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Review

From Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction

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ABSTRACT

Kratom (or Ketum) is a psychoactive plant preparation used in Southeast Asia. It is derived from the plant *Mitragyna speciosa* Korth. Kratom as well as its main alkaloid, mitragynine, currently spreads around the world. Thus, addiction potential and adverse health consequences are becoming an important issue for health authorities. Here we reviewed the available evidence and identified future research needs. It was found that mitragynine and M. speciosa preparations are systematically consumed with rather well defined instrumentalization goals, e.g. to enhance tolerance for hard work or as a substitute in the self-treatment of opiate addiction. There is also evidence from experimental animal models supporting analgesic, muscle relaxant, anti-inflammatory as well as strong anorectic effects. In humans, regular consumption may escalate, lead to tolerance and may yield aversive withdrawal effects. Mitragynine and its derivatives actions in the central nervous system involve μ-opioid receptors, neuronal Ca^{2+} channels and descending monoaminergic projections. Altogether, available data currently suggest both, a therapeutic as well as an abuse potential.

Contents

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1. Introduction

Humans regularly engage in the consumption of substances that are not necessary for survival. Those substances may change physiological parameters in the body and/or subjective perception and behaviour (Müller and Schumann, 2011). One group of these substances comprises the psychoactive compounds, which are consumed with the intention to change mental state and behaviour of the consumer (Sullivan and Hagen, 2002; Sullivan et al., 2008; Hagen et al., 2009). It is a common behaviour in virtually all known human cultures and can be traced back to oldest human records and artefacts (Abel, 1980; Dudley, 2002; Heath, 2000; Streatfeild, 2001). However, the substances consumed and their 'instrumentalization' has been and is changing in many cultures (Müller and Schumann, 2011). There are *de novo* synthesized substances emerging which target well known signalling proteins in the brain (Lindigkeit et al., 2009; Fattore and Fratta, 2011; Schmidt et al., 2011; Zawilska, 2011). On the other hand, drug markets draw from local natural sources. These compounds are naturally occurring in plants in particular regions of the world, where the use of the plant may already have a long history of use. While the use is initially a local one, the constant search of new psychoactive drugs pushes them to the global markets (Rosenbaum et al., 2012). One problem with these drugs is often that while a more 'natural use' as a plant preparation in the countries of origin may be less associated with addiction and health problems, they may have a strong addiction potential as purified substances (e.g. Streatfeild, 2001). For early prevention measures and classification of newly emerging psychoactive compounds, it is therefore pivotal to learn fast about their addiction potential.

Since time immemorial, plant-derived (phyto-) pharmaceuticals had been the concoction to treat and/or prevent a wide range of human maladies. Although many standard scientific and medical facets of these various phytopharmaceutical sources are yet to be investigated, their pool of consumers showed minimal or no signs of retreat, notably in economically disadvantaged countries where access to modern medicine remains scantily affordable (Chin et al., 2008). One such phytopharmaceutical source is a plant known as *Mitragyna speciosa* Korth (*M. speciosa*) of the Rubiaceae (coffee) family, a medicinal herb indigenous to Malaysia and Thailand (Gong et al., 2012). *M. speciosa* grows primarily in tropical and subtropical regions of Southeast Asia and Africa. It is also known as *biak-biak* or *Ketum* in Malaysia and *Kratom*, *Kakuam*, *Kraton*, *Ithang* or *Thom* in Thailand (Jansen and Prast, 1988a; Ingsathit et al., 2009; Maruyama et al., 2009; Adkins et al., 2011). *Kratom* and *Ketum* are used synonymously in this review as it was used in the original references.

According to anecdotal reports, the use of the leaves of this plant seems to have shifted from its folks remedy label to that of an opioid accomplice, branding it with an abuse potential. It is now apparent that the international use of various *Kratom/Ketum* chemotype preparations has spread beyond its traditional geographical boundaries. It is the aim of this review to provide an overview about what is currently known about the physiological, psychoactive, and behavioural effects of *M. speciosa* and its active ingredients and their metabolites. This shall serve as a decision making base for current classification, potential medical application, as well as to identify future research needs.

2. Botanical origin

M. speciosa trees can grow to a normal height of 4-9 m and 5 m wide. Certain plants can reach a height of up to 15-30 m. The stem is erect and branching. The leaves are of a dark glossy green colour (Fig. 1). They grow to over 18 cm long and 10 cm wide with an ovate-acuminate shape and tapered ends. The deep yellow flowers grow in globular clusters attached to the leaf axils on long stalks, bearing up to 120 florets each. The seeds are winged (Shellard and Lees, 1965; Emboden, 1979; Shellard, 1974). The leaves are constantly being shed and replaced, but there is some quasi-seasonal leaf shedding due to environmental conditions. The leaves fall abundantly during the dry season of the year and new growth is produced during the rainy season. The tree grows best in wet, humid, fertile soil, with medium to full sun exposure in areas protected from strong winds (Macko et al., 1972; Fig. 1). The plant parts used for consumption are the leaf and smaller stems of the trees. A genetic identification of *M. speciosa* and authentication compared to other *Mitragyna* species (Gong et al., 2012), is now possible by internal transscribed spacer sequence analysis of the nuclear ribosomal DNA (Sukrong et al., 2007; Maruyama et al., 2009).

3. Preparation of plants and consumption

The dried leaves of *M. speciosa* can be chewed fresh, smoked, or made into an extract (Grewal, 1932a,b; Wray, 1907b; Tanguay, 2011). It can also be powdered, brewed with hot water and drunk as a tea. Lemon juice is often added to facilitate the extraction of plant alkaloids. Sugar or honey may be added to mask the bitter taste of the brew. Another method of preparation involves powdering of the dried leaves and boiling in water until syrup is produced. The syrup can be mixed with finely chopped leaves of the palas palm (*Lincuala paludosa*) and made into pills. The pill is known as 'madatin' in Malaysia and is smoked in long bamboo pipes (Macmillan, 1991). The fresh leaves can be chewed with betel nuts (*Areca catechu*) (Scholz and Eigner, 1983) or alone with removal of the veins before eating. Salt is usually added to prevent constipation. In southern Thailand and northern Malaysia, *Kratom* use is not perceived as 'drug use', it rather is part of the way of life closely embedded in local traditions and customs (Tanguay, 2011). In southern Thailand, in recent years homemade ice-cold cocktails called '4 × 100', have become popular for their alleged alcohol-mimicking effect among young Muslim people. The cocktails are made from *M. speciosa* leaves, a caffeine-containing soft drink, and codeine- or diphenhydramine-containing cough syrup as the three basic ingredients to which an anxiolytic, an antidepressant, or an analgesic drug is added (Tanguay, 2011). Consumption of this cocktail can have fatal consequences due to multidrug action (Tungtananuwat and Lawanprasert, 2010).

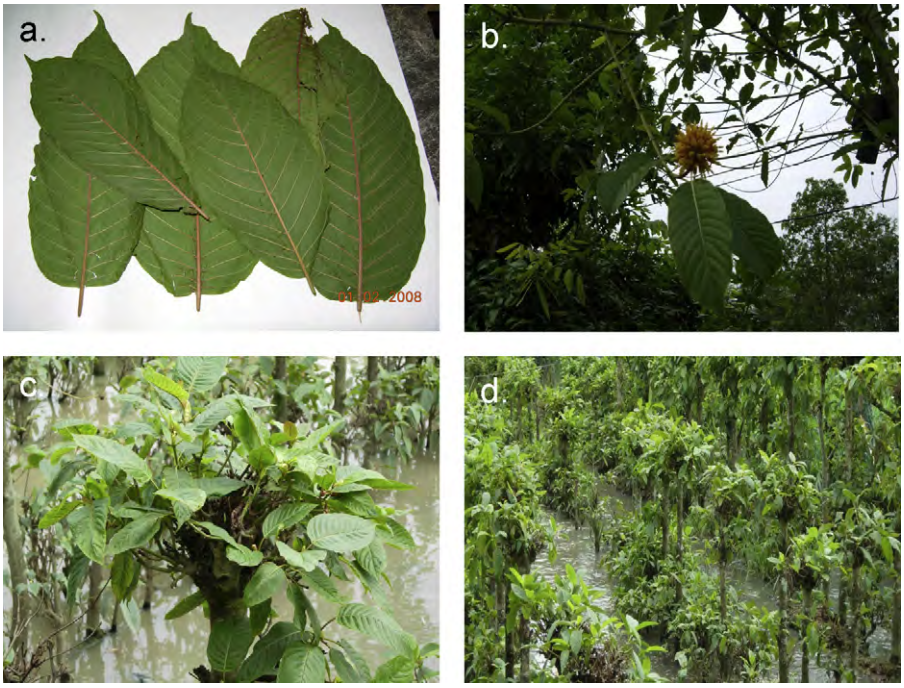

Fig. 1. The plant *Mitragyna speciosa* Korth. (a) Leaves of the plant, (b) naturally occurring trees, (c and d) cultivated plants.

Suwanlert (1975) investigated 30 Thai *Kratom* users, who were older and married men abusing *Kratom* over 5 years. They reported stimulant effects 5–10 min after chewing the leaves which lasted 1–1.5 h. Users reported an increase in work output and tolerance of hot sunlight (Grewal, 1932a,b; Macko, 1972).

Vicknasingam and colleagues performed a survey of current *M. speciosa* use in 136 active users in northern Malaysia. They found that *M. speciosa* (*Ketum*) users were relatively older (mean 38.7 years). About 77% of the users had previous drug use history. Long-term consumers with more than 2 years of use had higher odds of being married, of consuming more than the average three glasses of *Ketum* a day and reporting better appetite. Short-term users (<2 years of use) had higher odds of having ever used heroin, testing positive for heroin in a urine sample and of using *Ketum* to reduce addiction to other drugs. Both, short- and long-term consumers reported that they used *Ketum* in order to reduce their intake of more expensive opiates, to manage withdrawal symptoms and because it was cheaper than heroin. Only very few consumers (5.6–12.5%) report 'euphoria induction' as a reason to use *Ketum*. Drugs can be consumed in order to instrumentalize their psychoactive effects to better achieve other, non-drug related goals (Müller and Schumann, 2011). Ketum users report as major self-perceived benefits of their drug use that the drug 'helps to work harder' (76.6–87.5%), that it 'makes more active' (76.6–86.1%), it 'increases sexual desire' (73.4–84.7%), and an increase in appetite (57.8–77.8%). Interestingly, self-perceived use was higher in short-term than in long term users, thus suggesting a loss or reduction of the self-perceived instrumentalization. These findings differ from those in neighbouring Thailand where *Ketum* was used primarily to increase physical endurance. According to this study, the daily consumption of *Ketum* solution is 3×250 mL to ease opiate withdrawal symptoms, which contains approximately 68–75 mg mitragynine (Vicknasingam et al., 2010).

Commercial *M. speciosa* products are now widely available on the Internet (Hillebrand et al., 2010; Schmidt et al., 2011). They are offered as resin, dried leaf, or powder under the names 'Kratom', 'Mitragyna', 'Concentrated Kratom' or 'Plant sample Kratom' and many more. However, qualities vary and preparations may not always be *M. speciosa* products (Hanna, 2012). Kikura-Hanajiri et al. (2009) developed a method to simultaneously detect mitragynine, 7-Hydroxymitragynine (7-HMG) and other indole alkaloids in these products using liquid chromatography–electrospray ionization mass spectrometry (LC–ESI-MS). The content of mitragynine in these products ranged from 1.2 to 6.3% and that of 7-HMG from 0.01 to 0.04% (Kikura-Hanajiri et al., 2009). In contrast to newly designed psychoactive drugs, about which very little is known when they start to spread, the long history of *M. speciosa* use in Southeast Asia allows users via the Internet to access balanced and occasionally scientifically confirmed information about safety issues, dose patterns, potential side effects, and addiction potential of the consumption (e.g. Siebert, 2012).

4. Medical use

In Malaysia and Thailand, the leaves are traditionally used to treat intestinal infections, muscle pain, to reduce coughing and diarrhoea (Suwanlert, 1975; Jansen and Prast, 1988a; Said et al., 1991; Chuakul et al., 1995; Watanabe et al., 1997; Vicknasingam et al., 2010). *M. speciosa* preparations have been used by Malay and Thai natives for its opium and coca-like effects to enhance tolerance for hard work under the hot sun (Grewal, 1932a,b; Suwanlert, 1975; Tanguay, 2011). According to Burkill (1935), the earliest reports of *Kratom* use in Malaysia date back to 1836, when its use as opium substitution was reported. Holmes (1895) later confirmed this and identified the leaves as those from the *M. speciosa* tree. The methods of consumption in humans were first described by Wray (1907a). For a review of early Kratom use in humans see: Jansen and Prast (1988a).

In the nineteenth century, *M. speciosa* was reported to work as an opium substitute in the treatment of opium addiction in Malaysia and Thailand (Burkill and Haniff, 1930; Burkill, 1935; Beckett et al., 1965a; Wray, 1907a,b; Tanguay, 2011). Thuan (1957) reported withdrawal effects after *M. speciosa* consumption.

Norakanphadung (1966) described the medical use of the leaves in Thailand where *Kratom* had been used to replace morphine in addicts during detoxification in treatment programmes. *Kratom* has weaker effects than morphine with a shorter duration. Recently two surveys in Malaysia and one in Thailand among current users in the community have been published. These studies also found that *Ketum/Kratom* was used to increase physical endurance and as a cheaper substitute for opiates (Vicknasingam et al., 2010; Ahmad and Aziz, 2012). In Thailand, *M. speciosa* preparations are consumed by the three wheeled motorized 'taxis' as an amphetamine substitute (Schuldes, 1995). In Western societies, plant preparations are easily accessible from the local coffee shops and web-based 'legal highs' pharmacies (Boyer et al., 2008; Hillebrand et al., 2010). This had enticed many consumers there to use the plant as self-treatment in modulating opiate withdrawal, alcohol withdrawal, and chronic pain (Boyer et al., 2008; Havemann-Reinecke, 2011; Ward et al., 2011). In fact, it is a cheaper alternative to the established opioid-replacement therapies and is obtainable without medical prescription.

There is a general effect of 'cocaine-like' stimulation in small doses, while at high doses 'morphine-like' sedation and nausea are reported (Babu et al., 2008). Several studies suggest that *M. speciosa* preparations have analgesic, antipyretic, antidiarrheal, euphoric, anti-depressant, and anxiolytic effects. They may work as immune booster, lower blood pressure, and have anti-viral, diabetes- and appetite suppressing effects (Macko et al., 1972; Burkill, 1935). Besides this, they can also cause anorexia, dry-mouth, diuresis and constipation after long term use at high doses (Suwanlert, 1975; Perry, 1980). While there was no evidence of a dosage increment among long-term and repeated users, withdrawal symptoms were reported which suggest an addiction potential. These symptoms range from hostility, aggression, aching of muscles and bones, jerky movements of the limbs, and anorexia to weight loss and insomnia (Suwanlert, 1975). Long term effect of the consumption can also cause darker skin although the user remained indoors (Norakanphadung, 1966). The darker skin is due to the increase in the melanocyte-stimulating substance. It was suggested that in particular mitragynine may increase the production of melanocyte-stimulating substance. Long term users were reported to be thin with distended stomachs, unhealthy complexions, dark lips and dry skin (Grewal, 1932a,b; Suwanlert, 1975).

5. Epidemiology

According to a recent report, in Thailand *Kratom* is the most popular illicit substance used. Lifetime prevalence among high-school students in southern Thailand was between 2.3 and 4.9% in 2002–2004 (Assanangkornchai et al., 2007a). The prevalence for past year use among the 12–65-year olds was 4.73% and for current use 3.76% in the year 2007 (Assanangkornchai et al., 2007b, 2008). The use of *Kratom* among humans is no more confined to Southeast Asia. Recent reports indicate that its use has spread to the United States and Europe. It is reported to be widely sold on the internet (Hillebrand et al., 2010; Schmidt et al., 2011). Single case reports on the effects of Kratom use in humans emerged recently in Europe and the US (Boyer et al., 2007, 2008; McWhirter and Morris, 2010; Kapp et al., 2011). In some cases, *M. speciosa* and/or mitragynine may also serve as an ingredient of 'legal- or herbal high' preparations, which are distributed under various names, such as *Krypton* or *K2* (Lindigkeit et al., 2009; Fattore and Fratta, 2011; Schmidt et al., 2011; Zawilska, 2011; Logan et al., 2012). Urine screens after *Krypton* consumption revealed the presence of mitragynine and other *M. speciosa* alkaloids, but also of synthetic drugs, such as O-desmethyltramadol (Dresen et al., 2010; Arndt et al., 2011).

6. Legal status

M. speciosa preparations were scheduled for control in Thailand in 1943. In 1979, the Thai government placed *Kratom* under Schedule 5 of the Thai Narcotics Act, which is the least restrictive and punitive level. This makes it illegal to buy, sell, import, or possess it. The law also makes planting trees illegal and requires cutting down existing ones, however, with mixed success among native people. In Malaysia, use was permitted until 2003, when it was placed under the Poison Act. This made selling of *M. speciosa* leaves or preparations an offence with a penalty and/or jail sentence (Vicknasingam et al., 2010). In Indonesia, *Kratom* is legally cultivated and exported on large scale to Asia, North America and Europe (Tanguay, 2011). *M. speciosa* and/or mitragynine and 7-HMG are controlled drugs in many EU countries such as Denmark, Poland or Sweden. In other countries they are under the control of the narcotic laws, including Australia and Myanmar. In the US, the UK and Germany they are currently not controlled substances but under surveillance (EMCDDA, 2012). The US Drug Enforcement Administration (DEA) has placed *Kratom* on its *Drugs and Chemicals of Concern* list, which suggests that the agency may eventually try to ban it in the US once more reliable data on its addictive properties and/or health hazards become available.

7. Phytochemistry

Since the 1960s, 25 alkaloids were isolated and chemically characterized from *M. speciosa*. The alkaloid content varies according to geographical region and season. The alkaloid profile of *M. speciosa* is summarized in Table 1. The main indole alkaloids present in the young leaves of *M. speciosa* are mitragynine and its analogues, speciogynine, paynantheine and speciociliatine. In addition, a new alkaloid, 7α-hydroxy-7H-mitragyine (7-hydroxymitragynine; 7-HMG) was isolated as a minor constituent (Fig. 2; Seaton et al., 1960; Beckett et al., 1965b, 1969; Lee et al., 1967; Shellard et al., 1978a, 1978b; Ponglux et al., 1994; Leon et al., 2009; Orio et al., 2012). These alkaloids were also found in the methanolic extract of the mature leaves together with mitragynaline, pinoresinol, mitralactonal, mitrasulgynine and 3,4,5,6-tetradehydromitragynine as minor constituents (Takayama et al., 1998). In the ethyl acetate extract, nine corynanthe-type indole alkaloids were isolated namely, mitragynine, speciogynine, speciociliatine, paynantheine, 7-HMG, mitragynaline, corynantheidaline, corynantheidine and isocorynoxeine, whereas 9-methoxymitralactonine and mitralactonine were obtained as minor constituents (Takayama, 2004). Investigation of Malaysian *M. speciosa* found new types of alkaloids namely mitragynaline, corynantheidaline, mitragynalinic acid and corynantheidalinic acid (Houghton et al., 1991). The total alkaloid content from the leaves varies from 0.5% to 1.5%. An additional indole alkaloid found in the fruits of *M. speciosa* is 7-hydroxyspeciociliatine (Kitajima et al., 2007). Microbial transformation of the leaves was shown to yield two major metabolites: mitragynine pseudoindoxyl and hydroxyl mitragynine pseudoindoxyl (Zarembo et al., 1974).

Mitragynine is, with 66% of the total alkaloid mixture, the most abundant active alkaloid derived from the leaves of *M. speciosa* (Shellard, 1974, 1989; Shellard et al., 1978a, 1978b; Jansen and Prast, 1988a; Takayama et al., 1998; Chittrakarn et al., 2008). It was first isolated by Hooper (1907) and again by Field (1921) and Ing and Raison (1939). Field (1921) isolated two new alkaloids from *Mitragyna* species: mitragynine (from *M. speciosa*) and mitraversine (from *M. parvifolia*). Mitragynine was assumed to be a physiologically active constituent having morphine-like properties. However, it should be noted that it may not be the most potent psychoactive component. In particular over more chronic

Table 1
Alkaloid profile of *Mitragyna speciosa* Korth. The percentage is the estimated content in the alkaloid extracts.

Alkaloid	Percentage	Effect	Reference
Mitragynine	66%	Analgesic, antitussive, antidiarrheal, adrenergic, antimalarial	Hooper (1907); Field (1921); Lee et al. (1967); Ponglux et al. (1994)
Paynantheine	9%	Smooth muscle relaxer	Ponglux et al. (1994)
Speciogynine	7%	Smooth muscle relaxer	Lee et al. (1967); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
7-Hydroxymitragynine	2%	Analgesic, antitussive, antidiarrheal	Ponglux et al. (1994)
Speciociliatine	1%	Weak opioid agonist	Lee et al. (1967); Ponglux et al. (1994)
Mitraphylline	<1%	Vasodilator, antihypertensive, muscle relaxer, diuretic, antiamnesic, immunostimulant, anti-leukemic	Seaton et al. (1958); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
Isomitraphylline	<1%	Immunostimulant, anti-leukemic	Seaton et al. (1960); Shellard and Philipson (1966); Ponglux et al. (1994)
Speciophylline	<1%	Anti-leukemic	Shellard and Philipson (1966); Beckett et al. (1966)
Rhynchophylline	<1%	Vasodilator, antihypertensive, calcium channel blocker, antiaggregant, anti-inflammatory, antipyretic, anti-arrhythmic, antithelmintic	Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Isorhynchophylline	<1%	Immunostimulant	Seaton et al. (1958); Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Ajmalicine	<1%	Cerebrocirculant, antiaggregant, anti-adrenergic, sedative, anticonvulsant, smooth muscle relaxer	Beckett et al. (1966)
Corynantheidine	<1%	Opioid agonist	Takayama et al. (2002)
Corynoxine A	<1%	Calcium channel blocker, anti-locomotive	Shellard et al. (1978a)
Corynoxine B	<1%	Anti-locomotive	Shellard et al. (1978a)
Mitrafoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Isomitrafoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Oxindale A	<1%		Shellard et al. (1978a)
Oxindole B	<1%		Shellard et al. (1978a)
Speciofoline	<1%	Analgesic, antitussive	Hemmingway et al. (1975)
Isospeciofoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Ciliaphylline	<1%	Analgesic, antitussive	Trager et al. (1968)
Mitraciliatine	<1%		Lee et al. (1967)
Mitragynaline	<1%		Houghton et al. (1991)
Mitragynalinic acid	<1%		Houghton et al. (1991)
Corynantheidalinic acid	<1%		Houghton et al. (1991)

utilization this may be the less abundant 7-HMG (Horie et al., 2005; Matsumoto et al., 2005a; 2008). The structure of mitragynine was first fully determined in 1965 by Zacharias et al. (1965) through X-ray crystallography. A computational study recently identified the lowest energy conformation of mitragynine, which was in excellent agreement with X-ray crystal structure geometry (Liu et al., 2010). The first synthesis of mitragynine was reported by Takayama et al. (1995). Alternative synthesis ways were reported later by Ma et al. (2009). The molecular structures of *M. speciosa* alkaloids were found to be either indoles with a methoxy group in the C19 position and an open E ring with substitution occurring at the C9 position, or oxindoles without substitution in the C9 position and having a closed E ring (Fig. 2; Seaton et al., 1958; Beckett et al., 1966; Shellard and Philipson, 1966). Most of the alkaloids in *M. speciosa* have similarities to *yohimbe* and *Uncaria* alkaloids (Matsumoto et al., 2004). Mitragynine is a white amorphous powder. It is soluble in alcohol, chloroform and acetic acid. The chemical structure of mitragynine is related to both yohimbine and voacangine. Chemically, mitragynine is 9-methoxy-corynantheidine (Fig. 2).

8. Pharmacokinetic

The pharmacokinetic of mitragynine was investigated in the rat after oral and intravenous administration. A high performance liquid chromatography method with ultraviolet detection (HPLC–UV) was developed by Janchawee et al. (2007) to measure mitragynine in the plasma of humans and rats. The authors describe pharmacokinetic parameters from a non-compartmental analysis after the oral administration of 40 mg mitragynine in rats. This dose led to a peak plasma concentration (C_{max}) of 0.63 μg/mL after (T_{max}) 1.83 h. The elimination was slow with an elimination rate constant (λ_z) of 0.07 h^{-1}. The clearance was 1.60 L/h (Janchawee et al., 2007). De Moraes and colleagues described a method to detect mitragynine in rat plasma using HPLC and tandem mass spectrometry (LC–MS/MS). In this study an oral dose of 20 mg/kg mitragynine led to a C_{max} of 423.68 ng/mL after a T_{max} of 1.26 h. Elimination half life ($t_{1/2}$) was 3.85 h. Total clearance (CL) was 6.35 L/h/kg. Mitragynine could still be quantified in the plasma after 24 h (de Moraes et al., 2009). Mitragynine was determined in the plasma with solid-phase extraction and rapid HPLC–UV analysis in a study by Parthasarathy et al. (2010). After intravenous administration of 1.5 mg/kg, the C_{max} was 2.3 ± 1.2 μg/mL after $T_{max} = 1.2 \pm 1.1$ h. Elimination half life ($t_{1/2}$) was 2.9 ± 2.1 h. The CL was 0.29 ± 0.27 L/h/kg. After oral administration of 50 mg/kg mitragynine, C_{max} was 0.7 ± 0.21 μg/mL after T_{max} 4.5 ± 3.6 h with $t_{1/2}$ of 6.6 ± 1.3 h. The apparent total CL was 7.0 ± 3.0 L/h/kg. The bioavailability after oral administration was $3.03 \pm 1.47\%$ in this study (Parthasarathy et al., 2010).

9. Metabolism and detection

The main alkaloids of *M. speciosa* are mitragynine, paynantheine, and speciogynine. Macko et al. (1972) suggested that the mitragynine is metabolized into 7-HMG or another more active compound. The confirmation of the exposure and the abuse of *M. speciosa* are permitted by identification of mitragynine and its metabolites in urine samples using gas chromatography with mass spectrometry (GC–MS; Kaewklum et al., 2005), liquid chromatography with linear ion trap mass spectrometry (LC–LIT-MS; Philipp et al., 2009, 2010a, 2010b; Arndt et al., 2011) or with electrospray tandem mass

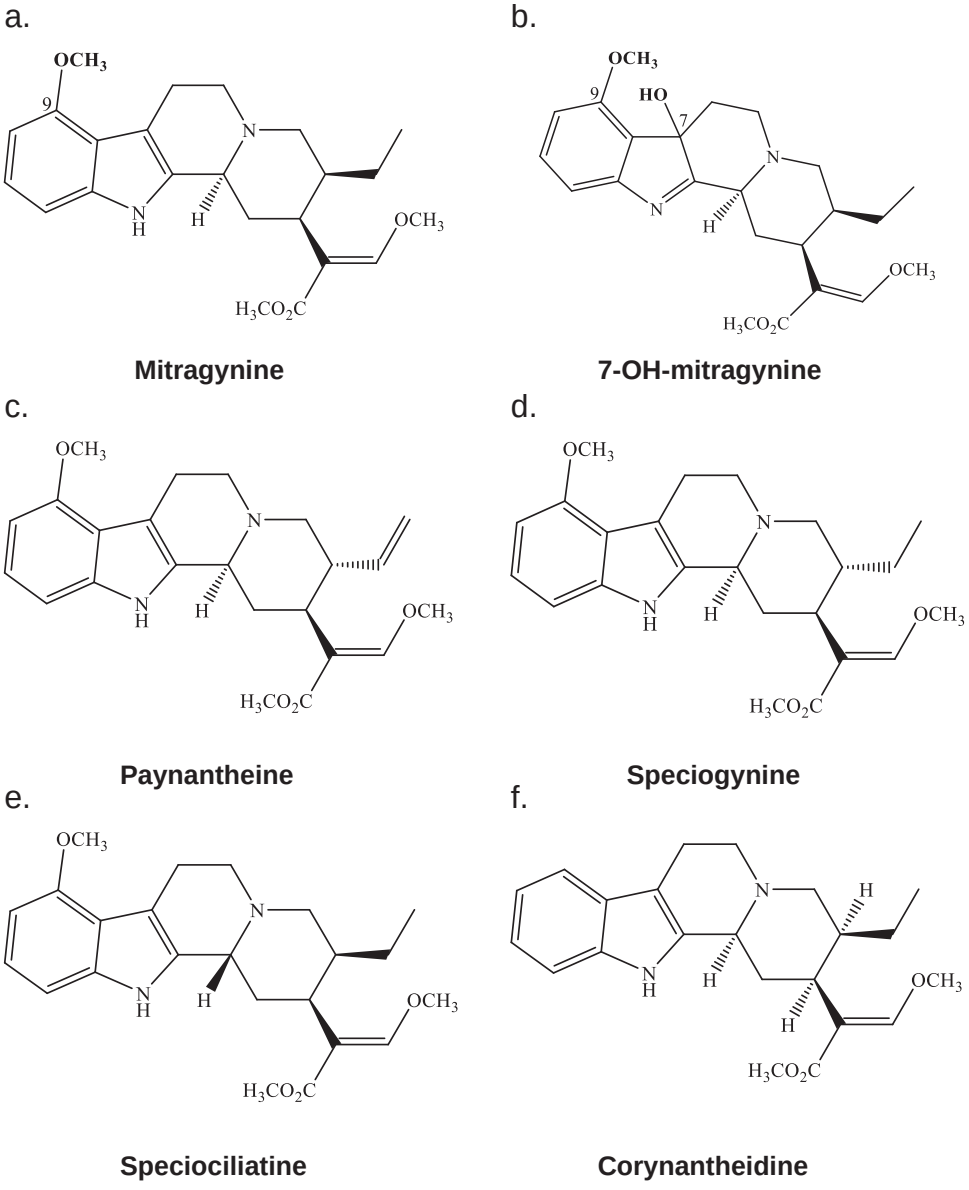

Fig. 2. Chemical structure of mitragynine and its major analogues.

spectrometry (HPLC–ESI/MS/MS; Lu et al., 2009; Le et al., 2012). Phase I and II metabolism studies in rats indicate that mitragynine undergoes hydrolysis of the methylester in position C16, O-demethylation of the 9-methoxy group and of the 17-methoxy group. The intermediate aldehydes undergo oxidation and reduction to form carboxylic acids and alcohol. Finally, conjugation of four phase I metabolites formed glucuronides and one sulphate in rats and three glucuronide metabolites and three sulphates in humans (Philipp et al., 2009; Maurer, 2010). Full metabolic pathways in rats and humans were recently proposed by Maurer and colleagues (Philipp et al., 2011).

More recent use of *Kratom* in Thailand and Malaysia suggest that *M. speciosa* preparations are mixed with other psychoactive drugs. To detect those, Chittrakarn et al. (2012) recently developed a simple HPLC assay which measures mitragynine, codeine, caffeine, chlorpheniramine and phenylephrine in parallel. In a study to evaluate Phase I drug metabolism, *M. speciosa* methanolic extract gave inhibition of more than 90% for CYP 2D6. The IC50 value of *M. Speciosa* methanolic extract was 3.6 ± 0.1 μg/mL, which is in the same concentration range as the CYP 2D6 inhibitor, quinidine (1.09 ± 0.36 μg/mL). Thus, the potential of herb-drug interaction should be taken into account when *M. speciosa* extracts are taken together with drugs mainly metabolized by CYP 2D6 isozymes. At present, the active *M. speciosa* constituents responsible for CYP inhibition are unknown. Therefore, further research is warranted (Hanapi et al., 2010).

10. Toxicology

In animal models, the toxicity of mitragynine was claimed to be relatively low. Macko et al. (1972) found no evidence of toxicity, measured as tremors or convulsions, at doses as high as 920 mg/kg in dogs. However, a more recent study in rats reported lethal effects of 200 mg/kg total alkaloid extract of *M. speciosa* (Azizi et al., 2010). Janchawee et al. (2007) reported lethal effects after an oral dose of 200 mg mitragynine in rats. In an acute toxicity test, the LD50 for oral administration of the methanolic and alkaloid extracts of *M. speciosa* were 4.90 g/kg and 173.20 mg/kg in mice, respectively (Reanmongkol et al., 2007). Acute oral administration of 100, 500 and 1000 mg/kg doses of standardized methanolic

extract of *M. speciosa* did not affect spontaneous behaviour, or food and water consumption in rats. The methanolic extract, however, led to a significant increase in alanine transaminase (ALT) and argininosuccinate lyase (ASL). Nephrotoxicity was seen only at a 1000 mg/kg dose as evidenced by elevated creatinine. A histological examination showed congestion of sinusoids, haemorrhage hepatocytes, fatty change, centrilobular necrosis and increased number of Kuppfer cells in the liver. However, an acute treatment with the methanolic extract did not induce damage in the axons and dendrites of hippocampal neurons (Harizal et al., 2010).

Both, *M. speciosa* preparations and mitragynine, are cytotoxic in human neuronal cells in vitro. Toxicity could be reduced by the opioid antagonist naloxone. However, no genotoxicity was found in the mouse lymphoma gene mutation assay (Saidin et al., 2008). There was also no mutagenic activity using the Ames test in the presence and absence of metabolic activator S9 systems. The aqueous *M. speciosa* extract may even show antimutagenic properties (Ghazali et al., 2011).

Several case studies that emerged more recently provide accumulating evidence for long term toxic effects of *M. speciosa* preparations in humans. Roche et al. (2008) reported the case of a 32-year-old male who was found having seizure-like movements and foaming at the mouth. Movements persisted despite of benzodiazepine treatment and intubation. The patient developed fever, aspiration pneumonia and showed a hypotension episode to intravenous fluids. After extubation 24 h after arrival, the patient admitted the consumption of *Kratom* obtained from the Internet (Roche et al., 2008).

A 64-year-old male was witnessed to have a seizure after acute Kratom consumption followed by a period of unresponsiveness. A urine screen detected a mitragynine concentration of 167 ± 15 ng/mL (Nelsen et al., 2010). The proposed mechanism for this seizure reaction, however, is unclear.

An increase of self-administration of *Kratom* was observed in a 44-year-old patient admitted for detoxification. Initial consumption of *Kratom* developed from 4 g single dose to twice daily after 3 months. In order to attain desirable effect of euphoria, the dose was further increased to 8 g as tolerance developed after 9 months. The patient was reported to experience withdrawal symptoms from opioids and elevated γ-glutamyltransferase of 107 U/L after regular dosing of 40 g every 6 h. The adverse effect of long term *Kratom* use included anorexia, weight loss, hyperpigmentation, psychosis, constipation, insomnia, fatigue, and poor concentration. However, the patient also showed a history of alcohol dependence and anxiety disorder (McWhirter and Morris, 2010).

One case report described a 44-year-old patient with history of alcohol abuse and '*Kratom* addiction', who developed severe primary hypothyroidism after *Kratom* use for 4 months. The patient presented for treating chronic abdominal pain. The patient became lethargic and developed a myxedematous face following opiate withdrawal symptoms. Improvement of his thyroid functions were seen after fifteen months oral opiates (methadone and oxycodone) combined with levothyroxine (Sheleg and Collins, 2011). A causal relationship between *Kratom* use and thyroid dysfunction has not been identified yet. Possibly, a high dose of mitragynine may reduce the normal response of the thyroid gland and result in an imbalance of thyroid-stimulating hormone (TSH). It was found that morphine suppresses TSH in animal models (Meites et al., 1979; Rauhala et al., 1998) and in stressed patients (Ogrin and Schussler, 2005).

A case report from Germany describes a 25-year-old man admitted to hospital with noticeable jaundice and pruritus after taking an overdose of *Kratom* powder over the course of 2 weeks. A subsequent liver biopsy identified drug-induced intrahepatic cholestasis. Both urine and serum samples confirmed presence of mitragynine and absence of paynantheine and other synthetic adulterants (Kapp et al., 2011).

The psychoactive preparation *Krypton* consist of powdered *Kratom* leaves mixed with the μ-opioid receptor agonist, O-desmethyltramadol, an active metabolite of the commonly prescribed analgesic tramadol (Dresen et al., 2010). In a series of 9 lethal cases from Sweden, both mitragynine (0.02–0.18 μg/g) and O-desmethyltramadol (0.4–4.3 μg/g) were detected in the post mortem blood samples of *Krypton* users over a 1-year time. It was suggested that the addition of both, μ-opioid receptor agonists, mitragynine and O-desmethyltramadol, to the herbal mixture may have caused the unintentional death (Bäckstrom et al., 2010; Kroonstad et al., 2011). However, since no data for lethal doses in humans are available yet, the contribution of mitragynine to polytoxic causes of death is currently hard to estimate (Holler et al., 2011).

Overall, a number of animal and human case studies suggest toxic and potentially lethal effects of *M. speciosa* preparations. The cases were either due to long term consumption with an accumulating dose regimen or an acute overdose. It is currently unclear which substances at what dose ranges may be responsible for these effects. Further studies are clearly warranted here.

11. Pharmacology

11.1. Receptor interactions

Mitragynine displays a high affinity to μ-opioid receptors (Yamamoto et al., 1999). Also its oxidative derivative, mitragynine pseudoindoxyl, exhibits potent opioid agonistic properties in vitro. Pharmacological investigations have shown that mitragynine acts at supraspinal μ- and δ-opioid receptors for its antinociceptive effects (Matsumoto et al., 1996a; Tohda et al., 1997; Thongpradichote et al., 1998). However, for other psychoactive effects, central opioid receptors may be more relevant. The affinity of mitragynine to δ- and κ-opioid receptors is considerably lower, but higher than that of morphine. It was shown that the methoxy group at the C9 position as well as the *N*b lone electron pair in the fundamental structure are essential for the opioid agonist activity (Takayama et al., 2002; Taufik Hidayat et al., 2010). A high opioid receptor potency was found for the minor *M. speciosa* constituent 7-HMG, suggesting full agonist properties. *Kratom* powder was found to have a 350-fold less affinity to the μ-opioid receptor than morphine in a 3H-[D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin (3H-DAMGO) radioligand binding assay in HEK 293 cells (Havemann-Reinecke, 2011).

11.2. Cellular effects

At cellular level, mitragynine inhibits neurotransmitter release from the nerve endings at the vas deferens, partly through the blockade of neuronal Ca^{2+} channels (Matsumoto et al., 2005b). The authors proposed the neuronal Ca^{2+} channel-blocking effect of mitragynine as a general mechanism for the analgesic and other physiological actions of mitragynine. In addition, mitragynine was shown to inhibit forskolin-stimulated cAMP formation in NG108-15 cells in vitro. This effect could be blocked by the opioid receptor antagonist naloxone, but not by the alpha-2-adrenoceptor antagonist idazoxane (Tohda et al., 1997).

12. Physiological effects

12.1. Antinociceptive effects

The opioid receptor agonistic action was assessed using the twitch contraction of the guinea pig ileum induced by electrical stimulation. Opioid agonist activity is measured as the inhibition

of the twitch contraction, which is reversed by the opioid receptor antagonist naloxone. *M. speciosa* preparations, mitragynine, and other isolated *M. speciosa* indole alkaloids as well as mitragynine derivatives inhibited the electrically stimulated contraction (Takayama et al., 2002; Horie et al., 2005; Matsumoto et al., 2005b).

The oral administration of *M. speciosa* preparations has antinociceptive effects. Methanolic and alkaloid *M. speciosa* extracts prolonged the latency of a nociceptive response to noxious stimulation in the hot-plate test, but not in the tail-flick test (Reanmongkol et al., 2007). In accordance with these findings was a study by Shaik Mossadeq and colleagues who showed that the methanolic extract of *M. speciosa* increased the latency of nociceptive responses in hot-plate test in mice. Findings in acetic-acid-induced writhing and the formalin test further proved that the methanolic extract has an antinociceptive activity as it significantly inhibits the writhing responses and pain sensation in both tests (Shaik Mossadeq et al., 2009). Sabetghadam et al. (2010) compared the antinociceptive effects of various orally administered *M. speciosa* extracts with that of morphine in rats. Alkaloid (20 mg/kg), methanolic (200 mg/kg) as well as aqueous (100–400 mg/kg) *M. speciosa* extracts significantly prolonged the latency of nociceptive responses in both, the hot plate and the tail flick tests. These and the morphine effects could be blocked by pre-administration of the opioid antagonist naloxone, which suggests an opioid-receptor mediated effect for the *M. speciosa* extracts (Sabetghadam et al., 2010). The anti-nociceptive effect of 100 mg/kg (p.o.) *M. speciosa* alkaloid extract could be further potentiated by co-administration of caffeine (25 mg/kg, p.o.) and codein (3 mg/kg, p.o.) in a hot plate test in rats (Botpiboon et al., 2007).

Mitragynine and mitragynine pseudoindoxyl administered intracerebroventricularly had an antinociceptive effect in the tail-flick test in mice. The ED_{50} estimate for this effect was 60.22 nM and 6.51 nM, respectively. The antinociceptive effects of both substances could be blocked by naloxone, suggesting an opioid receptor mediated mechanism (Takayama et al., 2002; Horie et al., 2005). Also orally administered mitragynine (200 mg/kg) had antinociceptive effects in mice when tested in the acetic acid induced writhing, and the hot and cold tail-flick tests. Those effects were less pronounced than that of 5 mg/kg morphine but more evident than after 100 mg/kg paracetamol (Idid et al., 1998). In other studies, Watanabe and colleagues showed that the antinociceptive effect of mitragynine is approximately 13 times more potent than that of morphine (Matsumoto et al., 1996a; Watanabe et al., 1997). A further study revealed that the minor constituent of *M. speciosa*, 7-HMG, is a 46-fold more potent analgesic than mitragynine (Matsumoto et al., 2005a). 7-HMG, has been found to have a more potent antinociceptive activity than morphine in the tail-flick and hot-plate tests when administered orally or subcutaneously. The higher potency and more rapid effect of 7-HMG, compared to morphine, was hypothesized to depend on its more lipophilic character and its ability to easily penetrate the blood brain barrier (BBB; Matsumoto et al., 2006). However, compared to mitragynine, the additional hydroxyl group makes 7-HMG more polar, which might in fact reduce BBB penetration. Thus, the actual mechanisms for the high potency of 7-HMG are currently unknown. The antinociceptive effect of 7-HMG was dose-dependent and primarily mediated through μ_1-opioid receptors because the effect in both, tail-flick and hot-plate tests, was completely abolished through blockade of this receptor (Takayama, 2004). In addition, supraspinal δ- and κ-opioid receptors have also been considered partially responsible for the antinociceptive activity of 7-HMG (Matsumoto et al., 2005a, 2006). Moreover, the two naturally derived *M. speciosa* indole alkaloids, 7-HMG and (E)-methyl 2-(3-ethyl-7a, 12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate (MGM-9), produced a potent μ-opioid receptor-mediated antinociceptive effect, much stronger that the effect of morphine (Matsumoto et al., 2004, 2005a,b, 2006, 2008).

The suppressive action of mitragynine on nociceptive responses differed from that of morphine in mice (Watanabe et al., 1997) and from that of codeine in dogs (Macko et al., 1972; Jansen and Prast, 1988b). It exhibited different sensitivities to serotonin (5-HT) depletion. Thus, both types of drugs may interact with different opioid receptor subtypes involving serotonergic pathways. The dorsal raphe nucleus, a major serotonergic brain area, has been shown to be one of sites of *M. speciosa* action in the CNS (Kumarnsit et al., 2007b). A significant increase in the expression of the immediate early gene, *cfos*, in this region was observed following 60 days of treatment with an alkaloid extract of *M. speciosa* in male Wistar rats. Acute administration, however, slightly increase the expression with no significant changes compared to the control. These findings suggest that chronic treatment with *M. speciosa* extract activates cells in the dorsal raphe nucleus. Despite containing various cell types, a major sub-population in the dorsal raphe nucleus are serotonergic neurones. There is a possibility that induction of Fos-like immunoreactivity by *M. speciosa* extract is localized at least in part in the serotonergic neurons (Matsumoto et al., 1996b; Kumarnsit et al., 2007b). Both, descending noradrenergic and serotonergic systems appear to be involved in the antinociceptive activity of mitragynine in mechanical noxious stimulation (e.g. tail-pinch) tests. In contrast, the descending noradrenergic system seemed to contribute predominantly to the action of mitragynine on thermal noxious stimulation (e.g. hot-plate test) (Matsumoto et al., 1996b). Mitragynine and the 5-HT_{2A} receptor antagonist ritanserine are able to attenuate the head-twitch response in mice induced by stimulating postsynaptic α_2-adrenoceptors (Matsumoto et al., 1997).

12.2. Anti-inflammatory effects

Inflammation is a response to pathogens, chemical or mechanical injury, or based on neurogenic loops (neurogenic inflammation). The methanolic extract of *M. speciosa* also has anti-inflammatory properties. An intraperitoneal administration of an *M. speciosa* extract was able to inhibit the development of a carrageenan-induced paw oedema with a maximal inhibition during first 3 h after the challenge. The extract may exert its anti-inflammatory effect by inhibiting the synthesis, release and action of a number of hyperalgesic mediators. Thereby, it suppresses the early phase of the oedema, which is the characteristic of acute inflammation. Arachidonic acid and its metabolites might be responsible for the inhibitory activity of the extract for a period of 4 h. Daily administration of the *M. speciosa* extract was also able to inhibit the growth of granuloma tissue as characterized by proliferation of modified macrophages, fibroblasts and highly vascularized and reddened mass tissue. The authors suggested that inhibition of pro-inflammatory mediator release and vascular permeability in combination with enhanced immunity, stimulation of tissue repair and healing processes may have contributed to the anti-inflammatory properties of *M. speciosa* (Shaik Mossadeq et al., 2009).

An inflammatory response is mediated by a series of inducible genes that control host immune defence, downstream signalling, and vascular regulation. The cyclooxygenase isoforms, COX-1 and COX-2, are critical oxygenases involved in the inflammatory pathway and catalyse prostaglandin PGE_2 formation. PGE_2 is one of the strongest inflammatory mediators. Mitragynine was shown to inhibit COX-2 mRNA and protein expression as well as PGE_2 formation in a dose-dependent manner in RAW264.7 macrophage cells. It did not affect COX-1 mRNA and protein expression at lower concentrations, but may inhibit them at higher doses (Utar et al., 2011).

M. speciosa preparations are traditionally used for its antibacterial effects to treat intestinal infections. Azizi and colleagues tested the effects of aqueous and alkaloid extracts of *M. speciosa* on glutathione transferase activity (GST) in rats. GST is involved in the detoxification of toxic and carcinogenic compounds in cells and protects against toxic injuries. The authors report a significant increase in GST in vivo after treatment with the aqueous, but not with the methanolic extract for 14 days (Azizi et al., 2010). The aqueous, alkaloid and methanolic extracts showed antioxidant properties using the 2,2-diphenyl-1-picrylhydrazyl radical scavenging method. Also antimicrobial activity against *Salmonella typhi* and *Bacillus subtilis* were found (Parthasarathy et al., 2009).

12.3. Gastrointestinal effects

Acute and chronically *M. speciosa* extract treated rats showed a suppression of food- and water intake. Also, weight gain was reduced. (Kumarnsit et al., 2006). The methanolic extract of *M. speciosa* reduced the defecation frequency and faecal weight in castor oil-induced diarrhoea in rats. However, the methanolic extract of *M. speciosa* may affect mechanisms other than opioid-receptor mediated since naloxone pre-treatment showed no effect on the inhibition of the defecation frequency and faecal weight. A single dose of the methanolic extract of *M. speciosa* also resulted in a dose-dependent reduction of the intestinal transit. Repeated treatments with this extract, however, did not cause any significant change of the intestinal transit and fluid (Chittrakan et al., 2008). The level of cholecystokinin, a peptide hormone of the gastrointestinal system which is associated with hunger suppression, was not affected by the methanolic extract of *M. speciosa.* These findings suggest that the anorectic effect of the plant extract may be attributed to other factors (Chittrakan et al., 2008). In a cellular model in rat L8 myotubes, however, it was shown that *M. speciosa* preparations increase the rate of glucose uptake and protein levels of glucose transporters, which may contribute to anti-diabetic effects (Purintrapiban et al., 2011).

Central administration of mitragynine into the lateral ventricle did not alter the basal gastric acid secretion, but administration into fourth ventricle of anesthetized rats caused an inhibition of 2-deoxy-D-glucose-stimulated gastric acid secretion in a dose-dependent manner. This inhibition was reversed by naloxone indicating the involvement of opioid receptors. The effects of mitragynine, particularly anorexia and weight loss, might be related to direct inhibition of neurons in the lateral hypothalamus (Tsuchiya et al., 2002). Subcutaneous 7-HMG also caused an inhibition of the gastrointestinal transit in mice (Matsumoto et al., 2006).

12.4. Other physiological effects

Acute oral administration of 100, 500 and 1000 mg/kg doses of standardized methanolic extract of *M. speciosa* increased blood pressure in rats 1 h after administration (Harizal et al., 2010).

Chittrakarn et al. (2010) reported that a methanolic *Kratom* extract caused muscle relaxation in rats. Thereby, the extract had a greater effect at the neuromuscular junction than on the skeletal muscle or at the somatic nerve. The *Kratom* extract and mitragynine (2 mg/mL) blocked the nerve conduction, amplitude and duration of compound nerve action potential (Chittrakarn et al., 2010).

In addition to the above reviewed effects of *M. speciosa*, the plant preparation may also interact with the effects of other drugs by changing their metabolism. Phase I metabolism involves redox and hydrolysis reactions which are catalysed by cytochrome P450 enzymes. Hanapi and colleagues tested the effects of a methanolic *M. speciosa* extract on the activity of three main CYP450 enzymes, CYP2C9, CYP2D6, and CYP3A4. A *M. speciosa* preparation inhibited the activity of all three tested CYP450s with the most potent effect on CYP2D6 (Hanapi et al., 2010).

Altogether, *M. speciosa* extracts and mitragynine have a number of physiological effects. Present evidence strongly supports analgesic, anti-inflammatory, as well as anorectic effects. Mitragynine and 7-HMG interact with μ-opioid receptors in the CNS. However, a number of these physiological effects appear to be opioid receptor independent and may involve neuronal Ca^{2+} channels and descending noradrenergic and serotonergic projections. It may thus be a challenge for future studies to fully characterize binding sites and mechanisms of action for mitragynine and related compounds.

13. Neurophysiological effects

The investigation of the nervous system involvement in the action of *M. speciosa*, as well as its alkaloids and derivatives, receives growing scientific interest. Dating back to 1932, Grewal distinguished two ways of action for mitragynine in the nervous system. First, there are the effects on the autonomic nervous system, which consist of a facilitation of the passage of impulses affecting both the crania-sacral and sympathetic divisions. Second, there are the effects on the central nervous system, which consist of an excitation of the medulla, probably the motor centres (Grewal, 1932a). Farah Idayu et al. (2011) suggest antidepressant effects of mitragynine at the behavioural level, which could be mediated by a restoration of monoamine neurotransmitter levels including serotonin, noradrenalin and dopamine, and/or 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. An increase in corticosterone activity is a response to natural stressors. Abnormal production of corticosterone, however, is associated with depression. These findings are in line with the outcomes observed using different antidepressant compounds by other researchers, but with the same approach for screening novel antidepressant compounds (Farah Idayu et al., 2011).

Recent studies on acute and chronic administrations of mitragynine in mice showed contrasting impact on cognitive function. Chronic mitragynine (5-15 mg/kg; i.p.) administration for 28 days significantly reduced locomotor activity in an open field test and object recognition, a test of working memory, in mice (Apryani et al., 2010). In contrast, acute oral exposure of either mitragynine or an *M. speciosa* extract had no significant effect on short term memory and motor coordination in mice using Y-maze test and rota-rod, respectively. However, it increased exploratory activity in the Y-maze (Hazim et al., 2011).

Another study using an avoidance task demonstrated that mitragynine given orally facilitated learning but had no benefit on the long-term memory consolidation. Post-training administration of methanolic extract of *M. speciosa* (100-1000 mg/kg) facilitated learning as shown by the decreased number of trials during retention test. The step-through latency showed an impairment in memory consolidation of a passive avoidance task. Long-term memory consolidation in a two-way active avoidance task demonstrated no significant changes between methanolic extract of *M. speciosa*-treated groups and control groups (Senik et al., 2012a). In order to elucidate the physiological mechanism for putative cognitive effects of *M. speciosa*, Senik et al. (2012b) investigated the effects of a methanolic *M. speciosa* extract on field excitatory post-synaptic potentials (fEPSP) and the induction of long term potentiation (LTP) in hippocampal slices of rats. They found a significant inhibition of hippocampal fEPSP with an IC_{50} of 0.008%. The same concentration of the *M. speciosa* extract prevented LTP induction, but induced a short term potentiation. These findings may

be one mechanisms of how *M. speciosa* compounds might affect learning and memory pathways in the brain (Senik et al., 2012b).

Taken together, at present studies on the cognitive and neurophysiological effects of mitragynine and *M. speciosa* preparations are scarce. In some tests mitragynine and *M. speciosa* preparations appear to have ambiguous effects on learning and memory, possibly by an interaction with synaptic transmission and plasticity. However, the understanding of the short- and long term effects on cognitive function and underlying mechanisms is still in its infancy and warrants further investigation.

14. Behavioural effects in humans

A survey in Malaysian short- and long-term users of *M. speciosa* revealed subjectively perceived effects. Users reported that the drug could enhance the capability of one's hard work, made the person more energetic and improve the sex libido. On the other hand, the long-term consumption caused weight loss, constipation and dehydration with excessive thirst. However, it could not be completely ascertained if these symptoms were due to the effects of *M. speciosa* alone or due to a combination with other drugs (Vicknasingam et al., 2010).

The behavioural effects of mitragynine are little investigated in humans. Also the consequences of *Ketum/Kratom* consumption are little understood so far. Alamdari (2012) and Singh (2012) attempted to objectively measure some of the effects of *Ketum* use in non-treatment settings. It was found that *Ketum* users had poorer performance compared to heroin users in visu-spatial perception while there were no impairment among long-term and short-term *Ketum* users in logical reasoning, executive function and visual memory. While these studies are of very recent origin, they need to be cautiously interpreted. Also in this area, well controlled experimental studies with dose-response estimates and clearly described test methods are needed.

15. Putative addictive properties

It has long been claimed that *M. speciosa* would have both, narcotic and stimulant-like effects. Both of them might constitute an abuse potential (Suwanlert, 1975; Jansen and Prast, 1988b). There are historical records that confirm a systematic use and potential abuse of *M. speciosa* preparations, and more recently of mitragynine itself (Boyer et al., 2007, 2008; McWhirter and Morris, 2010; Sheleg and Collins, 2011; Kapp et al., 2011). The use of *M. speciosa* as a substitute for opium was first described in early 1800s by Low (for review see: Burkill, 1935) and later by Holmes (1895). The leaves of *M. speciosa* contain a number of active alkaloids that produce narcotic-like actions when smoked, chewed, or drunk as a suspension (Wray, 1907a). Regardless of the method of administration, it produced opium-like effects, and was taken when opium was unavailable or unaffordable (Burkill, 1935). Despite the ban on *M. speciosa*, its sale and use remains active in Southeast Asia as local people continue assuming it as traditional remedy. There are reports published from two countries where *M. speciosa* consumption has always been popular; Thailand and Malaysia (Suwanlert, 1975; Vicknasingam et al., 2010; Ahmad and Aziz, 2012). Traditionally, *M. speciosa* is consumed to enhance physical effort and endurance. The *M. speciosa* users rely upon it to give them strong desire to work, especially under a scorching sun. The users described themselves as feeling happy, strong and active after five to ten minutes of *M. speciosa* consumption (Suwanlert, 1975). This may be seen as a systematic 'drug instrumentalization', which precedes addictive consumption of many psychoactive drugs (Müller and Schumann, 2011). The psychomotor stimulant effects lead them to continue consuming *M. speciosa* until consumption develops into a habit. Cheapness and relative local availability may be contributing factors when *M. speciosa* users gradually increase their daily dosage (Suwanlert, 1975; Chan et al., 2005; Vicknasingam et al., 2010).

Suwanlert (1975) reported that the chronic exposure to *M. speciosa* preparations can be followed by withdrawal symptoms in humans. Typical withdrawal symptoms include hostility, aggression, excessive tearing, inability to work, aching of muscle, bones, and jerky limb movements. Long term users experienced anorexia, weight loss, insomnia, and darkening of the skin, particularly on the cheeks. Other side effects include dry mouth, frequent micturition, and constipation coupled with small blackish stools. Some case reports indicate psychotic symptoms due to *M. speciosa* abuse (Suwanlert, 1975; Sheleg and Collins, 2011). Putative *M. speciosa* addicts are able to meet their work requirements in the early stage of the abuse. However, after prolonged consumption working activities are disturbed due to physical and psychiatric problems.

Anxiety, restlessness, tremor, sweating and craving for *M. speciosa* were some of the withdrawal symptoms caused by *M. speciosa* dependence in an old man with an additional history of alcohol and anxiety disorder (McWhirter and Morris, 2010). Given mitragynine affinity to μ-opioid receptors, it is tempting to speculate that dependence and withdrawal syndromes may be mediated via this pathway. Although descriptive reports suggest that *M. speciosa* users might become addicted (Suwanlert, 1975), scientific reports on the rewarding properties of the plant or its active compounds are scarce at present. A systematic investigation of the epidemiology of *M. speciosa* addiction as well as of the health problems related to it is strongly warranted. This is especially important in the light of the increasing availability of the major constituent, mitragynine, as a pure substance.

It is known that the rewarding properties of a drug can lead to dependence and addiction. This issue has been addressed by Matsumoto et al. (2008), whereby the rewarding properties of *M. speciosa* metabolites and its derivatives have been studied in animals using a place conditioning procedure. In this paradigm, animals are trained to associate a specific environment with the incentive properties of a drug. Following the conditioning procedure, a single test is performed to determine the establishment of conditioned place preference (CPP). Using this approach, the subject developed a CPP when it spends a significantly greater amount of time in the drug-paired environment compared to a baseline or a saline control group (Sanchis-Segura and Spanagel, 2006; Olmstead, 2006). 7-HMG, which has a hydroxyl group at the mitragynine C7 position, induced a significant CPP compared to the vehicle group in mice. On the other hand, the ethylene glycol-bridged and C10-fluorinated derivative of mitragynine, MGM-9, did not exhibit significant rewarding effects using the same procedure (Matsumoto et al., 2008). To the best of our knowledge, there is no clear evidence showing the rewarding effect of either *M. speciosa* extracts or mitragynine itself so far. Also self-administration studies are currently lacking.

Drugs of addiction are well known to activate the dopaminergic and serotonergic systems, which are key mechanism in their habit forming properties (McBride et al., 1999; Wise, 2002; Müller et al., 2007, 2010). Since mitragynine action resembles morphine activities, one may speculate that mitragynine may as well activate dopaminergic and serotonergic activity. However, this still awaits experimental proof.

Drug tolerance is commonly encountered when a subject's reaction to a specific drug is progressively declined, requiring an increase in concentration to achieve the desired effect. Repeated administration of 7-HMG and MGM-9 for 5 consecutive days produced tolerance in mice. The development of tolerance was noted as a significant reduction of the analgesic effect of each substance. The antinociceptive tolerance to 7-HMG is mediated by

μ-opioid receptor, while the antinociceptive tolerance to MGM-9 is mediated by both, μ- and κ-opioid receptors (Matsumoto et al., 2005a, 2008). Animals rendered tolerant to 7-HMG also displayed cross-tolerance to morphine's antinociceptive action and vice versa. 7-HMG induces physical dependence as shown by the significant withdrawal signs after naloxone injection (Matsumoto et al., 2005a).

To the best of our knowledge there are currently no systematic studies investigating the potential of mitragynine or its derivatives for the treatment of opiate withdrawal symptoms in humans or rodent models. However, a recent study addressed this question in a morphine withdrawal model in zebra fish. Morphine was shown to induce a significant dose-dependent CPP in zebra fish. Twenty four hours after these animals were withdrawn from a 2-week chronic morphine (1.5 mg/L) treatment they showed anxiety-related swimming behaviours with decreased exploration and increased erratic movements. The morphine withdrawal effects could be attenuated by mitragynine (2 mg/L). Morphine withdrawal increased whole body cortisol levels, suggesting withdrawal to be a stressful situation for zebra fish. Also the expression of corticotropin releasing factor (CRF) receptor 1 and 2, as well that of prodynorphine transcripts was significantly elevated during withdrawal. Mitragynine was able to reduce the effects on cortisol levels and to normalize transcript levels (Khor et al., 2011). These findings suggest that mitragynine may indeed be effective in ameliorating opiate withdrawal effects. There is also evidence which suggests beneficial effects of an aqueous extract of *M. speciosa* (300 mg/kg) on symptoms of alcohol withdrawal in mice (Kumarnsit et al., 2007a).

Taken together, the available evidence from human reports and animal studies suggests that *M. speciosa* extracts and its psychoactive compounds may have an addiction potential. The drug is initially used for rather well defined purposes, thus suggesting systematic instrumentalization. There is evidence for tolerance development during prolonged use which may drive an increase in dose to maintain the desired effects. Escalating doses appear to enhance aversive side effects, which makes the consumption an increasing health risk. Abandoning consumption appears to induce aversive withdrawal effects. At present it can only be speculated that these effects may be driven by interactions with monoaminergic systems, in particular serotonergic and noradrenergic systems, as well as with opioid receptors. However, evidence for the acute and long term neurophysiological effects in the reward and memory systems of the brain are currently missing and warrant further research.

16. Conclusion

Kratom/Ketum is a psychoactive plant preparation with a long established use in Southeast Asia. It is derived from the plant *M. speciosa* in various preparations. While the abuse constitutes a local problem in this region of the world, *M. speciosa* preparations *and* the purified active compound of this preparation, mitragynine, currently spread on a world wide scale. In that the question of addiction potential and adverse health consequences of the consumption is no longer a local one but may soon affect wider regions of the world. Currently, law makers are very much restricted in their handling of *M. speciosa* derived compounds by limited evidence on pharmacological, toxicological, neurophysiological, and behavioural effects of these substances. Here we summarized the available evidence and identified future research needs. This review shows that mitragynine and *M. speciosa* preparations are systematically consumed with rather well defined instrumentalization goals in Southeast Asia. There is indeed scientific evidence accumulating which strongly supports antinociceptive, anti-inflammatory and gastrointestinal effects, which might allow the use as medical treatment for various conditions. On the other hand, an uncontrolled consumption of both, plant preparations as well as mitragynine, may escalate upon tolerance development and yield aversive withdrawal effects upon abstaining from consumption. Although the available data may still show a lack of power and systematic approach, available evidence points towards an addiction potential of mitragynine and *M. speciosa* preparations. However, the mechanisms of action in the brain are still poorly understood. Future studies need to monitor the epidemiology of use, instrumentalization patterns and risk of addiction development. For a proper classification of mitragynine and other *M. speciosa* derived compounds, a full understanding of neurophysiologic and behavioural effects is required.

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