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Lipid-Modulating Effects of *C. argentea* In Phenylhydrazine-Induced Dyslipidaemia: Implications for Cardiovascular Risk

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Abstract- ***Phenylhydrazine-induced haemolytic anaemia is associated with oxidative disruption of hepatic lipid metabolism, leading to a pro-atherogenic dyslipidaemia characterized by elevated levels of total cholesterol (TC), LDL cholesterol, and triglycerides (TG), with concomitant suppression of cardioprotective HDL cholesterol. Celosia argentea is a nutritious green vegetable with reported antioxidant and anti-inflammatory activity. However, its lipid-regulatory effects under PHZ-induced oxidative dyslipidaemia have not been thoroughly explored. The present work aimed to examine the lipid-modifying property of aqueous leaf extract of C. argentea in PHZ, which caused dyslipidaemia in Wistar rats. Sixty adult male Wistar rats were divided into six groups (n = 10). PHZ (50 mg/kg) was administered intraperitoneally for 3 consecutive days to produce dyslipidaemia. Standard enzymatic colourimetric techniques were used to measure serum TC, TG, HDL-C, and LDL-C. The results showed that PHZ significantly increased the levels of TC (105.33 ± 5.03 mg/dl), LDL-C (55.00 ± 3.00 mg/dl) and decreased HDL-C (32.67 ± 2.87 mg/dl) as compared to controls (TC: 66.00 ± 11.38; LDL-C: 16.25 ± 3.20; HDL-C: 37.40 ± 2.51 mg/dl; p < 0.05). C. argentea post-treatment considerably lowered TC (71.00 ± 7.81 mg/dl), and LDL-C (38.67 ± 0.58 mg/dl), and partially restored HDL-C (35.75 ± 2.06 mg/dl) levels, which were comparable to Vitamin C. Pre-treatment also showed substantial activity in lipid normalization. The study showed that the aqueous leaf extract of C. argentea had significant lipid-modulating effects in PHZ-induced dyslipidaemia through antioxidant, cholesterol absorption-inhibiting, and hepatic lipid-regulatory pathways. The results provide a scientific basis for considering C. argentea as a plant-based nutraceutical supplement for the control of cardiovascular risk.***

Keywords: ***Celosia argentea, dyslipidaemia, phenylhydrazine, total cholesterol, LDL cholesterol, HDL cholesterol***

I. INTRODUCTION

Cardiovascular disease (CVD) continues to be the foremost cause of death globally, accounting for an estimated 18.6 million deaths yearly, or roughly one-third of all fatalities worldwide (Vaduganathan *et al*., 2022). Dyslipidaemia is a pathological change in the concentration of one or more circulating lipoproteins, including high levels of total cholesterol (TC), LDL cholesterol (LDL-C), triglycerides (TG) and/or low levels of HDL cholesterol (HDL-C) (Berberich & Hegele, 2022). It is one of the most frequent and essential modifiable risk factors for cardiovascular disease worldwide. In 2025, a systematic review and meta-analysis of over 200 population studies provided pooled estimates for the prevalence of dyslipidaemia in adults, with hypercholesterolaemia at 24.1%, hypertriglyceridaemia at 28.8%, and low high-density lipoprotein cholesterol (HDL-C) at 38.4%, confirming dyslipidaemia as one of the most common cardiometabolic disorders worldwide (Huertas-Bello *et al*., 2025). In 2019, high TC alone was estimated to account for 3.5 million deaths and 34.7 million disability-adjusted life years (DALYs) worldwide, with 80% of cardiovascular deaths occurring in low- and middle-income countries (LMICs) (Pirillo *et al*., 2021).

The epidemiology of dyslipidaemia is changing fast and alarmingly in sub-Saharan Africa and Nigeria, notably, due to urbanization, dietary westernization, physical inactivity and the increased prevalence of type 2 diabetes mellitus and obesity. A 16-year retrospective review of CVD admissions in Lagos, Nigeria, revealed a continued rising trend in CVD admissions and mortality in hospitals with dyslipidaemia identified as a major co-aggregating

risk factor alongside hypertension, diabetes and obesity (Amadi *et al*., 2022). Studies in Nigerian and West African diabetic populations have estimated the incidence of dyslipidaemia to be 55–80%, with low HDL-C and hypertriglyceridaemia being the prevalent trends, corroborating the global epidemiological shift towards atherogenic mixed dyslipidaemia (Emmanuel et al., 2024). The burden is high, but access to lipid-lowering medication, especially statins, is still quite limited in LMICs. Statins are available in public facilities in Africa at an average of only 13.3%, and when they are available, economic barriers hinder consistent use (Chaoyang *et al*., 2024). This stark inequality in treatment highlights a pressing need for safe, evidence-based, economical and culturally accessible lipid-regulating treatments, and plant-based nutraceutical alternatives.

The relationship between oxidative stress and dyslipidaemia is complex and bidirectional, and constitutes one of the main axes in the aetiology of atherosclerotic cardiovascular disease. According to Adegbaju *et al*. (2020), oxidative stress leads to the generation of reactive oxygen species (ROS), which directly attack LDL particles, which are particularly vulnerable to oxidative modification because of their high content of polyunsaturated fatty acids (PUFAs) and cholesterol esters. The oxidation of LDL is a three-step process, namely initiation (attack of free radicals on the PUFA side chains resulting in the formation of lipid peroxyl radicals), propagation (a chain reaction that propagates lipid peroxidation through neighbouring fatty acids) and termination (quenching of the radicals by antioxidants or other molecules) (Babakr, 2025). The classical LDL receptor does not recognize oxidized LDL (Ox-LDL). However, it is actively taken up by macrophage scavenger receptors (SR-A and CD36), resulting in intracellular cholesterol accumulation and foam cell development, the clinical hallmark of early atherosclerotic lesions (Vekic *et al*., 2023).

Phenylhydrazine (PHZ) is a commonly used experimental haemolytic drug that induces a systemic oxidative state by generating free radicals that affect hepatic and other tissue lipid metabolism and erythrocyte function. PHZ-induced haemolysis releases free haemoglobin and haem iron into circulation, which act as catalytic substrates for Fenton chemistry and widespread lipid peroxidation. The liver, as the principal site of lipoprotein production and processing, is particularly vulnerable to PHZ-induced oxidative hepatotoxicity, resulting in alterations in cholesterol homeostasis, lipoprotein assembly, and the activity of enzymes involved in lipid regulation (Berger, 2007; Hamzah *et al*., 2018). Thus, PHZ-induced dyslipidaemia represents a mechanistically relevant, experimentally validated model for the study of oxidative disruption of lipid metabolism and lipid-regulatory potential of antioxidant interventions.

Celosia argentea Linn. (family Amaranthaceae) is a common leafy vegetable in West Africa and has a phytochemical profile associated with numerous lipid-regulatory mechanisms. *Celosia argentea* is known as "sokoyokoto" (Yoruba), "inine" (Igbo) and "farar kalangu" (Hausa) in Nigeria. Its main bioactive components include: (i) triterpenoid saponins (oleanolic acid and its glycosides, celosin E, F, G) which are known as inhibitors of intestinal cholesterol absorption and as bile acid sequestrants; (ii) flavonoids (quercetin, luteolin, rutin, kaempferol) which modulate HMG-CoA reductase activity, enhance hepatic LDL receptor expression, and provide antioxidant protection against LDL oxidation; (iii) phenolic acids (gallic acid, caffeic acid, chlorogenic acid) which are potent inhibitors of lipid peroxidation and protect lipoprotein particles from ROS-mediated oxidative modification; and (iv) betalains, nitrogen-containing antioxidants that may contribute to membrane-associated lipid protection (Supriya *et al*., 2018; Ying *et al*., 2016; Mueangnak *et al*., 2025). Furthermore, the fibre content of *C. argentea* (1.8 g/100 g) also supports cholesterol lowering by binding bile acids in the intestinal lumen, thus decreasing enterohepatic cholesterol recycling. The molecular phytochemical richness of *C. argentea* has not been previously examined for its lipid-regulating action on PHZ-induced oxidative dyslipidaemia.

Dyslipidaemia is a major cardiovascular risk factor in Nigeria and sub-Saharan Africa and remains inadequately investigated. Cost and availability significantly limit access to evidence-based lipid-lowering medicine. Simultaneously, the PHZ-induced oxidative dyslipidaemia is a well-established experimental model for evaluating the lipid-modulatory effects of plant-derived therapeutics in a

controlled pro-oxidant milieu. A wide spectrum of phytochemicals, including saponins, flavonoids, and phenolic acids, has been identified in *C. argentea* and is known to impact cholesterol metabolism through various molecular processes. However, thus far, no study has comprehensively assessed the effects of *C. argentea* on the full serum lipid profile (TC, TG, LDL-C and HDL-C) in the setting of PHZ-induced oxidative dyslipidaemia. The absence of this evidence is a key scientific gap that hinders the appraisal of the plant as a nutraceutical candidate for the management of dyslipidaemia and reduction of cardiovascular risk in resource-limited settings. Against this background, this study aims to evaluate the lipid-modulating effects of aqueous leaf extract of *Celosia argentea* in phenylhydrazine-induced dyslipidaemia in Wistar rats and its implications for cardiovascular risk management.

II. MATERIALS AND METHODS

Plant Material and Extraction

Fresh leaves of *Celosia argentea* were purchased in Auchi, Edo State and identified by a taxonomist in the Department of Plant Biology and Biotechnology, Edo State University, Uzairue. The Fresh leaves were thoroughly rinsed, air-dried at room temperature (24ºC), then pulverized into a fine powder using a manual blender and weighed. Aqueous extracts of the plants were prepared by soaking 2000g of the dry, powdered plant material in 10 litres of double-distilled water and incubating at room temperature for 48 hours (to ensure thorough extraction). At the end of the 48 hours, the extracts were first filtered through a Whatman No. 42 filter paper (125mm) and then through cotton wool. The filtrate was then concentrated using a rotary evaporator set at 40ºC to one-tenth its original volume, and finally in a freeze-drier. The dried residue (crude extract) was then stored at 4ºC afterwards. Aliquot portions of the crude plant extract residue were weighed at 276.5g and dissolved in normal saline for use on each day of the experiments.

Experimental Animals

In the experiment, sixty (60) adult male Wistar rats, randomly assigned into six (6) groups of ten (10) animals, were employed as experimental animals. At the start of the study, they weighed between 110 and 220 grams. The animals were acquired and placed in washed and disinfected conventional cages at the Department of Anatomy's Animal House, Edo State University. The rats were allowed to acclimate for two (2) weeks before the commencement of the treatment. All animals were fed livestock growers' mash (Top Feed Limited, Sapele, Delta State, Nigeria) and water.

Experimental Design

After acclimatization to laboratory conditions for three days, animals were randomly divided into the following groups:

Group 1 (control): Normal control (without treatment) received normal saline orally once daily.

Group 2: Anaemic control (without treatment), but also received normal saline orally once daily.

Group 3: Anaemic rats treated with 400 mg/kg of the leaf extract of *Celosia argentea* orally once daily for 14 days.

Group 4: Rats treated with 400 mg/ kg of *Celosia argentea* orally once daily for 14 days and thereafter induced PHZ from day 12 for three consecutive days.

Group 5: anaemic rats treated with Vitamin C in a dose of 100 mg/kg orally once daily for 14 days.

Group 6: Non-anaemic rats treated with 400 mg/kg of the leaf extract of *Celosia argentea* orally once daily for 14 days.

Administration was done at 9:00–10:00 am each day. The animals' body weight was measured on the first and last days. Morphological and behavioural changes were monitored daily.

Sacrifice of Rats

The rats were euthanized 24 hours after the last extract treatment (day 15). Euthanasia was by cervical dislocation, and blood was collected in EDTA (haematology) and plain tubes (serum) via the ocular vein without the use of an anticoagulant. The blood collected in plain tubes was allowed to stand for 45 min before being centrifuged at 5,000 rpm for 45 min to obtain serum for analysis. Serum was stored at -20ºC until analyzed.

Lipid Profile Assays

Estimation of Serum Total Cholesterol in Plasma Sample

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The total cholesterol in plasma samples was estimated based on enzymatic hydrolysis and oxidation. Cholesterol reacts to form a coloured quinoneimine complex, the intensity of which is proportional to cholesterol concentration. Blank, standard, and sample tubes are prepared using distilled water, a cholesterol standard, a plasma sample, and a reagent. After incubation at 37 °C, absorbance is read at 500 nm against the reagent blank. Cholesterol concentration is calculated using the standard value of 200 mg/dl.

Estimation of Serum Triglycerides

Serum triglycerides were quantified using an enzymatic colourimetric method. Blank, standard, and test sample mixtures were prepared by combining specified volumes of distilled water, triglyceride standard, serum sample, and reagent. The reagent catalyzes the enzymatic reaction that generates a colored product, the intensity of which is proportional to the triglyceride concentration. Absorbance of the reaction mixtures is measured spectrophotometrically, with the reagent blank used to calibrate the instrument and the standard used as a reference for quantification.

HDL-Cholesterol Estimation

The estimation of high-density lipoprotein (HDL) cholesterol in serum was carried out using a precipitation-based method. The assay involves pipetting defined volumes of serum sample or cholesterol standard along with a precipitating reagent into test tubes. The reagent selectively precipitates non-HDL lipoproteins, leaving HDL cholesterol in the supernatant for subsequent quantification. The standard serves as a reference for calculating HDL cholesterol concentrations in the test samples.

LDL-Cholesterol Assay

The estimation of low-density lipoprotein (LDL) cholesterol in serum was carried out using an enzymatic colorimetric assay. The assay involves preparing a reagent blank, a standard, and a test sample by combining specified volumes of distilled water, serum or standard supernatant, and reagent. The reagent reacts with LDL cholesterol to produce a coloured complex, the intensity of which is proportional to the LDL concentration. Absorbance measurements of the mixtures allow for quantification, with the blank used to calibrate the spectrophotometer and the standard serving as a reference for calculation.

Statistical Analysis

Data obtained from this study were expressed as mean value ± standard deviation. Differences between means of groups were determined by One-way ANOVA and Tukey multiple comparison Post-Hoc Test using the IBM Statistical Package for the Social Sciences (SPSS) version 24. Differences in means were considered significant at $p < 0.05$.

III. RESULTS

A. Effect on Total Cholesterol and Triglycerides

PHZ administration significantly elevated serum TC (105.33 ± 5.03 mg/dl) compared to the normal control (66.00 ± 11.38 mg/dl), confirming PHZ-induced hypercholesterolaemia. TC was markedly reduced in all treatment groups: PHZ + CA (71.00 ± 7.81 mg/dl), CA + PHZ (59.71 ± 5.15 mg/dl), and PHZ + Vitamin C (72.80 ± 12.52 mg/dl), all significantly lower than the anaemic control ($p < 0.05$). The non-anaemic + CA group maintained TC within the normal range (62.33 ± 6.84 mg/dl). Notably, triglycerides were lower in the anaemic control (60.33 ± 23.62 mg/dl) compared to normal controls (92.00 ± 15.21 mg/dl), a finding that likely reflects PHZ-mediated disruption of VLDL assembly and TG secretion. CA treatment partially restored TG toward normal values (PHZ + CA: 73.20 ± 16.02; CA + PHZ: 46.16 ± 12.04 mg/dl).

B. Effect on HDL and LDL Cholesterol

PHZ induced a marked elevation in LDL-C (55.00 ± 3.00 mg/dl) relative to normal controls (16.25 ± 3.20 mg/dl), consistent with impaired LDL receptor-mediated hepatic clearance and oxidative LDL modification. All treatment groups showed significant reductions in LDL-C: PHZ + CA (38.67 ± 0.58 mg/dL), CA + PHZ (34.75 ± 6.65 mg/dL), and PHZ + Vitamin C (26.75 ± 6.24 mg/dL). HDL-C declined modestly in PHZ-treated rats (32.67 ± 2.87 vs 37.40 ± 2.51 mg/dl), consistent with PHZ-related LCAT oxidative inhibition. HDL-C partially recovered in all treatment groups, with the PHZ + CA group achieving 35.75 ± 2.06 mg/dl and the non-anaemic + CA group demonstrating values comparable to normal controls (35.56 ± 1.51 mg/dl).

Table 1: Effect of *C. argentea* on Serum Lipid Profile Parameters in PHZ-Induced Dyslipidaemia

Animal Group	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Normal Control	66.00±11.38^{ab}	92.00±15.21^{c}	37.40±2.51^{c}	16.25±3.20^{a}
Anaemic Control (PHZ)	105.33±5.03^{c}	60.33±23.62^{ab}	32.67±2.87^{a}	55.00±3.00^{d}
PHZ + CA	71.00±7.81^{ab}	73.20±16.02^{abc}	35.75±2.06^{bc}	38.67±0.58^{c}
CA + PHZ	59.71±5.15^{a}	46.16±12.04^{a}	34.00±1.58^{ab}	34.75±6.65^{c}
PHZ + Vitamin C	72.80±12.52^{b}	60.00±34.33^{ab}	34.60±1.77^{ab}	26.75±6.24^{b}
Non-anaemic + CA	62.33±6.84^{ab}	85.33±10.05^{bc}	35.56±1.51^{c}	17.50±2.52^{a}

Values are mean ± SD (n = 6). Different superscript letters indicate significant differences (p < 0.05, One-way ANOVA with Duncan's post-hoc test). TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; CA: Celosia argentea*; PHZ: Phenylhydrazine.*

IV. DISCUSSION

The observed substantial increases in TC and LDL-C and the concomitant reduction in HDL-C in PHZ-treated rats constitute a pro-atherogenic lipid profile, consistent with PHZ's mechanistic potential to induce systemic oxidative stress and affect hepatic lipid metabolism. Free radicals from PHZ, especially phenyl radicals and superoxide anions, promote lipid peroxidation of hepatocyte membranes and circulating lipoprotein particles, thereby influencing the enzymatic mechanisms of cholesterol homeostasis at multiple steps (Hamzah *et al*., 2018; Vekic *et al*., 2023).

The 59.6% increase in total cholesterol (from 66.00 to 105.33 mg/dl) suggests increased de novo hepatic cholesterol synthesis and decreased LDL receptor-mediated cholesterol clearance. Hepatic SREBP-2 overexpression under oxidative stress increases cholesterol production and HMG-CoA reductase expression. On the other hand, concomitant oxidative alteration of LDL particles leads to decreased recognition by the traditional hepatic LDL receptor, and hence to an increase in circulating LDL-C (Berberich & Hegele, 2022). The lipid peroxidation induced by PHZ leads to the formation of oxidized LDL (Ox-LDL), which is recognized by macrophage scavenger receptors (SR-A and CD36) and is selectively internalized by macrophages in the arterial intima, resulting in foam cell formation and the development of atherosclerotic plaques, a well-established process in the oxidative modification hypothesis of atherogenesis (Babakr, 2025; Vekic *et al*., 2023).

The 3.4% increase in LDL-C (from 16.25 to 55.00 mg/dl) is particularly concerning for cardiovascular risk. Banach *et al*. (2023) stated that LDL particles are the main cause of atherosclerotic cardiovascular disease and that there is a continuous and causal relationship between cardiovascular risk and LDL-C concentrations (Piko *et al.*, 2023). The magnitude of PHZ-induced increases in LDL reflects a clinically meaningful atherogenic risk that correlates with cardiovascular sequelae found in animal models of extended PHZ exposure.

The small drop in HDL-C induced by PHZ must be carefully examined at the mechanistic level. The cardioprotective role of HDL relies not only on its serum levels but also critically on its functional integrity, especially its capacity to induce reverse cholesterol transport (RCT) by stimulating the process of cholesterol efflux from macrophage foam cells through ABCA1 and ABCG1 transporters (Maduado *et al*., 2024) and its antioxidant, anti-inflammatory and

endothelial-protective properties. PHZ-induced ROS oxidatively modify apolipoprotein A-1 (Apo A-1), the major structural and functional protein of HDL, impairing its interaction with ABCA1 and reducing its ability to promote cholesterol efflux, despite only small decreases in absolute HDL-C levels. This dysfunctional HDL phenotype, characterized by near-normal HDL levels but poor quality, may be an underestimated contributor to PHZ-induced atherogenic risk.

The unexpected decrease in TG levels in the anaemic PHZ group (60.33 mg/dl) compared with normal controls (92.00 mg/dl) warrants further investigation. PHZ-induced oxidative liver damage may disrupt microsomal triglyceride transfer protein (MTP) activity and inhibit VLDL formation. This key enzyme loads triglycerides onto the apolipoprotein B (ApoB) as VLDL is synthesized. Decreased MTP activity reduces hepatic VLDL-TG production, leading to lower circulating TG levels despite intrahepatic TG accumulation. Also, splenic haemolysis and the haematopoietic system's stress response may alter lipoprotein metabolism, leading to a transient fall in circulating triglycerides. This observation is consistent with findings in acute haemolytic situations in which the conflicting metabolic needs of tissue haem-iron handling and compensatory erythropoiesis constantly alter lipoprotein profiles.

The saponins of *C. argentea* have a well-characterised lipid-regulatory mechanism: they can form insoluble micellar complexes with cholesterol in the intestinal lumen, thereby decreasing the bioavailability of dietary and biliary cholesterol for uptake by enterocytes. Triterpenoid saponins, such as oleanolic acid glycosides (celosin E, F, G) isolated from *C. argentea*, are structurally similar to bile acids and competitively inhibit cholesterol micellarisation, thus reducing ileal cholesterol absorption and increasing faecal cholesterol excretion (Ying *et al*., 2016; Xiao *et al*., 2025). This procedure is similar to the pharmacological action of ezetimibe, which prevents the Niemann-Pick C1-like 1 (NPC1L1) transporter in enterocytes, and to dietary phytosterols, which competitively displace cholesterol in intestinal micelles. Saponins prevent the absorption of cholesterol and reduce hepatic delivery of cholesterol from the intestine, resulting in stimulation of hepatic LDL receptor expression by upregulating SREBP-2 and enhanced clearance of LDL-C from the bloodstream. This is an ancillary mechanism that augments the direct reduction in TC and LDL-C observed in CA-treated groups.

In summary, the flavonoids of *C. argentea*, mainly quercetin, luteolin, rutin and kaempferol, control the hepatic cholesterol metabolism through at least two converging molecular routes. The first step is inhibition of HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway of endogenous cholesterol synthesis. Recent molecular modelling and in vitro studies suggest that quercetin and related flavonols bind to the active site of HMG-CoA reductase, thereby reducing endogenous cholesterol synthesis in hepatocytes via a mechanism partially analogous to that of statins, but with reduced potency and a better safety profile (Xiao *et al*., 2025). The second is an increase in hepatic LDL receptor (LDLR) expression. Bjune et al. (2024) demonstrated that dietary flavonoids regulate LDLR expression via structure-specific mechanisms. Flavonoids with catechol moieties, such as quercetin in *C. argentea*, have been shown to induce LDLR gene transcription via PCSK9-independent mechanisms, thereby increasing hepatic LDL-C uptake and plasma clearance. The observed dramatic decreases in LDL-C levels in the CA-treated groups are due to the synergistic reduction in hepatic cholesterol production and increased LDL clearance from the circulation via the LDL receptor.

The phenolic acids (gallic acid, caffeic acid and chlorogenic acid) and betalains present in *C. argentea* constitute an important antioxidant barrier that directly prevents the PHZ-induced oxidative modifications of lipoprotein particles. These compounds scavenge lipid peroxyl radicals (LOO•) at the initiation and propagation phases of LDL lipid peroxidation, thus maintaining the native recognition of LDL by the classical LDL receptor and diverting its clearance away from the atherogenic macrophage scavenger receptor pathway (Vekic *et al*., 2023). Simultaneously, the antioxidant shield provided by apolipoprotein A-1 maintains the structural integrity of HDL and enhances cholesterol efflux via ABCA1/ABCG1 during reverse cholesterol transport (Maduado *et al*., 2024). This antioxidant lipoprotein protection occurs in addition to

the saponin and flavonoid pathways, creating a multi-layered lipid-protective effect that exceeds the efficacy of any single phytochemical class acting alone. The greater fall in TC and LDL-C in the CA + PHZ (pre-treatment) groups compared with the PHZ + CA (post-treatment) groups supports the antioxidant hypothesis: pre-existing antioxidant phytoconstituents are effective in reducing oxidative stress due to subsequent PHZ administration, leading to less lipid peroxidation and its dyslipidaemic effects.

The dietary fibre content of *C. argentea* (1.8 g/100 g) is low yet contributes to lowering cholesterol by sequestering bile acids in the intestinal lumen. Soluble fibres bind bile acids, produced from hepatic cholesterol, in the intestine and prevent their reabsorption in the ileum and enterohepatic recycling, increasing hepatic cholesterol demand for bile acid synthesis. This results in depletion of hepatic cholesterol pools, then upregulation of LDL receptor expression, and increased plasma LDL-C clearance, a pharmacological mechanism of action for cholestyramine and other bile acid sequestrant resins (Berberich & Hegele, 2022). The route, although presumably less potent than the saponin and flavonoid pathways in the aqueous extract, also contributes to the dietary lipid-lowering effects observed.

The partial recovery of HDL-C in *C. argentea*-treated groups is clinically relevant and needs a molecular explanation. HDL has cardioprotective effects through a complex mechanism that includes (i) promotion of reverse cholesterol transport (RCT) efflux of excess cholesterol from macrophage foam cells in arterial walls to the liver for biliary excretion via cholesterol efflux (ABCA1/ABCG1) and hepatic SR-BI uptake; (ii) antioxidant properties via HDL-associated enzymes (paraoxonase-1 [PON1], platelet-activating factor acetyl hydrolase [PAF-AH]) that hydrolyze oxidized lipids and protect LDL from oxidation; (iii) anti-inflammatory actions via inhibition of vascular cell adhesion molecule expression; and (iv) endothelial protection via nitric oxide (NO) stimulation (Maduado *et al*., 2024).

While the absolute HDL-C content decreases slightly, the decrease in HDL-C by PHZ is presumably attributed to oxidative alteration of Apo A-1 by the ROS produced by PHZ, which inhibits the interaction of Apo A-1 with ABCA1 and decreases the cholesterol efflux capacity. The phenolic antioxidants of *C. argentea* scavenge the reactive oxygen species and prevent oxidative modification of Apo A-1 before they can react with the apolipoprotein methionine residues necessary for LCAT activation and cholesterol esterification. The recovery of HDL-C in CA-treated groups observed in this study would be likely to reflect both quantitative restoration of circulating HDL particles and qualitative preservation of HDL functionality. However, direct measurement of cholesterol efflux capacity and HDL-associated enzyme activities (PON1, PAF-AH) in future studies would validate this mechanistic interpretation.

There are significant trends in lipid values between the *C. argentea* and Vitamin C groups. Both PHZ + CA (71.00 mg/dl) and PHZ + Vitamin C (72.80 mg/dl) had similar decreases in total cholesterol from the PHZ baseline (105.33 mg/dl), showing similar antioxidant processes that lower total cholesterol by protecting hepatic lipid-regulatory enzymes. The greatest decrease in LDL-C (26.75 mg/dl, closest to normal) was observed with vitamin C compared with PHZ + CA (38.67 mg/dl), suggesting that the direct radical-scavenging ability of ascorbic acid may more efficiently prevent LDL oxidation and promote LDL receptor-mediated clearance than the more complex formulation of *C. argentea* at the 400 mg/kg dose. However, the lowest total cholesterol (TC) (59.71 mg/dl) and low-density lipoprotein cholesterol (LDL-C) (34.75 mg/dl) were observed in the combination of CA and PHZ pre-treatment among all treatment groups, including Vitamin C, thus emphasizing the efficacy of preventive phytochemical conditioning prior to toxin exposure. The study strategy was validated by the comparable efficacy of *C. argentea* and Vitamin C in the key lipid measures. In all groups, the main pharmacologic mechanism was antioxidant-mediated lipid protection.

V. CONCLUSION

The aqueous leaf extract of *Celosia argentea* (400 mg/kg) exhibits significant multifaceted lipid-modulating effects in PHZ-induced dyslipidaemia in Wistar rats, resulting in substantial reductions in total cholesterol and LDL cholesterol, a partial restoration of HDL cholesterol, and the normalization of

triglycerides to physiological levels, with effects largely analogous to those of Vitamin C. The mechanisms regulating lipids are complex: inhibition of intestinal cholesterol absorption by saponins; suppression of HMG-CoA reductase and upregulation of LDL receptors by flavonoids; antioxidant protection of LDL and HDL particles from oxidative modification by phenolic compounds and betalains; and bile acid sequestration by dietary fibre. The lipid-modulating efficacy of *C. argentea* is demonstrated in both post-PHZ therapeutic and pre-PHZ protective contexts, affirming its role as both a treatment and a preventative nutraceutical. In light of the increasing burden of dyslipidaemia and the significant pharmaceutical treatment gap in sub-Saharan Africa, these findings offer a robust scientific rationale for considering *C. argentea* as an evidence-based dietary and nutraceutical intervention for cardiovascular risk management. Molecular mechanistic research, dose-response analyses, bioavailability evaluations, and finally clinical trials are necessary to determine its therapeutic potential comprehensively.

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