• **Chair:** Vicknasingam B Kasinather, Universiti Sains Malaysia, Malaysia, vickna@usm.my

• **Pharmacology of Ketum/Kratom**
  – Sharif Mahsufi Mansor, Universiti Sains Malaysia, Malaysia, smahsufi@usm.my
  – Surash Ramanathan, Universiti Sains Malaysia, Malaysia, srama@usm.my

• **Neurobiology of Ketum/Kratom**
  – Zurina Hassan, Universiti Sains Malaysia, Malaysia, zurina_hassan@usm.my

• **Human Field Studies on Ketum/Kratom**
  – Darshan Singh, Universiti Sains Malaysia, Malaysia, darshan@usm.my

• **Plans for Human Laboratory Studies on Ketum/Kratom**
  – Marek C. Chawarski, Yale School of Medicine, marek.chawarski@yale.edu
Pharmacology
Of Kratom
*(Mitragyna speciosa)*

Professor Dr. Sharif Mahsufi Mansor

Centre For Drug Research (CDR)
Universiti Sains Malaysia
MGN is chemically unrelated to any known analgesic agents or opioid medications.

MGN is qualitatively different from narcotic analgesics, in terms of activity and side effect profile.

Controlled clinical trials need to be conducted to evaluate MGN as a new class of analgesics and for potential treatment of conditions/disorders related to opioid use.
PHARMACOLOGY OF KRATOM

Surash Ramanathan Ph.D.

Centre For Drug Research (CDR)
Universiti Sains Malaysia
Case report on Kratom poisoning and death

No direct evidence of death related to Kratom

Death: unintentional or accidental:

(i) due to adulterated Kratom products (synthetic adulterants: amphetamines, benzodiazepines or opioids amitriptyline, oxycodone etc)

(ii) Most cases the victims are poly drug users of other substance of abuse.

(iii) Underlying medical conditions e.g. alcohol abuse, depression, anxiety disorder.
Conclusions

- MGN has a very low bioavailability (3%) in rats
- In kratom users, MGN has a long elimination half life (24hr)
- The current MGN dispersion may offer a more uniform dosage form of MGN with better bioavailability for future preclinical studies
- MGN is safe at low dose (1-10mg/kg) but toxic at high dose (100mg/kg) in rats
- Evidence on death related to Kratom poisoning is lacking.
NEUROBIOLOGY OF KRATOM

Zurina Hassan, Ph.D

Centre For Drug Research (CDR)
Universiti Sains Malaysia
Conclusions

**Rewarding properties of MGN:**

- MGN at high doses (10 and 30mg/kg) exhibited a CPP effect, an indicator of addictive properties of MGN but not at low doses (1 and 5 mg/kg).
- Locomotor sensitization only observed after 10 days treatment in high dose (20mg/kg).
- There are participations of the opioidergic and GABAergic systems in modulating the effects of MGN in MGN-induced CPP.
- There are pharmacological similarities between MOR and MGN; suggesting that MGN should be evaluated as a potential agent for treatment of opioid use disorder.
Continued..

Cognitive effects of MGN:

- MGN at high doses (5 and 10mg/kg) impaired spatial learning but not at low dose (1mg/kg).
- There are contribution of opioidergic and GABAergic mediated during memory and learning functions.
- Memory impairment in a new learning task during abstinence was only observed at a high dose of MGN (10mg/kg).
Current studies in CDR

Assessment of the effectiveness of MGN, methadone & buprenorphine in morphine addicted model

Microdialysis
Measuring the extracellular neurotransmitters release in certain brain sites

Intravenous self administration (IVSA) is the best model to assess addictive liability of psychoactive substances
Field Studies on Ketum/Kratom Use

Darshan Singh, PhD
Centre for Drug Research
Universiti Sains Malaysia (USM)
## Overview of Field Findings on Kratom Effects.

**Kratom Studies in Southeast Asia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grewal, 1932.</td>
<td>Increased tolerance to heat, steadiness &amp; work capacity.</td>
</tr>
<tr>
<td>Burkill, 1936.</td>
<td>As an opium substitute.</td>
</tr>
<tr>
<td>Assanangkornchaisri et al., 2007.</td>
<td>Its use does not lead to harmful consequences.</td>
</tr>
<tr>
<td>Vicknasingam et al., 2010.</td>
<td>Males used kratom more frequently in social context.</td>
</tr>
<tr>
<td>Saingam et al., 2012.</td>
<td>Chronic use is associated with severe dependence &amp; withdrawal effects.</td>
</tr>
<tr>
<td>Trakulsrichai et al., 2013.</td>
<td>Used to reduce dependence &amp; suppress opiate (heroin) withdrawal.</td>
</tr>
<tr>
<td>Singh et al., 2014.</td>
<td>Regular use does not impair social-functioning.</td>
</tr>
<tr>
<td>Singh et al., 2015.</td>
<td>Traditional consumption (e.g. brewed kratom tea) does not lead to serious health problems.</td>
</tr>
<tr>
<td>Singh et al., 2018a.</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2018b.</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2018c.</td>
<td></td>
</tr>
</tbody>
</table>
Self-report surveys in Malaysia found that regular consumption was associated with kratom dependence. Kratom dependence was associated with higher frequency & heavy kratom consumption.

Being dependent on kratom was not affiliated with impaired social functioning, though users had difficulty abstaining from kratom use. Regular users were more likely to increase their kratom intake overtime.

(Singh et al. Drug and Alcohol Dependence, 2014).
Kratom Withdrawal Symptoms.

Kratom withdrawal symptoms are claimed to resemble opioid-like withdrawal symptoms.

Most users have never sought treatment for kratom withdrawal symptoms.

Kratom produces dose-dependent withdrawal effects during abrupt cessation.

However, users have their own ways to overcome (e.g. shower, sleep, sweat profusely, etc.) kratom withdrawal symptoms.

Kratom users with long-term (>1 year) & chronic kratom use history (daily ingestion of >1 litter of brewed kratom tea) have difficulty ceasing from kratom use.

Most users have never sought treatment for kratom withdrawal symptoms.
Safety.

Long-term kratom effects are poorly elucidated.

Current toxicity cases stem from the co-used of kratom with other substances & unresolved medical problems.

In the West, kratom use (regardless of duration & quantity) was associated with kratom exposure (poisoning & death).

Users have elevated risk of experiencing gastrointestinal (e.g. constipation, abdominal pain, etc.) & cardiovascular (e.g. tachycardia, hypertension, drowsiness, etc.) related effects.

Long-term users appeared thin, have darker skin & hepatic face, experience skin & hepatic face, experience constipation, dehydration, psychological problems & experienced fatigue.

So far, there have been no kratom toxicity incidents in Malaysia.

Perhaps, consumption of brewed kratom tea could be less toxic than the ingestion of powdered kratom extracts.

Users have elevated risk of experiencing gastrointestinal (e.g. constipation, abdominal pain, etc.) & cardiovascular (e.g. tachycardia, hypertension, drowsiness, etc.) related effects.

Despite the unpleasant effects, majority have not sought medical or mental health care treatment for kratom use.

(Kronstrand et al., Journal of Analytical Toxicology, 2011; Singh et al., Brain Research Bulletin, 2016; Lydeker et al., 2016; Anwar & al., ODC, 2016; Grundmann, Drug and Alcohol Dependence, 2017)
Current research gaps:

Current studies on kratom effects in humans are based on anecdotal observations, surveys among kratom users, clinical case-reports, in-depth interviews & review articles.

There are conflicting findings on dependence, withdrawal & the toxic effects of kratom use.

Controlled-clinical trials are needed to establish kratom (Mitragyna speciosa Korth.) effects and safety profile in humans.

(Singh et al., Brain Research Bulletin, 2016; Singh et al., Journal of Ethnopharmacology, 2018a).
Kratom studies at University Sains Malaysia (USM): Human Laboratory and Clinical Research

Marek C. Chawarski, PhD
Yale School of Medicine
Vicknasingam B. Kasinather, PhD
University Sains Malaysia
Findings overview

• Mitragyna speciosa plant (leaves) contains 57 compounds, 37 unique alkaloids (Brown et al. 2017)
  • Known active alkaloids are Mitragynine (12% - 66%) & 7-Hydroxy Mitragynine (2%) (Ponglux et al. 1994)
  • Content of Mitragynine varies depending on type and source of the raw material and geographical, climate, and seasonal factors (Adkin et al. 2011; Shellard et al. 1978)
• Mitragynine appears chemically unrelated to any known analgesic agents or opioids and is qualitatively different from other analgesics
• The current data is inadequate to establish the safety profile of kratom
  • There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term, daily users or kratom
Reported effects of kratom use in humans

• Pain relieve or increased pain tolerance
• Relieve or alleviation of opioid withdrawal symptoms
• Mood alteration, anti-depressive properties
• However, kratom use effects in humans are based primarily on anecdotal reports, observational findings, or self-reports collected using surveys, interviews, and focus groups
• Only one small study of mitragynine pharmacokinetics in humans published to date (Trakulsrichai, et al., 2015; N=10 in Thailand)