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Dichlorvos Evokes Systemic Lipid Dysmetabolism in Wistar Rats: Rescindment Influence of Curcumin

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Abstract

Organophosphorus pesticides such as dichlorvos (DDVP) are often employed to eradicate pests, especially in low and medium-income countries. However, they have several negative impacts on the visceral organs. Astonishingly, curcumin protects organs from the detrimental effects of xenobiotics via the maintenance of redox homeostasis; unfortunately, its role in dichlorvos-provoked multi-organ impairment vis-à-vis lipid homeostasis has not been examined. Therefore, this undertaking probed the remedial efficacy of curcumin on DDVP-prompted combined systemic toxicity and major lipid distribution. Randomization was engaged to dedicate rats (40) into seven groups (6 rats/group): control, DDVP only (20 mg kg^{-1}day^{-1}), DDVP administered with either curcumin (50 and 100 mg kg^{-1}day^{-1}) or reference medication atropine (0.2 mg kg^{-1}day^{-1}), and curcumin only (50 and 100 mg kg^{-1}day^{-1}). DDVP was dispensed orally for one week, followed by two weeks of curcumin treatment. Twenty-four hours after the last administration, we sacrificed the rats and collected their blood and viscera (liver, kidney, heart, lung, and brain) for bioassays. Curcumin remarkably ($p<0.05$) rescinded DDVP-mediated increases in plasma, LDL, and systemic cholesterol; markedly ($p<0.05$) attenuated DDVP-elicited decreases in HDL-cholesterol and TAG contents in all the compartments except erythrocyte and liver; and significantly ($p<0.05$) abated DDVP-induced plasma phospholipidaemia, multi-organ phospholipidosis, and up-regulation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA-R) activity. This finding demonstrated that curcumin reverses DDVP-triggered anomalous lipid dynamics by abating cholesterogenesis and phospholipidosis and restoring HMG-CoA-R activity.

Keywords: Dichlorvos, curcumin, visceral, cholesterogenesis, phospholipidosis

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INTRODUCTION

Over the last ten years, more than 100 organophosphorus (OP) substances have been exploited as insecticides to handle ectoparasitic infestations in agrarian food products (Leskovac and Petrović 2023). Low- to high-pernicious OP mixtures, such as dichlorvos and trichlorfon, are considerably employed (Fu et al., 2022). DDVP is commercially available in Nigeria as an agricultural concoction in a 100 bottle under the brand name "Sniper" by a chemical business that operates in both Switzerland and Nigeria. While OPs are no longer allowed in most advanced economies, they remain in circulation in many underdeveloped countries, negatively impacting human health and ecosystems (Okoroiwu & Iwara, 2018; Thredgold et al., 2019). OPs can be encountered acutely or chronically through occupational or non-occupational activities or inadvertently by ingesting pesticide residues that may persist in food (fruits, vegetables, grains) and drinking water, breathing air containing dichlorvos after home application, and skin contact with contaminated surfaces (Sinyangwe et al., 2016). Pesticide residues and their metabolites have the potential to pollute soils and water, infiltrate the dietary chain, and ultimately cause detrimental impacts on human well-being (Fu et al., 2022, Leskovac, 2022; Leskovac and Petrović, 2023).

Every year, millions of individuals worldwide experience poisoning from organophosphates (OPs), resulting from their use in agriculture, accidental exposure, suicide attempts, and, seldom, deliberate acts of harm (Ikizceli et al., 2005). The gastrointestinal and respiratory systems readily take in DDVP, but the liver and kidneys, respectively, handle its breakdown and removal. Both immediate and prolonged exposure to DDVP have been linked to a range of internal organ disorders such as hepatotoxicity (El-Saad et al., 2016), nephrotoxicity (Celik et al., 2015), cardiotoxicity (Salem et al., 2023), pulmonary toxicity (Taylor et al., 2008), neurotoxicity (Camacho-Pérez et al., 2022), pancreas (Leonel et al., 2020), reproductive deficit (Okoroiwu & Iwara, 2018), Acute and chronic DDVP exposure has also been shown to elicit mild to grave consequences ranging from sudden biliousness, nervous, agitated, teary eyes, dense sweating, bladder control loss, muscle vibrations, arduous breathing, delayed polyneuropathy, coma, incapability to breathe, and death (Sinyangwe et al., 2016; Leskovac and Petrović, 2023).

DDVP has been claimed to provoke the above biotic detrimental effect in target organisms (pests) and various tissues of non-target organisms (including human tissues) via two major mechanisms: (1) anti-acetylcholinesterase (anti-AChE) enzyme kinetics initiated by its phosphoric and phosphinic functional groups ensuing AChE inhibition and ACh accretion in nervous system (Farkhondeh et al., 2020; Salem et al., 2023), and (2) generation of DDVP reactive metabolites, metabolic free radical induction of free radicals leading to declined cellular anti-oxidative machineries, induction of oxidative stress, and disruption of vital cellular functions like apoptosis and ATP formation (Taylor et al., 2008; Celik et al., 2015; El-Saad et al., 2016; Okoroiwu & Iwara, 2018; Leonel et al., 2020; Camacho-Pérez et al., 2022; Salem et al., 2023).

Lipids, including cholesterol, triacylglycerol, and phospholipids, are essential components of liver, kidney, heart, lung, and brain cytomembrane structure, fluidity, and functions. The physiological functions of these lipids in these viscera include bile and vitamin synthesis, energy storage, transport, signaling (Hauton, 2016; Gupta et al., 2019; Yamaguchi & Ishimatu, 2020), and distortion in their optimal range, which will lead to negative consequences.

Why DDVP has been documented to provoke dyslipidemia (Agudelo et al., 2020; Tlatelpa-Romero et al., 2022), curcumin, a flavonoid found in turmeric, has been reported along with its antioxidant and anti-inflammatory functions against a myriad of xenobiotics-induced cytotoxicity in various visceral to also elicit anti-dyslipidemia capacity (Lin et al., 2009;

Mirzaei et al., 2017). Regrettably, curcumin's role in dichlorvos-triggered multi-organ impairment vis-à-vis lipid dysmetabolism has not been assessed. Hence, this study researched the antidotal capacity of curcumin on DDVP-occasioned combined systemic toxicity and major lipid distribution.

MATERIALS AND METHODS

Chemicals and reagents

Dichlorvos (DDVP, $C_4H_7Cl_2O_4P$) 5-dione,1,7-bis(4-hydroxy-3-methoxyphenyl)-6-heptadiene-3 ($C_{21}H_{20}O_6$). Besides what was explicitly mentioned, all additional kits and chemicals came from Sigma-Aldrich Chemical Co. The chemicals employed in this analysis were of the highest possible quality and purity.

Animal welfare

For this work, forty-two male Wistar rats were purchased from the College of Biosciences, Federal University of Agriculture, Abeokuta (FUNAAB), at 11 weeks of age and weighing 175 ± 19 g. The rats resided in well-ventilated plastic hanging cages with enough aspen matting; in a vivarium with a standard 12:12 diurnal period; and in temperature- and humidity-controlled environments (28 ± 2°C and 47 ± 2%, respectively). The rats were given standard rodent pellets and provided access to clean water on an unlimited basis. Acclimatization of all the animals was observed for one week before the beginning of the experiment. The rats were treated compassionately per the guidelines outlined by the FUNAAB Ethical Committee and the Animal Research: Reports of In vivo Experiments (Percie du Sert, 2020). The FUNAAB Research Ethical Committee approved the research procedures (license number: FUNAAB/COLBIOS/BCH/PG/17-0135); therefore, the study could proceed as planned.

Experimental architecture

After 7 days of adaptation, the rats were arbitrarily assigned to 7 clusters: control, DDVP (20 mg $kg^{-1}day^{-1}$), DDVP supplemented with curcumin (50 and 100 mg $kg^{-1}day^{-1}$) or reference prescription atropine (0.2 mg $kg^{-1}day^{-1}$), and curcumin (50 and 100 mg $kg^{-1}day^{-1}$). Seven days of DDVP administration via gavage were followed by fourteen days of uninterrupted curcumin chemotherapy from 7:30 a.m. to 8:30 a.m. daily. The chosen curcumin doses are effective antioxidants, anti-inflammatory, anti-lipidemic, and protect visceral from oxidative insult (Forouzanfar et al., 2020). Consequently, DDVP (20 mg/kg) is the 25% oral LD50 (Nwamba et al., 2018). In addition, based on the findings of the previous tests, sub-acute treatment (7 days for DDVP and 14 days for curcumin) was chosen (Nwamba et al., 2018; Forouzanfar et al., 2020). Described below is the experimental design.

Table 1. Groups and interventions used in the study.

Group	Treatments
Control (n = 6)	Received purified water (2 mL/kg) for seven days, then olive oil (2 mL/kg) for fourteen days
DDVP alone (n = 6)	Treated with dichlorvos (20 mg/kg) for seven days, then olive oil for fourteen days
DDVP + atropine (n = 6)	Treated with dichlorvos (20 mg/kg) for seven days, then atropine (0.2 mg/kg) for fourteen days
DDVP + C-50 (n = 6)	Treated with dichlorvos (20 mg/kg) for seven days, then curcumin (50 mg/kg) for fourteen days
DDVP + C-100 (n = 6)	Treated with dichlorvos (20 mg/kg) for seven days, then curcumin (100 mg/kg) for fourteen days
C-50 alone (n = 6)	Received purified water for seven days, then curcumin (50 mg/kg) for fourteen days
C-50 alone (n = 6)	Received purified water for seven days, then curcumin (100 mg/kg) for fourteen days

Blood and visceral (liver, kidney, heart, lung, and brain) collection and processing procedures and lipid parameters assessment

The rat was administered DDVP for seven straight days and/or curcumin for fourteen days. As stated by Wellington et al. (2013), rats were anesthetized with ketamine/xylazine [100–/10 mg kg^{-1}, 10% (w/w), intraperitoneally] twenty-four hours after the last curcumin exposure (i.e., day twenty second). The rats' blood via retro-orbital bleeding was collected in standard 10 mL Lithium heparinized vessels. We recovered the plasma by reeling the vials for 15 minutes at 3,000 x g at an ambient temperature (28 ± 2°C). The rats were terminated humanely by cervical disarticulation. The organ (liver, kidney, heart, lung, and brain) samples were homogenized (10%) in potassium phosphate solution (0.1 M, pH 7.4, 2°C), and reeled for 15 minutes at 10,000 g for 15 min at 4°C. The supernatant was used for the determination of triacylglycerol, cholesterol, and phospholipids concentration according to the LABKIT manual (Tietz, 1995) and the β-hydroxy-β-methyl-glutaryl-CoA reductase activity (Rao and Ramakrishnan, 1975).

Statistical analysis

The mean ± S.E.M. of six replicates per group was provided for quantitative variables. ANOVA was implemented in order to ascertain group homogeneity. The Duncan Multiple Range Test examined diverse groupings, with significance at $p < 0.05$. All statistical calculations were accomplished using Statistical Package for the Social Sciences 20.0. Plots were generated using GraphPad Prism 8.0.

RESULTS

The data presented in Figure 1 illustrates the impact of DDVP and curcumin on triacylglycerol levels across various tissues and lipid fractions. In comparison to the control group, significant reductions ($p < 0.05$) in triacylglycerol levels were noted in plasma (Fig. 1a), kidneys (Fig. 1f), heart (Fig. 1g), lungs (Fig. 1h), brain (Fig. 1i), and HDL (Fig. 1b) by 58.39%, 72.17%, 63.75%, 72.58%, 89.79%, and 32.08%, respectively. Conversely, elevated triacylglycerol levels were noted in erythrocytes (273.63%), liver (10.44%), and VLDL+LDL (176.98%) relative to the control group.

Administering curcumin (at 50 mg/kg or 100 mg/kg) or atropine to DDVP-treated rats significantly ($p < 0.05$) attenuated the lipid-altering effects induced by DDVP, restoring triacylglycerol levels in plasma, erythrocytes, liver, kidneys, heart, lungs, brain, HDL, and VLDL+LDL to near-normal levels. The percentage changes were as follows: 38.54%, 27.42%, 44.06%, 78.70%, 141.97%, 33.91%, 520.06%, 37.04%, and 69.61%, respectively, for atropine; 87.29%, 3.41%, 183.39%, 48.52%, 238.18%, 549.07%, 16.67%, and 43.38%, respectively, for curcumin at 50 mg/kg; 65.40%, 41.94%, 1.85%, 87.63%, 166.07%, 264.46%, 564.99%, 55.56%, and 65.45%, respectively, for curcumin at 100 mg/kg. Notably, curcumin at 100 mg/kg failed to counteract the reduction induced by DDVP in plasma.

Interestingly, administering curcumin alone to healthy rats resulted in significant ($p < 0.05$) alterations in triacylglycerol levels, with increases or decreases noted by: 17.73%, 40.27%, 12.38%, 45.46%, 1.00%, 18.22%, 26.70%, 22.64%, and 83.45%, respectively, for curcumin at 50 mg/kg; and 29.29%, 75.84%, 8.40%, 47.78%, 3.56%, 0.08%, 32.13%, 5.66%, and 4.32%, respectively, for curcumin at 100 mg/kg.

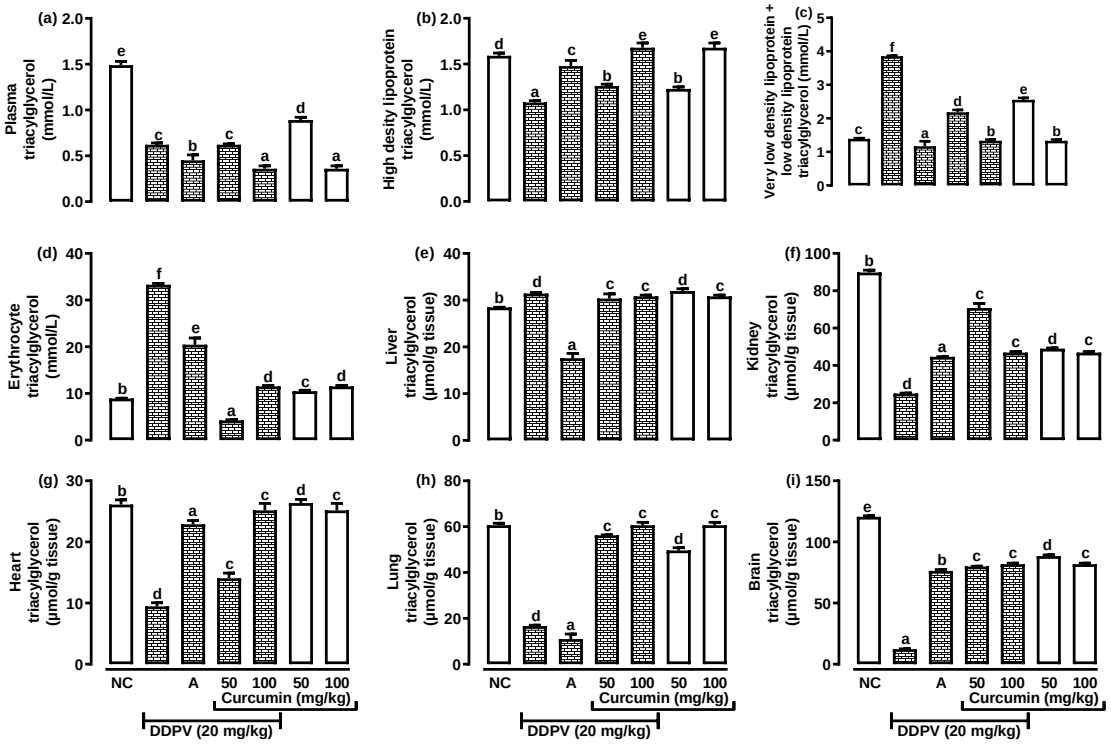

Figure 1: Efficacy of turmeric curcumin 14-day subacute chemotherapeutic on triacylglycerol in the plasma (graph a), HDL (graph b), VLDL+LDL (graph c), erythrocytes (graph d), liver (graph e), kidney (graph f), heart (graph g), lung (graph h), and brain (graph i) of rats exposed to DDVP for 7 days. NC implies normal control, the letter 'A' implies atropine, whereas DDPV implies 2,2-dichlorovinyl dimethyl phosphate or dichlorvos. The results are depicted as the mean ± SEM (the number of rats per group equals six). Bars represented by distinct lower-case letters differ from one another statistically substantially ($P < 0.05$).

Figure 2 depicts the impact of DDVP exposure followed by intervention with either curcumin or atropine on cholesterol levels across various biological tissues and components, including erythrocytes, plasma, liver, kidneys, heart, lungs, brain, HDL, and VLDL+LDL.

DDVP-treated rats exhibited significant ($p < 0.05$) increases in cholesterol levels compared to the control group, with fold increases of 7.69, 36.55, 20.74, 24.25, 20.22, 15.73, 18.18, 10.96, and 4.50 observed in plasma, erythrocytes, liver, kidneys, heart, lungs, brain, and VLDL+LDL, respectively. Conversely, there was a significant ($p < 0.05$) 6.45-fold decrease in HDL levels in the DDVP-treated group.

However, both curcumin and atropine interventions significantly ($p < 0.05$) mitigated the rise in cholesterol levels induced by DDVP. Atropine reduced cholesterol levels by 12.54%, 22.28%, 30.84%, 42.34%, 32.69%, 32.01%, 23.02%, 89.47%, and 33.00% in erythrocytes, plasma, liver, kidneys, heart, lungs, brain, HDL, and VLDL+LDL, respectively. Curcumin at doses of 50 mg/kg and 100 mg/kg resulted in reductions of 93.41%, 32.26%, 39.34%, 30.83%, 33.16%, 42.24%, 11.91%, 116.84% and 47.98%, and 81.25%, 26.24%, 24.22%, 31.47%, 22.42%, 29.81%, 20.06%, 222.11%, and 61.53%, respectively. Furthermore, atropine, curcumin at 50 mg/kg, and curcumin at 100 mg/kg attenuated the DDVP-mediated HDL cholesterol by 89.47%, 189.47%, and 222.11%, respectively.

Moreover, in normal rats treated with curcumin alone, cholesterol levels were statistically altered (either decreased or increased) compared to the normal control group. At a dose of 50 mg/b.tw, the alterations were -85.00%, -17.15%, 34.17%, 139.25%, 34.81%, -17.48%, 15.27%, -

72.10%, and 79.87%, respectively. At a dose of 100 mg/b.tw, alterations were -50.09%, 138.66%, 111.39%, 384.00%, 111.43%, 52.65%, 42.99%, -50.08%, and 73.16%, respectively.

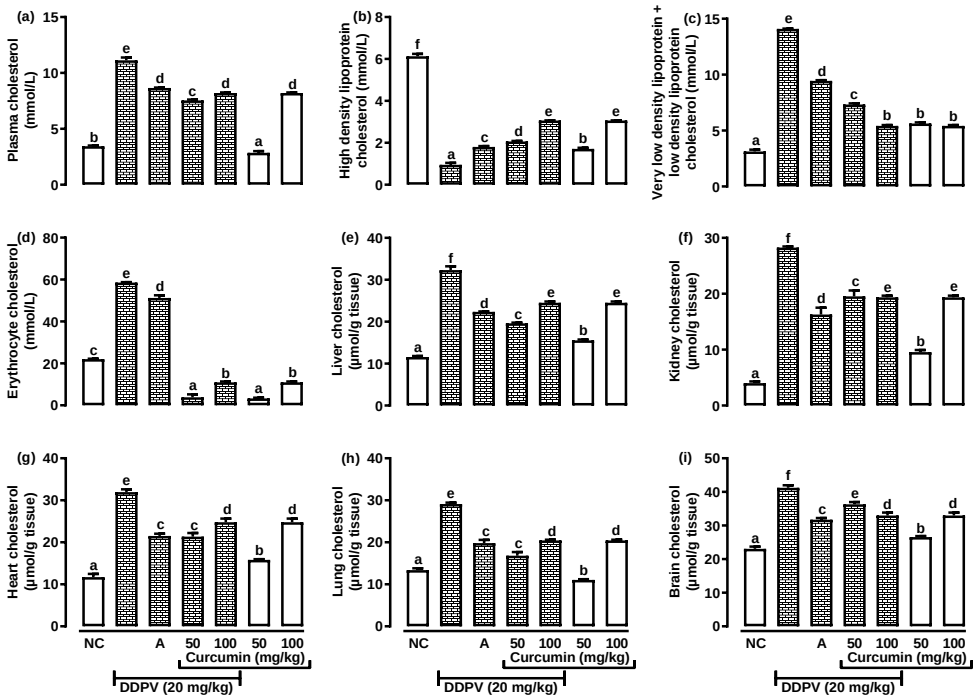

Figure 2: Efficacy of turmeric curcumin 14-day subacute chemotherapeutic on cholesterol in the plasma (graph a), HDL (graph b), VLDL+LDL (graph c), erythrocytes (graph d), liver (graph e), kidney (graph f), heart (graph g), lung (graph h), and brain (graph i) of rats exposed to DDVP for 7 days. NC implies normal control, the letter 'A' implies atropine, whereas DDPV implies 2,2-dichlorovinyl dimethyl phosphate or dichlorvos. The results are depicted as the mean ± SEM (the number of rats per group equals six). Bars represented by distinct lower-case letters differ from one another statistically substantially ($P < 0.05$).

Figure 3 demonstrates the effects of DDVP, atropine, and curcumin on phospholipids in various organs and 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity.

In DDVP-treated rats, phospholipid levels in plasma and kidney increased significantly ($p < 0.05$) compared to normal control rats, with corresponding increase in liver 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA-R) activity by 76.19%, 72.08% and 55.83%, respectively. However, phospholipid levels decreased in the liver by 82.07%, in the heart by 94.78% and in the lung by 38.13% (Fig. 3A–F).

Interestingly, treatment with curcumin and atropine resulted in remarkable reversal of DDVP-induced impairments in phospholipid levels and 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity.

Atropine administration attenuated the DDVP-induced increases in plasma phospholipids, kidney phospholipids and liver HMG-CoA-R by 33.06%, 26.42% and 49.73%, respectively. Atropine also attenuated the DDVP-triggered decreases in phospholipids levels in liver, heart, and lung by 515.56%, 433.33%, and 82.48%, respectively.

Meanwhile, administration of 50 mg/kg of curcumin reduced the DDVP-evoked increases in plasma phospholipids, kidney phospholipids and liver HMG-CoA-R by 24.00%, 44.15% and 43.85%, respectively. Curcumin at 50 mg/kg also reduced the DDVP-instigated decreases in phospholipids levels in liver, heart, and lung by 237.78%, 500.00%, and 54.98%, respectively.

Furthermore, curcumin administration oat a dose of 100 mg/kg of diminished the DDVP-incited increases in plasma phospholipids, kidney phospholipids and liver HMG CoA-R by 28.97%, 53.58% and 44.92%, respectively. Curcumin at 100 mg/kg equally mitigated the DDVP-elicited decreases in phospholipids levels in liver, heart, and lung by 237.78%, 733.33%, and 55.44%, respectively.

Moreover, a significant difference ($p < 0.05$) was observed in phospholipid concentration and 3-hydroxy-3-methylglutaryl-coenzyme reductase activity between the two doses of curcumin-only groups (50 and 100 mg/kg) and the standard control. Expressly, changes were noted by 8.16%, -24.30%, 7.14%, -57.39%, 540.59%, and -27.50%, for phospholipids levels in plasma, liver, kidney, heart, lung, and liver HMG-CoA-R, respectively, at 50 mg/kg body weight, and by 12.32%, -45.82%, -8.44%, -53.04%, 510.59%, and -24.17%, respectively, at 100 mg/kg body weight.

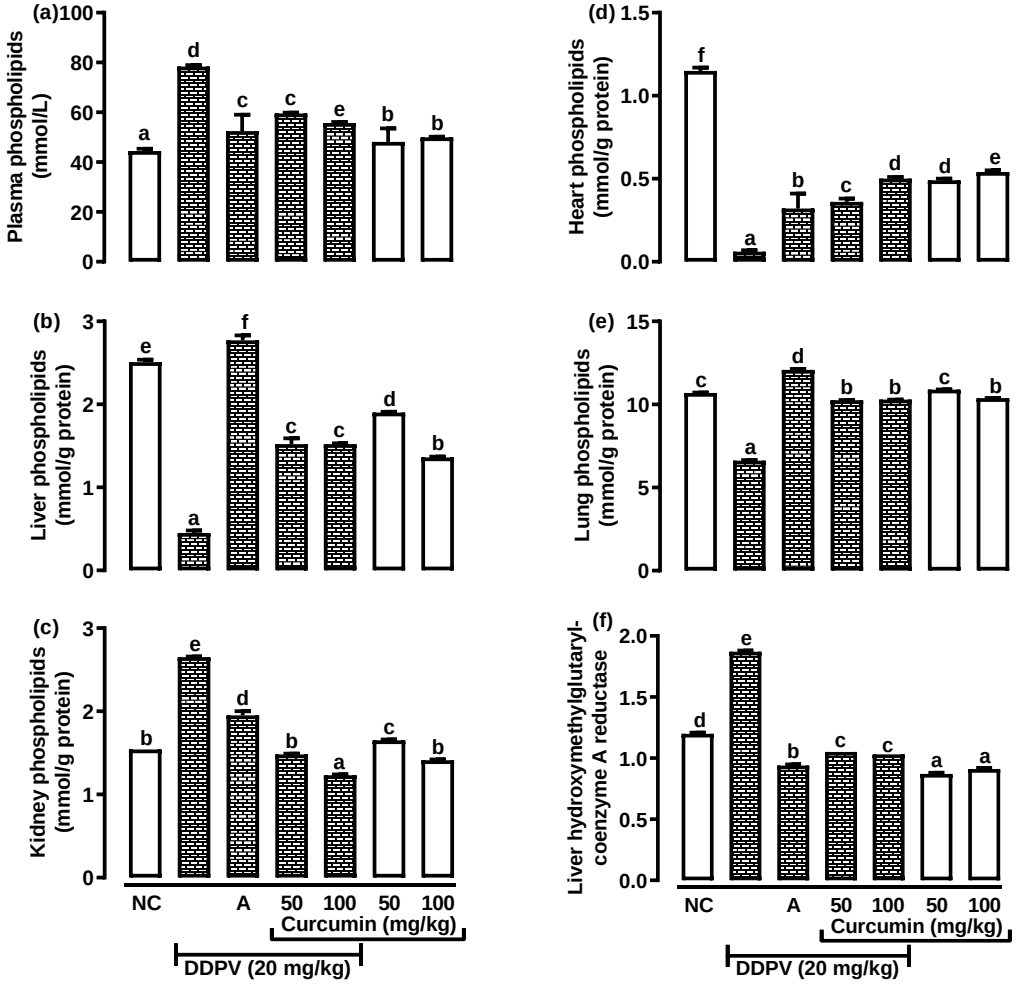

Figure 3: Efficacy of turmeric curcumin 14-day subacute chemotherapeutic on phospholipids in the plasma (graph a), liver (graph b), kidney (graph c), heart (graph d), and lung (graph e); and liver 3-hydroxy-3-methylglutaryl-coenzyme A reductase (graph f) of rats exposed to DDVP for 7 days. NC implies normal control, the letter 'A' implies atropine, whereas DDPV implies 2,2-dichlorovinyl dimethyl phosphate or dichlorvos. The results are depicted as the mean ± SEM (the number of rats per group equals six). Bars represented by distinct lower-case letters differ from one another statistically substantially ($P < 0.05$).

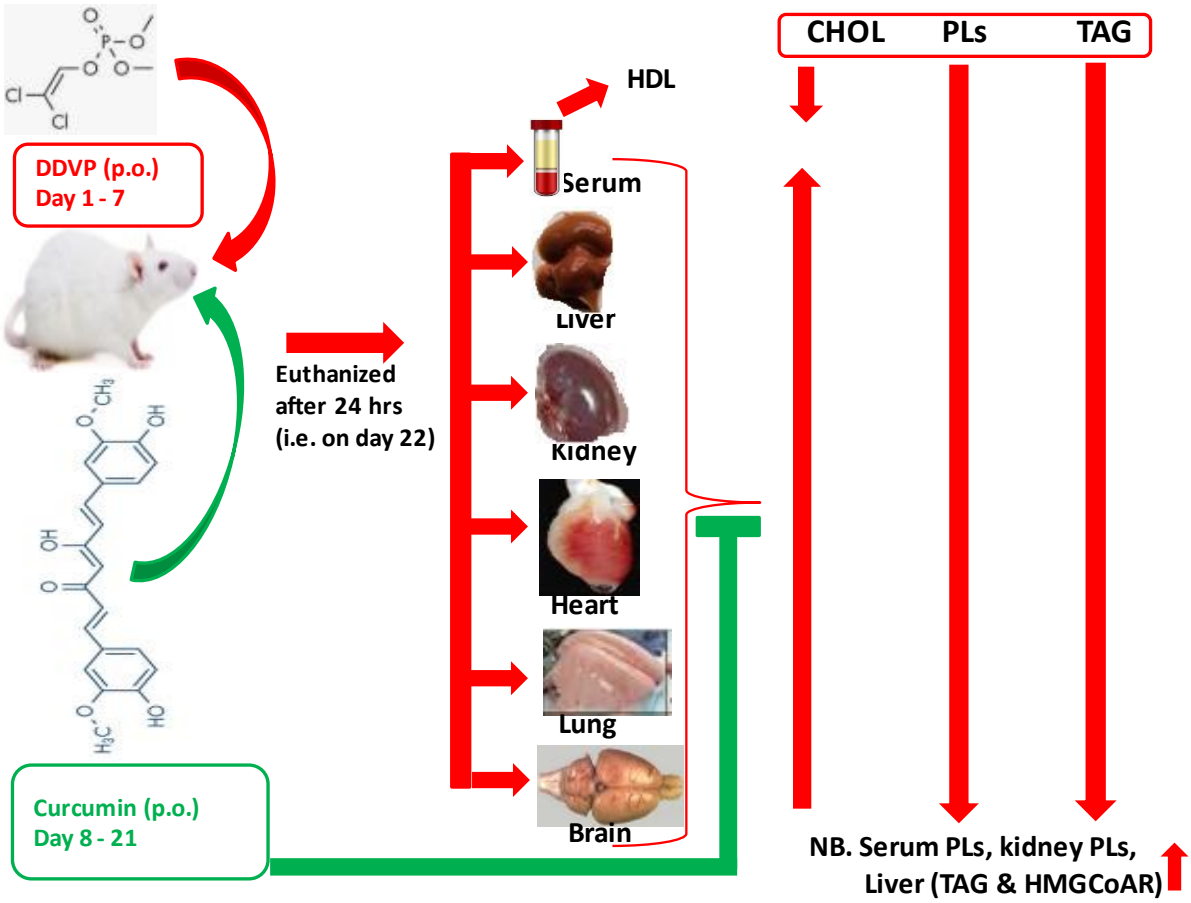

Figure 4: Graphical summary and the anticipated mechanism of the dichlorvos evokes systemic lipid dysmetabolism in Wistar rats: rescindment influence of curcumin. The Red arrows indicates the reaction pathways of the detrimental impact of DDVP, while the green symbol embodied the inhibition by curcumin intervention.

DISCUSSION

We examined the consequences of dichlorvos (DDVP) exposure on lipid metabolism across various tissues and the potential mitigating effects of curcumin intervention in Wistar albino rats. Our findings depicted marked modifications in lipid parameters and enzyme activity following DDVP exposure, underscoring the systemic dysmetabolism induced by this OP.

This current study shows that DDVP (20 mg/kg/day, 25% oral LD50) administered for a week elicited marked hypotriglyceridemia in the plasma, kidneys, heart, lungs, brain, and HDL lipid milieu. Triacylglycerols (TAGs) primarily store fatty acids in the cells, which are metabolized via β-oxidation to yield ATP for cellular activities. Generally, the DDVP-activated TAG depletion in these compartments may provoke diminished ATP production (Evans & Hauton, 2016; Gupta et al., 2019), leading to fatigue, weakness, and difficulty maintaining visceral functions.

Depleted TAG could occasioned other physiological consequences, including impaired lipid transport and free choline in plasma; compromised lipid metabolism and excretion affecting the filtration, reabsorption, and renal dysfunction; reduced ATP availability results in diminishes cardiac function and possibly individuals susceptible to cardiac ailments such as heart failure or ischemic heart disease (Evans & Hauton, 2016); TAG diminution instigates disrupt surfactant synthesis resulting in respiratory distress and diminished lung function (Tlatelpa-Romero et al., 2022); reduced brain TAG could impair neuronal membrane integrity, neurotransmitter biosynthesis, synaptic transmission resulting in cognitive deficits and neurological disorders (Tracey et al., 2018); and depleted HDL TAG could alter HDL composition, leading to impaired reverse cholesterol transport, which remove surplus cholesterol from peripheral tissues to liver for elimination, ultimately predisposing an individual to atherosclerosis and cardiovascular diseases (Ouimet et al., 2019).

The underlying mechanisms for the DDVP-evoked hypotriglyceridemia in the plasma, lipoprotein, and visceral could be that DDVP pesticide (1) enhances TAG excretion or inhibits enzymes involved in TAG biosynthesis, (2) disrupts lipid transport pathways, and (3) decreases fat mobilization, lipolysis, (4) augments activated fatty acid β-oxidation (Evans & Hauton, 2016; Ding et al., 2021; Tlatelpa-Romero et al., 2022).

Reports on antidotes for DDVP-induced hypotriglyceridemia are scarce in the literature. In this present investigation, the reversal effect of curcumin on DDVP-engendered hypotriglyceridemia to optimal ranges in the plasma, kidneys, heart, lungs, brain, and HDL could be by enhancing the genes expression or enzymes activities involved in TAG biosynthesis, fat mobilization, and lipolysis, thereby attenuating the detrimental consequences of hypotriglyceridemia and other concomitant impediments. Curcumin has been reported to have lipid-modulating potentials (Yuan et al., 2019; Rafiee et al., 2021).

We noted that DDVP instigated remarkable hypertriglyceridemia in the erythrocytes, liver, and VLDL+LDL lipid milieu. Our result agrees with several authors who reported that DDVP promoted elevated triacylglycerol (Yang & Park, 2018; Czajka et al., 2019.).

While TAGs are a high energy density molecule, elevated TAG in VLDL+LDL has been implicated in cardiovascular complications, including atherosclerosis, heart attacks, and strokes (Balling et al., 2023). Also, elevated liver TAG is associated with decreased TAG catabolism and elevated TAG anabolism, prompting liver dysfunction, predisposing an

individual to non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), inflammation, and fibrosis (Lee et al., 2023). Furthermore, elevated RBC TAG has been known to evoke decreased RBC membrane flexibility, alter blood viscosity and flow, impair RBC-taxi function, and ultimately contribute to anaemia and cardiovascular health anomalies (Wandersee et al., 2015). Also, elevated TAG in multiple tissues is associated with metabolic syndrome (Lee et al., 2023).

The causal mechanism stimulating the observed increased erythrocytes, liver, and VLDL+LDL TAG contents in DDVP-treated rats could be DDVP OP (1) phosphorylated the -OH group of serine in the active site of lipoprotein lipase, leading to decreased TAG clearance; (2) increased TAG biosynthesis; (3) increased fat mobilization, lipolysis, (4) compromised lipoprotein (VLDL and LDL) particle clearance from the circulation; (5) promoted liver inflammatory cytokines and other inflammatory mediators; (6) inhibited pseudocholinesterase activity (Wandersee et al., 2015; Balling et al., 2023; Lee et al., 2023).

The present assessment of hypertriglyceridemia in erythrocytes, liver, and VLDL+LDL agrees with prior experiments, in which the authors reported the anti-hypertriglyceridemia impact of curcumin against high-fat fed rats induced hyperlipidemia (Kempaiah& Srinivasan, 2006), poloxamer-407-induced hyperlipidemia (Manzoni et al., 2019), and 5/6 nephrectomy-induced hyperlipidemia (Ceja-Galicia et al., 2022).

This assessment shows that DDVP incited pounced hypercholesterolemia in the plasma and VLDL+LDL and enhanced cholesterogenesis erythrocytes, liver, kidneys, heart, lungs, and brain lipid microenvironment. Our findings agree with several authors who reported that DDVP mediated elevated cholesterol in various visceral and circulatory systems (Yang & Park, 2018; Czajka et al., 2019). Plasma and VLDL+LDL hypercholesterolemia have been implicated in atherosclerosis, resulting in narrowing or occluding arteries and cardiovascular ailments, including myocardial infarction and stroke.

Cholesterol is an essential component of the erythrocyte membrane (Yamaguchi & Ishimatu, 2020). However, erythrocyte cholesterol build-up has been shown to impair the RBC biomembrane's structural integrity and fluidity, disrupting RBC-O2 transport function and haemolysis (Yamaguchi & Ishimatu, 2020). Cholesterol synthesis and storage occur in the liver. Nonetheless, cholesterol accumulation in the liver could lead to hepatic steatosis and deranged liver activity (Horn et al., 2022). The backlog of cholesterol in the kidney perturbs its function and promotes kidney disorders, including glomerulosclerosis, renal artery stenosis, and kidney failure (Yasui et al., 2011). Enhanced CHOL contents in cardiac cells reduce blood flow to the muscle and stimulate the development of cardiovascular complications. Increased CHOL contents in the lungs could perturb pulmonary function and induce the formation of respiratory disorders, including pulmonary hypertension and interstitial lung disorders (Cao et al., 2020).

While cholesterol is a critical component of neuronal biomembrane structure and plays a role in neurosignaling, its enhanced accumulation in neuronal cells deranges lipid metabolism. It evokes the development of neurodegenerative complications, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and frontotemporal dementia (Zhang & Liu, 2015; She et al., 2020).

The hypercholesterolemia in plasma and VLDL+LDL and cholesterogenesis effect of DDVP in erythrocytes, liver, kidneys, heart, lungs, and brain could be accredited to DDVP pesticide

capability to elicit (1) cholesterol synthesis via upregulation/stimulation of HMG-CoA synthesis/activity, which was also noted in this current study (2) deranged cholesterol clearance via inhibition of cholesterol transporter activity or stimulating the expression of scavenger receptors (Zhang & Liu, 2015; Cao et al., 2020; Yamaguchi & Ishimatu, 2020; Horn et al., 2022)

Nonetheless, curcumin administration mitigated the DDVP-invoked enhanced CHOL level in plasma, VLDL+LDL, erythrocytes, liver, kidneys, heart, lungs, and brain. Our research aligns with multiple authors who have documented the anti-hypercholesteric effect of curcumin against capsaicin in induced hypercholesterolemic rats (Manjunatha et al., 2007), high-fat diet-induced hypercholesterolemic rats (Kim & Kim, 2010). This therapeutic strategy of curcumin could be due to its ability to inhibit HMG-CoA reductase, which was also observed in this present investigation. It has also been postulated that curcumin inhibits cholesterol synthesis via 7-alpha-hydroxylase suppression (Kim & Kim, 2010). Another mechanism could be that curcumin occasioned enhanced (1) cholesterol efflux in the liver, thereby diminishing the intrahepatic cholesterol contents (Favari et al., 2015)., and (2) expression and activity of enzymes and receptors involved in VLDL and LDL metabolism, leading to maintenance of the optimal range of VLDL and LDL cholesterol in the circulation (Dergunov et al., 2008).

Our observed decreased HDL cholesterol (HDL-C) following DDVP poisoning could lead to negative impacts, including impaired reverse cholesterol transport, leading to cholesterol build-up, which in turn leads to atherosclerosis, heart attacks, and strokes. Additionally, HDL particles possess antioxidant and anti-inflammatory properties, protecting against CVD; decreased HCL-C compromises these protective functions, resulting in enhanced blood vessel oxidative stress and inflammation (Rohatgi et al., 2021). Furthermore, HDL contributes to wound healing, so reduced HCL-C could motivate slower wound healing

The decreased HDL-C could be due to DDVP-elicited HDL synthesis inhibition in the liver, enhanced HDL particle clearance/catabolism from bloodstream/circulation, and disruption of HDL function due to oxidative stress (Gordts et al., 2014).

Regardless, curcumin administration substantially abrogated the DDVP-engendered decline in HDL-C content by (1) activating the expression and activity of proteins responsible for transporting cholesterol in HDL, leading to upregulation of cholesterol contents, improved reverse cholesterol transport, and decreased atherosclerosis (Favari et al., 2015), and (2) improving the corresponding antioxidant and anti-inflammatory properties of HDL (Zimetti et al., 2021). Our results align with previous studies, such as those conducted by Ganjah et al. (2017), which indicated that curcumin improved HDL functionality.

The marked increase in plasma and kidney phospholipid (PHOL) content observed in DDVP-exposed rats disagrees with the previous report of Tayyaba and Hassan (1980), who reported that DDVP- prompted reduced PHOL. Phospholipids, as an essential component of plasma and kidney biomembrane, dictate the membrane structural integrity of these compartments (Szachowicz-Petelska et al., 2013), so PHOL disruption could contribute to compromised structural integrity, perturb lipid transport, inhibit signaling pathways, impaired filtration and reabsorption processes, and upset ion and water balance, resulting in CVD, renal function, and other health aberrations (Afshinnia et al., 2021). The underlying mechanism for the DDVP-instigated hypophospholipedemia in the plasma and kidney could be that DDVP enhances the gene expression or enzyme activity involved in phospholipid biosynthesis in the hepatocytes, deceased degradation, decline transport, and oxidative cell damage.

The attenuation impact of curcumin on DDVP-incited elevated phospholipids suggests that curcumin could prevent phospholipids accumulation in the plasma and kidney by attenuating phospholipids synthesis, increasing phospholipids clearance, and reversing cyto-oxidative injury, thereby restoring cytomembrane integrity and improving plasma and kidney health (Nwamba et al., 2018; Forouzanfar et al., 2020). Curcumin has been shown to stabilize phospholipids concentration (Mirzaei et al., 2017).

The substantial drop in liver, heart, and lung phospholipids observed in rats subjected to DDVP aligns with earlier research suggesting that DDVP provokes multi-visceral hypophospholipedemia, as documented by Tayyaba and Hassan (1980). Decreased phospholipids disrupt visceral cell membrane integrity, lipid metabolism, signaling, and biological roles. For the liver, such impaired functions include bile synthesis, detoxification, and non-alcoholic fatty liver disease prevention (Svegliati-Baroni et al., 2019). For the heart, such perturbed activity could, among others, be electrolyte transport and contractile function, resulting in cardiac dysfunction and enhanced vulnerability to heart disease, arrhythmias, and heart failure (Yamamoto et al., 2018). For the lung, such a deranged role could be compromised gas exchange, declined lung compliance, diminished surfactant production, and enhanced vulnerability to pulmonary distress, pneumonia, and other lung ailments (Agudelo et al., 2020).

The DDVP-evoked decreased phospholipids could be because DDVP and its generated reactive metabolites (1) inhibit phospholipid synthesis, (2) enhance phospholipid degradation, and (3) trigger oxidative stress (Svegliati-Baroni et al., 2019; Yamamoto et al., 2018; Agudelo et al., 2020).

The ameliorative efficacy of curcumin in DDVP-induced hypophospholipedemia, as noted in this study, could be attributed to its ability to (1) enhance phospholipid synthesis, (2) inhibit phospholipid degradation and (3) rescind oxidative stress, thereby repudiating the DDVP-mediated hypophospholipedemia consequences listed above (Lin et al., 2009). Curcumin has been associated with maintaining and stabilizing phospholipid levels (Lin et al., 2009; Mirzaei et al., 2017).

Taken together, curcumin abated DDVP-invoked systemic and multi-visceral dyslipidemia by attenuating hypotriglyceridemia, hypertriglyceridemia, cholesterogenesis and phospholipidosis, and restoring HMG-CoA-R activity.

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