Lipid and cardiac profile assessment following the co-administration of Cisplatin and methanolic extract of *Portulaca oleracea* in adult Wistar rats: an experimental study

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**ABSTRACT**

**Introduction:** There is a need for continual evaluation of the effective use of plant-based medicine as combination therapies as more therapeutic potentials are being associated with phytomedicine. The changes in the lipid and cardiac profile of adult Wistar rats following the co-administration of Cisplatin and methanolic extract of *Portulaca oleracea* (MEPO) were investigated.

**Methods:** Twenty-four (24) rats with an average weight of 154 kg were randomly divided into six (6) groups (A-F). Group A was given no treatment and served as the normal control group. Group B received only a cisplatin injection and served as the cisplatin control group. Group C and D were given 400 mg/kg and 800 mg/kg MEPO six hours after cisplatin injection. Group E and F were administered 400 mg/kg and 800 mg/kg MEPO 6 hours before cisplatin injection. All cisplatin injections were single-dose intraperitoneal injection (2 ml/kg) and MEPO administration lasted for 7 days. Animals were euthanized under diethyl ether anesthesia at the end of the experiment and blood collected for serum lipid profile investigations. Some cardiac and lipid parameters were estimated from standard formulae.

**Results:** There was a significant increase in the serum levels of TG and TC (p=0.01 and p < 0.001) and some estimated parameters – LDL, VLDL, CRR, HDL-LDL and TG-HDL (p<0.001, p<0.049, p<0.001, p<0.001 and p=0.001 respectively) while HTR was significantly decreased (p<0.001) due to cisplatin treatment. LDL and AI levels were unchanged by cisplatin treatment. MEPO significantly reversed (p<0.05) the cisplatin-induced changes in the serum lipid parameters (TG and TC) and estimated parameters (VLDL, CRR and TG-HDL) across all MEPO-treated groups.

**Conclusion:** MEPO shows evidence of attenuating cisplatin-induced hyperlipidemia and cardiac risk.

**Keywords:** *Portulaca oleracea*, Purslane, hyperlipidemia, Cisplatin, lipid profile, cardiac profile

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**INTRODUCTION**

Advancements in modern therapeutics have encouraged a global search for natural remedies against different illnesses and diseases.¹ The cost, accessibility and side effects of some orthodox medical drugs have further increased the need for alternative therapeutic intervention. Herbs have been described as a powerhouse of nutrition. If used wisely and regularly can replace costly pills, supplements, and even some drugs.² Among known medicinal plants, *Portulaca oleracea* (PO) is one that should fascinate researchers. PO, commonly known as Purslane, is listed as one of the most used medicinal plants by the World Health Organization and has been given the term “global panacea” for its numerous medicinal attributes.³

PO contains numerous biologically active compounds like flavonoids, saponins, alkaloids, cardiac glycosides, vitamins (A, C, and E), calcium, magnesium, and other minerals.⁴⁵ PO has been reported to possess several biological properties like anti-septic, diuretic,⁶ antioxidant, anti-inflammatory, bronchodilatory, and analgesic effects.⁷⁸ The plant is also a very rich source of omega-3 fatty acids, a compound that has been shown to reduce the risk of sudden death caused by coronary heart disease.⁹ Other reported properties of *Portulaca oleracea* include antispasmodic, anti-bacterial, anti-scrotular,¹⁰¹¹ and hypcholesterolemic effects.¹² Cisplatin is a platinum-containing anticancer agent used in the treatment of varying forms of cancer.¹³ Cisplatin exerts severe toxic side effects against cells of the body, and often triggers apoptosis by reacting in vivo, binding to and causing crosslinks of DNA.¹⁴ Asides well-known major side effects of Cisplatin like nephrotoxicity, hepatotoxicity, and neurotoxicity; disorders like dyslipidemia, acute coronary syndrome, acute vascular toxicity, and cardiotoxicity have been reported in patients on Cisplatin chemotherapy.¹⁵¹⁶ Cisplatin has been reported to trigger cardiotoxicity through lipid
peroxidation and direct induction of oxidative stress on cardiac cells, which causes physical injury and damages to myocytes. The drug has also been reported to elevate levels of cholesterol, triglycerides, and low-density lipoprotein. A study by Hanchate and colleagues recommended regular cardiovascular monitoring of patients on Cisplatin therapy due to its effect on the cardiovascular system and lipid profile. The continuous treatment of different kinds of solid tumors with high-dose Cisplatin chemotherapy has necessitated the need to investigate agents that can safely and effectively reverse or neutralize different toxic side effects of Cisplatin without altering its anticancer efficacy. This study investigated changes in the lipid and cardiac profile of adult Wistar rats following the co-administration of Cisplatin and methanolic extract of Portulaca oleracea (MEPO).

**METHODS**

This experimental study was carried out in the research laboratory of the Department of Anatomy, Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, College of Health Science, Nnewi Campus, Anambra State and lasted about three months as part of a thesis in the Anatomy Department of Nnamdi Azikiwe University.

The aerial parts of the plant (Portulaca oleracea) were obtained from marshy areas at Awka, Anambra state. The botanical identification and authentication were confirmed in the Department of Pharmacognosy and Traditional Medicine, College of Pharmacy, Nnamdi Azikiwe University, Agulu Campus, Anambra State, Nigeria, with reference number PCG477. A large amount of the harvested plant was washed free of soil, roots separated from the aerial part. Fresh aerial parts of Portulaca Oleracea were cut into smaller parts (for easy drying), shade-dried for two weeks, and finely powdered with a mechanical grinder yielding 300g of powder. Methanolic extract of the powdered Portulaca oleracea (270g) was prepared using the soxhlet apparatus, and the extract concentrated using a rotary evaporator at a reduced pressure of 40°C yielding 40 g dry extract. The extract was made up of solution at varying doses per ml on each day of administration and given according to body weight and group treatment doses.

Cisplatin injection (Zuplatin, 50 mg/50 ml) manufactured by Taj pharmaceuticals Limited India was obtained from Christ the king pharmacy, Nnewi, Anambra State, Nigeria, and was certified by the Faculty of pharmacy, Nnamdi Azikiwe University, Agulu Campus.

Twenty-four (24) female Wistar rats were obtained from the animal house of College of Health Sciences, Nnamdi Azikiwe University, Okofia Nnewi Campus and acclimatized for two (2) weeks (to exclude any intercurrent infection) under standard housing condition (ventilated room with 0-12/12-hour light/dark cycle at 24 ± 2°C). The rats were fed ad libitum with water and standard rat chow.

The aforementioned 24 rats with an average weight of 154 g were randomly divided into six (6) groups (A-F). Group A was given no treatment and served as the normal control group. Group B received only a cisplatin injection and served as the cisplatin control group. Group C and D were given 400 mg/kg and 800 mg/kg MEPO six hours after cisplatin injection. Group E and F were administered 400 mg/kg and 800 mg/kg MEPO 6 hours before cisplatin injection. All cisplatin injections were single-dose intraperitoneal injection (2 ml/kg), while all MEPO administration were done orally for seven days using the oral cannula. The animals fasted overnight after the 7th day of drug administration, and on the 8th day, a 5 ml blood sample was collected from each animal by cardiac puncture into centrifuge tubes after euthanization under diethyl ether anaesthesia. The blood samples were allowed to stand for 15 minutes at 25°C, and the serum was separated and kept in plastic vials at -20°C until analysis after allowing for centrifugation at 4000 rpm for 20 minutes.

Serum values of high-density lipoprotein (HDL), total cholesterol (TC) and triglycerides (TG) were measured using a standard biochemical enzymatic method. Low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were calculated by Friedwald’s formula as VLDL = TG ÷ 5; LDL= TC - (VLDL + HDL). Cardiac risk ratio (CRR) and Atherogenic index (AI) were both given as CRR = TC ÷ HDL; AI = log

All data were analyzed using IBM SPSS (version 21), and values were expressed as mean ± standard error of the mean. The difference between groups was determined using a one-way analysis of variance (ANOVA). All tests were considered significant at p<0.05.

The experimental procedures of this study complied with ARRIVE guidelines, National Institutes of Health (NIH) guidelines, and National Health Research ethics committee of Nigeria (NHREC) guidelines for the care and use of laboratory animals. Animal health status was monitored throughout the experiment according to the federation of European Laboratory Animal
Science Associations (FELASA) guidelines.\textsuperscript{24} The ethical approval for this study was obtained from the Research Ethics Committee of Anatomy Department, Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus. AREC Registration Number: AREC/ANA/2019/0017. No informed consent was required for this study.

**RESULTS**

Animals in groups A, C, D, E and F all had a significant weight increase when the pre and post-administration body weight were compared, while animals in group B (treated with Cisplatin only) showed no significant change in body weight compared to the normal control (p<0.05) (Table 1).

| Groups          | MEAN±SEM (g) | p-VALUE | t-VALUE |
|-----------------|--------------|---------|---------|
| A (Normal Control) |              |         |         |
| Pre-administration | 150.20±1.172 | 0.009*  | -10.654 |
| Post-administration | 166.07±0.64  | 0.060   | 3.912   |
| B (Cisplatin Control) |            |         |         |
| Pre-administration | 150.07±1.10  | 0.030*  | -5.691  |
| Post-administration | 143.90±0.70  | 0.009*  | -10.429 |
| C (MEPO 400 A)  |              |         |         |
| Pre-administration | 152.00±1.15  | 0.030*  | -5.691  |
| Post-administration | 175.00±2.89  | 0.009*  | -10.429 |
| D (MEPO 800 A)  |              |         |         |
| Pre-administration | 155.80±0.12  | 0.004*  | -15.148 |
| Post-administration | 175.10±1.16  | 0.004*  | -15.148 |

Values were expressed as mean ± Standard error of the mean (SEM), and data were considered significant at P<0.05. MEPO means methanolic extract of *Portulaca oleracea*. * means significant at p<0.05.

Table 2. The lipid and cardiac parameters following the co-administration of Cisplatin and MEPO in adult Wistar rats

| Parameters | Group A (Normal Control) | Group B (Cisplatin control) | Group C (MEPO 400 A) | Group D (MEPO 800 A) | Group E (MEPO 400 B) | Group F (MEPO 800 B) |
|------------|--------------------------|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| HDL        | 43.09±1.59               | 42.39±1.58                  | 41.06±0.59           | 41.90±0.93           | 46.62±1.24*          | 50.71±1.45*          |
| LDL        | 20.76±3.72               | 46.20±3.05                  | 32.69±1.09*          | 52.87±1.38*          | 26.38±1.05*          | 20.30±1.19*          |
| VLDL       | 24.14±2.15*              | 33.03±3.63*                 | 25.17±0.68*          | 28.63±1.18           | 26.38±1.05*          | 24.06±1.42*          |
| TC         | 76.85±2.73               | 154.72±11.39                | 88.07±5.73*          | 122.72±12.0*         | 128.54±11.0*         | 115.9±5.03*          |
| TG         | 137.99±4.24*             | 149.20±4.57                 | 127.40±1.63*         | 135.54±3.45*         | 140.62±1.63          | 131.40±3.45*         |
| AI         | 0.50±0.03                | 0.54±0.01                   | 0.49±0.01*           | 0.51±0.00            | 0.47±0.01*           | 0.41±0.01*           |
| CRR        | 1.78±0.02*               | 3.67±0.36                   | 2.15±0.15*           | 2.93±0.04*           | 2.82±0.06*           | 2.29±0.19*           |
| HTR        | 56.08±0.68*              | 27.79±2.84                  | 47.00±2.98*          | 34.13±0.42*          | 35.47±0.75*          | 44.22±4.04*          |
| HDL/LDL    | 0.48±0.07*               | 1.09±0.06                   | 0.82±0.02*           | 1.26±0.02*           | 1.14±0.02*           | 0.40±0.01*           |
| TG-HDL     | 3.21±0.18*               | 3.52±0.06                   | 3.10±0.04*           | 3.23±0.02           | 3.02±0.10*           | 2.60±0.08*           |

Values are expressed as mean ± standard error of mean. HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein, TC = total cholesterol, TG = triglyceride, AI = atherogenic index, CRR = cardiac risk ratio and, HTR = HDL-cholesterol/total-cholesterol ratio. * means values were significantly different compared to the control group at p<0.05. * means values were significantly different compared to Cisplatin treated animals at p<0.05.

The lipid and cardiac marker results of each group are detailed in Table 2. In summary, there was no significant change in the HDL levels of all treated groups when compared to the normal control group except for group F, which was significantly higher than the control (p<0.05). The HDL levels of groups E and F were significantly increased compared to the cisplatin-only group (Table 2). LDL was significantly increased across all groups, except F, when compared to the normal control. Although it was significantly reduced across all groups except D when compared to the cisplatin control (p<0.05). VLDL levels were significantly increased in group B when compared to the control group but were reduced in all MEPO-treated groups when compared to Cisplatin only treatment.
group except in group D (p<0.05). TC levels were increased significantly in all the treated groups when compared to the control except for group C but decreased significantly across all groups when compared to the cisplatin control group (p<0.05). TG levels were significantly increased (p<0.05) in group B when compared to the normal control group but were reduced significantly across all groups except group E when compared to the cisplatin control group.

Overall, a similar pattern was observed in the four derived indexes. There was no difference seen in the AI ratio across all groups except E when compared to the normal control. However, the AI ratio in groups C, E and F was reduced significantly compared to the cisplatin control group (p<0.05). CRR was significantly increased in groups B, D and E when compared to the control group but were significantly decreased across all groups when compared to the cisplatin control group (p<0.05). The mean HTR was significantly decreased in all treated groups when compared to the control. However, all MEPO-treated groups showed a slightly increased HTR when compared to the Cisplatin control group (p<0.05). HDL-LDL ratio was significantly increased in group B and F when compared to the normal control. Groups C and F showed a significant decrease in HTR when compared to the cisplatin control group (p<0.05). TG-HDL ratio was significantly increased in the cisplatin control group (group B) when compared to the normal control group. However, when compared to the cisplatin control group, groups C, E, and F showed a significantly reduced TG-HDL ratio (p<0.05).

DISCUSSION

Lipid profile evaluation, particularly the assessment for hyperlipidemia, is commonly used to assess cardiovascular risks given the high correlation of hypercholesterolemia and hypertriglyceridemia with cardiovascular risk. A standard lipid cardiovascular risk assessment often involves the measurement of plasma or serum high-density lipoprotein (HDL), total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels. Also, novel indices like Cardiac Risk Ratio (CRR), Atherogenic Index (AI) and very-low-density lipoprotein (VLDL) are evaluated alongside the standard lipid profile to quantify blood lipid levels. They are optimal indicators of dyslipidemia, hyperlipidemia, atherosclerosis and cardiovascular diseases (CVDs). The casual relationship between elevated serum lipid levels and cardiovascular diseases like atherosclerotic plaques and coronary heart diseases has been well established over the years.

Increased lipid metabolism plays a critical role in weight reduction, and cytotoxic agents like Cisplatin have the potential of causing bodyweight loss. However, our study showed no significant difference (p=0.06) between the pre and post-administration body weights of the animals treated with Cisplatin alone, though the average post-administration body weight was slightly lower (143.90±0.69 g) than the pre-administration body weight (150.07±1.10 g) (Table 1). This finding drifted from several findings which have shown Cisplatin’s ability to cause a significant reduction in animal body weight. The drift observed in this study may be due to the low single dose of Cisplatin used (2 ml/kg) used. On the other hand, the administration of MEPO caused a significant increase in the body weight of animals across all MEPO-treated groups (p=0.03, 0.009, 0.01 and 0.004) (Table 1). This may be attributed to the presence of a high percentage of saponin in PO, which has been linked with a critical role in nutrient absorption.

Hyperlipidemia is characterized by elevated TC, TG, LDL, VLDL and a decreased level of HDL. It has been shown to increase cardiac risk ratio by up to ten times. Our result showed that the administration of Cisplatin causes hyperlipidemia, as evident in the significant elevation of serum LDL, VLDL, TG, and TC observed in group B (treated with Cisplatin only) when compared to the control group (p=0.00, 0.007, 0.01 and <0.001 respectively) (Table 2). The hyperlipidaemic effect of Cisplatin observed in the present study is comparable with the findings of Wang and co-authors, who reported a similar increase in serum LDL, TG, TC and VLDL following cisplatin treatment. The co-administration of MEPO was able to attenuate this observed hyperlipidaemic effect of Cisplatin. LDL and VLDL levels were significantly decreased in groups C, E and F when compared to Cisplatin control (group B). This finding agrees with the report of Movahedian and colleagues, who observed a similar decrease in LDL levels following the oral administration of 200, 400 and 800 mg/kg MEPO. TG level decreased significantly in groups C, D, and F (p=0.01, 0.01 and 0.003 respectively). Also, he TC levels were significantly decreased in all MEPO-treated groups (groups C to F) when compared to cisplatin control (<0.001, 0.003, 0.019 and 0.001) and normal control (p=0.217, <0.001, <0.001 and 0.001).

Our findings revealed no change in the HDL levels as a result of cisplatin treatment, as group B showed no difference in its mean HDL level compared to the control group (p=0.76). However,
HDL levels were increased significantly in groups E and F when compared to the cisplatin control group \((p=0.38\) and 0.001, respectively). HDL, also called the 'good cholesterol' transports cholesterol from tissues to the liver for catabolism through a reverse cholesterol transport process. An increased HDL level is desirable, being associated with a decreased risk of CVDs. The elevation of serum HDL levels following the administration of 400mg/kg and 800mg/kg MEPO before cisplatin injection is indicative of an anti-dyslipidemia potential of MEPO.

AI calculated as \(\log_{10}(TG/HDL)\) was found to be slightly higher in group B when compared to the control \((p=0.054)\). An increase in AI levels was observed in groups C and E. Increase AI has been reported to be associated with cardiovascular risks, thus our study provides preliminary evidence that cisplatin may not increase cardiovascular risks. This present study observed an increase in CRR \((p<0.05)\) due to cisplatin treatment, which was reversed across all MEPO treated groups (Table 2), indicating a direct reversal of the effect of cisplatin by MEPO. We also noted a significantly increased HDL/LDL and TG/LDL ratios in group B when compared to the control group \((p=0.001, <0.0001)\). The administration of MEPO significantly decreased HDL/LDL ratios across all MEPO-treated groups \((p<0.001)\) except group E when compared to the normal control; but increased only in groups D and E when compared to the cisplatin control group \((p=0.016, <0.0001)\). MEPO administration also caused a significantly decreased TG/LDL ratio in groups C, E and F when compared to group B but only group E when compared to the normal control \((p=0.01)\). Our study shows evidence of a reversal of a significantly reduced HTR following cisplatin administration. Except for group D, the mean HTR was significantly increased in all groups treated with MEPO \((p<0.001)\) (Table 2).

Most of the therapeutic properties of Portulaca oleracea have been attributed to its rich content of biologically active compounds like flavonoids, saponins, alkaloids and omega-3 fatty acids. The observed hypolipidaemic property of Portulaca oleracea may be due to its high content of saponins and flavonoids, both of which have been stated to be antioxidative and to reduce serum lipid levels, while saponins have been reported to interfere with the entero-hepatic circulation of cholesterol, thus preventing its absorption. Other constituents of MEPO like omega-3, ascorbic acid, β-carotene and glutathione have been shown to have antioxidant activity and this antioxidant property of MEPO may explain its hypolipidemic and cardio-protective effects as epidemiological evidence has implicated lipid peroxidation, especially the oxidation of LDL in the pathogenesis of atherosclerosis and congestive heart disease.

In summary, our study provided evidence of lipid profile changes caused by cisplatin administration. It causes significant increased LDL, VLDL, TC, TG, CRR, HDL-LDL ratio and TG-HDL ratio. It also caused a significant decrease in HTR but did not distort the AI and HDL levels. All these changes were observed with a single dose \((2 \text{ ml/kg})\) of cisplatin injection. More importantly, our study reported the efficacy of MEPO in attenuating the toxic effects of cisplatin on the lipid and cardiac parameters when administered at different doses. MEPO showed the most promising therapeutic potential against the above-described changes at the dose of 400mg/kg for VLDL, TC, TG, CRR and TG-HDL and 800mg/kg for TG. While MEPO showed more promising prophylactic potential at the dose of 400mg/kg for VLDL and TG-HDL and 800mg/kg for TG-HDL, HDL-LDL, CRR, TG, VLDL and LDL. There is a need for a high-powered clinical study to determine the best dose at which MEPO could achieve an optimal hypolipidaemic effect. It is important to note that the administration of MEPO also showed the potential of significantly increasing the HDL levels \((p=0.001)\) and decreasing AI \((p=0.000)\) at a higher dose of 800mg/kg when given before cisplatin injection.

Overall, we can say that MEPO offers protective or effective treatment for cisplatin toxicities depending on the dose and the time of administration through some cardiac and lipid profiles based on our findings could be equally affected at both doses used for this study – 400 and 800mg/kg. According to our findings, any dose of MEPO can reverse the toxic effects of cisplatin on TG levels more effectively when given after the cisplatin injection. The same is also true for VLDL and TG-HDL levels but when MEPO is given before cisplatin injection. From our study, animals administered 400mg/kg of MEPO after cisplatin injection, and 800mg/kg of MEPO before cisplatin injection showed the best lipid outcome with the least cardiovascular risks according to their lipid profiles though this argument could be contestable at this level of evidence. The mechanism behind the time and dose variations of these effects are yet to be understood. The protective and therapeutic effects of MEPO seen in this study against cisplatin-induced lipid and cardiac changes were seen with the crude extract of PO. There is a need to re-evaluate the claimed potency of MEPO using specific active compounds to make a more guided targeting of its effective component.  

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CONCLUSION
MEPO shows a clear protective and therapeutic potential in cisplatin-induced lipid and cardiac parameter changes. The result of the study reveals that MEPO had a dose-dependent protective and therapeutic hypolipidaemic effect against Cisplatin-induced hyperlipidemia. This evidence gives a lead for further investigations into the specific active component and mechanisms behind the effects and possible clinical experimentation of the identified compounds. PO may be useful not just in combination therapy with Cisplatin but also for acute dyslipidemia or hyperlipidemia if the mechanism of its dose-dependent efficacy is well understood.

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CONFLICT OF INTEREST
There is no conflict of interest to declare.

AUTHOR CONTRIBUTION
IAO and USN designed the study concept and protocol. IAO executed the project. JN analyzed the data and wrote the first draft. All the authors reviewed and approved the final draft of the manuscript.

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