SSR Journal of Medical Sciences (SSRJMS)

Homepage: https://ssrpublisher.com/ssrjms/

Volume 3, Issue 5, 2026 ISSN: 3049-0375

Attenuation of High-Salt Diet-Induced Renin–Angiotensin–Aldosterone System (RAAS) Activation and Endothelial Dysfunction by Omega-3 Fatty Acids and Quercetin Supplementation in Wistar Rats

Ekerette Sampson Udo[1], Ezeani Chidiebere[2], Egharevba Jovita Eghe[2], Udeh Owen Chikere[2], Onurah Sylvester[1], Ofem Effiong Ofem[3]

[1]Department of Physiology, Faculty of Basic Medical Sciences, State University of Medical and Applied Sciences (SUMAS), Igbo-Eno Enugu State, Nigeria
[2]Department of Physiology, School of Basic Medical Science, College of medicine, Federal University of Technology, Owerri, Imo State, Nigeria.
[3]Department of Physiology, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Nigeria

Received: *11.04.2026* | ***Accepted:*** *28.04.2026* | ***Published:*** *02.05.2026*

***Corresponding author:** Ekerette Sampson Udo

DOI: *10.5281/zenodo.19983809*

Abstract **Original Research Article**

Excessive dietary salt intake is a major contributor to hypertension and many other cardiovascular dysfunctions. The mechanism of actions usually involves; activation of the renin–angiotensin–aldosterone system (RAAS), increased oxidative stress, and impaired endothelial nitric oxide signaling.

This study investigated the effects of omega-3 fatty acids and Quercetin, individually and in combination, on biomarkers of RAAS activation, oxidative status, and endothelial function in high-salt diet-fed Wistar rats.

Thirty-Five (35) male Albino Wistar rats(180-220g) were randomly assigned into seven groups(n=5). Group 1 (Control) received rat chow and water only, Group2 (Sham control-1) received 1ml/kg bw of DMSO , Group 3(Sham control -2) received 0.1ml/kg bw of Olive oil, Group 4 (HSF) received 8%NaCl diet + 1% drinking water. Group 5 (HSF + Omega-3) and Group 6 (HSF + Quercetin) received 14.29mg/kg bw of Omega-3 and 20mg/kg bw of Quercetin plus HSF respectively. Group7 (HSF+Omega-3+Quercetin) received a combination of Omega-3 and Quercetin plus HSF. Olive oil and DMSO served as vehicles of administration for omega 3 fatty acids and Quercetin respectively. Administration was done once orally for 42days(6weeks).After 42 days, blood samples were collected and serum levels of angiotensin11 (Ang.11) angiotensin-converting enzyme (ACE), nitric oxide (NO), nitric oxide synthase (NOS), and total antioxidant capacity (TAC) were evaluated.

The results indicated no significant difference among the different control groups. For high salt diet (HSF) group; Ang 11, ACE were significantly ($P< 0.05$) decrease compared to control groups. While serum levels of NO, NOS and TAC were significantly ($P< 0.05$) decreased. Indicating RAAS activation, endothelial dysfunction, and oxidative stress. For Omega 3 and Quercetin Supplementation groups; serum levels of angiotensin 11 and ACE were significantly ($P< 0.05$) decreased while NO, NOS and TAC were significantly increased, suggesting ameliorative potential of these agents.

Interestingly, the combined group was more effective. These findings suggest that omega-3 fatty acids and Quercetin exert synergistic protective effects against salt-induced cardiovascular dysfunction via modulation of the RAAS–oxidative stress–nitric oxide axis.

Keywords: High-salt diet, omega-3 fatty acids, quercetin supplementation, RAAS modulation, oxidative stress and endothelial function.

Citation: Udo, E. S., Ezeani, C., Egharevba, J. E., Udeh, O. C., Onurah, S., & Ofem, E. O. (2026). Attenuation of high-salt diet-induced renin–angiotensin–aldosterone system (RAAS) activation and endothelial dysfunction by omega-3 fatty acids and quercetin supplementation in Wistar rats. *SSR Journal of Medical Sciences (SSRJMS)*, *3*(5), 8-21.

1.0 INTRODUCTION

Hypertension remains one of the leading causes of cardiovascular morbidity and mortality globally (Donghao et al; 2018; WHO,2025). It has been estimated that hypertension caused about 1.02million CVD deaths forming 53% of global burden of CVDs in 2021 (World Heart Federation,2023; British Heart Foundation,2024). Among the various contributory factors, excessive dietary salt intake has been directly associated with increased blood pressure and cardiovascular disease (Grillo et al; 2019; Han et al; 2025). High salt consumption contributes to the development of hypertension through multiple interrelated mechanisms. These include activation of the renin–angiotensin–aldosterone system (RAAS), increased oxidative stress, and endothelial dysfunction (Raisa et al; 2025).

The RAAS is a key neurohormonal regulatory pathway that maintains cardiovascular hemodynamic stability via modulation of arterial blood pressure, vascular tone, and extracellular fluid volume (Montani et al; 2004; Agnese et al; 2025). Angiotensin 11 is the main effector peptide in the RAAS pathway. It's a potent vasoconstrictor that als o promotes inflammation and oxidative stress (Kaschina et al; 2003; Jasleen et al; 2026). Angiotensin converting enzyme (ACE) mediates its traditional function of enzymatic conversion of Angiotensin-I into angiotensin-II (Arrighi et al; 2024). Thus, ACE serves as the chief regulator of this system. Althoughthe RAAS pathway is functionally important in cardiovascular physiology, persistent activation of this pathway is implicated in various cardiovascular pathologies. Overactivity of this system normally provokes sympathetic overexcitation, sustained increased total peripheral resistance, oxidative stress, inflammation and vascular remodeling (Montani et al.,2004; Paz et al.,2020; Jasleen et al; 2018). All these are key indices in the pathogenesis of hypertension, atherosclerosis and other cardiovascular complications.

Oxidative stress is one of the key initiators of cardiovascular disorders. It represents an imbalance between reactive oxygen species (ROS) production and antioxidant defense systems (Udo et al; 2023; Guillem et al; 2025). Total antioxidant capacity (TAC) serves as an important indicator of the overall antioxidant status of the body (Uquetan et al; 2026). It could reflect the cumulative effect of all antioxidants present in serum or tissues (Stefano et al; 2020).

Endothelial dysfunction is a critical underlying

pathogenic factor in the development of cardiovascular diseases (CVDs) (Hai-Jian et al ;2020; Hadi et al; 2025). It precedes atherosclerosis, which is central in many cardiovascular disorders (Hadi et al; 2025). Endothelial dysfunction is characterized by reduced NO production, impaired vasodilation, inflammation and increased risk of blood clots (Xia et al; 2024; Ewelina et al; 2025). Nitric oxide (NO), synthesized by nitric oxide synthase (NOS), maintains vascular tone and controls vasodilation. It also inhibits platelet aggregation, leukocyte adhesion, and smooth muscle proliferation (Costa et al; 2019; Theofilis et al; 2021). NO bioavailability insufficiency often results from oxidative stress or enzyme dysregulation leading to endothelial dysfunction (Hasnae et al; 2022; Roy et al; 2023). Studies suggest that high salt diets could impair NO production, disrupt endothelial functions and thus exacerbate cardiovascular risk (Zhu et al ;2006; Suma et al; 2025).

Recently, Omega-3 fatty acids and Quercetin have been extensively studied for their health benefits including cardioprotective potential (Aribo et al; 2024).

Omega-3 fatty acids are a group of polyunsaturated acids needed for a number of body functions. It is commonly found in fatty fish and in plants such as flaxseed, chia seeds and walnuts (National Institutes of Health, 2022). These polyunsaturated fatty acids have been shown to improve endothelial function, reduce inflammation, reverse oxidative stress and modulate lipid metabolism (Lu et al ;2023).

Quercetin, a naturally occurring flavonoid found in fruits, vegetables, and grains (Nutmakul, T, 2022). It has been shown to possess antioxidant, anti-inflammatory, and antihypertensive

properties (Carrillo-Martinez et al ;2024). It has been reported to improve enhanced nitric oxide production and improve overall cardiovascular function (Mila et al ;2025).

Despite the well-documented individual effects of omega-3 fatty acids and quercetin, limited studies have examined their individual and combined effects on RAAS activation, oxidative stress, and endothelial dysfunction under high dietary salt intake. Hence, this study aimed to investigate the individual and combined effects of these agents on angiotensin II, ACE, nitric oxide, nitric oxide synthase, and total antioxidant capacity in high-salt diet-fed Wistar rats.

2.0. Materials and Method

2.1. Drugs and Chemical

Omega-3 Fatty Acids manufactured by Nicholson Ltd, India. was purchased from BEZ pharmaceuticals stores and Ltd. Calabar.

Quercetin (BN: 1002181952) produced by Sigma-Aldrich (India) purchased at Eyamson Scientific Stores, Calabar, was used for the study.

1 kg of Dangote Salt was bought from Watt market, Calabar and used for the study

The Diethyl sulfoxide (DMSO) (BN: 20190422) produced by GHTECH, China, was obtained from the Biochemistry Department, University of Calabar, Nigeria.

Olive oil was purchased from Bez pharmacy, Calabar, Nigeria.

2.2. Experimental animals

A total of Thirty Five (35) male albino Wistar rats weighing between 180-220g were bought from the local breeder in Calabar and kept in the animal house of the Department of Physiology, University of Calabar, Calabar, Nigeria and were used for the study.

The animals were acclimatized for one week, then weighed and distributed into seven groups of five animals each. All the animals were allowed free access to rat chow and water. Ethical approval (No.: 307PHY3724; Ref.: FAREC/PA/UC/049; was obtained from the Faculty of Basic Medical Sciences animal ethical committee.

2.3. Preparation and administration of experimental drugs

Omega-3 was given at a dose of 14.29 mg/kg (extrapolated from a human dose of 1000 mg / 70 kg) orally, once daily by dissolving 1 capsule in 10mL of Olive oil and 0.1mL was given to 100g of rats.

Quercetin was administered at a dose of 20mg/kg body weight to the rats orally, once daily. 1g of quercetin was dissolved in 50ml of 50% dimethyl sulfoxide (DMSO) solvent, then given at 0.1ml/100g bw, orally once daily, (Allan-Ndoul et al ;2017).

100g of salt were dissolved into 10 litres of water to produce 1% NaCl drinking water and 92% of feed were mixed in 8g of salt to produce an 8% high salt diet (HSF) (Ofem et al ;2015).

DMSO (50%) was given at the dose of 1mL/kg orally and once daily to the sham control-1 group while olive oil was given at a dose of 0.1 mL/kg orally and once daily to the sham control-2 group.

2.4. Experimental Protocol

A total of Thirty-Five (35) male albino Wistar rats were randomly assigned into 7 groups of 5 rats each and were treated thus:

Group 1 (Normal control): Received normal rat chow + drinking water

Group 2 (Sham control-1): DMSO (50%) 1mL/kg orally and once daily.

Group 3 (Sham control-2): Olive oil (0.1 mL/kg orally and once daily)

Group 4 (HSF): (8% NaCl feed +1% NaCl drinking water).

Group 5 (Omega-3 + HSF): Omega-3 (14.29/kg) + HSF orally once daily

Group 6 (Quercetin + HSF): Quercetin (20mg/kg) + HSF orally once daily.

Group 7: (Omega-3 + Quercetin + HSF): Omega-3 (14.29mg/kg) + Quercetin (20mg/kg,) + HSF (8% NaCl feed +1% NaCl drinking water) orally once daily.

The animals were housed in wooden cages. Wooden shavings were used as bedding and routinely changed daily to maintain proper hygiene. The feeding period lasted for 42 days (six weeks).

2.5. Collection of Experimental samples

Animals were fasted overnight after the last administration, weighed and anesthetized with 5% chloroform. The animals were dissected via the linea alba in order to expose the heart. Blood was collected via cardiac puncture with a 5 ml sterile syringe into plain sample bottles for biochemical analysis. The blood samples collected in plain sample bottles were allowed to clot for two hours at room temperature at 4°C before centrifugation for 15 minutes at 1000 ×g. The serum was then collected and stored at -80°C.

2.6. Biochemical Assay

2.6.1. Determination of Angiotensin11 and Angiotensin converting enzymes (ACE).

Angiotensin II assay was done using Cusabo Elisa kit. This assay employs the quantitative sandwich enzyme immunoassay technique, while ACE inhibitory activity was determined by modification of the method of Cushman and Cheung, 1971

2.6.2. Determination of NO and NOS concentration

Serum levels of Nitric oxide were assayed using the colorimetric assay kit. The Nitric Oxide Colorimetric test provides an accurate, convenient measure of total nitrate/nitrite in a simple two-step process, while NOS were determined using the Elisa Kit.

2.6.3. Determination of total antioxidants capacity

The Total antioxidants capacity level was estimated spectrophotometrically at 532nm following the method earlier described by Galaktionova et al; 1998

2.7. Statistical analysis

The data obtained were presented as mean ±SEM. Data were analyzed using one way analysis of variance (ANOVA) followed with Tukey post hoc test. This was done with the aid of a statistical package, SPSS Version 25.0 for windows. $P<0.05$ was considered significant.

3.0. RESULTS

3.1. Angiotensin II (Ang II) Serum concentration in the different experimental groups

The mean values of Ang II (*ng/mL)* was 102.00 ± 0.91 for normal control, 105.75 ± for Sham control 1, 104.00 + 1.47 for Sham control 2, 175.75 ± 1.11 for HSF, 123.00 ± 2.12 for HSF + Omega-3 , 139.25 + 1.31 for HSF + Quercetin , 128.00±1.73 for HSF + Omega-3 + Quercetin respectively.

As shown in fig.1, the results indicated that there was no significant difference in the different control groups. But a significant increase ($p < 0.05$) was observed in the HSF group compared to control groups. However, there was significant decrease ($p < 0.05$) in the HSF + Omega-3, and HSF + Quercetin group compared to the HSF group.

Similarly, a significant decrease ($p < 0.05$) was observed in the HSF + Omega-3 + Quercetin group compared to all the other treatment groups.

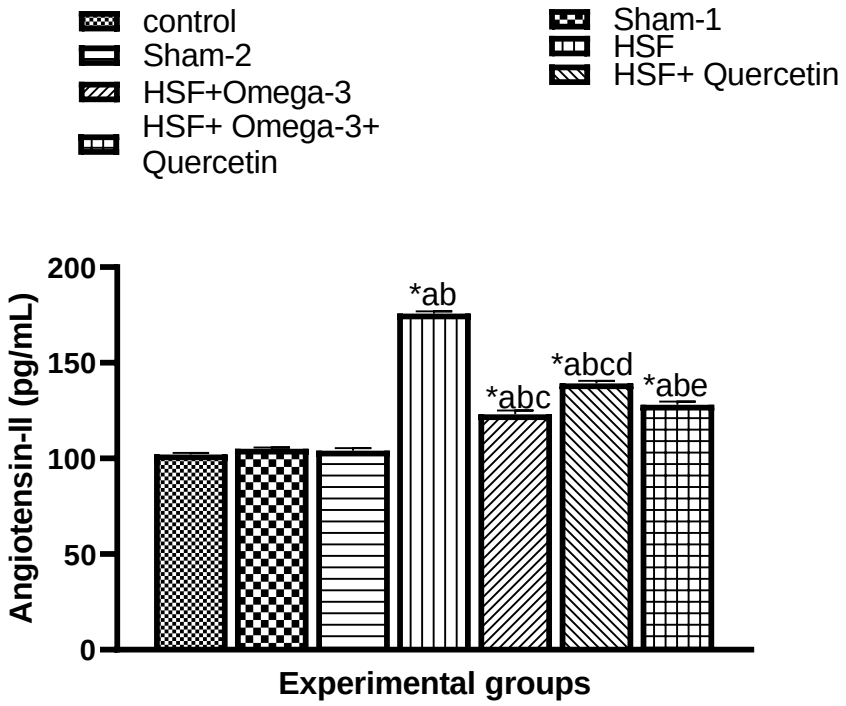

Fig. 1: Comparison of angiotensin-ll across groups
Values are expressed as mean ± SEM, n=6.
*=significantly different from control at P<0.05
a= significantly different from sham-1 at P<0.05
b= significantly different from sham-2 at P<0.05
c= significantly different from HSF at P<0.05
e= significantly different from HSF+Quercetin at P<0.05

3.2. Angiotensin Converting Enzyme (ACE) activity in the different experimental groups

The mean ACE (*pg/mL)* were 1.32 ± 0.04, 1.30 ± 0.04, and 1.34 ± 0.04 for normal control, Sham control 1 and Sham control 2, while 2.58 ± 0.07, 2.08 ± 0.07, 1.94 ± 0.05 and 1.68 ± 0.07 were for HSF, HSF + Omega-3, HSF + Quercetin, HSF + Omega-3 + Quercetin respectively .

As shown in Fig.2, there was no significant difference among the different control groups. But there was a significant increase ($p < 0.05$) in the HSF group compared to the control groups. However, significant decrease ($p < 0.05$) was observed in the HSF + Omega-3, and HSF + Quercetin compared to the HSF group. Similarly, a more significant decrease ($p < 0.05$) was observed in the HSF + Omega-3 + Quercetin group compared to all the other treatment groups.

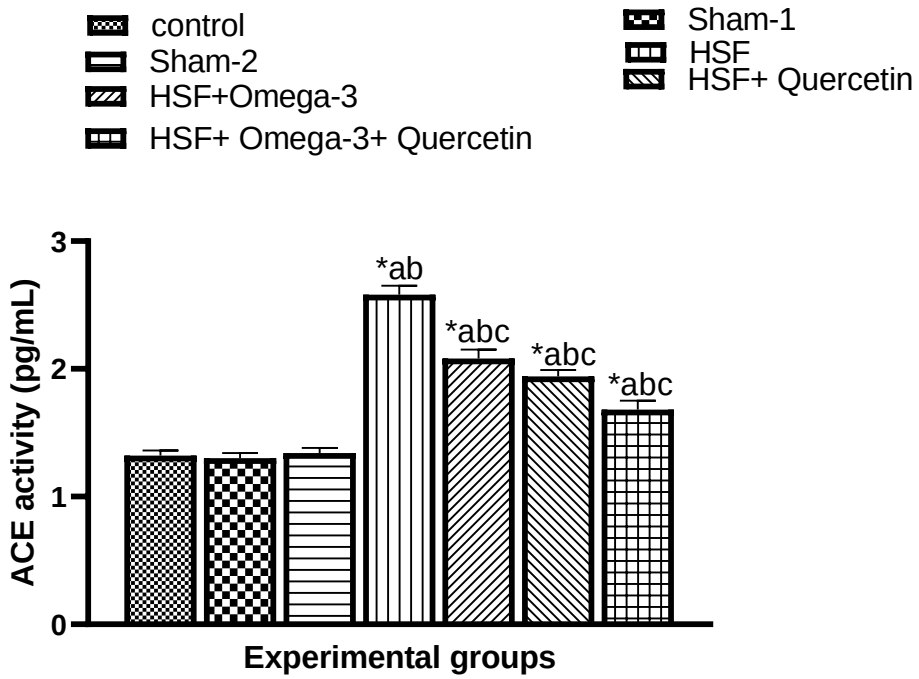

Fig. 2: Comparison of angiotensin converting enzyme across groups
Values are expressed as mean ± SEM, n=6.
*=significantly different from control at P<0.05
a= significantly different from sham-1 at P<0.05
b= significantly different from sham-2 at P<0.05
c= significantly different from HSF at P<0.05

3.3. Nitric oxide (NO) concentration in the different experimental groups

The results of NO level in the different experimental groups were presented in fig.3.

The mean NO (*umol/L)* for normal control, Sham control 1,Sham control 2 were 211.89 ± 3.83, 211.00 ± 4.26, and 218.56 ± 2.05 while the mean NO level for HSF, HSF+Omega-3, HSF+ Quercetin and HSF+ Omega-3+ Quercetin were 167.87 ± 4.26, 189.56 ± 2.01, 195.60 ± 3.80, and 209.20 ± 5.89 respectively. The results show that there is no significant difference among the different control groups. But a significant decrease ($p < 0.05$) was observed in the HSF group compared to the control groups. However, there was significant increase ($p < 0.05$) in the HSF + Omega-3, and HSF + Quercetin group compared to the HSF group. Also, a significant increase ($p < 0.05$) was observed in the HSF + Omega-3 + Quercetin group compared to all the other treatment groups.

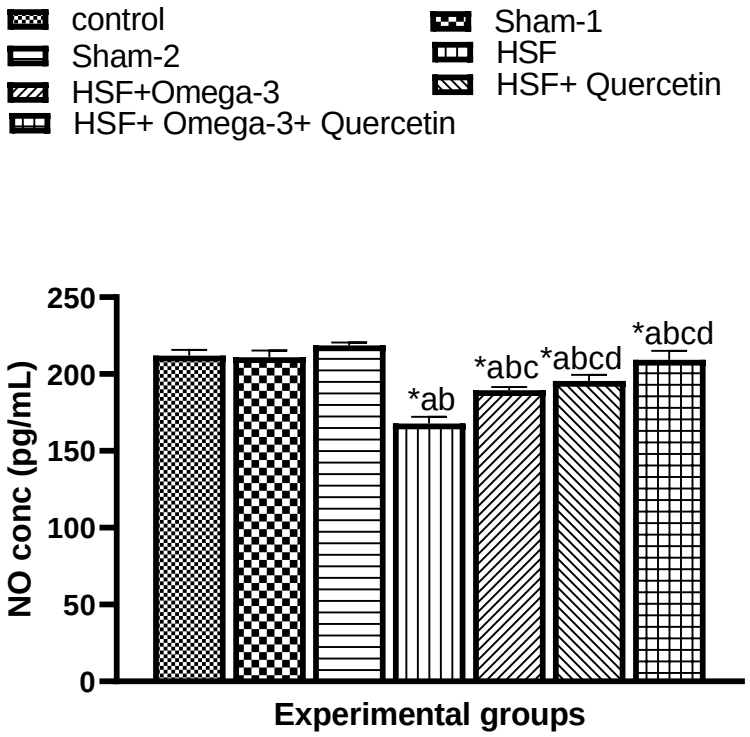

Fig. 3: Comparison of nitric oxide concentration across groups
Values are expressed as mean ± SEM, n=6.
*=significantly different from control at P<0.05
a= significantly different from sham-1 at P<0.05
b= significantly different from sham-2 at P<0.05
c= significantly different from HSF at P<0.05

3.4. Nitric Oxide Synthase (NOS) activity in the different experimental groups.

The mean NOS activity (*ulu/ml)* was 73.62 ± 1.57 for normal control, 71.92 ± 2.97 for Sham control 1, 70.02 ± 2.68 for Sham control 2, 61.23 ± 0.37 for HSF, 65.40 ± 1.69 for HSF + Omega-3, 68.98 +1.40 for HSF + Quercetin, and 71.98 ± 0.88 for HSF + Omega-3 + Quercetin respectively.

As shown in Fig 4, no significant difference was observed among the different control groups. There was a significant decrease ($p < 0.05$) in the HSF group compared to control groups. However, significant increase ($p < 0.05$) was observed in the HSF + Omega-3, and HSF + Quercetin compared to the HSF group Notably, in the HSF + Omega-3 + Quercetin group , there was a significant increased ($p < 0.05$) compared to all the other treatment groups.

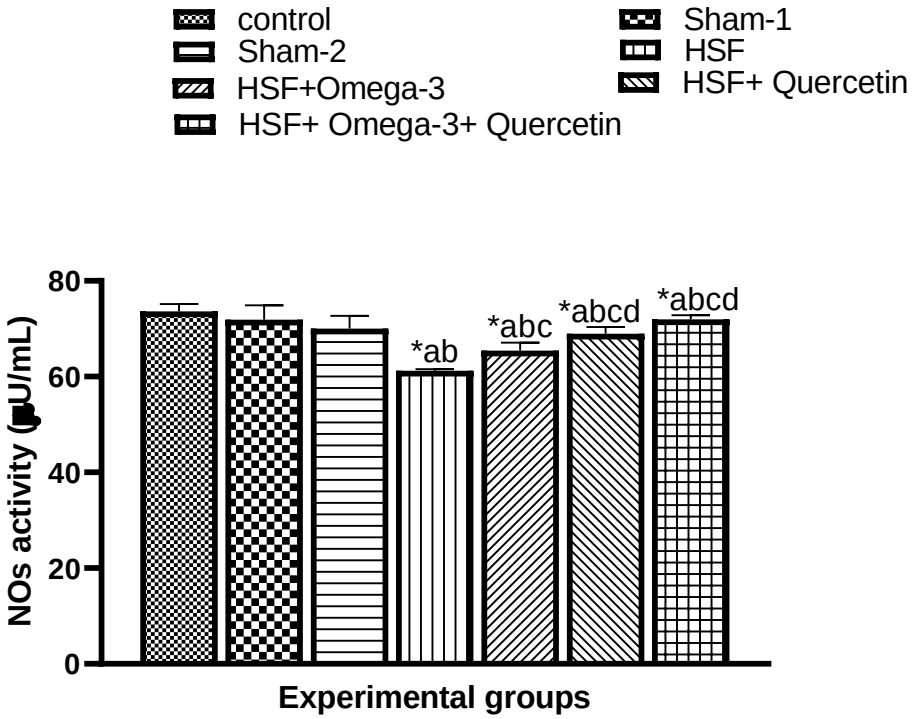

Fig. 4: Comparison of nitric oxide synthase activity across groups
Values are expressed as mean ± SEM, n=6.
*=significantly different from control at P<0.05
a= significantly different from sham-1 at P<0.05
b= significantly different from sham-2 at P<0.05
c= significantly different from HSF at P<0.05

3.5. Total antioxidants capacity (TAC) concentration in the different experimental groups

The results of TAC conc. in the different experimental groups were presented in fig.5.

The mean TAC (*umol/L)* for normal control, Sham control 1,Sham control 2 were 9.48 ± 1.48, 9.63 ± 1.44, and 9.44 ± 1.50 while the mean TAC level for HSF, HSF+Omega-3, HSF+ Quercetin and HSF+ Omega-3+ Quercetin were 2.98 ± 1.14, 6.78 ± 1.15, 7.83 ± 1.19, and 8.91 ± 1.58 respectively. The results show that there is no significant difference among the different control groups. But a significant decrease ($p < 0.05$) was observed in the HSF group compared to control groups. However, there was significant increase ($p < 0.05$) in the HSF + Omega-3, and HSF + Quercetin group compared to the HSF group. Also, a significant increase ($p < 0.05$) was observed in the HSF + Omega-3 + Quercetin group compared to all the other treatment groups.

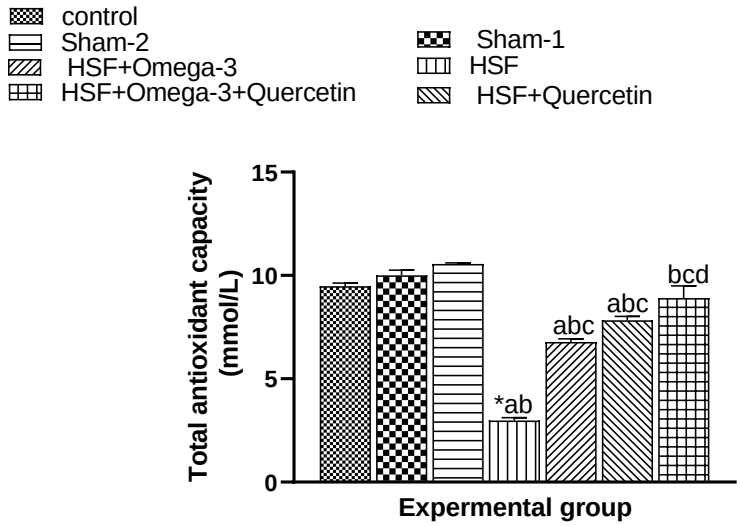

FIG. 5: Total antioxidant capacity across experimental groups
Values are expressed as mean ± SEM, n=6.
*=significantly different from control at P<0.05
a= significantly different from sham-1 at P<0.05
b= significantly different from sham-2 at P<0.05
c= significantly different from HSF at P<0.05

Discussion

The present study demonstrated that a high-salt diet induces significant activation of the renin–angiotensin system, increased oxidative stress, and impaired endothelial function in Wistar rats. These findings are consistent with established reports that excessive salt intake is associated with adverse cardiovascular outcomes including hypertension and vascular damage (Ofem et al; 2019; Xue et al; 2022**).**

The elevated serum levels of Ang.11 and ACE observed in the HSF group confirmed the activation of the RAAS pathway, Consequent to high dietary salt intake. Ang II and ACE are important regulators of cardiovascular hemodynamic (Agnese et al; 2025**).** ACE mediates conversation of inactive Ang 1 to active Ang II, which is the principal actor in the RAAS pathway (Jasleen et al; 2026**).** Reports have shown that they are elevated in hypertensive states and Ang11 are implicated in various cardiovascular disorders including atherosclerosis, ventricular hypertrophy and heart failure (Paz et al; 2020; Oudit et al; 2007**).** Angiotensin II not only promotes vasoconstriction but also stimulates the production of reactive oxygen species (ROS), and vascular inflammation (Kaschina et al; 2003; Jasleen et al; 2026**).** This provides the link between RAAS activation with oxidative stress and inflammation. Evidence established that oxidative stress and inflammation are the drivers of cardiovascular pathogenesis (Raelene, J, 2021; Gimblet et al; 2025**).**

The significant reduction in total antioxidant capacity (TAC) in the HSF group as observed in this study, depicts the presence of oxidative stress. A decrease in TAC reflects depletion of the endogenous antioxidant defense system (Stefano et al; 2020**).** This could make the vascular system susceptible to oxidative damage resulting in vascular dysfunction (Adela et al; 2026**).** In addition, excessive ROS can interfere with nitric oxide (NO) production, thereby reducing its bioavailability and impairing endothelial function (Roy et al; 2023**).** Nitric oxide is one of the most potent endogenous vasodilators that plays a major role in regulation

of vascular resistance in both regional and systemic hemodynamics (Ahmad et al; 2018). Nitric oxide is generated by NOS isoforms. In this study, the observed significant reduction in NO and NOS levels in the HSF group suggests endothelial dysfunction. Deficient bioavailability of NO has been implicated in several cardiovascular outcomes especially endothelial dysfunction and hypertension ((Roy et al; 2023. It is likely that excessive salt promotes angiotensin II-induced oxidative stress which downregulates NOS expression and reduces serum NO activity as earlier reported (Zhu et al; 2006).

Omega-3 fatty acids treated group indicated significant reduction in Ang.11 and ACE levels, improved total antioxidant capacity (TAC) and endothelial function. It could be speculated that these fatty acids might inhibit RAAS activation, reduced blood pressure, and attenuated oxidative stress. Additionally, omega 3 fatty acids may facilitate NO synthesis by improving endothelial nitric oxide synthase activity. These opinions are consistent with earlier research findings that omega 3 fatty acids could lower blood pressure, (Lu et al; 2023**),** reduce oxidative stress (Heshmati et al; 2019**)** and improve endothelial function (Kei et al; 2025**).**

Similarly, Quercetin supplementation significantly improved TAC, suggesting its potent antioxidant capacity as earlier documented (Nutmakul, T, 2022; Carrillo-Martinez et al; 2024**).** By scavenging reactive oxygen species, quercetin could preserve nitric oxide bioavailability and protect endothelial function. (Mateusz et al; 2025). Besides, its inhibitory effect on RAAS activation, might contribute to reduced angiotensin II levels, thus, attenuating RAAS-mediated oxidative stress.

Interestingly, co-administration of Omega-3 fatty acid and Quercetin produced the most significant inhibition of the salt induced RAAS activation and enhanced endogenous antioxidants capacity and endothelial markers. This suggests a synergistic interaction between these agents, probably resulting from complementary mechanisms of actions. It is therefore safe to speculate that the combination of Omega-3 fatty acid and Quercetin provide a comprehensive and most effective strategy in mitigating high dietary salt induced cardiovascular derangements including vascular damage.

Finally, this study did not measure blood pressure or assess markers of inflammation, which could provide further insight into the underlying mechanisms. It is therefore recommended that future studies should incorporate blood pressure determination, molecular and histological analysis to better authenticate and elucidate on all the pathways involved.

Conclusion

This study demonstrates that a high-salt diet induces RAAS activation, oxidative stress, and endothelial dysfunction in Wistar rats.

Omega-3 fatty acids and Quercetin Supplementation individually attenuated these effects by reducing angiotensin II and ACE levels, enhancing nitric oxide signaling, and improving total antioxidant capacity. Combined supplementation provides the most effective protective effects, suggesting a synergistic role in modulating the RAAS–oxidative stress–nitric oxide axis. Hence, Omega-3 and quercetin combination present promising dietary supplements that could mitigate the detrimental effects of high salt consumption on the cardiovascular system.

ACKNOWLEDGEMENTS

This is part of a Ph.D. thesis. The authors are grateful to Prof. A.E. Eno, Dr. Icha and Mr. A. D Collins for their technical assistant.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding Statement

This research was funded by the authors and received no specific donations from government,

corporate, commercial or non-profit organizations.

Conflict of interest

The authors declare that they have no conflicts of interest.

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