

Changes in blood pressure, vascular reactivity and inflammatory biomarkers following consumption of heated corn oil

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Abstract: Consumption of corn oil for cooking purpose is gaining popularity. The present study examined the effect of heated corn oil on blood pressure and its possible mechanism in experimental rats. Thirty male Sprague-Dawley rats were randomly divided into 5 groups and were fed with the following diets, Group I was fed with basal diet only; whereas group II, III, IV and V were fed with basal diet fortified with 15% (w/w) either fresh, once-heated, five-times-heated or ten-times-heated corn oil, respectively for 16 weeks. Body weight, blood pressure were measured at baseline and weekly interval for 16 weeks. Inflammatory biomarkers which included soluble intracellular adhesion molecules (sICAM), soluble vascular adhesion molecules (sVCAM) and C reactive protein (CRP), were measured at baseline and the end of 16 weeks. The rats were sacrificed and thoracic aorta was taken for measurement of vascular reactivity. There was significant increase in the blood pressure in the groups fed with heated once, five-times (5HCO) and ten-times-heated corn oil (10-HCO) compared to the control. The increase in the blood pressure was associated with an increase in CRP, sICAM and sVCAM, reduction in vasodilatation response to acetylcholine and greater vasoconstriction response to phenylephrine. The results suggest that repeatedly heated corn oil causes elevation in blood pressure, vascular inflammation which impairs vascular reactivity thereby predisposing to hypertension. There is a need to educate people not to consume corn oil in a heated state.

Keywords: Corn oil, Heating, Blood pressure, Vascular reactivity, Inflammation

INTRODUCTION

Hypertension is reported to be associated with cardiovascular morbidity and mortality resulting from stroke, myocardial infarction and kidney failure (Klag *et al.*, 1996). The prevalence of hypertension amongst Malaysians aged more than 30 years has increased from 32.9% in 1996 to 40.5% in 2004 (Rampal *et al.*, 2008). By the year 2025, 29% of the world's adult population is expected to suffer from hypertension (Ueshima *et al.*, 2000). Many factors contribute to the variation in blood pressure (BP) and these include genetic constitution, dietary habits and the life style of the individual.

Various studies in humans and animals were performed to determine the role of saturated and unsaturated fatty acids in hypertension. Consumption of diet rich in unsaturated fatty acids was found to decrease BP (Bairati *et al.*, 1992; Mensink *et al.*, 1988). Olive oil, a main ingredient of the Mediterranean diet, was found to decrease systolic and diastolic BP (Psaltopoulou *et al.*, 2004).

There is a high tendency for public to reuse the frying oils while cooking in order to save the cost of food preparation (Azman *et al.*, 2012). This practice is

detrimental to health as repeatedly heated oils undergo a series of chemical reaction known as thermal oxidation. Thermal oxidation products of heated oils include free radicals which are implicated in the pathogenesis of many diseases including hypertension (Soriguer *et al.*, 2003). Oxidative stress which is the imbalance between the production of reactive oxygen species (ROS) and antioxidant dependence system is capable to induce lipid per oxidation and free radicals formation. Oxidative stress and lipid per oxidation were implicated in the pathogenesis of hypertension and atherosclerosis (Nurul-Iman *et al.*, 2013; Rodrigo *et al.*, 2007; Ono *et al.*, 2013). Oxidative stress-induced endothelial injury impairs endothelial-dependent vasodilation which subsequently increases the vascular reactivity and resistance. ROS may enhance sequestration of nitric oxide-forming peroxynitrite which itself is a free radical. Furthermore, ROS causes vascular inflammation and activation of growth signalling pathway (Hausding *et al.*, 2013; Chatterjee and Fisher, 2014). There may be a link between oxidative stress and hypertension. Hypertensive patients were reported to have high level of malondialdehyde (MDA) which is a breakdown product of lipid per oxidation and lower antioxidant activities. A recent study has demonstrated linear positive correlation between blood pressure and oxidative stress (Korkmaz *et al.*, 2013). On the other hand, a negative correlation

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between blood pressure and antioxidant activities were reported (Muhammad *et al.*, 2012).

Previous studies showed that heated oils increase the risk of atherosclerosis (Adam *et al.*, 2008) and cause lipid per oxidation (Adam *et al.*, 2009). Osim *et al.*, (1996) reported that rats which were given diet of either fresh or oxidized palm oil for 18 weeks were found to have significant increase in the mean arterial pressure compared to the fresh palm oil diet. Leong *et al.*, (2009) and Jaarin *et al.*, (2011) also reported that heated palm and soy oil, respectively increased blood pressure with impaired vasodilatation in rats. The degree of thermal oxidation of the oil is determined by the presence of the unsaturated double bond, which indicates the degree of oil saturation. Unsaturated fatty acid which is present in the unsaturated oils such as soy oil and corn oil are more susceptible to lipid per oxidation compared to the monosaturated palm oil.

Heated oil causes oxidative stress and subsequently vascular inflammation, which plays an important role in cardiovascular diseases including hypertension (Korkmaz *et al.*, 2013; Muhammad *et al.*, 2012; Adam *et al.*, 2009). The present study was undertaken to determine the effect of heated corn oil (a polyunsaturated oil) on blood pressure (BP) and to elucidate the possible mechanism by measuring vascular reactivity and inflammatory biomarkers.

MATERIALS AND METHODS

Experimental animal and study design

A total of thirty adult male Sprague-Dawley rats aged 3 months (weighing 200-280g) were obtained from the Animal Housing Facility, Universiti Kebangsaan Malaysia and were randomly divided into five groups comprising of six animals per group. Prior ethical approval was obtained from the University Research Secretariat and the University Animal Ethics Committee (PP/ANAT/2011/SRIJIT/19-MAY/370-MAY-2011-AUGUST-2012). The animal management and procedures were performed as per the recommended guidelines. The rats were kept in plastic cages and maintained at room temperature of 25°C±2°C with a 12 hour light-dark cycle. All rats had free access to food and water *ad libitum* during the study period.

The rats were allowed to acclimatize for one week prior to the treatment with the test diets. Following one week of acclimatization, the following diets were fed to each group of rats: the group I (control) was fed only with commercial rat chow (basal diet); group II was fed with basal diet fortified with 15% weight/weight (w/w) of fresh corn oil (FCO); group III was fed with basal diet fortified with heated once corn oil (1HCO); group IV was fed with basal diet fortified with heated five times corn oil

(5HCO) and group V was fed with basal diet fortified with heated ten times corn oil (10HCO) for 16 weeks.

BP was measured at baseline and at intervals of four weeks for 16 weeks using non-invasive method. Blood was collected through orbital sinus prior to the treatment and at the end of study. The blood was then centrifuged to obtain plasma for the biochemical analyses. Following 16 weeks of study, the animals were sacrificed with overdose of diethyl ether. The thoracic aorta were harvested and freshly used for vascular reactivity study as described by Ajay *et al.*, (2006) with some modifications.

Preparation of oil diet

Corn oil used in this study was purchased from local manufacturer Organic Gain Sdn Bhd. It was used either in fresh form, heated once, five times or ten times following method described by Owu *et al.*, (1998) with some modifications. Briefly, 2.5L of oil was heated to 180°C in a stainless steel wok and used to deep-fry 1kg sliced sweet potatoes. The heating process lasted for 15 min. The hot oil was then left to cool at room temperature for five hours. This procedure resulted in the once heated corn group (1HCO). The pre-cooled hot oil was used to deep-fry another new batch of sweet potatoes. The frying process was carried out without adding any fresh oil to compensate for oil losses. In order to obtain heated five times (5HCO) and heated ten times (10HCO) corn oil, the same heating procedure was repeated four and nine times, respectively. The experimental diets were prepared twice in a week. Standard rat chow (Gold Coin, Port Klang, Selangor, Malaysia) was ground and mixed with some water and fresh or the heated corn oil prepared. The weight ratio of rat chow to the oil was 100:15. The mixture was then dried at 70°C overnight in an oven.

Measurement of BP

Non-invasive method was used to measure systolic BP as described by Jaarin *et al.*, (2011) using Power Lab data acquisition systems (AD Instruments, Castle Hill, NSW, Australia). A monitoring cuff was placed on proximal tail to detect changes in blood flow which occur during occlusion or releases of the cuff. The rats were put in an approximately body sized plastic container prior to BP measurement. This step ensured acclimation and faster BP measurement. The animals were pre-warmed for 15 minutes to increase blood flow to the tails. Minimum five measurements were recorded and the mean was used for analysis. The BP was recorded every 4 weeks over the 16 weeks feeding period.

Biochemical analysis

Measurement of plasma VCAM-1 and ICAM-1

The quantification of soluble VCAM-1 and soluble ICAM-1 were determined using commercially available ELISA kit from USCN Life Science Inc (Wuhan, China) and Abnova (Taipei, Taiwan) as described by Amran *et*

al., (2011). Absorbance at 450 nm was determined using VERSA micro plate reader (USA). Values of samples were calculated by the software provided with the micro plate reader and compared to the standard curve generated.

Measurement of plasma C-reactive protein

The level concentration of CRP was determined using commercially available ELISA kit (Abnova, Taipei, Taiwan) as described by Amran *et al.*, (2011). The intensity of colored product was measured using VERSA micro plate reader (USA) at 450 nm absorbance. Values of samples were calculated by the software provided with the micro plate reader and compared with the standard curve generated.

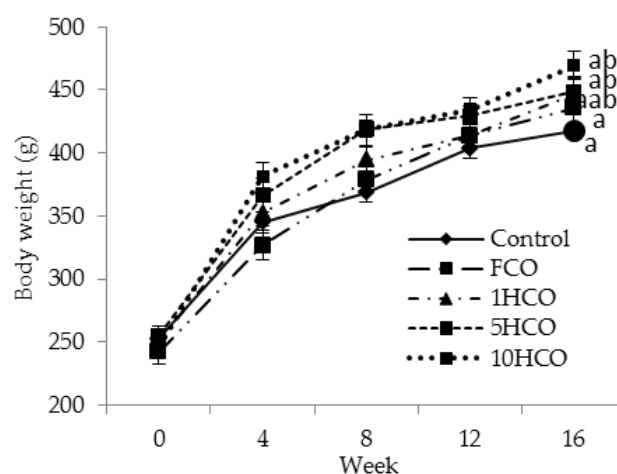


Fig. 1: Body weight gained following of 24 weeks consumption of fresh and heated corn oil (CO) in adult male rats. Data are shown as means $\pm$ SEM (n = 6).

Vascular reactivity

The vascular reactivity was determined using an aortic ring as determined by Ajay *et al.*, (2006). The descending thoracic aorta was dissected and excess fat and connective tissues were removed. The aorta was cut into ring segments with the width of 3-5mm. Aortic rings were suspended in 5ml tissue baths containing Krebs physiological salt solution of the following composition (mM): NaCl 118.0, KCl 4.7, CaCl₂•2H₂O 2.5, KH₂PO₄ 1.2, MgSO₄ 1.2, glucose 11.7, NaHCO₃ 25.0, and EDTA 0.026. The bathing solution was maintained at 37°C and continuously gassed with mixture of 95% oxygen and 5% carbon monoxide. Measurement of tissue isometric tension (g) was recorded by a force-displacement transducer (FT03E, Grass Instruments, West Warwick, RI, USA) attached to a MacLab recording system (MacLab model 8 S, AD Instruments, Castle Hill, NSW, Australia). The aortic rings were allowed to equilibrate for 30 to 45min prior to the initiation of experimental protocol. The bathing solution was replaced every 15 min and resting tension was readjusted to basal tension 1 g whenever it is needed.

Following the equilibration period, the aortic rings were allowed to achieve maximal tension by exposure to stimulation of isotonic KCl solution (high K⁺, 80 mM). Following the washout of responses to high K⁺, the rings were constricted with phenylephrine (PE, 10⁻⁷ M) to confirm the presence of the endothelium by the occurrence of relaxations induced by a single addition of acetylcholine (ACh 10⁻⁵M). Only the endothelial intact rings with more than 50% relaxation to ACh were used. All experiments were performed on different aortic rings with endothelium: (1) the cumulatively increasing concentration of relaxation responses to acetylcholine (ACh 10⁻¹⁰M to 10⁻⁵M) or sodium nitroprusside (SNP 10⁻¹¹M to 10⁻⁶M) was recorded in phenylephrine (PE 10⁻⁶M) pre-contracted aortic rings. Dose-response curves were plotted as percentage of relaxation against the maximal PE (10⁻⁶M) contraction; (2) the contractile responses to cumulatively increasing concentration of PE (10⁻¹⁰M to 10⁻⁵M) were recorded in the rings and expressed as percentage of maximum contraction obtained with high K⁺.

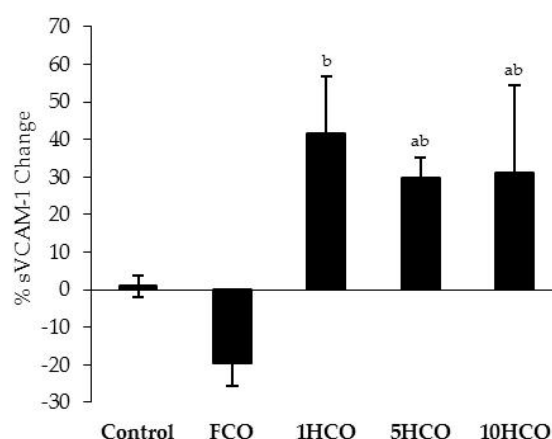


Fig. 2: Percentage of sVCAM change in rats fed heated corn oil diets. ^aVs control (p<0.05), ^bvs FCO (p<0.05).

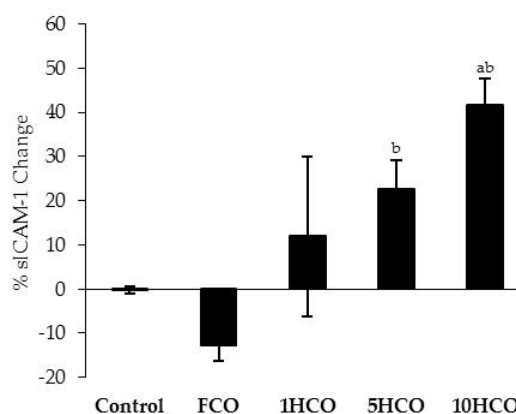


Fig. 3: Percentage of sICAM change in rats fed heated corn oil diets. ^aVs control (p<0.05), ^bvs FCO (p<0.05).

STATISTICAL ANALYSIS

The data were expressed as mean $\pm$ standard error of mean (SEM). Normality test was done by using Kolmogorov-Smirnov test. The normally distributed data were analysed using analysis of variance (ANOVA) and Tukey HSD post-hoc test. Data were not normally distributed were analysed by using Kruskal-Wallis test. Differences were considered significant if $p < 0.05$. Correlation test was also performed to observe the relationship between two parameters. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) software version 19.

RESULTS

Body weight

After the 16-week feeding period: All groups showed an increase pattern of body weight. The body weight increase was significant ($p < 0.05$) in all groups when compared to their respective baseline values. The increase of body weight in 1HCO, 5HCO and 10HCO groups was significantly higher compared to the control group ($p < 0.05$) (fig. 1).

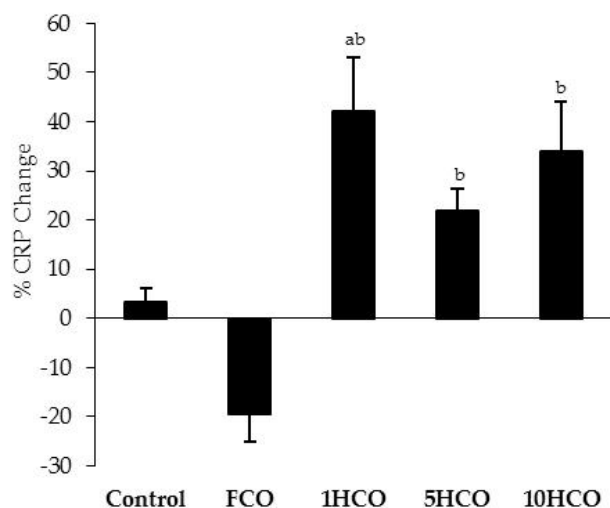


Fig. 4: Percentage of sICAM change in rats fed heated corn oil diets. ^aVs control ($p < 0.05$), ^bvs FCO ($p < 0.05$).

Vasodilation response to acetylcholine (ACh)

All groups showed a concentration-dependent relaxation of contraction induced by PE. At the highest concentration of ACh 10-5M, the percentage of vasodilation was significantly lower in the aortic rings of 1HCO ($88.49\% \pm 7.91$), 5HCO ($68.15\% \pm 3.70$) and 10HCO ($63.44\% \pm 6.91$) when compared to the control ($105.54\% \pm 9.76$) and FCO ($101.54\% \pm 3.72$) groups ($p < 0.05$). The percentage of vasodilation was significantly lower in 5HCO and 10 HCO compared to 1HCO ($p < 0.05$) (table 1).

Inflammatory biomarkers

There were significant increase in percentage changes in sVCAM-1 and sICAM-1 concentration in both 5HCO and 10HCO control and FCO group respectively (fig. 2 and fig. 3). A similar finding was noted for C-reactive protein in which 1HCO, 5HCO and 10HCO caused a significant increase in soluble C-reactive protein (fig. 4). figs. 5 and 6 showed correlation between blood pressure and sICAM-1 and sVCAM-1. There was significant positive correlation between the BP and sICAM-1 ($r = 0.345$, $p < 0.05$). However, there was no significant correlation between blood pressure with sVCAM-1 ($r = 0.126$).

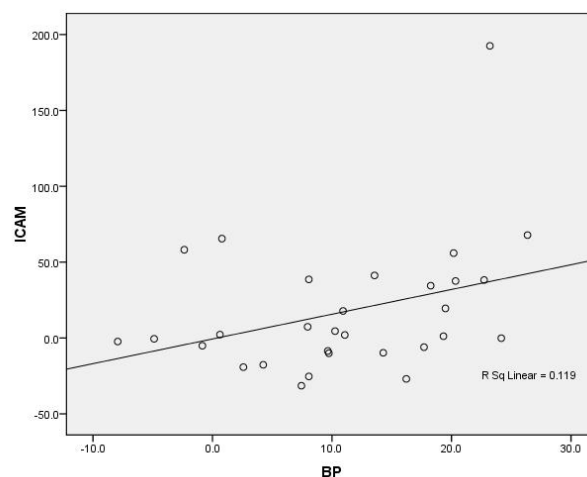


Fig. 5: Correlation between sICAM and BP.

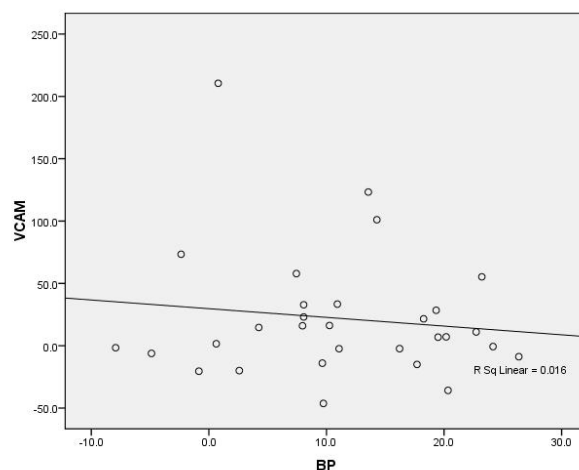


Fig. 6: Correlation between sVCAM and BP.

DISCUSSION

The present study showed that heated corn oil increased BP. The magnitude of the increase in BP was higher with heated five and ten times compared to once heated oil. In the present study, once heated, five times and ten times heated corn oil caused 9%, 14.5% and 15.30% increase in BP, respectively compared to the fresh corn oil. The

Table 1: Percentages changes in blood pressure, vasorelaxation and vasoconstriction response with heated corn oil.

Type of diet	FCO	1HCO	5HCO	10HCO
Blood pressure	2.00±0.80	9.00±1.50*	14.50±3.00*#	15.30±2.00*#
Vasorelaxation response	105.54±3.70	88.50±7.91*	68.15±3.70*#	63.44±6.91*#
Vasoconstriction response	119.32±4.78	128.49±5.95*	187.66±27*#	185.41±18*#

Data are mean± SEM. *p<0.05 compared to FCO, #p< 0.05 compared to 1HCO.

effect of heated oil on blood pressure was comparable to a study by Leong *et al.*, (2009) and Jaarin *et al.*, (2011) who reported that repeatedly heated palm oil and soy oil increases blood pressure. However, in contrast the magnitude of rise in BP with corn oil appeared to be lower at the smallest and highest heating frequency compared to the soy oil. Jaarin *et al.*, (2011) reported that heated once, five times and ten time soy increased BP by 16%, 25.9% and 34.4%, respectively. In the light that lipid per oxidation may play an important role in the pathogenesis of hypertension, it was expected that the percentage increase in BP to be more with polyunsaturated oil such as soy and corn oil as they are more prone to lipid per oxidation compared to the monounsaturated palm oil. Hence, it was expected that, the percentage increase in BP with corn and soy oil would be comparable. However, in contrast, heated corn produced a less increase in BP compared to soy oil. A reason for this was not clearly understood. It may be suggested that corn oil was more stable compared to the soy oil for lipid per oxidation. The stability of corn oil could not be concluded as the peroxide value and vitamin E content of the corn oil was not determined in the present study. Peroxide values and vitamin E content of the heated corn oil and soy oil should be determined in future studies in order to compare the oil stability.

In the present study, the increase in BP with corn oil was associated with an increase in vascular reactivity as reflected by attenuation of vascular relaxation response to acetylcholine and enhanced vasoconstriction response to phenylephrine. The effect of heated oil on vascular reactivity in the present study was similar to what was reported by Leong *et al.*, (2009) and Jaarin *et al.*, (2011). Therefore, this finding again suggests that heated oil increased BP due to vasoconstriction which increases the total peripheral resistance of the blood vessels. The vasoconstriction may be due reduction in bioavailability of endothelium-derived vasoactive compounds such as nitric oxide and prostacyclin which impairing endothelial function (Amran *et al.*, 2011).

In the present study, heated corn oil increased soluble VCAM-1, soluble ICAM-1 and C-reactive protein concentration which indicate that heated corn oil increases inflammatory biomarkers and vascular inflammation. A positive correlation between BP changes and ICAM-1 suggests that the increase in the BP with heated corn oil was attributed to vascular inflammation.

Again, this finding was in agreement with Ng *et al.*, (2012) which reported that vascular inflammation may contribute to BP raising effect of heated soy oil. The association between adhesion molecules and cardiovascular diseases particularly hypertension and atherosclerosis were reported in previous studies (Schneemann *et al.*, 1993; Schmidt *et al.*, 2009; Parker *et al.*, 2001). In this study although, heated corn oil cause significant increase in soluble VCAM-1 and ICAM-1, the positive correlation was observed only for ICAM-1 but not for VCAM-1. The reason for this was unclear. The possible role of inflammation in pathogenesis of heated oil-induced hypertension was further supported by an increase in CRP level with heated corn oil. The possible role of vascular inflammation in hypertension was also reported by previous studies (Demerath *et al.*, 2001; Bayorh *et al.*, 2005; Ganafa *et al.*, 2002; Mahfouz and Kummerow, 2004; Yamamoto *et al.*, 2008; Gebhard *et al.*, 2011; Gortan *et al.*, 2013).

We postulated that the detrimental effect of heated oil on BP was most likely due to lipid peroxidation as our previous study reported that heated oil increase peroxide value which was coupled with reduction in vitamin E content of heated oil (Adam *et al.*, 2007). Heating destroyed vitamin E particularly α -tocopherol and tocotrienol. After five-times heating, more than 90% of vitamin E in both palm and soy oil were destroyed thereby rendering the oil more prone to oxidation (Adam *et al.*, 2007). Lipid per oxidation of the oil was detrimental to vascular endothelium which leads to vascular inflammation. Vascular inflammation may interfere with the release of vascular endothelial derived relaxing factors such as nitric oxide and prostaglandin (Demerath *et al.*, 2001; Bayorh *et al.*, 2005; Ganafa *et al.*, 2002; Mahfouz and Kummerow, 2004; Yamamoto *et al.*, 2008; Gebhard *et al.*, 2011). The role of lipid peroxidation in pathogenesis of heated oil-induced hypertension was further supported by Nurul Iman *et al.*, (2013) as the blood pressure raising effect of palm oil was attenuated by administration of virgin coconut oil which is rich in antioxidant content mainly polyphenols.

However, the present study had few limitations. We could not really relate the aortic immunological staining for VCAM-1 and ICAM-1 (Ng *et al.*, 2012) with soluble adhesion molecules. It would be better in future if the adhesion molecules are measured by the same technique which is aortic immunological staining (Ng *et al.*, 2012).

Unfortunately, it could not be done due to time and financial constraint. The stability test of heated corn should be undertaken by measuring the peroxide value and vitamin E content of the heated corn oil. We also admit that measuring diastolic pressure may be more beneficial especially with relation to hypertension. Further studies are needed to observe the effect of heated oil on endothelial derived relaxing factors including nitric oxide and eicosanoids.

CONCLUSION

Heated corn oil increases BP. The increase in the BP was significantly higher with heated five-times and ten-times corn oil. The increase in BP with heated corn oil was associated with an increase in vascular reactivity, inflammatory biomarkers, which suggests the possible role of inflammation and lipid per oxidation in the pathogenesis of heated oil-induced hypertension. Future studies are required to determine the effect of heated corn oil on vascular derived relaxing factors such as nitric oxide and eicosanoids.

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