



Topical Administration of *Cymbopogon Citratus* Essential Oil Extract and Citral Drug in Response to Bilateral Carotid Occlusion Maintained Cardiovascular Function in Wistar Rats

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ABSTRACT: Several authors have reported contrasting effect of *Cymbopogon citratus* essential oil (CCEO) and citral on the cardiovascular function based on different routes of administration and experimental design, but they have not investigated cardiovascular function or mechanics in response to bilateral carotid occlusion (BCO). Consequently, the objective of this paper was to investigate the topical administration of *Cymbopogon citratus* essential oil (CCEO) extract and citral drug in response to bilateral carotid occlusion (BCO) maintained cardiovascular function in Wistar Rats using appropriate standard procedures. Mean arterial blood pressure (MABP) and heart rate (HR) were monitored. CCEO decreased MABP and HR, while citral increased MABP but reduced HR. There was dose graded beat per second decrease in MABP and HR by CCEO in a plateau form while citral caused dose graded increase in MABP in plateau form but with decrease in HR in a declining form in response to 30 sec BCO. However, there was positive decrease in beat-to-beat change in Δ MABP in an inclining form with negative increase in beat-to-beat change in Δ HR in declining form caused by CCEO while was dose-graded positive increase in beat-to-beat change in Δ MABP with dose-graded negative increase beat-to-beat change in Δ HR both in plateau forms during 30 sec BCO. CCEO or citral therefore blunted cardiovascular reflex fluctuations and protected cardiovascular function, maintaining cardiovascular homeostasis in response to BCO in the Wistar rats.

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Cymbopogon citratus is a tall perennial grass with rhizomes and dense tufted and fibrous root (Nour, 2013). Its leaves are dense, clustery, coarse and leathery leaves. The plant originally was found in northern and southern part of India and Asia. It is cultivated nationally for commercial benefits in some

Africa countries (Aftab *et al.*, 2011). There are also other species of lemongrasses such as *Cymbopogon citratus*, *C. ambiguus*, *C. bombycinus*, *C. nardus*, *C. oblectus*, *C. refractus*, *C. schoenanthus*, *C. flexuosus* and *C. pendulus* found in Africa, Australia, China and India (Aftab *et al.*, 2011). *C. citratus* is

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traditionally employed in the treatment of cardiovascular diseases in addition to being insects/mosquito's repellent (Ewansiha *et al.*, 2012). The phytochemical composition of *C. citratus* and its oil extract varies with the geographical location, genetic individuality, part of the plant used, extraction method, botanical age and season (Ewansiha *et al.*, 2012; Nuor, 2013). These differences still allow similar chemical compositions like, which are reproducible in this species, tannins, flavins, phenol-alkaloids, and anthraquinones. Geranial (α -citral) and neral (β -citral) are the major active compounds found in the oil (Idrees *et al.*, 2013) responsible for the lemon-like fragrance of the species (Saito *et al.*, 2000; Negielle *et al.*, 2007).

The basic function of cardiovascular system is the perfusion of body tissues with nutrient, oxygen, and mediators and drainage of waste product from tissues to maintain physiological homeostasis and effective circulation with adequate delivery of oxygen to all body cells, tissues, organ and systems by metabolic demands. The heart and vascular tissues play this role with metabolic changes demands (Smussen and Nielsen, 1960). Circulatory regulatory mechanisms annul hypoxia, fluctuations in arterial blood pressure owing to dehydration, temperature, gravity and postural change. Regulation of arterial blood pressure and oxygen saturation, blood volume, occlusion and body temperature are german in cardiovascular function and homeostasis via baroreceptor and chemoreceptor mechanics and mechanisms (Gandevia *et al.*, 1993). Citral is a major monoterpene found in CCEO. It has been reported to be responsible for reduction in peripheral resistance with a blood pressure reducing effect (Peixoto-Neves *et al.*, 2010), which also is beneficial for cardiovascular disease (Avoseh *et al.*, 2015).

In addition, monoterpenes have been observed to promote lowering of blood pressure and heart rate via vasorelaxation and parasympathetic system (Aydin *et al.*, 2007; Magalhaes *et al.*, 2008; Bastos *et al.*, 2010; Peixoto-Neves *et al.*, 2010), making it useful as remedy for cardiovascular illnesses (Lefkowitz and Willerson, 2001). Anigbogu and Olayemi (2007) have also investigated circulatory system in normal-blood pressure after *C. citratus* administration in rats, resulting in neutral effect of *C. citratus* on heart rate and blood pressure reflex response to bilateral-carotid-occlusion. In view of the above contrasting reports based on varying doses and methods of administration, the objective of this paper was to investigate the topical administration of CCEO extract and citral in response to BCO maintained cardiovascular function in Wistar Rats

MATERIALS AND METHODS

Plant material collection, identification, preparation and extraction of *Cymbopogon citratus* essential oil: Fresh *Cymbopogon citratus* leaves were collected from home grown garden in Ikorodu North Local Government Area, Ikorodu, Lagos State, Nigeria and identified at the Department of Botany, Faculty of Science, University of Lagos, Nigeria (Voucher Number LUH4687). The whole plant leaf sheath and blade were fetched for essential oil extraction. Five hundred gram (500 g) of chopped pieces of the plant was crushed in a mortar with pestle, increasing the surface area for essential extraction. The samples were dried in a freeze drier (Beta 1-8 LD, Martin Christ Germany) at -55°C and 0.070 mbar for 48 min in order to remove the moisture content. Freeze-dried sample (200 g) was then hydro-distilled. The hydro-distillation was done in the Clevenger apparatus at 100°C for 6 h in a modified all Dean and Stark apparatus for lowest phase return. 10.0 mL of n-hexane was added to trap the condensed oil, via the condenser top. Hexane was later collected every hour. So, new portion of hexane was added as described. The mixtures were dried over sodium sulphate (Na_2SO_4) anhydrous for 24 h and then filtered. The hexane solution was finally evaporated in a rotary evaporator (Eyela N-1001, Tokyo Rikakikai, Japan) at 40°C and gave a yellowish essential oil stored at 4°C for further analysis (Mirgani *et al.*, 2012).

Citral oil: A standard synthetic citral oil compound purchased from Sigma Aldrich, USA was used for citral administration.

Experimental animals: Eighty-four (84) male and female Wistar rats (160 to 180 g) were collected from the Animal House, Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria. They were identified in the Department of Zoology, Faculty of Science, University of Lagos, Lagos, Nigeria (Reference Number 002/2021). The rats were acclimatized for two weeks before the commencement of the study and fed with pelletized feed and had access to water (Oyedele *et al.*, 2000).

Experimental Protocol for topical application of the *Cymbopogon citratus* essential oil and citral drug: Rat right hind limb fur $4\text{ m}^2/\text{Kg}$ body weight portion was shaved with a new razor blade (Figure 2) and exposed their skin for topical application of CCEO, citral, paraffin and DEET. The rats were divided into 2 groups (A and B) and the 2 groups were further subdivided into 7 sub-groups (AI to AVII) and (BI to BVII) respectively. Each sub-group had 6 Wistar rats

for daily topical application of various standard concentrations of CCEO and citral for 8 weeks (Oyedele *et al.*, 2000). Rats in Group A (II-VII) were topically administered 2.0 mL of 0.5%, 1.0%, 10%, 15% CCEO, 15% paraffin, 15% DEET while rats in the Control Group (AI) was administered with 2.0 mL normal saline. Rats in Group B (II-VII) were topically administered 2.0 mL of 0.5%, 1.0%, 10%, 15% citral, 15% paraffin (as a diluent), 15% diethyltoluamide (DEET, as positive control) while rats in Control Group (BI) were administered with 2.0 mL normal saline. BCO test was carried out at the end of the 8 weeks of CCEO and citral topical application in order to study the baro-reflex rate-pressure responses to topical application of CCEO and citral in the Wistar rats.



Fig. 1: The shaved portion of the rat hind limb for topical application of substances (Oyedele *et al.*, 2000).

Measurement of blood pressure, heart rate and reflex response to bilateral carotid occlusion in rats: The rats in each group were anaesthetized with a mixture of 25% (w/v) urethane and 1% (w/v) alpha-chloralose at 5 mL/Kg⁻¹ body weight administered into the peritoneum. Tracheal cannulation was done to clear airway and prevents spontaneous aspiration. Left femoral artery and vein were cannulated with polyethylene micro cannulae (PE.50) filled with heparinized normal saline (0.9% NaCl) for infusions. Intra-arterial blood pressure was measured from the cannulated femoral artery connected to a pressure transducer linked to a PowerLab Data Acquisition and Analysis System (ADInstruments, Australia) attached to a computer. MABP was then calculated from the systolic upper border of the arterial pressure curve on the blood pressure tracings and diastolic lower border of the arterial pressure tracings (Berne and Levy, 1992). Heart rate was obtained directly as number of cycles of systolic or diastolic curves from the blood pressure tracing per minute. Cardiovascular reflex function/test was performed using bilateral carotid occlusion (Oloyo *et al.*, 2011).

The rats were laid supine on a sterile surface and the neck area was shaved and cleansed with a disinfectant (4% sodium hypochlorite and 70%

alcohol) to prevent contamination at the surgical site. Using sterilized scissors, a medially straight incision was in the neck from the chin to the sternum the ribcage. The skin was separated on both sides of the incision by blunt dissection. The fascia overlying the glandular tissue was separated to gently dissect the underlying muscular layer. The left common carotid artery aspect at the internal and external bifurcation was isolated freely from overlying fascia and adjacent nerves. Vagus nerve and all associated nerves were adjacent to the bifurcation were kept intact. The appropriate ligation placement for carotid artery was then performed.

The ascending pharyngeal, occipital, and superior thyroid branches of the external carotid artery were identified and ligated using sterile suture to avoid retrograde flow. During this BCO operation, the rat sedation was routinely checked and all exposed tissues were kept moist using sterile saline solution (Oloyo *et al.*, 2011). Mean arterial pressure (MABP) = (SBP + 2DBP) ÷ 3; where SBP = systolic blood pressure; DBP = diastolic blood pressure (Oloyo *et al.*, 2011). Heart rate (HR) is taken as cycles per minute of blood pressure upper (SBP) and lower (DBP) deflections on the arterial blood pressure tracings (Oloyo *et al.*, 2011).

Statistical Data Analysis: Data are presented as Mean ± SEM. And statistically significant level was accepted when $p < 0.05$. One-way-analysis of variance (ANOVA) was used for intergroup comparison using Graph Pad 9.0 software (Graph Pad Software, Inc., La Jolla, CA, USA) follow by post hoc test ($p < 0.0001$).

RESULTS AND DISCUSSION

Effect of topical application of cymbopogon citratus essential oil extract or citral drug on mean arterial blood pressure and heart rate in Wistar rat: The MABP in Group AII (0.5% v/v CCEO) Group AIII (1.0% v/v CCEO), Group AIV (10% v/v CCEO) and Group AV (15% v/v CCEO) were significantly reduced after chronic topical application of CCEO compared with MABP obtained in the Control Group AI ($p < 0.05$; Figure 2). There was also significant reduction in MABP obtained in Group AVI (15% v/v paraffin) and Group AVII (15% v/v DEET) after topical applications of Paraffin and DEET respectively compared with that of the Control Group AI ($p < 0.05$). However, a marked significant reduction in MABP obtained in Group AIII rats (1.0% v/v CCEO) compared with MABP in Group AII (0.5% v/v CCEO), Group AIV (10% v/v CCEO) and Group AV (15% v/v CCEO) and Control Group AI ($p < 0.05$). On the other hands, there were similar

reductions in the MABP in Group AII (0.5% v/v CCEO) and Group AIV (10% v/v CCEO) after topical application of CCEO respectively compared to the MABP in the Control Group AI ($p < 0.05$). Figure 3 shows significant reductions in the heart rate (HR) in Groups AII, AIII, AIV, AV and Group AVII respectively after topical application of 0.5% v/v, 1.0% v/v, 10% v/v, 15% v/v CCEO and 15% v/v DEET compared with the Control Group AI ($p < 0.05$), but in Group AVI, there was significant increase in the HR upon topical application of 15% v/v Paraffin compared with the HR obtained in Control Group AI ($p < 0.05$). On the other hand, Groups AII, AIII, AIV and AV show slight decrease in HR on topical application of 0.5% v/v, 1.0% v/v, 10% v/v, 15% v/v CCEO compared to the Control Group AI ($p < 0.05$).

The MABP obtained in Group BII (0.5% v/v citral), Group BIII (1.0% v/v citral), Group BIV (10% v/v citral) and Group BV (15% v/v citral) were high compared to the MABP obtained in the Control Group BI ($p < 0.05$), after topical application of citral. Nevertheless, the MABP obtained in Group BIII (1.0% v/v citral) was significantly higher than all other groups ($p < 0.05$). On the other hands, there were little or no differences in the MABP of Control Group BI and Group BVII compared to 15% v/v Paraffin and 15% v/v DEET topical application respectively (Figure 4). The heart rate (HR) in Groups BII, BIII, BIV, BV (after topical application of 0.5% v/v, 1.0% v/v, 10% v/v and 15% v/v citral respectively) and Group BVI (15% v/v paraffin) were low compared with the HR in Control Group BI ($p < 0.05$; Figure 7). Nevertheless, there was little or no difference between the HR in Groups BI compared to that of BVII (Figure 5). The fall in MABP and HR after topical CCEO application and the rise in MABP and reduction in HR after topical application of citral may suggest similar and complimentary but contrasting cardiovascular activities of the two stereoisomers (geranial and neral) in CCEO in contrast to the geranial isomer in citral. The simultaneous fall in MABP and HR after topical application of CCEO was in inverse dose-related manner. The utmost reduction been at 1.0% dose, followed by 15%, 10% and 5% respectively. This suggest that 1% dose possessed the most negative pressor effect compare to other 15%, 10%, and 0.5% doses of CCEO, a best possible complimentary effect of the stereoisomers at these doses. The similarity of MABP reduction between 15% Paraffin with 10% CCEO and 15% diethyltoluamide (DEET) with 15% CCEO indicate that 10% CCEO and 15% CCEO produced depressor effect similar to that of neutral diluents and positive control respectively. The

decrease in HR is a negative chronotropic effect similar to those of paraffin and DEET as negative and positive controls respectively. These results show these stereoisomers in the CCEO might have been absorbed via the rat integument into the blood vessels to affect their actions. Studies and reports have been published on the anti-hypertensive, vaso-relaxant and negative chronotropic activities of citral isomer extracts of lemon grass plant. In those studies, *Cymbopogon citratus* extracts relaxed the umbilical arterioles, aortic ring, and mesenteric vessels (Wierzejska *et al.*, 2020; Silva and Bárbara, 2022). The negative chronotropic activity was reported in isolated rat hearts (Gazola *et al.*, 2004; Silva and Bárbara, 2022). In most of these reports, the antihypertensive effect of *Cymbopogon citratus* extract is simultaneously produced with its bradycardic responses (Pereira *et al.*, 2013; Song *et al.*, 2016)..

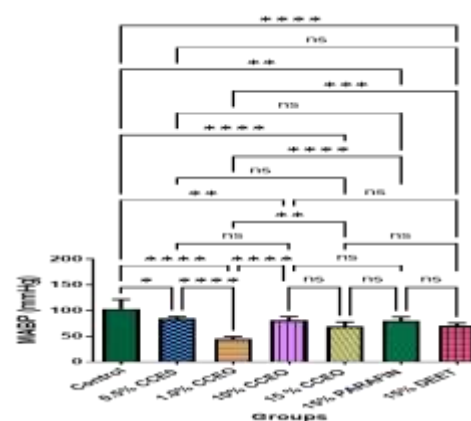


Fig. 2: Mean arterial blood pressure in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared with control group AI, group AVI after topical application of paraffin and group AVII after topical application of diethyltoluamide. MABP = mean arterial blood pressure; DEET = Diethyltoluamide; PARAFIN = Paraffin; CCEO = *Cymbopogon citratus* extract oil; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$, **** = $p < 0.0001$ = significant, ns = not significant.

The rise in MABP obtained in the BII to BV groups of Wistar rats topically administered with citral are in contrast to the decrease observed in AII to AV groups of Wistar rats topically administered with CCEO. However, the highest increase in MABP was obtained in Group BIII similarly to the highest decrease of the MABP in Group AIII topically administered with CCEO. This study does not show how increase in MABP were obtained in groups of Wistar rats topically administered with citral in contrast to the decrease in MABP obtained in the groups of Wistar rats topically administered with CCEO, however, this contrasting positive and negative pressor effects may be attributed to the fact

that CCEO contained majorly α -citral and β -citral while citral was purely α -citral. The findings then suggest that the MABP lowering effect of CCEO is attributable to the β -citral counterpart in the CCEO as the citral oil contains only α -citral

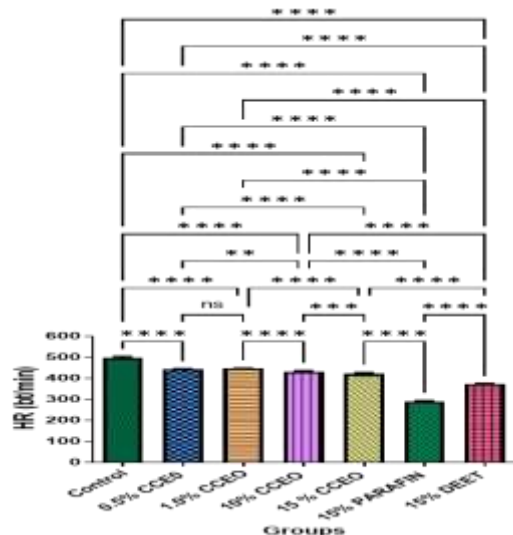


Fig. 3: Heart rate in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared with the control group AI, group AVI after topical application of paraffin and group AVII after topical application of diethyltoluamide. CCEO = *Cymbopogon citratus* extract oil; DEET = Diethyltoluamide; HR = heart rate, PARAFIN = Paraffin; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$ = significant; ns = not significant

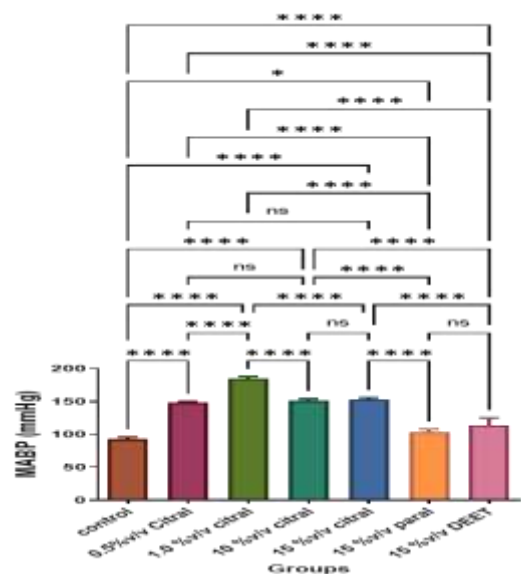


Fig. 4: Mean arterial blood pressure in Wistar rats Groups BII, BIII, BIV and BV after topical application of citral drug compared with control group BI, group BVI after topical application of paraffin and group BVII after topical application of diethyltoluamide. MABP = mean arterial blood pressure; parafin = Paraffin; DEET = Diethyltoluamide; * = $p < 0.05$; **** = $p < 0.0001$ significant; ns = not significant

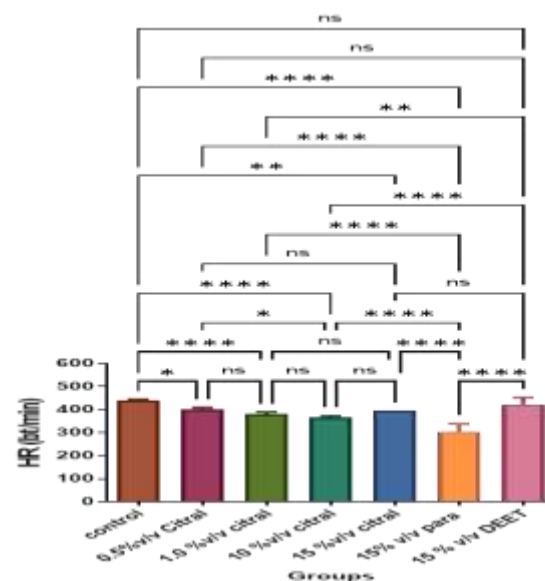


Fig 5: Heart rate in Wistar rats' groups BII, BIII, BIV and BV after topical application of citral drug compared with the control group BI, group BVI after topical application of paraffin and group BVII after topical application of diethyltoluamide. Para = Paraffin; DEET = Diethyltoluamide; HR = heart rate, * = $p < 0.05$, ** $p < 0.01$ and **** $p < 0.0001$ = significant; ns = not significant.

Effect of topical Application of Cymbopogon citratus essential oil or citral drug on the mean arterial blood pressure, heart rate responses to bilateral carotid occlusion in Wistar rats: The result of test of cardiovascular reflex function: reflex changes in blood pressure and heart rate following 30 sec BCO in CCEO-treated rats (Figure 4 and Figure 5). The 30 sec BCO in rats after topical application of CCEO produced a decrease in MABP in Groups AII, AIII, AIV, AV, AVI and AVII in general compared with MABP of Control Group AI. The rate of decrease in the MABP in Groups AII, AIV, and AV after topical application of 0.5% v/v, 10% v/v, 15% v/v CCEO were similar compared to those of Groups AVI and AVII after topical application of 15% v/v paraffin and 15% v/v DEET respectively and Control Group AI ($p < 0.05$). On the other hand, the decrease in MABP obtained in Group AIII after topical application of 1.0% v/v CCEO was much more than other Groups AII, AIV, AV, AVI and AVII compared with MABP of Control Group AI ($p < 0.05$). At the baseline level (i.e., 0 to 5 sec), there was a decrease in MABP obtained in Groups AII to AVII compared with MABP of Control Group AI (Figure 6). At 5 to 30 sec BCO, MABP decreased in Groups AII, AIII, AIV, AV, AVI and AVII but much more in Group AIII (1.0% v/v CCEO) than the MABP of Control Group AI. However, decrease in MABP continued in these groups up to 30 sec after which a plateau was reached at 20 to 30 sec in MABP in

Groups AII to AVII. Nevertheless, in overall, Group AII (1.0% v/v CCEO) produced the lowest MABP response after BCO followed by other Groups AIII (10% v/v CCEO), Group AVII (15%v/v paraffin), Group AV (15% v/v CCEO), Group AIV (10% v/v CCEO), Group AVI (15% v/v paraffin) and lastly the Control Group AI. On the other hand, from 0 to 30 sec, there were decreased HR responses in Groups AII, AIII, AIV, AV, AVI and AVII. The decreased HR response was lowest in Group AVII (15% v/v DEET) followed by Group AV (15% v/v CCEO), and Group AIV (10% v/v CCEO), Group AII (0.5% v/v CCEO), Group AIII (1.0% v/v CCEO) and lastly Group AVI (15% v/v Paraffin). More so, there were slightly low HR obtained after topical application of CCEO in Group AVI (15% v/v paraffin) and Group AVII (15% v/v DEET) compared with the HR obtained in the Control Group AI ($p < 0.05$). Changes in mean arterial blood pressure (Δ MABP) following BCO decreased from 0 to 5 sec in all the Groups compared to the Control Group AI ($p < 0.05$). There were also decreases in MABP in Group AII (0.5% v/v CCEO), Group AIII (1.0% v/v CCEO), Group AIV (10% v/v CCEO), Group AV (15% v/v CCEO) in 5 to 30 sec, responses to BCO after topical application of CCEO and Group AVI (15% v/v paraffin) and Group AVII (15% v/v DEET) after application of Paraffin and DEET. Changes in Groups AII, Group AIV, Group AV, Group AVI and Group AVII attained plateau in responses to BCO from 20 to 25 sec while that of Group AIII attained its plateau at 20 to 25 sec (Figure 6). At baseline (0 to 5 sec) there was a decrease in heart rate (Δ HR) in all the groups compared with the Control Group AI ($P < 0.05$ in each case), however, changes in HR in Group AIII (1.0% v/v CCEO) after topical application of CCEO was higher from 5 to 10 sec in response to BCO, followed by Group AVII (15% v/v DEET) 10 to 20 sec and Group AV (15% v/v CCEO) at 10 sec and 20 to 30 sec BCO compared to changes in HR in the Control Group AI ($p < 0.05$) Figure 7.

The results on test of cardiovascular reflex function, arterial blood pressure and heart rate following 30 sec BCO in citral treated rats is shown in figures 10 and 11. The 30 sec BCO in rats after topical application of citral produced high MABP in Group BII (0.5% v/v citral) Group BIII (1.0% v/v citral), Group IV (10% v/v citral) and Group BV (15% v/v citral), Group BVI (15% v/v paraffin) and BVII (15% v/v DEET) in general compared to MABP in Control Group BI. At the baseline level (i.e., 0-5 sec), there was significant high MABP obtained in Groups BII to BVII compared with Control Group BI ($p < 0.05$). At 5-15 sec BCO, MABP increased much more significantly in Groups BII to BVII than the MABP

of Control Group B1. The increase in MABP continued in these groups up to 20 sec after which a plateau was reached at 20-30 sec in MABP in Groups BII to BVII. Nevertheless, in overall, Group BIV (10% v/v citral) produced the highest MABP response after BCO followed by Group BIII (1.0% v/v citral), Group BV (15% v/v citral), Group BII (0.5% v/v citral), Group BVII (15% v/v DEET), and Group BVI (15% v/v paraffin) and lastly the Control Group BI. On the other hand, from 0-5 sec, decreased HR response was most in Group BIV (10% v/v citral) and followed by Group BII (0.5% v/v citral) and Group BIII (1.0% v/v citral) were similar, but Group BV (15% v/v citral) was the lowest (Figure 12). Conversely after 5 sec and onward, the HR response was lowest in control followed by group BV (with a big gap), then Group BIII and Group BIV and lastly Group BII (Figure 13). The changes in MABP following BCO increased from 0 to 5 sec across the Groups with the Group BII (1.0% v/v citral) being the highest followed by Group BIV (10% v/v citral), closely followed by Group BII (0.5% v/v citral), followed by Group BV (15% v/v citral), followed by Control Group BI, Group BVI (15% v/v paraffin) and Group BVII (15% v/v DEET), from 5-10 or 15 sec changes in MABP assumed plateaux across the groups. However, during plateaux formation, Group BIV came up with the highest increase in MABP responses to BCO followed by Group BIII, BII, BV, BVI and control Group BI respectively in that order (Figure 14). At baseline (0-5 sec) there were decrease in heart rate (Δ HR) in all the groups compared with the Control Group BI ($p < 0.05$), while changes within 5-15 s in response to BCO in Group BIII (1.0% v/v citral) after topical application of CCEO was much more and similar to each other Groups (BII, BIV, BV, BVI and BVII) compared to the Control Group BI. However, from 20-30 sec response to BCO, there were continuous decrease in HR in Groups BII, BVII followed by Group BIII, BIV, BV and BVI compared with the Control Group BI ($p < 0.05$; Figure 13).

The decrease in the MABP and HR in a plateau form with time following 30 sec BCO after topical application of CCEO and the increase in MABP in plateau form with time with reduction in HR in declining form with time following 30 sec of BCO after topical application of citral suggest a blunt baroreceptor response of the cardiac and vascular function against BCO. This blunt baroreceptor reflex shows that both CCEO isomers and citral isomer have cardiovascular protective mechanism in the Wistar rats as shown by the plateau. The complimentary reduction in MABP and HR following BCO after CCEO topical application and

the complimentary contrast of increase MABP and decrease HR following BCO after citral topical application are what translated to the blunting or attenuation of the baro-receptor reflex as indicated by the plateau form (CCEO groups of rats) or declining form (citral groups of rats) of responses.

Several studies on *Cymbopogon citratus* extract have shown and demonstrated that it possesses vaso-relaxation activities via a series of mechanisms which includes: inhibition of calcium entry (by calcium channel deactivation) into vascular smooth muscle cells; hyperpolarisation of vascular smooth muscle cells; inhibition of Rho-associated protein kinase; activation of guanyl cyclase and subsequent myosin light-chain phosphatase; activation of nitric oxide synthase and nitric oxide production with subsequent reactive oxygen species depletion; suppression of vasomotor centre and sympathetic activity; diuretic activities; inhibition of rennin-angiotensin-aldosterone system (Galán, 2020; Tchetchonaet *et al.*, 2022; Silva and Bárbara, 2022).

On the other hand, mechanism for its bradycardic might have included as have been suggested by earlier scholars: bradycardic response via activation of muscarinic receptors on the sino-atrial node; slowing down SA nodal depolarization and transmission frequency; or activation of cardiac inhibitory centre and vagal tone and subsequent deactivation of sodium and calcium channels and suppression of cardio-excitatory centre; suppression sympathetic activity and inactivation of adrenergic receptors (Silva and Bárbara, 2022). The citral's effect on vascular smooth muscle might have included the opposite mechanisms of these ones above.

The bases of our findings may rest on the above mechanisms so far as early reported. Although, there are little or no reports on the effect of CCEO on blunting or attenuation of the baro-receptor reflex using BCO in Wistar rats, nevertheless, the above mechanisms stand as bases for the mechanics for beat-to-beat baro-receptor reflex blunting responses in this study. In addition, reports have been shown that the mechanisms for CCEO cardiovascular protecting activities include boosting of antioxidants and depletion of hydrogen peroxides (Mediesse *et al.*, 2018; Safaeian *et al.*, 2020; Silva and Bárbara, 2022). This study shows coexistence these cardiovascular findings with boosting of serum, kidney and heart antioxidant enzymes and suppression of hydrogen peroxides.

So, the decrease in MABP and HR responses to 30 sec BCO after topical application of CCEO suggest a concurrent negative pressor and chronotropic synergy which may be cardio- and vasculo-protective against BCO maneuvering in the Wistar rats, having possibly attenuated cardiac and vascular contractions and rates via desensitizing sympathetic vaso-motor and cardio-acceleratory centres with concomitant sensitization of vagal tone pressure-rate reflex response in the rats (Barret *et al.*, 2019). On the other hand, the decrease in HR reflex response to the increase in MABP reflex response is a compensatory reflex response to BCO after Citral topical application in the rats. This difference in reflex responses to BCO in rats after topical applications are attributable to the Geranial and the Neral stereoisomers identified in CCEO as a counterpart to Citral. In disagreement to the findings in this study, exposure of rats to petroleum hydrocarbons (diesel, kerosene and engine oil by inhalation had increased MABP, HR and the consequent baroreflex sensitivity (instead of blunt reflex effect of CCEO in this study) and resetting of arterial blood pressure (unlike improvement of cardiovascular homeostasis produced by CCEO in this study) (Azeez *et al.*, 2012) by increasing vascular responses to circulating adrenalin and impairing both endothelial-dependent and non-endothelial-dependent cardiovascular function and baroreceptor reset in response to BCO in the Sprague-Dawley rats (Barret *et al.*, 2019).

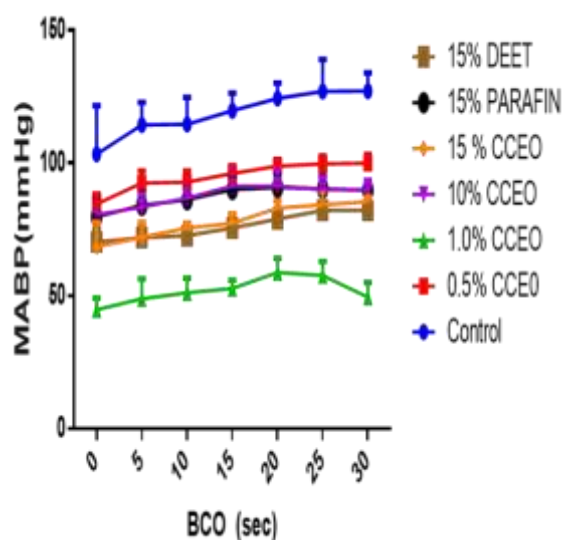


Fig 6: Mean arterial blood pressure responses during 30 sec bilateral carotid occlusions in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared with the control group AI, Group AV1 after topical application of paraffin and group AVII after topical application of diethyltoluamide. MABP = mean arterial blood pressure; CCEO = *Cymbopogon citratus* extract oil; DEET = diethyltoluamide; * = $p < 0.05$ = significant

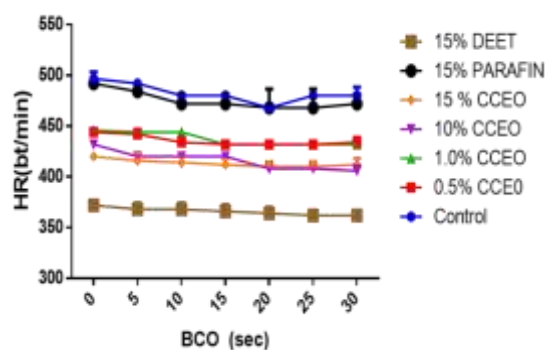


Fig. 7: Heart rate responses during 30 sec bilateral carotid occlusions in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared to the control group AI, group AVI after topical application of paraffin and group AVII after topical application of diethyltoluamide. HR = heart rate; DEET = diethyltoluamide; CCEO = *Cymbopogon citratus* extract oil; * = $p < 0.05$ = significant

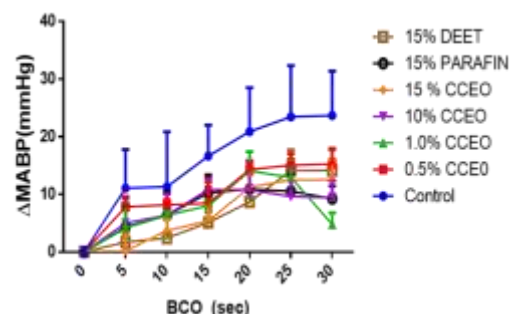


Fig. 8: Changes in mean arterial blood pressure responses during 30 sec bilateral carotid occlusions in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared with the control group AI, group AVI after topical application of paraffin and group AVII after topical application of diethyltoluamide. ΔMABP = change in mean arterial blood pressure; CCEO = *Cymbopogon citratus* extract oil; * = $p < 0.05$ = significant

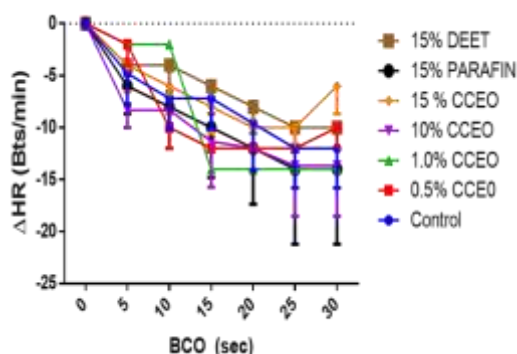


Fig. 9: Changes in heart rate responses during 30 sec bilateral carotid occlusions in Wistar rats' groups AII, AIII, AIV and AV after topical application of *Cymbopogon citratus* essential oil extract compared with the control group AI, group AVI after topical application of paraffin and group AVII after topical application of diethyltoluamide. ΔHR = change in heart rate; CEO = *Cymbopogon citratus* extract oil; * = $p < 0.05$ = significant

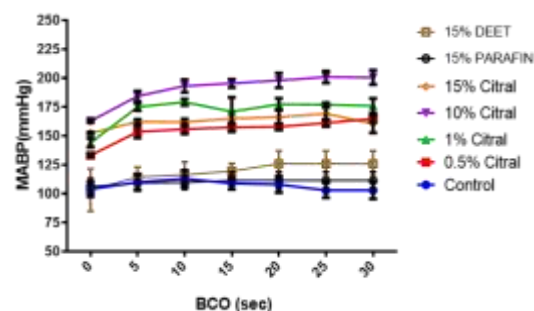


Fig. 10: Mean arterial blood pressure responses during 30 sec bilateral carotid occlusions in Wistar rats' groups BII, BIII, BIV and BV after topical application of citral drug compared with the control group BI, group BV1 after topical application of paraffin and group BVII after topical application of diethyltoluamide.

MABP = mean arterial blood pressure; DEET = Diethyltoluamide; * = $p < 0.05$ = significant

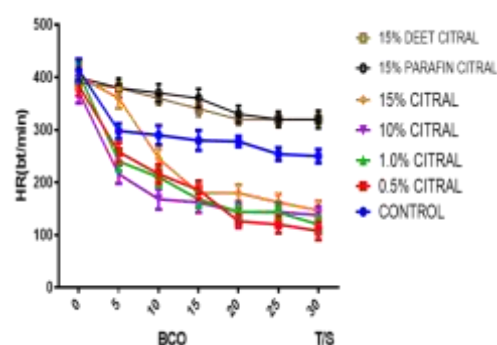


Fig. 11: Heart rate responses during 30 sec bilateral carotid occlusions in Wistar rats' groups BII, BIII, BIV and BV after topical application of citral drug compared with the control group BI, group BV1 after topical application of paraffin and group BVII after topical application of diethyltoluamide. HR = heart rate; DEET = diethyltoluamide; * = $p < 0.05$ = significant

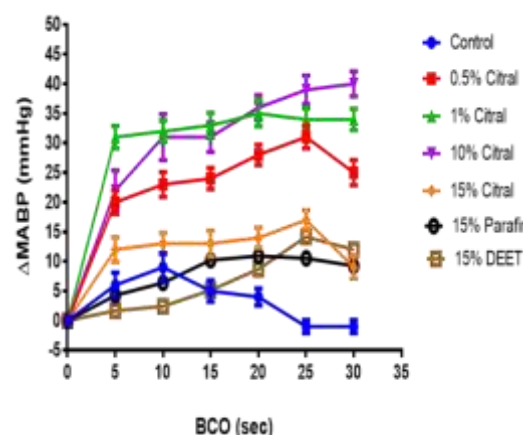


Fig. 12: Changes in mean arterial blood pressure responses during 30 sec bilateral carotid occlusions in Wistar rats' groups BII, BIII, BIV and BV after topical application of citral drug compared with the control group BI, group BV1 after topical application of paraffin and group BVII after topical application of diethyltoluamide. ΔMABP = change in mean arterial blood pressure, ΔHR = change in heart rate, * = $p < 0.05$ = significant

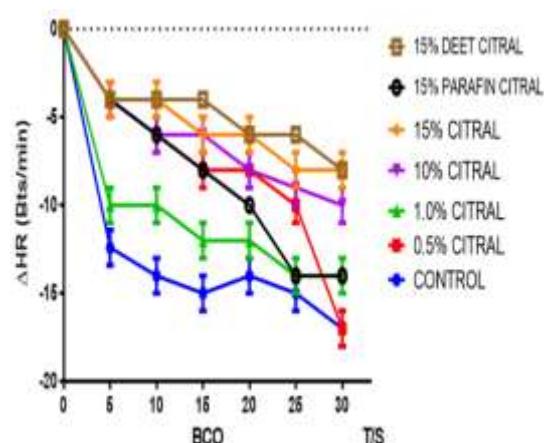


Fig. 13: Changes in heart rate responses following 30 sec bilateral carotid occlusions in Wistar rat groups BII, BIII, BIV and BV after topical application of citral drug compared with the control group BI, group BV1 after topical application of paraffin and group BVII after topical application of diethyltoluamide. ΔHR = change in heart rate; DEET = diethyltoluamide; * = $p < 0.05$ = significant

Conclusion: Therefore, the cardiovascular protecting benefits of CCEO are attributable to possible sympatho-vagal maneuvering, antioxidant boosting and suppression of peroxidation in the Wistar rats. In conclusion, our findings revealed that no significant changes in the mean arterial blood pressure ($\Delta MABP$) after topical application of CCEO and citral in response to bilateral carotid occlusion (BCO) despite significant decrease in MABP and HR upon topical application of CCEO and significant changes in MABP and HR upon topical application of citral). Therefore, topical application of CCEO or citral blunted possible alteration of the cardiovascular function that might be impacted from BCO.

DECLARATIONS

Ethical Approval: this study is an animal experimental studies with ethical approval obtained from College of Medicine Health Research Ethics Committee (Approval Number CMUL/HREC/10/19/629).

Disclaimer (artificial intelligence): we declare that there were no generative artificial intelligence (AI) aids or technologies such as Chat GPT, Copilot, or similar models were used during the writing or editing of this manuscript.

Declaration of conflict of interest: the authors declare no such things known as conflict of interest regarding the publication of this manuscript.

Declaration of data availability: data are available upon reasonable request from the first author, Dr. J. P. Akinbosola.

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