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Full length Research Article

The Effect of Acute Administration of the Aqueous Calyx Extract of *Hibiscus sabdariffa* on Blood pressure, Heart rate and Double Product of Apparently Healthy Human Subjects during Different Postures

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Summary: The aqueous calyx extract of *Hibiscus sabdariffa* (HS) is widely consumed as a beverage in Northern Nigeria and other parts of the world. HS has been reported to lower blood pressure (BP) in animals and man. However, not much is known about the effect of HS on BP in different postures. We tested the hypothesis that HS may lower BP, heart rate (HR) and heart rate-pressure product or double product (DP) by attenuating the discharge of the autonomic nervous system in different postures. Experiments were performed in accordance with the Principles of the Declaration of Helsinki. Following ethical approval and informed consent, BP and HR were measured in different postures (supine, sitting and standing) in apparently healthy human subjects (n=20) before and after (+HS) the oral administration of 15mg/Kg HS. Mean arterial pressure (MAP; taken as representative BP) and DP were calculated. Results are expressed as mean ±SEM. Paired t test and ANOVA with a post hoc Bonferroni test were used for statistical analyses. P<0.05 was considered significant. In the supine position MAP, HR and DP were significantly (P<0.0001 each) reduced in the presence of HS (85.6±1.7mmHg, 72.1±1.1/min and 8716±320mmHg.bpm) compared to its absence (89.6±2.0mmHg, 73.7±1.6/min and 8921±444mmHg.bpm). Similar trends were observed in the sitting position in the presence of HS (85.4±2.7mmHg, 73.7±1.8/min and 9098±345mmHg.bpm vs its absence: 91.4±2.3mmHg, 77.1±1.9/min and 9388±478mmHg.bpm; P<0.0001, P<0.0001 and P=0.007 respectively) and in the standing position (+HS: 89.3±2.0mmHg, 78.1±1.8/min and 10164±230mmHg.bpm vs its absence: 94.3±2.1mmHg, 81.8±2.3/min and 10742±268mmHg.bpm; P<0.0001, P<0.0001 and P=0.007 respectively). In the absence of HS, HR and DP were significantly higher in the standing posture (81.8±2.3/min, 10742±268mmHg.bpm) compared to the sitting (77.1±1.9/min, 9388±478mmHg.bpm; P<0.05 and P<0.0001 respectively) and the supine (73.7±1.6/min, 8921±444mmHg.bpm; P<0.001 each) postures while the BP remained similar. A similar trend was observed across the three postures in the presence of HS although the parameters were significantly lower. It is concluded that HS lowered BP, HR and DP by modulating autonomic mechanisms through the inhibition of both parasympathetic withdrawal and sympathetic nervous system discharge across the postures. Also the standing posture is associated more with a higher sympathetic nervous system discharge and a higher cardiac oxygen demand and workload than the sitting and supine postures in the absence or presence of HS.

Keywords*: Hibiscus sabdariffa calyces, Posture, Blood pressure, Heart rate, Double product, Autonomic nervous system*

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INTRODUCTION

The calyces of *Hibiscus sabdariffa* linn (family: Malvaceae) are used in many parts of the world, including Sokoto and much of Northern Nigeria, to make a delectable beverage locally called soborodo. The calyx extract of *Hibiscus sabdariffa* (HS) is also used in folk medicine in the treatment of hypertension. This has been scientifically validated by some studies (Mojiminiyi *et al*., 2007: Mojiminiyi *et al*., 2012). Changes in position of the human body are known to affect cardiovascular, endocrine, and renal functions (Norsk, 1992). While assuming the standing posture from sitting, for example, blood is pooled to the lower extremities due to gravitational forces. This leads to decreased venous return, stroke volume, arterial blood pressure and subsequent decrease in blood flow to the brain (Olufsen *et al*., 2005). This reduction in arterial blood pressure stimulates the baroreceptors located in the carotid sinus and aortic arch to a lesser extent, leading to withdrawal of parasympathetic discharge and activation of sympathetic discharge through the baroreflex-mediated autonomic control (Olufsen *et al*., 2005). The parasympathetic withdrawal induces fast increase in heart rate, while the sympathetic activation causes a slower increase in vascular resistance, vascular tone, cardiac contractility and a further increase in heart rate (Smith and Kampine, 1990; Bullock *et* *al*., 2001; Guyton and Hall, 2011). These responses combine to increase the blood pressure back to normal and ensure that blood flow to the brain is preserved. So the standing or erect posture may be associated with a state of parasympathetic withdrawal and activation of the sympathetic nervous system.

Other postural changes appear to affect blood pressure and heart rate as well. In the recumbent or horizontal posture, changing from the prone to supine and vice versa are associated with changes in blood pressure and heart rate (Pump *et al*., 2002; Tabara *et al*., 2005; Watanabe *et al*., 2007) with little or no change in the balance of the autonomic nervous system (Watanabe *et al*., 2007). However changes from the recumbent or horizontal posture (prone or supine) to the vertical (sitting or standing) are associated with significant differences in the balance of autonomic discharge to the heart, such that there is a shift towards the dominance of the sympathetic nervous system in the sitting position (Watanabe *et al*., 2007). In general, the parasympathetic nervous system (PNS) seems to be predominant in the recumbent postures while the sympathetic nervous system (SNS) appears to be predominant in the vertical postures (Watanabe *et al*., 2007). From the above, it is apparent that maintenance of blood pressure and heart rate in the different postures are dependent on the activity of the autonomic nervous system. An earlier work from our laboratory suggests that one mechanism by which HS lowers blood pressure is by inhibiting the discharge of the SNS (Aliyu *et al*., 2014). We therefore hypothesized that HS, being an inhibitor of the SNS, may lower the blood pressure and heart rate in the vertical postures of standing and sitting and perhaps in the recumbent posture as well.

The cardiac heart rate-pressure product or double product (DP) is the product of heart rate and systolic blood pressure. It is an index of cardiac oxygen consumption and workload (Katz and Feinberg, 1958; Kitamura *et al*., 1972; Hermida *et al*., 2001). Since HS lowers both heart rate and systolic blood pressure (Mojiminiyi *et al*., 2007; Aliyu *et al*., 2014), it is conceivable that it may lower DP too. However, this is yet to be examined.

Consequently, this study tested the hypotheses that HS may lower BP, heart rate (HR) and double product (DP) by attenuating the discharge of the autonomic nervous system across the postures and that this effect may be associated with a reduction in myocardial oxygen consumption and workload.

MATERIALS AND METHODS

Plant materials: The dried red calyces of HS were obtained from the Talata Mafara Central Market, Zamfara State, Nigeria. The dried red calyces of HS were previously identified and a voucher specimen (voucher number PCG/UDUS/MLV 001) deposited in the herbarium of the Department of Pharmacognosy and Ethnopharmacy, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria (Aliyu *et al*., 2014).

Extraction procedure: This was done as described earlier (Aliyu *et al*., 2014). Briefly, the dried calyces of HS were pounded into coarse powder. 500g of the powder was mixed with 2.7 litres of hot water (50°C) in a conical flask and stirred continuously with a magnetic stirrer. It was left overnight and later filtered using a filter paper (0.5µ). It was then decanted and evaporated to dryness in a water bath at 60°C leaving a powdery extract.

Tableting of powdery extract of HS: The powdery extract was then prepared into tablets containing 500mg of extract per tablet using the wet granulation method as earlier described (Aliyu *et al*., 2014). The granules were tableted using the single pouch machine (ART 400 Eureka Gmbh, Germany).

Ethical Clearance: Before the commencement of the study, ethical approval was obtained from the ethical committee of Specialist Hospital Sokoto, Nigeria, and informed consent was obtained from the subjects. The protocol number of the ethical committee approval was: SHS/SUB/133/1. Indeed, the experiments were performed in accordance with the Principles of the Declaration of Helsinki.

Participants: 20 apparently healthy male human volunteers aged 29.9±1.6 years and weighing 67.3±2.7 kg were randomly selected for the study. They were not on any medication that affects blood pressure and heart rate and were not consuming alcohol, tobacco or caffeine-containing beverages. They were also not involved in strenuous exercise twenty four hours before the test. Participants were excluded if they had cardiovascular, renal or endocrine diseases.

Data acquisition: The blood pressure and heart rate were measured using the EchoMax plus BP-400 digital sphygmomanometer (HuBDIC Co. Ltd., Gyeonggi-do, Korea) with the cuff at the level of the heart. In order to minimize the impact of cardiovascular adjustments during postural changes on our observations, the subjects were made to maintain each posture for at least 5 minutes before the blood pressure and heart rate were measured (Watanabe *et al*., 2007). Since we started with the supine position the subjects were allowed to rest for a minimum of twenty-five minutes in the supine position (Nardo *et al*., 1999) in order to allow sufficient time for the blood pressure and heart rate to reach the resting level after which these parameters were recorded in this position. They were then asked to sit up and the parameters measured after more than a five-minute rest (Tabara *et al*., 2005). They were then asked to stand up, and the blood pressure and heart rate recorded after more than five minutes. Thereafter, the HS tablets were given orally at a dose of 15mg/kg and the subjects were allowed to rest. One hour after HS administration, the above procedures were repeated.

The mean arterial pressure (MAP) was calculated using the formula:

Mean arterial pressure=
diastolic blood pressure + 1/3 pulse pressure
(Ganong, 1991; Jaja *et al*., 2000)
Where pulse pressure= systolic - diastolic blood pressure

In addition, the heart rate-pressure product or double product (DP) was calculated by multiplying the heart rate and the systolic blood pressure (Katz and Feinberg, 1958; Kitamura *et al*., 1972; Hermida *et al*., 2001).

Statistical analysis: Data were presented as Mean ± SEM. Paired student t-test was used to analyse the data that fell in pairs i.e. before the administration of HS compared to after its administration. However, when data from the three different postures were compared, ANOVA with a Bonferroni post hoc test was used for analysis. P<0.05 was considered statistically significant.

RESULTS

The systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), heart rate (HR) and double product (DP) obtained in the supine position in the absence and presence of HS are shown in table 1. The SBP, DBP, MAP, HR and DP were significantly (P<0.0001 each) lower in the presence of HS (Supine +HS) compared to its absence (Supine).

Table 2 shows the blood pressure parameters, heart rate and DP obtained in the sitting position in the absence and presence of HS. The blood pressure parameters and heart rate were significantly (P<0.0001 each) lower in the presence of HS compared to its absence. In addition, the double product was significantly (P=0.007) lower in the presence of HS compared to its absence.

Table 1:
The Blood pressure, heart rate and double product of apparently healthy subjects (n=20) in the supine position in the absence and presence of 15mg/kg HS

Parameter	Supine	Supine+HS
SBP (mmHg)	123.0 ±2.0	120.2 ± 1.9*
DBP (mmHg)	72.9 ± 2.0	68.4 ± 1.8*
MAP (mmHg)	89.6 ± 2.0	85.6 ± 1.7*
HP (beats/min)	73.7 ± 1.6	72.1 ± 1.1*
DP (mmHg/min)	8921 ± 444	8716 ± 320*

***=P< 0.0001 standing + HS vs standing*
**=P = 0.007 standing + HS vs standing*
SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure
MAP= Mean Arterial Blood Pressure; HR= Heart Rate
DP= Heart rate-pressure product or double product

The blood pressure parameters, heart rate and DP obtained in the standing position in the absence and presence of HS are shown in Table 3. The blood pressure parameters and heart rate were significantly (P<0.0001 each) lower in the presence of HS compared to its absence. Furthermore, DP was also significantly (P=0.007) lower in the presence of HS compared to its absence.

The SBP, DBP, MAP, HR and DP obtained in the supine, sitting and standing positions in the absence of HS are shown in figures 1 to 5. The blood pressure parameters (SBP, DBP and MAP) followed the same trend. They were highest in the standing position, followed by sitting and were least in the supine posture. However these parameters did not differ significantly across the three postures (Figs. 1-3). The HR was significantly (P<0.05) higher in the standing position compared to the sitting (Fig. 4). It was also significantly (P<0.001) higher in the standing posture compared to the supine (Fig. 4). The HR, however, showed no significant difference between the sitting and supine positions. The DP or heart rate-pressure product (Fig. 5) was also significantly higher in the standing posture than in the supine (P<0.001) and sitting (P<0.05) postures.

TABLE 2:
The Blood pressure, heart rate and double product of apparently healthy subjects (n=20) in the sitting position in the absence and presence of 15mg/kg HS

Parameter	Supine	Supine+HS
SBP (mmHg)	124.9 ±2.2	122.3 ± 2.3*
DBP (mmHg)	75.1± 2.1	70.0 ± 1.8**
MAP (mmHg)	91.4 ± 2.3	85.4 ± 2.7**
HP (beats/min)	77.1 ± 1.9	73.7 ± 1.0**
DP (mmHg/min)	9388 ± 478	9098 ± 345*

***= P< 0.0001 sitting + HS vs sitting*
**=P = 0.007 sitting + HS vs sitting*
SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure
MAP= Mean Arterial Blood Pressure; HR= Heart Rate
DP= Heart rate-pressure product or double product

TABLE 3:
The Blood pressure, heart rate and double product of apparently healthy subjects (n=20) in the standing position in the absence and presence of 15mg/kg HS

Parameter	Supine	Supine+HS
SBP (mmHg)	126.7 ±2.3	123.3 ± 2.5**
DBP (mmHg)	78.1 ± 2.3	72.4 ± 2.1**
MAP (mmHg)	94.3 ± 2.1	89.3 ± 2.0**
HP (beats/min)	81.8. ± 2.3	79.3 ± 2.0**
DP (mmHg/min)	10742 ± 268	10164 ± 230*

***=P< 0.0001 standing + HS vs standing*
**=P = 0.007 standing + HS vs standing*
SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure
MAP= Mean Arterial Blood Pressure; HR= Heart Rate
DP= Heart rate-pressure product or double product

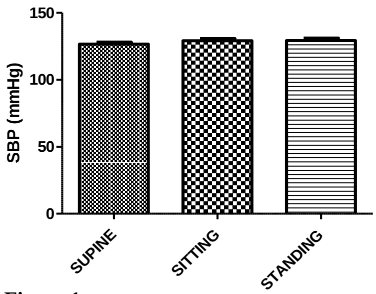

Figure 1:
The SBP (systolic blood pressure) of apparently healthy subjects (n=20) in the absence of HS in the supine, sitting, and standing positions. The SBP showed no significant difference across the postures.

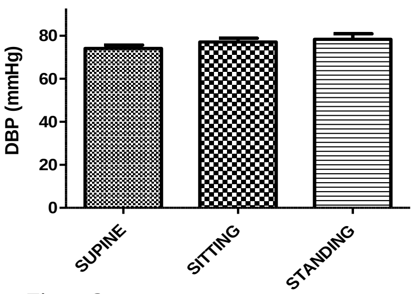

Figure 2:
The DBP (diastolic blood pressure) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the absence of HS. The DBP did not show a significant difference across the postures.

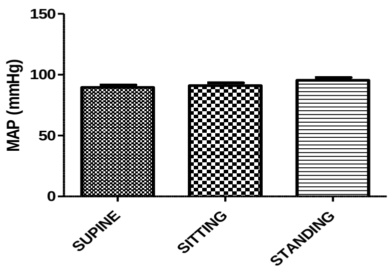

Figure 3:
The MAP (mean arterial pressure) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the absence of HS. The MAP showed no significant difference across the postures

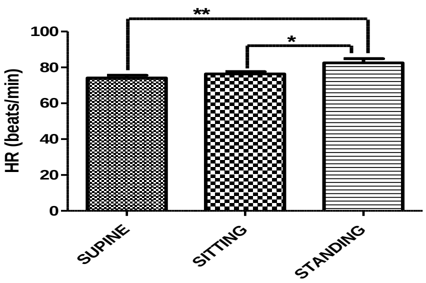

Figure 4:
The HR (heart rate) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the absence of HS. The HR was significantly higher in the standing position than in the supine and sitting positions. *=P<0.05 standing vs sitting; **=P<0.001 standing vs supine

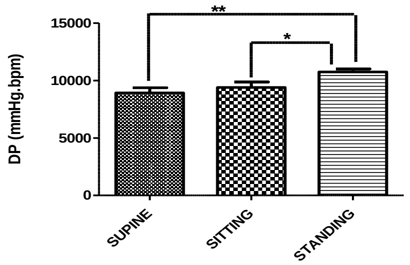

Figure 5:
The DP (Double Product or heart rate-pressure product) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the absence of HS. The DP was significantly higher in the standing position than in the supine and sitting positions.

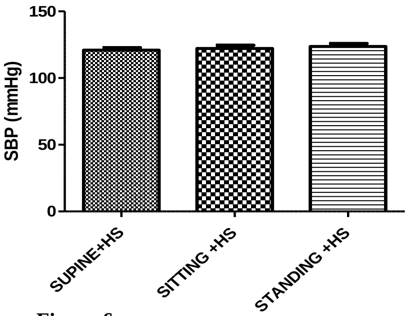

Figure 6:
The SBP (systolic blood pressure) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the presence of HS. The SBP showed no significant difference across the postures.

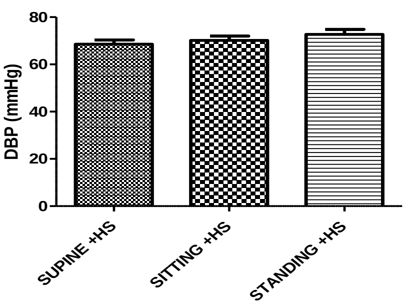

Figure 7:
The DBP (diastolic blood pressure) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the presence of HS. The DBP showed no significant difference across the postures.

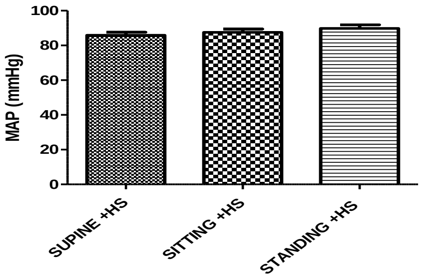

Figure 8:
The MAP (mean arterial blood pressure) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the presence of HS. The MAP showed no significant difference across the postures

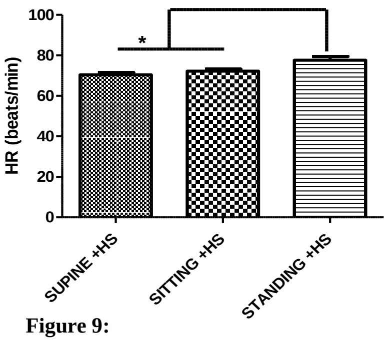

Figure 9:
The HR (heart rate) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the presence of HS. The HR was significantly higher in the standing position than in the supine and sitting positions.
**=P<0.001 standing +HS vs supine + HS and standing +HS vs sitting +HS*

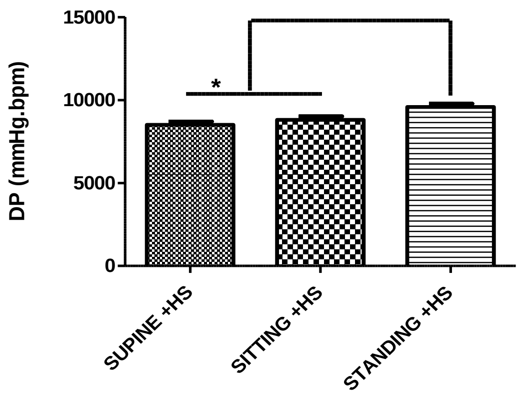

Figure 10:
The DP (Double Product) of apparently healthy subjects (n=20) in the supine, sitting, and standing positions in the presence of HS. The DP was significantly higher in the standing position than in the supine and sitting positions.
**=P<0.001 standing + HS vs supine +HS and standing + HS vs sitting +HS*

The SBP, DBP, MAP, HR and DP obtained in the supine, sitting and standing positions in the presence of HS are shown in figures 6 to 10. The blood pressure parameters (SBP, DBP and MAP) also followed a similar trend as in the absence of HS. They were highest in the standing posture, followed by sitting and were least in the supine position. However, these parameters showed no significant difference across the three postures (Figs. 6-8). The HR was significantly (P<0.001 each) higher in the standing position compared to the sitting and supine postures although it did not differ between the sitting and supine postures (Fig. 9). The DP was significantly (P<0.001 each) higher in the standing position compared to the supine and sitting postures (Fig. 10). However, the DP did not differ significantly between the supine and sitting postures.

DISCUSSION

The major finding of this study is that HS consistently lowered blood pressure, heart rate and double product across the postures studied. An additional finding is that in the absence of HS, HR and DP were significantly higher in the standing posture compared to the sitting and the supine postures while the BP remained similar across these postures. Furthermore, in the presence of HS a similar trend was observed for these parameters although the values were significantly lower. To the best of our knowledge, this study is the first to report that HS lowers the BP, HR and DP across the different postures.

This study found that HS lowered BP, HR and DP in the supine position compared to its absence. Since the supine posture is associated with a predominance of the parasympathetic nervous system discharge to the heart (Watanabe *et al*., 2007), this finding suggests that HS may act by stimulating the parasympathetic nervous system, or inhibiting parasympathetic withdrawal, resulting in the lowering of BP, HR and DP.

The vertical postures of sitting and standing are associated with parasympathetic withdrawal and sympathetic activation of the heart (Watanabe *et al*., 2007). HS reduced the BP, HR and DP in these postures suggesting that it might be acting by inhibiting parasympathetic withdrawal and inhibiting the discharge of the SNS. So the notion that HS might act by inhibiting the SNS activation as hypothesized in this study appears to be correct.

The decrease in DP caused by HS across the postures as seen in this study is an interesting observation that is being reported for the first time to the best of our knowledge. DP is a measure of cardiac work load as well as myocardial O_2 consumption (Katz and Feinberg, 1958; Kitamura *et al*., 1972) and it closely relates more with the left ventricular mass than the daily blood pressure mean (Hermida *et al*., 2001). In this study HS significantly lowered the DP across the supine, sitting and standing postures compared to its absence. This suggests that HS reduced the cardiac workload and myocardial O_2 consumption across the postures. This finding implies that HS enables the heart to utilize O_2 more efficiently as well as reduce the cardiac workload in the different postures. It is not clear how HS does this. A likely explanation may be that since HS is a known vasodilating agent (Adegunloye *et al*., 1996; Abubakar *et al*., 2019), it may be dilating the coronary arteries thereby leading to an increase in blood flow to the heart.

A comparison of the BP parameters across the postures in the absence and presence of HS showed no significant difference. It is not clear why this is so but it may suggest that the autonomic control of BP may be similar across these postures. However, the HR and DP were significantly higher in the standing posture compared to the sitting and supine postures in the absence and presence of HS. While changing posture from the supine to sitting and from sitting to standing, the immediate rise in HR is due to parasympathetic withdrawal followed later by sympathetic activation (Smith and Kampine, 1990; Bullock *et al*., 2001; Guyton and Hall, 2011). Since the HR was measured at least five minutes after the assumption of the posture by which time the autonomic adjustments are over, the increased HR may be due to the predominant autonomic system associated with that posture. Since the predominant autonomic system associated with standing is the sympathetic nervous system (Watanabe *et al*., 2007), the increased HR seen in the standing posture compared to the sitting and supine may be due to the increased discharge of the SNS. DP tended to follow a similar trend with HR since it is the product of HR and systolic pressure implying that the increased DP seen in the standing posture compared to the sitting and supine may also be due to the increased discharge of the SNS associated with standing. The increased SNS discharge associated with the standing position may be an effort to increase the cardiac output and ensure blood supply to the brain thereby overcoming the gravitational forces predominant in this position compared to the sitting and supine postures. Although the HR and DP were reduced in the presence of HS the significant difference in these parameters remained in the standing position compared to the sitting and supine postures.

The findings of this study showing that the BP parameters did not differ significantly across the postures in the absence of HS is in agreement with the findings of Silvani *et al*., (2017) with respect to systolic pressure. These workers reported no difference in systolic pressure across the supine, sitting and standing postures. However our findings are not in agreement with the findings of Silvani *et al*., (2017) with regards to the diastolic pressure. They found that the diastolic pressure was significantly higher in the vertical postures of standing and sitting compared to supine. They also reported that the BP was significantly higher in the standing compared to the sitting posture (Silvani *et al*., 2017). Tabara *et al*., (2005), also found that the blood pressure increased significantly in the sitting position compared to supine which is also not in accord with our findings. The disparity between our findings and those of these earlier workers may be due to differences in experimental protocol. It may also be due to the fact that they used older subjects than us. Silvani *et al*., (2017) used subjects with a mean age of 39±5years while Tabara *et al*., (2005) used subjects with a mean age 50±11 years some (33.9%) of whom were hypertensive. We used younger subjects with a mean age of 29.9±1.6 years all of whom were normotensive. In addition, our findings concerning HR in the absence of HS are dissimilar to those of Tabara *et al*., (2005) who reported that the heart rate increased in the sitting posture compared to supine. Tabara *et al*., (2005) however, did not study subjects in the standing posture.

HS tablets were used in this study in order to ensure that the exact dose required was administered to the subjects. This was also done in our earlier study (Aliyu *et al*., 2014). One of the limitations of this study was that direct evidence of the involvement of the PNS and SNS through microneurography and/or or heart rate variability techniques was not provided. This is because we do not have the equipment to perform these techniques due to poor funding. But it will be interesting to confirm the findings of this study using microneurography and/or heart rate variability techniques.

This study provides further evidence that the blood pressure lowering effect of HS may occur through the modulation of the autonomic nervous system across the postures of supine, sitting and standing. This supports the earlier finding from our laboratory suggesting that the hypotensive effect of HS was due to the inhibition of the discharge of the SNS (Aliyu *et al*., 2014). HS may also lower BP and HR through other mechanisms including: angiotensin-converting enzyme inhibitory action (Ojeda *et al*., 2010), diuretic (Mojiminiyi *et al*., 2000; Alarcon-Alonso *et al*., 2012), cholesterol-lowering (Ochani and D'Mello, 2009), direct vasorelaxant effect through acetylcholine-like and histamine-like actions (Adegunloye *et al*., 1996), through Ca2+ influx inhibition (Ajay *et al*., 2007; Alsayed *et al*., 2020), through antioxidant effects (Wang *et al*., 1997; Hopkins *et al*., 2013) and through the nitric oxide-cyclic Guanosine Monophosphate (NO-cGMP) relaxant pathway (Ajay *et al*., 2007; Sarr *et al*., 2009).

In summary, the BP, HR and DP of apparently healthy normotensive subjects were significantly lowered by HS across the supine, sitting and standing postures. In addition, in the absence and presence of HS, the HR and DP were significantly higher in the standing posture compared to the sitting and supine postures while the BP remained unchanged. It is concluded that HS may lower BP, HR and DP through the modulation of autonomic nervous system activity predominant in each posture. Such autonomic modulation may involve stimulation of the parasympathetic nervous system or inhibition of parasympathetic withdrawal and inhibition of the discharge of the sympathetic nervous system. These autonomic effects of HS are associated with a reduction in cardiac oxygen demand and reduction in cardiac workload as evidenced by its lowering of the DP. In addition, the standing posture, regardless of the presence or absence of HS, is associated predominantly with increased sympathetic nervous system discharge to the heart which is accompanied by an increase in cardiac oxygen demand and cardiac workload compared to the sitting and supine postures.

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