

Genus *Mitragyna*: Ethnomedicinal uses and pharmacological studies

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Abstract

Mitragyna genus, belongs to Rubiaceae family, distributed in Africa and Asia. Many species in *Mitragyna* genus have a history of use as a medicinal plant. Traditionally, it has been used to treat fever, malaria, diarrhea, muscle pain, inflammation and hypertension. Phytochemical research has showed that alkaloids, triterpenoids and flavonoids were main compounds in *Mitragyna* genus. Pharmacology investigation demonstrated that plant of *Mitragyna* possess wide pharmacological effects, in antitumor, cardiovascular disease and antibacterial activity. This review aims to update information on its pharmacological effects.

Keywords: Genus *Mitragyna*; ethnomedicinal; Mitragynine

Introduction

The genus *Mitragyna* belongs to Rubiaceae family and is found in swampy territory in the tropical and subtropical regions of Asia and Africa (Shellard et al., 1978). Six species, *M. speciosa* (Korth.) Havil., *M. tubulosa* (Arn.) Havil., *M. parvifolia* (Roxb.) Korth., *M. hirsuta* Havil., *M. diversifolia* (Wall. ex G. Don) Havil. and *M. rotundifolia* (Roxb.) O. Kuntze, widely grow in India and Asia (Puff C et al., 2005). Other four species, *M. ciliate*, *M. inermis*, *M. stipulosa* and *M. africanus*, widely grow in west African.

Traditional (ethnomedicinal) uses

The genus *Mitragyna* have been used in local folklore medicine for a wide variety of diseases such as fever, malaria, diarrhea, cough, muscular pains and used for the expulsion of worms (Shellard and Phillipson, 1964; Shellard et al., 1971). *M. speciosa* (Korth.) Havil, a species of particular medicinal importance, is known as “Kratom” in Thailand and “Biak-Biak” in Malaysia, and the leaves have been traditionally used by natives for their opium-like effect and coca-like stimulant ability to combat fatigue and enhance tolerance to hard work under the scorching sun. It has been used also as a substitute for opium and for weaning addicts off morphine (Sangun Suwanlert, 1975). However, the use of this plant has been banned in those countries because of its narcotic effect. Other African species, *M. ciliate*, *M. inermis*-

and *M. stipulosa* are used for inflammation, hypertension, headache, rheumatism, gonorrhea and bronchopulmonary diseases. *M. africanus* which is one of an African species is used in Nigeria to treat mental illness (Moklas et al., 2008).

Indole alkaloids (Shellard et al., 1967; Shellard and Houghton, 1974) and triterpenoid saponins (Cheng et al., 2002a,b; Takayama et al., 2004; Kang et al., 2006) were reported in previous phytochemical investigations on *Mitragyna* genus isolation of, and mitragynine, an indole alkaloid, was the major constituent of this plant, accounting for about half of the total alkaloid contents. At the same time, *in vivo* and/or *in vitro* and clinical practice have demonstrated that *Mitragyna* and its active compounds possess wide-reaching pharmacological actions, including antitumor, cardiovascular disease and antibacterial activity. In this review, the advances in pharmacological activities of *Mitragyna* genus are presented.

Pharmacology studies

Antinociceptive activities

Mitragynine, a major indole-alkaloid, isolated from leaves, has effects on guinea-pig ileum, radioligand binding assay and the tail-flick test in mice, and found that mitragynine acts on opioid receptors and possesses analgesic effects (Watanabe et al., 1997; Yamamoto et al., 1999; Takayama et al., 2002). Mitragynine pseudoindoxyl and 7-hydroxymitragynine, exhibited a potent opioid effect on the electrically stimulated contraction in guinea-pig ileum and orally active analgesic effect based on activation of mu-opioid receptors (Horie et al., 2005; Takayama, 2004; Matsumoto, 2004; Matsumoto et al., 2005b). 9-Hydroxycorynantheidine (Figure 1), synthesized from mitragynine, has partial agonist properties on mu-opioid receptors in the guinea-pig ileum (Matsumoto et al., 2005c). In addition, the MeOH extract of *M. speciosa* and *M. ciliate* also exhibited potent analgesic activity by significantly increasing the threshold of sensitivity to pain in the rats (Reanmongkol et al., 2007).

Anti-inflammatory activities

The extracts plants in *Mitragyna* genus showed significant anti-inflammatory effects using carrageenan-induced paw edema tests in mice (Winter et al., 1962). Results showed th-

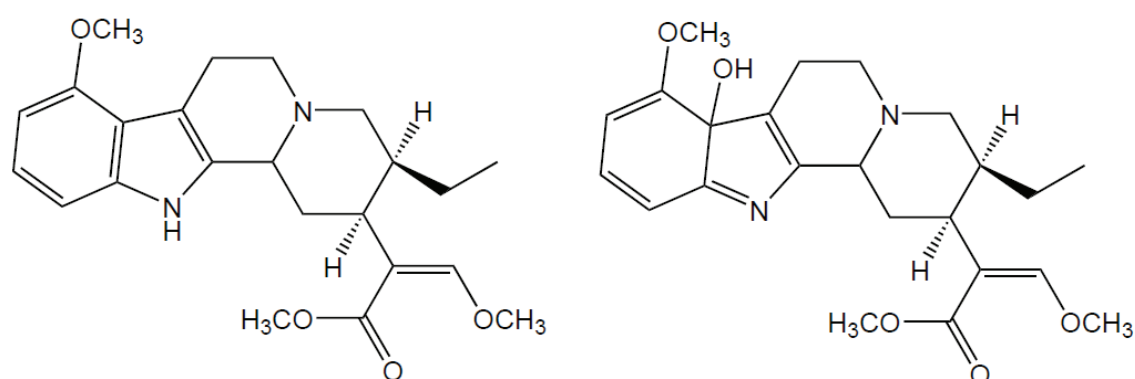


Figure 1. Chemical structures of Mitragynine (left) and 7-hydroxymitragynine (right).

at intraperitoneal administration of the methanol extract of *M. speciosa* (100 and 200 mg/kg, respectively) significantly and dose-dependently suppressed the development of carrageenan-induced rat paw edema ($P < 0.05$). In addition, the maximum anti-inflammatory effect of the extract of *M. parvifolia* was found to be at 300 mg/kg in carrageenan test and this effect was equivalent to phenyl buta zone (PBZ) (80 mg/kg, orally) ($P < 0.05$). The anti-inflammatory activity could be due to the inhibition of cyclooxygenase leading to the inhibition of prostaglandin synthesis, result from a combination of inhibition of pro-inflammatory mediator release and vascular permeability in addition to enhanced immunity, stimulation of tissue repair and healing processes (Dongmo et al., 2003; Gupta et al., 2009; Shaik Mossadeq et al., 2009). The cellular mechanism involved in the anti-inflammatory effects of mitragynine as major bioactive constituent. Results suggested that mitragynine suppressed PGE₂ production by inhibiting COX-2 expression in LPS-stimulated RAW264.7 macrophage cells. It is for the first time to explain the anti-inflammatory pathway of mitragynine, which provide support to the traditional utilization of this plant in pain and inflammation (Utar et al., 2011).

Anticancer activities

Aqueous extract of *M. speciosa* was screened for potential of mutagenic and antimutagenic activity using Ames test (Salmonella/microsome mutagenicity assay). Ames test involved the pre-incubation assay against *Salmonella typhimurium* TA 98 and TA 100 in the presence and absence of metabolic activator S9 system. Every extract was evaluated using two-fold value of the number of revertant's colony in negative control plate as cut-off point, to determine the mutagenicity effects. No mutagenic activity was found for frameshift mutation (TA98) and base-pair substitution (TA100) in all concentrations of *M. speciosa* in the presence and absence of metabolic activator S9 system. Inhibition percentage of revertant's colony was used to evaluate the antimutagenic activity of *M. speciosa* aqueous extract by simultaneous addition of mutagen. Significant antimutagenic activity ($P < 0.001$) were observed in three concentrations of *M. speciosa* as compared with mutagenicity induced by 2-aminoanthracene for both TA 98 and TA 100 with the presence of metabolic activator S9 system. Therefore, *M. speciosa* did not show any mutagenicity effects in both tester strains in the presence and absence of metabolic activator S9 system. However, *M. speciosa* showed strong antimutagenicity properties in both strains with the presence of metabolic activator S9 system (Ghazali et al., 2011).

Arjunolic acids (Figure 2) were isolated from *M. ciliate*, and tested in uiuo on a two-stage carci-nogenesis assay in mouse skin, using dimethyl-benz [a] anthracene (DMBA) as initiator and 12-0-tetradecanoylphorbol-13-acetate (TPA) as promoter. The activities were evaluated by both rate (YO) of papilloma-bearing mice and average number of papillomas per mouse and compared with the control. The mice treated with arjunolicacid triacetat methyleste and arju-nolicacid triacetate, the occurrence of papillomas was delayed compared with the control. With arjunolicacid triacetate methyleste, papillomas occurred in 100% animals only at week 15. The results suggest that arjunolic acid derivatives could be valuable compounds as antitu-mour-promoters (Diallo et al., 1995).

Cardiovascular activities

Mitragyna species is largely growing in West Africa, have been used in traditional medicine in West Africa to cure fever, manage hypertension, and to facilitate delivery (Halle,

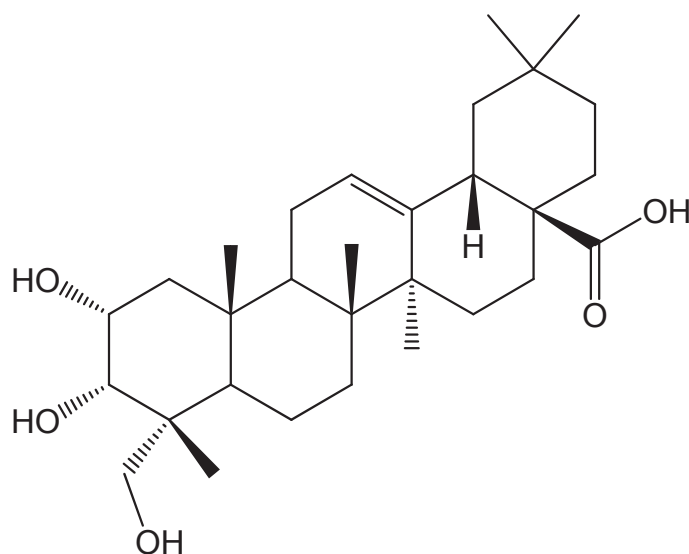


Figure 2. Chemical structures of Arjunolic acid.

1966; Adjanohoun et al., 1985). In order to understand the pharmacological basis for the use of *M. ciliata* in folk medicine for the treatment of cardiovascular diseases, the vascular relaxant effect in the rat and guinea-pig were investigated. The extract induced aortic relaxation in a concentration-dependent manner, with an EC_{50} of 1.3 and 7 $\mu\text{g/mL}$ for the noradrenaline- and KCl-induced contractions, respectively. The relaxant effect of the extract on KCl-induced contractions was five times greater than that on noradrenaline-induced contractions. Moreover, the relaxant effect of the extract was higher in rat aortic rings with endothelium (104.67%) than that without endothelium (49.44%). Results showed that MeOH extract induced a relaxation (vasodilatation action) on aorticvascular rings precontracted with noradrenaline or KCl. The effects might be due to the presence of alkaloids and/or flavonoids (Dongmo *et al.*, 2004).

Aqueous extracts of *M. inermis* used traditionally as antihypertensive agents produced a concentration-dependent (0.1–3 mg/mL) *ex vivo* increase in cardiac contractile response and coronary flow but did not modify heart rate in the rat. Results showed that aqueous extract from *M. inermis* possessed cardiactropic effect and induces an increase in coronary flow without inducing tachycardia in isolated heart. Furthermore, *M. inermis* is able to induce the release of endothelial NO and EDHF in porcine coronary arteries and to produce smooth muscle relaxation in the rat tail arteries (Ouédraogo *et al.*, 2004).

Antidiarrheal activities

The ethanolic extract of *M. diversifolia* bark showed significant ($P < 0.05$) antidiarrheal activity on gastrointestinal motility with barium sulfate milk model and castor oil-induced diarrheal model in rats. The antidiarrheal effects of bark ethanolic extracts may be due to the inhibition of prostaglandin biosynthesis (Jebunnessa *et al.*, 2009). Similarly, *M. speciosa* extract at 50, 100, 200 and 400 mg/kg (p.o.) respectively caused a dose dependent protection against castor oil-induced diarrhea in rats and also inhibited intestinal transit. The effects may occur via pathways in addition to the action on opioid receptors (Chittrakarn *et al.*, 2008; Ma-

tsumoto et al., 2006). These result obtained revealed that the bark extract possess Pharmacological activity against diarrhea and may possibly explain the use of the plant in traditional medicine.

Antioxidant and antibacterial activities

Antioxidant properties for leaves and barks of *M. rotundifolia* were evaluated by DPPH, ABTS, and FRAP assays, respectively. In six extracts of the leaves and barks, ethyl acetate extract from leaves had the highest DPPH and ABTS free radical scavenging activity ($IC_{50} = 2.24$ mg/L and $IC_{50} = 1.165$ mg /L respectively). Which was higher than that of BHA ($IC_{50} = 3.43$ mg/L and $IC_{50} = 1.675$ mg/L respectively) and BHT ($IC_{50} = 18.79$ mg/L and $IC_{50} = 4.555$ mg/L respectively). *n*-Butanol extract from leaves exhibited the highest ferric reducing antioxidant power with FRAP value of 1395.94 μ mol TE/g, *n*-butanol extract from barks (FRAP value =1275.43 μ mol TE/g) was slightly lower than that of the *n*-butanol extract from leaves, and both of them had ferric reducing antioxidant power higher than that of BHT (the FRAP value = 2381.1 μ molTE/g), lowered than that of PG (FRAP value = 5159.97 μ molTE/g) and BHA (FRAP value = 2573.96 μ molTE/g). The results indicate that *n*-butanol and ethyl acetate extracts showed higher antioxidant activity than that of the petroleum ether extract, and the leaves and bark extract of the same solvent had similar antioxidant activity (Kang et al., 2010; Kang WY and Li CF, 2009).

The antioxidant properties of water, methanolic and alkaloid *M. speciosa* leaf extracts were evaluated using the DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging method. The amount of total phenolics and flavonoid contents were also estimated. The DPPH IC_{50} values of the aqueous, alkaloid and methanolic extracts were 213.4, 104.81 and 37.08 μ g/mL, respectively. The total phenolic content of the aqueous, alkaloid and methanolic extracts were 66.0, 88.4 and 105.6 mg GAE/g, respectively, while the total flavonoid were 28.2, 20.0 and 91.1 mg CAE/g respectively. Result showed that the relatively high antioxidant activity of the methanolic extract compared with aqueous and alkaloid extract could be due to its high phenolic content. The extracts showed antimicrobial activity against *Salmonella typhi* and *Bacillus subtilis*. The minimum inhibitory concentrations (MICs) of extracts determined by the broth dilution method ranged from 3.12 to 6.25 mg/mL. The alkaloid extract was found to be most effective against all of the tested organisms (Parthasarathy et al., 2009).

Antioxidant activities for ethanolic extract of *M. parvifolia* leaves were concentration dependent which were compared with standard antioxidants such as BHA and ascorbic acid. The extract was screened for antioxidant and free radical scavenging effects at various concentrations (100, 300 and 500 μ g/mL) by reducing power assay, superoxide radical and DPPH free radical scavenging method. The highest antioxidant activity of *M. parvifolia* leaves extract was observed at a concentration of 500 μ g/mL. The extract in different concentrations was also tested for antibacterial activity using agar well diffusion method. The extract significantly inhibited *S. aureus* and showed some degree of inhibition against *P. aeruginosa* and *E. coli* (Kaushik et al., 2009; Kaushik et al., 2009).

Antiplasmodial and anthelmintic activities

M. inermis and *M. ciliate* were selected by ethnobotanical survey as plants commonly

used by traditional healers for the treatment of malaria. Extracts of these plants were tested on three strains of *Plasmodium falciparum*, FcB1-Colombia and FcM29-Cameroon (chloroquine-resistant strains) and a Nigerian chloroquine-sensitive strain for an evaluation of antiplasmodial activity and cytotoxicity *in vitro*. Extracts were obtained by preparing decoction in water of the powdered plant, the technique used by most of the traditional healers. A radioactive micromethod allowed the evaluation of the activity of the extracts on *P. falciparum in vitro*. Concentrations inhibiting 50% of the parasite growth (IC₅₀) ranged from 2.34 to more than 500 mg·mL⁻¹. The tested plants revealed weak or very low activities. These plants could be effectively more active on *P. falciparum* in man, as it is the case for plants containing prodrugs nonactive by themselves but which can be metabolised to active drugs (Mustofa et al., 2000; M'enan et al., 2006).

The effects of the ethanolic and aqueous extracts of leaves from *M. parvifolia* were examined for their anthelmintic activity against *Pheritima posthuma*. The results suggest that the ethanolic and aqueous extracts significantly demonstrated paralysis and also caused death of worms especially at higher concentration of 50 mg/mL, as compared with albendazole (10 mg/mL) as standard reference (Sahu et al., 2009).

Antidiabetic activities

The inhibitory activities of α -glucosidase of leaves, barks extracts and compounds from *M. rotundifolia* Kuntze. were screened *in vitro*, and the results were compared with acarbose as positive control. The results showed that leaves and barks extracts from *M. rotundifolia* all had inhibitory activity of α -glucosidase, and the activity of leaves was higher than that of barks. The *n*-butanol and ethyl acetate extract from the same part of *M. rotundifolia* had higher inhibitory activity of α -glucosidase than that of the petroleum ether extract. Scopletin had higher inhibitory activity of α -glucosidase (IC₅₀ = 35.03 μ g/mL), and IC₅₀ value was lowered about thirty times than that of acarbose (IC₅₀ = 1081.27 μ g/mL) as positive control (Kang et al., 2010).

The water, methanolic and crude alkaloidal extracts from *M. speciosa* leaves and its major constituent mitragynine for the enhancement of glucose transport had been studied. The results showed that test samples significantly increased the rate of glucose uptake, and the increased glucose transport activity of *M. speciosa* is associated with increases in activities of the key enzymes dependent to then sulin-stimulated glucose transport for its acute action, and increases in the GLUT1 content for its long-term effect. This study demonstrated the effect of *M. speciosa* in stimulating glucose transport in muscle cells, implicating the folkloric use of *M. speciosa* leaves for treating diabetes (Purintrapiban et al., 2011).

Hepatoprotective activities

The effects of *M. speciosa* alkaloid extract (MSE) on human recombinant cytochrome P450 (CYP) enzyme activities using a modified Crespi method. The results indicated that MSE has the most potent inhibitory effect on CYP3A4 and CYP2D6 (IC₅₀ = 0.78 μ g/mL and 0.636 μ g/mL, respectively). In addition, moderate inhibition was observed for CYP1A2 (IC₅₀ = 39 μ g/mL), and weak inhibition was detected for CYP2C19. This study showed that *M. speciosa* alkaloid extract may contribute to an herb-drug interaction if administered conc-

omitably with drugs that are substrates for CYP3A4, CYP2D6 and CYP1A2 (Kong et al., 2011). *n*-Butanol extract from *M. rotundifolia* barks (MRBBU) and leaves (MRLBU) were investigated, and played a protective role against carbon tetrachloride (CCl₄)-induced acute liver injury in mice. The level of MDA decreased significantly ($P < 0.01$ and $P < 0.05$, respectively), except for the group of MRLBU (75 mg/kg) ($P > 0.05$). The level of SOD in liver only in administration of MRLBU (150 and 75 mg/kg, respectively) had no significant increase ($P > 0.05$), the other treatment groups had significantly increase ($P < 0.001$ and $P < 0.05$, respectively). The level of glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) in each treatment group significantly decreased ($P < 0.001$). The result indicates that MRBBU and MRLBU had very good hepatoprotective activity and the hepatoprotective effect may be correlated with its antioxidant effects (Gong et al., 2012).

Other pharmacological activities

The anticonvulsant effect of ethanolic extract from the leaves of *M. parvifolia* was investigated by studying the effects of seizures induced by pentylenetetrazole (PTZ) and maximal electroshock convulsive methods in mice. The extract suppressed tonic hind limb extensions (THLE) induced by MES at the doses of 250 and 500 mg/kg ($P < 0.05$) and also exhibited protector effect in PTZ-induced seizures only at 500 mg/kg ($P < 0.05$). The activity reported was dose dependent in both the models (Kaushik et al., 2009). In other study, mitragynine at dose of 10 mg/kg and 30 mg/kg i.p. injected significantly reduced the immobility time of mice in both FST and TST without any significant effect on locomotor activity in OFT. Moreover, mitragynine significantly reduced the released of corticosterone in mice exposed to FST and TST at dose of 10 mg/kg and 30 mg/kg. The study demonstrated that mitragynine exerts an antidepressant effect in animal behavioral model of depression (FST and TST) and the effect appears to be mediated by an interaction with neuroendocrine HPA axis systems (Idayu et al., 2011). In addition, oral administration of standardized methanolic extraction of *M. speciosa* Korth resulted in increasing rat blood pressure after an hour of drug administration. The highest dose (1000 mg/kg) of extract also induced acute severe hepatotoxicity and mild nephrotoxicity. However, *M. speciosa* Korth showed no effects on body weight, food and water consumption, absolute and relative organ weight and also hematology parameters (Harizal et al., 2010).

Conclusion

Medicinal plants are the local heritage with the global importance. World endowed with a rich wealth of medicinal plants. Medicinal plants also play an important role in the lives of rural people, particularly in remote parts of developing countries with few health facilities. *Mitragyna* genus has a history of use as a medicinal plant, pharmacological studies reported in the present review confirm the therapeutic value of *Mitragyna* genus. The indole alkaloids are the major chemical constituents in *Mitragyna* genus. The plant has been studied for their various pharmacological activities like antinociceptive, anti-inflammatory, anticancer, antidiarrheal, antioxidant and antibacterial, antidiabetic activity, and so on. Then it is necessary to exploit its maximum potential in the field of medicinal and pharmaceutical sciences for novel and fruitful application.

Conflict of interest

There is no conflict of interest associated with the authors of this paper.

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