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Research Article

Preclinical evidence of a rapid-onset antidepressant-like effect of *Pseudospondias microcarpa* hydroethanolic leaf extract in a chronic depression model

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ABSTRACT

Background: Depression is a widespread, devastating mental illness and currently available treatments have significant limitations including low response rates and delayed onset of action. N-methyl-D-aspartate (NMDA) receptor antagonists exert fast-acting antidepressant effects. *Pseudospondias microcarpa* produces an antidepressant-like effect via inhibition of the glycine/NMDA receptor complex, and could therefore possess a rapid onset of action. Therefore, the present study investigated the possible rapid-onset antidepressant action of *P. microcarpa* in mice.
Methods: In this study, rapid-onset and sustained antidepressant effects of the hydroethanolic leaf extract of *P. microcarpa* (PME) was investigated in the open-space swim test, a chronic model of depression. Antidepressant effect was further assessed in the tail suspension test (TST). In addition, the effect of the extract on cognitive function in the Morris water maze (MWM) test was investigated.
Results: Depressed mice showed a significant increase in immobility and decrease in distance swum. However, treatment with PME and the classical antidepressants significantly decreased immobility time and increased distance swum. Furthermore, unlike the classical antidepressants which required 10-14 days to significantly improve mobility behaviour, PME treatment significantly decreased immobility time ($P<0.001$) on the first day of treatment (day 5 of stress procedure). This effect was also sustained for the remainder of the experiment. The extract also significantly decreased immobility time in the TST ($F_{3,16}=4.881$, $P=0.0135$) and decreased escape latency ($F_{4,24}=12.07$, $P<0.0001$) in the MWM procedure.
Conclusions: The leaves of *P. microcarpa* exhibits rapid and sustained antidepressant effects and improve cognitive function in depressed mice.

Keywords: Pseudospondias microcarpa, Depression, Open-space swim, NMDA, MWM, Tail suspension test

INTRODUCTION

Depression is one of the most devastating mental illnesses which results in enormous personal suffering and economic loss, with a lifetime prevalence of about 17%.[1,2]

Although in the last few decades agents that modulate the monoaminergic system are used in treating depression, their efficacies are unsatisfactory and they produce multiple unwanted side effects.[3,4] Furthermore, they require several weeks to achieve therapeutic response.[5] This treatment delay is a major limitation to current depression therapies, leading to increased morbidity, suicidal ideation, and loss of quality of life.[6-8] For these reasons, developing faster-acting and more effective antidepressants is important, especially for depressed patients at risk for suicide.[9]

During the past years, several evidences have implicated the NMDA class of glutamate receptors in the pathophysiology of major depression and the mechanism of action of antidepressant treatment.[10] Extensive preclinical research indicates that both competitive and non-competitive NMDA receptor antagonists, polyamine site antagonists and inorganic inhibitors of NMDA receptor function (zinc and magnesium) possess antidepressant-like activity.[4,11,12] In addition, clinical evidence also shows a rapid and sustained antidepressant activity for NMDA receptor antagonists such as ketamine.[13] Similar to NMDA antagonists, research has also shown that antagonists and partial agonists at the glycine site of the NMDA receptor complex exhibit rapid antidepressant-like activity in both preclinical and clinical studies.[9,14]

Pseudospondias microcarpa, the African grape tree, is a plant used traditionally for managing various central nervous system (CNS) disorders.[15] The hydroethanolic leaf extract (PME) of the plant showed antidepressant-like effects in acute models of depression employed in the search for new antidepressants, forced swimming test (FST) and tail suspension test (TST).[16] Furthermore, we demonstrated in this study that the extract elicits its antidepressant-like effect via interaction with the 5-HT system, nitric oxide pathway and glycine/NMDA receptor complex. Since the antidepressant effect of PME acts through inhibition of the glycine/NMDA receptor, we hypothesize that it could modulate glutamatergic synapses to effect a rapid-onset antidepressant-like action.

Therefore, this study assessed the onset of antidepressant effect of the extract in the open-space swim procedure, a chronic model of depression with greater face, construct, and predictive validity than the acute behavioural measures used for screening. This depression model responds to chronic but not acute or subacute administration of a variety of antidepressants, including tricyclics, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors but not anxiolytics or antipsychotics.[17,18] In addition, the effects of PME on cognitive function in the Morris water maze task was assessed in this chronic model of depression.

METHODS

Plant collection and extraction

Fresh leaves of *P. microcarpa* were collected from the campus of Kwame Nkrumah University of Science and Technology (KNUST), Kumasi (6º 40.626'N, 1º 34.041'W) and authenticated at the Department Of Herbal Medicine, Faculty of Pharmacy And Pharmaceutical Sciences, KNUST, Kumasi, Ghana. Leaves of the plant were room-dried for seven days and pulverised into fine powder. The powder was extracted by cold percolation with 70 % (v/v) ethanol in water over a period of 72 hours and the resulting extract concentrated into a syrupy mass under reduced pressure at 60 °C in a rotary evaporator. It was further dried in a hot air oven at 50 °C for a week and kept in a refrigerator for use. The yield was 20.5 % (w/w). In this study the crude extract is subsequently referred to as PME or extract.

Animals

Male ICR mice (20-25 g) were purchased from the Noguchi Memorial Institute for Medical Research, Accra, Ghana and kept in the animal house of the Department of Pharmacology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. They were housed in standard cages and allowed free access to food and water. Prior to testing, animals were allowed to acclimatize to laboratory conditions of temperature, humidity and light. The studies were conducted in accordance with accepted principles for laboratory animal use and care.[19] Approval for this study was obtained from the faculty ethics committee.

Chemicals

Desipramine hydrochloride was purchased from Sigma-Aldrich Inc., St. Louis, MO, USA and fluoxetine hydrochloride (Prozac®), Eli Lilly and Company Ltd., Basingstoke, England.

Repeated open-space swim model

This test is a modification of the acute forced swim paradigm.[17,18] In this procedure, mice are swum for 15 min/d for 4 days in rat tub cages (24 cm × 43 cm × 23 cm, w × h × l) filled with lukewarm water (13 cm deep, 32-34 ºC) with these cages divided into 4 imaginary quadrants. This schedule produces a progressive reduction of active swimming along with a concomitant increase in immobility (floating) which persists unaltered for weeks after the last test.

Drug treatments begun on the fifth day. Briefly, mice were divided into 10 groups (n=5) and pre-treated with vehicle (10 ml kg^{-1} of 0.9 % NaCl, i.p), PME (30, 100 and 300 mg kg^{-1}, p.o.), fluoxetine (3, 10 and 30 mg kg^{-1}, p.o.) or desipramine (3, 10 and 30 mg kg^{-1}, i.p.) 60 minutes (p.o.) or 30 minutes (i.p.) before being placed individually into the rat tub cages. The time of onset of drug action was assessed by swimming the mice at days 5, 8, 11, 14 and 18 after i.p. or oral administration. All swims were videotaped with a digital video camera placed 80 cm above the tub cage. Videos were rated for immobility time (drifting with no observable movements of the limbs or tail) and distance swum (number of tank quadrants entered). No special procedures were used to dry or warm the animals as they rapidly dried themselves with no observable episodes of shivering. Active swimming is defined as those swimming motions a mouse makes to move around in the pool.

Tail suspension test

Twenty four (24) hours after the last swim, animals were assessed in the TST. Briefly, mice were individually suspended by the tail from a horizontal ring-stand bar raised 30 cm above the floor using adhesive tape placed 1 cm from the tip of tail. The mice were positioned such that the base of their tail was aligned with the horizontal plane. Test sessions lasted for 6 minutes and were videotaped. Behaviours for the last 4 of the 6-minute test period were then analysed for mobility and immobility duration.

Spatial working memory (Morris water maze)

On day 21, the effects of mice behaviour on hippocampal-dependent spatial learning and memory was evaluated with the Morris water maze task.[20]

The MWM equipment consisted of a tank that was 120 cm in diameter and 60 cm in height, which was filled with water to the depth of 45 cm and maintained at 23±1 °C. Black non-toxic ink was added to make the water opaque. The tank was divided into four equal quadrants (NE, SE, NW and SW) by two imaginary perpendicular lines crossing the centre of the tank. A movable black circular platform (5 cm in diameter) was located in the centre of SW quadrant (target quadrant) and submerged 2 cm below the water surface so that a mouse could easily climb and escape from water. Each session was recorded with a video camera approximately 100 cm above the centre of the maze. The environment was kept lightless, maintaining visual extra-maze cues and minimizing the noise disturbance.

The MWM task consisted of two sections: place navigation and spatial probe trial. In the place navigation test, animals were subjected to 4 training trials of 2 minutes per day for five consecutive days (days 21-25 of treatment). It assessed the animal's motivation and ability to swim and escape from the aversive situation of being placed into the water by associating the platform with the escape. For each trial the platform was located at the centre of SW quadrant. The mouse entered the pool facing the wall from a different starting point each time so that the direct route to the platform differed. Briefly, the location of the platform remained constant and mice were allowed to swim for 60 s or until they located the platform. Mice that failed to locate the platform within 60 s were guided manually to the platform and remained for at least 5 s before returning to their home cage.

Twenty four (day 26) hours after the last training trial in the escape acquisition test, mice were submitted to the probe trial in which the platform was removed. In the 60-s probe trial, the time in the target quadrant (the quadrant in which the platform was located in the training sessions) was obtained as a measure for spatial memory. Performance parameters measured in the MWM included latency to the platform, quadrant dwell time and swimming speed.

Data analysis

In all experiments, a sample size of 5 animals was utilized. All data are presented as mean±SEM. To compare differences between groups, one-way ANOVA was performed with Newman-Keuls' test as *post hoc*. The time-course curves were subjected to two-way (treatment × time) repeated measures analysis of variance (ANOVA) with Bonferroni's *post hoc* test. GraphPad Prism for Windows 5 (GraphPad Software, San Diego, CA, USA) was used for all statistical analysis. $P<0.05$ (Newman-Keuls' test or Bonferroni's test) was considered statistically significant. Doses for 50 % of the maximal effect (ED^{50}) for each drug were determined by using an iterative computer least squares method, with the following nonlinear regression (three-parameter logistic) equation.

$$Y = \frac{a + (b - a)}{\left(1 + 10^{(LogED_{50} - X)}\right)}$$

Where, X is the logarithm of dose and Y is the response. Y starts at a (the bottom) and goes to b (the top) with a sigmoid shape.

RESULTS

Effect in the open-space swim test

Mice showed a gradual and significant reduction in the distance moved as well as an increase in immobility over trials as they swum in the rat tub cages 15 minutes/day for four consecutive days. Unlike the behaviour patterns observed in the classical forced swimming test, no climbing on the wall was observed. As the trials progressed, the control mice showed a significant decrease in swimming. A maximal reduction in their mobility was reached at the 3rd trial in these control mice. At this point,

control mice did not make any movements other than those just sufficient to keep their heads above the water surface (immobility), a characteristic behaviour that is taken as an indicator of depression in the forced swimming test.

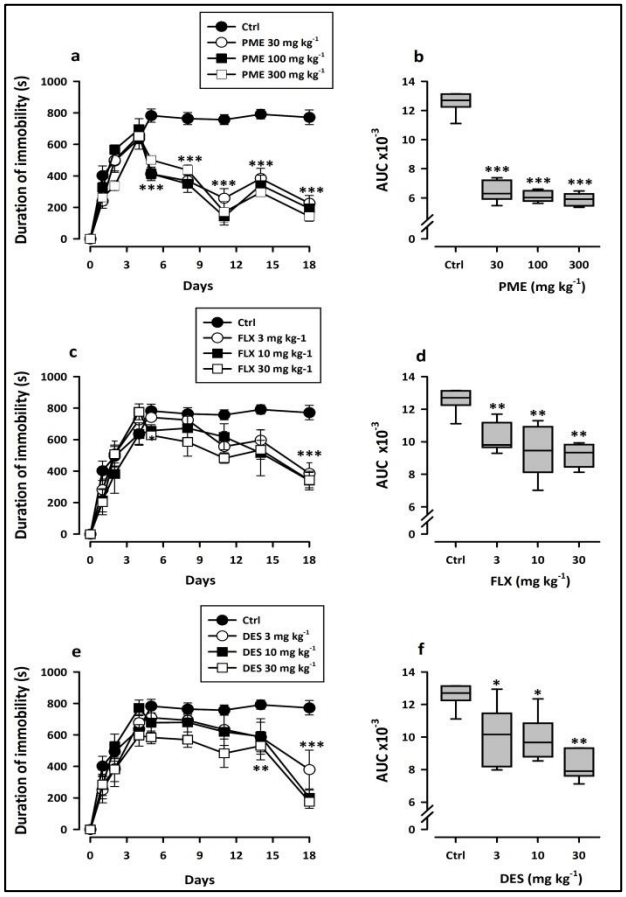

Figure 1: Effect of PME (30-300 mg kg^{-1}), fluoxetine, FLX (3-30 mg kg^{-1}) and desipramine, DES (3-30 mg kg^{-1}) treatment on the total duration of immobility in the open space swim test. Data are presented as both time course curves (a, c and e) and mean±SEM (n=5) of their areas under the curves (AUCs) (b, d and f). The lower and upper margins of the boxes (b, d and f) represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box and symbols represent outliers. Significantly different from control: *P<0.05, **P<0.01, ***P<0.001 One-way ANOVA followed by Newman-Keuls' test for the AUCs or Two-way ANOVA followed by Bonferroni's *post hoc* test for time-course curves.

From the time course curves in Figure 1, without antidepressant drug (depressed group with vehicle injection), the open space swim test induced a significant increase in immobility for almost the entire duration of the experiment. However, treatment with PME and the classical antidepressants significantly increased the reduction in immobility time over the entire duration of the experiment when compared with the vehicle-treated stressed group [PME: $F_{3,128}$=89.81; P<0.0001 (Figure 1a); fluoxetine: $F_{3,128}$=9.732, P=0.0007 (Figure 1c); desipramine: $F_{3,128}$=8.139, P=0.0016 (Figure 1e); two-way ANOVA (treatment x time)]. Importantly, Bonferroni's *post hoc* analysis revealed a significant anti-immobility effect of PME on day 5 (treatment day 1) (P<0.001). In contrast, treatment with the classical antidepressants (fluoxetine and desipramine), which started 24 hours after the four open-space swim test trials, was not immediately effective. The first week of treatment did not significantly improve mobility of the mice (P>0.05, when compared with the stressed group). The improvement was observed on day 10 of continued antidepressant treatment (P<0.05) and achieved its peak 2 weeks after the continued treatment (P<0.001).

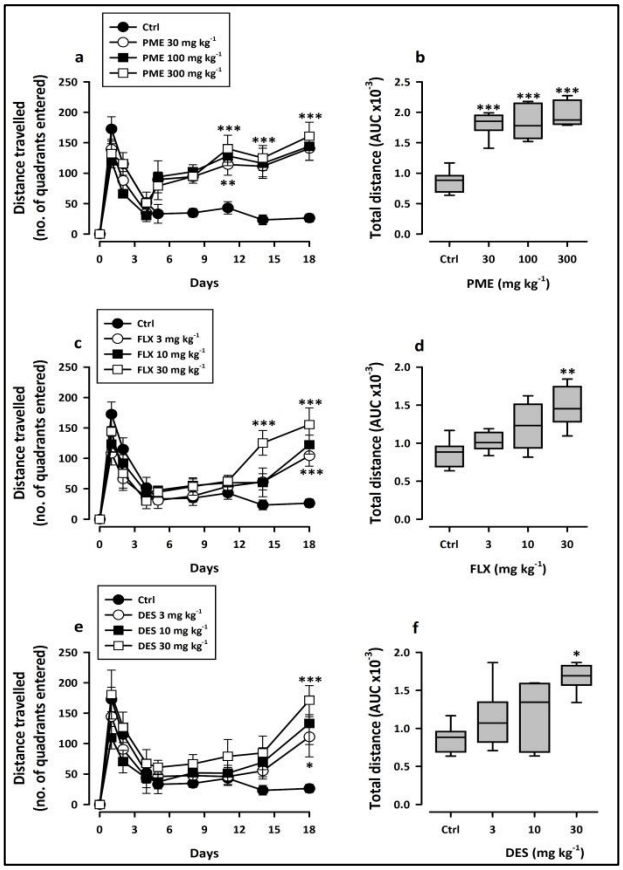

Figure 2: Effect of PME (30-300 mg kg^{-1}), fluoxetine, FLX (3-30 mg kg^{-1}) and desipramine, DES (3-30 mg kg^{-1}) treatment on the distance travelled in the open-space swim test. Data are presented as both time course curves (a, c and e) and mean±SEM (n=5) of their areas under the curves (AUCs) (b, d and f). The lower and upper margins of the boxes (b, d and f) represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box. Significantly different from control: *P<0.05, **P<0.01, ***P<0.001 One-way ANOVA followed by Newman-Keuls' *post hoc* test for the AUCs or two-way ANOVA followed by Bonferroni's *post hoc* test for time-course curves.

From the time course curves in Figure 2, all drug-treated groups displayed significant increase in the distance moved over trials when compared with the vehicle-control stressed group [PME: $F_{3,128}$=12.94, P=0.0002 (Figure 2b); fluoxetine: $F_{3,128}$=3.752, P=0.0325 (Figure 2d); desipramine: $F_{3,128}$=3.970, P=0.0272 (Figure 2f); two-way ANOVA (treatment x time)].

From the AUC's of the time course curves, oral administration of PME (30-300 mg kg^{-1}) significantly decreased the immobility time ($F_{3,16}$=119.8, P<0.0001; (Figure 1b) and increased the total distance swum ($F_{3,16}$=22.29, P<0.0001; figure 2b). Similar effects were also observed for fluoxetine [immobility: $F_{3,16}$=8.946, P=0.001 (Figure 1d); distance swum: $F_{3,16}$=5.671, P=0.0077 (Figure 2d)] and desipramine [immobility: $F_{3,16}$=7.562, P=0.0023 (Figure 1f); distance swum: $F_{3,16}$=4.554, P=0.0172 (Figure 2f)].

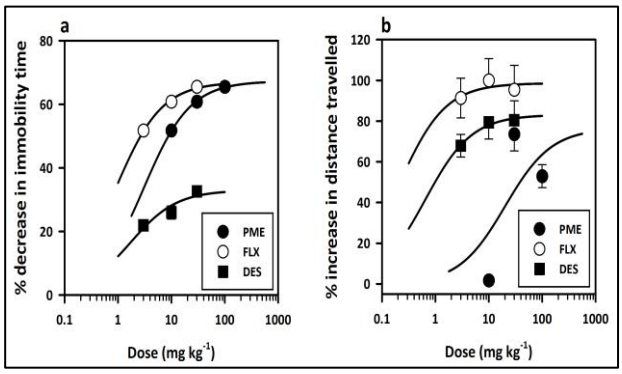

Figure 3: Dose response curves for PME (30-300 mg kg^{-1}, p.o.), fluoxetine, FLX (3-30 mg kg^{-1}, p.o.) and desipramine, DES (3-30 mg kg^{-1}, i.p.) with respect to % decrease in immobility time (a) and % increase in swimming time (b) in the open space swim test in mice. Each point represents the mean±SEM (n=5).

In Figure 3, PME showed more efficacy than desipramine and fluoxetine though less potent in decreasing the immobility time. The extract was however the most potent of the test compounds with regards to increase in distance travelled [PME (ED_{50}=5.84 mg kg^{-1}); FLX (ED_{50}=15.29 mg kg^{-1}); DES (ED_{50}=15.57 mg kg^{-1})].

Effect in the TST

The effects on mice behaviours in the TST 24 hours after behavioural assessment in the repeated open-space swim procedure are shown in Figure 4. One-way ANOVA revealed a significant reduction in the immobility effect of all drug-treated groups when compared to control [PME: $F_{3,16}$=4.881, P=0.0135; fluoxetine: $F_{3,16}$=4.391, P=0.0195; desipramine: $F_{3,16}$=8.358, P=0.0014].

Effect of extract on spatial learning and memory

A day after the behavioural assessment in the TST, the effects of induced depressive behaviour was tested on spatial learning in mice, using the Morris water maze (MWM). All groups showed no significant changes in escape latency during the first day as compared to the depressed control group (P>0.05). However, the depressive behaviour-induced increase in escape latency was eliminated by the administration of PME, fluoxetine and desipramine.

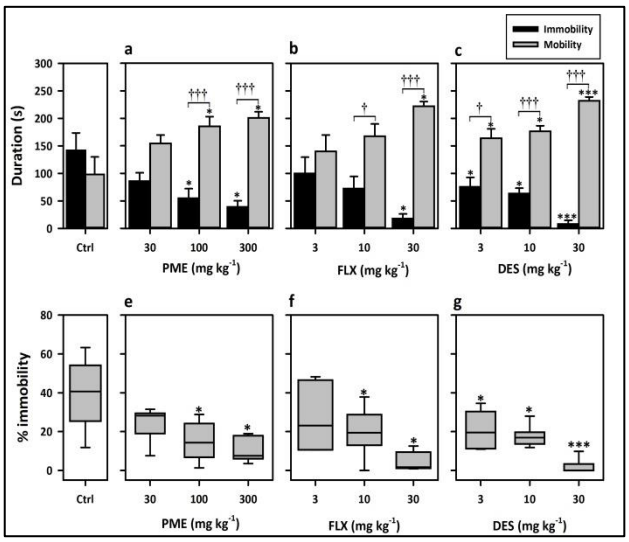

Figure 4: Effects of PME (30-300 mg kg^{-1}), fluoxetine, FLX (3-30 mg kg^{-1}) and desipramine, DES (3-30 mg kg^{-1}) treatment on immobility and mobility duration (a, b and c) and % immobility (e, f and g) in the TST performed after the repeated open-space swim procedure. Significantly different from control: *P<0.05, ***P<0.001 (One-way ANOVA followed by Newman-Keuls' test) and significant difference when immobility and mobility were compared: †P<0.05, †††P<0.001 (two-way repeated measures ANOVA followed by Bonferroni's *post hoc* test). Data are presented as group mean±SEM (n=5).

The change in latency to escape to the platform in all drug treated groups of mice decreased significantly following the training sessions, indicating that all mice showed some degrees of learning [PME: $F_{4,100}$=12.86, P<0.0001 (Figure 5a); fluoxetine: $F_{4,100}$=9.572, P<0.0002 (Figure 5c); desipramine: $F_{4,100}$=16.46, P<0.0001 (Figure 5e); two-way ANOVA (treatment x time)]. One-way ANOVA revealed a significant decrease in the change in escape latency for PME ($F_{4,24}$=12.07, P<0.0001; Figure 5b), fluoxetine ($F_{4,24}$=7.555, P=0.0007; Figure 5d) and desipramine ($F_{4,24}$=10.93, P<0.0001; Figure 5f) when compared with depressed mice. Moreover, a *post hoc* analysis revealed significant differences from the third trial for all treated groups (P<0.001). Although a decreased change in escape latency was observed for naive group when compared to the depressed mice, this was not statistically significant. In the place navigation test, swimming speed of mice treated with the extract, fluoxetine and desipramine were not significantly affected when compared with the depressed and naïve controls (Figure 7).

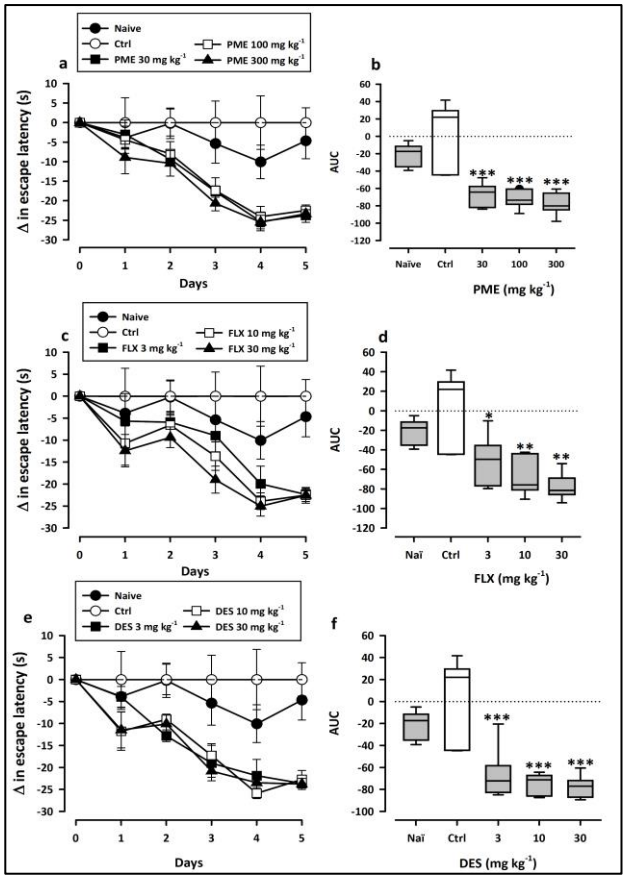

Figure 5: Effects of PME (30-300 mg kg^{-1}), fluoxetine, FLX (3-30 mg kg^{-1}) and desipramine, DES (3-30 mg kg^{-1}) treatments on escape latency from the place navigation session in the Morris water maze test. Data are presented as both time course curves (a, c and e) and mean±SEM (n=5) of their areas under the curves (AUCs) (b, d and f). The lower and upper margins of the boxes (b, d and f) represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box. Significantly different from control: *P<0.05, **P<0.01, ***P<0.001 (One-way ANOVA followed by Newman-Keuls' *post hoc* test).

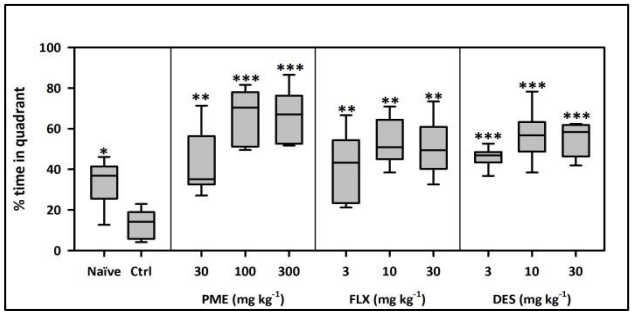

Figure 6: Effect of PME (30-300 mg kg^{-1}), fluoxetine, FLX (3-30 mg kg^{-1}) and desipramine, DES (3-30 mg kg^{-1}) treatments on % time in quadrant from the probe trial session in the Morris water maze test. Data are presented as group mean±SEM (n=5). The lower and upper margins of the boxes represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box. Significantly different from control: *P<0.05, **P<0.01, ***P<0.001 (One-way ANOVA followed by Newman-Keuls' *post hoc* test).

Memory retention was evaluated after the training trials. Spatial probe trial tests 24 hours after the last training trial revealed that the mice after the depressive behaviour induction did not show significant preference for the target quadrant (quadrant 4), where the platform was previously placed during the training trials. In Figure 6, administration of PME ($F_{4,24}$=13.33, P<0.0001, fluoxetine ($F_{4,24}$=6.885, P=0.0012) and desipramine ($F_{4,24}$=14.81, P<0.0001) significantly increased the percentage time spent in the target quadrant. Newman-Keuls' *post hoc* analysis also showed that naïve mice significantly increased percentage time spent in the target quadrant as compared to depressed mice (P<0.05).

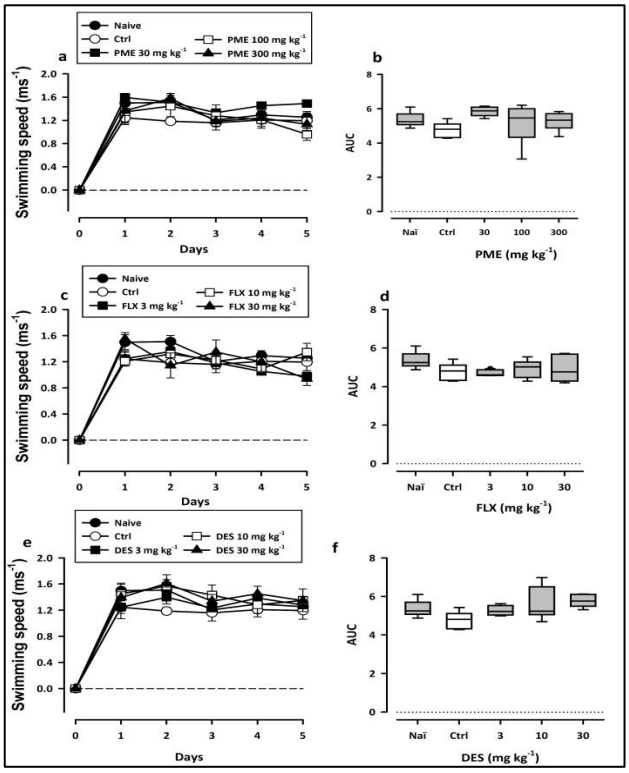

Figure 7: Effects of PME (30-300 mg kg-1), fluoxetine, FLX (3-30 mg kg-1) and desipramine, DES (3-30 mg kg-1) treatments on swimming speed from the place navigation session in the Morris water maze test. Data are presented as both time course curves (a, c and e) and mean±SEM (n=5) of their areas under the curves (AUCs) (b, d and f). The lower and upper margins of the boxes (b, d and f) represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box.

DISCUSSION

The present study provides evidence that the leaves of *Pseudospondias microcarpa* reverse the depressive-like behaviour induced in the repeated open-space swim test and improves cognitive function. In addition, it possesses a rapid and sustained antidepressant-like effect.

In this study, mice showed a progressive decrease of active swimming and a corresponding increase in floating behaviour that persisted for weeks with occasional repeated open-space swims. This increased inactivity was selectively reversed by the extract and the classical antidepressant drugs (desipramine and fluoxetine), in that they increased swimming behaviour as well as total distance travelled indicating antidepressant-like effects. Further evidence for a depressing effect of repeated open-space swimming was observed in the tail suspension test. Mice subjected to repeated swims were found to show increased immobility behaviour in the tail suspension test. This immobility is known to be characteristic of rodent models of depression.[21] However, this effect was significantly reversed by treatment with the extract and classical antidepressants, fluoxetine and desipramine, further indicating antidepressant-like effects.

It has been demonstrated in previous experiments that the reversal of immobility and inactivity in this mouse model of depression requires about 2 weeks of antidepressant drug administration.[18,22] This is further confirmed in the present study in which 2 weeks of daily treatment with both desipramine and fluoxetine, starting 24 hours after the depressive behaviour was induced, was required to produce a significant improvement in mobility in the open space swim test. In addition, results indicate that the open-space swim test induces a depressive behaviour that is not only lasting but also resemble the time course of clinical effectiveness during antidepressant drug treatment in humans.[17,18] In contrast, a single administration of the extract was found to produce an immediate and significant reduction in immobility together with an increase in distance swum which was sustained for the entire duration of the experiment. This finding indicates that PME has a rapid and sustained antidepressant-like action giving it an advantage over the classical antidepressants. Moreover, the extract was the most efficatious in reducing immobility behaviour in depressed mice.

Research has shown that NMDA receptor antagonists such as ketamine, produce a rapid (within hours) and sustained (1-2 weeks) antidepressant effect in patients with treatment-resistant depression.[13] This rapid and sustained antidepressant effects has been hypothesized to be the result of synaptic potentiation and early neuroplastic changes respectively.[23,24] Similar to the results obtained for ketamine, glycine site NMDA receptor antagonists or partial agonists also possess rapid and sustained antidepressant effects in animal models as well as in clinical trials.[9,14] However, unlike the severe side effects induced by competitive and noncompetitive NMDA antagonists which limit their use as antidepressants,[4] research has proven that glycine site NMDA receptor antagonists and partial agonists have favorable safety profile.[25] This therefore makes them potential candidates for the treatment of depression.[4]

In a previous study, we have demonstrated in our laboratory that the antidepressant-like activity of PME acts via inhibtion of the glycine/NMDA receptor complex.[16] Therefore, this rapid and sustained antidepressant effect observed for PME in the repeated open-space forced swim procedure could possibly be through its interaction with NMDA receptors. This therefore gives it an advantage over the conventional antidepressants and further suggests that modulation of the glutamatergic system may be a critical therapeutic target for obtaining rapid antidepressant actions. Moreover, since the extract acts via inhibition of the glycine site of the NMDA receptor complex, it can be suggested that its rapid-onset antidepressant effects could be devoid of side effects which limits the use of non-competitive NMDA receptor antagonists such as ketamine as antidepressants.

Lines of evidences have suggested that impaired cognition is an element of depression and that antidepressant therapy may improve cognitive function.[26,27] Thus, the effects of PME on cognitive function in the Morris water maze task was asssessed in depressed mice. The Morris water maze (MWM) task is a well-validated method for evaluating learning and memory. It can reliably express hippocampus-related acquisition and the persistence of spatial memory.[28,29] Learning is measured as a decreased latency to discover the hidden platform whereas memory is the increased time spent in the area of the platform during a test session in which the platform has been removed.[30]

Data from this study indicates that the depressive-behaviour induced by the repeated open-space swim test impairs hippocampal-dependent spatial learning and memory performance. This finding is in agreement with a study showing similar deficits in spatial learning and memory following repeated open-space forced swim procedure.[22] The learning ability was mainly reflected by the performances in place navigation section. Results of this study revealed that with increase of training days, escape latencies were consistently decreased and there was prominent improvement during the last three days in mice treated with the extract and antidepressants. Furthermore, the persistence of spatial memory was mainly reflected through mouse performances in spatial probe trial. It was observed that quadrant dwell time was significantly decreased in depressed mice. However, treatment with the extract and the classical antidepressants ameliorated this defect efficiently indicating improved memory. These findings therefore indicate improved cognitive function of the extract in depressed mice.

Several reports have shown that the 5-HT system plays an important role in cognitive function, such as learning and memory, demonstrated through the activation or blockade

of 5-HT receptor subtypes as well as its reuptake sites.[31-33] For example, it was observed that fluoxetine and tianeptine reversed memory impairments induced by scopolamine (a cholinergic antagonist) and dizocilpine (a glutamatergic antagonists).[26,34] Furthermore, although blockade of NMDA receptors leads to impairment of neuronal plasticity (learning),[35] studies have also indicated cognitive enhancing effects.[36,37] For instance, memantine, a non-competitive NMDA receptor antagonist, has demonstrated cognitive and behavioural improvements in both humans,[38] and animals.[39,40] As indicated earlier, the extract exerts its antidepressant effects *via* interaction with the 5-HT system and glycine/NMDA site. Therefore, reversal of the chronic depression-induced memory deficits by PME could possibly be due to its interaction with the 5-HT system and glycine/NMDA receptor complex.

Although pretreatment with PME and the classical antidepressants improves spatial learning and memory of depressed mice in the repeated open-space procedure, it is necessary to deduce whether altered acquisition reflects impairment of learning or memory. Analysis of swimming velocity to reach the platform revealed no differences between depressed and treated animals, ruling out any non-specific effects of induced-depressive behaviour on spatial acquisition and memory. This finding demonstrates that improvement of spatial learning and memory by PME and the classical antidepressants in depressed mice are not due to any nonspecific changes in gross motor activity or motivational state.

CONCLUSION

The present study provides preclinical evidence that the hydroethanolic leaf extract of *P. microcarpa* exerts a rapid and sustained antidepressant-like effect and improves cognitive function.

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