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RESEARCH ARTICLE

THE INVOLVEMENT OF DOPAMINERGIC, SEROTONERGIC AND NORADRENERGIC RECEPTORS IN THE ANTIDEPRESSANT EFFECT OF METHANOL EXTRACT OF ASYSTASIAVOGELIANA IN THE TAIL SUSPENSION TEST USING MICE

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Abstract

Background: Research shows that significant deficiencies in monoaminergic transmitters can lead to severe depression. Asystasiavogeliana (AV) has been shown to improve neuropsychological injuries by regulating the action of monoamine transporters. Therefore, this study aimed to assess the role of monoaminergic systems in the antidepressant-like effect of AV extract using the tail suspension test (TST) in mice.

Materials and Methods: The mice were pretreated with AV extract (125-1000 mg/kg, i.p) one hour before they were subjected to the tail suspension test. To establish the role of monoaminergic systems in the antidepressant-like effects of the extract, the mice were administered receptor antagonists 15 minutes before receiving the AV extract at a dose of 1000 mg/kg (i.p.) and one hour prior to the TST.

Results: Findings indicated that AV extract (125–1000 mg/kg, i.p) induced a dose-dependent antidepressant-like effect ($P<0.001$) without causing changes in spontaneous locomotor activity during the open-field test. Pretreatment of mice with haloperidol and cyproheptadine inhibited the antidepressant-like effects of AV extract (1000 mg/kg, i.p.), but this effect was not observed with prazosin.

Conclusion: This study revealed that the antidepressant-like effect of the methanol extract **o**f Asystasiavogeliana is mediated through interactions with the dopaminergic and serotonergic pathways. These results support the traditional use of this plant extract in managing depression.

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Introduction:-

Depression impacts a significant portion of the global population (Nemeroff, 2007). Severe depression is marked by notable changes in behavior, sleep patterns, energy levels, appetite, and weight (Neal, 2012). It is believed that a major deficiency in monoaminergic transmitters contributes to the onset of severe depression as previously described(Howland et al., 2006). Meyers (Meyers, 2000) described various drugs that can elevate the levels of monoaminergic neurotransmitters in the central nervous system (CNS), making them suitable for antidepressant treatment. These antidepressant treatments increase the synaptic levels of certain monoaminergic neurotransmitters, such as serotonin (5HT) and noradrenaline (NA), or help to normalize their levels (Hasler, 2010). Meyers described various drugs that can elevate the levels of monoaminergic neurotransmitters in the central nervous system (CNS), making them suitable for antidepressant treatment. These antidepressant treatments increase the synaptic levels of certain monoaminergic neurotransmitters, such as serotonin (5HT) and noradrenaline (NA), or help to normalize their levels (Hasler, 2010).

Furthermore, the dopaminergic system is modulated during depression therapy (Papakostas, 2006). These medications are effective in treating depression, but their use is limited because of potential side effects (Trevor et al., 2010). It is essential to discover new antidepressants that are more effective and have fewer side effects, particularly in combination with commonly used antidepressants. Therefore, medicinal plants and their extracts could be a promising option for treating psychiatric disorders, as they have shown psychotherapeutic benefits in various animal models. It is essential to discover new antidepressants that are more effective and have fewer side effects, particularly in combination with commonly used antidepressants. Therefore, medicinal plants and their extracts could be a promising option for treating psychiatric disorders, as they have demonstrated psychotherapeutic benefits in various animal models (Zhang, 2004).

During a screening of medicinal plants traditionally used in Nigeria for managing different conditions, Asystasiavogeliana was identified based on local knowledge. This plant, Asystasiavogeliana belonging to the Acanthaceae family), is a sprawling herb recognized for its various ethnomedicinal benefits in Nigeria. The leaves of A. vogeliana, or the entire plant, can be crushed in clean water to produce an extract. This solution is used to treat malaria, gastric disorders, and gonorrhea (Popoola et al., 2017). Additionally, the whole plant of A. vogeliana is boiled together with the leaves of Cassia alata, the fruits of Citrus aurantifolia (lime), and the leaves of Cymbopogoncitratus. A combined extract or infusion of the plant is consumed as a remedy for various ailments, including malaria, fever, hypertension, gonorrhea, gastric disorders, cancer, tumors, epilepsy, and diabetes (Popoola et al., 2017).

Additionally, the leaf extract of A. vogeliana is used as a treatment for hepatitis in Nsukka, a city located in Enugu, Nigeria (Ugwuanyi et al., 2020). In southwestern Nigeria, the leaves of A. vogeliana are boiled in clean water to create an infusion, which is consumed as a tonic to increase blood volume in cases of anemia. Similarly, in Cameroon, a decoction made from the leaves of A. vogeliana is used as a remedy for treating reproductive diseases and managing HIV (Gildas et al., 2017). Many health conditions treated with various extracts of Asystasiavogeliana were found to share similar physiological mechanisms related to inflammation. Therefore, the objective of this study was to evaluate the acute oral toxicity and anti-inflammatory properties of different solvent extracts of Asystasiavogeliana.

In this study, we aim to provide important insights into the safety profile and potential therapeutic value of A. vogeliana extracts, thereby enhancing our understanding of their potential pharmaceutical applications. In Nigerian ethnomedicine, the leaves and the entire plant of Asystasiavogeliana are used for various medicinal purposes (Popoola et al., 2017).

Materials and Methods:-

Plant Collection, Identification and Preparation

In 2024, the leaves of Asystasiavogeliana were collected at the Medicinal Herbarium, ObafemiAwolowo University, Ile-Ife, Osun State, Nigeria. The plant was identified at the Department of Botany, Faculty of Sciences, ObafemiAwolowo University, Ile-Ife, Nigeria, by taxonomist Mr. G.A. Ademoriyo, and a voucher specimen was deposited (voucher IF E-18270). The collected materials were allowed to air-dry in the shade for two weeks. The dried leaf was ground into a powder using a pestle and mortar. The powdered leaves were weighed and then extracted with absolute ethanol using cold maceration techniques. A rotary evaporator was used to dry the filtrate obtained, yielding a black residue weighing 10.7% w/w, which was then stored in a desiccator for future use.

Animal Material

Male and female Swiss albino mice, weighing between 22 and 25 grams, were used in this study. They were housed in a well-ventilated room at the animal facility of the Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, LadokeAkintola University of Technology (LAUTECH), Ogbomoso, Oyo State, Nigeria. The animals were kept under standard conditions at room temperature. They had free access to standard animal feed produced by the animal house at LAUTECH and were provided with clean water ad libitum in hygienic conditions. Before conducting any experiments, the animals were given time to acclimate to the laboratory environment. Each experimental group in this study consisted of six mice. The investigation adhered to the guidelines for the use and care of laboratory animals which was published by the United State National Institutes of Health (NIH No. 85-23, revised 1996).

Tail suspension test

The total duration of immobility caused by tail suspension was calculated using a standard procedure (Yousuf et al., 2020). Animals that were acoustically and visually isolated were suspended 40 cm above the floor, and adhesive tape was used to hold the tail of mice 1 cm from the tip. The mice were divided into six groups, and each group consisted of six mice (n = 6). The treatments were as follows: Group I received normal saline (10 ml/kg, intraperitoneally), Groups II to IV were administered AV extract at doses of 250, 500, and 1000 mg/kg (intraperitoneally), respectively. Groups V and VI received fluoxetine (20 mg/kg, intraperitoneally) and imipramine (30 mg/kg, intraperitoneally), respectively. During the test, the total duration of immobility was recorded using a chronometer for 4 minutes, following a 2-minute accumulation period. A reduction in immobility time was considered an indication of antidepressant activity (Voiculescu et al., 2015).

Possible Mechanism of Antidepressant-Like Effect Of AV Extract

Involvement of the dopaminergic receptor in the antidepressant-like effect of AV extract

To investigate of the role of dopaminergic system in the antidepressant-like effect of AV extract, mice were pretreated with a dopamine D1 receptor antagonist (SCH23390, 0.05 mg/kg), a dopamine 2 receptor antagonist (sulpiride, 50 mg/kg), non-selective DA receptor antagonist (haloperidol (0.2 mg/kg), 15 min before i.p treatment of AV (1000 mg/kg, i.p) or vehicle (10 ml/kg, i.p), 1 hr post-treatment, the mice were exposed to TST (Guet al., 2012;Piotrowska et al., 2013;Tanyeri et al., 2013;Onasanwo et al., 2015;Zhang et al., 2021).

Involvement of the serotonergic receptor in the antidepressant-like effect of AV extract

To investigate the possible role 5HT plays in the antidepressant-like effect of AV extract in the TST. The mice were pretreated with a 5-HT synthesis inhibitor (PCPA, 150 mg/kg, i.p.) or saline, once a day, for 3 consecutive days. Thereafter, the mice were treated with AV (1000 mg/kg, i.p.). Fifteen minutes after the last pCPA, one hour after administration, they were subjected to the Tail Suspension Test (26). Also, to investigate 5HT2 receptor role on the antidepressant effect of AV in TST, mice were pretreated with ketanserin (5 mg/kg, i.p) and cyproheptadine (3 mg/kg, i.p), a selective 5HT2A/C receptor antagonist and 5HT2A receptor antagonist respectively or saline and 15 min later, AV extract (1000 mg/kg, i.p) was prtreated for 1 hr before Tail Suspention Test was performed (Zheng et al., 2014).

Involvement of the noradrenergic receptor in the antidepressant-like effect of AV extract

To examine the possible involvement of noradrenergic system in the antidepressant-like effect of AV methanol extract, mice were pretreated with a α1-adrenorecep- tor antagonist (prazosin 1 mg/kg, i.p) and a α2-adrenoreceptor antagonist (yohimbine, 1 mg/kg, i.p), 15 min prior to intraperitoneal treatment of AV extract (1000 mg/kg, i.p) or vehicle (10 ml/kg), 1 hr after, the mice were then subjected to TST (Onasanwo et al., 2015).

Open field test (OFT)

The psychomotor stimulant activity effect of AV extract in mice was evaluated using the method as previously described (Brown et al.). The mice were individually put into OFT to determine the effect of AV on explorative behaviour (Brown et al., 1999). The animals were individually positioned in a Plexiglas box measuring 40×60×50 cm. The floor was separated into 12 squares. We recorded the number of squares crossed with all paws, and the number of rising with the front paws (rearings) using a counter for 5 min. The numbers of squares crossed with four paws were noted as an index of locomotor activity, and the count of rearing was a sign of exploratory behavior.

Results:-

Open field test

Table 1 revealed no significant changes in the counts of crossings and rearing behaviour in animals treated with AV (250-1000 mg/kg; i.p) as compared to the control group.

Table 1:- Effect of AV on open field.

Pretreatment	Doses (mg/kg)	Crossing behavior**	Rearing behavior**
Control	0	9.2±2.35	2.5±0.05
AV	250	8.7±2.23	2.5±0.10
AV	500	8.3±1.06	2.3±0.03
AV	1000	8.1±3.13	2.3±0.01

**Values are mean ± SEM (n=5).

*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett's post-hoc test.

Tail suspension test

Table 2 shows that the duration of immobility time in the TST significantly decreased in mice administered with AV extract in a dose-dependent manner ($p<0.05$). The 1000 mg/kg dose administered produced the most effective antidepressant action, hence, was used in the later experiments. ANOVA results indicated that there were no significant differences in immobility time among the AV extract and the common antidepressants, fluoxetine and imipramine. However, the reduction in immobility time observed with the AV extract (1000 mg/kg) was comparable to that of the mice treated with fluoxetine and imipramine.

Table 2:- Effect of AV on Tail Suspension Test.

Pretreatments	Doses (mg/kg)	Immobility(s)**
Control	0	250±9.27
Fluoxetine	20	41±1.22
Imipramine	30	35±1.35
AV	250	195±6.73
AV	500	120±5.61
AV	1000	45±3.91

**Values are mean ± SEM (n=5).

*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett's post-hoc test.

Involvement of the dopaminergic system

Table 3 demonstrated that mice treated with haloperidol (0.2 mg/kg) significantly inhibited the antidepressant-like effects of AV extract in the Tail Suspension Test (TST). In contrast, mice treated with SCH23390 (0.05 mg/kg) and sulpiride (50 mg/kg) did not show a significant blockage of the antidepressant-like effects of AV extract in the TST.

Table 3:- Involvement of the dopaminergic receptor antagonist on antidepressant effect of AV.

Pretreatments	Doses (mg/kg)	Immobility(s)**
SCH23390	0.05	235±7.67
AV	1000	57±2.24
AV+ SCH23390	1000&0.05	63±2.21*
Sulpiride	50	239±9.41
AV+ Sulpiride	1000&50	61±4.01*
Haloperidol	0.2	229±6.68
AV+Haloperidol	1000&0.2	231±7.53

**Values are mean ± SEM (n=5).

*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett's post-hoc test.

Involvement of the serotonergic system

The results presented in Table 4 indicated that pretreatment of animals with WAY100135, ketanserin, and cyproheptadine significantly reduced the antidepressant-like effect induced by the AV extract at a dosage of 1000 mg/kg in the tail suspension test (TST).

Table 4:- Involvement of the serotonergic receptor antagonist on antidepressant effect of AV.

Pretreatments	Doses (mg/kg)	Immobility(s)**
WAY100135	10	238±8.43
AV	1000	65±3.23
AV+WAY100135	1000&0.10	232±6.53
Ketanserin	5	225±7.56
AV+Ketanserin	1000&5	223±8.34
Cyprohetadine	3	229±8.12
AV+Cyproheptadine	1000&3	231±5.17

**Values are mean ± SEM (n=5).

*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett's post-hoc test.

Involvement of the noradrenergic system

The results of the animal pretreatment with α1- and α2-adrenoceptor antagonists are presented in Table 5. The administration of α1-adrenoceptor antagonist (prazosin; 1 mg/kg) and an α2-adrenoceptor antagonist (yohimbine; 1 mg/kg) did not prevent the antidepressant-like effect of the AV extract at a dosage of 1000 mg/kg in the tail suspension test (TST).

Table 5:- Involvement of the noradrenergic receptor antagonist on antidepressant effect of AV.

Pretreatments	Doses (mg/kg)	Immobility(s)**
Prazosin	1	238±7.15
AV	1000	68±4.03*
AV+prazosin	1000&1	65±4.17*
Yohimbine	1	229±7.43
AV+Yohimbine	1000&1	63±2.21*

**Values are mean ± SEM (n=5).

*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett's post-hoc test.

Discussion:-

Our findings reveal that acute administration of AV extract via the intraperitoneal route significantly induces antidepressant-like activity in the TST in mice for the first time. It is noteworthy that both AV extract and the common antidepressants, fluoxetine and imipramine, did not exhibit significant differences in immobility time. Additionally, the AV extract did not alter locomotor activity in the Open Field Test (OFT). An increase in locomotor activity is not a valid indicator of antidepressant activity, as such an increase may be a false positive response. Furthermore, our findings indicate that the AV extract has an antidepressant-like effect, most likely as a result of interactions between the dopaminergic and dopaminergic systems, but not with the adrenergic system. The Tail Suspension Test (TST) is a well-established behavioral model used to assess antidepressant activity. In TST, mice were placed inescapably, as a reduction in immobility time indicates antidepressant-like action (Yousuf et al., 2020). The TST is an index used to differentiate between psycho-stimulant drugs and antidepressants (Küpeli-Akkol et al., 2019). So far, we have not found any study demonstrating that AV extract modulates antidepressant-like activity. Consistent with our findings, other researchers have shown that certain herbal extracts exhibit antidepressant-like effects (Shahamatet al., 2016;Hieronymuset al., 2021). Elhwuegi reported that monoamine neurotransmitters, norepinephrine (NA), dopamine (DA), and serotonin (5HT), play significant roles in the pathophysiology and treatment of depression(Jawaher et al., 2021). It is well-documented that most drugs used to treat depression work by increasing the levels of these monoamine neurotransmitters (Risch, Nemeroff, 1992). Our results indicated that pretreating animals with dopamine receptor antagonists, specifically sulpiride or haloperidol, significantly prevented the decrease in immobility time caused by the extract. This suggests that the dopaminergic system is involved in the antidepressant-like effects of the AV extract observed in the tail suspension test (TST) in

mice. Our results indicated that pretreating animals with dopamine receptor antagonists, specifically sulpiride or haloperidol, significantly prevented the decrease in immobility time caused by the extract. This suggests that the dopaminergic system is involved in the antidepressant-like effects of the AV extract observed in the tail suspension test (TST) in mice. The dopaminergic system is reported to play a significant role in mood regulation and is effective in the treatment of depression (Willner, Hale, 2005). Earlier studies indicated that antagonists of the D1 and D2 receptors could inhibit the antidepressant-like effects, highlighting their role in depression(Hirano et al., 2007). D2 receptor agonists have been suggested for the treatment of depression based on clinical studies(Machado et al., 2007). Therefore, AV extract may partially influence the dopaminergic system in the tail suspension test (TST) in mice. Monoamine neurotransmitters, such as norepinephrine (NA) and dopamine (DA), are essential for the proper functioning of cognition, emotion, and other processes(Shahamat et al., 2016). It was reported that Zhao et al. showed that AV extracts interact with activators of dopamine (DA), norepinephrine (NA), and/or serotonin (5HT) transporter inhibitors(Haider et al., 2007). Therefore, it is reasonable to conclude that AV extract may help improve neuropsychological injuries, such as depression, by modulating these activators and inhibitors. WAY100135 and ketanserin pretreated mice inhibited the reduction in immobility time caused by the AV extract. This suggests that the serotonergic system is involved in the antidepressant effects of the methanol extract of AV in the tail suspension test (TST) in mice. Some studies have identified serotonin (5HT) as a key neurotransmitter in depression, as it plays a role in modulating symptoms of severe depression, such as memory issues(Haider et al., 2007). The 5HT1A receptors play a direct role in the action of antidepressants because they are located on the soma and dendrites of serotonin (5HT) neurons in the dorsal raphe, inhibiting the release of 5HT. The 5HT1A receptors play a direct role in the action of antidepressants(Celada., 2004) because they are within the soma and dendrites of serotonin (5HT) neurons in the dorsal raphe, inhibiting the release of 5HT (Bohra et al., 2015). The 5-HT2 receptors found in brain regions like the hippocampus are linked to the development of depression (Bohra et al., 2015). Research has demonstrated that ketanserin can inhibit the antidepressant effects of certain medicinal plants in the tail suspension test (TST) conducted on mice. Our findings indicate a connection between the serotonergic system and AV extract in the TST. It is well established that tryptophan serves as the substrate for serotonin (5HT) synthesis.

In this study, when mice were pretreated with α1-adrenoceptor antagonist (prazosin) and an α2-adrenoceptor antagonist (yohimbine), the decrease in immobility time did not reverse with the AV extract in the tail suspension test (TST). This suggests that the noradrenergic system is not involved in the antidepressant-like effects of the AV extract. Several studies have indicated the involvement of noradrenergic system in the pathophysiology of depression and the mechanisms of action of antidepressant agents. (Shahamat et al., 2016). Unfortunately, we cannot find any studies showing that AV extract involves the noradrenergic system. We discovered that AV extract does not act through this system, according to our results.

Conclusion:-

Our observations indicate that the AV extract produces its effects through the dopaminergic and serotonergic systems. These findings support the traditional use of AV extract in the management of depression. The results of this study indicate that the AV extract produces its effects through the dopaminergic and serotonergic pathways. Additionally, the AV extract can enhance the antidepressant effects of commonly used antidepressant medications, suggesting that it may improve their effectiveness. These findings support the traditional use of AV extract in the management of depression.

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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