

An Insight into the Effect of *Mitragyna speciosa* Korth Extract on Various Systems of the Body

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Abstract: *Mitragyna speciosa* (MS) Korth is a tropical plant which has been widely used by locals for treatment of various diseases. However, the abuse of ketum has gained a lot of attention all over the world. Mitragynine is a major alkaloid of the plant which is widely used as a recreational drug because of its morphine-like properties. Several studies have been conducted based on the effects of MS crude extract and its alkaloid components. Toxicological effects of MS crude extract on experimental animals are still lacking. The present review was an effort to summarize the effects of MS on different systems of the body such as central nervous system, gastrointestinal system and urinary system. Better understanding of the toxicological effects on different organs may help in better diagnosis and treatment.

Key words: *Mitragyna speciosa* • Toxicity • Brain • Spinal Cord • Gastrointestinal • Urinary System

INTRODUCTION

Mitragyna speciosa

Geographical Distribution: *Mitragyna speciosa* (MS) belongs to the family Rubiaceae (Coffee) and sometimes known as Nauclea tribe from subfamily Naucleoideae [1]. It is commonly known as Ketum or Biak-biak in Malaysia and Kratom, Kraton, Kakuam, Ithang or Thom in Thailand [2]. Genus *Mitragyna* was coined by Korthlas due to its stigma shape similar to mitra bishop [3]. It is a type of tropical evergreen and non-seasonal plant, commonly found in swamps and valleys. It grows abundantly in wet, humid areas rich with humus [3]. This plant is found in tropical and subtropical Asian regions such as Thailand, Laos, Cambodia and Malaysia. It is also found in Borneo, Philippines, New Guinea, East and West Africa and India [3, 4]. In Malaysia, this plant is widely found in northern half of the Peninsular and Selangor [5].

Description of the Plant: It is a large trunk tree and usually grows to an usual height of 4-9 metres. Its flowers are in globular in shape with 120 dark yellow florets



Fig. 1: Photograph showing MS plant.

attached to the leaf axils on long stalks (Fig. 1). It consists of fruit-like capsule with flat seeds. The ovate acuminate shaped leaves are dark shiny green colour and arranged opposite to one another [6]. The leaves fall abundantly during the dry season. The MS plant is very sensitive to extreme cold and drought. The leaves will fall abundantly during extremely hot season and grow during

the rainy season [7]. There are two types of *MS* based on the color of veins in the leaves like green and red. The taste of red vein is bitterer and its effect can last longer than the green vein. Therefore, most of the local people prefer red vein leaves than green one [8].

Traditional Use of *MS* Plant: *MS* is one of the traditional medicinal plants used to treat various types of diseases especially in Thailand and Malaysia. The villagers used the leaves to treat diseases such as cough, fever, diarrhea and even common cold. Sometimes, they crushed the leaves and applied it on the body to treat pain [9-11]. *MS* also has been used as a medication for animals such as buffalos and cows. When the animals are affected by diseases like diarrhoea, the owner feed them food mixed with ketum leaves. The animals recovered following consumption of 2-3 meals [8].

Ketum leaves are commonly used as a source of energy among local people to stimulate and increase their work efficiency. They felt strong, had power to work harder and longer, were awake during working and could tolerate and work under heat and hot sun for the whole day. The *MS* leaves are also reported to be used to prolong sexual intercourse [9- 11].

The use of *MS* leaves is related to culture-bound and ritualistic in rural villages [12]. The leaves are used as valuable gift to spirit or God. When the locals prayed to God for any help and if it was successful, they served God with ketum leaves. This tradition was followed by generation to generation during ancient time. Apart from that, ketum leaves were used during local ceremonies. Usually, the owner prepares ketum leaves free of charge for audience who came for watching the competitions. In Thailand, villagers welcome their guests by offering ketum leaves with betel nut and served with hot coffee or tea. Ketum leaves consumption is socially accepted by the rural people. They felt that people who consume ketum leaves were better than those who smoked tobacco or consume alcohol. Interestingly, this was thought because ketum users did not fight, bully or hurt others [8].

Medicinal and Therapeutic Use: The villagers also believed that *MS* leaves could prevent some chronic diseases such hypertension, diabetes, herpes zoster, cancer and HIV [13]. Previous studies reported that *MS* possessed antipyretic, antidiarrheal, euphoric, analgesic, anxiolytic and anti-depressant effects. *MS* also acted to boost immune, lower blood pressure and proved to possess anti-viral, anti-diabetic and appetite suppressing effects [14-18].

The leaves possess opium-like effect and cocaine-like stimulant which used as a substitute for morphine in treating addicts [11]. *MS* leaves were used to replace morphine in addicts during detoxification in treatment programs. *MS* possess less effect than morphine with a shorter duration. Previous studies reported that *MS* was used to increase physical endurance and as cheaper substitute for opiates [19, 20]. The effect of *MS* which has cocaine-like effect in small doses and morphine- like effect in high dose was reported in previous studies [21]. *MS* effect was first reported as ‘calming the mind’ in Thailand. Mitragynine is widely used as a recreational drug because of the similar effects like morphine. *MS* use is illegal in Thailand, Malaysia, Myanmar, Vietnam, Australia and Denmark but the use is still uncontrolled in most of the world [22].

Recently, the abuse of ketum has gained a lot of attention in South-east Asia. In Malaysia, *MS* was listed in the First Schedule and the Third Schedule (Psychotropic substances) of the Poisons Act 1952 of January 2003. The maximum penalty for selling *MS* leaves in Malaysia has been set at RM 10,000 (Approximately 3143 USD, 1 USD=3.2 RM) and a four-year jail sentence or even both [20].

Recently, there has been a growing trend among drug addicts to use bitter-tasting ketum leaves to get kick when they are unable to get cannabis or heroin. This is because of the easy availability and lower price of ketum leaves compared to any other controlled drugs. Fresh *MS* leaves and powdered leaves are sold locally at 4 Malaysian Ringgits (1 Ringgit = 0.30 USD) and small packet drinks for RM 1 [23]. Its availability via the internet has increased the potential for use and abuse [24].

Even ketum users had their own ketum trees hidden in some places such as orchard, rubber plantation, paddy field and house yard. Heavy users may chew ketum between 10- 80 leaves a day while new users may only need a few leaves to obtain the desired effects. Recently, ketum cocktail or 4x100 (Sii koon roi) became popular among youngsters. The drink is prepared by boiling ketum leaves with codeine cough syrup and cola soft drinks. It is usually served with ice. Other than that, other toxic substances such as sleeping pills, bleaching liquid, benzodiazepines and mosquito repellent stick are also added to the drink [8].

Recently, several case studies provide evidence of long term consumption of *MS* extract in humans. A 44-year-old patient developed severe primary hypothyroidism after *MS* use for 4 months. A relationship between *MS* use and thyroid dysfunction has not been studied yet. It is due to high dose of mitragynine that

Effects of MS consumption	Effects experienced on stopping MS consumption
<ul style="list-style-type: none"> • Energized and increased alertness • Euphoria, feeling relax and contented • Light headed • Sedated • Hot and sweaty • Improve sexual performance • Hallucination/ induce fantasy • Pigmentation • Others (e.g. vomiting, increase appetite and bitter taste) 	<ul style="list-style-type: none"> • Hostility • Aggression • Excessive tearing • Inability to work • Aching of muscles and bones • Jerky movement of limbs • Loss of appetite • Weight loss • Insomnia • Malaise • Restlessness

Fig. 2: Effects of MS consumption and effects experienced on stopping MS consumption.

reduces the normal response and results in imbalance of thyroid stimulating hormone (TSH) [25]. Another case described a 25-year-old man admitted to hospital having pruritus and jaundice following consumption of MS powder for a period of two weeks. Both serum and urine samples confirmed presence of mitragynine [26]. A 64-year-old man was reported to suffer from seizure following consumption of MS. Mitragynine was detected in the urine samples [27].

The regular users of MS show some symptoms of addiction such as aggression, difficulty to work, muscle and bones aching, jerky movement of limbs, anorexia, weight loss and insomnia [23]. It also causes other harmful effects including dry mouth, diuresis, loss of appetite, weight loss; darken skin and constipation [9]. The effects of MS consumption and the effects experienced following the discontinuity in its usage were shown in Fig.2.

Misuse of Ms as an Addictive Agent: The leaves and smaller stems of the tree are consumed by local people in Malaysia and Thailand [28]. However, the leaves are the most commonly used and effective part of MS tree [29]. It is widely available in the form of drink and tea. The drinks are easily available in the villages and are also cheap. Other ways of consumption include chewing fresh leaves or dried leaves, grinding up and in cooking. The effect of dried ketum and fresh leaves are same. The fresh MS leaves are chewed with removal of the veins or with betel nuts [29]. Other substances are also added during the preparation of MS leaves prior to before chewing or swallowing. Lemon juice usually added during preparation to facilitate the extraction of MS leaves. Salt is often added to prevent constipation. Besides that, sugar or honey also added to mask the bitter taste of the extract

Table 1: Table showing alkaloid components of MS and its effect.

Alkaloid Compounds	Percentage (%)	Effect
Mitragynine	+++++	Antinociceptive, antidepressant
Paynanthine	++	Smooth muscle relaxer
Speciogynine	++	Smooth muscle relaxer
7-Hydroxymitragynine	+	Antidiarrheal, analgesic
Speciociliatine	+	-
Speciofoline	+	-
Mitraphylline	+	-
Ajmalicine	+	Sedative
Corynanthidine	+	-
Mitraversine	+	-
Rhynchophylline	+	Calcium channel blocker
Stipulatine	+	-

[30, 31]. The dried leaves have been ground, powdered and boiled in water to produce syrup. Then, the syrup is mixed with palas palm leaves (*Lincuala paludosa*) and made into pills. Local people have reportedly smoked these pills in long bamboo pipe. It is known as ‘madatin’ in Malaysia [31].

Active Compounds in Ms and Their Resultant Action:

MS contains abundant of indole alkaloids [32]. It contains at least 25 alkaloids which may be biologically active [33-35]. The most abundant alkaloids are three indoles and two oxindoles. The three indoles are mitragynine, speciogynine and paynanthine wherever the two oxindoles are speciofoline and mitraphylline. Other alkaloids present in MS extract are ajmalicine, corynanthidine, mitraversine, rhychophylline and stipulatine [36-38]. Table 1 showed the alkaloid components of MS and its effect.

Mitragynine is the primary alkaloid of MS which accounts for two-thirds of the total alkaloid extract. Mitragynine was obtained as the major constituent which was 66.2% based on the crude base. It was followed by its analogues such as speciogynine (6.6%), speciociliatine (0.8%) and paynantheine (8.6%) [39]. According to Takayama [40], mitragynine maybe the key for the effects of MS. It has opiod like properties which may lead to addiction [20]. It has a molecule formula of 9-methoxycorynantheidine (C₂₃H₃₀N₂ O₄) with molecular weight of 398.5 [18]. Mitragynine was first isolated by Hooper [41] and its structure was first discovered by Zacharias *et al.* [42].

Effect of Ms on Various Systems of the Body

Central Nervous System (CNS): Majority of the research has focused on mitragynine for its antinociceptive action on CNS which is mediated by opiod receptor [19, 20]. Mitragynine also inhibited the electrically stimulated

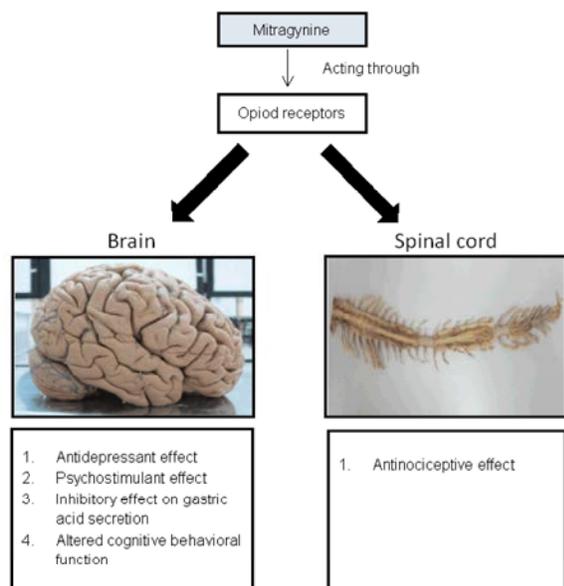


Fig. 3: Schematic diagram showing the effect on central nervous system

guinea-pig ileum through the opioid receptor [43]. Other than that, mitragynine also exhibited inhibitory effect on forskolin-stimulated cAMP formation in NG108-15 cells [44] and on 5-methoxy-N, N-dimethyltryptamine-induced head-twitch response in mice [45]. Chronic administration of mitragynine altered the cognitive behavioural function (Working memory) in mice using object location task and the motor activity in open-field test [46].

Farah Idayu *et al.* [47] described antidepressant effects of mitragynine at the behavior level which could be mediated by a restoration of monoamine neurotransmitter levels due to an interaction with neuroendocrine hypothalamic-pituitary- adrenal axis. It was shown that mitragynine significantly reduced the corticosterone concentration in mice exposed to the forced swim test and tail suspension test.

Another study using an avoidance task demonstrated that mitragynine administered orally facilitated learning but had no benefit on the long term memory consolidation. There were no significant changes between methanolic extract of MS groups and control groups in two-way active avoidance task [48]. Other than that, alkaloid and aqueous extract of MS showed antidepressant-like effects in models of behavioral despair tests. However, antidepressant mechanisms of MS not clearly stated in both studies [22, 23].

Acute toxicity study of MS extract using 3 different doses 100, 500 and 1000 mg/kg did not reveal any

morphological changes in brain. This indicated that acute dose used did not induce damage in axons and dendrites of the hippocampal neurons [49]. The effects on central nervous system i.e. brain and spinal cord was depicted in Figure 3.

Gastrointestinal System: Acute and chronic MS extract treated rats showed a suppression of food and water intake. It caused reduction in weight gain [10]. It also reduced the defecation frequency and faecal weight in castor oil-induced diarrhea in rats. A single dose of the methanolic extract of MS resulted in a dose dependent reduction of the intestinal transit. Repeated treatment with this extract did not cause any significant change of the intestinal transit and fluid [34].

The dose of 1000 mg/kg of the MS extract has also been reported to induce acute severe hepatotoxicity in male Sprague Dawley rats. The dose marked a significant damage in liver tissue such as congestion of sinusoids, lipid accumulation, centrilobular necrosis and presence of kuppfer cells [49]. Biochemistry results showed significant changes in ALT, albumin and triglycerides which indicate impairment of the liver function. In another study, the repeated dose of 100 mg/kg of mitragynine for 28 days caused damage in liver tissue such as dilation of sinusoids and hemorrhage in hepatocytes [50].

Urinary System: Acute dose of 1000 mg/kg MS crude extract caused no morphological changes in kidney tissue. However, biochemical studies showed significant increase in urea and creatinine [49]. In another study which used repeated dose of 100 mg/kg mitragynine for 28 days showed histopathological changes such as hemorrhage and swollen glomerulus capsule in female rats. However, the same dose did not cause any significant changes in the kidney tissues of male rats [50].

Endocrine System: Interestingly, it has been reported earlier that glucose levels were reduced in aquatic animals treated with immunostimulants [51]. Although, immunostimulant action of MS has not been observed, it remains to ascertain such in future. Interestingly, recent studies showed the beneficial effect of MS extract on glucose transport in muscle cells through the activity of many vital enzymes [52]. The antioxidant action of the MS extract may be beneficial for the endocrine system.

CONCLUSION

Herbal products are widely used as a self-medication by local people. MS plant as a traditional remedy to cure

various diseases. However, the MS leaves are misused as an addictive agent because of its morphine like properties. Majority of the animal studies were performed to observe the effect of MS crude extract and its major alkaloid component, mitragynine with regard to its antidepressant, antinociceptive and psychostimulant actions. There is lack of studies on toxicity of MS plant on various organs. A few researches proved toxicity in various organs especially in liver and kidney. The present review article highlighted the effect of MS plant which may be important for clinicians and physicians for better diagnosis of the toxicity symptoms and planning adequate treatment.

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