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Research Article

Antidepressant-like properties of *Antiaris toxicaria* aqueous extract

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ABSTRACT

Background: Depression is a global burden whose therapy is plagued with inconsistent efficacy. Hence, the need for the discovery of newer therapies.
Methods: In this study, *Antiaris toxicaria* extract (200, 400 and 800 mg/kg, p.o.), was evaluated for antidepressant activity using behavioral tests battery particularly the forced swim test (FST) and tail suspension test (TST). In order to investigate its mechanism of action, animals groups were pretreated with α-methyldopa (α-MD), para-chlorophenylalanine (PCPA), reserpine, D-serine and 5-hydroxytryptophan.
Results: It increased the mobility periods and decreased immobility periods significantly in both the FST and the TST when compared to the control group. But the TST showed more promising effect than the FST. Pre-treatment with α-MD reversed the antidepressant property of *A. toxicaria* aqueous extract as did PCPA, reserpine and reserpine combined with α-MD. The extract increased the number of head twitches produced by 5-hydroxytryptophan confirming the involvement of serotonin in the antidepressant property and inhibited carbachol-induced contractions on the isolated rat uterus, which was non-competitively antagonized by propranolol. Treatment with D-serine produced no significant increase in the immobility time produced by the extract at the doses studied. This excludes the involvement of N-methyl-d-aspartate in the possible mechanisms of action.
Conclusion: *A. toxicaria* possesses antidepressant-like action in rodents.

Keywords: Antiaris, Para-chlorophenylalanine, Head twitches, N-methyl-d-aspartate, Tail suspension, Uterus

INTRODUCTION

Depression will be the second largest global burden and the second leading cause of disease-related disability by 2020, according to the World Health Organization.[1,2] It is associated with a consistently high prevalence worldwide[3] and is one of the most important causes of morbidity and disability in developing countries.[4]

However, therapy for depression has been plagued with inconsistent efficacy of currently available regimens and untoward side-effects in a significant number of patients.[5,6]

Herbs are usually resorted to because of the belief that they are safer.[7] Even though traditionally used herbs do not always transition into the primary health care system, some herbs have been found to be useful antidepressants. A leading

example is Saint John's Wort (*Hypericum perforatum)* L., Hypericaceae.

Antiaris toxicaria (family Moraceae) is a plant used locally for treating mental illness, pain and epilepsy in Africa.[8] The specie has been evaluated for anti-tumor and central activity.[9,10] It has also been previously shown to possess anticonvulsant activity in our lab.[11] Antidepressant-like activity has been reported with the aqueous leaf extract using a single model of depression.[12] This present study, however, aims is to establish the effects of *A. toxicaria* stem bark aqueous extract in various animal models of depression as well as investigate effects of the extract on the monoaminergic system and the glycine/N-methyl-d-aspartate (NMDA) receptor complex in order to elucidate the possible mechanism(s) of action of the extract.

METHODS

Plant material

The stem bark of *A. toxicaria* was harvested from the KNUST campus, Kumasi and identified by a staff member of the Pharmacognosy Department of the Faculty of Pharmacy and Pharmaceutical Sciences, KNUST, and Kumasi, Ghana.

Preparation of A. toxicaria aqueous extract

The dry stem bark was milled into powder using a commercial grinder. Coarse powder was extracted with distilled water by cold maceration at room temperature for 5 days. The filtrate was concentrated in a rotary evaporator. *A. toxicaria* aqueous extract (AAE) was obtained by drying the resultant filtrate with an oven. The final yield was 23.40% w/w.

Animals

Male ICR mice (20-25 g) were obtained from the Noguchi Memorial Institute for Medical Research. Animals were cared for in the Departmental Animal House for use in this study. Prior to testing, animals were allowed to acclimatize to laboratory conditions of temperature, humidity and light. They were also allowed free access to water and food and housed in standard cages. Groups of 8-10 animals were used. Animals were treated according to the Guide for the Care and Use of Laboratory Animals[13] and experiments were approved by the Faculty Ethics Committee.

Drugs and chemicals

Fluoxetine hydrochloride (Prozac®) (FLX), imipramine hydrochloride (IMI), α-methyldopa (Aldomet®) (α-MD), reserpine, para-chlorophenylalanine (PCPA), α-methyl-ρ-tyrosine (AMPT), D-tubocurarine (d-TC), diazepam (DZP), D-serine, D-cycloserine (D-CS), desipramine (DES), 5-hydroxytryptamine (5-HTP), noradrenaline (NE) and propranolol (PROP) were purchased from Sigma-Aldrich Inc., St. Louis, MO, USA.

Evaluation of antidepressant property

Forced swimming test (FST)

The test was performed as previously described by Porsolt et al. in 1977.[14] Mice were placed in vertical cylindrical plastic containers (25 cm high, 10 cm internal diameter) filled with water (25-28°C) up to a level of 20 cm for 7 mins. Five identical cylinders were used separated by opaque screens. Each session was recorded by a video camera suspended approximately 75 cm above the cylinders. Five animals were tested simultaneously. After each session, animals were removed from the cylinders, dried with absorbent towels and then returned to their home cages. Water was changed for each mouse. Scored behaviors were defined as mobility (swimming and struggling) and immobility (floating with only minimal movements needed to keep the head above water). Mice were divided into seven groups (n=8) and received either the extract (200, 400 or 800 mg/kg, p.o.), the vehicle (10 ml/kg, p.o.) or the standard reference drug IMI and FLX (3, 10 or 30 mg/kg, p.o.).

Tail suspension test (TST)

The test was carried out as previously described by Steru et al. in 1985.[15] Mice were divided into 10 groups of 5 (n=10) and received either extract (200, 400 or 800 mg/kg, p.o.), the vehicle (10 ml/kg, p.o.) or the standard reference drug IMI and FLX (3, 10 or 30 mg/kg, p.o.). Mice were individually suspended by the tail from a horizontal bar raised 30 cm above the bench top using adhesive tape (distance from the tip of tail=1 cm). Scored behavior was defined as mobility (struggling) and immobility (lack of movement).

Effect of catecholamine depletion on the antidepressant actions of AAE

The possible role of noradrenergic and serotonergic systems in the actions of AAE was investigated by carrying out serotonin (5-HT) and catecholamines depletion in the TST. Doses of PCPA, α-MD and reserpine were chosen based on previous work by O'Leary et al.,[16] To selectively deplete 5-HT, mice were pre-treated with PCPA, a tryptophan hydroxylase inhibitor, at a dose of 300 mg/kg; i.p. twice daily for 3 consecutive days. Animals were tested on the 4th day 20 hrs after the last dose. Mice were treated with a single dose of α-MD (200 mg/kg, i.p.) 3½ hrs before behavioral testing, in order to deplete newly synthesized pools of NE and dopamine (DA). To deplete vesicular pools of NE and DA, mice received a single dose of reserpine

(1 mg/kg, s.c.) 24 hrs before behavioral testing. Both the vesicular and cytoplasmic pools of NE and DA were depleted with a combination of reserpine (1 mg/kg, s.c.) 24 hrs and α-MD (200 mg/kg, i.p.) 3.5 hrs, before behavioral testing, respectively. All control animals received normal saline.

Involvement of NMDA receptors

Investigation into the possible involvement of NMDA in the mechanism of action was carried out. The procedure as described by Poleszak et al.[17] was used with slight modifications. D-serine (320 mg/kg; i.p), a partial agonist at the glycine/NMDA receptor was used to antagonize the antidepressant effects of the extract and standard antidepressants.

5-Hydroxytryptophan potentiation

Groups of 10 mice (20-30 g) were used. They were treated with either AAE (400 mg/kg; p.o), FLX (20 mg/kg; p.o) or distilled water. 30 mins later, the mice received 200 mg/kg of 5-hydroxytryptophan via intraperitoneal route. The number head twitches exhibited by the mice were recorded for the next 30 mins and presented as the head twitch score.[18]

Opioidergic involvement in the TST

This evaluation was done as described by Berrocoso et al.[19] Swinging behavior was defined as when the animal moved alternately from side to side with the body straight. Pedaling behavior was when the animal moved its paws continuously without moving its body. When the animal raised its head towards it hind paws, it was defined as curling. Behaviors were assessed in the TST.

β_2-Adrenoceptor activity

This was tested using the isolated rat uterus preparation. The rat uterus muscle was obtained from a freshly killed Sprague-Dawley rat (200 g). The muscle was suspended under a resting tension of 0.5 g in a 10 ml organ bath containing De Jalon's solution. The solution was maintained at 32°C and aerated with oxygen (95%) and carbon dioxide (5%). Isotonic contractions were recorded on a single channel pen recorder. Dose-response curves to carbachol were produced and mean (n=3) EC_{80} (8.76×10^{-7} M) was chosen. Increasing concentrations of the extract were administered in the presence of the EC_{80} of carbachol and responses compared to the carbachol control response. PROP (10^{-7}-10^{-5} M) was then added to the physiological saline solution for the remainder of the experiment and the above procedure repeated. Responses to adrenaline were used as a standard following the same protocol. The % inhibition of carbachol-induced contractions was calculated.

Motor co-ordination - rotarod test

The effect of the extract was assessed using the rotarod apparatus. The rotarod apparatus (model 7600, Ugo Basile, Cormerio, Italy) rotated at a speed of 18 rpm. This apparatus consists of a base platform and a rotating rod of 3 cm diameter with a non-skid surface. The rod, 50 cm in length, is divided into five equal sections by six disks. Before the start of the experiment, animals were trained to stay on the rotarod for 300 sec. Mice that did not achieve 300 sec endurance were excluded from the study. The mice were taken through five training runs. On the test day, five mice were tested simultaneously. The length of time each mouse remained on the rod (maximal score 300 sec) was measured after administration of the test compounds or vehicle. The integrity of motor coordination was assessed by the time spent on the rotating rod. Animals received either distilled water (10 ml/kg; p.o), extract (200, 400 and 800 mg/kg; p.o), DZP (0.1, 0.3 and 1 mg/kg, i.p.) or d-TC (3, 10 and 30 mg/kg, i.p.).

Data analysis

Analysis of variance (ANOVA) followed by Newman–Keuls' *post-hoc* test was used to determine significant differences between means. Two-way ANOVA followed by Bonferroni test was used in the FST and TSTs. Statistical analyses were carried out with Graph Pad Prism® Version 5.0 (GraphPad Software, San Diego, CA, USA). Values were presented as mean±standard error mean and $p<0.05$ was considered significant.

RESULTS

Effect in forced swimming

In the FST, mobility time was increased significantly ($p<0.05$; $F_{3,16}=3.703$; Figure 1a) only by the 800 mg/kg dose of the extract. FLX showed a similar increase while IMI showed higher increases, which were significant ($p<0.01$; $F_{3,16}=7.059$; Figure 1c) at the 10 and 30 mg/kg doses. Immobility time was significantly ($p<0.05$; $F_{3,16}=3.434$; Figure 1a) decreased by the middle dose of AAE. A significant ($p<0.05$; $F_{3,16}=4.809$; Figure 1b) decrease in immobility period occurred at all at doses for FLX. IMI showed significant ($p<0.05$; $F_{3,16}=6.841$; Figure 1b) decrease in immobility periods in a non-dose-dependent manner.

Effect in the TST

All doses showed a significant decrease in immobility periods for extract treated groups ($p<0.01$; $F_{3,16}=7.826$;

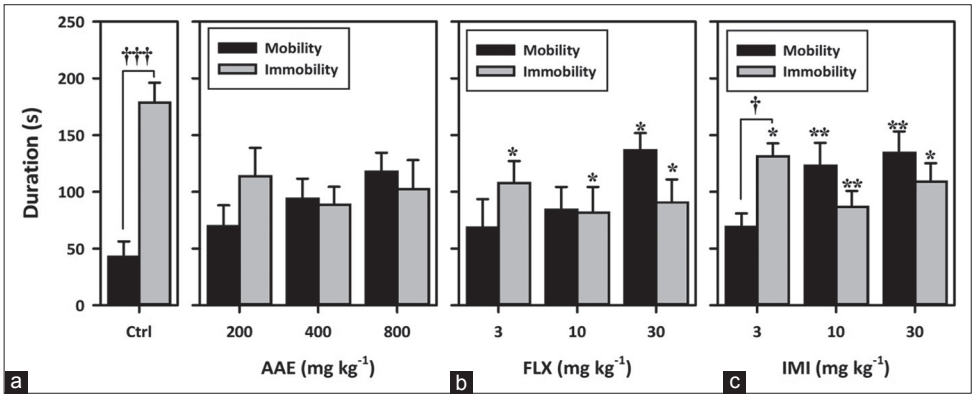

Figure 1: Effects of acute *Antiaris toxicaria* aqueous extract (200, 400 and 800 mg/kg, p.o.), fluoxetine (3, 10 and 30 mg/kg, p.o.) and imipramine (3, 10 and 30 mg/kg, p.o.) treatment on mobility and immobility times in forced swim test. Data are presented as group means (±standard error mean). Significantly different from control: *p<0.05, **p<0.01, by one-way ANOVA followed by Newman–Keuls' *post-hoc* test, †p<0.0.5, †††p<0.001 by two-way ANOVA followed by Bonferroni test.

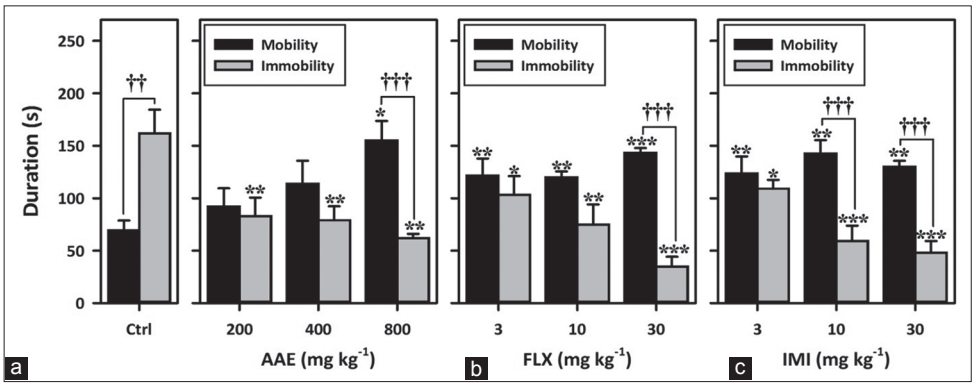

Figure 2: Effects of acute *Antiaris toxicaria* aqueous extract (200, 400 and 800 mg/kg, p.o.), fluoxetine (3, 10 and 30 mg/kg, p.o.) and imipramine (3, 10 and 30 mg/kg, p.o.) treatment on mobility and immobility times in tail suspension test. Data are presented as group means (±standard error mean). Significantly different from control: *p<0.05, **p<0.01, ***p<0.001 by one-way ANOVA followed by Newman–Keuls' *post-hoc* test. ††p<0.01, †††p<0.001 by two-way ANOVA followed by Bonferroni test.

Figure 2a) with only the highest dose showing a significant ($p<0.05$; $F_{3,16}=4.321$; Figure 2a) increase in mobility periods. IMI produced a significant ($p<0.001$; $F_{3,16}=11.77$; Figure 2c) decrease in immobility time, which was dose dependent. The increase in mobility period was also significant ($p<0.01$; $F_{3,16}=7.574$; Figure 2c) at all doses. FLX produced a decrease in immobility periods as well ($p<0.01$; $F_{3,16}=8.910$, Figure 2b) in addition to a significant increase in mobility time ($p<0.01$; $F_{3,16}=9.531$; Figure 2b).

Opioidergic evaluation

Swinging frequency was not affected by the extract. The duration, however, showed significant ($p<0.05$; Figure 3a) increase at the highest dose. A significant decrease in both pedaling frequency and duration ($p<0.01$; Figure 3b) in a non-dose-dependent manner was obtained.

AAE showed no significant increase in curling frequency, but a significant ($p<0.01$; Figure 3c) increase in the duration of curling.

Effect of monoamine depletion on the effect of AAE

Figure 4a shows the effects of α-MD pre-treatment on the behavioral effects of antidepressants in the TST. AAE, IMI and FLX were not able to significantly attenuate or reverse the immobility induced by α-MD. Two-way ANOVA shows significant ($p<0.0001$; $F_{1,18}=25.70$; Figure 4a) increase in immobility periods by α-MD.

The extract was also not able to significantly reverse the immobility periods induced by pretreatment with PCPA just as FLX. IMI, however, significantly ($p<0.001$; Figure 4b) reversed the increase in immobility time compared with

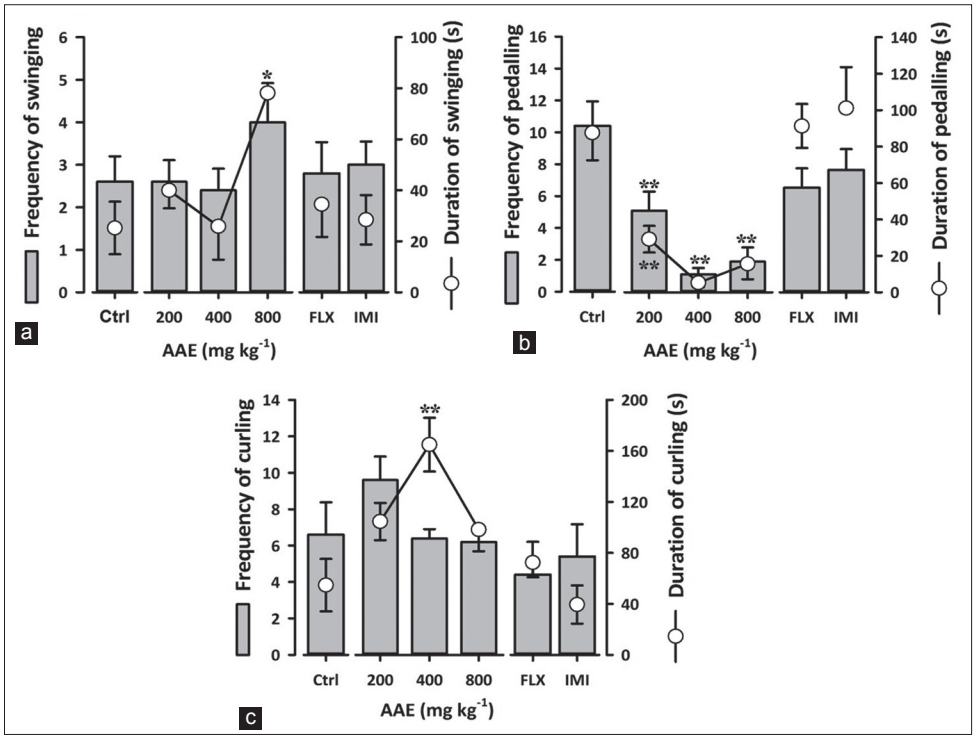

Figure 3: Effects of acute *Antiaris toxicaria* aqueous extract (200, 400 and 800 mg/kg), imipramine (30 mg/kg) and fluoxetine (30 mg/kg) treatment on swinging (a) pedaling (b) and curling behavior (c) in tail suspension test. Data are presented as group means (±standard error mean). *p<0.05, **p<0.01 by one-way ANOVA followed by Newman–Keuls' *post-hoc* test.

control. PCPA caused significant ($p<0.05$; $F_{1,18}=5.64$, Figure 4b) depletion of serotonin hence the inability of FLX to act.

From the effects of pre-treatment with reserpine, FLX, AAE and IMI were not able to cause any significant change in reserpine-induced immobility (Figure 4c).

Pre-treatment with a combination of reserpine (1 mg/kg, s.c.) 24 hrs before the TST and α-MD (200 mg/kg, i.p.) 3.5 hrs before the TST was to deplete both the newly formed stores of catecholamines by α-MD and also vesicular storage by reserpine. The behavioral effects of all the tested antidepressant drugs were completely blocked by this combination (Figure 4d).

Effect of 5-hydroxytryptophan potentiation

The extract was able to significantly ($p<0.05$; Figure 5) increase the number of head twitches produced by 5-HTP in a similar manner to FLX.

NMDA involvement

The extract alone produced significant ($p<0.001$; Figure 6a) decrease in immobility time as did FLX, DES and D-CS ($p<0.001$; Figure 6b-d). Treatment with D-serine produced no significant increase in the immobility time produced by the extract (Figure 6a). FLX ($p<0.01$; $F_{1,18}=12.85$; Figure 6b) and D-CS ($p<0.01$; $F_{1,18}=14.05$; Figure 6d) showed significant increases in immobility time after D-serine treatment at the doses studied.

PCPA significantly ($p<0.05$; $F_{1,18}=6.12$; Figure 6e) increased the immobility period at the highest dose only of the extract just as FLX ($p<0.05$; $F_{1,18}=14.34$; Figure 6f). DES was not affected significantly as expected. The immobility time for the extract was significantly ($p<0.0001$; $F_{1,54}=204.18$; Figure 6i) reversed by AMPT but FLX was unaffected. DES was affected ($p<0.0001$; $F_{1,54}=48.27$; Figure 6k) at all doses except the highest dose. D-CS was also not affected.

β_2-adrenoceptor activity

The extract produced inhibition of carbachol-induced contractions in a dose-dependent fashion with a maximum inhibition of 100%. PROP (10^{-7}-10^{-5} M) produced a non-parallel rightward shift of increasing concentrations of AAE (Figure 7a). Adrenaline, however, produced a parallel rightward shift in the presence of PROP (Figure 7b).

Locomotor activity

Results show that AAE at the doses used has no significant effect on motor coordination. d-TC and DZP however caused

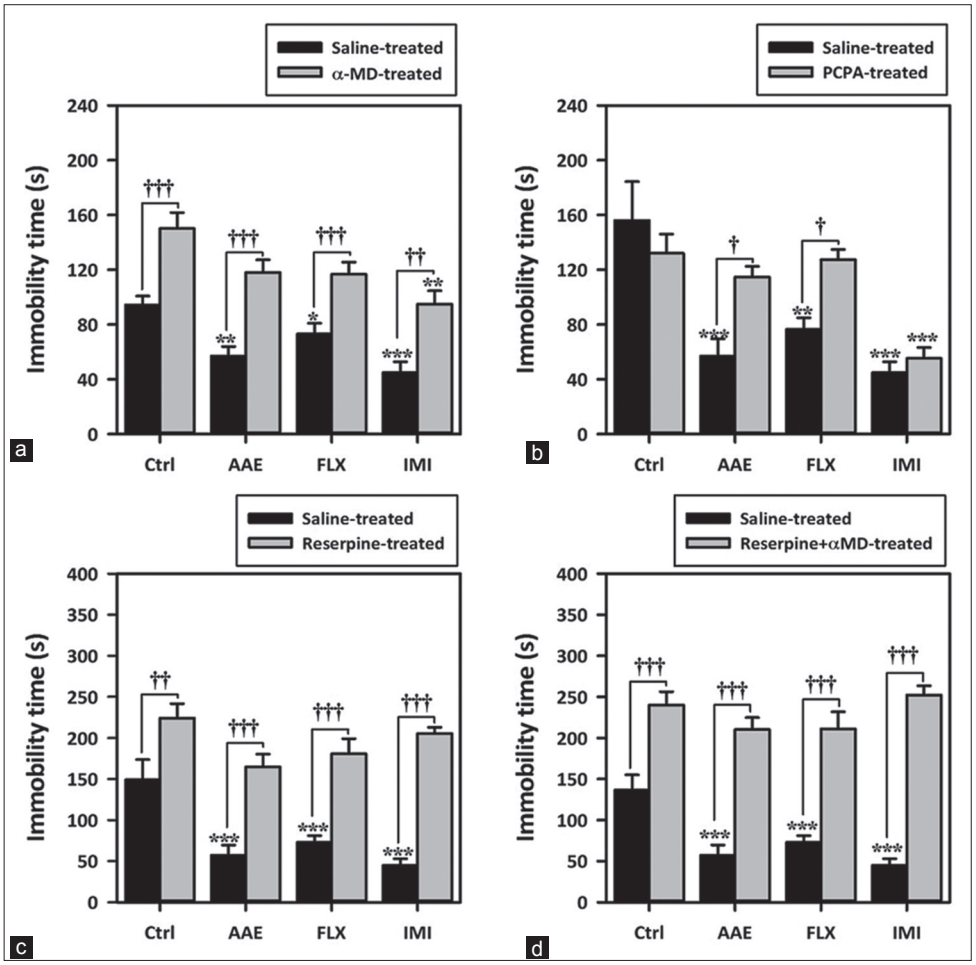

Figure 4: Effects of α-methyldopa (α-MD) (200 mg/kg, i.p.) (a) para-chlorophenylalanine (300 mg/kg bd, i.p.) (b) reserpine (1 mg/kg, s.c.) (c) and reserpine + α-MD (d) pretreatment on the behavioral response of *Antiaris toxicaria* aqueous extract (400 mg/kg p.o.), fluoxetine (10 mg/kg p.o.) and imipramine (10 mg/kg p.o.) in the tail-suspension test. Data are presented as group means (±standard error mean). Analysis was done by one-way analysis of variance followed by Newman–Keuls' *post-hoc* test. Significantly different from control: *p<0.05, **p<0.01, ***p<0.001. And by two-way ANOVA †p<0.05, ††p<0.01 †††p<0.001 by Bonferroni post-test.

significant (p<0.01) dose-dependent decrease in time spent on the rod (Figure 8).

DISCUSSION

Results of the present study indicate that *A. toxicaria* may possess antidepressant-like effect in the models of depression used.

The FST evaluates "behavioral despair;" a measure of failure to seek escape from an aversive stimulus.[20] FST has high predictive validity and has shown sensitivity to major classes of antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors (Borsini and Meli, 1988; Dalvi and Lucki, 1999). In the TST, mice attempt to "escape" by agitation. In both tests, immobility is reduced by a broad range of pharmacological treatments. AAE showed reduced immobility in both tests. It was however more effective in the TST showing it is more sensitive in that test.

To eliminate the involvement of compromised motor activity and coordination, the rotarod test was used to show that AAE at the doses used did not have such effects.

Berrocoso et al. in 2011 have shown that opioids produced stereotyped behavioral patterns by decreasing pedaling behavior and increasing the curling behavior in the TST. This may help differentiate between standard antidepressants and other compounds possessing antidepressant-like properties but with different mechanisms of action. The extract showed a significant increase in duration of curling and pedaling behavior implicating opioidergic properties. Some opioids such as pethidine and methadone have shown a tendency to increase swinging behavior. As AAE showed some significant increase in duration of swinging, it is likely

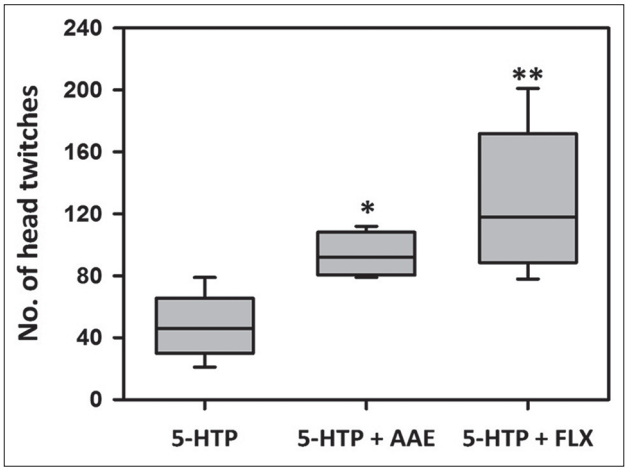

Figure 5: Effects of *Antiaris toxicaria* aqueous extract (400 mg/kg, p.o.) and fluoxetine (15 mg/kg, p.o.) on head twitches in 5-hydroxytryptophan potentiation test. Data are presented as group means (±standard error mean). The lower and upper margins of the boxes represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles respectively. The median is shown as a horizontal line within the box. Analysis was done by one-way analysis of variance followed by Newman–Keuls' *post-hoc* test. Significantly different from control: *p<0.05, **p<0.001.

that its opioidergic properties are more similar to that of pethidine and methadone than to that of morphine.

An attempt was made to investigate the mechanism of the antidepressant action of AAE by monoamine depletion. Pre-treatment of mice with PCPA, α-MD and reserpine are mechanistic models known to alter the monoamine levels in the frontal cortex. These monoamines are crucial in mood, cognition and motor behavior functions that are compromised in depression.[21] Acute administration of many antidepressants is accompanied by an increase in extracellular monoamine levels since they block transporters that control neurotransmission.[21] This implies that elevated levels of monoamines are crucial in the management of depression.[22-24]

α-MD is a 3,4-dihydroxyphenylalanine decarboxylase inhibitor which hampers synthesis of catecholamines and 5-HT.[25-27] α-MD gives rise to "false transmitters;" α-methyldopamine and α-methylnoradrenaline.[27,28] Presynaptic feedback inhibition of NE occurs since these false transmitters are powerful α_2-adrenoceptor agonists.[29] This implies that pre-treatment with α-MD is expected to have a more sustained effect on catecholamine depletion rather than on the serotoninergic pathway. Results did not confirm this as the effect of FLX was largely blocked though not completely. This, however, confirms the findings of Carlsson and Lindqvist.[27] Pre-treatment with α-MD, similar to IMI, abolished the antidepressant effects of the extract pointing to the possible involvement of catecholamines in the antidepressant-like properties of *A. toxicaria*. IMI is a non-selective inhibitor of both monoamine transporters norepinephrine transporter and serotonin transporter. Hence, α-MD was not expected to block its action completely - and this was rightly so.

Pre-treatment with PCPA did not alter baseline immobility significantly. This agrees with previous reports which demonstrate the depletion of 5-HT with PCPA does not alter baseline behavior in many antidepressant animal models.[16] It reversed the antidepressant effect of FLX as expected since 5-HT had been depleted. The effect of the extract was reversed similarly, again implicating serotoninergic involvement in its mechanism of action. IMI, however, showed no significant reversal of activity consistent with earlier findings.[16]

Pre-treatment with reserpine increased immobility periods reversing the antidepressant effects of IMI and AAE in the TST. Effect of FLX was also reversed, though not completely. Reserpine irreversible inhibits vesicular monoamine transporter 2 which is responsible for transporting monoamines from the cytoplasm into secretory vesicles mainly in the central nervous system.[30] Vesicular monoamine stores of both serotonin and NE are depleted by reserpine.[31] This helps to further implicate both serotonin and NE in the antidepressant effects of AAE. Pre-treatment with a combination of reserpine and α-MD completely inhibited the effects of all three treatments.

Involvement of serotonin in the effects of AAE was confirmed using the 5-hydroxytryptophan potentiation test. 5-HTP is a precursor for serotonin and is known to produce head twitches while increasing serotonergic transmission.[32,33] 5-HTP head twitch response was significantly potentiated by AAE further confirming its antidepressant properties are modulated by serotonin. This test is considered as further evidence for antidepressant activity based on synaptic serotonin uptake inhibition.[33]

Some antidepressants are known to increase synaptic concentrations of NE while others act directly on adrenoceptors.[34] β_2-adrenoceptor agonists have been shown to possess antidepressant-like activity in animals and man, but possess peripheral side-effects that prevent their therapeutic use.[35] The extract showed β_2-adrenoceptor agonist activity by producing reduced contractions induced by carbachol on the isolated rat uterus.[36-38] Various concentrations of PROP blocked the relaxation effect of the extract non-competitively.

The role of the excitatory neurotransmitter glutamate in the pathophysiology of depression is evident. Disturbances of glutamate levels in depressed patients have been found in clinical studies.[39] The antidepressant property shown by the extract was not antagonized by a pre-treatment with D-serine. D-serine is a full agonist at the glycine/NMDA

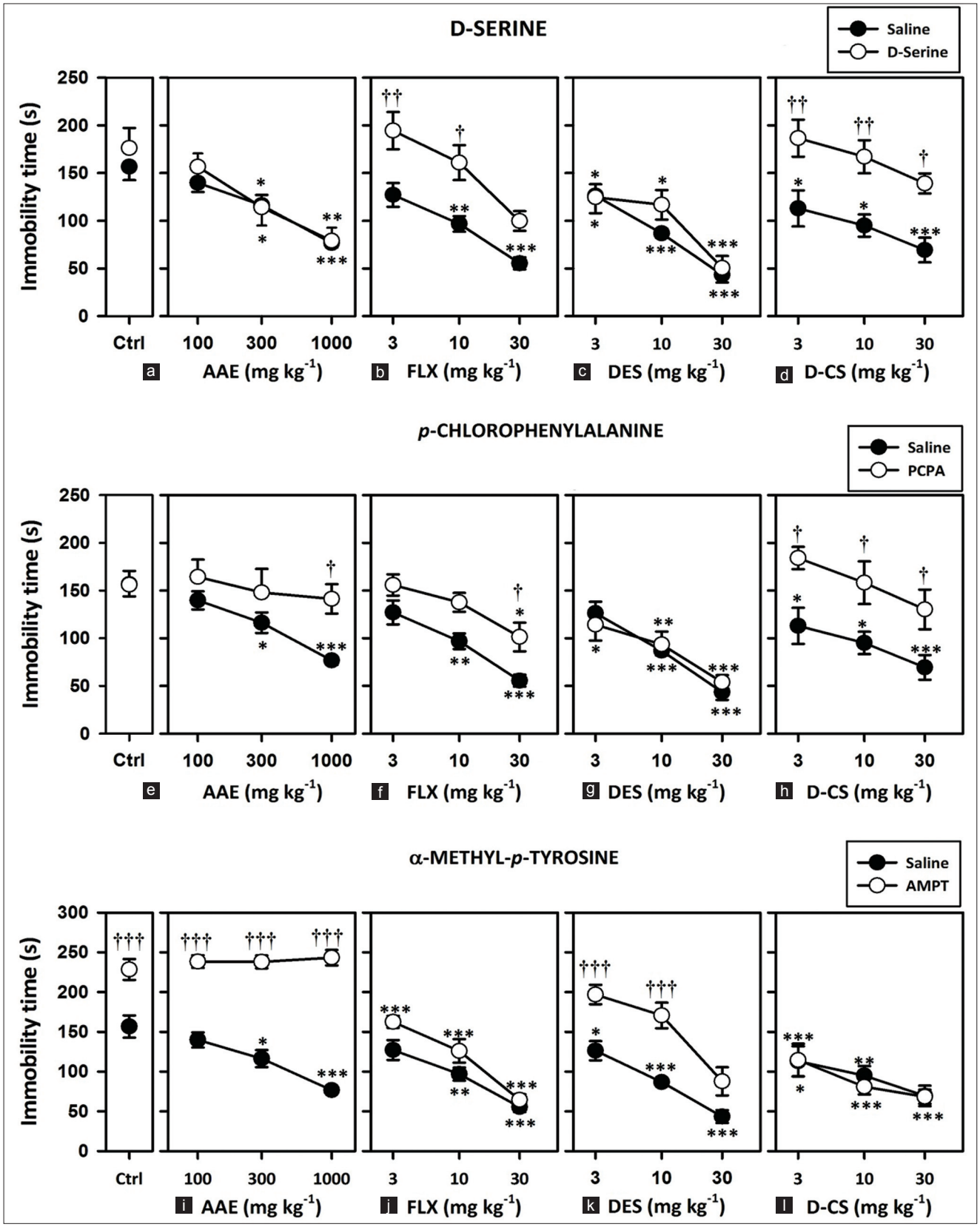

Figure 6: Effects D-serine (320 mg/kg; i.p) on behavioural response of *Antiaris toxicaria* aqueous extract (AEE) (100-1000 mg/kg) (a) fluoxetine (3-30 mg/kg) (b) desipramine (DES) (3-30 mg/kg) (c) and D-cycloserine (D-CS) (3-30 mg/kg) (d) para-chlorophenylalanine (200 mg/kg) pre-treatment on the behavioral response AEE (100-1000 mg/kg) (e) fluoxetine (3-30 mg/kg) (f) DES (3-30 mg/kg) (g) and D-CS (3-30 mg/kg) (h) α-methyl-ρ-tyrosine pre-treatment on the behavioral response AEE (100-1000 mg/kg) (i) fluoxetine (3-30 mg/kg) (j) DES (3-30 mg/kg) (k) and D-CS (3-30 mg/kg) (l) in the forced swimming test. Data are presented as group means (±standard error mean). Analysis was done by one-way analysis of variance followed by Newman–Keuls multiple comparisons test.

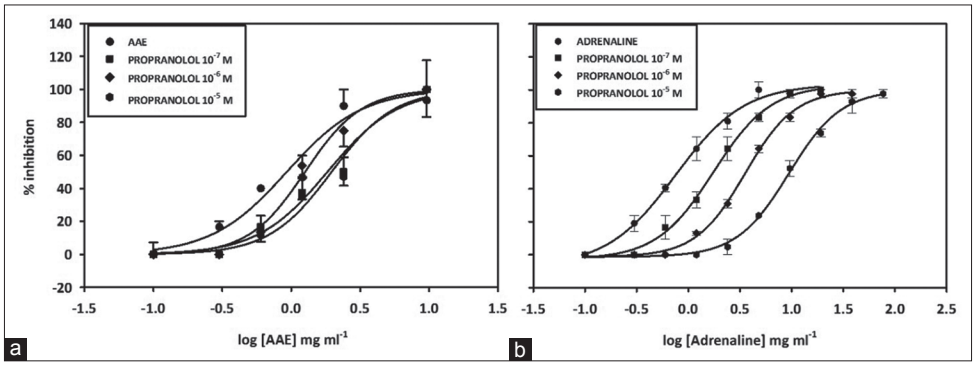

Figure 7: Mean concentration-response curves obtained for *Antiaris toxicaria* aqueous extract (a) and adrenaline (b) in the absence and presence of propranolol on the response of isolated rat uterine preparation to the EC_{80} (8.76×10^{-7} M) of carbachol. Each point represents mean±standard error mean. % maximum response were calculated as % inhibition of carbachol responses.

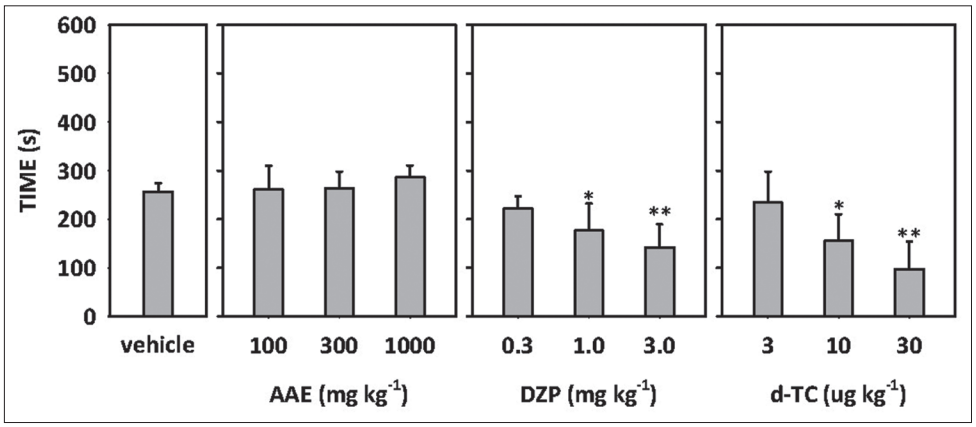

Figure 8: Effects of acute *Antiaris toxicaria* aqueous extract (100, 300 and 1000 mg/kg), diazepam (0.3-3.0 mg/kg) and D-tubocurarine (3-30 mg/kg) on motor coordination in the rotarod test. Data are presented as group means (±standard error mean). *p<0.05, **p<0.01 by one-way ANOVA, followed by Newman–Keuls' *post-hoc* test.

receptor. AAE's antidepressant effects were still apparent in the presence of D-serine indicating that its actions are independent of the NMDA-glycine receptor B. Glycine/NMDA receptor antagonists are known to enhance antidepressant-like effects of serotonin-based, but not NE-based antidepressants.[17] This was confirmed by monoamine depletion with PCPA and AMPT.

CONCLUSION

The aqueous extract of *A. toxicaria* stem bark possesses antidepressant-like activity and may be acting via adrenergic and serotoninergic mechanisms.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602.
2. Rybnikova E, Mironova V, Pivina S, Tulkova E, Ordyan N, Vataeva L, et al. Antidepressant-like effects of mild hypoxia preconditioning in the learned helplessness model in rats. Neurosci Lett. 2007;417(3):234-9.
3. Piato AL, Rizon LP, Martins BS, Nunes DS, Elisabetsky E. Antidepressant profile of *Ptychopetalum olacoides* Bentham (Marapuama) in mice. Phytother Res. 2009;23(4):519-24.
4. Abas M, Broadhead J. Mental disorders in the developing world. BMJ. 1994;308(6936):1052-3.
5. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatr Res. 2007;41(3-4):189-206.
6. Healy D. Did regulators fail over selective serotonin reuptake inhibitors? BMJ. 2006;333(7558):92-5.
7. Rates SM. Plants as source of drugs. Toxicon. 2001;39(5):603-13.
8. Mshana RN, Abbiw DK, Addae-Mensah I, Adjanouhoun E, Ahyi MRA, Ekpere JA, et al. Traditional Medicine and Pharmacopoeia; Contribution to the Revision of Ethnobotanical and Floristic Studies in Ghana. Accra, Ghana: Science and Technology Press, CSIR; 2001.
9. Levrier C, Kiremire B, Guéritte F, Litaudon M. Toxicarioside M. A new cytotoxic 10ß-hydroxy-19-

nor-cardenolide from *Antiaris toxicaria*. Fitoterapia. 2012;83(4):660-4.
10. Li YN, Huang FY, Mei WL, Dai HF, Guo JL, Tan GH, et al. Toxicarioside A, isolated from tropical Antiaris toxicaria, blocks endoglin/TGF-ß signaling in a bone marrow stromal cell line. Asian Pac J Trop Med. 2012;5(2):91-7.
11. Mante PK, Adongo DW, Woode E, Kukuia KK, Ameyaw EO. Anticonvulsant effect of *Antiaris toxicaria* (Pers.) lesch. (Moraceae) aqueous extract in rodents. ISRN Pharmacol. 2013;2013:519208.
12. Agbaje EO, Ishola IO, Oniyire JA. Antidepressant, anxiolytic, and anticataleptic effects of aqueous leaf extract of *Antiaris toxicaria* Lesch. (Moraceae) in mice: possible mechanisms of actions. J Basic Clin Physiol Pharmacol. 2014.
13. Institute of Laboratory Animal Research, C.o.L.S., National Research Council. Guide for the Care and Use of Laboratory Animals. 7th edition. Washington, D.C: The National Academies Press; 1996.
14. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977;266(5604):730-2.
15. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl). 1985;85(5):367-70.
16. O'Leary OF, Bechtholt AJ, Crowley JJ, Hill TE, Page ME, Lucki I. Depletion of serotonin and catecholamines block the acute behavioral response to different classes of antidepressant drugs in the mouse tail suspension test. Psychopharmacology (Berl). 2007;192:357-71.
17. Poleszak E, Wlaź P, Szewczyk B, Wlaź A, Kasperek R, Wróbel A, et al. A complex interaction between glycine/NMDA receptors and serotonergic/noradrenergic antidepressants in the forced swim test in mice. J Neural Transm. 2011;118(11):1535-46.
18. Koe BK, Weissman A, Welch WM, Browne RG. Sertraline, 1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine. a new uptake inhibitor with selectivity for serotonin. J Pharmacol Exp Ther. 1983;226(3):686-700.
19. Berrocoso E, Ikeda K, Sora I, Uhl GR, Sánchez-Blázquez P, Mico JA. Active behaviours produced by antidepressants and opioids in the mouse tail suspension test. Int J Neuropsychopharmacol. 2013;16(1):151-62.
20. Crawley JN, Belknap JK, Collins A, Crabbe JC, Frankel W, Henderson N, et al. Behavioral phenotypes of inbred mouse strains: implications and recommendations for molecular studies. Psychopharmacology (Berl). 1997;132(2):107-24.
21. Millan MJ, Lejeune F, Gobert A. Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: relevance to the actions of antidepressant agents. J Psychopharmacol. 2000;14(2):114-38.
22. Brunello N, Mendlewicz J, Kasper S, Leonard B, Montgomery S, Nelson J, et al. The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. Eur Neuropsychopharmacol. 2002;12(5):461-75.
23. Stone EA, Lin Y, Rosengarten H, Kramer HK, Quartermain D. Emerging evidence for a central epinephrine-innervated alpha 1-adrenergic system that regulates behavioral activation and is impaired in depression. Neuropsychopharmacology. 2003;28(8):1387-99.
24. Gobert A, Rivet JM, Cistarelli L, Millan MJ. Potentiation of the fluoxetine-induced increase in dialysate levels of serotonin (5-HT) in the frontal cortex of freely moving rats by combined blockade of 5-HT1A and 5-HT1B receptors with WAY 100,635 and GR 127,935. J Neurochem. 1997;68(3):1159-63.
25. Oates JA, Gillespie L, Udenfriend S, Sjoerdsma A. Decarboxylase inhibition and blood pressure reduction by alpha-methyl-3,4-dihydroxy-DL-phenylalanine. Science. 1960;131(3417):1890-1.
26. Hess SM, Connamacher RH, Ozaki M, Udenfriend S. The effects of alpha-methyl-DOPA and alpha-methyl-metatyrosine on the metabolism of norepinephrine and serotonin *in vivo*. J Pharmacol Exp Ther. 1961;134:129-38.
27. Carlsson A, Lindqvist M. *In-vivo* decarboxylation of alpha-methyl DOPA and alpha-methyl metatyrosine. Acta Physiol Scand. 1962;54:87-94.
28. Sjoerdsma A. Alpha-methyldopa: antihypertensive drug with unusual mechanism of action. Heart Bull. 1963;12:1-4.
29. Hey JA, Ito T, Koss MC. alpha-Methyldopa produces mydriasis in the rat by stimulation of CNS alpha 2-adrenoceptors. Br J Pharmacol. 1988;94(3):834-8.
30. Metzger RR, Brown JM, Sandoval V, Rau KS, Elwan MA, Miller GW, et al. Inhibitory effect of reserpine on dopamine transporter function. Eur J Pharmacol. 2002;456(1-3):39-43.
31. Fukui M, Rodriguiz RM, Zhou J, Jiang SX, Phillips LE, Caron MG, et al. Vmat2 heterozygous mutant mice display a depressive-like phenotype. J Neurosci. 2007;27(39):10520-9.
32. Ortmann R, Martin S, Radeke E, Delini-Stula A. Interaction of beta-adrenoceptor agonists with the serotonergic system in rat brain. A behavioral study using the L-5-HTP syndrome. Naunyn Schmiedebergs Arch Pharmacol 1981;316(3):225-30.
33. Pandey DK, Rajkumar R, Mahesh R, Radha R. Depressant-like effects of parthenolide in a rodent behavioural antidepressant test battery. J Pharm Pharmacol. 2008;60(12):1643-50.
34. Elhwuegi AS. Central monoamines and their role in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(3):435-51.
35. Consoli D, Leggio GM, Mazzola C, Micale V, Drago F. Behavioral effects of the β3 adrenoceptor agonist SR58611A: is it the putative prototype of a new class of antidepressant/anxiolytic drugs? Eur J Pharmacol. 2007;573(1-3):139-47.
36. Mattsson H, Andersson T, Carlsson E, Hedberg A, Lundgren B, Olsson T. beta 1-and beta 2-adrenoceptor stimulatory effects of prenalterol. Naunyn Schmiedebergs Arch Pharmacol. 1982;321(4):302-8.
37. Tanaka Y, Horinouchi T, Koike K. New insights into beta-adrenoceptors in smooth muscle: distribution of receptor subtypes and molecular mechanisms triggering muscle relaxation. Clin Exp Pharmacol Physiol. 2005;32(7):503-14.
38. Liu YL, Nwosu UC, Rice PJ. Relaxation of isolated human myometrial muscle by beta2-adrenergic receptors but not beta1-adrenergic receptors. Am J Obstet Gynecol. 1998;179(4):895-8.
39. Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. Increased cerebrospinal fluid glutamine levels in depressed patients. Biol Psychiatry. 2000;47(7):586-93.

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