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Original Research Article

Evaluation of Antidepressant-Like Activity of Solvent Partitioned Fractions of *Olax subscorpioidea* Oliv. (Olacaceae) Leaf Extract in Rodents

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ABSTRACT

Olax subscorpioidea is a medicinal plant with a long history in traditional medicine for the treatment of mental illness in Nigeria. The current study investigated antidepressant-like activity of solvent partitioned fractions. The crude extract was partitioned in increasing order of polarity to yield ethyl-acetate fraction (EAF), butanol fraction (BF) and aqueous fraction (AF). They were evaluated for antidepressant activity at doses of 5-20 mg/kg in mice using the forced swim test, tail suspension and reserpine tests. The BF, the most active was adsorbed on silica gel and subjected to vacuum liquid chromatography to yields several fractions which were subsequently pooled into five sub-fractions, F1-F5 and screened for antidepressant action. F1 being the most active one was subjected to column chromatography with n-hexane, dichloromethane and ethyl-acetate. The yields of twenty-six fractions were pooled into four fractions *f1-f4* and were screened with the FST and TST only. The EAF, BF, F1, *f1, f2, f3 and f4* fractions significantly ($P<0.05$) reduced immobility in the FST and TST without locomotor effect. The BF and F1 significantly ($P<0.05$) reversed reserpine-induced hypothermia. From the data obtained, it was observed that among all the fractions, BF, F1, *f1, f2, f3 and f4* possess prominent antidepressant-like and antiimmobility effects in both FST and TST. This activity increases as the extract and fractions were further separated. This shows that the plant may have important phytochemicals with great potential for the development of a new antidepressant, thus justifying the traditional use of the plant in mental illness.

***Keywords*:** Antidepressant; *Olax subscorpioidea*; Olacacea; Vacuum Liquid Chromatography

Introduction

Olax subscorpioidea (Olacacea) is a tree commonly found in Nigeria, and some other parts of sub-Sahara Africa. It is known as 'Ifon' in Yoruba in Southwest Nigeria.[1] Different parts of the plant from time immemorial have been used mainly to treat central nervous system related diseases, inflammatory diseases and pain.[1] The plant has been used in treating parasitic infections, diabetes mellitus and gastrointestinal disorders.[2,3] The search for potential candidates in the management of some refractory diseases like mood disorders has singled out this plant among others. Investigation and scientific screening of the plant based on its traditional claims have been intensified in recent time. Among the reports found in literature are; antinociceptive and anti-inflammatory.[4,5] anticonvulsant and sedative[6] and antidepressant.[7] Other biological activities of this plant like pro-apoptotic activity[8], antiprotease[9], antimicrobial[10] and antihyperglyceamic[11] effects were reported. Preliminary investigation of its photochemistry shows that alkaloids, steroids, glycosides, saponins, flavonoids and terpenoids were present .[3,10] Since previous study of antidepressant effect of this plant was only limited to ethanol extract, further investigation of various fractions will be worthwhile.

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Thus, this study was designed to evaluate antidepressant-like activity of solvent partitioned fractions of *Olax subscorpioidea* leaf extract in rodents.

Materials and Methods

Plant materials

The part of the plant, leaves of *O. subscorpioidea* were obtained from Ibadan, at Gambari forest reserve, Oyo state, Nigeria (latitude 7° 261 N and longitude 3°541 E) in April 2011. Ugbogu O.A. and Shasanya O.S. carried out the authentication of the plant at Forestry Research Institutes of Nigeria (FRIN) Ibadan. Thereafter, an identification number 109924 was assigned.

Extraction procedure

The leaves were air-dried and pulverized into fine powder. About 500 g of the pulverized leaves was macerated in 50% ethanol for forty-eight hours before filtration. Rotary evaporator at 40°c was used to concentrate the filtrate to dryness. The dry extract about 38.04 g was reconstituted in distilled water and later partitioned between the solvents into ethyl acetate fraction (EAF), n-butanol fraction (BF) and aqueous fraction (AF). The BF (1.00 g) being the most active after screening was then adsorbed on silica gel (without binder mesh 90% < 45µm) and subjected to vacuum liquid chromatography using gradient elution with n-hexane, ethyl acetate, and methanol to yield thirteen fractions which were subsequently pooled into five fractions (F1, F2, F3, F4 and F5). After biological screening, the most active F1 was then subjected to column chromatography (silica gel 70-230 mesh) with n-hexane, dichloromethane and ethyl acetate as the solvent system in gradient elution to yield 26 impure fractions, which were later pooled into four impure fractions (*f*1, *f*2, *f*3, *f*4) according to their R_f value.

Experimental animals
Mice weighing between 20 to 25 g were purchased from a standard animal house at Faculty of Basic Medical Science, University of Ibadan. The animals were housed in a standard cages and temperature controlled environment with relative humidity of 40-70%. They were allowed to access food and water *ad libitum*. prior to the investigation, the University of Ibadan Animal Care and Use Research Ethics Committee approved the proposal (UI-ACUREC/App/2015/064).

Drugs and chemicals
Reserpine (Pfizer Inc., New York, NY, USA), imipramine (Shanghai Zhongxi Pharmaceutical Co., Ltd. Shanghai, China).
All animals were treated thirty minutes before subjecting them to open field, tail suspension, forced swim and reserpine tests.

Antidepressant screening
The forced swim test (FST)
Animals were subjected to this despair test in line with the previously described protocol.[12] A mouse was forced to swim in a Plexiglas cylinder (18 cm diameter × 30 cm height) filled with water at a depth of 18 cm (22–24 ºc) for 6 minutes. The total immobility time in the last 4 minutes was recorded. A mouse was adjudged immobile when there was no active movement except for the little movement required to keep its head above the water[12]

Tail Suspension Test (TST)
Animals were subjected to the TST, another form of despair test for screening antidepressant agent according to the previously described protocol.[13] After treating the animals with the various agents, adhesive tape was used to hold the tip of the tail against the strain force gauge and left to hang freely in the air. The total immobility time was recorded. A mouse was adjudged immobile when there was no active struggling and body movement and animal hangs passively in the air.

Open field Test
Psychostimulants are not effective clinically as antidepressant, but they exhibit antidepressant-like action in FST and give false positive.[14] To rule out any unspecific locomotor effect and possibility of false positive results in the FST and TST, we thus seek to evaluate the effect of the fractions on activities of the animal in the open field arena. The effect on the locomotor activity of the animals were determined using a computerized open field square box (activity cage). Animals were made to habituate for at least one hour in the test room before the real test. This was followed by introducing animals individually into the activity cage to freely explore for five minutes. The total distance traveled was recorded. In between tests, the cage was cleaned with seventy percent ethanol.

Reserpine-induced temperature change test
Baseline rectal body temperature of the animals was determined in line with Bakre *et al*.[15] Mice received reserpine 30 min after treatment and thereafter, rectal body temperature was taken by gently hand-restraining and inserting lubricated digital thermometer into the rectum and recorded at 0, 60, 120, 180 and 240 minutes.

Statistical analysis
All data were subjected to parametric test using one-way analysis of variance (ANOVA). Student's-Newman-Keuls post hoc analysis was used to check significance among the group with $p < 0.05$. All results are presented as Mean ± SEM.

Results and Discussion

Effect of the fractions of Olax subscorpioidea on immobility in forced swim test and tail suspension test
Fractions of *O. subscorpioidea* were subjected to the despair tests to evaluate their antidepressant-like potentials. The result in Figure 1 shows the effect of the EAF, BF and AF on the immobility time of mice in FST. One-way ANOVA revealed a significant difference between the treatment groups [F (10, 44) = 9.573, p< 0.001]. Post hoc analysis showed a significant (p<0.05) decrease in immobility time with BF (10 mg/kg) relative to control. However, EAF and AF showed no significant effect on immobility time. Furthermore, effect of the BF fractions (F1- F5) on immobility in FST (Figure 2) were significantly different among the treatment groups [F (16, 68) = 28.453, p< 0.001]. It was further revealed that there is a significant (p <0.05) decrease in immobility with F1 (5, 10 and 20 mg/kg), F2 (5 mg/kg) and F3 (20 mg/kg) compared to control. Figure 3 shows anti-immobility effect of F1 impure fractions (*f1-f4*). Post hoc analysis showed a significant (p < 0.05) decrease in immobility time with *f1* (10 mg/kg), *f2* (10 mg/kg) and *f4* (10 mg/kg) compared to control.

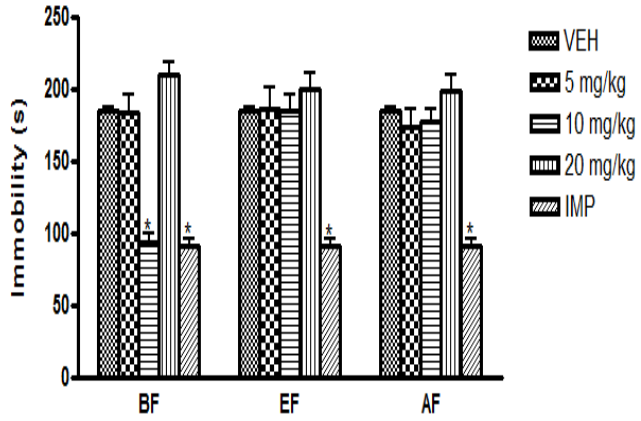

Figure 1: Effect of fractions of *Olax subscorpioidea* on immobility time in FST
* P < 0.05 compared with control.

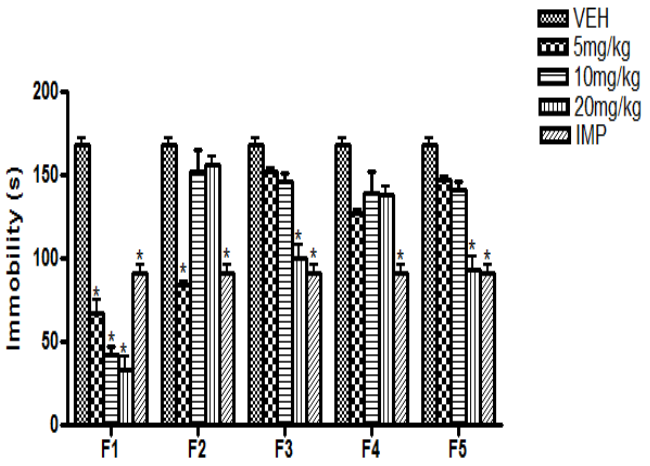

Figure 2: Effect of subfractions of BF on immobility time in FST
* P < 0.05 compared with control.

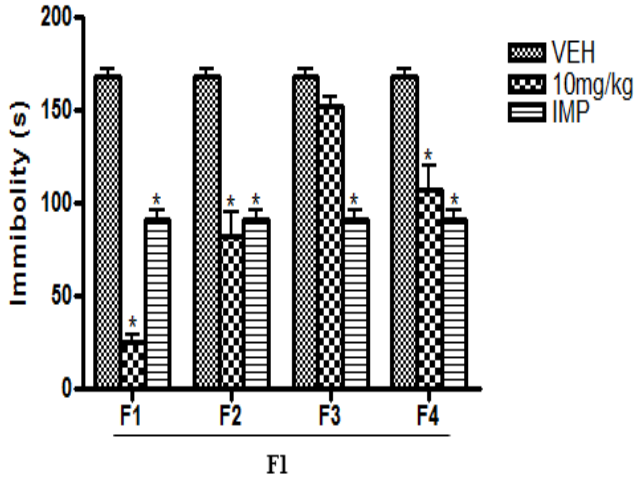

Figure 3: Effect of impure fraction of F1 on immobility time in FST
* P < 0.05 compared with control.

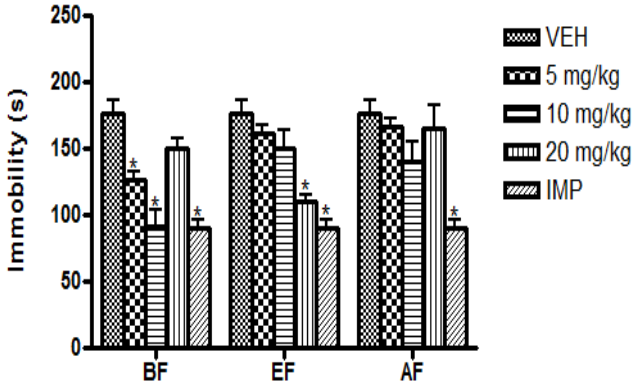

Figure 4: Effect of fractions of *Olax subscorpioidea* on immobility time in TST
* P < 0.05 compared with control.

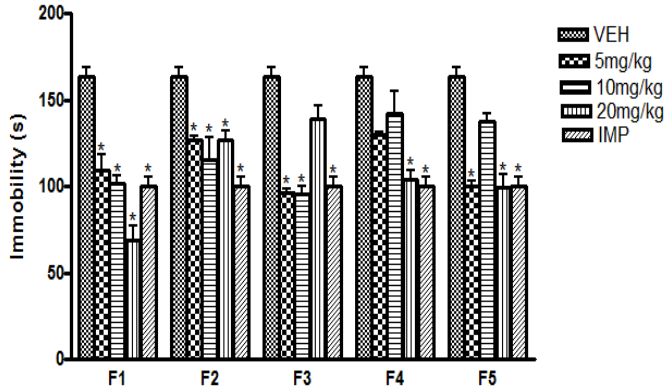

Figure 5: Effect of subfraction of BF (F1) on immobility time in TST
* P < 0.05 compared with control.

Similarly, effects of the fractions on the TST were evaluated and shown in Figure 4-6. One-way ANOVA revealed a significant difference between the treatment groups [F (10, 44) = 7.73, p< 0.001]. Post hoc analysis showed a significant (p< 0.05) decrease in immobility time with administration of BF (5 and 10 mg/kg) and EAF (20 mg/kg) compared to control (Fig. 4). However, AF showed no significant effect on immobility (Fig. 4). The anti-immobility effect of BF sub fractions (F1- F5) in the TST is shown in figure 5. One-way ANOVA showed a significant difference between the treatment groups [F (16, 68) = 9.573, p< 0.001], as F1 (5, 10 and 20 mg/kg), F2 (5, 10 and 20 mg/kg), F3 (5 and 10 mg/kg), F4 (20 mg/kg) and F5 (5 and 20 mg/kg) significantly decrease immobility compared to control. In addition, figure 6 shows F1 impure fractions (*f1-f4*). Following one-way analysis of variance, post hoc analysis showed a significant (p < 0.05) decrease in immobility time with *f1* (10 mg/kg), *f2* (10 mg/kg), *f3* (10 mg/kg) and *f4* (10 mg/kg).The antiimmobility of butanol fraction with its sub fractions and the impure fractions in the TST and FST is indicative of the antidepressant-like activity. This observation is consistent with the previous finding that hydro-alcoholic extract and butanol fraction of the leaves *O. subscorpioidea* showed antidepressant-like effect in FST and TST.[7,13] This finding thus justifies ethno-pharmacological use of the plant for the treatment of mental disease.[13] The presence of flavonoids in the butanol fraction may account for the antidepressant-like activity. Flavonoids like quercetin and rutin have demonstrated antidepressant activity in rodents.[12,16] An et al.[17] reported that flavonoids reversed chronic stressed-induced behavioural alteration and serotonergic dysfunction in rats

Effect of the fractions of Olax subscorpioidea on spontaneous motor activity in open field

In order to assess the influence of the test substance on the baseline spontaneous motor activity of the animals, effects of EAF, BF and AF, and BF sub fractions (F1–F5) on locomotor activity of mice in open field test were investigated and shown in Figure 7 and Figure 8 respectively. The fractions showed no significant (P<0.05) effect on spontaneous motor activity of the animals compared to control. The results thus, suggest that the decrease in the immobility by these fractions in the FST and TST was unrelated to psychostimulant effect. This furthers strengthens our observation that the extract antidepressant-like effect is not associated with hyperkinetic effect on the locomotor activity of the animals in TST and FST. False positive results have been recorded in FST and TST with drug or agents that cause hyperkinesia or hyper-locomotion. [18] Stimulants like amphetamine, convulsants and anticholinergics stimulate spontaneous motor activity in open field and produce false antidepressant-like effect in FST and TST.[12,19] Generally, psychostimulants will cause hyperkinesia in open field and give false positive result in FST, while a genuine antidepressants will not would not cause general increase in locomotor activity.[20]

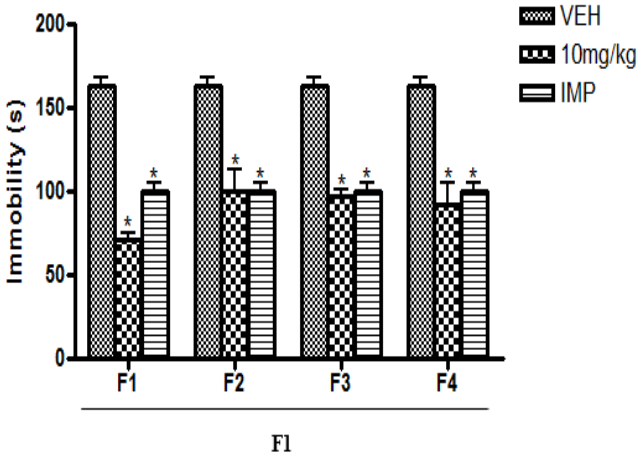

Figure 6: Effect of impure fraction of F1 on immobility time in TST

* P < 0.05 compared with control.

Effect of the fractions of Olax subscorpioidea on reserpine-induced hypothermia

The result in Table 1 shows the effect of the EAF, BF and aqueous fraction AF on reserpine-induced hypothermia. One-way ANOVA showed there were significant difference between the treatment groups [F (10, 44) = 19.3, p<0.001]. Post hoc analysis showed that reserpine induced a significant (p< 0.05) reduction in rectal body temperature of mice compared to control at 120 min, 180 min and 240 min. The BF (5, 10 and 20 mg/kg) significantly (p< 0.05) reversed hypothermic effect of reserpine while EAF and AF did not reverse the reduction in rectal body temperature induced by reserpine. In addition, Table 2 shows the effect of Butanol sub fractions (F1, F2, F3, F4 and F5) on the reserpine-induced hypothermia. One-way ANOVA revealed that a significant difference exists between the treatment groups [F (16, 68) = 24.59, p< 0.001]. Post hoc analysis showed that reserpine induced a significant (p< 0.05) reduction in rectal body temperature compared to control at 120 min, 180 min and 240 min. Only F1 (5, 10 and 20 mg/kg) significantly (p< 0.05) reversed hypothermic effect of reserpine. However, F2-F5 did not reverse the change in rectal body temperature induced by reserpine. Reserpine test has been used successfully to investigate involvement of α-adrenoceptor, β-adrenoceptor and serotonergic receptors in the antidepressant mechanisms of agents. The associated behavioural abnormalities and induction of ptosis, diarrhea and hypothermia are reversed by the antidepressants.[15] Hence, the ability of butanol fraction and its sub fraction (F1) to reverse reserpine-induced hypothermia is indicative of the involvement of monoaminergic systems in its antidepressant mechanism.

Conclusion

The study shows that of all the fractions, only butanol fraction and its sub fractions have significant antidepressant-like activity in the predictive model of depression. The presence of the bioactive constituents like quercetin, rutin, morin and caffeic acid in the butanol fraction,[13] may account for the antidepressant effect of this extract. Although some active principles of the plants have not been identified, further studies are needed to isolate and identify the unknown active principles present in the plant.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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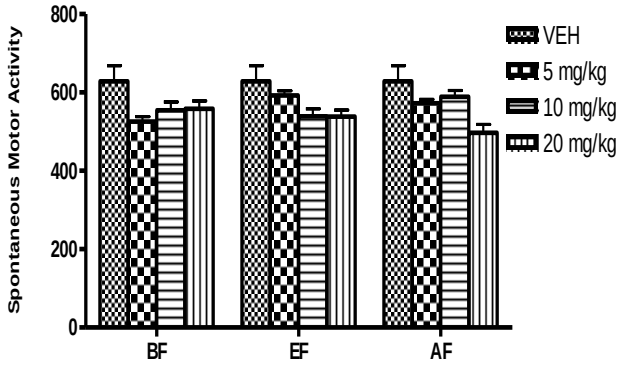

Figure 7: Effect of the fraction of *Olax subscorpioidea* on the locomotor activity of mice in Open Field

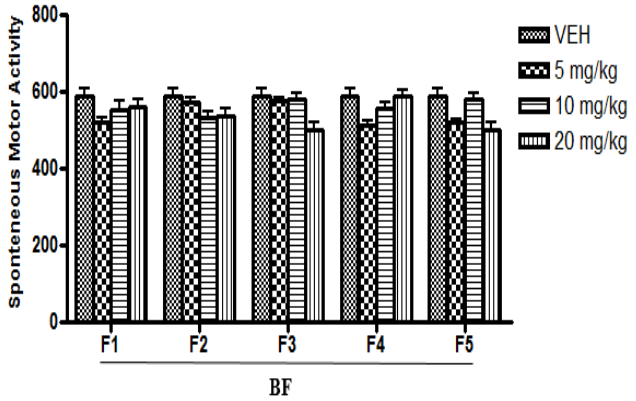

Figure 8: Effect of the subfraction of BF on the locomotor activity of mice in Open Field

Table 1: Effect of Ethyl-acetate fraction (EAF), Butanol fraction (BF) and Aqueous fraction (AF) on the reserpine-induced temperature change

Treatments	Dose (mg/kg)	0 min	60 min	120 min	180 min	240 min
Vehicle (control)	10 mL/kg	38.80 ± 0.13	37.08 ± 0.18	37.90 ± 0.13	37.5 ± 0.18	38.00 ± 0.11
Vehicle + Reserpine	10 mL/kg	37.80 ± 0.13	37.18 ± 0.18	36.84 ± 0.32*	36.42 ± 0.34*	36.18 ± 0.24*
Butanol fraction +	5	37.26 ± 0.06	37.42 ± 0.07	37.24 ± 0.11#	37.46 ± 0.14#	37.52 ± 0.13#
Reserpine	10	37.50 ± 0.14	37.12 ± 0.36	37.78 ± 0.27#	37.28 ± 0.27#	36.88 ± 0.35
	20	37.70 ± 0.13	37.04 ± 0.21	37.40 ± 0.08#	37.52 ± 0.18#	36.98 ± 0.33
Ethyl acetate fraction	5	38.00 ± 0.2	36.40 ± 0.10	36.53 ± 0.08	36.93 ± 0.37	36.57 ± 0.74
+ Reserpine	10	38.03 ± 0.23	37.03 ± 0.48	36.77 ± 0.06	36.90 ± 0.26	36.60 ± 0.66
	20	38.13 ± 0.17	36.80 ± 0.10	36.53 ± 0.26	36.03 ± 0.48	36.70 ± 0.49
Aqueous fraction +	5	37.97 ± 0.14	37.37 ± 0.42	36.72 ± 0.39	36.70 ± 0.08	36.22 ± 0.36
Reserpine	10	38.03 ± 0.20	37.20 ± 0.32	37.32 ± 0.25	37.00 ± 0.35	36.38 ± 0.17
	20	38.07 ± 0.14	36.50 ± 0.30	36.18 ± 0.11	35.80 ± 0.25	36.34 ± 0.16
Imp + Reserpine	10	38.07 ± 0.14	37.50 ± 0.30	38.08 ± 0.11#	37.720 ± 0.25#	37.24 ± 0.16#

* P < 0.05 compared with control.; # P < 0.05 compared with vehicle/reserpine

Table 2: Effect of sub-fractions on reserpine-induced temperature change

Treatments	Dose (mg/kg)	0 min	60 min	120 min	180 min	240 min
Vehicle (Control)	10 mL/kg	38.80 ± 0.13	37.08 ± 0.18	37.90 ± 0.13	37.50 ± 0.18	38.00 ± 0.11
Vehicle + Reserpine	10 mL/kg	37.80 ± 0.13	37.18 ± 0.18	36.84 ± 0.32*	36.42 ± 0.34*	36.18 ± 0.24*
$BF_{(F1)}$+ Reserpine	5	37.26 ± 0.06	37.42 ± 0.07	37.24 ± 0.11#	37.46 ± 0.14#	37.52 ± 0.13#
	10	37.50 ± 0.14	37.12 ± 0.36	37.78 ± 0.27#	37.28 ± 0.27#	36.99 ± 0.35#
	20	37.70 ± 0.13	37.04 ± 0.21	37.40 ± 0.08#	37.52 ± 0.18#	37.98 ± 0.33#
$BF_{(F2)}$+ Reserpine	5	38.00 ± 0.2	36.40 ± 0.10	36.53 ± 0.08	36.93 ± 0.37	36.57 ± 0.74
	10	38.03 ± 0.23	37.03 ± 0.48	36.77 ± 0.06	36.90 ± 0.26	36.60 ± 0.66
	20	38.13 ± 0.17	36.80 ± 0.10	36.53 ± 0.26	36.03 ± 0.48	36.70 ± 0.49
$BF_{(F3)}$+ Reserpine	5	37.97 ± 0.14	37.37 ± 0.42	36.72 ± 0.39	36.70 ± 0.08	36.22 ± 0.36
	10	38.03 ± 0.20	37.20 ± 0.32	37.32 ± 0.25	37.00 ± 0.35	36.38 ± 0.17
	20	38.07 ± 0.14	36.50 ± 0.30	36.18 ± 0.11	35.80 ± 0.25	36.34 ± 0.16
$BF_{(F4)}$+ Reserpine	5	38.00 ± 0.2	36.40 ± 0.10	36.46 ± 0.08	36.83 ± 0.37	36.47 ± 0.74
	10	38.03 ± 0.23	36.03 ± 0.48	36.67 ± 0.06	36.80 ± 0.26	36.48 ± 0.66
	20	38.13 ± 0.17	36.80 ± 0.10	36.43 ± 0.26	36.13 ± 0.48	36.60 ± 0.49
$BF_{(F5)}$+ Reserpine	5	37.97 ± 0.14	36.37 ± 0.42	36.72 ± 0.39	36.67 ± 0.08	36.12 ± 0.36
	10	38.03 ± 0.20	36.20 ± 0.32	36.32 ± 0.25	36.00 ± 0.35	36.28 ± 0.17
	20	38.07 ± 0.14	36.50 ± 0.30	36.08 ± 0.11	35.72 ± 0.25	36.24 ± 0.16
IMP + Reserpine	10	38.07 ± 0.14	37.50 ± 0.30	38.08 ± 0.11#	37.72 ± 0.25#	37.24 ± 0.16#

* $P < 0.05$ compared with control.
# $P < 0.05$ compared with vehicle/reserpine
F1 – F5: Sub-fractions from butanol fraction

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