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Original article

Cardioprotective Efficacy of *Ageratum conyzoides* Leaf Extract in Paroxetine-Administered Male Rats

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Abstract
Chronic use of paroxetine, a selective serotonin reuptake inhibitor, is increasingly linked to cardiovascular complications. Owing to safety concerns and the cost of synthetic drugs, plant-based therapies are gaining attention. This study evaluated the cardioprotective potential of Ageratum conyzoides leaf extract (EEACL) via its effects on the Arginase/NO/PDE5 axis and lipid homeostasis. Thirty male Wistar rats were divided into six groups (n=5): naive control, paroxetine-only (10 mg/kg), sildenafil (4 mg/kg), and EEACL-treated groups (15, 30, 45 mg/kg). Paroxetine (21 days) significantly ($P < 0.05$) increased cardiac PDE5 (0.98±0.05 vs 0.78±0.02 mmol/min/mg) and arginase (6.32±0.31 vs 5.35±0.41 mmol/min/mg), reduced NO (61.87±1.36 pg/mL), elevated troponin I (4.72±0.18 pg/mL), and raised total cholesterol (26.33±0.22 mmol/L). Seven-day EEACL treatment reversed these effects. At 45 mg/kg, arginase (5.11±0.22 mmol/min/mg) and troponin I (1.45±0.42 pg/mL) improved, while 15 mg/kg increased NO (72.92±5.29 pg/mL). EEACL at 15 and 30 mg/kg reduced total cholesterol (19.98±3.15; 20.16±1.89 mmol/L) and normalized the atherogenic index (0.09±0.02). These findings suggest A. conyzoides may offer cardioprotection by restoring Arginase/NO/PDE5 balance and lipid stability, supporting its potential as an adjunct therapy for drug-induced cardiotoxicity.
Keywords: *Ageratum Conyzoides, Paroxetine-Administered, Arginase, Phosphodiesterase 5, Troponin I, Atherogenic Index.*

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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading global cause of morbidity and mortality, with ~11.3 million deaths in 2022 [1]. While many cases stem from modifiable risks, drug-induced cardiotoxicity is an increasing concern [2]. Paroxetine, a selective serotonin reuptake inhibitor (SSRI) used for depression and anxiety, has been linked to cardiac events ranging from arrhythmias to cardiomyopathy [3]. Its cardiotoxicity is associated with oxidative stress and disruption of key biochemical pathways essential for myocardial homeostasis [4]. The nitric oxide (NO) pathway is central to vascular tone and cardioprotection [5]. NO, produced by nitric oxide synthase (NOS), promotes vasodilation and inhibits platelet aggregation and inflammation [6]. However, in drug-induced cardiac stress, NO bioavailability declines due to arginase upregulation [7]. Arginase competes with NOS for L-arginine [8], and its overactivity depletes this substrate, causing NOS uncoupling and superoxide generation instead of NO, leading to oxidative stress and endothelial dysfunction [9].

Phosphodiesterase-5 (PDE5) further impairs NO signaling. Normally, NO stimulates cyclic guanosine monophosphate (cGMP) production, promoting cardiac relaxation and protection [7]. PDE5 degrades cGMP, and its overactivity in paroxetine toxicity reduces cGMP signaling, increasing myocardial stress [10]. Elevated cardiac troponin I (cTn-I) indicates cardiomyocyte membrane damage and myofibril injury [11]. Cardiac dysfunction is also associated with dyslipidemia, including increased cholesterol and triglycerides, which heighten atherosclerosis risk and membrane vulnerability to drug toxicity [12,13].

Medicinal plants are being explored for modulating these pathways. *Ageratum conyzoides* L. (Asteraceae), a pantropical herb rich in flavonoids, alkaloids, and polyphenols, has demonstrated antioxidant and anti-inflammatory properties [14,15]. However, its role in regulating the Arginase/NO/PDE5 axis remains underexplored. Evidence on its ability to restore NO levels, modulate arginase/PDE5 activity, and reduce troponin I and dyslipidemia is limited. This study, therefore, investigated the cardioprotective effects of *A. conyzoides* leaf extract in paroxetine-treated male Wistar rats, providing mechanistic insight into its potential as an adjunct therapy for drug-induced cardiotoxicity.

Methods

Animals

Thirty adult male Wistar rats (150–220 g) were obtained from the animal holding facility of the Department of Biochemistry, University of Ilorin. After two weeks of acclimatization under standard conditions (12 h

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light/dark, feed and water ad libitum), experiments were conducted in accordance with approved ethical guidelines.

Preparation of ethanol extract

Fresh leaves of *Ageratum conyzoides* were obtained from Oja-Oba market, Ilorin (8.49664 N, 4.54214 E), Kwara State, and authenticated at the Herbarium, Department of Plant Biology, University of Ilorin (voucher no. UILH/001/810/2024). Leaves were washed and air-dried.

Ethanolic extract was prepared with slight modifications to Adetuyi et al. [16], substituting ethanol for methanol. Dried leaves were pulverized, and 400 g of powder was extracted in 750 mL of ethanol for 48 h at room temperature, filtered (Whatman No. 1), concentrated in a water bath, and refrigerated.

Paroxetine Administration

Paroxetine was administered as described by Muritala and Bewaji [17]. Twenty-five rats received 10 mg/kg body weight of paroxetine orally via oropharyngeal cannula once daily for 21 days, prepared in Tween-80 with 0.9% saline.

Animal Grouping

Rats were grouped into 7 groups of 5 animals each: Group A (naïve/positive control) received normal saline for 21 days, followed by distilled water for an additional 7 days. Groups B (received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days); groups D, E & F received paroxetine for 21 days and 15, 30, 45 mg/kg body weight of ethanol extract of *Ageratum conizoides* leaf (EEACL), respectively.

Preparations of animal serum

After 24 h post-treatment, rats were anesthetized (diethyl ether), blood collected via jugular puncture, and serum was prepared as described by Muritala et al. [18]. Blood was allowed to clot (10 min), centrifuged using a Uniscope laboratory centrifuge (Model 5M800B, Surgifriend Medicals England) (3000 rpm for 10 min), and serum was stored refrigerated for analysis.

Arginase Activity

Cardiac arginase activity was determined by the method of Stickings et al. [19]. Briefly, 50 µL cardiac homogenate was mixed with 200 µL arginase buffer and incubated at 37 °C for 1 h. After adding 100 µL 0.5 M hypochlorite and centrifugation (8000 rpm, 3 min), 20 µL supernatant was reacted with 100 µL urea reagent, and absorbance was read at 380 nm.

Urea concentration was calculated as:

Concentration (mg/dL) = (A_sample × standard concentration) / A_standard,

where standard = 13.1 mg/dL.

Nitric Oxide Concentration

Nitric oxide concentration in heart tissue was determined using the Griess method of Green et al. [20]. Color intensity, measured spectrophotometrically, was used to estimate NO concentration from a standard curve.

PDE5 Activity

Cardiac phosphodiesterase-5 (PDE5) activity was assessed using Butcher and Sutherland [21]. Cardiac homogenate supernatant was incubated with cGMP, and products were measured spectrophotometrically. Activity was calculated as:

$EA = V\Delta C / V_3$ (units/mL)

where EA = enzyme activity, V = total reaction volume, ΔC = reaction velocity (Pi/20 min), V_3 = enzyme volume, and Pi = inorganic phosphate released.

Troponin I

Troponin I levels were measured using a modified Liu et al. [22] method. Samples were added to microplate wells coated with anti-TnI antibody, followed by biotin-conjugated secondary antibody and streptavidin-HRP. Color development was read at 450 nm, and TnI was quantified using a standard curve.

Lipid Profile

Total Cholesterol

Determined by enzymatic colorimetry (Fredrickson et al. [23]). Serum (20 µL), standard (5.10 mmol/L), and blank were mixed with 2000 µL reagent (cholesterol esterase/oxidase, peroxidase, 4-aminoantipyrine,

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phenol, buffer pH 6.8), incubated (37 °C, 5 min), and read at 546 nm. Calculated as: (A_sample × standard) / A_standard.

Triglycerides
Measured enzymatically (Warnick et al. [24]). Sample (10 µL), standard (2.21 mmol/L), and blank were mixed with 100 µL reagent (lipase, glycerol kinase, glycerol-3-phosphate oxidase, peroxidase, ATP, 4-chlorophenol), incubated (10 min, 20–25 °C), and read at 500 nm. Calculated as above.

High-Density Lipoprotein (HDL) Cholesterol Concentration
Determined by precipitation (Hafiane & Genest [25]). Sample (200 µL) was mixed with 500 µL phosphotungstic acid/$MgCl_2$, incubated (10 min), centrifuged (4000 rpm, 10 min), and supernatant analyzed as total cholesterol. Calculated as above.

Low-Density Lipoprotein (LDL) Cholesterol Concentration
Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald equation, as described by Friedewald *et al.* [26]. The formula used was: LDL-C (mmol/L) = Total Cholesterol − HDL-C − (Triglycerides / 2.2), where VLDL-C was estimated by dividing the triglyceride concentration by 2.2. This method is widely accepted for estimating LDL-C in fasting serum samples.

Very Low-Density Lipoprotein (VLDL) Cholesterol Concentration
The Friedewald formula was used to estimate the very low-density lipoprotein (VLDL) concentrations of the experimental animals [26]. The formula is as follows:

$$\text{VLDL} = \frac{\text{TAG}}{5} \text{ (mg/dL)}$$

Atherogenic Index
The atherogenic index was computed using the method described by Dobiasova [27]. The index was calculated as the base-10 logarithm of the ratio of triglycerides to HDL cholesterol, expressed as:

$$\text{AI} = \log\left(\frac{\text{TG}}{\text{HDL}}\right)$$

Statistical Analysis
Values were expressed as mean ± SEM based on five replicates. In order to evaluate the statistical differences among the groups, one-way analysis of variance (ANOVA) was carried out ($p < 0.05$) followed by Duncan's multiple comparison test. The results were analysed, and graphical representations were done using GraphPad Prism 8.

Results

Specific Activities of Cardiac Arginase in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf (EEACL)
The cardiac arginase activity in the paroxetine untreated group was significantly higher ($p < 0.05$) compared to the other groups (Figure 1). There was no significant difference ($p < 0.05$) in the arginase activity of the normal control, 15, and 45 mg/kg EEACL groups. Also, there was no significant difference ($p < 0.05$) in the arginase activity in the sildenafil and 30 mg/kg EEACL groups, and their arginase activity was significantly higher (p 0.05) compared to the normal control, 15 and 45 mg/kg EEACL groups.

Cardiac Nitric Oxide Concentration of Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf (EEACL)
The cardiac nitric oxide (NO) concentration in rats administered paroxetine for 21 days is presented in the figure 2. The NO concentration in the naive control group was significantly higher ($p < 0.05$) when compared to all other experimental groups. Following the 7-day treatment period, there was no significant difference ($p < 0.05$) in the NO concentration between the sildenafil citrate and 15 mg/kg EEACL groups; however, the NO levels in these two groups were significantly higher ($p < 0.05$) than those recorded for the paroxetine untreated, 30 mg/kg EEACL, and 45 mg/kg EEACL groups. Additionally, no significant difference ($p < 0.05$) was observed in the nitric oxide levels among the paroxetine untreated, 30 mg/kg EEACL, and 45 mg/kg EEACL groups, all of which remained significantly lower ($p < 0.05$) than both the naive control and the 15 mg/kg treatment groups.

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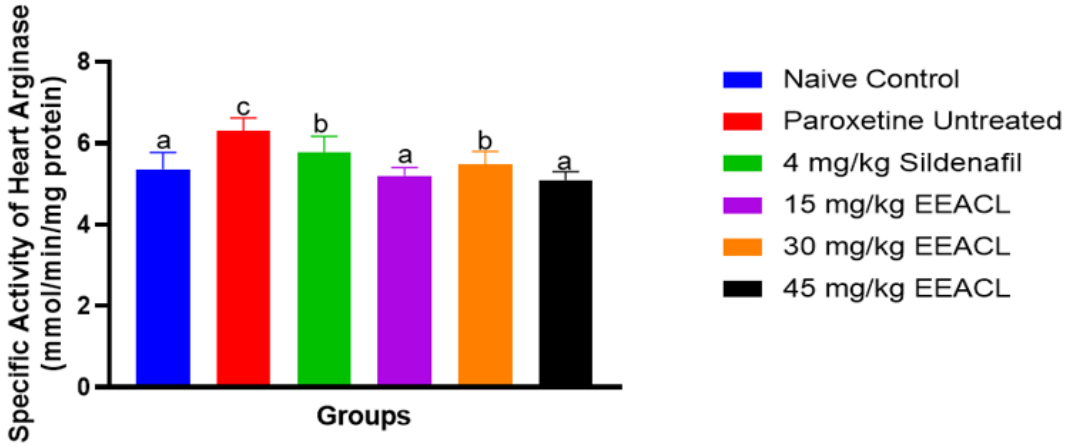

Figure 1: Specific Activities of cardiac Arginase in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

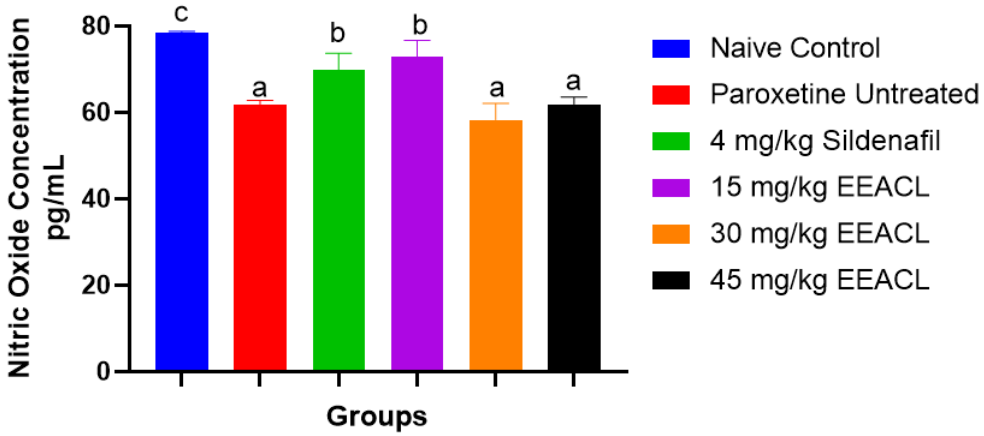

Figure 2: Cardiac Nitric Oxide Concentration of Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

Specific Activities of Cardiac Phosphodiesterase-5 in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

The cardiac PDE 5 activity in rats administered paroxetine for 21 days is presented in Figure 3. After 7 days of treatment, the PDE5 activity in the negative control group was significantly higher ($p < 0.05$) when compared to the other groups. There was no significant difference ($p < 0.05$) in the PDE5 activity in the 15 and 30 mg/kg EEACL groups. However, the PDE5 activity in the 15 and 30 mg/kg EEACL was significantly higher ($p < 0.05$) when compared with the normal control, sildenafil citrate, and 45 mg/kg EEACL groups. There was no significant difference ($p < 0.05$) in the PDE5 activities of the normal control, sildenafil citrate, and 45 mg/kg EEACL groups.

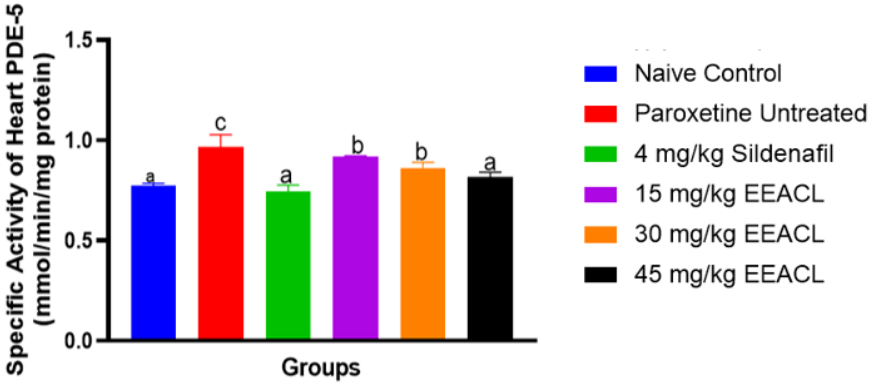

Figure 3: Specific Activities of Cardiac Phosphodiesterase-5 in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

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Troponin I Concentration in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

The troponin I concentration in the paroxetine untreated group was significantly higher ($p < 0.05$) compared to the other groups (Figure 4). There was no significant difference ($p < 0.05$) in the arginase activity of the normal control and 30 mg/kg EEACL groups. There was no significant difference ($p < 0.05$) in the troponin I level in the sildenafil and 45 mg/kg EEACL groups, and their troponin I levels were significantly lower ($p < 0.05$) compared to other groups. The troponin I level in the 15 mg/kg EEACL group was significantly higher ($p < 0.05$) compared to the normal control, sildenafil, 30, and 45 mg/kg EEACL groups.

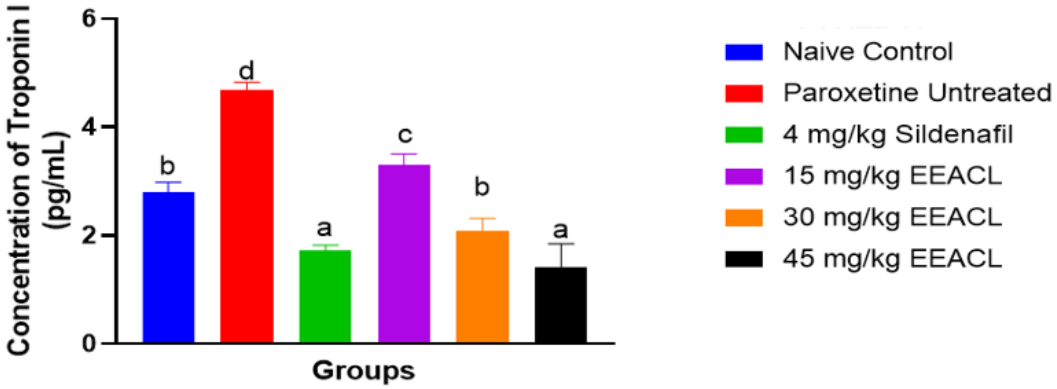

Figure 4: Troponin I Concentration in Paroxetine-Administered Rats Treated with Ethanol Extract of Ageratum conyzoides Leaf

Serum Lipid Profile of Ageratum conyzoides-treated Rats with Paroxetine-induced Erectile Dysfunction

Table 1 shows the serum lipid profile of paroxetine-induced erectile dysfunction in male Wistar rats. There was a significant increase ($P < 0.05$) in the serum total cholesterol concentration of the negative control group when compared with all other experimental groups. The groups administered with 15 and 30 mg/kg EEACL showed the lowest concentrations, which were significantly lower ($P < 0.05$) than all other groups. Furthermore, there was no significant difference ($P > 0.05$) in the cholesterol levels of the naive control, sildenafil citrate, and 45 mg/kg EEACL groups.

The concentration of TAG in the negative control group was significantly higher ($P < 0.05$) compared to other groups. There was no significant difference ($P > 0.05$) between the naive control and the three extract-treated groups (15, 30, and 45 mg/kg EEACL), and their concentrations were significantly lower ($P < 0.05$) compared to the sildenafil citrate group. The sildenafil citrate group, while higher than the extract groups, remained significantly lower ($P < 0.05$) than the negative control. The induction of paroxetine significantly decreased ($P < 0.05$) HDL concentration in the negative control group when compared with all other groups. There was no significant difference ($P > 0.05$) in the HDL levels of the naive control and sildenafil citrate groups, both of which were significantly higher ($P < 0.05$) than the extract-treated groups. No significant difference ($P > 0.05$) was observed among the 15, 30, and 45 mg/kg EEACL groups.

A significant increase ($P < 0.05$) in LDL concentration was observed in the negative control group compared to all other groups. There was no significant difference ($P > 0.05$) in the LDL levels of the sildenafil citrate and 30 mg/kg EEACL groups, and their concentrations were significantly lower ($P < 0.05$) than those of the naive control, 15 mg/kg, and 45 mg/kg EEACL groups. The 15 mg/kg and 45 mg/kg EEACL groups showed no significant difference ($P > 0.05$) when compared to the naive control.

The serum VLDL concentration of the negative control group was significantly higher ($P < 0.05$) than that of all other groups. Similar to the trend observed in TAG, there was no significant difference ($P > 0.05$) in the VLDL levels of the naive control and the 15, 30, and 45 mg/kg EEACL groups. These groups were all significantly lower ($P < 0.05$) than the sildenafil citrate group, which in turn was significantly lower ($P < 0.05$) than the negative control.

The atherogenic index of the negative control group was significantly higher ($P < 0.05$) compared to all other groups. There was no significant difference ($P > 0.05$) in the AI of the naive control and sildenafil citrate groups. While all extract-treated groups (15, 30, and 45 mg/kg EEACL) showed no significant difference ($P > 0.05$) among themselves and were significantly lower ($P < 0.05$) than the negative control, their index values remained significantly higher ($P < 0.05$) than those of the naive control and sildenafil groups.

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Table 1: Serum Lipid Profile of Ageratum conyzoides-treated Rats with Paroxetine-induced Erectile Dysfunction

Groups	Cholesterol (mmol/L)	TAG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	VLDL (mg/dL)	Atherogenic Index
Naive Control	22.74 ± 1.81^{b}	9.38 ± 0.12 ^{a}	8.76 ± 0.39^{c}	12.7 ± 1.80^{b}	1.88 ± 0.03^{a}	0.03 ± 0.02^{a}
Negative Control	26.33 ± 0.22^{c}	11.50±0.36 ^{c}	7.09± 0.12^{a}	17.19± 0.42^{d}	2.25 ± 0.06^{c}	0.19 ± 0.16^{c}
4 mg/kg Sildenafil	22.91 ± 0.51^{b}	10.12± 0.11^{b}	8.39 ± 0.39^{c}	8.14 ± 1.54^{a}	1.97 ± 0.02^{b}	0.08 ± 0.15^{a}
15 mg/Kg EEACL	22.91 ± 0.51^{b}	9.57 ± 0.22^{a}	7.78± 0.66^{b}	11.91± 1.27^{b}	1.91 ± 0.04^{b}	0.09 ± 0.03^{b}
30 mg/Kg EEACL	20.16 ± 1.89^{a}	9.26 ± 0.20^{a}	7.52± 0.25^{b}	9.79 ± 1.15^{a}	1.85 ± 0.04^{a}	0.09 ± 0.02^{b}
45 mg/Kg EEACL	22.71 ± 0.56^{b}	9.78 ± 0.21^{a}	7.82±0.37^{b}	13.59± 0.91^{c}	1.96 ± 0.05^{b}	0.09 ± 0.01^{b}

Discussion

The cardiotoxicity of the long-term use of paroxetine, a selective serotonin reuptake inhibitor, continues to be a major concern. *Ageratum conyzoides* is a plant reported to have antioxidant properties [28]. Arginase promotes cardiotoxicity by depleting L-arginine and uncoupling eNOS, leading to low NO [29]. The elevated expression of arginase in the paroxetine untreated rats suggests disruption of L-arginine metabolism and reduced NO concentration. The activity of the enzyme in this group also implies higher competitiveness of the enzyme over nitric oxide synthase, since they both share L-arginine as their substrate [30].

This imbalance might be accountable for the decrease in the NO concentration in the heart muscle of paroxetine-treated rats, and consequently, higher levels of cardiotoxicity, because NO is an essential mediator of vasodilation and heart cell preservation [31]. However, the administration of EEACL at all doses reduced the arginase activity, reducing the cardiotoxicity. It is noteworthy that the 15 and 45 mg/kg EEACL groups showed lower susceptibility to cardiotoxicity, as evidenced by their arginase activity, which showed no difference from that of the normal control group.

This biochemical imbalance in the paroxetine untreated group was further promoted by the activity of phosphodiesterase 5 (PDE5), resulting in rapid cGMP breakdown. Consequently, due to the interference of the signaling pathway, paroxetine interferes with the usual control of cardiac vascular tone and restorative relaxation [32]. The capacity of the leaf extract of Ageratum conyzoides (EEACL) to enhance NO level and inhibit arginase and PDE5 proves the potency of this plant against Paroxetine-induced cardiotoxicity.

Cardiac troponin I is a cardiac parameter that leaks into the systemic circulation as a result of cardiac tissue damage [33]. High troponin I observed in the paroxetine untreated group suggests cardiomyocyte membrane rupture and, therefore, it is possible that the oxidative stress generated by paroxetine caused myofibrillar damage or necrotic changes in the cardiac tissue [34]. The dose-dependent modulation of troponin I concentration by EEACL treatment indicates a strong membrane-stabilizing effect, which provides a defense mechanism for cardiomyocytes. The EEACL has also shown some levels of cardioprotection via its potential to reduce paroxetine-induced dyslipidemia. The decrease in the total cholesterol, triglycerides (TAG), and low-density lipoproteins (LDL), and an increase in high-density lipoproteins (HDL) observed in the EEACL groups suggest that EEACL can regulate the lipid biosynthetic pathways or increase the clearance mechanisms, which result in the cardioprotective effect of decreasing the atherogenic index. This supports cardioprotection, since the atherogenic index is a predictive factor of coronary artery disease, and the reduced index suggests a reduced cardiovascular risk in the long run [35].

It is noteworthy that at the point of designing this research, there was no evidence of Ageratum conyzoides leaf extract specifically activating the Arginase/NO/PDE5 axis and balancing the lipid profile in order to counteract the cardiotoxicity caused by paroxetine. Although the antioxidant effect of the plant, in general, has been previously reported [14], the new evidence that it can inhibit PDE5 and arginase activity at the same time and restore myocardial integrity and lipid homeostasis creates a new paradigm in the mechanisms of use as a cardioprotective agent. This multi-target efficacy indicates that Ageratum conyzoides exhibits an overall therapeutic benefit by attenuating drug-induced cardiotoxicity by protecting vascular signaling, myocardial structure, and mitigating metabolic risk factors. These results open the path to the use of this ethnomedicinal resource as a potential adjunctive therapy, which is both cheap and effective, to protect cardiac health in patients receiving chronic SSRI therapy.

Conclusion

Based on the findings in this study, *Ageratum conyzoides* leaf extract has a significant cardioprotective potential against cardiac issues arising from chronic paroxetine administration. As indicated in the research, the extract can considerably control the Arginase/NO/PDE5 pathway to raise the bioavailability of nitric oxide and lessen the phosphodiesterase-5 and arginase overexpression. The potency of the extract in preserving cardiovascular activity, which is achieved by enhancing signaling pathways and decreasing the levels of cardiac troponin I and the subsequent lipid profile and atherogenic index, can be observed by its effects on the significant decrease in cardiac troponin I concentration and the subsequent lipid profile and atherogenic index.

Conflict of Interest

There are no personal or professional conflicts of interest to declare.

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