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Effects of Aqueous Extract of Some Selected Vegetables on Halofantrine Hepato-cardiatoxicity in Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AJA, MSS designed the study, performed the statistical analysis, wrote the protocol, and write the first draft of the manuscript. Authors AMW and UL managed the analyses of the study. Authors AJA and UL managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: The protective effect of some selected vegetables {Moringa (*Moringa oleifera*), Cabbage (*Brassica oleracea*) and Tomato (*Solanum lycopersicum*)} against hepato-cardio toxicity of halofantrine (an antimalarial drug) was evaluated in 72 albino rats.
Study Design: The rats were grouped into eight of nine rats each. Three different doses; 7.1, 14.2 and 21.3mg/Kg of halofantrine were given to group II, III and IV respectively. Group V was co-administered with halofantrine and moringa extract 7.1 and 0.20mg/Kg respectively, Group VI co-administered with halofantrine and cabbage extract 7.1 and 0.10mg/Kg respectively, Group VII co-administered with halofantrine and Tomato extract 7.1 and 0.20mg/Kg respectively and Group VIII co-administered with halofantrine, moringa, cabbage and tomato extracts 7.1, 0.20, 0.10 and 0.20mg/Kg respectively). Group I was neither given the drug nor the vegetable extract serving as normal control.
Methodology: The liver and heart function indices were evaluated using standard methods.
Results: Serum liver enzymes, heart marker enzymes and concentration of malondialdehyde (MDA) were analyzed after 16, 96 and 192 hours of oral administration.

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Halofantrine administration caused significant increase ($p<0.05$) in the activities of all the enzymes with a peak at the 16th hour. Malondialdehyde had a peak at the 192 hours. The oral co-administration of vegetables extract showed a significant decrease ($p<0.05$) in the enzyme activities and concentration of malondialdehyde as compared sole administration of halofantrine. The result showed that Moringa, Cabbage and Tomato may have hepato and cardio protective effects against halofantrine toxicity. It may be concluded that consumption of vegetables may be beyond the nutritional needs but also for protective purposes.

Keywords: Halofantrine; hepato-cardiotoxicity; vegetables; malaria.

1. INTRODUCTION

Malaria is continuously associated with considerable morbidity and mortality, and significant socio-economic impact in developing countries. It is one the most important and oldest human diseases. According to the World Health Organization (WHO), malaria is endemic in 91 countries, predominantly in Africa, Asia and Latin America with about 40% of the world's population at risk [1]. It is caused by parasites that belong to the genius *Plasmodium* with four different species namely *Plasmodium falciparium, Plasmodium vivax, Plasmodium ovale*, and *Plasmodium malariae*. A large spectrum of clinical manifestations is observed, from asymptomatic infections stage to fulminant stage. The clinical characteristics of the infection depend on the *Plasmodium* species and on the age and immune status of the host. Clinical manifestations are linked to the replication cycles of the parasite. Rupture of infected red blood cells (iRBC) and release of toxic substances into the circulation are responsible for the repeated episode of chills, headaches and fevers, followed by profuse sweats [2]. The periodicity of this clinical presentation differs between species; either quartan cycle (*P. malariae*) or tertian cycle (*P. falciparum*, *P. vivax*, and *P. ovale*). The natural chronicity of these infections also leads to the development of splenomegaly, hepatomegaly, renal failure and severe anemia. Other complications, like acidosis, edema, respiratory problems, jaundice, hypoglycemia, and cerebral malaria (CM), can occur during a severe falciparum malaria episode [3].

Halofantrine, a lipophilic phenanthrene methanol belonging to the aryl amino alcohol is used for the treatment of acute uncomplicated multi-drug resistant malaria [4]. It is schizonticidal with high degree of activity against the erythrocytic stage of malarial infections caused by single or mixed infections of *Plasmodium falciparium* or *Plasmodium vivax.* It has limited effect against the exoerythrocytic or gametocyte stages of malaria parasites [5]. Clinical treatment with halofantrine is often accompanied by serious side effects such as abdominal pain, diarrhea, vomiting, rash, headache, and itching, elevated liver enzymes, prolongation of QTc interval and arrhythmias that could be fatal. However, an increasing number of reports describing serious complications in the last few years have raised some doubt about the safety of halofantrine [6]. Halofantrine has been reported to be cardiotoxic [6,7]. Also several studies have shown that other antimalarials such as chloroquine and quinine are hepatoxic [8,9]. Although halofantrine was reported as an effective antimalarial agent [10,11], but there are increasing reports of resistance to the drug by the malaria parasite [12]. The declining sensitivity of *P. falciparum* to halofantrine may necessitate an increase in dosage, but the hepato-cardiotoxic effects of the drug are a major concern, especially as they are plasma concentration-dependent [13] Uncomplicated malaria comprises the largest segment of the global malaria infestation (personal communication). Therefore it is important to devise strategies to prevent the further spread of halofantrine resistance and to delay its

onset in areas where the drug is still effective. One such approach is the use of combination therapy [7,14]. In order to find ways of reducing the hepato–cardio toxicity of halofantrine this study evaluated, the effect of its co–administration with some vegetables.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Albino rats weighing 100-120 grams were obtained from university of Jos, Plateau State and kept in the Animal House of Biological Science Department, Bayero University Kano, Nigeria. The rats were kept for two weeks to acclimatize before the commencement of the experiment.

2.2 Sample Collection and Preparation

The fresh vegetables (Moringa, Tomato and Cabbage) were obtained from Sharada Market, Municipal Local Government, Kano State, cleaned of dirt and blot, weighed and blended at room temperature (25ºC). The paste was filtered using cheesecloth and immediately evaporated by the use of Rotary evaporator and reweighed. The concentrations of the Moringa leaves, Cabbage leaves and Whole tomato extracts were adjusted to 0.05, 0.2 and 0.08g/ml respectively.

Halofantrine drug was purchased from a registered pharmaceutical store at Kofar Nassarawa, Kano Municipal Council and diluted to concentration of 5.0mg/ml. Three different doses of the drug, based on human dosage (mg/kg) were administered to review the pattern of its hepato-cardio toxicity.

2.3 Experimental Design

The seventy two (72) rats were randomly divided into eight (8) groups of nine (9) rats each.

Group I - Normal control, neither given the drug nor the extract (normal diet and Water only).
Groups II - Test control, orally administered with 7.10 mg/kg halofantrine drug
Group III – Test control, orally administered with 14.20mg/kg halofantrine drug
Group IV – Test control, orally administered with 21.30mg/kg halofantrine drug
GroupsV – Test control orally co-administered with halofantrine and Moringa extract; 7.10 and 0.20mg/Kg respectively.
Group VI – Test control orally co-administered halofantrine and cabbage extract; 7.10 and 0.10mg/Kg respectively.
Group VII – Test control orally co-administered halofantrine and tomato extract; 7.10 and 0.20mg/Kg respectively.
GroupVIII - Test control orally co-administer with halofantrine, Moringa extract, carbbage extract and tomato extract; 7.1, 0.20, 0.10 and 0.20 respectively.

Three rats were removed from each group after 16, 96 and 192 hours of administration and sacrificed. Serum was analyzed for liver marker enzymes; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities by the method of Reitman and Frankel [15], alkaline phosphatase (ALP) activity by the method of Rec [16] and cardiac marker enzymes; lactate dehydrogenase by the spectrophotometric (kinetic) method of Wroblewski and La

Due [17] as reported by Derek [18] and creatine kinase by the colorimetrical method of Ennor and Rosenberg [19] as reported by Derek [18] and serum malondialdehyde (MDA) by the method of Hunter et al. [20], modified by Guttridge and Wilkins [21].

2.4 Statistical Analysis

Results were statistically analyzed using ANOVA software developed by Microsoft Inc. P value of 0.05 was considered as significant.

3. RESULTS AND DISCUSSION

3.1 Results

Tables 1, 2 and 3 show the serum activities of liver maker enzymes {Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphate (ALP), heart marker enzymes; {Creatine kinase (CK) and Lactate dehydrogenase (LDH)}and concentration of Malondialdehyde (MDA) for G II-IV rats, administered with 7.1mg/Kg, 14.2mg/Kg and 21.3mg/kg halofantrine after 16, 96 and 192hours respectively, and a control GI which was not treated with the drug. There is significant difference (P=.05) in serum level of these parameters, commonly used as hepato – cardio toxicity indices between GI (control) and the test groups (II, III and V) 16 hours after oral administration of halofantrine. The result showed no significant difference (P=.05) in AST between G I and III, I and II as well as Groups II and III, within 96 hours of halofantrine administration. However, at 192 hours all the indices showed significant difference (P=.05) between the groups. Tables 4, 5 and 6 present the serum hepato–cardio toxicity indices for groups of rats treated with halofantrine and vegetable extracts concurrently for 16, 96 and 192hours.

The levels of ALP, CK and LDH in all the groups showed significant difference (P=.05) 16 hours after administration of extracts. There was no significant difference in ALT between Groups I and VI, V and VIII, V and VII as well as VII and VIII at 16hrs after extract administration. No significant difference was recorded in the levels of AST between Groups V and VII, V and VIII and also between VII and VIII within 16 hours of oral administration of the extracts. Similarly, the levels of MDA in Groups I and VI showed no significant difference after 16 hours of oral extract administration.

The results of oral administration of vegetable extract(s) after 96 hours revealed significant difference (P=.05) in all the parameters except in AST level, between Groups V and VIII, V and VI as well as VI and VIII. However, significant difference (P=.05) was recorded in all the parameters 192 hours after oral administration of extract(s), except for ALT in Groups V and VIII.

Table 1. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 16 hours after oral administration of Halofantrine drug

Group/treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
Group I	43.00[a]±0.09	16.00[b] ±0.02	1001.51[c] ±0.25	90.79[d]±0.02	17761.24[e]±0.13	6.49[f]±0.03
Group II	52.00[a] ±0.09	23.00[b] ±0.02	5737.73[c] ±0.36	19005.30[d]±0.37	14718.21[e] ±0.10	20.74[f] ±0.04
Group III	62.00[a] ±0.04	19.00[b] ±0.03	5235.41[c] ±0.43	705.72[d] ±0.07	12073.26[e] ±0.05	27.99[f] ±0.04
Group IV	94.00[a] ±0.02	13.00[b] ±0.02	4568.72[c] ±0.76	1109.48[d] ±0.28	15672.00[e] ±0.07	28.23[f] ±0.04

Results are in mean±SD, n=3 and values in the same column bearing similar superscript are significantly different at p<0.05

Table 2. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 96 hours after oral administration of Halofantrine drug

Group/treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
Group I	43.00[a]±0.09	16.00[b]±0.02	1001.51[e]±0.25	90.79[f]±0.02	17761.24[g]±0.13	6.49[h]±0.03
Group II	67.00[a]±0.05	16.00[c]±0.02	3316.60[e]±0.48	1646.67[f]±0.36	11183.60[g]±0.14	35.14[h]±0.04
Group III	77.00[a]±0.12	16.00[d]±	4214.83[e]±0.68	1188.58[f]±0.16	11945.02[g]±0.13	40.26[h]±0.01
Group IV	52.00[a]±0.09	13.00[b, c, d]±0.02	2314.72[e]±0.44	517.94[f]±0.01	14159.83[g]±0.12	57.46[h]±0.20

Results are in mean±SD, n=3 and values in the same column bearing similar superscript are significantly different at p<0.05

Table 3. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 192hours after oral administration of Halofantrine drug

Group/treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
Group I	43.00[a]±0.09	16.0[b]±0.02	1001.51[c]±0.25	90.79[d]±0.02	17761.24[e]±0.13	6.49[f]±0.03
Group II	94.00[a]±0.09	19.00[b]±0.04	3450.00[c]±0.60	1272.49[d]±0.17	10721.40[e]±0.05	35.87[f]±0.10
Group III	72.00[a]±0.08	13.00[b]±0.02	3946.80[c]±0.35	859.10[d]±0.17	10229.81[e]±0.10	48.09[f]±0.003
Group IV	48.00[a]±0.00	23.00[b]±0.03	3281.64[c]±0.06	878.02[d]±0.09	10876.36[e]±0.03	74.27[f]±0.25

Results are in mean±SD, n=3 and values in the same column bearing similar superscript are significantly different at p<0.05

Table 4. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 16 hours after oral administration of Halofantrine drug and vegetable extracts

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
I(Normal control)	$43.00^{a}\pm0.09$	$16.00^{i,j}\pm0.02$	$1001.51^{p}\pm0.25$	$90.79^{q}\pm0.02$	$17761.24^{r}\pm0.13$	$6.49^{s}\pm0.03$
II(Test control, 7.1mg/Kg halofantrine)	$94.00^{a,c}\pm0.09$	$19.00^{i,j}\pm0.04$	$3450.00^{p}\pm0.60$	$1272.49^{q}\pm0.17$	$10721.40^{r}\pm0.05$	$35.87^{s}\pm0.10$
V(7.1mg/Kg halofantrine +0.20mg/Kg moringa extract)	$21.00^{a,c,d}\pm0.04$	$89.00^{i,j,k}\pm0.02$	$6090.77^{p}\pm1.69$	$28.89^{q}\pm0.01$	$8351.63^{r}\pm0.00$	$3.93^{s}\pm0.09$
VI(7.1mg/Kg halofantrine +0.10mg/Kg cabbage extract)	$43.00^{b,c,d,g}\pm0.14$	$67.00^{i,j,k,n}\pm0.08$	$1078.61^{p}\pm0.10$	$235.24^{q}\pm0.07$	$5346.01^{r}\pm0.00$	$6.59^{t}\pm0.01$
VII(7.1mg/Kg halofantrine +0.20mg/Kg tomato extract)	$21.00^{a,c,e,g}\pm0.03$	$89.00^{i,j,l,n,o}\pm0.03$	$817.65^{p}\pm0.09$	$16.51^{q}\pm0.001$	$8708.30^{r}\pm0.01$	$11.71^{s}\pm0.04$
VIII (7.1mg/Kg halofantrine+0.20mg/Kg moringa+0.10mg/Kg cabbage+0.20mg/Kg tomato extracts)	$21.00^{a,c,f,g,h}\pm0.03$	$89.00^{i,j,m,n,o}\pm0.04$	$2570.25^{p}\pm0.00$	$134.95^{q}\pm0.04$	$3935.37^{r}\pm0.00$	$20.07^{s}\pm0.07$

Results are in mean±SD, n=3 and values in the same column bearing similar superscript are significantly different at p<0.05

Table 5. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 96 hours after oral administration of Halofantrine drug and vegetable extracts

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
Group I(Normal control)	$43.00^{a}\pm0.09$	$16.00^{b}\pm0.02$	$1001.51^{l}\pm0.25$	$90.79^{j}\pm0.02$	$17761.24^{k}\pm0.13$	$6.49^{l}\pm0.03$
II(Test control, 7.1mg/Kg halofantrine)	$94.00^{a}\pm0.09$	$19.00^{b}\pm0.04$	$3450.00^{i}\pm0.60$	$1272.49^{j}\pm0.17$	$10721.40^{k}\pm0.05$	$35.87^{l}\pm0.10$
V(7.1mg/Kg halofantrine+0.20mg/Kg moringa extract)	$77.00^{a}\pm0.01$	$89.00^{b,d}\pm0.01$	$1412.29^{i}\pm0.24$	$8.25^{j}\pm0.001$	$8936.73^{k}\pm0.00$	$16.35^{l}\pm0.13$
VI(7.1mg/Kg halofantrine+0.10mg/Kg cabbage extract)	$72.00^{a}\pm0.00$	$89.00^{b,c,f}\pm0.01$	$2117.20^{i}\pm0.69$	$10.32^{j}\pm0.002$	$9361.52^{k}\pm0.00$	$7.12^{l}\pm0.01$
VII(7.1mg/Kg halofantrine+0.20mg/Kg tomato extract)	$83.00^{a}\pm0.05$	$67.00^{b,d,f,h}\pm0.03$	$1374.48^{i}\pm0.25$	$17.75^{j}\pm0.002$	$6123.46^{k}\pm0.00$	$6.93^{l}\pm0.02$
VIII(7.1mg/Kg halofantrine+0.20mg/Kg moringa+0.10mg/Kg cabbage +0.20mg/Kg tomato extracts)	$67.00^{a}\pm0.03$	$89.00^{b,e,g,h}\pm0.01$	$501.63^{i}\pm0.12$	$6.19^{j}\pm0.001$	$7121.33^{k}\pm0.11$	$7.75^{l}\pm0.03$

Results are in mean±SD, n=3 and values in the same column bearing similar superscript are significantly different at p<0.05

Table 6. Serum ALT, AST, ALP, CK and LDH activities and MDA levels in rats 192 hours after oral administration of Halofantrine drug and vegetable extracts

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	CK (U/L)	LDH (U/L)	MDA (µM)
I (Normal control)	43.00[a]±0.09	16.00[d]±0.02	1001.51[e]±0.25	90.79[f]±0.02	17761.24[g]±0.13	6.49[h]±0.03
II (Test control, 7.1mg/Kg halofantrine)	94.00[a]±0.09	19.00[d]±0.04	3450.00[e]±0.60	1272.49[f]±0.17	10721.40[g]±0.05	35.87[h]±0.10
V (7.1mg/Kg halofantrine+0.20mg/Kg moringa extract)	77.00[a,b]±0.05	76.00[d]±0.09	501.70[e]±0.12	849.13[f]±0.16	9762.27[g]±0.00	28.02[h]±0.21
VI (7.1mg/Kg halofantrine+0.10mg/Kg cabbage extract)	72.00[a]±0.02	52.00[d]±0.01	2076.35[e]±0.36	895.56[f]±0.00	8960.77[g]±0.00	28.81[h]±0.19
VII (7.1mg/Kg halofantrine+0.20mg/Kg tomato extract)	83.00[a]±0.05	58.00[d]±0.02	7905.33[e]±1.97	903.35[f]±0.04	8281.19[g]±0.01	27.35[h]±0.17
VIII (7.1mg/Kg halofantrine+0.20mg/Kg moringa+0.10mg/Kg cabbage +0.20mg/Kg tomato extracts)	77.00[a,c]±0.03	89.00[d]±0.20	1068.53[e]±0.10	921.35[f]±0.07	8023.02[g]±0.03	12.73[h]±0.04

Results are in mean±SD, n=3 and values in the same column bearing similar super script are significantly different at p<0. 05

3.2 Discussion

Results from this study showed that group of rats orally administered with 7.1mg/Kg, 14.2mg/Kg and 21.3mg/Kg (II, III and IV respectively) in 16, 96 and 192 hours had mean serum ALT, AST, ALP, LDH and CK activities and MDA level significantly higher ($p<0.05$) than those in Control Group Tables 1, 2 and 3, except for AST in group IV Table 1 and 2, and LDH. It may be due to inhibitory effect of the drug on the enzymes at effective serum concentration. However, the increase in serum liver and cardiac marker enzymes and MDA, may be in supports of the assertion that Halofantrine administration even under therapeutic dose can cause increase in serum liver and heart enzymes [22]. The linear decrease in serum ALT with increase in halofantrine may further implicate the enzyme inhibitory effect of the drug. It is imperative for researchers to document both *in vitro* and *invivo* effect of halofantrine on non-plasma specific marker enzymes for the benefit of science and medicine. The linear increase of these hepato–cadio toxicity indices due to normal dose (7.10mg/kg) of halofantrine in 16, 96 and 192 hours, indicates that the effect of the drug increases with time. Due to probable inhibitory effect of the drug at higher dose on serum makers enzymes, this research choosed to work with the dose of halofantrine that show no inhibitory effects to evaluate the effect of *Moringa oleifera, Brassica olerace and Solanum lycopersicum* on the on halofantrine hepato–cardio toxicity.

In phase I Table 4, group of rats co–administered with halofantrine, separate doses (V–VII) and combination of the vegetable extract (V), show serum CK and LDH significantly higher ($P<0.05$) than the control group in 16 hours. While within same period the liver function indices except ALP were significantly lower than those of the control (GII). This may indicate hepato–protective effects of the vegetables within 16 hours of administration with no cardiac protective sign. It could be possible, liver being the central site of metabolism/biotransformation may stand to benefits early and more from the protective effect of the vegetables. In phase II Table 5, rat treated with the vegetables extract showed no significant decrease ($p<0.05$) of all the hepato–cardio toxicity indices after 96 hours compared to GII, except AST. This shows possible hepato-cardio protective effects of the vegetables extract against halofantrine toxicity and the trend was maintained in phase III Table 6.

The possible hepato and cardio protective effects of vegetables could be attributed to their chemical constituents that have antioxidant properties. Preliminary studies had shown that some of the potential applications for *Moringa oleifera* are as source of antioxidant [23]. *Moringa oleifera* was found to contain the following water-soluble vitamins; vitamin B_1, B2, B_3, and C. In addition, it contains fat-soluble vitamins as; vitamin A, and E (α-tocopherol), and also contains choline, lipitropic element, fiber and several key minerals; calcium, magnesium, phosphorous, potassium, copper, iron and selenium [24]. *Moringa oleifera*has the ability to provide protein (including 19 of the 20 prominent amino acids). It contains all the eight amino acids considered essential [24].

Cabbage (*Brassica oleracea*) is an excellent source of vitamins C and K, and a good source of vitamin A. It provides calcium, potassium, chlorine, iodine, phosphorous, sodium, sulphur and phytonutrient, polyphenol, that all act as antioxidants and/or coenzymes. Cabbage is a source of indole-3-carbinol, a chemical that boost DNA repair in cells and appears to block the growth of cancer cells [25,26] thereby facilitating cell regeneration.

Tomato (*Solanum lycopersicum*) contains the carotene lycopene (one of the most powerful natural antioxidants), zea-xanthine, lutein, vitamins A, B_1, B_3, B_6, C, E, and K, as well as

minerals such as magnesium, manganese, phosphorous and potassium that can act as antioxidants and/or coenzymes [27]. The cumulative effects of the active components of these vegetables may include, among others, promoting many cellular biochemical processes for the proper functioning of the cell, hence permitting for reversing the toxic condition imposed by the anti–malarial drug halofantrine.

4. CONCLUSION

The results obtained indicates that the elevation effects of both liver and cardiac marker enzymes and MDA even at therapeutic dose by the anti-malarial drug “halofantrine”, could be prevented by co–administrating the drug with moringa, cabbage and tomato extracts. Hence the vegetables may have medicinal properties, which may be due to their antioxidants and co–enzymatic roles. It is therefore advice sable to co–administer the anti-malarial drug with these vegetables, after proving that they do not interfere with the absorption of the drug.

CONSENT

Not applicable.

ETHICAL CONSIDERATION

Handling of experimental animals met the guidelines for Good Laboratory Practice (GLP) regulations of WHO. All authors hereby declare that principles of laboratory animal care (NIH publication No 85–23, revised 1985) where followed, as well as specific national laws where applicable. All experiment have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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