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Effects of high-oleic peanuts within a hypoenergetic diet on inflammatory and oxidative status of overweight men: a randomised controlled trial

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Abstract
The consumption of food with MUFA has been associated with improvement of inflammation and oxidative stress in overweight individuals. In the present study, we evaluate the effect of high-oleic peanut intake within a hypoenergetic diet on inflammatory and oxidative status markers in overweight men. Sixty-four overweight men (BMI 26–35 kg/m^2, 18–50 years old) participated in this randomised controlled study for 4 weeks, allocated into three groups: control (CT, *n* 22), conventional peanut (CVP, *n* 21) and high-oleic peanut (HOP, *n* 21). They followed a hypoenergetic diet (−250 kcal/d; −1045 kJ/d) with or without 56 g of high-oleic or conventional peanuts. After the intervention, the inflammatory markers did not show significant changes in fasting concentrations or postprandial response among the experimental groups ($P > 0·05$). The activity of oxidative status markers remained unchanged after the intervention. However, in the CT, malondialdehyde showed lower concentration in comparison with the baseline ($P = 0·020$) and among the groups ($P = 0·002$). In the present study, the daily intake of high-oleic peanuts within a hypoenergetic diet did not modify the inflammatory markers and oxidative status in overweight men. More studies are needed to better understand the effect of high-oleic peanut intake on health outcomes.

Key words: Inflammation: MUFA: Obesity: Oxidative stress: Peanuts

Currently, obesity becomes a major global health challenge[1]. In 2016, 39 % of men and 39 % of women aged 18 years and over were overweight (BMI ≥ 25 kg/m^2) and 11 % of men and 15 % of women were obese (BMI ≥ 30 kg/m^2)[2]. Both obesity and overweight lead to adverse metabolic effects on blood pressure, cholesterol, TAG and insulin resistance, all intermediated factors for several chronic diseases, most notably CVD, type 2 diabetes and certain types of cancer[2]. Recently, oxidative stress and inflammation have been postulated as the new risk factors linking obesity to chronic diseases[3].

Inflammation and oxidative stress are interrelated mechanisms which play a central role in the obesity pathogenesis[4]. The excessive adiposity is associated with antioxidant defence reduction and consequently higher oxidative product formation[5,6], while the subclinical inflammation in obesity is characterised by higher concentration of proinflammatory cytokines, such as C-reactive protein, IL-6, IFN-γ, TNF-α, all predictors of co-morbidities[7,8]. Furthermore, increases in oxidative stress induced by inflammation are the main factor responsible for the development and progression of obesity co-morbidities[3].

Recently, it has been demonstrated that the consumption of food with anti-inflammatory and antioxidant nutrients might bring benefits for overweight subjects[9,10]. Several studies show that oleaginous are sources of polyphenols, antioxidant vitamins and minerals and MUFA, which improve insulin resistance, lipid profile, inflammation and oxidative stress[11–13]. Although peanut is a legume, it shares similar nutritional properties to nuts or oilseeds and has anti-inflammatory and antioxidant components[13–15]. The high-oleic peanut cultivar contains about 83·0 % of MUFA from which approximately 80·0 % are oleic fatty acid[15,16]. This fatty acid has shown antioxidant and anti-inflammatory activities, reducing the expression of NF-κB by the activation of the AMP-activated kinase signalling pathway[17]. Scientific evidence indicates that the inclusion of moderate amounts of high-oleic peanuts in a diet can improve lipid profile, insulin sensitivity and body composition[15,16,18].

However, despite the health benefits attributed to peanuts, few clinical studies available in the literature have evaluated the direct effect of daily intake of high-oleic peanuts on inflammatory markers and oxidative status. Thus, the objective of this

Abbreviations: CT, control group; CVP, conventional peanut; HOP, high-oleic peanuts.

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nutrition intervention study was to evaluate the impact of the daily intake of conventional and high-oleic peanuts, associated with a hypoenergetic diet on the inflammatory and oxidative status in overweight men.

Methodology

Subjects

All participants were recruited in the local community by advertisements, flyers and posters. Afterwards, they were submitted to nutritional screening and completed self-administered questionnaires about medical history, food intake and physical activity practice. The participants eligibility was assessed according to the following inclusion criteria: men; adults (age 18–50 years); overweight (BMI 26–35 kg/m^2); non-smokers; without clinically diagnosed disorders, eating disorders or allergies, including to peanuts; do not taking lipid-lowering or anti-inflammatory medication and do not have a regular consumption of peanuts.

The present study has been approved by the ethics committee on human research of the Universidade Federal de Viçosa (protocol: 185/2011) and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to inclusion in the study.

Study design

The present study is part of a randomised controlled three-arm parallel group study, designed to investigate the health effects of the high-oleic peanut intake within a hypoenergetic diet[16,19,20]. Briefly, the subjects participated in a 4-week randomised clinical trial, assigned in three parallel arm: control (CT; hypoenergetic diet), conventional peanut group (CVP, hypoenergetic diet plus 56 g/d conventional peanut) and high-oleic peanut group (HOP; hypoenergetic diet plus 56 g/d high-oleic peanuts). The allocation to treatment groups was conducted by a simple randomisation method. At baseline and after the 4-week intervention, the participants were submitted for an experimental day, during which anthropometric and postprandial measurements were taken.

On each experimental day (final and initial), the participants consumed a test meal at fasting state (within 15 min), according to the allocation group, and stayed at the laboratory for 4 h without intake of any other food. Peripheral blood samples were collected at fasting (10–12 h) and 60, 120 and 180 min after the test meal consumption. Subjects were required not to consume caffeine and alcohol and to maintain their physical activity levels and regular sleep–wake schedule (8 h/night) during 72-h before experimental days. During the intervention period, all participants followed a hypoenergetic diet (−250 kcal; −1045 kJ) with similar macronutrient distribution among the groups. Also, the participants received face-to-face nutrition counselling weekly. In this occasion, the peanut packages were distributed to the participants allocated in peanut groups (CVP and HOP). The study compliance was monitored by the return of not consumed peanut packets and evaluation of food records (applied at the beginning and end of the study). The blood samples were used to measure the changes in inflammatory and oxidative status markers.

Nutritional intervention

For the dietary prescription, the energy requirement of subjects was estimated using indirect calorimetry as previously described by Alves *et al.*[20] and 250 kcal/d (1045 kJ/d) was restricted. All experimental diets provided 15 % of energy from protein, 30 % from fat and 55 % from carbohydrate. The CT diet did not include any peanuts, while the CVP and HOP diet included a daily portion of 56 g of conventional or high-oleic peanuts, respectively. The energy content provided by the daily peanuts portion was considered in the total energy of experimental diets. For the CT, the energy and macronutrient intake were adjusted with the food of the habitual diet. The peanut portion of 56 g was determined to meet the FDA recommendation about saturated fat disqualifying levels (up to 4 g saturated fat per food portion customarily consumed)[21]. Participants were free to eat the peanut portion any time of the day. Also, they were asked to consume the whole portion at once. The portions of the conventional and high-oleic peanuts contained, respectively, 13·6 and 12·8 g of carbohydrates, 16·8 and 16·3 g of proteins, 24·0 and 24·7 g of fat and 5·0 and 5·5 g of dietary fibre. Oleic fatty acid represents 51·0 and 81·5 % of the total fat present in the conventional and high-oleic peanuts, respectively. The peanuts' preparation was previously shown by Moreira Alves *et al.*[16].

Moreover, being an intervention study under free-living conditions, all the participants were instructed to use a self-selected exchange food list and do not intake any other oilseed/nuts during the intervention period. Before the baseline assessments and during the fourth-week intervention, the participants were also instructed to keep a 3-d dietary record (two nonconsecutive weekdays and one weekend day) for the compliance evaluation. Dietary data were analysed using Dietpro software (version 5.2i).

Test meal

In the initial and final experimental day, the participants consumed a test meal according to the allocation group. Each test meal consisted of a strawberry-flavoured milkshake with 56 g of high-oleic or conventional peanuts for the experimental groups and biscuit to the CT group. The test meals were prepared to provide 25 % of daily energy requirements and contained similar volume and macronutrient distribution (35 % carbohydrate, 16 % protein and 49 % fat relative to the total energetic value). The test meal preparation was previously described by Moreira Alves *et al.*[16].

Anthropometry and physical activity level

Anthropometrics measurements (height, weight, waist circumference, BMI) were collected at baseline and post-intervention. Height and weight were assessed in the standing position with the participants wearing light clothing. BMI was calculated as weight/height^2 (kg/m^2). Waist circumference was measured using an inelastic flexible tape positioned midway between the lower rib margin and the iliac crest. The physical activity level of each subject was evaluated by the International Physical activity Questionnaire and classified according to FAO/WHO/UNU[22–24].

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Blood sampling

Fasting and postprandial (60, 120 and 180 min) blood samples were collected into tubes precoated with EDTA. For this, a catheter was introduced into an antecubital vein by a trained phlebotomist at baseline and post-intervention. The blood samples were centrifuged (2200 ***g***, 15 min, 4°C), aliquoted and stored at −80°C for further analysis.

Inflammatory and oxidative status markers analyses

The inflammatory and oxidative status markers were assessed on fasting and postprandial state. As previously described[16], an automated analytical method was used to measure C-reactive protein concentration. For the determination of IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ and TNF-α cytokines plasma concentrations, the Human cytokine kit Th1/Th2/Th17 CBA (BD Biosciences) was used, according to instructions of the manufacturer by flow cytometry technique (BD FACSort™ cytometer; BD Immunocytometry Systems). The data were analysed using matrix FCAP Array Software version 3.0 (BD Biosciences), and the values were expressed in pg/ml.

Oxidative status markers were measured in plasma samples by colorimetric methods. Malondialdehyde was determined in duplicate, by the measurement of thiobarbituric acid reactive substances, described by Buege & Aust[25]. Nitric oxide concentration was determined in duplicate using the Griess reagent according to Grisham *et al.*[26]. The total activity of superoxide dismutase enzyme was determined in triplicate following the method described by Marklund & Marklund, and your activity was expressed as U of superoxide dismutase enzyme/l[27]. The enzymatic activity of glutathione S-transferase was determined as described by Habig *et al.*[28]. The glutathione S-transferase activity was expressed as μmol/min per g.

Statistical analysis

Statistical analysis was conducted using SPSS 22.0 for Windows (SPSS, Inc.). Data are expressed as mean values with their standard errors. The Shapiro–Wilk test was performed to check the normality of variables. Power analyses were calculated by the analyst procedures of the statistical analysis system considering IL-10 and TNF-α as the primary outcomes. It was indicated that a sample of twenty-one per group would permit detection of a 5 % change of IL-10 and TNF-α with 99 % of power at the 5 % level of probability. For all data analyses, the differences were considered statistically significant for $P < 0{\cdot}05$. To evaluate the postprandial cytokine responses, the AUC was calculated through the trapezoidal method by the Excel program (Microsoft® Excel 2013). Among the groups, variable changes (final fasting measurements – baseline fasting measurements) were compared by one-way ANOVA followed by Tukey's *post hoc* test or using the non-parametric Kruskal–Wallis test followed by Dunn's *post hoc* test. To compare differences between baseline and post-intervention within the groups, pairwise tests were performed (paired *t* test or Wilcoxon).

Results

From seventy-six randomised subjects, sixty-four completed the study (Fig. 1), all in compliance to study protocol. The mean of age and BMI was 27 (SEM 0·9) years and 29·76 (SEM 0·3) kg/m^2, respectively. Of the subjects, 61 % (*n* 39) were overweight, and the rest were obese. At baseline, anthropometric characteristics, energy intake, inflammatory markers and oxidative stress did not differ among the groups (Table 1).

After intervention, body weight reduction (CT −2·2 (SEM 0·3) kg, $P < 0{\cdot}001$; CVP −1·57 (SEM 0·23), $P < 0{\cdot}001$, HOP −1·58 (SEM 0·31), $P < 0{\cdot}001$) was not different among the

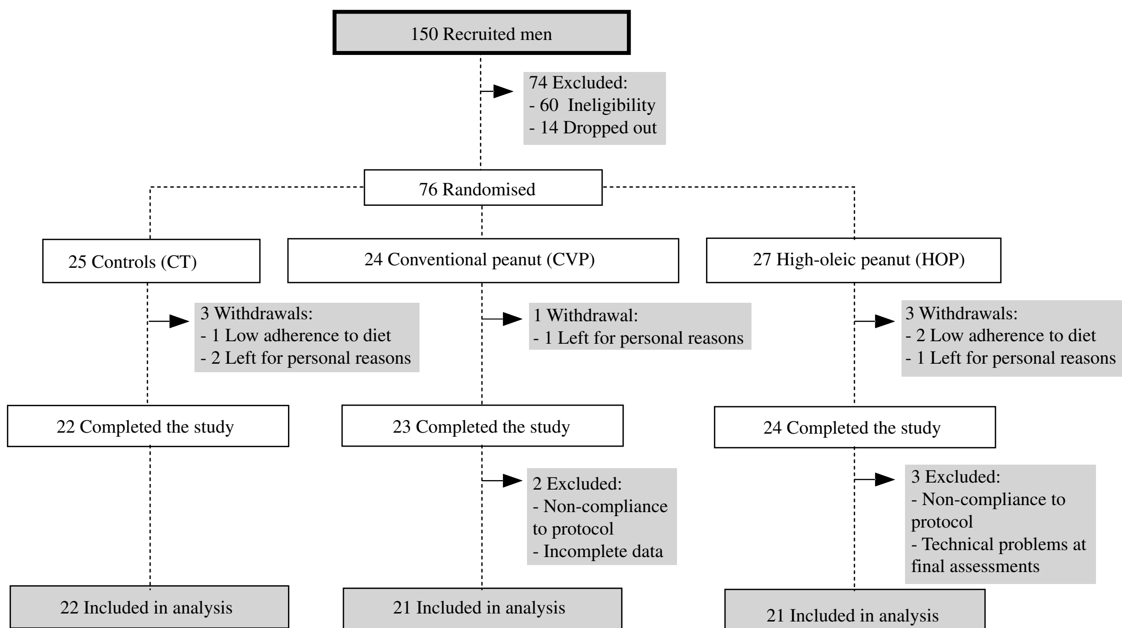

Fig. 1. Flow diagram of enrolment, randomisation, withdrawals and follow-ups of the study subjects.

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Table 1. Clinical and biochemical characteristics of the participants according to the experimental group at baseline
(Mean values with their standard errors)

	CT (*n* 22)		CVP (*n* 21)		HOP (*n* 21)		
	Mean	SE	Mean	SE	Mean	SE	*P**
Age (years)	27·4	1·6	28·0	1·5	27·2	1·8	0·728
Body weight (kg)	94·5	2·4	92·7	2·1	95·5	2·2	0·695
BMI (kg/m^2)	29·7	0·5	29·4	0·4	30·1	0·5	0·802
Waist circumference (cm)	102·2	1·9	100·5	1·2	102·3	1·6	0·697
NO (μmol/l)	34·6	3·3	27·9	3·9	40·8	7·3	0·413
MDA (μmol/l)	0·5	0·1	1·0	0·1	0·6	0·1	0·062
GST (μmol/min/g)	1·9	0·1	1·5	0·2	1·6	0·1	0·370
IL-17A (pg/ml)	6·0	2·2	6·5	3·4	18·6	5·8	0·147
TNF-*α* (pg/ml)	1·3	0·5	0·9	0·4	1·6	0·6	0·190
IL-10 (pg/ml)	1·5	0·9	0·4	0·2	0·6	0·2	0·643
IL-6 (pg/ml)	1·5	0·6	1·1	0·3	1·7	0·4	0·716
IL-4 (pg/ml)	0·3	0·1	0·2	0·1	0·5	0·1	0·305
hs-CRP (mg/l)	14	3	13	2	16	2	0·373

CT, control group; CVP, conventional peanut group; HOP, high-oleic peanut group; NO, nitric oxide; MDA, malondialdehyde; GST, glutathione S-transferase; hs-CRP, high-sensitivity C-reactive protein.
* *P* value column refers to differences among groups (ANOVA or Kruskal–Wallis test followed by Tukey or Dunn's test, respectively).

Table 2. Change (fasting values at week 4 – fasting baseline values) in inflammatory markers after intervention according to the experimental group
(Mean values with their standard errors)

	CT (*n* 22)		CVP (*n* 21)		HOP (*n* 21)		
	Mean	SE	Mean	SE	Mean	SE	*P**
Body weight (kg)	−2·2†	0·3	−1·5†	0·2	−1·5†	0·3	0·221
BMI (kg/m^2)	−0·6†	0·1	−0·5†	0·07	−0·4†	0·1	0·283
Waist circumference (cm)	−2·0†	0·3	−2·1†	0·4	−1·2†	0·2	0·223
IL-17A (pg/ml)	0·6	2·7	4·5	5·1	−3·6	6·9	0·222
TNF-*α* (pg/ml)	−0·2	0·1	0·005	0·2	0·2	0·2	0·940
IL-10 (pg/ml)	−0·4	0·4	−0·1†	0·06	0·03	0·07	0·200
IL-6 (pg/ml)	0·9	1·2	0·05	0·2	−0·05	0·3	0·743
IL-4 (pg/ml)	−0·1†	0·07	−0·1	0·09	−0·2†	0·08	0·830
hs-CRP (mg/l)	5	4	−2	1	−0·4	2	0·279

CT, control group; CVP, conventional peanut group; HOP, high-oleic peanut group; hs-CRP, high-sensitivity C-reactive protein.
* *P* value column refers to differences between groups (Kruskal–Wallis test followed by Dunn's test).
† Significant difference between final and baseline assessment within groups ($P < 0·05$; Wilcoxon test).

groups ($P = 0·860$). A similar result was verified for waist circumference (CT −2·0 (SEM 0·3), $P < 0·001$; CVP −2·1 (SEM 0·4), $P < 0·001$; HOP −1·2 (SEM 0·2), $P < 0·001$). The energy intake did not differ among the experimental groups at 4-week intervention (CT −291·0 (SEM 195·8) kcal (−1217·5 (SE 819·2) kJ); CVP −275·7 (SEM 258·0) kcal (−1077·1 (SE 1078·4) kJ); HOP −212·0 (SEM 163·7) kcal (−886·1 (SE 684·2) kJ), $P = 0·542$). As expected, the HOP group had a higher MUFA intake (CT −6·6 (SEM 2·1) g; CVP 5·0 (SEM 3·4) g; HOP 17·8 (SEM 5·5) g, $P < 0·001$). On the other hand, total lipid intake was lower in CT group (CT −17·9 (SEM 9·6) g; CVP −0·3 (SEM 11·2) g; HOP 8·2 (SEM 12·6) g, $P < 0·001$), which also show lower PUFA intake (CT −4·8 (SEM 2·2) g; CVP 0·9 (SEM 3·4) g, HOP −1·9 (SEM 1·5) g, $P < 0·021$). The other nutrients carbohydrate, protein, SFA and fibre were similar among groups after the intervention (data not shown). Furthermore, there was no difference between groups for physical activity levels ($P = 0·876$). Subjects did not change their physical activity level in comparison with baseline (CT, $P = 1·0$; CVP, $P = 0·73$; HOP, $P = 0·84$), and no difference among groups was observed ($P = 0·97$).

The fasting concentrations and postprandial responses of IL-17A, IL-10, IL-6, IL-4, TNF and C-reactive protein did not show significant differences among the experimental groups at the end of the intervention (Table 2) (Fig. 2). In the baseline assessments, for most of the volunteers (IFN-*γ*: 93·4 %, *n* 59 and IL-2: 95·3 %, *n* 61), IFN-*γ* and IL-2 cytokines concentrations were below the level of detection of used kit and were excluded from the statistical analysis. Similarly, the peanut consumption was not able to modulate the glutathione S-transferase and superoxide dismutase enzyme activity, as well as nitric oxide concentrations, within or among the group's comparison ($P > 0·05$) in the 4th week. However, malondialdehyde fasting concentration reduced significantly in the CT group compared with the baseline ($P = 0·020$) and among groups ($P = 0·002$) (Fig. 3).

Discussion

To our knowledge, this is the first randomised clinical trial to verify the effects of high-oleic peanut consumption on inflammatory and oxidative status markers in overweight men. The dietary

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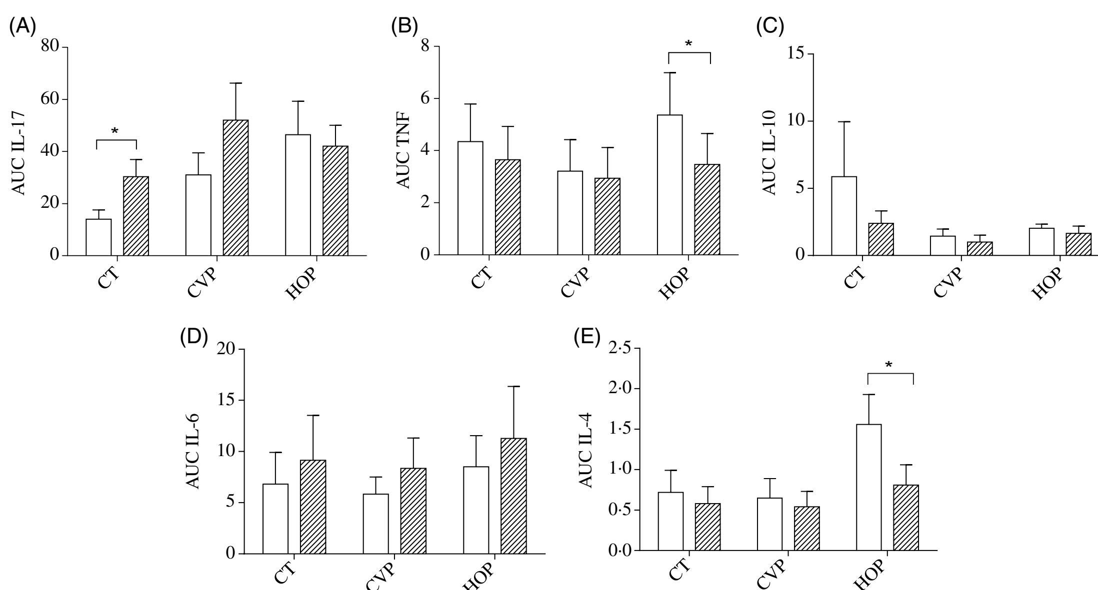

Fig. 2. Postprandial response of cytokines according to the experimental group. (A) IL-17A; (B) TNF; (C) IL-10; (D) IL-6; (E) IL-4. Empty bars indicate initial AUC, and striped bars indicate final AUC. Values are means, with their standard errors represented by vertical bars. The cytokines did not show difference between experimental groups. * Significant difference between final and baseline assessment within groups ($P < 0{\cdot}05$; Wilcoxon test). CT, control group; CVP, conventional peanut group; HOP, high-oleic peanut group.

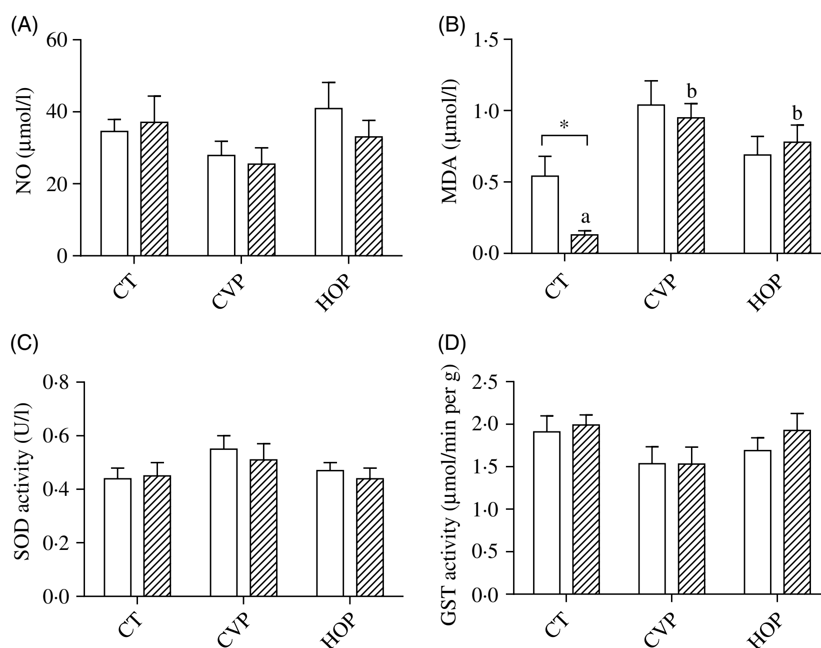

Fig. 3. Fasting oxidative stress markers. (A) Nitric oxide (NO); (B) malondialdehyde (MDA); (C) superoxide dismutase (SOD); (D) glutathione S-transferase (GST). Empty bars indicate initial mean, and striped bars indicate final mean. Values are means, with their standard errors represented by vertical bars. [a,b] Mean values with unlike letters were significantly different ($P<0{\cdot}05$; ANOVA or Kruskal–Wallis test followed by Tukey or Dunn's test, respectively). * Significant difference between final and baseline assessment within groups ($P < 0{\cdot}05$; paired t test or Wilcoxon test). CT, control group; CVP, conventional peanut group; HOP, high-oleic peanut group.

records assessment and the count of returned peanut bags consumed by the participants revealed that they had good adherence to the dietary intervention. The results of the present study demonstrate that daily consumption of high-oleic or conventional peanut within a hypoenergetic diet did not modify the inflammatory or oxidative status in overweight men.

Unhealthy changes in lifestyle and diet have resulted in the obesity increase, which is associated with inflammation and oxidative stress[29,30]. Previous studies have supported that excessive body fat induces TH17 proinflammatory cell proliferation and increase in the IL-17A blood concentration[31,32]. This cytokine has been associated with the induction of tissue

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inflammation and possibly with chronic low-grade inflammation in obese individuals[33]. The role of IL-4 is not fully understood in the inflammatory process[34]. Some evidence showed that IL-4 might be involved in lipid and glucose metabolism, proinflammatory chemokines regulation and inflammatory cell recruitment[34–37]. Both cytokines were not modified by peanut consumption after the intervention. Contrary to our results, Rocha *et al.* demonstrate that MUFA high-fat meal consumption leads to a significant reduction in IL-17A postprandial response in healthy women with a high percentage of body fat[38]. Similarly, an *in vitro* study demonstrated an increase in IL-4 concentration after incubation with oleic acid, but not with palmitoleic acid[39]. Monocytes extracted from healthy men exhibit a higher concentration of IL-4 after acute consumption of a fat-enriched meal with MUFA and PUFA in comparison with the meal rich in SFA[40]. The explanation for these results is unclear; IL-17A and IL-4 response in overweight patients is largely unexplored, especially after the nutritional intervention. Besides, kinetic mechanisms and the behaviour of IL-17A and IL-4 after a lipid stimulus are not known yet.

For IL-10, TNF, IL-6 and C-reactive protein, no changes were observed in fasting concentration or postprandial response after peanuts consumption. However, some studies have shown that acute or chronic consumption of oilseeds increases IL-10 concentration[41,42]. Also, contrary to our results, Richard *et al.*[43] verified that men with the metabolic syndrome who followed the Mediterranean Diet, with high amounts of MUFA, PUFA and polyphenols, showed lower TNF fasting concentration in plasma. Similar results have been observed by other studies that evaluated the MUFA effect on TNF-α concentration[44,45].

Nevertheless, studies evaluating the effect of nut consumption on inflammatory markers have observed conflicting results[46]. Although observational studies have shown anti-inflammatory effect associated with nuts consumption[47], clinical trials have failed to verify this result consistently. Barbour *et al.* showed that intake of 56–84 g of high-oleic peanut for 12 weeks by healthy subjects did not modify C-reactive protein concentrations. Other studies with walnut[48–51], almond[49,52], pistachio[53], hazelnut[54] and mixed nuts[55] have also not observed improvement in inflammatory markers. MUFA – especially oleic fatty acid – acts as an anti-inflammatory by acting on AMP-activated kinase phosphorylation, which inhibits NF-κB activation inhibiting the inflammatory process[17,56]. Taken together, this evidence highlights the complexity involved in the relationship between inflammation, overweight and diet. Only add MUFA-rich food to the habitual diet without other interventions in lifestyle seems not enough to improve inflammatory status in overweight and obese individuals under free-living conditions.

Besides low-grade chronic systemic inflammation, the oxidative stress is also a disturbance frequently observed in obesity[29,57]. This condition is influenced by the activation of the innate immune system in adipose tissue, which promotes the pro-inflammatory status and oxidative stress and triggers a systemic acute-phase response[29]. Also, the oxidative stress is associated with an irregular production of adipokines, which contributes to the development of obesity-associated co-morbidities[57].

The lipid peroxidation is involved in a variety of chronic diseases and has malondialdehyde – a product of the peroxidation of PUFA – as one of its final products[58]. Unexpectedly, the malondialdehyde showed significant reduction in the CT group. One possible explanation includes the significant reduction in the PUFA consumption observed in this group, which are known to be more susceptible to lipid peroxidation[59,60]. Despite peanut being the largest L-arginine source[61], after the 4-week intervention, the peanut consumption did not modify nitric oxide concentration. Studies that evaluate the enzymatic activity of superoxide dismutase enzyme and glutathione S-transferase after oilseeds intervention are still scarce. We believe that the constant supply of non-enzymatic antioxidants by the daily peanuts intake may have contributed to the antioxidant status equilibrium and prevented the free radicals increase. Thus, there was neither oxidative products formation nor stimulus for the increase in activity of antioxidant enzymes. Also, most volunteers of the present study had no obesity-associated co-morbidities, which may be associated with an antioxidant status balance. In this way, the impact of peanut consumption on oxidative status may have been attenuated, since other studies with nuts consumption seem to improve the oxidative stress mainly in subjects with higher imbalance in oxidative status[62].

There are some limitations to the present study that should be mentioned. The non-evaluation of phenolic compounds present in peanuts stands out as a limiting factor since they might interfere in inflammatory and oxidative stress markers[63,64]. Although food consumption, peanut intake and physical activity have been well controlled, any biomarkers of peanut intake were assessed. Future studies with this evaluation may be of greater utility. The short time of intervention may be another reason for the limited beneficial effect of peanut consumption. In addition, these results may not be generalisable to women because the sample consisted of men. Furthermore, the influence of the dietary intervention on IFN-γ and IL-2 was not possible to be measured.

In conclusion, the daily high-oleic peanut consumption within a hypoenergetic diet did not modify the plasma inflammatory markers in overweight men. Furthermore, the oxidative status markers remained unchanged after peanut consumption. Thus, more studies are needed to evaluate whether peanuts intake associated with habitual diet or specific dietary patterns might improve the antioxidant and anti-inflammatory status in overweight subjects.

Ethical statement

The authors declare that all protocols in the present study were performed in accordance with the ethical standards of the institutional research committee and Helsinki declaration.

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R. D. M. A. designed the research; A. P. S. C. and L. L. d. O. conducted the analyses; A. P. S. C. wrote the manuscript; J. B., H. H. M. H., R. D. M. A. and L. L. d. O. critically revised the manuscript. All authors read and approved the final manuscript.

There are no conflicts of interest.

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