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Studies of Behavioural and Neural Mechanism of Aridanin Isolated from *Tetrapleura tetraptera* in Mice

[1]A.O. Aderibigbe, [2]E.O. Iwalewa, [3]S.K. Adesina and [4]O.I. Agboola
[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy,
Niger-Delta University, Bayelsa State, Nigeria
[2]Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University,
Ile-Ife Osun State, Nigeria
[3]Drug Research and Production Unit, Faculty of Pharmacy, Obafemi Awolowo University,
Ile-Ife Osun State, Nigeria
[4]Department of Pharmacognosy, Faculty of Pharmacy, Niger-Delta University,
Bayelsa, Bayelsa State, Nigeria

Abstract: The aim of the present study was to investigate the central nervous system depressant effect and neural mechanisms of Aridanin in mice. Novelty-induced rearing, head dips, locomotor activity and effect on learning and memory were studied. Aridanin at 5, 10, 20 and 30 mg kg^{-1} b.wt. reduced novelty-induced rearing and locomotor activity in mice. Head dip reduction was noticed only with the highest dose (30 mg kg^{-1}, i.p.) while in Y-maze, a reduction in number of entrance (locomotion) with no change in percentage alternation on short term working memory was obtained. Aridanin reversed the central excitatory effect of flumazenil in the methods. These results confirm the central depressant properties of Aridanin which may be mediated through $GABA_A$ receptor.

Key words: Aridanin, *Tetrapleura tetraptera*, Y-maze, hole board, open field, rearing

INTRODUCTION

Tetrapleura tetraptera Taub (Mimosaceae) locally known as Aridan is a large tree growing throughout the rain forest belt of West Africa. It is generally found in the lowland forest of tropical Africa. The fruit consist of a fleshy pulp with small, brownish-black seeds. The plant has many traditional uses mainly in the management of convulsion, leprosy, inflammation and rheumatic pains, schistosomiasis, asthma and hypertension (Ojewole and Adesina, 1983). The dry fruit has a pleasant aroma (Aladesanmi, 2007). It is used as a popular seasoning spice, a medicine and a dietary supplement rich in vitamins in Southern and Eastern Nigeria (Okwu, 2003; Essien *et al*., 1994). The fruit is used to prepare soup for mothers from the first day of birth to prevent post partum contraction (Nwawu and Akali, 1986). The root extract has been proven to be useful for the treatment of gastrointestinal related clinical problem (Noamesi *et al*., 1994). The ethanol extract and saponins from the stem bark of *Tetrapleura tetraptera* exerted an inhibitory effect on luteinizing hormone released by pituitary cells, suggesting its use as contraceptive agent (El-Izzi *et al*., 1990). *Tetrapleura tetraptera* is a natural molluscicides as aqueous extract of it is effective against *Bulinus globosus* and *Lymnaea natalensis* (Adewunmi, 1991). The alleopathic potential of *Tetrapleura tetraptera* has led to its integration into an agro forestry system (Amoo *et al*., 2008). *Tetrapleura tetraptera* has been shown to improve the foaming ability of soaps (Adebayo *et al*., 2000). *Tetrapleura tetraptera* has no influence on cell proliferation and neither induced chromosomal aberration nor sister chromatid exchanges in Chinese hamster ovary cells (no genotoxic effect) (Adewunmi *et al*., 1991). *Tetrapleura tetraptera* has been shown to cause elevation in serum AST and alteration of various metabolites parameters and did not induce any marked pathological lesion in the liver (Lawal *et al*., 2009). The sedative, anticonvulsant and analgesic effect of Aridanin in mice have been reported by Aderibigbe *et al*. (2007 a, b) and Ojewole (2005). The aqueous extract of *Tetrapleura tetraptera* fruit have been shown to possessed anti-inflammatory and hypoglycaemic properties (Ojewole and Adewunmi, 2004). The ethanolic extract of *Tetrapleura tetraptera* fruit possessed antiplasmodial activity in mice (Okonkon *et al*., 2007). One

Corresponding Author: A.O. Aderibigbe, Department of Pharmacology and Toxicology, Faculty of Pharmacy,
Niger-Delta University, P.M.B. 071, Amassoma, Bayelsa State, Nigeria Tel: 08054327546

of the active constituents isolated from *Tetrapleura tetraptera* fruit is a mono-N-acetylglycoside of oleanoic acid (3β-hydroxyolean-12-en-28-oic) called Aridanin (Adesina and Reish, 1985). The present study was carried out in order to investigate further the neurobiology properties of Aridanin.

MATERIALS AND METHODS

Plant material: Structural elucidation and characterization of Aridanin (Fig. 1) from *Tetrapleura tetraptera* was carried out by Prof. S. K. Adesina (Adesina and Reish, 1985) of Drug Research and Product Unit, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife. Sample used for this experiment was collected from him.

Animals: Swiss albino male mice weighing between (20-25 g) were obtained in March 2009 from the animal house of the Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife. The animals were divided into five mice in each cage and were fed with a standard laboratory diet and tap water *ad libitum*. The animals were maintained at 25+1°C under natural 12 h daylight night conditions. All experiment was carried out in compliance with Obafemi Awolowo University Ethics Committee on research in animals and in accordance with NIH guide for the care and use of laboratory animals.

Drugs: Diazepam (Roche, Basel Switzerland), Atropine, Flumazenil, Yohimbine, Naloxone, Cyproheptadine (Sigma Chemicals Co. St. Louis, Missouri, USA).

Drug dissolution: Aridanin was dissolved in 5% Tween 80. Diazepam, flumazenil, atropine, yohimbine, naloxone and cyproheptadine were dissolved in normal saline. Tween 80 at 5% concentration did not affect behavioural studies in rodents (Castro *et al*., 1995). The resulting solution, control vehicle and test materials were usually administered intraperitoneally (i.p.).

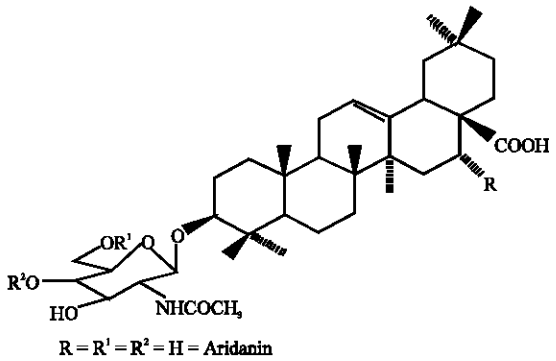

Fig. 1: The chemical structure of Aridanin

Toxicity: Acute toxicity studies of Aridanin in mice were carried out as described by Miller and Tainter (1944) and the lethal dose was calculated by the method of Lichtfield and Wilcoxon (1949). It was carried out by injecting Aridanin intraperitioneally (i.p.) into 5 groups of male mice containing 5 animals with the following dose levels 25, 37.5, 50, 75 and 100 mg kg^{-1}. The animals were observed for over 24 h and the LD_{50} was calculated.

Novelty-induced rearing: The behavioural profile of albino mice under the influence of Aridanin was assessed singly in a Plexiglass cage measuring (45×25×25 cm) containing wood shavings. Behavioural measurements were carried out after i.p. administration of 5% Tween 80 (0.2 mL/20 g) group 1 and Aridanin (5, 10, 20 and 30 mg kg^{-1}, i.p.) groups 2-5. Aridanin was administered for 30 min into animals before been placed singly into an opaque plexiglass observation cage with only one side transparent for observation. Each animal was used only once, with the saw dust bedding changed after each assessment to remove olfactory cue from one animal to the other. The time of the experiment was kept constant (9.00 a.m.-1.00 p.m.) daily to avoid changes in biological rhythm. The behavioural component employed in this observational analysis is rearing. Rearing is defined as the number of times the animal stood on its hind legs or with its forearm against the wall of the observation cage or in the free air (Ajayi and Ukponmwan, 1994). The frequency of rearing episodes was counted manually for 5 min.

Locomotor activity: Motor activity was measured in an open field apparatus consisting of a white plexiglas box (28 ×28 × 25 cm) with a painted back grid dividing the floor into 16 (7 × 7 cm) equal squares. The animals were divided into six groups. Group 1 was given 5% Tween 80 (0.2 mL/20 g i.p.), while groups 2-5 was given Aridanin (5, 10, 20 and 30 mg kg^{-1} i.p.). Aridanin was administered for 30 min into animals and were placed singly in one of the corners of the box; the number of squares crossed with all four paws was counted for 5 min. The cages were cleared with 70% ethanol at intervals when the animal is removed (Mandal *et al*., 2001). Diazepam (2.0 mg kg^{-1}, i.p.) group 6 served as reference drug.

Head dips: The effect of Aridanin on the rate of head dipping was determined in the holeboard with a number of holes (usually 16) in the floor through which the animal can poke its head. The animals were divided into six groups. Group 1 was given 5% Tween 80

(0.2 mL/20 g i.p.), while groups 2-5 was given Aridanin (5, 10, 20 and 30 mg/kg i.p.). Aridanin was administered for 30 min into animals and placed on top of a wooden box with 16 evenly spaced hole. The number of times that each animal dipped their head into the holes in 5 min was counted (Dorr *et al*., 1971). 70% ethanol was used to clean the cages at intervals. Diazepam (2.0 mg kg^{-1}, i.p.) group 6 served as reference drug.

Effect on learning and memory: The Y-maze test can be used as a measure for short term working memory and locomotor activity. Spontaneous alternation is a measure of spatial working memory. To alternate among spatial location, a mouse must remember its previous location. Spontaneous alternation performance was assessed using a Y-maze composed of three equally spaced arms (120°, 41 cm long × 15 cm high). The floors of each arm consist of wood (5 cm wide). This test was carried out using this apparatus to obtain results for spontaneous alternation performance (memory) and locomotor activity (total arm entries). The animals were divided into six group with (n = 5). Group 1 was given control solution 5% Tween 80 (0.2 mL/20 g, i.p.), while groups 2-5 was given Aridanin at the doses of (5, 10, 20 and 30 mg kg^{-1}, i.p.) for 30 min. Each mouse was placed in one of the arm compartments usually arm A for consistency and was allowed to move freely for 5 min without rein forcers. An arm entry is defined as the body of a mouse except for its tail completely entering into an arm compartment. The sequence of arm entries is manually recorded. An alternation is defined as an entry into all three arms on consecutive devices. The percentage alternation was expressed as the ratio of actual alternations to possible alternations (defined as the total number of arm entries minus two) multiplied by 100. 70% of ethanol was used to clean the Y-maze at interval (Akanmu *et al*., 2007). Diazepam (2.0 mg kg^{-1}, i.p.) group 6 was used as reference drug.

Mechanism of action: In another set of experiment, mice were pre-treated i.p. for 15 min with neurotransmitter blockers to evaluate the mode of actions of Aridanin on novelty-induced rearing (NIR) behaviour, locomotor activity, head dip and Y-Maze in mice. The following receptor blockers were used; atropine (muscarinic antagonist 0.5 mg kg^{-1}), yohimbine (α-2-adrenergic antagonist, 1.0 mg kg^{-1}), naloxone (μ-opioid antagonist, 2.0 mg kg^{-1}), flumazenil (GABA antagonist, 2.0 mg kg^{-1}) and cyproheptadine (5-HT antagonist, 0.5 mg kg^{-1}). The doses administered are the doses that have been found not to induce behavioural studies of their own in experimental animals and as such they only block the receptors involved (Ayoka *et al*., 2006).

Statistic analysis: All behavioural data was analysed by one way ANOVA and Post hoc tests (Student-Newman-Keuls) were carried out to determine the source of a significant mean effect or interaction. Results are expressed as Mean±SEM., $p<0.05$ is taken as accepted level of significant difference from control. In all these statistical determination, a computer programme the primer of biostatistics (version 3.01) was used (Glantz, 1992).

RESULTS

Results of toxicity testing: The intraperitoneal LD_{50} of Aridanin in mice was calculated to be 60.0 mg kg^{-1}.

Effect of Aridanin on novelty-induced rearing, locomotor activity and head dip in mice: Aridanin induced a decrease in NIR, locomotor activity and head dips in mice [$F(5, 24) = 225.2$, $p<0.001$]; [$F(5, 24) = 37.3$, $p<0.001$]; [$F(5, 24) = 54.1$, $p<0.001$] (Table 1).

Effect of Aridanin on learning and memory in mice: Aridanin (5-30 mg kg^{-1}, i.p.) induced a reduction in total arm entries (locomotion) [$F(5, 24) = 68.7$, $p<0.001$] (Table 2). The doses administered gave a percentage alternation that is approximately equal to that of 5% Tween 80 control (Table 2).

Table 1: Effect of Aridanin on novelty-induced rearing, locomotor activity and head dip in mice

Treatments	Dose	NIR/5min	LA/5min	HD/5min
5% TW80	0.2 mL/20 g	48.4±1.6	130.8±2.0	39.8±1.7
Aridanin	5 mg kg^{-1}	22.4±1.5*	83.4±4.1*	39.4±0.9
Aridanin	10 mg kg^{-1}	17.0±0.7*	76.8±9.2*	36.4±1.9
Aridanin	20 mg kg^{-1}	10.1±0.7*	58.2±4.0*	35.4±1.0
Aridanin	30 mg kg^{-1}	6.0±0.7*	42.8±6.1*	26.2±1.5*
Diazepam	2 mg kg^{-1}	7.0±0.7*	48.0±3.1*	13.0±1.2*

Results are expressed as Mean±SEM, (n = 5-7). One way ANOVA revealed that there is significant difference between various treatment groups. NIR: Novelty-Induced Rearing; LA: Locomotor activity; HD: Head dip; 5%TW 80: 5% Tween 80. *indicate significant difference from 5% Tween 80 control. $p<0.05$

Table 2: Effect of Aridanin on learning and memory in mice

Treatments	Dose	No. of entrance/5 min	% Alternation
5% TW	800.mL/20 g	23.0±0.7	60.0±2.7
Aridanin	5 mg kg^{-1}	11.0±0.7*	60.0±2.7
Aridanin	10 mg kg^{-1}	10.4±0.5*	65.3±4.7
Aridanin	20 mg kg^{-1}	10.6±0.5*	60.0±2.7
Aridanin	30 mg kg^{-1}	8.0±0.7*	66.2±5.1
Diazepam	2 mg kg^{-1}	12.4±0.7*	41.0±1.5*

Results are expressed as Mean±SEM, (n = 5-7). One way ANOVA revealed that there is significant difference between various treatment groups. 5%TW 80:5% Tween 80 *indicate significant difference from 5% Tween 80 control. $p<0.05$

Table 3: Effect of Aridanin on novelty-induced rearing, locomotor activity and head dip in the presence of antagonists

Treatments	Dose	NIR/5 min	LA/5 min	HD/5 min
5% TW80	0.2 mL/20 g	48.4±1.6	130.8±2.0	39.8±1.7
Aridanin	10.0 mg kg^{-1}	17.0±0.7*	76.8±9.2*	36.4±1.9
ATR	0.5 mg kg^{-1}	47.0±3.2	127.6±2.3	36.1±1.7
ATR+ARI	10.0 mg kg^{-1}	14.8±2.0*	55.2±5.1*	32.0±0.9
YOH	1.0 mg kg^{-1}	40.1±1.3	120.0±7.1	32.5±2.2
YOH+ARI	10.0 mg kg^{-1}	6.8±0.6*	50.2±7.0*	32.2±0.9
FLU	2.0 mg kg^{-1}	50.6±2.7	160.0±1.3	52.2±3.5*
FLU+ARI	10.0 mg kg^{-1}	5.0±0.3*	33.4±1.6*	20.6±1.1*
NAL	2.0 mg kg^{-1}	41.7±1.4	124.0±2.7	31.4±2.4
NAL+ARI	10.0 mg kg^{-1}	2.6±0.4*	13.8±7.3*	15.6±1.7*
CYP	0.5 mg kg^{-1}	40.6±1.4	127.1±4.2	33.1±2.1
CYP+ARI	10.0 mg kg^{-1}	7.0±0.7*	32.4±1.4*	28.6±1.3*

Result are expressed as mean±SEM, (n = 5-7). One way ANOVA revealed that there is significant difference between control and treatment groups. NIR: Novelty-Induced Rearing; LA: Locomotor activity; HD: Head dip; 5%TW 80: 5% Tween 80; ATR: Atropine; YOH: Yohimbine; FLU: Flumazenil; NAL: Naloxone; CYP: Cyproheptadine: ARI: Aridanin.*indicate significant difference from 5% Tween 80 control. $p<0.05$

Table 4: Effect of Aridanin on learning and memory in the presence of antagonists

Treatments	Dose	No. of entrance/5 min	% Alternation
5% TW80	0.2 mL/20 g	23.0±0.7	60.0±2.7
Aridanin	10.0 mg kg^{-1}	10.4±0.5*	65.3±4.7
ATR	0.5 mg kg^{-1}	24.2±0.8	63.1±3.1
ATR+ARI	10.0 mg kg^{-1}	8.6±1.1*	63.7±3.3
YOH	1.0 mg kg^{-1}	24.2±1.3	62.0±2.9
YOH+ARI	10.0 mg kg^{-1}	6.2±0.6*	63.4±3.2
FLU	2.0 mg kg^{-1}	45.2±2.1*	63.4±3.2
FLU+ARI	10.0 mg kg^{-1}	5.2±0.4*	64.4±4.5
NAL	2.0 mg kg^{-1}	22.7±0.9	61.0±2.7
NAL+ARI	10.0 mg kg^{-1}	6.2±0.6*	65.8±4.7
CYP	0.5 mg kg^{-1}	21.9±0.7	61.4±2.7
CYP+ARI	10.0 mg kg^{-1}	5.8±0.4*	64.6±4.7

Result are expressed as mean±SEM, (n = 57). One way ANOVA revealed that there is significant difference between control and treatment groups. 5%TW 80: 5% Tween 80; ATR: Atropine; YOH: Yohimbine; FLU: Flumazenil; NAL: Naloxone; CYP: Cyproheptadine: ARI: Aridanin *indicate significant difference from 5% Tween 80 control. $p<0.05$

Effect of Aridanin on novelty-induced rearing, locomotor activity and head dip in the presence of antagonists: Pretreatment of mice with atropine yohimbine, naloxone, flumazenil and cyproheptadine did not reverse the decrease in NIR, locomotor activity and head dips of Aridanin in mice. The antagonists potentiated the decrease in NIR and locomotor activity in mice [$F (11, 48) = 143.8$, $p<0.001$]; [$F (11, 48) = 95.7$, $p<0.001$] (Table 3). However, flumazenil and naloxone potentiated the reduction in head dip induced by 10 mg kg^{-1} of Aridanin in mice [$F (11, 48) = 22.6$, $p<0.001$] (Table 3).

Effect of Aridanin on learning and memory in the presence of antagonists: Pretreatment of mice with atropine, yohimbine, naloxone, flumazenil and cyproheptadine potentiated the reduction in total arm entries (locomotion) induced by Aridanin [$F (11, 48) = 164.7$; $p<0.001$] (Table 4).

DISCUSSION

Aridanin decreased the NIR behaviour in mice at (30 mg kg^{-1}) but with the other doses the decrease is not dose dependent. On exposure to a new environment mice displayed novelty-induced behaviour syndrome consisting of rearing, grooming, scratching and wet dog shakes. In this study, NIR which is a measure of central nervous system excitation (Ajayi and Ukponmwan, 1994; Labella *et al*., 1979) was used to test the sedative properties of Aridanin. This inhibition of NIR behaviour suggests that Aridanin possesses sedative action. The work is in agreement with some plants that have been shown to possess strong sedative effect such as *Cissus quadrangulensis*, *Spondia mombin*, *Ficus thoningii*, *Stachys lavandufolia*, *Nigella sativa* L. and *Cryptolepsis sanguinolenta* (Viswanatha Swamy *et al*., 2006; Musa *et al*., 2006; Rabbani *et al*., 2003; Al-Naggar *et al*., 2003; Ayoka *et al*., 2006; Ansah *et al*., 2008).

Aridanin produced a reduction in locomotor activity at (30 mg kg^{-1}) but with the other doses the reduction is not dose dependent. Locomotion is mediated mainly through dopaminergic pathway (Rang *et al*., 1999) but other neurochemical pathways have been reported to modulate locomotive activities in animals. This reduction in locomotor activity also confirms the central depressant properties of Aridanin. The reduction in locomotor activity is in agreement with plants that have been reported to inhibit locomotor activity such as *Cissus quadrangulensis*, *Spondia mombin* and *Ficus thoningii* (Viswanatha Swamy *et al*., 2006; Musa *et al*., 2006; Ayoka *et al*., 2006).

Aridanin at a dose of 5, 10 and 20 mg kg^{-1}, i.p. produced an increase in number of head dips comparable to 5% Tween 80 control; this shows that Aridanin may possess anxiolytic properties. However, 30 mg kg^{-1} i.p. of Aridanin produced a significant reduction in head dip when compared to 5% Tween 80 control, showing that Aridanin may be anxiogenic. Hence, at higher dose of Aridanin a sedative effect was produced. The effect of Aridanin is similar to benzodiazepine which at low doses has anxiolytic action and at high doses has anxiogenic effect and plants such as *Cissus cornifolia*, *Careya anboree* which has both anxiolytic and anxiogenic properties (Onaivi *et al*., 1992; Musa *et al*., 2008; Kumar *et al*., 2008). The study is also in conformity with a number of scientific reports which indicated that troterpenoids produced CNS depressant action, since Aridanin is a triterpenoid saponins (Chattopadhyay *et al*., 2003).

In the Y-maze test, Aridanin at (30 mg kg^{-1}) decrease total arm entries (locomotor activity) in mice, but with the other doses the decrease in total arm entries is not dose dependent. Aridanin at the doses administered do not affect percentage alternation in mice. Memory is a highly complex process that involved several brain structures as well as the role of several neurotransmitters and neuropeptides (Akanmu *et al*., 2007; Steckler *et al*., 1998). Aridanin at doses of (5-30 mg kg^{-1} i.p.) has no effect on working memory as the percentage alternation produced is not different from that of control.

The NIR behaviour response is regulated by multiple neurotransmitter systems; such transmitters include Ganima-Amino-Butyric-Acid (GABA), opioid and dopamine receptors (Walting, 1998). The administration of atropine, yohimbine, naloxone and cyproheptadine did not reverse the inhibitory effect of Aridanin on NIR, locomotor activity, and Y-Maze, this suggest that muscarinic, adrenergic, opioid and serotonin receptors are not involved in the inhibitory effect of Aridanin on NIR, locomotor activity and Y-Maze. However, yohimbine and naloxone potentiated the inhibitory effect of Aridanin on NIR. However the presence of atropine, yohimbine, naloxone and cyproheptadine potentiated the inhibitory effect of Aridanin on locomotor activity. Flumazenil, a $GABA_A$ antagonist increased novelty induced rearing, locomotor activity, head dips and Y-Maze which was blocked by Aridanin. This suggests that Aridanin may facilitate $GABA_A$ transmission (Garrett *et al*., 2003). The administration of atropine and yohimbine produced a reversal in the reduction of head dip produced by Aridanin. Naloxone potentiated the reduction in head dip produced by Aridanin. Cyproheptadine did not reverse the reduction in head dip produced by Aridanin. The results also show that both cholinergic and adrenergic receptor is partially involved in the exploratory head dip of Aridanin.

The results are in line with previous findings where it was shown that the plant has sedative, anticonvulsant and analgesic effect. Since Aridanin facilitate GABAergic transmission, this may the mechanism of the sedative and anticonvulsant effect of Aridanin.

In conclusion, Aridanin significantly reduced NIR, locomotor activity and head dip in mice. The reduction in NIR, locomotor activity and head dip may be related to an interaction with $GABA_A$ neurotransmission. This shows that Aridanin may facilitate GABA-ergic neurotransmission. It is known that the inhibitory action of GABA consists of the GABA receptor opening the chloride ion channel to allow more chloride ion to enter the cell, thus making the membrane less likely to polarize (Gottesmann, 2002). It is possible that the sedative effect of Aridanin is mediated by such GABAergic mechanism, since it is known that GABAergic transmission produced profound sedation in mice (Gottesmann, 2002).

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