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Antidepressant-like effect of aqueous extract of *Channa striatus* fillet in mice models of depression

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Abstract. – ***Background and Objectives:*** ***Channa (C.) striatus*** **(Malay-Haruan), is a fresh water snakehead fish, consumed as a rejuvenating diet in post-parturition period in local Malay population. The aqueous extract of *C. striatus* fillet (AECSF) was reported to act through serotonergic receptor system in a previous study. There is no scientific report on neuropharmacological effects of *C. striatus*. Based on these data, the antidepressant-like effect of *C. striatus* was evaluated in mice models of depression.**

Materials and Methods: **AECSF was prepared by steaming the fillets as described previously. Antidepressant activity was studied in male ICR mice using forced swimming test (FST) and tail suspension test (TST). Open-field test was used to evaluate any psychomotor stimulant activity. AECSF was administered intraperitoneally at the concentrations of 30%, 40% and 50% w/v at the dosage of 10 ml/kg. Amitriptyline (10 mg/kg) was used as positive control.**

Results: **All the three concentrations of AECSF (30%, 40% and 50% w/v) significantly reduced the immobility time ($p < 0.001$) in FST and TST. All the three concentrations of AECSF (30%, 40% and 50% w/v) significantly ($p < 0.001$) reduced locomotor activity in a dose-dependent manner in open-field test.**

Conclusions: **AECSF produced significant reduction of immobility time in both FST and TST. Amitriptyline produced a significant reduction of immobility time in both FST and TST similar to previous findings. The AECSF produced a dose-dependent decrease in locomotor activity in the open-field test. This hypolocomotion effect indicated the absence of any psychomotor stimulant activity thereby supporting the antidepressant-like effect of the AECSF. The pharmacological mechanisms of the observed antidepressant-like effect and hypolocomotion effect are not understood from our study. Hence, further studies are required.**

Key Words:

Channa striatus, Haruan, Antidepressant-like effect, Forced swimming test, Tail suspension test.

Introduction

Postpartum depression (PPD) is one of the global public health issue and affects 15% of child-bearing women[1]. The etiology of PPD was linked with abrupt decrease in the estradiol level after the delivery[2-4], alterations in the hypothalamo-pituitary-adrenal axis[5], decrease in docosohexaenoic acid level in the brain and involvement of serotonergic system[6].

Although, selective serotonin reuptake inhibitors (SSRI's) and tricyclic antidepressants are indicated for the treatment of postpartum depression[7], their safety is not well established on neurological development of infants during the breastfeeding period[8,9]. Hence, a safe antidepressant is warranted in the treatment of postpartum depression.

Channa striatus (called as haruan in Malay), is a fresh water snakehead fish indigenous to Malaysia[10]. *C. striatus* belongs to the family Channidae. Its flesh is included in post-parturition diet as a rejuvenating diet and to aid wound healing in local Malay population[11]. The aqueous extract of *Channa striatus* fillet (AECSF) produced wound healing effect in rodents[12-15], antinociceptive activity in rodents[16-22] and protective effect against experimentally induced osteoarthritis in rabbits[23]. The mucus extract of *C. striatus* showed antibacterial activity[24]. *C. striatus* was analysed for amino acid and fatty acid

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compositions and found to contain glutamic acid, aspartic acid and lysine as major amino acids and palmitic acid, stearic acid, arachidonic acid (omega-6 fatty acid) and docosahexanoic acid (omega-3 fatty acid) as major fatty acids[14,15,25].

The traditional usage of *C. striatus* for post parturition rejuvenation effect suggests a central effect. In a previous study, the aqueous extract of *Channa striatus* fillets (AECSF) produced antinociception in mice synergistically through various receptor systems including serotonergic receptor system[18,21,22].

The observation that *C. striatus* is already used in the local Malay population in the postpartum period without any reported side effects, involvement of serotonergic system in a previous report and lack of scientific studies on its neuropharmacological effects, stimulated our research interest to study the antidepressant activity of *C. striatus*. Hence, a study was set up to examine its antidepressant-like effect in mice models of depression.

Materials and Methods

Preparation of Aqueous Extract of C. striatus Fillet (AECSF)

Aqueous extract of *C. striatus* fillet (AECSF) was prepared according to the previously described method[17]. Throughout the study 3 month old (100-150 g) haruan fish were used. The fish were cultured in a fish farm in Pontian, Malaysia from where they were transferred to the aquarium at University Putra Malaysia, Malaysia, and acclimatized for at least 3 days before the extraction procedure was carried out. Cleaned boneless fish fillets were placed on a stainless steel wire mesh mounted on a tripod in a pressure cooker. Five volume of water was added and water level was kept low in order not to submerge the fillets. The extract was obtained through steaming for 1 hour. After 1 hour, fillet was discarded and extract was filtered, centrifuged and stored at 4°C until use. The resultant final concentration of the extract was 50% w/v (the weight refers to wet fish weight). The extract obtained thus was stored at –20°C until used. The extract was diluted with normal saline (NaCl 0.9% w/v) to desired concentrations (30% w/v and 40% w/v) and administered at the dosage of 10 mL/kg based on a previous study[17] in which the extract showed maximum antinociceptive activity at 40% w/v concentration.

Animals

Male ICR mice (25-30 g) were obtained from animal house, Faculty of Medicine and Health Sciences (FMHS), University Putra Malaysia (UPM). All the animals used in this study were cared for and treated in accordance with the protocols specified by the animal Ethics Committee of FMHS, UPM and also with the "Principles of Laboratory Animal Care" (NIH Publication No. 85-23, revised in 1985). The animals were housed for 1 week under controlled conditions for acclimatization before the experiments. These conditions were as follows: light (12 h light/dark cycle, lights on at 7:00 am), temperature (25 ± 1°C), free access to food and water. The animals were randomly assigned to different groups for the experiments (6-8 animals per group).

Drugs

AECSF was administered to three groups of animals in the concentrations of 50%, 40% and 30% w/v respectively at the dosage 10 mL/kg body weight. The 50% w/v concentration of AECSF was diluted to 40% w/v and 30% w/v with normal saline (NaCl 0.9% w/v). Control group animals were administered with normal saline (NaCl 0.9% w/v) at 10 mL/kg body weight. In forced swimming test and tail suspension test, positive control group animals were administered with amitriptyline (Sigma-Aldrich, Corp. St. Louis, MO, USA) at 10 mg/kg body weight[26-30] since amitriptyline was shown to produce antidepressant-like effect in six animal models of depression[31]. All drug administration was performed intraperitoneally (ip). All the test observations were made 30 min after injection of drugs. All the experiments were carried out between 9.00 a.m. and 3.00 p.m.

Forced Swimming Test (FST)

The FST has been used as an animal model predictive of antidepressant effect[32]. The procedure developed originally by Porsolt et al.[33, 34] with a slight modification[35] was employed in this study. Briefly, mice were individually forced to swim in an open cylindrical container (diameter 14 cm, height 20 cm), with a depth of 15 cm of water at 25 ± 1°C for 6 min. After the initial 2-3 min of vigorous activity, the animals showed a period of immobility by floating with minimum movements. Each mouse was judged to be immobile when it stopped struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. The number of seconds spent immobile by the animals were scored during 6 min with the help of a stop-watch, as described previously[36]. A decrease in the duration of immobility is indicative of an antidepressant-like effect[33,34]. The water was changed after each mouse was tested to eliminate the influence of odours from faeces and urine excreted by the animal in a previous session. The animals were used only once in each swimming test.

Tail Suspension Test (TST)

The tail suspension test was carried out as per the established method[26]. Briefly, mice both acoustically and visually isolated were suspended individually 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. After 2-3 min of vigorous activity characterised by struggling movements, attempts to catch the adhesive tape, or body torsions or jerks, the mice hung passively and completely motionless. Immobility was defined as the absence of any limb or body movements, except for those caused by respiration or when they hung passively and completely motionless. A decrease in the duration of immobility is indicative of an antidepressant-like effect[26]. The total immobility period in number of seconds was scored manually during 6 min test session with the help of stop-watch[35].

Open-Field Test

In order to rule out any nonspecific locomotor effect of AECSF on the observed antidepressant-like effect in the FST and TST, mice were evaluated in the open-field paradigm as previously described[37,38]. Before each test, animals were kept in the test room at least 1 hour before the open-field test for habituation. The apparatus consisted of a square box (50 cm × 50 cm × 40 cm) made up of plexiglass with the floor divided equally into twenty-five squares (10 cm × 10 cm) marked by black lines. Each mouse was placed individually into the centre of the arena and allowed to explore freely for 6 min. The number of squares crossed by the animal with its four paws was considered as indicative of locomotor activity and number of rearings was an indicative of exploratory behaviour[39,40]. The number of crossings and number of rearings were recorded for 6 min. The measurements were taken from another room through a video camera mounted over the square box[41]. All animals were used only once in this test. These animals were different from those used in the FST and TST. The apparatus was cleaned after each test session to prevent each mouse from being influenced by the odors present in the urine and faeces of the previous mouse.

Statistical Analysis

All the results were expressed as means ± S.E.M. and analysis of data was performed by means of one-way ANOVA followed by Dunnett's test as the *post hoc* test. All the treated groups were compared with their respective vehicle treated control groups. All analyses were performed using the software GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Effects were considered significant at $p < 0.05$.

Results

The AECSF produced a highly significant reduction ($p < 0.001$) in the immobility time in 30%, 40% and 50% w/v concentrations with the maximum effect at 40% w/v concentration in both the FST and TST in the treated animals (Figure 1). Amitriptyline produced highly significant ($p < 0.001$) reduction in the immobility time in both FST and TST (Figure 1). The AECSF produced significant ($p < 0.001$) dose-dependent reduction in the number of squares crossed and the number of rearings in the open-field test in treated animals (Figure 2).

Discussion

Forced swimming test (FST) and tail suspension test (TST) are the two well established animal models of depression[26,33,34] which are used to screen the potential drugs for antidepressant activity. In the present study, AECSF significantly reduced the immobility time in both FST and TST after single intraperitoneal administration in all the three concentrations used in this study when compared with the control group. The positive control drug amitriptyline significantly reduced the immobility time in both FST and TST similar to previous findings[33,35,42]. The pattern of dose-response produced by the three doses of AECSF used in this study in FST and TST

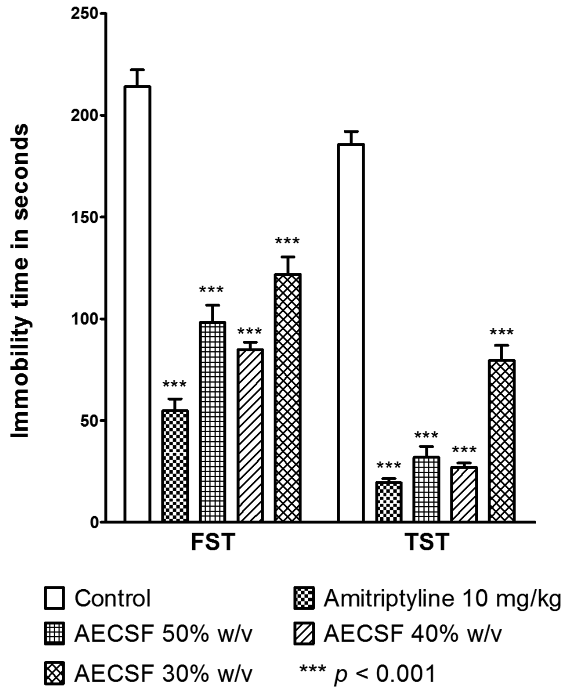

Figure 1. Effect of aqueous extract of *C. striatus* fillet (AECSF) (50%, 40% and 30% w/v) and amitriptyline (10 mg/kg) in forced swimming test (FST) and tail suspension test (TST) in male ICR mice. Data represent means ± S.E.M. (n = 6-8). ***$p < 0.001$, one-way ANOVA followed by Dunnett's test.

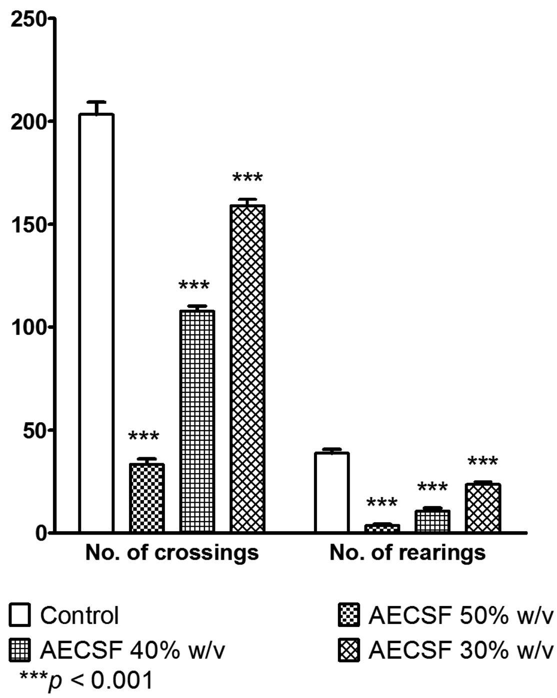

Figure 2. Effect of aqueous extract of *C. striatus* fillet (AECSF) (50%, 40% and 30% w/v) in open-field test in male ICR mice. Data represent means ± S.E.M. (n = 6-8). ***$p < 0.001$, one-way ANOVA followed by Dunnett's test.

showed a nonlinear relationship with a maximum response at 40% w/v concentration. In a previous study, AECSF produced maximum antinociceptive effect at 40% w/v concentration when compared to 30% and 50% w/v concentrations[17]. Interestingly, similar findings were observed in this study with a maximum antidepressant-like effect at 40% w/v concentration when compared to 30% and 50% w/v concentrations.

The pharmacological mechanism of the observed antidepressant-like effect of AECSF is not clear from this study. Previous studies indicated that *C. striatus* contain lipids and amino acids[14,15,25]. The level of palmitic and oleic acid concentrations seem to be relevant for sleep disturbances in depressive subjects, maybe due to their function as precursors of the sleep inducing oleamide[43], a fatty acid amide that has been shown to produce antidepressant-like effects[44]. Omega -3 fatty acids were also shown to be effective for depression[45]. Oral treatment with L-lysine and L-arginine was reported to reduce anxiety and stress[46]. Treatment with yeast hydrolysate, which was found to contain high concentrations of glutamic acid and aspartic acid, was reported to exhibit anti-stress activity in humans[47]. The *C. striatus* was reported to contain all these fatty acids and amino acids as major components[14,15,25]. Although the possible involvement of these fatty acids and amino acids might be anticipated in the observed antidepressant-like activity of AECSF, it cannot be concluded from this study.

In a previous study[21], AECSF exhibited antinociception in mice synergistically through muscarinic, $GABA_A$-ergic, alpha-adrenergic, and serotonergic receptor systems and not through opioid receptor system. The antinociception effect was observed to act through nitric oxide/cyclic guanosine monophosphate (cGMP) pathway also[22]. Hence, in an attempt to explain the mechanism of action, it may be speculated that the AECSF might have acted through one or more of these receptor systems to produce the observed antidepressant-like effect. However, it cannot be concluded from this study. Further investigations are needed in this aspect and further studies are in progress in our laboratory to evaluate the mechanism of action of the observed antidepressant-like activity of AECSF in mice.

Agents that enhance locomotor activity in open-field test including psychomotor stimulants, convulsants and anticholinergics, tend to produce a false positive result in FST and TST[48]. Therefore, locomotor activity was assessed in mice in open-field test to rule out any psychomotor stimulant activity[38]. The major difference between the antidepressants and the psychomotor stimulants is that the antidepressants would not cause significant increase in motor activity[49]. Surprisingly, the AECSF produced a dose-dependent decrease in number of crossings and number of rearings in the open-field test in this study. This hypolocomotion effect of the AECSF treated animals when compared with the control group animals in open-field test indicated the absence of any psychomotor stimulant activity, thereby supporting the antidepressant-like effect of the AECSF observed in the FST and TST. Although the pharmacological mechanism by which the AECSF caused a significant decrease of locomotion in the open-field test is not clearly understood from this study, decreased spontaneous locomotor activity suggests a possible sedation effect[50]. David et al[51] suggest that even if a sedative effect is observed in the open-field test, antidepressant-like activity may be perceived in the FST. In previous studies, clonidine[52], imipramine[53], desipramine[51], buspirone[53], ipsapirone[53] and gepirone[53] produced significant decrease in immobility time in FST and significant decrease in locomotor activity (number of crossings and number of rearings) at doses similar to those that decreased immobility. Furthermore, fluoxetine, zimeldine, and indalpine significantly reduced immobility time in TST and significantly reduced locomotor activity at doses similar to those that decreased immobility[54]. Collectively, these data indicate that antidepressants can produce decreased locomotor activity in open-field test in rodents. Hence, the decreased immobility time and decreased locomotor activity produced by AECSF in this study are similar to the previous findings[51-54]. Alternatively, the presence of high concentration of arachidonic acid (19.02% of total fatty acids) in *C. striatus*[14,15,20,25] may be considered as a reason for the decreased locomotor activity, since arachidonic acid was found to reduce locomotor activity in mice in open-field test in a previous research[55]. However, no conclusion can be derived from our study regarding the mechanism of the observed hypolocomotion, since it was a basic behavioural investigation to evaluate the potential antidepressant activity of *C. striatus*. Further researches are required and are in progress in our laboratory to assess the molecular mechanism of the observed hypolocomotion.

In conclusion, this study demonstrated that the aqueous extract of *C. striatus* fillet (AECSF) produced antidepressant-like effect in mice models of depression which was not due to any psychomotor stimulant activity thereby supporting the traditional usage of *C. striatus*. Despite the positive results of this research, only male ICR mice were used. A suitable animal model of induced-postpartum depression may be used in future to assess the postpartum antidepressant-like effect. Hence, further investigations are necessary to identify the bioactive principles, their respective mechanism of action and also toxicological assessment of *C. striatus*. Our findings have clinical importance since *C. striatus* is currently used by the local Malay population.

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