidity and demographic correlation

3.1 PRIMARY OBJECTIVE

- To determine the prevalence of Kratom use among settlers in Felda Chuping, Perlis.
- To assess the correlation between Kratom use and demographic data.
- To investigate the association between Kratom use and psychiatric illness.
- To determine the association between Kratom use and Quality of Life among its users.

3.2 RATIONAL OF STUDY

Kratom use is said to be predominant in Malaysia particularly in the northern region bordering Thailand. However, till date, there is no data on the prevalence of Kratom use especially among rural settlers in the northern regions of Malaysia. Illustrating the prevalence of its use, and determining its correlates, may help us understand the complexity and magnitude of the problem. There is also a scarcity with regards to studies about Kratom use and psychiatric comorbidities in Malaysia and worldwide. This study will help to determine if there is an association between psychiatric illnesses and Kratom use

4 METHODOLOGY

4.1 PREVALENCE STUDY SETTING

This study was conducted in FELDA Chuping, Perlis. FELDA Chuping is the largest and oldest FELDA settlement in Perlis. It is the only Felda in Perlis which houses only settlers originating from Perlis. It is located near the border town of Padang Besar and is merely a stones-throw away from Thailand.

The population in the area are currently in their third and fourth generation, with many families still working nearby the settlement. The demography of the population in the area is similar to the population of Perlis in general. In the Felda settlement, the housing areas are sub-divided into blocks, which allows randomization during the investigation. The area is as well close to the Thai border. Thus, the population of Chuping is known to consume Kratom as per other areas in Perlis.

4.2 TARGET POPULATION

Currently, there are 4 FELDA settlements in Perlis. The research focused on Chuping as mentioned before; it is the largest and oldest settlement in Perlis with a population of approximately 13000. The participants of the study are adults, 18 years of age and older, who are permanently staying in Chuping. The investigator interviewed each respondent in their home, mindful of the nature of the study, and the sensitivity of the questions. All the items were asked individually on a 1:1 basis with the interviewer and each respondent. The individual interview allowed a confidential setting for each participant.

4.3 LANGUAGE

The researcher used Bahasa Malaysia as the majority of the population in Perlis is ethnic Malay. All the questionnaires used were in Bahasa Malaysia. However, the team consisted of interviewers who are multiracial and multilingual. The multiracial and

multilingual group allowed the team to interview the respondents in the different languages if the need arises. The issue of language was monitored continuously during the data collection. The leading researcher would be alerted if there were significant numbers of respondents who required a translation.

4.4 INTERVIEWER BRIEFING

The research team had a total of 18 interviewers who helped collect the data. The team comprised of a consultant psychiatrist, a medical officer (the leading researcher), medical students from University Malaya, medical students from University Insaniah, research assistants from University Malaya Centre of Addiction Sciences (UMCAS), as well as staff nurses with post-basic qualifications in psychiatry.

The team comprised of a multiracial background with combined language proficiency in Bahasa Malaysia, English, Mandarin, and Tamil. The staffs were divided into pairs for the data collection. A series of briefings were conducted, headed by the consultant psychiatrist to allow for discussion and to familiarize the interviewers with the questionnaires. The heads of the team held practice sessions and role-played exercises before the data collection started. Each briefing lasted between 1-2 hours, and organized a total of 4 sessions to prepare every member before the data collection commenced.

All interviewers were provided with copies of the questionnaires and were briefed regarding the need to identify salient information from each respondent, to provide non-biased information regarding the study, methods of asking questions as well as the brief intervention as per ASSIST protocol. The interviewers were also informed to alert the researcher if any of the respondents were noted to be having any urgent medical/psychological need to ensure further help and continuity of care.

4.5 STUDY DESIGN AND SAMPLING METHOD

This is a cross-sectional study. Convenient sampling method was used to recruit the participants for the study.

A list of all the settlers and their family members of Felda Chuping was needed in order to randomise the study sample. However, this list was not available at the time of the study. Hence the researcher used computer-generated randomization of all the houses available in FELDA Chuping, from the 23 blocks. All 23 blocks were included in the study. Each block contained approximately 25 houses, out of which 100 houses were chosen randomly using a randomization software. Sampling was done from house to house, and all members of the household who met the inclusion criteria were invited to participate in the research

4.6 INCLUSION CRITERIA

1. Participants who are Malaysian citizen
2. Participants should be of age 18 and above
3. Participants are permanent resident of FELDA Chuping
4. Participants who are able to read and understand Bahasa Malaysia adequately.

4.7 EXCLUSION CRITERIA

1. Non-consenting individuals

4.8 DATA COLLECTION

Data collection was done from July 2017 to October 2017. A meeting was held with the authorities in the respected settlement, and a meeting was held with the manager and heads of all the blocks in FELDA Chuping. An approximately 50 heads of block (male and female) were present during the meeting. The meeting was to ensure that the participants in the respected blocks will respond to the group of researchers who will be

going from house to house during the following months. They were also informed that the selection of houses was randomized.

As part of a community outreach program, general talk about common psychiatric illnesses was organized with the help of the consultant psychiatrist from University Malaya. The main researcher then used this opportunity to explain briefly regarding the study to the heads of blocks and to inform them regarding the purpose of the study, methods used and who may take part in the study. This gesture was important taking into consideration the local culture of settlers in Perlis and in order to reduce response bias.

Data collection was performed mainly during weekends to ensure that as many settlers were around at home and were not out working. The time of sampling, as well as the weather, was also taken into consideration to ensure that most participants were available during the time of data collection. Based on the preliminary interview with the manager and other heads of the blocks, sampling should be done in the mornings during the weekends, preferably during rainy days. Most of the settlers are rubber tappers and would be indoors during those times. Interview was done from house to house and the interview was directed towards everyone in the household who fulfill the inclusion criteria mentioned.

During data collection, the researchers again informed the participants about the purpose of the study. A Patient information sheet was given and participants were allowed to ask questions or decline to participate. The researcher team assured each participant confidentiality concerning their responses, and there would be no risk to the participants. If the team found the participants had symptoms of any mental illness, the team will make a referral to nearby medical facilities. The reference would give the participants the opportunity to do a further assessment with their consent. Informed

consent was compulsory from all participants and the Patient Consent Form was provided to all respondents. Once consent was obtained, the sociodemographic data were obtained using the Demographic Data Questionnaire.

The Mini-international Neuropsychiatric Interview (MINI), The Alcohol, Smoking and Substance Involvement Screening Test-Malay version (ASSIST-M) are both interviewer rated tools that were used for the participants. The participants were then given a self-rated questionnaire, the World Health Organisation Quality of Life (WHOQOL). All participants were interviewed personally, in their own home and comfort. They were assisted by the investigators when needed, without influencing their selection or introducing bias. Data obtained were kept confidential in a specified box.

4.9 SAMPLE SIZE CALCULATION

Table 4-1- Sample Size Calculation

Population size (for finite population correction factor or fpc)(*N*):	13000
Hypothesized % frequency of outcome factor in the population (*p*):	8.6%+/-5
Confidence limits as % of 100(absolute +/- %)(*d*):	5%
Design effect (for cluster surveys-*DEFF*):	1

Sample Size(*n*) for Various Confidence Levels

Confidence Level (%)	**Sample Size**
95%	**116**
80%	50
90%	82
97%	142
99%	199
99.9%	322
99.99%	446

Equation

Sample size $\boldsymbol{n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]}$

Results from OpenEpi, Version 3, open source calculator--SSPropor

Felda Chuping is the largest Felda settlement in Perlis and has an estimated 13000 population. No similar study was found in Malaysia. However based on a study in Thailand, which reported a prevalence of Kratom use at 8.6% in the southern territories

bordering Malaysia (Administrative Committee of Substance Abuse Academic Network, 2012), hence this was used in the calculation of sample size. Based on the sample size calculation, a minimum number of 116 samples were needed for this study to achieve 95% level of confidence.

4.10 INSTRUMENTS

4.10.1 DEMOGRAPHIC DATA

The research team developed a questionnaire to collect relevant demographic data from the participants. The form included age, ethnicity, marital status, level of education, occupation, income, medical history, smoking, and substance use among participants and family members.

4.10.2 MINI- INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI)

Mini- International Neuropsychiatric Interview (MINI) is a short, structured interview based on the DSM-IV criteria, which has good psychometric properties and is reliable for diagnosing major psychiatric illnesses (Sheehan et al., 1998).

MINI has been used in various studies worldwide as a diagnostic tool in investigating psychiatric illness among its participants. it comprises of questions subdivided according to major psychiatric diagnosis according to DSM-IV. Trained individuals require approximately 15 minutes to administer MINI to respondents. The investigators were trained by a consultant psychiatrist to use MINI during the study period.

4.10.3 ASSIST-MALAY VERSION

The alcohol, Smoking, and Substance Screening Test (ASSIST) is an instrument developed by the World Health Organization (WHO) to study the use of tobacco and

psychoactive substances (WHO, 2002a). It consists of 8 items that investigate the use of substances and categorizes the risk scores into 'low,' 'moderate,' and 'high,' which is then used to determine the level of intervention needed for the particular respondent (no intervention, brief intervention, brief intervention with referral).

The Malay version of ASSIST was translated and validated in a recent study among alcohol users and demonstrated good internal consistency (Cronbach's alpha of 0.8) with the original ASSIST, as well as significant concurrent validity when compared with other established questionnaires (Yee, Salina, Rusdi, & al., 2017). For the current study, Kratom was inserted in item 'J-Other substances' of ASSIST-M.

4.10.4 WHOQoL-BREF-Malay Version

World Health Organization Quality of Life- Brief-Malay version is a translated and validated tool of the original WHOQoL-Bref (Hasanah, Naing, & Rahman, 2003), which may be used to assess the quality of life of respondents for the past two weeks. It contains four domains mainly physical, psychological, social relationship and environment. The use of WHOQoL-Brief-M in this study would allow the researcher to ascertain the relationship between Kratom use and quality of life if there is any.

4.11 STATISTICAL ANALYSIS

Data collected in this study were analyzed using Statistical Package for Social Sciences (SPSS) Version 24. The demographic data were summarized using descriptive statistics. The prevalence of Kratom use among Felda settlers was described. Independent t-test (parametric) was used to compare the mean differences between two independent variables that were normally distributed, while Mann-Whitney U test (non-parametric) was used to compare median between two independent variables that were not normally distributed.

Chi-Square was used for categorical data to compare two or more variable from the Kratom user population. Kratom users in the population were derived from ASSIST-M question one (Item-J) which describes the current and past use of Kratom. Univariate analysis was done to analyze the association between demographic data, ASSIST-M (tobacco, heroin), MINI, WHO-QoL and Kratom use. Wald's, Pearson's Chi-square test, and Fisher's Exact Test was used for the univariate analysis. Finally, multivariate analysis was performed among the statistically significant results from the univariate analysis and described.

4.12 ETHICAL CONSIDERATION

Ethical approval was obtained from University Malaya Medical Centre Ethics committee MREC ID NO: 2016927-4283 dated 21 August 2017. Permission to conduct research in Felda was also obtained dated 4th January 2017 (Refer Appendix). All participants who took part in the study were asked to sign the Patient Consent Form, following which a detailed explanation regarding the purpose of the study was explained. All data obtained were kept confidential.

5 RESULTS

5.1 SOCIO-DEMOGRAPHIC DATA

A summary of the socio-demographic data collected is presented in Table 5-1. A total of 144 subjects agreed to participate in this research. The mean age of participants was 47.5 (SD 17.22) whereby 56.9% were male participants (n=82) and 43.1% or, 62 were female. Majority of the participants 75.7% (n=109) were married while 17.4% (n=25) were single, and 7% (n=10) were either divorced or widowed at the time of data collection. The mean age of stopped schooling was 15.2 (SD=3.59), whereby the majority 54.2% (n=78) studied up to secondary level, while 34% (n=49) completed primary school education and 9% (n=13) achieved tertiary education. Four of the participants or 2.8% did not attend school.

The majority of participants or 71.5%, (n=103) were employed, 28.5% (n=41) were unemployed, and the mean income for the participants was RM1090 per month. The median amount of family members for the participants was 4 (IQR=3).Based on the demographic data, the majority of participants (65.3%, n=94) involved in the study were healthy participants, while 34.7% (n=50) experienced general medical illness. Only 1 of the participant (0.7%) reported having an underlying psychiatric illness during the initial interview and was at the time under the psychiatric follow up at Hospital Kangar. When asked regarding substance use, 13.2% (n=19) had experience of using illicit substance in the past while 86.8% (n=125) denied of any past substance use. A total of 7.6% (n=11) also had at least 1 of their family members who are currently abusing illicit substance Smoking seemed to be a norm among rural settlers in Felda Chuping as 42.4% (n=61) of respondents were smokers. They started smoking at the mean age of 16.1 (SD=7.17) and smoked 11 sticks per day (IQR=10). It is important to note that 61.7% (n=37) of the smokers had an intention to stop smoking.

Table 5-1- Descriptive Statistic of Demographic Data

Demographic	Participants (n =144)
Age, Mean (SD)	47.5 (17.22)
Gender, n (%) Male Female	 82 (56.9) 62 (43.1)
Marital status, n (%) Single Married Divorced Widowed	 25 (17.4) 109 (75.7) 1 (0.7) 9 (6.3)
Age when stopped schooling, years Mean (SD)	**n =140, four participants never went to school** 15.2 (3.59)
Education level, n (%) Primary Secondary Tertiary and above No	 49 (34.0) 78 (54.2) 13 (9.0) 4 (2.8)
Employment, n (%) Employed Unemployed	 103 (71.5) 41 (28.5)
Income, Mean (SD) [in RM/month]	1090 (1033.97)
Family members, Median (IQR)	4 (3)
General illness, n (%) No Yes	 94 (65.3) 50 (34.7)
Psychological illness, n (%) No Yes	 143 (99.3) 1 (0.7)
History of using drug, n (%) No Yes	 125 (86.8) 19 (13.2)
Family members using drug, n (%) No Yes	 133 (92.4) 11 (7.6)
Smoker, n (%) No Yes	 83 (57.6) 61 (42.4)
Age when started to smoke, Mean (SD)	**n = 60, 1 missing data** 16.4 (7.17)
Number of cigarettes (per day), Median (IQR)	**n = 56, 5 missing data** 11 (10)
Dedicate to stop smoking, n (%) No Yes	**n = 60, 1 missing data** 23 (38.3) 37 (61.7)

SD = Standard deviation.
IQR = Inter-quartile range

5.2 PREVALENCE OF KRATOM USE

Based on question 1, item J of ASSIST-M, all participants were divided into Kratom users and non-users. A comparison between Kratom users and non-users were cross-tabulated in Table 5-2, and the prevalence of Kratom use was found to be at 24.3% (n=35) at Felda Chuping. Comparison between Kratom users and non-user demographically is summarized below.

Table 5-2- Socio-Demographic Data Comparison Kratom User and Non-User

Demographic data	Kratom user	
	No (n = 109)	Yes (n = 35)
Age, Mean (SD)	50.4 (16.94)	38.5 (14.99)
Gender, n (%)		
Male	49 (45.0)	33 (94.3)
Female	60 (55.0)	2 (5.7)
Marital status, n (%)		
Singe	11 (10.1)	14 (40.0)
Married	91 (83.5)	18 (51.4)
Divorced	0	1 (2.9)
Widowed	7 (6.4)	2 (5.7)
Age when stopped schooling, Mean (SD)	15.0 (3.75)	15.7 (3.10)
Education level, n (%)		
Primary	43 (39.4)	6 (17.1)
Secondary	51 (46.8)	27 (77.1)
Tertiary and above	11 (10.1)	2 (5.7)
No	4 (3.7)	0
Employment, n (%)		
Employed	71 (65.1)	32 (91.4)
Unemployed	38 (34.9)	3 (8.6)
Income, Mean (SD) [in RM/month]	1077.5 (1121.72)	1128.86 (705.38)
Family members, Median (IQR)	4 (2)	4 (3)
General illness, n (%)		
No	65 (59.6)	29 (82.9)
Yes	44 (40.4)	6 (17.1)
Psychological illness, n (%)		
No	109 (100.0)	34 (97.1)
Yes	0	1 (2.9)
History of using drug, n (%)		
No	108 (99.1)	17 (48.6)
Yes	1 (0.9)	18 (51.4)
Family members using drug, n (%)		
No	106 (97.2)	27 (77.1)
Yes	3 (2.8)	8 (22.9)

Smoker, n (%) No Yes	81 (74.3) 28 (25.7)	2 (5.7) 33 (94.3)
Age when started to smoke, Mean (SD)	**(n = 27, 1 missing)** 17.5 (10.01)	**(n = 33)** 15.4 (3.35)
Number of cigarettes (per day), Median (IQR)	**(n = 23, 5 missing)** 10 (15)	**(n = 33)** 20 (10)
Dedicate to stop smoking, n (%) No Yes	**(n = 27, 1 missing)** 6 (22.2) 21 (77.8)	**(n = 33)** 17 (51.5) 16 (48.5)

It was found that the mean age for the Kratom users were lower (38.5 SD=14.99) as compared to non-users (50.4 SD=16.94). A total of 94% (n=33) among Kratom users were male, and 5.7% (n=2) were female respondents who used Kratom. Among the Kratom users, 51.4% (n=18) are married and 40% (n=14) were single.

The age of stopped schooling (mean years) among Kratom users and non-users were 15.7 (SD 3.10) and 15.0 (SD 3.75) respectively. Among Kratom users, 77.1% (n=27) reached secondary school education, while 17.1%(n=6) completed primary school. Two respondents (5.7%) among the Kratom users reached tertiary level of education.

With regards to employment, it was found that 91.4% (n=32) of Kratom users were employed at the time of data collecting, as compared to 65.1%(n=65) of non-users. The mean income for Kratom users was RM 1128.86 (SD 705.38) as opposed to non-users of RM1077.5 (SD=1121.72)

A total of 82.9% (n=29) of Kratom users did not complain of any general medical illness and, 97.1% (n=34) did not experience any psychiatric illnesses. As compared to non-users, 40.4% (n=44) has some form of general illness, and none of them (n=109) was under any psychiatric follow-up. One participant among Kratom users was known to have an underlying psychiatric illness. A total of 51.4% (n=18) of

Kratom users admitted to having a history of illicit substance use, and 22.9% (n=8) of them has another family member who are currently abusing substances.

Among Kratom users, 94.3% (n=33) are smokers, at an average of 20 sticks per day (IQR=10) and started smoking at a mean age of 15.4 (SD=3.35). Non-Kratom users, however, reported that 25.7% (n=28) were active smokers, at a median of 10 sticks per day (IQR=15), and started smoking at a mean age of 17.5 (SD=10.01). Among non-Kratom users who smoked, 77.8% (n=21) of them reported an intention to stop smoking, as compared to 48.5% (n=16) among Kratom users.

5.3 ASSOCIATION BETWEEN MINI AND KRATOM USERS

Univariate analysis to compare Kratom users and MINI was also done and presented in Table 5-3. There was only one diagnosis which corresponds significantly with Kratom use which is MINI- Item J -Substance Abuse and Dependance category. If was found that 28.6% (n=10) of Kratom users fulfilled the criteria to be diagnosed under Item-J of MINI (X^2=28.716, p <0.01). There were no other significant or strong associations found between Kratom users and psychiatric illness.

Table 5-3- Association Between MINI and Kratom Users

MINI Diagnosis	Kratom user		χ^2	p value
	No (n = 109) n (%)	Yes (n = 35) n (%)		
A. Major Depressive No Yes	 105 (96.3) 4 (3.7)	 35 (100.0) 0	1.321	0.572[a]
B. Suicidality No Yes	 107 (98.2) 2 (1.8)	 35 (100.0) 0	0.651	1.000[a]
C. Manic/Hypomanic No Yes	 107 (98.2) 2 (1.8)	 35 (100.0) 0	0.651	1.000[a]
D. Panic Disorder No Yes	 104 (95.4) 5 (4.6)	 34 (97.1) 1 (2.9)	0.199	1.000[a]
E. Agoraphobia No Yes	 106 (97.2) 3 (2.8)	 35 (100.0) 0	0.984	1.000[a]
F. Social Phobia No Yes	 109 (100.0) 0	 35 (100.0) 0	-	-
G. OCD No Yes	 108 (99.1) 1 (0.9)	 35 (100.0) 0	0.323	1.000[a]
H. PTSD No Yes	 107 (98.2) 2 (1.8)	 35 (100.0) 0	0.651	1.000[a]
I. Alcohol D/A No Yes	 109 (100.0) 0	 35 (100.0) 0	-	-
J. Substance D/A No Yes	 108 (99.1) 1 (0.9)	 25 (71.4) 10 (28.6)	28.716	< 0.01[a]
K. Psychotic Disorder				

No Yes	106 (97.2) 3 (2.8)	34 (97.1) 1 (2.9)	0.001	1.000[a]
L. Aneroxia Nervosa No Yes	 98 (89.9) 11 (10.1)	 32 (91.4) 3 (8.6)	0.070	1.000[a]
M. Bulimia Nervosa No Yes	 109 (100.0) 0	 35 (100.0) 0	-	-
N. GAD No Yes	 108 (99.1) 1 (0.9)	 35 (100.0) 0	0.323	1.000[a]
O. Medical/Organic/Drug No Yes Not sure	 91 (83.5) 16 (14.7) 2 (1.8)	 31 (88.6) 4 (11.4) 0	0.925	1.000[a]
P.Antisocial P. No Yes	 109 (100.0) 0	 33 (94.3) 2 (5.7)	6.316	0.058[a]

a = Fisher's exact test.

- = No statistics are computed due to constant variable.

5.4 ASSOCIATION BETWEEN ASSIST-M AND KRATOM USERS

Table 5-4 shows Mann Whitney U test analysis done to compare Kratom users and ASSIST-M scores for all substance. The mean score for Kratom users based on ASSIST-M was 11.46 (SD= 10.918). Among Kratom users, only two items namely opioid and tobacco were found to be used among Kratom users, and both showed a significant association. Item a (Tobacco Products) showed that Kratom users had a mean score of 16.74(SD- 8.936, r^2 0.326, $p < 0.01$) whereas for Item I (Opioid use) the mean score for ASSIST-M of 0.80 (SD 3.708, r^2 0.044. $p<0.05$). All other items in ASSIST-M were excluded from the summary table given no data.

Table 5-4- Association between ASSIST-M and Kratom users

WHO-ASSIST	Kratom user		r^2	*p* value*
	No (n = 109)	Yes (n = 35)		
	Mean (SD)	Mean (SD)		
a. Tobacco products	3.71 (8.047)	16.74 (8.936)	0.326	< 0.01
i. Opioids	0	0.80 (3.708)	0.044	< 0.05
j. Other (Kratom)	-	11.46 (10.918)	-	-

SD = Standard deviation.
r^2 = Mann-Whitney effect size.
* = Mann-Whitney U test.

5.5 UNIVARIATE ANALYSIS BETWEEN WHO-QoL-BREF AND KRATOM USERS

The scores of WHO-QoL Bref M among Kratom users were analyzed using Mann Whitney U Test and summarized in the table below.

Table 5-5- Univariate Analysis Between WHO-QoL and Kratom Users

WHO-QOL_BREF	Kratom user		Z*	p value	r^2
	No (n = 109) Mean (SD)	Yes (n = 35) Mean (SD)			
Overall quality of life	3.79 (0.747)	3.60 (0.651)	-1.307	0.191	0.012
Overall health	3.69 (0.742)	3.89 (0.677)	-1.477	0.140	0.015
Physical health	**15.65 (2.545)**	**16.64 (2.521)**	**-2.147**	**0.032**	**0.032**
Psychological	15.40 (2.315)	16.00 (2.200)	-1.193	0.233	0.010
Social relationships	15.85 (2.484)	15.89 (2.595)	-0.045	0.964	0.001
Environment	15.53 (2.385)	15.26 (2.088)	-0.804	0.422	0.004

SD = Standard deviation.
r^2 = Mann-Whitney effect size.
* = Mann-Whitney U test

The mean score for overall quality of life, overall health, psychological, social relationship and environmental domain among Kratom users and non-users did not show any significant correlation. However as for the physical health domain, the mean score for non-users was 15. 65 (SD 2.545) as compared to Kratom users 16.64 (SD=2.521) which shows a significant difference with a Z score of -2.147, and p-value 0.032 (<0.05).

5.6 FACTORS ASSOCIATED WITH KRATOM USE – UNIVARIATE ANALYSIS

Univariate analysis was performed to study Kratom use and its associating factors as summarized in Table 5-6.

Table 5-6: Univariate Analysis of Factors Associated With Kratom Use

Factors	Kratom user n (%)		χ^2	Odds Ratio	P value
	No	Yes			
Age (Mean/SD)	**50.4 (16.94)**	**38.5 (14.99)**	**11.646[a]**	**0.957**	**< 0.01**
Gender					
Male	**49 (45.0)**	**33 (94.3)**	**26.297[b]**	**0.049**	**< 0.01**
Female	**60 (55.0)**	**2 (5.7)**			
Marital status					
No	**18 (16.5)**	**17 (48.6)**	**14.799[b]**	**0.209**	**< 0.01**
Yes	**91 (83.5)**	**18 (51.4)**			
Education					
< Secondary	**47 (43.1)**	**6 (17.1)**	**7.686[b]**	**3.664**	**< 0.01**
≥ Secondary	**62 (56.9)**	**29 (82.9)**			
Employment					
unemployed	**38 (34.9)**	**3 (8.6)**	**8.992[b]**	**5.709**	**< 0.01**
employed	**71 (65.1)**	**32 (91.4)**			
Monthly income In (RM)	1077.5 (1121.72)	1128.9 (705.38)	0.066[a]	1.000	0.798
Family members (Median/IQR)	4 (2)	4 (3)	0.624[a]	1.062	0.430
General illness					
No	**65 (59.6)**	**29 (82.9)**	**6.304[b]**	**0.306**	**< 0.05**
Yes	**44 (40.4)**	**6 (17.1)**			
Psychiatry illness					
No	109 (100.0)	34 (97.1)	3.136	0.238[#]	0.243[c]
Yes	0	1 (2.9)			
History of using drug					
No	**108 (99.1)**	**17 (48.6)**	**59.016**	**114.353**	**< 0.01[c]**
Yes	**1 (0.9)**	**18 (51.4)**			
Family using drug					
No	**106 (97.2)**	**27 (77.1)**	**15.178**	**10.469**	**< 0.01[c]**
Yes	**3 (2.8)**	**8 (22.9)**			
Smoker					
No	**81 (74.3)**	**2 (5.7)**	**51.058[b]**	**47.732**	**< 0.01**

Yes	**28 (25.7)**	**33 (94.3)**			
Substance use disorder					
No	**108 (99.1)**	**25 (71.4)**	**28.716**	**43.200**	**< 0.01[c]**
Yes	**1 (0.9)**	**10 (28.6)**			
Tobacco					
Low	**87 (79.8)**	**5 (14.3)**	**Reference**	**-**	**-**
Moderate	**18 (16.5)**	**26 (74.3)**	**34.026[a]**	**25.133**	**< 0.01**
High	**4 (3.7)**	**4 (11.4)**	**11.468[a]**	**17.400**	**< 0.01**
Opioid					
Low / none	109 (100.0)	33 (94.3)	6.316	0.232[#]	0.058[c]
Moderate	0	2 (5.7)			

a = Wald's chi square.
b = Pearson's chi square.
c = Fischer's exact test.

Based on the analysis, a number of factors were determined to be associated with Kratom use cohort as compared to non-users.

Comparison between age and Kratom use among respondents were analyzed. The mean age of Kratom users (38.5, SD=14.99) were significantly younger as compared to non-user (50.4 SD=16.94), with a chi-square (χ^2) value of 11.646, odds ratio (OR) of 0.957 (P<0.001) which shows a significant correlation.

Gender comparison between Kratom users and non-users showed statistically significant correlation in which the majority of Kratom users were male respondents (χ^2=26.297, OR= 0.049, P<0.001)

Marital status among respondents was significantly associated with Kratom use (χ^2= 14.799, OR= 0.209, p<0.01). Non-Kratom users were mostly married (n=91, 83.5%) whereas among Kratom users, only 51.4% (n=18) were married and 48.6% (n=17) were single.

Analyzing the education level among users and non-users of Kratom showed that there is a significant association between users who underwent primary level of education as

compared to secondary level education (χ^2= 7.686, OR= 3.664, p<0.01). Twenty-nine (82,9%) of Kratom users studied up to secondary level, whereas 17% (n=6) completed primary level of education. In contrast, 59.9% (n=62) of non-users underwent secondary level education, and 43.1% (n=47) completed primary level education

There were no statistically significant associations between the average monthly income and amount of family members in the household for both Kratom and Non-Kratom users. Employment status was another factor analyzed, and it was found that employment status was significantly associated with Kratom usage (X^2= 8.992, OR= 5.709, p<0.01). It was found that 91.4% (n=32) of Kratom users were employed and only 8.6% (n=3) were unemployed, whereas for non-users 65.1% (n=71) were employed and 34.9%(n=38) were unemployed.

Analysis of the presence of an underlying general medical illness showed that there was a statistically significant association between users and non-users of Kratom (X^2=6.304, OR 0.306, p<0.05). The majority of Kratom users (82.9%) did not experience an underlying medical illness, while only 59.6% (n=65) non-users had an underlying condition.

History of drug use was also found to be highly associated with Kratom usage (X^2= 59.016, OR= 114.353, p<0.01). It was found that among Kratom users, 48.6% (n=17) has had a history of illicit substance use, whereas only 0.9%(n=1) of non-users had a similar history.

A significant association between family members who are abusing substances was also found among Kratom users (X^2= 15.178, OR= 10.469, p<0.01) as compared to non-users. Among non-users, a total of 106 respondents (97.2%) did not have any family members who were abusing illicit substance, and only 3 (2.8%) admitted to having a family member abusing illicit substance during data collection. In comparison

to Kratom users, 77.1% (n=27) did not have any family members abusing illicit substance, while 8 of them (22.9%) admitted to having other family members who were abusing illicit substances.

Kratom users showed significant association with MINI Item-J diagnosis (X^2=28.716, OR 43.200, p<0.01). As mentioned before, 28.6% (n=10) of Kratom users were found to fulfill criteria to be diagnosed as substance dependence and abuse according to MINI, whereas only 1 participant (0.9%) among non Kratom users fulfilled the same criteria.

Analyzing the data from ASSIST-M scores (item tobacco and opioid) and comparing them to Kratom users, it was shown that both moderate and high use of tobacco use were significantly associated with Kratom use (X^2= 34.026, OR= 25.133, p= <0.01 and X^2=11.468, OR=17.400, p<0.01 respectively).It is important to note that variable such as the age of stopped schooling, the age of starting to smoke, and the number of cigarettes consumed per day were not included in the univariate analysis due to missing values.

5.7 COLLINEARITY TESTING

A number of potential highly correlated variables were to be included in the multivariate analysis. Based on available data, it was determined that the smoking variable was highly correlated ($r > \pm 0.7$) with gender (negatively) and tobacco (positively), hence this variable was removed in multivariate analysis to avoid potential multicollinearity issue (Table 5-7). The multivariate analysis did not lose any information as tobacco and smoking are of the same variables.

Table 5-7- Potential highly correlated variables (Testing of collinearity)

	Smoking	Gender
Gender	-0.745**	
Tobacco	0.866**	-0.645**

5.8 FACTORS ASSOCIATED WITH KRATOM USE-MULTIVARIATE ANALYSIS

Among Kratom user's population, univariate analysis showed that significant correlates were age ($p<0.01$), gender ($p<0.01$), marital status ($p<0.01$), education level ($p<0.01$), and employment status ($p<0.01$). General illness ($p<0.05$), history of drug use and family members using substances ($p<0.01$), drug dependency ($p<0.01$) as well as tobacco use ($p<0.01$) were also noted to be significantly associated with Kratom use.

Multivariate binary logistic regression analysis on these variables was performed to further assess the significant correlation among Kratom users. The results of the multivariate analysis showed that history of drug use was significantly associated with Kratom user with an adjusted odds ratio (AOR) of 58.204, 95% CI= 2.847-1190.077 and p-value <0.01. The use of tobacco was also found to be significantly correlated

with Kratom users whereby the adjusted OR was 5.717, 95% CI= 1.106- 29.548 and P value <0.01). All the other factors were found not to be statistically significant in the multivariate analysis as shown Table 5-8.

Table 5-8-Multivariate Analysis of Factors Associated with Kratom Use

Factors	Odd ratio (OR) [a]	Adjusted odd ratio (AOR) [b]	95 % confidence interval (CI)	p value
Age	0.957	1.006	0.954 – 1.060	0.834
Gender Male*	0.049	0.382	0.044 – 3.330	0.384
Marital status Non-married*	0.209	0.477	0.116 – 1.968	0.306
Education level < Secondary*	3.664	1.565	0.246 – 9.968	0.635
Employment Non-employed*	5.709	1.590	0.237 – 10.693	0.633
General illness No illness*	0.306	0.318	0.058 – 1.745	0.187
History of using drug No*	**114.353**	**58.204**	**2.847 – 1190.077**	**< 0.01**
Family using drug No*	10.469	1.881	0.104 – 33.865	0.668
Drug dependency No*	43.200	2.786	0.146 – 53.128	0.496
Tobacco Low*	**25.133 (M) 17.400 (H)**	**5.717 6.233**	**1.106 – 29.548 0.546 – 71.107**	**< 0.05 0.141**

* Reference group.
a: based on univariate analysis
b: based on multivariate binary logistic regression analysis
M = Moderate ASSIST Score 4-26
H = High ASSIST Score 27+

6 DISCUSSION

For centuries Kratom has been indigenously used in Thailand and Malaysia, (Chan et al., 2007; P. Tanguay, 2011; Vicknasingam et al., 2010). Its predominant use in the northern states of Malaysia as well as in Southern Thailand (Singh et al., 2016; P. Tanguay, 2011) continues to date. Research in Malaysia about the prevalence of Kratom use and impact on its users is scarce (Ahmad & Aziz, 2012; Singh et al., 2014). Additionally, it is uncommon to locate in the literature on using Kratom and its associating factors. Thus, there is the need for more continued research of its use and impact on users. Studies concerning Kratom and its association with mental health issues is also lacking.

The current research is the earliest prevalence study in a Malaysian setting, particularly among the rural settlers in Perlis. The study attempted to discover vital queries, focusing on the rural settlers in a FELDA settlement located in Perlis. The variables discussed in this study are about Kratom users which looks into their past and current use of the named substance. There are currently no other screening tools specific for Kratom use.

A total of 144 participants took part in the study. The study found close to a quarter (n=35) out of all the participants (n=144) reported the use of Kratom in their lifetime. Nearly all of the users are working (91.4%, n=32) of Kratom users, and the Kratom users were of younger age group (38.5 SD=14.99), and predominantly males (94%, n=33). Further analysis regarding marital status revealed the non-Kratom users were mostly married (n=91, 83.5%) whereas, among Kratom users, only 51.4% (n=18) are married while 48.6% (n=17) were single.

The initial analysis showed a significant association in the level of education between user and non-users. More Kratom users proceeded to the secondary school

level. In the non- users group, only half went to up to secondary school level, while the rest reached primary school level.

Employment status was another factor analyzed. The initial analysis found the employment status and Kratom usage, is significantly related. Expectedly, among Kratom users and non-users, the overall quality of life, overall health, psychological, social relationship and environmental domain did not show any significant correlation. Amid the users, the majority (65.3%, n=94) were healthy, 34.7% (n=50) experienced general medical illness, and only one (0.7%) reported having an underlying psychiatric illness.

Other than the Substance Abuse and Dependence category, the study revealed there was no other significant association found between Kratom users and psychiatric illness. In the screening for substance use and related problems, the analysis showed the use of opioids and tobacco and using Kratom, is notably correlated. About substance use, close to 50% (n=17) admitted to having experience using illicit substances, with about 20% also had at least 1 of their family members who are currently abusing substances. Regarding current substance use, close to three quarters (94.3%, n=33) of users are smokers. A quarter of the non-users were smoking as well. They smoke an average of 20 sticks per day (IQR=10), and they started smoking at a mean age of 15.4 (SD=3.35).

The further analysis of all the results showed the current use of Kratom and a history of drug usage, is significant. All the studies done locally were among present and active Kratom users.

6.1 PREVALENCE OF KRATOM USE

The study found a total of 24.3% (n=35) out of all participants (n=144) reported the use of Kratom in their lifetime. The finding is compared to available prevalence study of Kratom users. Many studies about the prevalence of Kratom use has come from Thailand where its usage is high. The (Administrative Committee of Substance Abuse Academic Network, 2012) reported a prevalence of 8.6% usage in Southern Thailand. The number varies however according to the location of the study. (Assanangkornchai et al., 2008) conducting a National Household Survey on Substance and Alcohol Use in Thailand in 2001 and the second in 2003, found Kratom, cannabis, yaba, and inhalants, were the most popular substances for both the past 12 months and the past 30 days before the survey. The study revealed users of Kratom had increased. (Talek, Cottler, & Assanangkornchai, 2017) looking at substance use in three southern Thailand provinces and among 13,545, subjects found Kratom had the highest number of current users with 85.2% of all users surveyed.

In another study looking into the prevalence of overall NPS use in Thailand, found that the lifetime use of NPS was 49.7% and current use was 14.9% (Wonguppa & Kanato, 2017). The survey studied the Thai population aged 15-64 years and found 15% of the 48,541,501 individuals surveyed reported using Kratom leaves, and Kratom cocktail. Comparable to (Assanangkornchai et al., 2008), the study concluded the use of MS leaves had increased more than twice Kratom cocktail increased above ten times over five years. Researchers voiced the presence of new methods of usage boosts its traditional usage while making it more harmful to the consumers (Assanangkornchai et al., 2008; Assanangkornchai, Pattanasattayawong, et al., 2007; Chongrattanakon, Bang-On, & Ah Hong, 2017; Wonguppa & Kanato, 2017). Interestingly (Assanangkornchai, Pattanasattayawong, et al., 2007) cautioned Kratom is the most popular illicit substance

use and is increasing among the youths. It is not unexpected knowing to the abuse potential of Kratom (Henningfield et al., 2017; Wonguppa & Kanato, 2017; Yusoff et al., 2016).

What are the concerns regarding the high prevalence and continued pattern of Kratom use and its impact on mental health of users? Reports have suggested the evolution of Kratom from recreational element to misuse and abuse. The Kratom juice cocktail has become popular among youths and in the Southernmost provinces of Thailand (Chongrattanakon et al., 2017; Hassan et al., 2013; Tungtananuwat & Lawanprasert, 2010). The Kratom juice consumption increases the high-risk situations. Likewise, (Tungtananuwat & Lawanprasert, 2010) reported a death in a 21-years-old youth after consumption of the cocktail with the report suggesting the cause of death might be due to the multiple drugs in the cocktail including Kratom. The intoxication of the many additives in the cocktail affected the CNS and respiratory systems. Scientists have raised alerts of deaths related to, but not openly attributable to Kratom use (Domingo et al., 2017; Hassan et al., 2013; Holler, 2011).

In recent years, Kratom use in the West has increased (Cinosi et al., 2015; Grundmann, 2017; Prozialeck et al., 2012). To date, the prevalence of kratom use is not well established in the USA. Isolated reports have emerged including from several poison centers handling medical emergencies of Kratom usage.

A recently published study investigating the prevalence of Kratom use found that 20.8% respondents admitted to lifetime use of Kratom, and 10.2% had used Kratom in the past 12 months (Smith & Lawson, 2017). There is a scarcity in literatures pertaining to FELDA settlers and Kratom use. Studies exploring social problems in FELDA settlements have noted that substance use is one of the major social problems faced by FELDA settlers in Malaysia (Hisham, Kamaruddin, & Nordin, 2010). It is postulated

that due to the location and availability of Kratom in northern region plays and important role in explaining the high prevalence of its use. The finding of the study shows that the prevalence of Kratom use in Malaysia is comparable if not more than other countries, particularly at FELDA Chuping, Perlis. Similarly, the beneficial effects have been overshadowed by concerns of abuse and dependency (Anwar et al., 2016; Smith & Lawson, 2017; Warner et al., 2016).

6.2 KRATOM USE AND HISTORY OF SUBSTANCE USE & SMOKING

Two significant findings of the present study were:

1. The present Kratom users has history of using illicit substances. Users who have had history of substance use are 58 times more likely to be a kratom user (AOR 58.204, CI 2.847-1190.077, $p<0.01$).
2. Kratom users are likely to use tobacco. The analysis found moderate smokers were five times likely to presently take kratom; while heavy smokers were six times more likely to take kratom.

Many studies state Kratom is used as an opioid substitute as well as its use in association with other illicit substances use (Boyer et al., 2007; Cinosi et al., 2015; Henningfield et al., 2017; M.T. Swogger & Walsh, 2017). Mitragyna speciosa (MS) is known for its psychoactive effects (Smith & Lawson, 2017) and is not surprisingly commonly used for management of opioid withdrawal (Boyer et al., 2008; Boyer et al., 2007; Nelson et al., 2014). Users recognize Kratom is an as alternative therapy for their opioid withdrawal in order to replace or decrease the use of another substance that is deemed undesirable (Chan et al., 2007; Nelson et al., 2014). However, the medical field is cautious about its long-term administration in these individuals.

Centuries before in Malaya, in the literature stated people use Kratom as an opium substitute during the during the times of opium scarcity (Chan et al., 2007;

Hassan et al., 2013; Jansen & Prast, 1988). Based on the univariate analysis of the present study, a history of substance use is significantly associated in the Kratom users surveyed. The investigation found among the Kratom users, a staggering 51.4% of the responders has had a history of substance use in the past.

(Cinosi et al., 2015) categorized consumers into two main groups:

1. Users who solely use kratom to improve their physical tolerance due to their laborious work, and
2. The poly-drug users. The second group is individuals who attempt to cope with their drug withdrawal symptoms or to reduce the intake of other opiates such as heroin. Kratom then presents a cheaper alternative.

Thus, it is not surprising the study found a substantial percentage of the present users have a history of substance use. The finding is in par with various studies done showing significant links of Kratom users to past substance use and attempted opioid replacement or a substitute for other illicit substances, past and present substance use (Singh et al., 2016; Talek et al., 2017; Tungtananuwat & Lawanprasert, 2010). (Vicknasingam et al., 2010) reported in his study that 53% of the subjects reported ever using other opioids in the past. In the current kratom users and ever used heroin in the past, (Vicknasingam et al., 2010) uncovered almost all relied on kratom to reduce their addiction to other drugs, and in 15% admitted kratom helped ameliorate the effects their opiate addiction withdrawal. In the same study, three-quarters of the respondents reported using other substances concomitantly with the kratom. The current study and using the MINI, discovered among the kratom users, 28.6% (n=10) of Kratom users fulfilled the criteria having a substance dependence and abuse disorder, while only 1 participant (0.9%) among non Kratom users fulfilled the same criteria. The study did not however, confirm the state via a urine test. Thus, the study supports (Cinosi et al., 2015)'s hypothesis of poly-drug users among the regular Kratom users.

In (Ahmad & Aziz, 2012)'s study among 530 respondents, the majority of the respondents (96%) did not report concomitant using other substances of abuse, while only two respondents (4.2%) declared using MS together with marijuana, amphetamine, heroin or cough syrup.

Many communities recognize 'herbal' or 'botanical' remedies, and they are acceptable to its usage (Newman & Cragg, 2012; Prozialeck et al., 2012). Thus, many individuals see Kratom represents an acceptable and cheaper means of opioid replacement (Chan et al., 2007; Vicknasingam et al., 2010). Moreover, its use is less associated with addiction properties with modest abstinence symptoms (Ahmad & Aziz, 2012; Boyer et al., 2008; Hassan et al., 2013).

Up to present times, kratom is much cheaper and widely available in the northern states of Malaysia (Ahmad & Aziz, 2012; Hassan et al., 2013). In the area surveyed, Kratom juice is readily available in many small coffee shops along the roadside, as well as in individual houses which produces and sell the juice. Despite the more accessible and cheaper substitute, the literature shows evidence of Mitragyna Speciosa is addictive, and there is a likely potential individual may misuse the produce (Brown et al., 2017; Henningfield et al., 2017; Warner et al., 2016; Yusoff et al., 2016).

Interestingly, in (Singh et al., 2015)'s study group, none of the kratom users reported problems directly related to their kratom use, and none felt the need to treat their kratom use or dependency problems. The belief is despite almost 83% respondents were aware of kratom's capacity to be addictive and can cause dependency. In 15% of the subjects stating they use Kratom as a substitute for their illicit drugs habits, such as heroin and cannabis. (Singh et al., 2015)'s study did not report a history of substance use in the 293 regular kratom responders. However, the respondents reported experiencing a few impairments in their social functioning and recognized they were

unable to stop using kratom for prolonged periods. Moreover, all the respondents believed that kratom could curatively allay their medical symptoms (Singh et al., 2015). However, (Singh et al., 2014) assessing for Kratom dependence, withdrawal symptoms and craving in the 293 regular Kratom users, found 45% showed a moderate Kratom dependence.

Similarly, in Thailand, the continued use and potential abuse of Kratom use has raised concerns. (Suwanlert, 1975), alerted people about the abuse with Kratom use, and warn individuals can become addicted. While users focused on the perceived advantages of Kratom use in the increased work endurance and pain reduction (M.T. Swogger et al., 2015; P. Tanguay, 2011), using higher and regular doses of Kratom causes difficulties (Chan et al., 2007; Nelson et al., 2014; Suwanlert, 1975). Kratom withdrawal is indistinguishable from opioid withdrawal and is much more tolerable (Ahmad & Aziz, 2012; K. M. Babu et al., 2008; Boyer et al., 2008; Hassan et al., 2013). Consequently, it explains the increasing and continued use of Kratom for the self-management of withdrawal from and dependency on opioid drugs. (Suwanlert, 1975) reported among individuals using Kratom to wean off heroin addiction experience withdrawal symptoms of Kratom such as hostility, aggression, and the inability to work with long-term consumption.

The review highlights not only are Kratom use related to history of drug use, there is a risk of using other substances concomitantly with kratom, i.e. the presence of poly-substance users among the regular Kratom users.

In a National Household Survey over three years, (Assanangkornchai et al., 2008) found Kratom is very popular among substance users. (Assanangkornchai et al., 2008) found when compared with the other substances while other illicit substances such as yaba, heroin, and cannabis, has reduced dramatically, the rate of Kratom use has

not decreased. (Assanangkornchai et al., 2008) concluded Kratom recorded the highest substance use.

Another factor which has received headlines is Kratom, consumed in combination with alcohol or other drugs. The combination with alcohol or other drugs use may lead to severe and potentially deadly adverse effects (Anwar et al., 2016; Tungtananuwat & Lawanprasert, 2010). A study by (Chongrattanakon et al., 2017) showed among 458 youths in Surat Thani Province, youths who consume alcohol were more likely to use Kratom juice.

(Smith & Lawson, 2017) investigated the prevalence and motivations to use kratom in a sample of individuals receiving SUD treatment. The study found the Kratom-users were younger and reported a more extensive substance use history. They have experimented using a variety of substances, preferring heroin and amphetamines. The majority of users stated Kratom as a means of reducing or abstaining from the non-prescription opioids (NPO) and/or heroin, with more than half recounted using kratom as a substitute for the NPO and heroin. Almost all of the users were as well smokers using both cigarette and e-cigarette. (Smith & Lawson, 2017) determined that individuals in the U.S. were motivated to use kratom for an assortment of purposes, some of which are similar to those observed in the Asian-based studies. Among factors for continued Kratom use is to address their drug dependency, an aid for their chronic pain, and for reducing anxiety, as well as to improve their well-being. (Smith & Lawson, 2017) highlighted individuals with higher number of substances used, were more likely to endorse using kratom more often.

The apparent fact of a strong association between Kratom use and smoking and tobacco use has thus far been under-reported, thus under-analyzed. In the present study, the demographic data shows 94.3% (n=33) of the Kratom users are smokers compared

to 25.7% (n=28) of non-users. Comparing the age of onset of smoking the Kratom users started smoking at an earlier age of 15.4 (SD=3.35) compared to non-users. Interestingly, the number of cigarettes per day showed among the Kratom users was twice more (20, IQR =10) to non-users (10, IQR=15). The number of cigarette used per day is also almost double compared to the mean number of cigarettes smoked per day recorded in other studies done in Malaysia (Institute of Public Health & Ministry of Health Malaysia, 2006; Lim et al., 2013).

A further analysis using the univariate and multiple logistic regression models continues to support a robust association between Kratom users and smoking. In the univariate analysis, a significant association of Kratom use with moderate and high tobacco use showed a significant association ($p<0.01$). The multivariate analysis also showed a similar pattern showing low, moderate and high tobacco use was five times likely to be a Kratom user (AOR=5.717, 95%CI=1.106-29.548, $p <0.05$).

With regards to the finding of this study, a possible perspective is that Kratom users tend to combine the effects of nicotine, on the endogenous opioid system, as well as the exogenous opioids obtained from Kratom to reduce the unwanted withdrawal effects of opiates (Boyer et al., 2008). Studying exogenous opioids such as heroin and Kratom, one will likely encounter the term endogenous opioid. Endogenous opioids consist of mainly three opioid peptide systems which act as precursors for the production of *beta*-endorphin, the met- and Leu-enkephalins, and the dynorphins (Waldhoer, Bartlett, & Whistler, 2004). Animal studies have shown that nicotine protected tested animals against opioid withdrawals by inducing the release of endogenous opioids (Davenport, Houdi, & Van Loon, 1990). Human and animal research has shown that nicotine and tobacco smoking modulates the endogenous opioid system (Xue & Domino, 2008). Further studies are needed to understand the complexity of its interaction. Studies have found that nicotine helps to reduce opioid withdrawal

symptoms such as restlessness, irritability, and depression, and attenuate the effects of methadone, which may explain the high prevalence of smokers among methadone users (Elkader, Brands, Selby, & Sproule, 2018).

There is a high and documented occurrence of tobacco use in an individual with substance use disorders (SUDs) (Mannelli, Wu, Peindl, & Gorelick, 2013; McClure, Baker, & Gray, 2014; McClure et al., 2015; Pajusco et al., 2012). The studies on the prevalence of smoking among opioid-dependent individuals demonstrate rates higher than in the other addictions (Haas et al., 2008; Mannelli et al., 2013; M. A. Sullivan & Covey, 2002). The (Center for Disease Control, 2005) reported rates of concurrent smoking and opioid use is higher even more than the general U.S. population, with (M. A. Sullivan & Covey, 2002) stating the risk of any opioid user is four times likely to use tobacco. Moreover, high smoking rates are associated with higher levels of illicit drug use and lower rates of smoking cessation (Mannelli et al., 2013; Shoptaw et al., 2002). Additionally, tobacco users are less likely to successfully withdraw from using opioids (M. A. Sullivan & Covey, 2002; Ziedonis et al., 2009).

The literature analysis would possibly support the findings of the study. Polysubstance use among kratom-users is not uncommon (Smith & Lawson, 2017; Vicknasingam et al., 2010). The present study discovered a high number of Kratom users who are as well heavy smokers, and the possible association with previous opioid use and current abstinence. It would be interesting to study the synergistic effect of Kratom use and nicotine with the opioid receptors, and how it helps to ameliorate opioid withdrawals. However, the researcher understands that it may be impossible to find the actual causal relationship between tobacco use and Kratom use due to the design of this study. It is interesting to state that there is a lack of data pertaining to the interaction between Kratom and nicotine, which opens up a new gap in knowledge for further studies. Looking into the data available from the Malaysian National Health and

Morbidity Survey, Kratom use has yet to be included in the survey, hence the data was never captured and could not be analyzed for future use.

Thus, the highlights of the present study and past reports are despite there are a variety of beneficial effects of kratom, the study demonstrates:

1. Kratom has addictive properties,
2. Usage is common among individuals with past and possible concurrent use of illicit substance,
3. Its usage has evolved, and remains worrying,
4. Among individuals using Kratom, there is a significant association with tobacco use which adds to the concerns among the medical professionals.

6.3 KRATOM USE AND ITS ASSOCIATIONS

The study tried to look for other significant factors associated with its usage. However, these factors were only significant via univariate analysis but not multivariate analysis. The study explored factors relating to gender and age group as reported in the additional studies done particularly in Thailand.

The analysis of the study population revealed that the mean age for Kratom users was lower than non-users. The mean age for Kratom users was 38.5 years (SD 14.99) whereas among the non-users they were older age, with a mean age of 50.4 years (SD=16.94). The finding was almost similar to the other research done locally. (Vicknasingam et al., 2010), in the study, among 150 active Kratom users, in Kedah and Penang, found the users had a mean age of 39 years. The majority (65%) of the responders in (Singh et al., 2015)'s group were younger between 18 and 30 years old, with an average mean age of 28 years. The age of the respondents were not stated in (Ahmad & Aziz, 2012)'s study. In the other studies, the respondents and using Kratom the male were of middle-aged (Assanangkornchai et al., 2008; Talek et al., 2017; Pascal

Tanguay, 2011).

Correspondingly, (Vicknasingam et al., 2010) as well found a higher preponderance of males and using Kratom in their study. The other studies also showed that Kratom use was more predominant among male and working adults (Ahmad & Aziz, 2012; Suwanlert, 1975; P. Tanguay, 2011). In (Vicknasingam et al., 2010)'s study, amongst 150 active Kratom users, only one was female. Similarly, (Ahmad & Aziz, 2012) among 530 respondents were all males, except for two females. In a more recent survey, (Singh et al., 2015) among 293 regular kratom users and from 15 different communities, all the respondents were males. (Ahmad & Aziz, 2012) stated the expected low number of female respondents was because among females MS is not commonly used. Culturally, using Kratom is something males-do (Ahmad & Aziz, 2012; Suwanlert, 1975; P. Tanguay, 2011). Thus, the community disapproved its use in females (Ahmad & Aziz, 2012; Suwanlert, 1975; P. Tanguay, 2011). In fact, (Vicknasingam et al., 2010) discovered in the survey, the females were reluctant for the researchers to interview them. About substance use, more men are more likely to use illicit substances as compared to women (S. A. SAMHSA, Mental Health Services Administration, 2010). In the analysis of the study, (Vicknasingam et al., 2010) hypothesized married men had higher probabilities of being long-term users.

A recently published study by (Wonguppa & Kanato, 2017) concurred with the findings in this cross-sectional study. According to Wonguppa, the majority of NPS users in Thailand were males ($p<0.01$), aged between 25 to 44-years-old ($p <0.01$), and employed ($p<0.01$).

The same study however noted that the majority of the NPS users completed only primary school studies, while is similar to (Vicknasingam et al., 2010)'s findings. (Vicknasingam et al., 2010) reported in a quarter of the kratom-users, had lower

secondary education or lesser number of years schooling. This was in contrasts to the findings in the current study. The present study found the majority of Kratom users completed secondary education ($p<0.01$). In another local study by (Singh et al., 2015), found that among the 293 respondents, 66% had completed upper-secondary schooling, 95% were employed of which close to 90% were manual laborers.

It is postulated that in the Malaysian setting, the second generation of FELDA settlers who are currently in the mid-30s or early 40s and has had more prospects to better schooling. The second generation of FELDA settlers had a different pathway compared to their predecessors. The change is due to the nature of FELDA scheme and the integration of free education. Through the years, the government has given scholarships for the FELDA settlers and their families and structured their living into the core of its establishment. This could explain why in the study, 43.1% (n=47) of non-users only completed primary school education and the mean age for the group studied was significantly higher at 50.4 years old (SD=16.94) at the time of survey. The present study found that 82.9%(n=29) of Kratom users were employed and only 8.6% (n=3) were unemployed. Though the employment status was significant in the univariate analysis, however in the multivariate logistic regression analysis only history of drug use and current tobacco use was significant.

The presence of a general medical illness was also found to be associated with Kratom use. It was found in this study that non-users reported a higher number of an underlying general medical illness ($p<0.01$). This could be again explained by the higher mean age among non-Kratom user respondents as compared to Kratom users. Another plausible explanation would be that Kratom users are healthier in general. The causal effect of this could not be ascertained in this study due to the nature of this study being cross sectional. This question could further be explored in future studies. It is also

important to take into consideration the association between Kratom users and physical health which will be discussed later.

6.4 KRATOM AND QUALITY OF LIFE

Based on this study, Kratom users and non-users did not show a marked difference regarding their quality of life. The Self-reported WHOQOL questionnaire consists of 4 major domains namely physical health, psychological, social relationship and environment. In the study, the research added two domains were namely overall quality of life and the overall health comparing both the groups. The univariate analysis revealed a significant difference between both groups in the physical health domain. The Kratom users reported a higher mean score of 16.64 (SD=2.512, r^2 0.032, $p < 0.05$). With regards to other scores, the study was unable to find a statistically significant association between the two groups in other domains.

The result appears on par with a social study done in a Malaysian setting by (Singh et al., 2015) which showed that regular Kratom users did not show any significant impairment in their social functioning. (Singh et al., 2015) found the respondents experienced few impairments in their social functioning, despite being dependent on kratom for prolonged periods. Comparing Kratom and any other substances, Heroin, for example has shown to reduce the quality of life among users and their relatives in all domains of WHOQOL-BREF (Moreira et al., 2013). The fact that Kratom users remain employed, actively participating in the community and having equal quality of life as to non-users, maybe the impetus for continued Kratom use particularly among regular users. The finding is consistent with the literature affirming MS helps improves mood and relieves pain (Prozialeck et al., 2012; M.T. Swogger & Walsh, 2017; P. Tanguay, 2011). Thus, among its regulars, Kratom is known for its energizing and pain-relieving effects (Singh et al., 2015; Yusoff et al., 2016). Unknown

to many users, the research has shown evidence has of cognitive impairments related to its chronic use (Yusoff et al., 2016). One wonders why despite the majority of the participants (71.5%, n=103) are employed, their mean income remains around RM1090 per month.

Looking at the impact on physical health, it is understandable why Kratom users generally 'feel' better and hence self-reported better physical health. Kratom in small or moderate doses can produce mild stimulant effects (Adkins et al., 2011; Macdonald & Nacapew, 2013; Thongpradichote et al., 1998; Ulbricht et al., 2013). Users rely on its stimulant effects to help reduce fatigue, in particular for those individuals carrying out manual labor (Warner et al., 2016) such as the respondents in the study. Thus, among the rural folks and doing laborious work, as in the group surveyed, the produce is well-liked. Kratom helps these workers to reduce their fatigue, promote work desire, and enhance their physical tolerance to the debilitating work (Hassan et al., 2013; Singh et al., 2015; Singh et al., 2016).

However, the researcher recommends careful consideration of the results as the initial demographic data showed that there are discrepancies in the general demography of Kratom users as compared to non-users. Kratom users in the study were on average younger, employed, as well as healthier (without any underlying medical illness). Besides, the team did not do any other medical examination to substantiate the physical health of the respondents. Hence the report of better physical health via WHOQOL could be expected and should be interpreted carefully. The situation suggests the need for comprehensive education, prevention and control strategy for all kinds of substances and further detailed studies to monitor the situation.

7 CONCLUSION

The current research has found Kratom use is prevalent among settlers in Felda Chuping, Perlis. Despite the current users stating they are physically and socially well, the research team remains concern. The risk of misuse and abuse is real.

Among the responders, 13.2% (n=19) had experience using illicit substance in the past while 28.6% (n=10) of users fulfilled the criteria of substance dependence and abuse. Almost all of the users are smokers (94.3%, n=33). The correlation with the polysubstance use and Kratom usage poses an imminent hazard to its users and may place them in potentially dangerous consequences. The high prevalence and significant association substance use and tobacco as seen in the study, adds to the medical professionals' concerns. Tobacco use and dependence are highest among individuals with substance-use disorders (C. Kelly & McCreadie, 2000; C. Kelly & McCreadie, 1999; Robson & Gray, 2007; Roick et al., 2007).

The impact of smoking and morbidity and mortality related to smoking is staggering (Surgeon General, 2014). Poor treatment outcomes, more severe illness with additional lifetime medical conditions thus frequent service utilization is linked with tobacco use and comorbid mental health disorders (Anda et al., 1990; Kessler et al., 2011; Mendelsohn, Kirby, & Castle, 2015). Ironically, the users may not show or have any impairment related to Kratom-use they may have the impairment related to tobacco use. Smoking poses substantial health burden and costs (Surgeon General, 2014; U. S. D. o. H. a. H. S. Surgeon General, 2012; Williams & Ziedonis, 2004; World Health Organization, 2009), with tobacco being a leading cause of preventable and premature death (Breslau, 1995; U. S. D. o. H. a. H. S. Surgeon General, 2012).

8 LIMITATIONS AND STRENGTHS

8.1 LIMITATIONS

There were a few limitations in the study conducted:

1. This study was only done in one settlement in Perlis. Hence it may limit the generalizability of the findings.
2. The sampling was done from house to house. Only participants who consented were recruited into this study. Hence the study might fail to capture respondents who are users of Kratom but refused to provide consent for the study or persons who were not around during the time of the survey.
3. This study was only able to determine the presence of associations between two variables. The causal relationship was not able to be determined between Kratom users and its associating factors due to the nature of the study is cross-sectional.
4. Response bias among participants may occur due to the sensitive topic of study. The demeanor of the researcher and how the questions were being asked, types of questions, and various other factors may influence the participants to answer in a certain way which may affect the results of the study.
5. Kratom users in this study were derived from ASSIST-M questions, without confirmatory testing using blood investigations or urine sampling method.
6. Sample size calculation in this study was only for the prevalence but was not for each association.

8.2 STRENGTHS

Despite the many limitations in this study, there were a few strengths worth mentioning

1. This is the first of study of its kind attempting to identify the prevalence of Kratom use among rural settlers in northern Malaysia.

2. The interview was performed by trained researchers, under the direct supervision of a consultant psychiatrist.

3. As part of a community outreach programme, the researcher was able to identify participants who required psychiatric needs and referred them to the appropriate centers. Additionally, participants who scored moderate and above in ASSIST –M were also given brief intervention according to the ASSIST guideline.

8.3 RECOMMENDATIONS

Given the limitation of the study, there are several recommendations for future studies

1. The researcher recommends that Kratom use be included in the national health and morbidity survey to enable the government to collect more data and monitor the on-going problem of Kratom use mainly in the northern region.

2. Further studies should include more centers and not only limited to the northern regions of Malaysia, as Kratom use may also be present elsewhere.

3. Currently, there are no tools available that can be used to gauge the dependence level of Kratom users in Bahasa Malaysia. Hence there is a need for the translation of Kratom Dependence Scale or the development of new screening tools for Kratom users.

4. Further studies regarding the use of Kratom and its potential use as an opioid replacement should be taken into consideration.

5. The relationship between Kratom use and tobacco use may be further explored, to better understands the effect of Kratom and nicotine.

6. Further studies should consider increasing the sample size and take into consideration each of the associations discussed.

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