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The Antidepressant-like Effect of Mitragyna Speciosa Korth

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Abstract: *Mitragyna Speciosa* Korth (MS) was used as an opium substitute in Southeast Asia. It has been shown to have addictive properties and to produce tolerance and dependence. The methanolic leaf extract of *Mitragyna Speciosa*is Known to contain several alkaloids including mitragynine which structurally has an indole moiety. This moiety is also a feature of serotonin which is an important neurotransmitter in depression. This would tend to suggest some activities of MS at the brain serotonergic system. On the other hand, current strategy in designing antidepressants in the form of selective serotonin reuptake inhibitors (SSRIs), this study has investigated whether the methanolic leaf extract of MS possesses antidepressant-like effect. The Porsolt swim test method (PST) for screening antidepressants had been used. Female mice were forced to swim for 6 minutes. This was followed 24h later with a second swim session of 6 min. Drugs were administered (n=10) orally1, 5 and 24h after the first swim session to record chronic effect. The oral administration of MS methanolic leaf extract at doses 100, 200, 400 mg/kg, significantly reduced the immobility time.

Keywords: Mitragyna Speciosa, Mitragynine, Selective Serotonin Reuptake Inhibitors, Antidepressant effects.

1 Introduction

Mitragyna Speciosa (MS) is a large tree belongs to the family *Rubiaceae*. It grows to a height of about 3-4 meters in swampy ground and is native to countries in Southeast Asia.

MS have been traditionally used in Southeast Asia for its medicinal properties. This plant is locally known as “Daun Biak” or “Kratom”.It was used as an opium substitute in Southeast Asia [1]. It has been shown to have addictive properties and to produce tolerance and dependence [2]. In Thailand the labourers use it to increase work efficiency, and is also used by drug abusers when the drug itself is not available [3,4,5]. The methanolic leaf extract of MS contains several alkaloids including mitragynine ($C_{23}H_{30}N_2O_4$) which has a structure with an indole moiety [6,7]. This would tend to suggest some activities at the brain serotonergic receptors. Mitragynine has been reported to exhibit analgesic and antitussive properties in experimental animals [8,9]. It has a low p Ka value and is reported as a lipid soluble compound [10]. It appears to be the only centrally active alkaloid from *Mitragyna Speciosa.*

Depression is common and is characterized by a disturbance of mood with alterations in behaviour, energy, appetite, sleep and weight. The illness is phasic and there is a return to full normality during periods of remission. The drugs used most often to treat endogenous depression inhibit the uptake of neurotransmitters such as noradrenaline and 5-hydroxytryptamine (tricyclics) or are specific inhibitors of 5-hydroxytryptamine uptake (non-tricyclics or monoamine oxidase inhibitors and second generation or atypical antidepressants). The main action of the tricyclic antidepressant drugs is to block the re-uptake of noradrenaline and 5-hydroxytryptamine into their respective nerve terminals in the brain. This results in increased amounts of these neurotransmitters being available at the synapse and hence, increased noradrenergic and serotonergic activity in the brain [10]. Imipramine (antidepressant) is a potent inhibitor of neuronal catecholaminesup take in rat brain including noradrenaline and 5-hydroxytryptamine [11]. It was consistent with the earlier proposed “amine theory of depression” which was thought to be the basis of the pharmacological action of these drugs [12].

Thus, as the alkaloid mitragynine has a structure similarity

to the neurotransmitter serotonin as mentioned above, this study has therefore been carried out to investigate whether the methanolic leaf extract of MS possesses antidepressant-like effect through the central serotonergic system.

2 Materials and Methods

2.1 Materials

2.1.1 Plant Materials

The fresh leaves of MS were collected from Seberang Perai, West Malaysia. Samples were confirmed at Herbarium specimen at the School of Biological Science, UniversitiSains Malaysia. Leaves were dried, milled and macerated in methanol at 50º C for three days. The methanolic leaf extract was then screened for the presence of the alkaloid mitragynine using a precoated TLC plate (UV $_{254}$) with chloroform: acetone (5:4) as a solvent system. Fresh suspension of powdered methanolic leaf extract (50mg/ml containing 5% v/v Tween 80) was prepared. Solutions required are then prepared by adding distilled water.

2.1.2 Animals

Female albino mice weighing (25-40g) were used. Animals were brought into laboratory at least one day preceding an experiment and were housed 10 per cage at a constant temperature (25-30º C). Food and water were available ad lib.

2.1.3 Drug Treatment

Methanolic leaf extract 100, 200, 400 mg/kg was used. The tricyclic antidepressant imipramine HCl 15mg/ ml was from sigma Chemical Company, USA. Control animals were given distilled water with Tween 80.

2.1.4 Data Analysis

The data were analysed by one-way analysis of variance (ANOVA) statistical test that included the four test groups and the untreated control followed by Duncan test, with $p< 0.05$ as the significant level for all.

2.2 Methods

2.2.1 Induction and Measurement of Immobility by Forced Swim Test

The forced swim test was carried out in this study according to the method of Porsolt et al [13,14] with minor modification. Mice were randomly allocated to five groups (n=10) and their body weight were recorded.

They were individually forced to swim for 6 min in a vertical glass cylinder (height: 27cm, diameter 16.5cm) containing 11cm of fresh tap water maintained at 27ºC. This was followed 24 hours later with a second swim session of 6 min.

Drugs were administered (n=10) orally for the methanolic leaf extract 50, 100, 200, 400 mg/kg and for imipramine hydrochloride 15mg/kg, intraperitoneally at 1, 5, 24h prior to the test to record the chronic effect, this schedule has been shown to be suitable by Porsolt [14]. the total amount of time (in seconds) spent immobile during the final 4 min of the second swim session was measured and analysed for statistical difference against controls (n=10). Imipramine was used to serve as a control for an antidepressant (Table1).

2.2.2 Measurement of Loco Motor Activity

In another separate experiment, motor activity was measured. Mice was placed in an open field box (size: 30 × 25cm), and the number of movement each 10 min was recorded by using Animex apparatus. The activity and tuning of the instrument were adjusted to 35uA to enable the measurement of loco motor activity. Yohimbine, was given i.p. at 1mg/kg and 1ml injection volume as a control drug. It is a CNS stimulant and is also known to enhance the loco Motor activity [15]. Each animal was individually observed for 80 min and the arbitrary unit of activity was recorded at the first 20 min and the last 60 min. The animals were tested only once and did not have any prior exposure to the experimental apparatus [16].

3 Results

The effect of treatment with different doses of the methanolic leaf extract of *Mitragynaspeciosa*50, 100, 200, 400 mg/kg, orally or imipramine 15mg/kg, i.p. on the forced swim test or mice, are presented in Table 1. An analysis of data between the groups (n=10) by one-way analysis of variance (ANOVA) statistical test is followed by a Duncan test, $p<0.05$ for all, indicated a significant decrease in the immobility time in seconds), compared to control.

Mitragyna Speciosa methanolic leaf extract significantly reduced the immobility time at doses of 100, 200, and 400mg/kg to 126.0 $\pm$ 13.4 s, 113.0 $\pm$14.9 s, and 129.3 $\pm$ 13.5 s respectively, verses control (170.0 $\pm$ 11.5 s, $p<0.05$). Comparison between the imipramine and control group, imipramine was also showed a significant reduction in the time of immobility (100.9 $\pm$21.8 s, $p<0,05$). However, no significant decrease was recorded for the dose of 50 mg/kg of the extract.

The effects of treatment with *Mitragyna Speciosa* methanolic leaf extract 100 and 200mg/kg, orally and yohimbine 1mg/kg, i.p. on loco motor activity (Fig. 1).

The analysis of the data, for single treatment, using one-way analysis of variance (ANOVA) statistical test showed a

significant increase in loco motor activity by yohimbine 1mg/kg during the first 20 min $p<0.05$. There was no change in loco motor behavior in any of the methanolic lead extract groups. Furthermore, no significant differences were found during the last 60 min, except for the methanolic leaf extract group 100mg/kg, which recorded a significant decrease in loco motor behavior (Fig.1).

Table 1: Effects of different doses of Mitragyna extract 50, 100, 200, 400mg/kg and imipramine on the immobility time. Mean ± s.e.m. (n=10), *p<0.05 as compared to control.

Drug	Dose (mg/kg)	Duration of immobility (sec) Mean ± (s.e.m.)
Control	10	170± 11.5
Imipramine HCL	15	10.9± 21.8*****
Mitragyna extract	50	154.1± 8.6
	100	126.0± 13.4*****
	200	113.0± 14.9*****
	400	129.3± 13.5*****

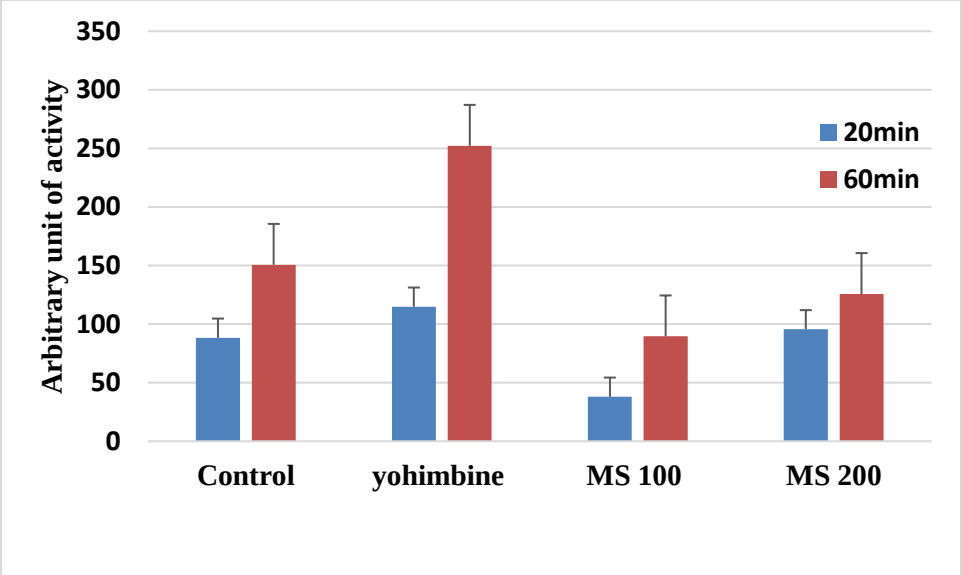

Fig.1: Effects of MS (100, 200mg/kg) on locomotors activity during the first 20 min and last 60 min. Mean ± s.e.m., *p<0.05 as compared to control.

4 Discussions

The main findings in this study are that the methanolic leaf extract of MS (100, 200, 400 mg/kg) has clear antidepressant- like activity as seen in the forced swim test model of depression. This effect was demonstrated by the decrease in the total amount of time spent immobile posture during the final 4 min of the second swim session without any increase in the loco motor activity. This confirms that the antidepressant - like effect is not due to the increase in loco motor behaviour. The present result also suggests that the optimum doses of this extract are 100 and 200mg/kg.

MS may exert its anti-immobility effect through facilitated transmission of the serotonergic and/or noradrenergic System, supporting the hypothesis that diminished central 5-HT function may be involved in the pathophysiology of some types of depression [17, 18].

Serotonin receptor subtype [3] among the 7 subtypes recognised is the only known 5-HT receptor that directly gates ion channels (sodium and potassium) resulting in rapid neuronal depolarisation followed by rapid desensitisation [19]. The consequences of neuronal depolarisation resulting from 5-HT_3 activation is the release of other stored neurotransmitters suggesting a potentially important role in neuronal circuitry involved in drug abuse [20].

MS has a rewarding effect and is effective in alleviating the morphine and ethanol withdrawal effects [21]. However, studies on human revealed that prolonged consumption of this plant led to dependence and tolerance while cessation caused a series of averse withdrawal symptoms [22] Findings also showed that MS extracts possess antinociceptive, anti-inflammatory, and muscle relaxant properties [23] Available evidence further supports the adverse effects of MS preparations, mitragynine on cognition [24] Pharmacological activities of mitragynineare mainly mediated via opioid receptors as well as neuronal calcium channels, expression of cAMP via descending monoaminergic system [25,26]. Physicochemical properties of mitragynine may further explain the variation in pharmacological responses.

The present study clearly demonstrated that mitragynine exerts an antidepressant effect in animal behavioral model of depression (PST) and the effect appears to be mediated by an interaction with serotonergic system. Based on the hypothesis of the structural similarity of the mitragynine to serotonin, which further emphasized that; the in dole alkaloid present in the leaf extract of MS is responsible for such behavioural effect. Compatible with other previous studies which highlighted that mitragynine is the psychoactive compound of MS Korth [27].

In summary, further purification of alkaloids of MS will be necessary for more precise in detecting the active constituents of this plant.Despite its addictive properties and reported side effects, scientific clinical human studies are necessary to determine its potential therapeutic value.

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