Serum VCAM-1 reduction by phytosomal curcumin formulation in rats on a high-fat diet

Rima Abdul Razzak
Department of Physiology, College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain
Ghada Al Kafaji
Princess Al-Jawhara Center for Molecular Medicine and Inherited Disoders, Arabian Gulf University, Manama, Bahrain
Mohammad Nadir Khan
Department of Physiology, College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain
Amar Muhsin Marwani
College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain, and
Yahya M. Naguib
Department of Physiology, College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain

Received 28 February 2023
Revised 17 May 2023
Accepted 30 May 2023

Abstract

Purpose – This paper aims to evaluate the effect of consumption of a high-fat diet (HFD) rich with total saturated fats on adiposity and serum levels of vascular cell adhesion molecule (sVCAM-1), a biomarker of endothelial inflammation/dysfunction. Another aim is to evaluate whether supplementation of a phytosomal formulation of curcumin would reduce adiposity measures and sVCAM-1 levels in HFD rats.

Design/methodology/approach – The study was conducted on 17 male rats which were allocated to one of three feeding regimen groups: normal diet (ND); HFD, or HFD with dietary phytosomal curcumin (HFD-C). Anthropometric measures were recorded weekly up to 20 weeks of feeding intervention, at the end of which, sVCAM-1 levels were also compared with one-way ANOVA and Tukey *post-hoc* analysis.

Findings – The HFD group had the greatest values for raw anthropometric data, and there was a group difference in anthropometric measures, however there was no significant difference between HFD and HFD-C for any measure. The gain at 20 weeks from initial values did reveal significant differences in weight and abdominal circumference between HFD and HFD-C groups. There were significant group differences in sVCAM-1 levels, with only HFD-C displaying significant lower levels than HFD group.

Originality/value – This is the first study that shows the capacity of a phytosomal formulation of curcumin in reducing adiposity and sVCAM-1 levels during daily intake of saturated fats above the recommended level. The results are promising in that this formulation can protect against endothelial

This work was supported by a grant from the Arabian Gulf University (Grant number: G02/AGU 11/19).
Conflict of interest: The authors declare that they have no conflict of interest of any kind.

Arab Gulf Journal of Scientific Research
Emerald Publishing Limited
e-ISSN: 2536-0051
p-ISSN: 1985-9899
DOI 10.1108/AGJSR-02-2023-0092

inflammation/dysfunction, and can be used as complimentary therapy to suppress dyslipidemia/obesity-related cardiovascular complications.

Keywords High-fat diet, Adiposity, Phytosomal curcumin, sVCAM-1 level, Endothelial inflammation
Paper type Research paper

Introduction

Cellular adhesion molecules (CAMs) are glycoproteins expressed on the surface of various cells in response to signals of inflammation and mediate binding with the extracellular matrix (Mulhem, Moulla, Klöting, *et al.*, 2021). In response to pathophysiological stimuli, the expression of CAMs on the endothelial cell surface mediates the interaction between the endothelium and blood. For example, during inflammation, CAMs are involved in migration of leukocytes to inflammatory sites (Mulhem *et al.*, 2021), with E-selectin mediating the first adhesion step of monocytes to the vascular wall, whereas ICAM-1 and VCAM-1 both mediate firm adhesion to endothelial cells and transmigration of leukocytes into the subendothelial space (Nourshargh & Alon, 2014; Kreuger & Phillipson, 2016). CAMs can exist as both transmembrane proteins and soluble circulating forms, formed by proteolytic cleavage of the extracellular domain and release into the circulation. As such, soluble CAMs (sCAMs) correlate with their cellular surface expression (Drake, Chambers, Ott, & Daiello, 2021; Troncoso *et al.*, 2021) and are considered sensitive molecular indicators and accepted markers of vascular endothelial dysfunction (Drake *et al.*, 2021; Troncoso *et al.*, 2021).

In general, hyperlipidemic states are associated with increased levels of CAMs. With elevated levels of serum FFAs, that may result from consumption of high amounts of saturated fats (Silva Figueiredo *et al.*, 2017), as well as with obesity and hyperlipidemia (Henning, Venable, Vingren, Hill, & McFarlin, 2018; Troncoso *et al.*, 2021), there is elevated production of pro-inflammatory cytokines (i.e. IL-6, and tumor necrosis factor (TNF-α)) that induce systemic inflammation (Duan *et al.*, 2018; Berg, Seyedsadjadi, & Grant, 2020) and increased concentrations of soluble endothelial activation markers including E-selectin, VCAM-1, and ICAM-1 (Mathew, Tay, & Cusi, 2010).

Curcumin is a polyphenol and effective ingredient of Curcuma longa (turmeric). Curcumin has been reported to have many health and therapeutic properties, and previous evidence has shown that it has strong anti-inflammatory and antioxidant properties (Uchio *et al.*, 2021; Peng *et al.*, 2021; Fuloria *et al.*, 2022). Different animal studies have established curcumin's anti-atherosclerotic effect, its effect in alleviating hyperlipidemia (Panahi, Ahmadi, Teymouri, Johnston, & Sahebkar, 2018; Ashraf *et al.*, 2022), and on the expression of CAMs levels (Um *et al.*, 2014; Pradana *et al.*, 2019). These studies relied on different delivery curcumin formulations including solid dispersions, complexation with cyclodextrins, co-administration with piperine, as nano-particles/emulsions, and as microencapsulation/emulsions. A phytosomal delivery system has also emerged to enhance the systemic bioavailability of curcumin (Mirzaei *et al.*, 2017; Zheng & McClements, 2020), but according to our knowledge, its effect on soluble CAM levels, especially in HFD-induced animals, has not been investigated.

The purpose of this current study was to evaluate the effect of consumption, for 20 weeks, of a HFD with total fat of 34.5 % of which the total saturated fats comprise 15.2% of total energy intake, on adiposity induction and sVCAM-1 levels. Another aim was to evaluate whether supplementation of phytosomal curcumin would reduce adiposity measures, and sVCAM-1 levels in rats placed on an HFD.

Materials and methods

The Research Ethics Committee at our university approved (Ethical approval No. E03-PI-11/19) all experiments that were carried out in accordance with the internationally accepted guide for the care and use of laboratory animals.

Experimental animals and curcumin supplementation

Seventeen Sprague-Dawley male rats (8 – 10 weeks old, 190 to 240 g) were individually housed in cages at 22 ± 2° C temperature while a 12 h on/12 h off light cycle was maintained. All animals had free access to water. One group of 6 rats was on normal chow/diet (ND) *ad libitum* in pellet form. The ND contained 14.0 MJ/kg digestible energy with 23% protein, 65% carbohydrate and 12% fat. To induce adiposity in another group of 11 rats, a semi-pure high-fat diet (HFD) (Specialty Feeds Pty Ltd, Australia: SF13-092) was provided in the form of 12 mm diameter pellets. The calculated nutritional parameters of the HFD are protein: 25.50 %, total fat: 34.50 % (15.18% Total saturated fats), crude fiber: 6.00%, AD fiber: 6.00 %. The HFD contained 21.7 MJ/kg digestible energy, of which 60.1% was from fat. A weighed amount of fresh high-fat-diet was given every morning. The remaining food in the cage was collected and weighed 24 hours later.

A well-absorbed curcumin formula, curcumin phytosome as Meriva-SF (THORNE RESEARCH, INC, Summerville, South Carolina) was used in this study, with each capsule containing 500 mg of curcumin phytosome complex. The composition of the curcuminoid mixture is 75% curcumin, 15% dimethoxy-curcumin, and 10% bisdemethoxycurcumin. The recommended daily serving of *this formulation* for humans is two capsules, thus providing 1000 mg of curcumin phytosome complex per day (1,000 mg/day, corresponding to 200 mg pure curcumin mixture/day).

For a 70 kg person, 200 mg pure curcumin mixture/day would provide 2.86 mg curcumin mixture/kg/day. To deliver the equivalent dose to rats, the Animal Equivalent Dose (AED) was calculated by multiplying the human dose by the rat conversion factor of 6.2 (Nair & Jacob, 2016). The calculated AED of pure curcumin mixture in this study corresponds to 17.73 mg/kg/day, which was supplemented to rats by providing 88.65 mg curcumin phytosome complex/Kg/day. For the whole duration of HFD regimen (20 weeks), 6 of the 11 rats were daily supplemented, by once-a-day oral gavage, with the curcumin phytosome dissolved in 5 ml of 50% aqueous dimethyl sulfoxide (DMSO).

Energy intake (MJ/day) was calculated as the product of food intake (kg/day) by the digestible energy (MJ/kg) of the food.

Adiposity measures

Individual rat body weights, (g) naso-anal length (cm), abdominal circumference (cm) and thoracic circumference (cm) were recorded at the beginning of the experiment, then weekly. The naso-anal length (cm) was measured by a non-extensible thread, and readings were taken using a ruler with an accuracy of 0.1 cm. Measurements of the level of adiposity at the end of the feeding period include the body weight and body weight gain, body mass index (BMI), abdominal and thoracic circumference. The BMI was calculated as:

$$BMI = \frac{Weight\,(g)}{Naso - anal\,Length\,(cm)^2}$$

Measurement of sVCAM-1 concentration

At the end of 20 weeks of feeding regimen, blood samples were collected to determine the levels of sVCAM-1. Plasma concentrations of sVCAM-1 were measured by enzyme-linked immunosorbent assays (ELISA) in rats from each of the three feeding groups (ND, HFD and HFD-C). sVCAM-1 concentration was expressed in ng/ml.

Statistical analysis

Data are shown as means ± SD. Statistical analysis was performed using SPSS version 12.0 (Chicago, IL). The Kolmogorov-Smirnov test was used to assess whether the distribution of

variables followed a Gaussian pattern. Analysis of variance (ANOVA) was used for multiple between-group comparisons. The Tukey test was used for post-hoc analysis. The Pearson product-moment correlation coefficient was used to measure linear correlation between two sets of data. P values < 0.05 were considered statistically significant.

Results

Energy intake and adiposity measures

For both groups of rats on HFD (with and without curcumin supplementation), food consumption was about 20 g of food per day, corresponding to 0.434 MJ energy intake per day.

Values for all raw adiposity measures were greatest in the HFD group, except for the initial weight measure. One-Way ANOVA showed significant group differences for all adiposity measures (Table 1). Post-hoc Tukey analysis revealed significant pairwise differences as follows: Weight, BMI (ND and HFD, $P < 0.05$; ND and HFD-C, $P < 0.05$); and for abdominal circumference (ND and HFD, $P < 0.05$). There was no significant difference in these adiposity measures between the HFD and HFD-C groups. As for the initial weight, both ND and HFD-C were significantly greater than HFD ($P < 0.01$), with no significant difference between ND and HFD-C ($P > 0.05$).

For adiposity measures representing change in values (Table 2) between 20 weeks of feeding regimen and beginning of experimentation, there was significant group differences for all measures. For all rat groups, all measures showed a positive change, with the greatest change in the HFD group. Pairwise comparison revealed a significant difference between HFD and HFD-C groups in weight change ($P < 0.01$) and change in abdominal circumference

Table 1.
Initial weight and raw adiposity measures after 20 weeks of feeding regimen for the three groups of rats

	Initial weight (g)	Weight (g)	BMI (g/cm^2)	Abdominal C (cm)	Thoracic C (cm)
ND	223.00 ± 9.47	394.67 ± 26.73	0.65 ± 0.03	17.00 ± 0.32	15.92 ± 0.42
HFD	204.80 ± 7.26	433.40 ± 16.30	0.72 ± 0.02	18.10 ± 0.82	16.90 ± 0.96
HFD-C	225.33 ± 7.26	414.00 ± 16.33	0.70 ± 0.03	17.42 ± 0.74	16.50 ± 0.32
F(*P*-value)	9.71 (*0.002*)	4.81 (*0.026*)	6.92 (*0.008*)	3.94 (*0.044*)	3.51 (0.058)

Note(s): F (P value) obtained with one-Way ANOVA. ND: normal diet ($n = 6$); HFD: high-fat-diet ($n = 5$) HFD-C: high-fat-diet supplemented with phytosomal curcumin ($n = 6$)
Source(s): Tables were produced by the authors of this publication

Table 2.
Change in adiposity measures after 20 weeks of feeding regimen from initial values, for the three groups of rats

	Weight (g)	BMI (g/cm^2)	Abdominal C (cm)	Thoracic C (cm)
ND	171.67 ± 19.42	0.09 ± 0.03	3.92 ± 0.58	4.75 ± 0.42
HFD	228.60 ± 16.73	0.18 ± 0.07	5.50 ± 0.79	6.10 ± 1.08
HFD-C	188.67 ± 18.96	0.13 ± 0.04	4.25 ± 0.82	5.17 ± 0.61
F(*P*-value)	3.33 (< *0.001*)	4.60 (*0.030*)	6.85 (*0.008*)	4.84 (*0.025*)
Ratios				
HFD/ND	1.33	2.00	1.40	1.28
HFD-C/ND	1.10	1.40	1.08	1.09
HFD-C/HFD	0.83	0.72	0.77	0.85

Note(s): F (P-value) obtained with one-Way ANOVA. ND: normal diet ($n = 6$); HFD: high-fat-diet ($n = 5$) HFD-C: high-fat-diet supplemented with phytosomal curcumin ($n = 6$)
Source(s): Tables were produced by the authors of this publication

($P < 0.05$), but not for BMI or thoracic C. Not for any measure was there a significant difference in change of that measure between ND and HFD-C rats. When plotting the cumulative weight gain every 2 weeks from the initial weight (Figure 1), it is obvious that the HFD rats, at most time points, displayed significantly higher weight gains than either ND or HFD-C rats.

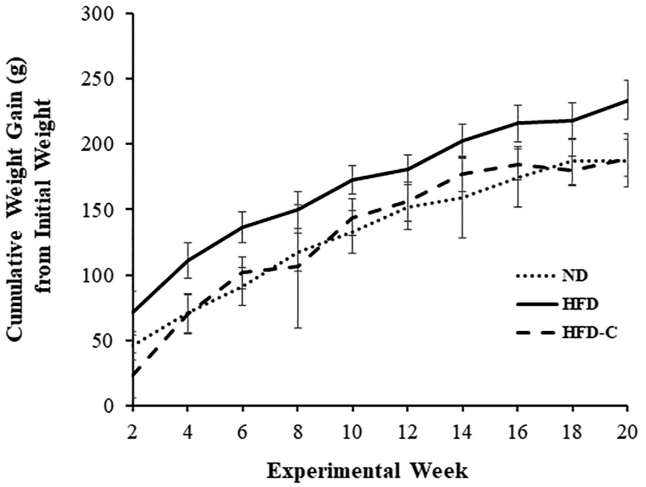
Soluble VCAM-1 concentrations

The mean concentration of sVCAM-1 was highest in the HFD group, with almost 58% increase in comparison to the ND group. sVCAM-1 concentration was lowest in the HFD-C group, about 75% the concentration in ND group and only 47% that for the HFD group. Interestingly, the highest concentration of sVCAM-1 level in the HFD-C group was less than the lowest value in the HFD group.

ANOVA analysis reveals a significant effect of feeding regimen $F_2 = 4.618$, $P = 0.029$ on sVCAM-1concentrations, however post-hoc Tukey analysis shows that the difference in sVCAM-1 mean concentration was only significant between HFD and HFD-C rats ($P = 0.025$). Figure 2 is a box and whiskers plot depicting the plasma concentrations of sVCAM-1 in the three groups of rats.

Correlation between sVCAM-1 and adiposity measures

Table 3 displays that there was an inverse correlation between sVCAM-1 and all adiposity measures in rats fed on a normal diet, but it was only statistically significant for BMI and Abdominal circumference. For HFD rats, the correlation between sVCAM-1 was positive, but not statistically significant, with adiposity measures related to weight (weight, BMI) and was negative, but not significant, with measures related to circumference.



Note(s): ND: normal diet ($n = 6$); HFD: high-fat-diet ($n = 5$); HFD-C: high-fat-diet supplemented with phytosomal curcumin ($n = 6$)

Source(s): Figures were produced by the authors of this publication

Figure 1.
Line plots depicting the cumulative weight gain every 2 weeks from the initial weight in the three groups of rats

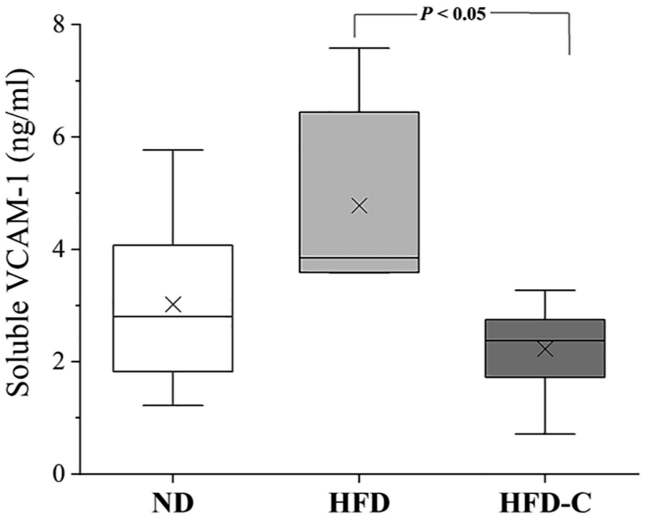


Figure 2.
Box and Whisker plots of circulating serum levels of sVCAM-1 in the three groups of rats on different feeding regimen

Note(s): ND: normal diet (n = 6); HFD: high-fat-diet (n = 5); HFD-C: high-fat-diet supplemented with phytosomal curcumin (n = 6). The middle line in the box represents the median and "X" represents the mean of the data points

Source(s): Figures were produced by the authors of this publication

Table 3.
Association between sVCAM-1 concentration and raw adiposity measure after 20 weeks of feeding regimens

sVCAM-1	ND	HFD	HFD-C
Weight (g)	−0.68 (0.140)	0.85 (0.068)	−0.57 (0.237)
BMI (g/cm^2)	−0.92 (*0.010*)	0.70 (0.189)	0.18 (0.732)
Abdominal C (cm)	−0.91 (*0.010*)	−0.68 (0.202)	0.54 (0.268)
Thoracic C (cm)	−0.36 (0.484)	−0.08 (0.900)	0.01 (0.978)

Note(s): Pearson correlation coefficient and (P-value). ND: normal diet (n = 6); HFD: high-fat-diet (n = 5); HFD-C: high-fat-diet supplemented with phytosomal curcumin (n = 6). Italic font indicates statistical significance
Source(s): Tables were produced by the authors of this publication

Discussion

The recommendation by the World Health Organization (WHO) is that total fat should not exceed 30% of total energy intake, and intake of saturated fats should be less than 10% of total energy intake (World Health Organization, 2018). In the present study, we used a diet rich in saturated fats (15% of total energy intake), exceeding the amount recommended by WHO, to investigate whether 20 weeks intervention with this HFD can induce some level of adiposity. Moreover, we evaluated the effect of this HFD on the plasma concentration of sVCAM-1, a biomarker of inflammation and atherosclerosis, and explored whether a dietary curcumin phytosome could modulate adiposity measures and sVCAM-1 levels.

We found significantly greater measures related to weight (weight, BMI) and central adiposity (abdominal circumference) after 20 weeks of feeding in the HFD rats, compared to the ND rats. Additionally, the significantly greater cumulative weight gains every 2 weeks in the HFD group, compared to ND group indicates that rats on HFD consistently had higher

energy intake than ND rats, even when ND rats had *ad libitum* access to food. This could be related to the fact that the amount of digestible energy from fat was about 5 times greater in the HFD than ND. The greater adiposity measures observed in the HFD rats indicate that the HFD used in the current study was effective in inducing some degree of adiposity. consistent with other studies reporting that several weeks into a regimen of a diet with a high fat content can lead to increased adiposity in rodents (Marques *et al*., 2015; Rosnah *et al*., 2022).

The lack of significant difference in raw adiposity measures between the HFD and HFD-C groups may suggest a lack of effect of phytosome curcumin on adiposity, but this is refuted by the findings that despite having significantly greater initial weight, HFD-C rats showed, at the end of 20 weeks of feeding regimen, significantly less gain in body weight and abdominal circumference in comparison to HFD rats. This indicates that phytosomal curcumin not only reduced body weight gain but may have also affected body fat distribution. As curcumin phytosome did not affect the daily food/energy intake in HFD rats, this suggests that curcumin's effect in reducing adiposity was most likely not related to central mechanisms for body weight regulation.

These findings of phytosomal curcumin reducing adiposity measures in HFD rats are in agreement with indings in clinical studies reporting that a daily phytosomal curcumin supplementation of 200 – 400 mg of curcumin given for a period of one to two months showed significant reductions on anthropometric indices among overweight or obese adults (Di Pierro *et al*., 2015; Panahi *et al*., 2017; Cicero *et al*., 2019; Zeng *et al*., 2023). Such an effect could be evidence of proper absorption and tissue distribution of the phytosomal curcumin (Mirzaei *et al*., 2017; Zheng & McClements, 2020; Mohseni *et al*., 2021). Indeed, this curcumin formulation has demonstrated 29-times greater absorption than ordinary unformulated curcumin in humans (Cuomo *et al*., 2011), and has accumulated significant clinical documentation of efficacy for the management and treatment of a variety of conditions including diabetic microangiopathy and retinopathy, cancer, osteoarthritis, inflammatory diseases (Mirzaei *et al*., 2017), and most recently against migraine headaches (Shojaei *et al*., 2023).

The soluble isoforms of cell adhesion molecules (CAMs) have been considered biomarkers of severity of inflammation (Xing, Murthy, Liles, & Singh, 2012), and increases in their levels have been correlated with a variety of inflammatory diseases (Garton, Gough, & Raines, 2006) and to development of endothelial dysfunction/atherosclerosis, especially in patients with obesity (Barton, Baretella, & Meyer, 2012). In the current study, the significant increase in the concentration of sVCAM-1 by almost 60% in the HFD group compared to the ND group, even if not statistically significant, indicates that the HFD used to induce adiposity can increase the endothelial expression of VCAM-1. This could be related to the diet's high content of saturated fat (15% saturated fat), as it has been reported that excessive consumption of saturated and trans-fat is associated with a chronic subclinical inflammatory response (Duan *et al*., 2018), and increased expression of VCAM-1 on endothelial cells (Shrethta *et al*., 2013). This results from consistent increase in free fatty acids (FFA) and pro-inflammatory markers (TNF-α and IL-1ß) in the circulation (Duan *et al*., 2018). Even transient increase in FFAs due to lipid infusion has been shown to have a pro-inflammatory effect and increase in CAM levels in healthy individuals (Mathew *et al*., 2010). Under such pro-inflammatory stimuli, VCAM-1 is expressed in the plasma membrane through the increased transcription induced by the IKK/NF-kB pathway (Troncoso *et al*., 2021). Once VCAM-1 is expressed in the endothelial cell surface, it interacts with integrin $\alpha_1\beta_4$ present at the surface of circulating leukocytes, allowing their entrapment, rolling, and activation of intracellular signaling. VCAM-1 is then proteolytically cleaved by ADAM matrix metallopeptidase domain 17 (ADAM-17) and shed into the circulation. Since sVCAM-1 is recognized as a biomarker of inflammation and endothelial activation (Troncoso *et al*., 2021), its increased level in the current study suggests that some degree of inflammation-induced endothelial dysfunction, an important contributor

to atherosclerosis and cardiovascular diseases (Zhang, 2022), has developed along the course of the 20-week HFD feeding intervention.

The beneficial effects of different formulations of curcumin on dysglycemia, dyslipidemia, inflammation and oxidative stress markers in obese or overweight people are well documented in a recent review (Zeng *et al.*, 2023). Curcumin has been reported to alleviate generalized inflammation through reducing TNF-α, IL-6 and CRP levels in obese or overweight subjects (Zeng *et al.*, 2023). However, obesity, even in the absence of overt cardio-metabolic risk factors, is also associated with an increase in serum CAMs (Mulhem *et al.*, 2021), and a reduction of CAMs may indicate a lowering of risk of atherosclerosis and cardiovascular diseases in obese or overweight subjects. According to our knowledge, only a few studies have investigated the effects of curcumin on sVCAM-1 levels in conditions of increased adiposity. For instance, results from a human study have also shown that sVCAM-1 levels in obese people could be reduced by 1 g/day supplementation of curcumin complexed with piperine, for a period of 30 days (Saberi-Karimian *et al.*, 2020). As for animal studies, Pradana *et al.* (2019) experimented on Wistar rats on an HFD and described a reduction of sVCAM-1 concentrations by curcumin with nanoparticle formulations. In the current study, the addition of dietary phytosomal curcumin significantly decreased the concentration of sVCAM-1 in HFD-C rats to levels not significantly different from those for ND rats, indicating that this phytosomal curcumin formulation is effective in reducing sVCAM-1 to normal levels in HFD-induced rats. An outstanding finding in the current study is that the degree of reduction in sVCAM-1 levels (53% reduction) in HFD-C rats is very comparable to that reported by Pradana *et al.* (2019), while using nanocurcumin formulation (52.5 % reduction). These results can be very significant if translated to, and established in clinical settings.

One of the mechanisms of action for phytosomal curcumin to reduce sVCAM-1 levels may be similar to other formulations and includes suppressing the NF-κB signaling pathway (Hasanzadeh *et al.*, 2020) and downregulating inflammatory cytokines that lead to inflammatory activation of endothelial cells and endothelial dysfunction (Troncoso *et al.*, 2021). For instance, other formulations of curcumin have been shown to reduce IL-6 levels in HFD-induced rats (Pradana *et al.*, 2019) and in several preclinical studies and in clinical trials, to effectively block TNF-α (Sahebkar, Cicero, Simental-Mendía, Aggarwal, & Gupta, 2016; Subedi *et al.*, 2020; Zeng *et al.*, 2023), which in turn induces expression of VCAM-1 (Troncoso *et al.*, 2021).

Body composition and dietary pattern can modulate the levels of CAMs in general (Adrielle, Nascimento de Freitas, & Volp, 2014). Despite that the relationship between sVCAM-1 concentrations with anthropometric markers is controversial, we still investigated this relationship for all feeding regimen. In the current study, there was a negative correlation between anthropometric measures and sVCAM-1 levels, but was only significant for BMI and abdominal circumference in rats on a normal diet. This finding is consistent with those reported by Souza *et al.* (2012), who also observed an inverse correlation between VCAM-1 and BMI, when studying apparently healthy women.

In the context of adiposity/obesity-induced inflammation, soluble CAM levels are expected to increase with increasing anthropometric measures. This is observed in the current study for the HFD group for which there was reversal of relationship between sVCAM-1 and BMI or weight, and the correlation with weight was almost statistically significant. It may well be that with a larger sample size, these associations would be represented better and may reach statistical significance, or it might be that CAM-anthropometry relations will never be absolute, just as in human researches. For instance, some researches show a positive correlation with BMI (Demerath, Towne, Blangero, & Siervogel, 2001; Ponthieux *et al.*, 2004; Ziccardi *et al.*, 2002), WC and WHR (Couillard *et al.*, 2005), while another (Miller & Cappuccio, 2006) did not show any

significant results between sVCAM-1 and BMI after adjustment for age, sex, smoking status and ethnicity.

This study has few limitations including not measuring baseline sVCAM-1levels on a weekly basis to monitor any changes along the course of feeding intervention. Also, lipid profile testing was not conducted at the end of 20 weeks feeding, in order to confirm hyperlipidemia as a result of the HFD used. Based on previous studies on rodents and not necessarily using the same HFD as in the current study, we believe that the HFD we used can model the metabolic disorders of human adiposity/obesity, since it induced a significant increase in adiposity. As a reported example, a study on Wistar rats established that several weeks into a regimen of HFD lead to obesity and dyslipidemia (Rosnah *et al.*, 2022). Another study (Karam, Ma, Yang, & Li, 2018) on the same species of rats as in the current study (Sprague-Dawley rats) has also reported significant increase in hyperlipidemia biomarkers after only 7 weeks of consumption of HFD with the following macronutrients (41.5% lipids, 40.2% carbohydrates, and 18.3% proteins (kcal)).

Conclusions

Our findings confirm the effectiveness of the high fat diet, with 15% saturated fat, in inducing adiposity along 20 weeks of intervention. This HFD diet also induced an increase in sVCAM-1 levels in comparison to a normal diet. The effectiveness of phytosomal curcumin in reducing adiposity and sVCAM-1 levels in this study emphasizes that this formulation of curcumin, which enhances its absorption and tissue distribution, may offer protection against some cardiovascular complications in hyperlipidemic states and/or obesity due to consumption of diets rich in saturated fats.

References

Adrielle Lima Vieira, R., Nascimento de Freitas, R., & Volp, A. C. (2014). Adhesion molecules and chemokines; relation to anthropometric, body composition, biochemical and dietary variables. *Nutricoin Hospitalaria*, *30*(2), 223–36. doi: 10.3305/nh.2014.30.2.7416.

Ashraf, H., Butt, M. S., Iahtisham-Ul-Haq, Nadeem, M., Aadil, R. M., Rusu, A. V., & Trif, M. (2022). Microencapsulated curcumin from Curcuma longa modulates diet-induced hypercholesterolemia in Sprague Dawley rats. *Frontiers in Nutrition*, *9*, 1026890.

Barton, M., Baretella, O., & Meyer, M. R. (2012). Obesity and risk of vascular disease: Importance of endothelium-dependent vasoconstriction. *British Journal of Pharmacology*, *165*(3), 591–602.

Berg, J., Seyedsadjadi, N., & Grant, R. (2020). Saturated fatty acid intake is associated with increased inflammation, conversion of kynurenine to tryptophan, and delta-9 desaturase activity in healthy humans. *International Journal of Tryptophan Research*, *13*. doi: 10.1177/1178646920981946.

Cicero, A., Sahebkar, A, Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2019). Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: A double-blind, placebo-controlled clinical trial. *European Journal of Nutrition*, *59*, 477–483.

Couillard, C., Ruel, G., Archer, W. R., Pomerleau, S., Bergeron, J., Couture, P., & Bergeron, N. (2005). Circulating levels of oxidative stress markers and endothelial adhesion molecules in men with abdominal obesity. *The Journal of Clinical Endocrinology and Metabolism*, *90*(12), 6454–6459.

Cuomo, J., Appendino, G., Dern, A. S., Schneider, E., McKinnon, T. P., Brown, M. J., . . . Dixon, B. M. (2011). Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. *Journal of Natural Products*, *25;74*(4), 664–669.

Demerath, E., Towne, B., Blangero, J., & Siervogel, R. M. (2001). The relationship of soluble ICAM-1, VCAM-1, P-selectin and E-selectin to cardiovascular disease risk factors in healthy men and women. *Annals of Human Biology*, *28*(6), 664–78.

Di Pierro, F., Bressan, A., Ranaldi, D., Rapacioli, G., Giacomelli, L., & Bertuccioli, A. (2015). Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: Preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. *European Review of Medical and Pharmacological Sciences*, *19*, 4195–4202.

Drake, J. D., Chambers, A. B., Ott, B. R., & Daiello, L. A. (2021). Alzheimer's disease neuroimaging initiative. peripheral markers of vascular endothelial dysfunction show independent but additive relationships with brain-based biomarkers in association with functional impairment in Alzheimer's disease. *Journal of Alzheimers Disease*, *80*(4), 1553–1565.

Duan, Y., Zeng, L., Zheng, C., Song, B., Li, F., Kong, X., & Xu, K. (2018). Inflammatory links between high fat diets and diseases. *Frontiers in Immunology*, *9*, 2649.

Fuloria, S., Mehta, J., Chandel, A., Sekar, M., Rani, N. N. I. M., Begum, M. Y.... & Wu, Y. S., (2022). A comprehensive review on the therapeutic potential of *curcuma longa* linn. in relation to its major active constituent curcumin. *Frontiers in Pharmacology*, *13*, 820806.

Garton, K. J., Gough, P. J., & Raines, E. W. (2006). Emerging roles for ectodomain shedding in the regulation of inflammatory responses. *Journal of Leukocyte Biology*, *79*, 1105–1116.

Hasanzadeh, S., Read, M. I., Bland, A. R., Majeed, M., Jamialahmadi, T., & Sahebkar, A. (2020). Curcumin: An inflammasome silencer. *Pharmacological Research*, *159*, 104921. doi: 10.1016/j.phrs.2020.104921.

Henning, A. L., Venable, A. S., Vingren, J. L., Hill, D. W., & McFarlin, B. K. (2018). Consumption of a high-fat meal was associated with an increase in monocyte adhesion molecules, scavenger receptors, and propensity to form foam cells. *Cytometry B Clinical Cytometry*, *94*(4), 606–612.

Karam, I., Ma, N., Yang, Y. J., & Li, J. Y. (2018). Induce hyperlipidemia in rats using high fat diet investigating blood lipid and histopathology. *Journal of Hematology and Blood Disorders*, *4*(1). doi: 10.15744/2455-7641.4.104.

Kreuger, J., & Phillipson, M. (2016). Targeting vascular and leukocyte communication in angiogenesis, inflammation and fibrosis. *Nature Reviews Drug Discovery*, *15*(2), 125–42.

Marques, C., Meireles, M., Norberto, S., Leite, J., Freitas, J., Phestana, D., . . . Calhau, C. (2015). High-fat diet-induced obesity rat model: A comparison between Wistar and sprague-dawley rat. *Adipocyte*, *5*(1), 11–21.

Mathew, M., Tay, E., & Cusi, K. (2010). Elevated plasma free fatty acids increase cardiovascular risk by inducing plasma biomarkers of endothelial activation, myeloperoxidase and PAI-1 in healthy subjects. *Cardiovascular Diabetology*, *9*, 9.

Miller, M. A., & Cappuccio, F. P. (2006). Cellular adhesion molecules and their relationship with measures of obesity and metabolic syndrome in a multiethnic population. *International Journal of Obesity*, *30*, 1176–82.

Mirzaei, H., Shakeri, A., Rashidi, B., Jalili, A., Banikazemi, Z., & Sahebkar, A. (2017). Phytosomal curcumin: A review of pharmacokinetic, experimental, and clinical studies. *Biomedicine Pharmacotherapy*, *85*, 102–112.

Mohseni, M., Sahebkar, A., Askari, G., Johnston, T. P., Alikiaii, B., & Bagherniya, M. (2021). The clinical use of curcumin on neurological disorders: An updated systematic review of clinical trials. *Phytotherapy Research*, *35*, 6862–6882.

Mulhem, A., Moulla, Y., Klöting, N., Ebert, T., Tonjes, A., Fasshauer, M., ... & Bluher, M. (2021). Circulating cell adhesion molecules in metabolically healthy obesity. *International Journal of Obesity*, *45*, 331–336.

Nair, A. B., & Jacob, S. (2016). A simple practice guide for dose conversion between animals and human. *Journal of Basic and Clinical and Pharmacy*, *7*(2), 27–31.

Nourshargh, S., & Alon, R. (2014). Leukocyte migration into inflamed tissues. *Immunity*, *20;41*(5), 694–707.

Panahi, Y., Kianpour, P., Mohtashami, R., Jafari, R., Simental-Mendía, L., & Sahebkar, A. (2017). Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: A randomized controlled trial. *Drug Research*, *67*, 244–251.

Panahi, Y., Ahmadi, Y., Teymouri, M., Johnston, T. P., & Sahebkar, A. (2018). Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms. *Journal of Cellular Physiology*, *233*(1), 141–152.

Peng, Y., Ao, M., Dong, B., Jiang, Y., Yu, L., Chen, Z., ... Xu, R. (2021). Anti-inflammatory effects of curcumin in the inflammatory diseases: Status, limitations and countermeasures. *Drug Design, Development and Therapy*, *15*, 4503–4525.

Ponthieux, A., Herbeth, B., Droesch, S., Haddy, N., Lambert, D., & Visvikis, S. (2004). Biological determinants of serum ICAM-1, Eselectin, P-selectin and L-selectin levels in healthy subjects: The stanislas study. *Atherosclerosis*, *172*, 299–308.

Pradana, D. A., Ardhi, M. F., Hasyono, A. C., Meytasari, D., Nabilah, F., Istikharah, R., & Chabib, L. (2019). Nanocurcumin preparation for reducing Vcam-1 and IL-6 in high fat diet-induced hyperlipidemic rats. *Indonesian Journal of Pharmacy*, *30*(1), 58.

Rosnah, R., Taslim, N., Aman, A., Idris, A., As'ad, S., Buchari, A., ... & Nugraha, G.I. (2022). The formulation and evaluation of high-fat pellet on lipid profiles and body mass index of male Wistar rats. *Iraqi Journal of Pharmaceutical Sciences*, *31*(1). doi:10.31351/vol31iss1pp285-292.

Saberi-Karimian, M., Rezaei, M., Ghazizadeh, H., Nikbakht-Jam, I., Orooji, A., Tavallaie, S., ... & Ghayour-Mobarhan, M. (2020). Effect of curcumin supplements on serum cell adhesion molecule (CAM) concentrations in obese subjects. *Austin Journal of Obesity & Metabolic Syndrome*, *4*(1), 1014.

Sahebkar, A., Cicero, A. F. G., Simental-Mendía, L. E., Aggarwal, B. B., & Gupta, S. C. (2016). Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. *Pharmacological Research*, *107*, 234–242.

Shojaei, M., Sahebkar, A., Khorvash, F., Fallahpour, S., Askari, G., & Bagherniya, M. (2023). The effects of phytosomal curcumin supplementation on clinical symptoms, and inflammatory and oxidative stress biomarkers in patients with migraine: A protocol for a randomized double-blind placebo-controlled trial. *Avicenna Journal of Phytomedicine*, *13*(1), 45–57.

Shrestha, C., Ito, T., Kawahara, K., Shrestha, B., Yamakuchi, M., Hashiguchi, T., & Maruyama, I. (2013). Saturated fatty acid palmitate induces extracellular release of histone H3: A possible mechanistic basis for high-fat diet-induced inflammation and thrombosis. *Biochemical and Biophysical Research Communications*, *437*(4), 573–8.

Silva Figueiredo, P., Carla Inada, A., Marcelino, G., Maiara Lopes Cardozo, C., de Cássia Freitas, K., de Cássia Avellaneda Guimarães, R., ... Aiko Hiane, P. (2017). Fatty acids consumption: The role metabolic aspects involved in obesity and its associated disorders. *Nutrients*, *9*(10), 1158.

Souza, C. I., Rosa, D. D., Ettrich, B., Cibeira, G. H., Giacomazzi, J., Tusset, P., ... & Graudenz, M.S. (2012). Association of adipokines and adhesion molecules with indicators of obesity in women undergoing mammography screening. *Nutrition and Metabolism*, *50*, 1529–35.

Subedi, L., Lee, S. E., Madiha, S., Gaire, B. P., Jin, M., Yumnam, S., & Kim, S. Y. (2020). Phytochemicals against TNFα-mediated neuroinflammatory diseases. *International Journal of Molecular Sciences*, *21*(3), 764. doi: 10.3390/ijms21030764.

Troncoso, M. F., Ortiz-Quintero, J., Garrido-Moreno, V., Sanhueza-Olivares, F., Guerrero-Moncayo, A., Chiong, M., ... Lavandero, S. (2021). VCAM-1 as a predictor biomarker in cardiovascular disease. *Biochimica et Biophysica Acta Molecular Basis of Disease*, *1867*(9).

Uchio, R., Kawasaki, K., Okuda-Hanafusa, C., Saji, R., Muroyama, K., Murosaki, S., ... & Hirose, Y. (2021). Curcuma longa extract improves serum inflammatory markers and mental health in healthy participants who are overweight: A randomized, double-blind, placebo-controlled trial. *Nutrition Journal*, *20*, 91.

Um, M. Y., Hwang, K. H., Choi, W. H., Ahn, J., Jung, C. H., & Ha, T. Y. (2014). Curcumin attenuates adhesion molecules and matrix metalloproteinase expression in hypercholesterolemic rabbits. *Nutrition Research*, *34*(10), 886–93.

World Health Organization (2018). *Healthy Diet*. Fact Sheet No. 394. Updated August 2018.

Xing, K., Murthy, S., Liles, W. C., & Singh, J. M. (2012). Clinical utility of biomarkers of endothelial activation in sepsis – a systematic review. *Critical Care*, *16*, R7–10. doi: 10.1186/cc11145.

Zeng, Y., Luo, Y., Wang, L., Zhang, K., Peng, J., & Fan, G. (2023). Therapeutic effect of curcumin on metabolic diseases: Evidence from clinical studies. *International Journal of Molecular Science*, *7;24*(4), 3323.

Zhang, J. (2022). Biomarkers of endothelial activation and dysfunction in cardiovascular diseases. *Reviews in Cardiovascular Medicine*, *22;23*(2), 73.

Zheng, B., & McClements, D. J. (2020). Formulation of more efficacious curcumin delivery systems using colloid science: Enhanced solubility, stability, and bioavailability. *Molecules*, *25*(12), 2791.

Ziccardi, P., Nappo, F., Giugliano, G., Esposito, K., Marfella, R., Cioffi, M., ... & Giugliano, D. (2002). Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation*, *105*, 804–809.

Corresponding author
Rima Abdul Razzak can be contacted at: reemala@agu.edu.bh