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Full length Research Article

Methanolic Leaf Extracts of *Ricinus communis* Ameliorated Cardiovascular Dysfunction in Dichlorvos-exposed Rats

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Summary: Cardiovascular diseases are the leading causes of death globally resulting in 17-19 million death every year. The search for an effective medicine to manage cardiovascular disorder without any side effect has led to the use of traditional based medicine. 75% of the world's population has been reported to depend on traditional medicine as their basic form of health care and this has resulted to the use of herbal medicine in the treatment and management of metabolic diseases. The study evaluated the effect of methanolic extract of *Ricinus communis* on DDVP-induced cardiotoxicity in male Wistar rats. Thirty-two (32) male Wistar rats were randomly divided into four groups of eight (8) rats each. Group A served as control rats, received 10mL/Kg of dimethyl sulfoxide (DMSO) and distilled water solution (vehicle) for six weeks. Group B served as DDVP-induced rats and were exposed to DDVP (15 minutes daily) for 3 weeks without any treatment. Group C rats received DDVP as in group B and then administered 300mg/kg of *R. communis* extract for 42days. While Group D rats were administered 300mg/kg of *R. communis* extract daily, for 6 weeks in addition to normal feed and water. Exposure to DDVP caused significant cardiac dysfunction evidence by alteration in cardiovascular variables and electrocardiac function, compromised lipid profile and reduced antioxidant enzymes. However, treatment with methanolic extract of *Ricinus communis* improved antioxidant defense system, attenuate hemodynamic impairment and left ventricular dysfunction, as well as inhibit lipid peroxidation and prevent hyperlipidemia in rats. In addition, histopathology observation showed that *Ricinus communis* extract was able to regenerate the myocardial injury caused by exposure to dichlorvos. In conclusion, *Ricinus communis* exhibited cardioprotective properties and may be a potential remedy for cardiovascular diseases with low risk of toxicity.

Keywords*: Cadiovascular diseases, Ricinus communis, cardiovascular variable, electrocardiac function, dichlorvos (DDVP)*

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INTRODUCTION

Cardiovascular diseases (CVD) currently stand as the predominant cause of disability and mortality worldwide (WHO, 2017). In 2015, approximately 17 million deaths were attributed to cardiovascular diseases, accounting for 30% of the total global mortality (WHO, 2017). Among these deaths, 7.2 million resulted from heart attacks, and 5.7 million were due to stroke (Forreira, 2020). Notably, about 80% of these fatalities occurred in low and middle-income countries, affecting both men and women almost equally (Leone, 2015). Estimations suggest that if the current trend persists, by 2030, around 23.6 million people will succumb to cardiovascular diseases, primarily from heart attacks and strokes (Forreira, 2020). This positions cardiovascular diseases among the most prevalent non-communicable diseases (WHO, 2017).

Cardiovascular diseases encompass a broad spectrum of conditions that impact the cardiac muscles and/or vascular systems. This category includes coronary heart disease (heart attacks), cerebrospinal disease, hypertension, rheumatoid heart disease, peripheral artery disease, and heart failure (Forreira, 2020). Recognized potential risk factors for CVD comprise tobacco use, physical inactivity, elevated Low-Density Lipoprotein (LDL) Cholesterol, diabetes, and a constellation of interconnected metabolic risk factors (Cannon, 2007). The Framingham Heart Study, initiated in 1961, pioneered the concept of risk factors, establishing connections between high cholesterol, hypertension, tobacco usage, and diabetes mellitus with future cardiovascular diseases (Mahmood *et al*., 2014). Additionally, environmental toxic substances, including pesticides like dichlorvos, may influence novel risk pathways such as inflammation and oxidative stress (Anna, 2010). Consequently, ecological toxicants should be considered significant risk factors for cardiovascular disease (Mostafalou *et al*., 2013).

Dimethyl 2,2-dichlorovinyl phosphate, commonly abbreviated as DDVP, is an organophosphate (OP) insecticide and pesticide that exerts its toxic effects on humans and animals by inhibiting the enzyme acetylcholinesterase (USEPA, 2007). Due to its chemical properties, the most likely route of exposure to dichlorvos in human is through the inhalation of air contaminated with

it. Another reported route of exposure is through skin contact (with soil or surfaces contaminated with dichlorvos) or oral exposure by ingesting DDVP-contaminated food (USPH, 1995). Reported side effects resulting from acute exposure to DDVP are palpitations, nausea, vomiting, diarrhea, headache, fatigue, drowsiness, eye irritations and at very high concentrations, convulsions and coma (Saka *et al*., 2022a). Tests involving acute exposure of rats, mice, and rabbits have demonstrated that dichlorvos has high to extreme acute toxicity through oral, dermal, or inhalation exposure (WHO, 1992). Evidence from previous studies has revealed that organophosphates (OP) poisonings lead to cardiovascular abnormalities, such as alterations in the normal conducting activity and capacity of the heart, and ventricular arrhythmias expressed in electrocardiography (ECG) (Mostafalou and Abdollahi, 2013; Karki *et al*., 2004). Other risk effects of exposure to OP include neurotoxicity (Henshaw and Iwara, 2018), carcinogenicity (Greim *et al*., 2015), mutagenicity (Bhinder and Chaudhry, 2013), hepatotoxicity, and nephrotoxicity (Soboleve *et al*., 2021; Saka *et al*., 2022a).

The utilization of medicinal plants in traditional healing dates back to the origin of humanity (Ameh and Eze, 2010). Approximately two-thirds of the global population, primarily in developing countries, is estimated to depend on traditional medicine as their primary healthcare approach (Oladeji, 2016). The practice of traditional medicine remains prevalent in treating diseases in the African continent, attributed to the socio-cultural and socio-economic lifestyle of Africans, the lack of adequate basic healthcare facilities, and a shortage of qualified medical personnel (Singh *et al*., 2015). However, since the advent of civilization, medicinal plants have been an essential aspect of life (Singh *et al*., 2015). Globally, it is estimated that over 80,000 plant species have been utilized as medicinal plants. The significance of medicinal plants lies in their availability, relevance, acceptability, minimal side effects, and affordability.

Ricinus communis L. (*R. communis*), commonly known as the castor plant, is an erect, rapidly growing shrub characterized by dark red stems and can reach a height of about 6 meters. It is found across various continents worldwide, including the Arabian Peninsula, and has been cultivated for at least 6000 years (Scarpa and Guerci, 1982). The plant is often referred to as the castor oil plant due to the abundant oil that can be extracted from it (Chan *et al*., 2010). Many researchers believe it originated from Tropical Africa, and in Saudi Arabia, it is commonly known as Kherwa (Scarpa and Guerci, 1982). In Nigeria, it is called Laara or Ilarum/Iru by the Yorubas, Ogili Ugba or Ogili Isi by the Igbos, and Cika-gidaa by the Hausas (Toplak, 2005). *Ricinus communis* leaves have a historical therapeutic use spanning 4000 years, predominantly in herbal medicine for treating various diseases, disorders, and infections. All parts of *Ricinus communis* , including leaves, roots, bark, and various components, have been employed for medicinal purposes. The plant has been used as a laxative for over 2500 years in Greece and Rome (Scarpa and Guerci, 1982). Furthermore, *Ricinus communis* is utilized in the treatment of tumors and various diseases. Phytochemicals found in the castor plant include steroids, saponins, alkaloids, terpenoids, flavonoids, coenzyme Q10, vitamins A and E, and glycosides (Waseem *et al*., 2018). The combined effects of vitamin C and vitamin E have been observed to have a positive impact on carotid atherosclerosis (Shargorodsky *et al*., 2010). *Ricinus communis* has been reported to possess numerous medicinal properties (Waseem *et al*., 2018). However, there is paucity of information on the metabolic effect of *Ricinus communis* leaves extract on cardiovascular function and heart tissue disease. Hence, the medicinal properties of methanolic extract of the leaf on cardiovascular function parameters in DDVP-induced rats were investigated in this study.

MATERIALS AND METHODS

Animals: Thirty-two (32) male Wistar rats were used in this study. The animals were obtained from Animal House of the Department of Physiology, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso. The animals ranged from 200 – 250g. They were acclimatized for 2 weeks under suitable environmental conditions (standard conditions of 12 hours light and dark cycles) and housed in plastic cages at the Animal House. They were fed with standard grower's mash rat pellets *ad libitum*, with care to avoid any unnecessary stress and cages kept clean and odor-free at all times.

Ethical Review: This study was approved by the Ethics Review Committee of the Faculty of Basic Medical Sciences, LAUTECH, Ogbomoso, with Ethic Number: FBMS/AEC/P/074/22.

Treatments

Group A: Control groups: rats were administered 10mls/kg of (DMSO and distill water, prepared at 1:19mls respectively) daily, for a period of 6 weeks.

Group B: DDVP-exposed group: rats were exposed to 1ml of concentrated DDVP for 15 minutes daily via inhalation, for a period of 3 weeks.

Group C: DDVP+ 300mg/kg of *R.communis*: exposed to DDVP as in B above and were concomitantly administered with 300mg/kg solution of *R. communis* extract dissolved in DMSO and distilled water (as prepared for group 1 rats above) for 42days.

Group D: Extract Only: rats were administered 300mg/kg of *R. communis* extract dissolved in DMSO and distilled water (as prepared for group 1 rats above) daily, for 6 weeks.

Collection, extraction and preparation of methanolic extract': Fresh *Ricinus communis* leaves were plucked from a farm in Aduin area of Ogbomoso town, Oyo state, Nigeria. The castor plants were identified by Dr. (Mrs) Ogundola, a botanist in the Department of Pure and Applied Biology, LAUTECH, Ogbomoso, Oyo State. The leaves were thoroughly washed with running tap water 2-3times and then finally washed with distilled water and shade-dried for seven days, then dried in an oven below 50^{o}C and powdered using electric grinder and stored in air tight containers for later use. A standard dose of 300mg/kg was administered to the rats in groups III and IV for 42days.

Drugs and Chemicals: The trade name of the local pesticide used for this study is **Sniper^{TM}.** DDVP, containing 1000g/liter of 2,3-dichlorovinyl dimethyl phosphate (DDVP); manufactured by (Forward (Beinaj)

Hepu Pesticide Co. Limited, China, for Saro Agrosciences Limited, Oyo State, Nigeria) was used. The pesticide, which contains dichlorvos as the active ingredient, was purchased from New Waso market, Ogbomoso, Oyo State. Other chemicals used in this study include 96.4% methanol, Dimethyl sulfoxide (DMSO), formalin, distilled water and chloroform.

Exposure to DDVP: Animals in Group II and III were exposed to 98.54g/m^3 of DDVP via inhalation, as modified by Saka *et al*. (2022a). In addition, 1ml of the pesticide was soaked in cotton wool and placed in a desiccator. The rat was also placed inside the desiccator and allowed to inhale the dichlorvos for 15 minutes daily for 21 days to induce cardiotoxicity. The medium follows the diffusion principle.

Blood Collection and Preparation of Tissues homogenate: After 6 weeks of experimental procedure, the animals were taken to the Department of Veterinary Medicine of University of Ibadan, Oyo State, Nigeria, where the blood pressure and ECG were measured. The animals were later fasted overnight few days after getting back to Ogbomoso. After overnight fast, the animals were anesthetized via chloroform inhalation using a desiccator, blood sample was collected via cardiac puncture into lithium heparinized bottles, centrifuged, and plasma obtained for estimation of lipid profile. The heart tissues were excised, weighed and fixed in 10% buffered formalin inside plain sample bottles for histopathological study. The supernatant obtained from homogenized tissues was assayed for the assessment of oxidative stress markers (GPx, CAT, MDA and SOD)

Phytochemical screening of methanolic extract of *Ricinus communis* : Qualitative phytochemical analysis of *Ricinus communis* extract using methanol was performed and reported as previously documented by Nortjie *et al*. (2022) and Saka *et al*. (2022).

Saponins: 5ml of the extract was boiled in 20ml of distilled water in a water bath and filtered. Approximately 10ml of the filtrate was mixed with 5ml of distilled water and shaken vigorously to obtain a stable, persistent foam. The resulting foam was then mixed with three drops of olive oil and shaken vigorously. The formation of emulsion indicated the presence of saponin

Alkaloids: 1ml of the extract was stirred with 5ml of 1% (v/v) aqueous HCl on a steam bath and filtered when hot. Distilled water was added to the residue, and then 1ml of the filtrate was treated with a few drops of Mayer's reagent, Wagner's reagent, and Dragendoff's reagent. Alkaloids were confirmed by forming a yellow color with Mayer's reagent, red precipitate with Dragendoff's reagent, and reddish-brown precipitate with Wagner's reagent.

Terpenoids: 5ml of the extract was added to 2ml of chloroform. 3ml of concentrated H_2SO_4 was then carefully added to form a layer. Reddish-brown discoloration of the interfaced was observed, indicating the presence of terpenoid.

Steroids: 2ml of acetic anhydride was mixed with 2ml of the extract, followed by the addition of 2ml of concentrated H_2SO_4. A color change confirmed the presence of steroids from violet to blue or green.

Glycosides: 5ml of the extract was mixed with 2ml of glacial acetic acid containing one drop of ferric chloride solution. This was then underplayed with 1ml of concentrated sulphuric acid. The presence of glycoside was confirmed by forming a violet-green ring below the brown circle.

Flavonoids: One milliliter (1ml) of 10% (w/v) NaOH was added to 3ml of the extract. The formation of yellow color confirmed the presence of flavonoids.

Tannins: One millimeter (1ml) of the extract was boiled with 20ml of distilled water in a test tube and filtered. Three drops of 0.1% ferric chloride were added to the filtrate. The formation of green color confirmed the presence of tannin.

Anthraquinones: Five millimeters (5ml) of the seed oil was mixed with 10ml of benzene and filtered. Five millimeters (5ml) of 10% NH3 solution was added to the filtrate. The presence of anthraquinones was established by developing red color in the ammoniacal (lower) phase

Test for saponins: Extract was mixed with 5 ml of distilled water in a test tube and then it was shaken vigorously, formation of stable foam indicated the presence of Saponins.

Test for Phenol: Extract was mixed with 3-4 drops of ferric chloride solution. Bluish black or blue green color indicated positive test for phenol.

Test for amino acids (Ninhydrin test): Extract was boiled with 2 ml of 0.2% Solution of Ninhydrin. Violet color indicated the presence of amino acids.

Test for Carbohydrates (Benedict's test): 2 ml of Benedict's reagent was added to the extract and heated on boiling Water bath for 2 minutes, reddish brown precipitate indicated the presence of Carbohydrates.

Blood Pressure (BP) & Heart Rate (HR): Blood pressure and heart rates of the animals were taken using the tail cuff method (as designed by Rogers (2000) at the Department of Veterinary Medicine, University of Ibadan. Blood pressure readings were taken with a computerized system that automatically performs rapid, simultaneous, multiple measurements of cardiac parameters (CODA). It involves the use of a tail-cuff placed on the tail of the rat to occlude blood flow and at all-cuff incorporating the volume pressure recording (VPR) sensor placed distal to the occlusion cuff to measure BP parameters. As the occlusion cuff is slowly deflated the VPR cuff measures the physiological characteristics of the returning systolic blood flow resulting in values for systolic and diastolic BP, mean BP, heart pulse rate, tail blood volume and flow.

Waveform acquisition is described below: Mouse tails were passed through cuffs (13mm long, with a 9mm diameter) and immobilized by adhesive tape in a V-shaped block between a light source above and a photoresistor below the tail. Evaluated photoelectrically, blood flow in the

tails produces oscillating waveforms that are digitally sampled 200times per second per channel. The waveforms displayed on the monitor are computer analyzed before and during a programmable routine of cuff inflation and deflation. Tail-cuff BP is defined as the cuff inflation pressure at which the waveform amplitude falls below a programmable percentage of its original amplitude for a specified number, of waveform cycles. Adjustment of these parameters allows BPs to be determined without interference from background noise.

Mean Arterial Blood Pressure (MAP): The mean arterial blood pressure was calculated using the mathematical relation of:

$$MABP = DBP + \frac{(SBP - DBP)}{3}$$

Where *MABP = Mean Arterial Blood Pressure*
DBP = Diastolic Blood Pressure
SBP = Systolic Blood Pressure

Pulse Pressure (PP)
Pulse pressure was calculated using the following formula:

$$PP = SBP - DBP$$

Where *PP= Pulse Pressure*
SBP= Systolic blood pressure (mmHg)
DBP=Diastolic blood pressure (mmHg).
It refers to the force that the heart generates each time a contraction occurs.

Rate Pressure Product (RPP): The Rate Pressure Product was calculated using the following formula:

$$RPP = \frac{HR \times SBP}{100}$$

Where *RPP = Rate Pressure Product*
HR= Heart Rate (bpm)
SBP= Systolic Blood Pressure (mmHg).

Electrocardiogram (ECG): Electrocardiography readings were taken using EdanVE-1010 machine, a PC-based diagnostic tool intended to acquire, process and store electrocardiograph (ECG) signals from pets such as rats undergoing resting test. After the BP analysis, the rats were sedated with ketamine (50mg/kg) and xylazine (0.75mg/kg) administered subcutaneously, there after gel was applied to the four limbs and chest of the rats. Five veterinary ECG leads, one for chest (V) and four for the limbs (RA, LA, RL, LL), with each lead attached to an atraumatic alligator lip electrode were then connected to the gels pot and the cardiogram was recorded for 60s with the custom-made software accompanying the system.

Determination of Lipid Profile: Total cholesterol, triglyceride, and HDL cholesterol were determined using Randox Commercial Kits. The chylomicrons' very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) serum are precipitated by phosphotungstic acid and magnesium ions. Therefore, LDL was calculated from the results of Total cholesterol, Triglyceride, and High-density lipoprotein (Saka *et al.,* 2022).

Determination of Oxidative stress marker: The activity of superoxide dismutase (SOD) in the heart was determined by the method of Misra and Fridovich (1972) and modified by Kakkar *et al*. (1984). GPx activity was estimated using calorimetric method (Saka *et al.,* 2020). The level of lipid peroxidation as malondialdehyde (MDA) and Catalase (CAT) activity were determined based on the principle of Varshney and Kale (1990) and Aebi (1974), respectively.

Histopathology of the Excised Organs: The fixed organs were analyzed at the Histopathology Laboratory of the University College Hospital, Ibadan following standard protocol (Abiona *et al.,* 2019). Photomicrography, H & E were done in accordance to the principle of (Avwioro, 2010).

RESULTS

Phytochemical screening of methanolic-extract of *Ricinus communis* : Table 1 shows the findings of the qualitative phytochemical studies. *Ricinus communis* extract was found to contain alkaloid, tannin, saponin, flavonoids, phenol, terpenoids, carbohydrate and glycosides.

Table 1:
Phytochemical screening of methanolic-extract of *Ricinus communis*

Phytochemical test	Results
Alkaloid	+
Tannin	+
Saponin	+
Flavonoids	+
Phenol	+
Terpenoids/Isoprenoids	+
Amino acids	-
Carbohydrate	+
Glycoside	+

+: Present; - :Absent

Estimation of cardiovascular variables: The effects of dichlorvos and methanolic extract of *Ricinus communis* leaf on cardiovascular variable is summarized in Table 2. Administration of Dichlorvos induced extensive cardiovascular dysfunction evident by significant increase ($P< 0.05$) in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), blood volume, rate pressure product (RPP) as well as heart rate (HR) in rats exposed to DDVP when compared to control group. However, treatment with *Ricinus communis* extract in pathogenic rats significantly reduced SBP, blood volume, RPP, HR with a non-significant difference in DBP, PP and MAP when compared to DDVP-exposed rats. Also, *Ricinus communis* treated rats has significantly decreased cardiovascular variables when compared to DDVP-exposed rats at $p<0.05$.

Estimation of electro-cardiac function

Effects of Methanolic extract of *Ricinus communis* leaf on Electrocardiogram (ECG) in male Wistar rats exposed to DDVP: The result (Table 3) revealed an alteration in electro-cardiac function evident by significant increase ($p\leq 0.05$) in P-duration, QRS Complex, QT interval, corrected QT interval, R-Amplitude with a non-significant difference in PR-Interval in DDVP-exposed rats

when compared to control group. However, administration of methanolic leaf extract of *Ricinus communis* significantly decreased PR-Interval, QRS-complex and QTC-Interval with a corresponding non-significant difference in P-Duration, QT-Interval and R-Amplitude when compared with DDVP-exposed rats. Electro-cardiac function in *Ricinus communis* leaf extract recorded a normal range as compared to control rats.

Estimation of lipid profile: The effects of dichlorvos and methanolic extract of *Ricinus communis* on lipid profile such as cholesterol (CHOL), Triglyceride (TAG), High density lipoprotein (HDL) and low density lipoprotein (LDL) is summarized in Table 4. Exposure of rats to DDVP caused abnormalities in lipoprotein metabolism as shown by increase in CHOL ($p<0.05$), LDL ($p<0.05$), TAG ($p>0.05$) with a corresponding decrease in HDL ($p<0.05$) when compared with control rats. However, treatment with methanolic extract of *Ricinus communis* decreases elevated level of CHOL ($p<0.05$), LDL ($p>0.05$), TAG ($P>0.05$) with significant increase in HDL ($p<0.05$) when compared with DDVP-exposed rats. Also, administration of *Ricinus communis* methanolic leaf extract revealed a significantly normal lipid profile as compared to DDVP-exposed rats.

Estimation of oxidative stress: The effect of DDVP and *Ricinus communis* on oxidative stress marker such as glutathione peroxidase (GPx), malondialdehyde (MDA), superoxide peroxidase (SOD) and Catalase (CAT) were assessed and summarized in table 5. Administration of DDVP induced oxidative damage to rats evident by generation of free radicals (significant increase in MDA concentration) and suppression of antioxidant enzymes (significant decrease in GPx, SOD and CAT activities) as compared to control rats ($p<0.05$).

Table 2:
Effects of Methanolic extract of *Ricinus communis* leaf on cardiovascular variable in DDVP-exposed rats

Parameters	I	II	III	IV
Systolic blood pressure (mmHg)	116.0 ± 2.10	146.5 ± 2.39[a]	132.2 ± 2.51[a,b]	123.0 ± 1.32[b,c]
Diastolic blood pressure (mmHg)	83.33 ± 2.06	93.67 ± 1.05[a]	93.00 ± 1.63[a]	86.50 ± 1.78[b]
Pulse Pressure (mmHg)	32.67 + 1.73	52.83 ± 2.14[a]	39.17 ± 1.54[a]	32.00 ± 1.51[b,c]
Mean arterial blood pressure (MAP) (mmHg)	94.22 ± 1.91	111.3 ± 1.28[a]	106.1 ± 1.83[a]	101.7 ± 0.72[a,b]
Blood volume (ml/kg)	65.51 ± 7.20	116.9 ± 3.14[a]	67.06 ± 3.54[b]	87.09 ± 7.08[b]
Rate Pressure Product	31.76 ± 1.70	41.62 ± 0.61[a]	34.17 ± 0.89[b]	27.81 ± 2.30[b,c]
Heart Rate (HR) (bpm)	291.7 ± 0.88	351.3 ± 2.91[a]	286.0 ± 3.00[b]	238.3 ± 2.19[a,b,c]

Values are expressed in Mean ± SEM (n=8)
Groups with different superscript(s) are significantly different at p≤0.05.
[a]Represent significant difference when compared with Group I. [b]Represent significant when compared with Group II. [c] Represent significant difference when compared with Group III.
Group I = Control; Group II = DDVP-exposed rats; Group III = DDVP + 300mg/kg of Ricinus communis ; Group IV: Ricinus communis only

Table 3:
Effects of Methanolic extract of *Ricinus communis* leaf on Electrocardiac-function in DDVP-exposed rats

Parameters	I	II	III	IV
P-Duration (ms)	35.33 ± 3.38	43.33 ± 4.67[a]	40.67 ± 3.48	35.00 ± 5.13[a]
PR-Interval (ms)	44.00 ± 2.08	55.33 ± 0.33	45.67 ± 2.33[b]	41.67 ± 0.88[c]
QRS Complex (ms)	16.33 ± 0.88	35.00 ± 0.58[a]	18.00 ± 0.58[b]	23.33 ± 1.76[a,b,c]
QT-Interval (ms)	124.00 ± 2.33	100.7 ± 2.85[a]	86.33 ± 5.36[a]	113.0 ± 3.61[c]
QTC Interval (ms)	262.7 ± 1.86	218.0 ± 9.07[a]	165.0 ± 5.69[a,b]	231.7 ± 6.01[a,c]
R-Amplitude (mV)	0.329 ± 0.02	0.528 ± 0.02[a]	0.474 ± 0.03	0.449 ± 0.02[b,c]

Values are expressed in Mean ± SEM (n=8)
Groups with different superscript(s) are significantly different at p≤0.05.
[a]Represent significant difference when compared with Group I. [b]Represent significant when compared with Group II. [c] Represent significant difference when compared with Group III.
Group I = Control; Group II = DDVP-exposed rats; Group III = DDVP + 300mg/kg of *Ricinus communis* ; Group IV: *Ricinus communis* only

Table 4:
Effects of Methanolic extract of *Ricinus communis* leaf on lipid profile in DDVP-exposed rats

Parameters	**I**	**II**	**III**	**IV**
CHO (mg/dL)	47.68 ± 1.03	66.67 ± 4.05[a]	60.55 ± 3.37[a,b]	46.33 ± 1.57[b,c]
TAG (mg/dL)	60.38 ± 3.55	62.53 ± 0.60	61.07 ± 2.19	48.96 ± 1.27[a,b,c]
HDL (mg/dL)	13.68 ± 0.61	10.37 ± 0.56[a]	12.59 ± 0.87[b]	14.57 ± 0.37[b,c]
LDL (mg/dL)	22.05 ± 2.59	37.43 ± 1.69[a]	36.21 ± 1.93[a]	22.49 ± 1.97[b,c]

Values are expressed in Mean ± SEM (n=8)
Groups with different superscript(s) are significantly different at p≤0.05.
[a]Represent significant difference when compared with Group I. [b]Represent significant when compared with Group II. [c] Represent significant difference when compared with Group III.
Group I = Control; Group II = DDVP-exposed rats; Group III = DDVP + 300mg/kg of *Ricinus communis* ; Group IV: *Ricinus communis* only.

Table 5:

Effects of Methanolic extract of *Ricinus communis* leaf on oxidative stress marker in DDVP-exposed rats

Parameters	I	II	III	IV
GPx (µg/mL)	0.11 ± 0.01	0.05± 0.01[a]	0.07± 0.02[a,b]	0.09± 0.00[b]
SOD (U/mL)	5.66 ± 0.36	2.07 ± 0.42[a]	5.23 ± 0.25[b]	4.57 ± 0.2150[b]
CAT (mU/g)	0.52 ± 0.01	0.24 ± 0.15[a]	0.51 ± 0.03[b]	0.76 ± 0.01[a,b,c]
MDA (nmol/mL)	15.77 ± 1.00	24.05 ± 1.37[a]	17.26 ± 0.52[b]	14.47 ± 1.59[b]

Values are expressed in Mean ± SEM (n=8)
Groups with different superscript(s) are significantly different at p≤0.05.
[a]Represent significant difference when compared with Group I. [b]Represent significant when compared with Group II. [c] Represent significant difference when compared with Group III.
Group I = Control; Group II = DDVP-exposed rats; Group III = DDVP + 300mg/kg of *Ricinus communis* ; Group IV: *Ricinus communis* only

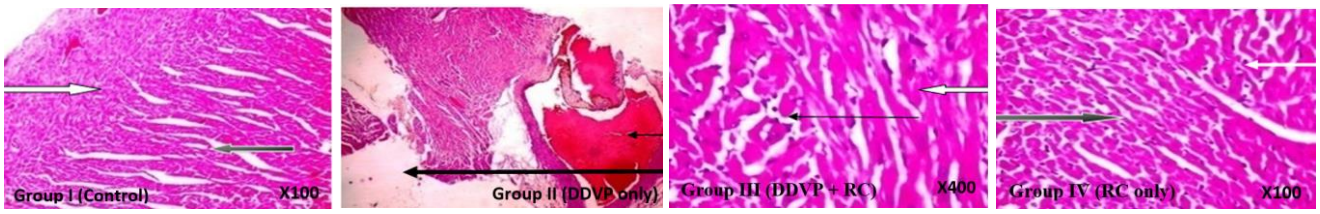

Plate 1:
Photomicrographs of heart section of normal control rats (Group I) depicts normal myocytes, epicardial layer (white arrow) and normal myocardial layer seen (black arrow), no pathological lesion seen but a photomicrograph of heart section of Group II induced with dichlorvos revealed normal epicardial layer (slender arrow) and marked fat degeneration and necrosis of the myocardial layer seen (black arrow), emblic myocytes vessels and valves (slender arrow). A photomicrograph of heart section of Group III treated with 300mg/kg of *Ricinus communis* methanolic extract after administration of dichlorvos showed normal epicardial layer (white arrow) and the mild infiltration of inflammatory cells of myocardial layer (slender arrow). Administration of methanolic extract of *Ricnius communis* extract to rats (Group IV) revealed a normal myocyte, epicardial layer (white arrow) and normal myocardial layer seen (black arrow) with no pathology.

However, treatment with methanolic extract of *Ricinus communis* significantly increases GPx, SOD, CAT and decreases MDA concentration when compared with DDVP-exposed rats. Also, administration of *Ricinus communis* extract to rats significant improved antioxidant enzymes and reduced peroxidation of lipid when compared to DDVP-exposed rats at $p<0.05$

DISCUSSION

The frequent utilization of pesticides and insecticides has heightened human exposure to environmental pollutants, potentially leading to both acute and chronic adverse health effects. The synthetic chemicals present in pesticides may contribute to long-term environmental repercussions. Within homes, individuals are exposed to insecticides, the toxicity profiles of which have not been thoroughly investigated. Dichlorvos (DDVP), a highly hazardous chemical classified by the WHO as (Class Ib) (WHO, 1992), accumulates in humans and induces toxic effects in various organs of the body (Tsitsimpikoua *et al*., 2013). Despite the wealth of knowledge regarding cardiovascular diseases (CVDs), their prevalence continues to escalate. Cardiovascular disease (CVD) remains the foremost cause of premature deaths globally (Kumar *et al*., 2010). Consequently, there is an immediate need for new, safe, effective, and relatively affordable drug candidates.

In the present study, dichlorvos induced cardiovascular dysfunction evidenced by significant alterations in cardiovascular variables such as increased arterial blood pressure (both systolic and diastolic pressure), mean arterial pressure (MAP), pulse pressure (PP), volume, rate pressure product (RPP), and heart rate. These findings align with a prior report by Saka *et al*. (2020). The ability of DDVP to induce changes in cardiovascular variables may stem from its stimulation of adrenergic responses or dysfunction in left ventricular contraction. Rats exposed to DDVP exhibited a substantial increase in arterial blood pressure (DBP, SBP, and MAP), contrary to the findings of Jun *et al*. (2018). However, administration of the methanolic extract of *Ricinus communis* restored DDVP-induced alterations in cardiovascular variables.

This study has also disclosed that *Ricinus communis* leaves possess a significant capacity to reduce systolic and diastolic blood pressure, pulse pressure, mean arterial blood pressure, and rate pressure product induced by exposure to DDVP. The blood pressure regulatory activity of *Ricinus communis* could be attributed to the presence of phytochemicals such as tannins and saponins embedded in the extract. Tannins exert physiological effects such as accelerating blood clotting, reducing blood pressure, decreasing serum lipid levels, inducing liver necrosis, and modulating immune responses, as reported by Chung *et al*. (1998). Saponins also aid in controlling cardiovascular disease and cholesterol in humans (Oladeji, 2016). Additionally, it has been revealed that *Ricinus communis* leaves extract exhibits a significant antioxidant capacity on cardiac tissues. Therefore, *Ricinus communis* is effective and possesses sufficient potency in the management of high blood pressure, which could otherwise lead to conditions like cardiac failure, stroke, and other cardiovascular diseases or potentially result in death. Thus, this finding suggests that R.communis may be a potential remedy for cardiovascular diseases with low risk of toxicity.

Electrocardiac function parameters, including P-duration, PR-interval, QRS-complex, QT-interval, QTC-Interval, and R-Amplitude, were evaluated in this study. Administration of DDVP to rats resulted in abnormal electrocardiac function evidenced by a significant increase in P-duration, QRS-complex, QT-Interval, QTC interval, R-Amplitude, and a non-significant difference in PR-Interval compared to control rats (as shown in Table 3). P-duration reflects the depolarization of the atrium of the heart, while PR-Interval represents the time of conduction of electric signals through the atrial and atrioventricular (AV) node. Therefore, the observed prolongation in P-wave and PR-Interval duration in DDVP-exposed rats indicates an increased risk of atrial fibrillation, myocardial fibrosis, and even death in the study population (Cheng *et al*., 2009). QRS-Complex duration corresponds to conduction through the ventricular myocardium and serves as a predictor of sudden cardiac death (Kurl *et al*., 2012). The widening of QRS-complex duration observed in DDVP-exposed rats indicates impairment in hemodynamic performance and mitral regurgitation (Kass *et al*., 1999). QT-Interval and corrected QT Interval signify the electrical activity of the ventricles, while R-Amplitude measures the heart rate. The observed fluctuations in QT-interval, corrected QT Interval, and increased R-Amplitude in DDVP-exposed rats suggest that DDVP predisposes rats to ventricular arrhythmia (torsades de pointes) and attendant seizures (Trinkley *et al*., 2013). This possibly contributes to the observed DDVP-induced increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and pulse pressure, as seen in this study. However, treatment with the methanolic extract of *Ricinus communis* significantly ameliorated the deviations in electrocardiac parameters compared to dichlorvos-induced rats. This reveals the cardioprotective effect of the extract, which aligns with the findings of Charan *et al*. (2009).

The alteration in the lipid profile observed in DDVP-exposed rats as demonstrated in this study, is characterized by a significant increase in serum total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) levels, accompanied by a corresponding reduction in high-density lipoprotein (HDL) levels. These changes in the lipid profile of DDVP-exposed rats indicate abnormalities in lipoprotein metabolism. Lipoproteins play roles in various metabolic processes, such as immune reactions, coagulation, and tissue repair. Oxidative alteration of lipoproteins, particularly LDL, along with the suppression of lipoprotein antioxidants, especially Vitamin E, has been associated with the accumulation of cholesterol and an increased susceptibility to atherosclerosis (Olayinka *et al*., 2011). Elevated levels of TG, TC, and LDL, along with a concurrent decrease in HDL, generally signify an increased risk of cardiovascular disease. However, treatment with the methanolic extract caused a significant increase in HDL, coupled with a corresponding decrease in LDL, serum cholesterol, and TG. The leaf extract of *Ricinus communis* demonstrated hypolipidemic activity by significantly reducing triglycerides, cholesterol, LDL, and increasing HDL in rats' plasma, suggesting the herb's potential as a remedy for hyperlipidaemia and cardiovascular diseases (Kwiterovich, 2000). This aligns with the ethnobotanical use of the leaf extract as a natural remedy against cardiovascular disease in the West Africa Sub-Region. The present results support previous findings by Oyewole *et al*. (2016), who reported the modulatory effect of *Ricinus communis* leaf extract on cadmium-chloride-induced hyperlipidaemia and pancytopaenia in rats. The hypolipidaemic and blood-boosting activities of the leaf can be attributed to its phytochemical constituents present in the extract, as reported earlier (Oyewole *et al*., 2010; Kensa and Syhed, 2011). Some of these phytochemicals have been reported to have positive physiological actions on haematopoiesis and lipid metabolism in animals and humans (Brown, 1996).

Oxidative stress which has been described as an imbalance between pro-oxidants and antioxidants is a major contributor to cardiac injury. It is widely accepted that antioxidant enzymes play a crucial role in defending against prooxidants, protecting cellular integrity, and preventing the pathogenesis of various degenerative diseases (Saka *et al*., 2022b). In situations of oxidative stress, disturbances in the normal redox state within cells can lead to an overwhelming effect on the enzymatic antioxidant enzymes, notably SOD, CAT, GST, and GPx, due to the excessive production of free radicals. Oxidative stress has been implicated in various conditions, including inflammatory diseases, alcoholism, smoking-related disorders, ischemic diseases, and more (Lobo *et al*., 2010; Dailiah *et al*., 2012; Prabu *et al*., 2013). The overall decrease observed in the status of enzymatic antioxidants in the heart homogenates of dichlorvos-exposed rats in the present study indicates a net suppression of the total antioxidant capacity in the tissue. This finding aligns with other reports (Ahmed *et al*., 2015; Saka *et al*., 2020; 2021). Treatment with methanolic extract of *Ricinus communis* ameliorated this effect, highlighting the antioxidant potential of the extract, as reported by Waseem *et al*. (2018). This result suggests that the plant extract contains bioactive constituents capable of donating hydrogen ions to free radicals, thereby scavenging them and preventing their potential to induce cellular damage. This affirms the protective influence of *Ricinus communis* extract on oxidative stress induced by dichlorvos exposure.
Lipid peroxidation, a crucial pathogenic event in myocardial necrosis, serves as a sensitive marker of oxidative stress induced by DDVP. The elevated level of MDA, a product of lipid peroxidation, reflects the extent of damage to cardiac tissues (Khalil *et al*., 2015). Malondialdehyde levels are commonly utilized as markers of oxidative stress (Maddock and Pariante, 2001). In this study, there was an observed increase in MDA levels in the DDVP-treated group. The findings presented in this study indicate that the methanolic extract of *Ricinus communis* could mitigate the elevation of DDVP-induced MDA content. The reduction in MDA levels in heart tissues might be attributed to the enhanced activities of antioxidant enzymes like SOD and GPx. It is plausible that the free radicals induced by DDVP were effectively neutralized and/or scavenged by the extract, resulting in the cardioprotective effect of the extract. Histopathological findings also revealed that exposure to DDVP altered the histoarchitecture of heart tissue, evidenced by marked fat degeneration and necrosis of the myocardial layer, embolic vessels, and valves in the myocytes compared to control rats. However, treatment with the methanolic extract of *Ricinus communis* resulted in a normal epicardial layer and mild infiltration of inflammatory cells in the myocardium.

In conclusion, *Ricinus communis* positively modulates cardiovascular dysfunctions, as evidenced by its attenuation of abnormal cardiovascular function, cardiac electrical activity, and lipid profile caused by DDVP in rats. The findings also indicate that the methanolic extract of *Ricinus communis* can mitigate DDVP-induced oxidative stress. Consequently, this study suggests that *Ricinus communis* alleviates cardiovascular dysfunction either through the reduction of cardiac oxidative stress or its hypolipidaemic effect. Therefore, the study infers that the leaf of *Ricinus communis* may serve as a potential remedy for cardiovascular diseases with a low risk of toxicity.

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