

Effects of high-fat diets on inflammation and antioxidant status in rats: Comparison between palm olein and olive oil

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Palm olein (PO) and olive oil (OO) are widely consumed in the world. PO is considered harmful to health, whereas OO is considered healthy. This study aims to discover the effects of consumption of these oils on antioxidant status and inflammation that can be beneficial for consumer. This was an experimental study in male wistar rats fed a diet containing 30% of each oil. Rats had free access to food and water. After being fed for 12 weeks, animals were sacrificed and liver and aortic blood were collected. Plasma was used for the determination of interleukin-6 and oxidative stress parameters (Superoxide dismutase, Glutathione peroxidase, Thiobarbituric acid reactive substances, Thiol groups and isoprostane). The inflammation and oxidative stress status as well as the expression of several genes/proteins were also analyzed in liver homogenate. No significant differences were observed between PO and OO in plasma and liver levels of the studied inflammation and oxidative stress parameters. We noted that the consumption of PO does not promote inflammation and oxidative stress. This study will help the researchers to uncover the critical areas of antioxidant and anti-inflammatory effects of olive oil and palm olein consumption.

Key words: palm olein, olive oil, oxidative stress, inflammation, high fat diet

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Abbreviations: AU, arbitrary Unit; CD68, Cluster of differentiation 68; GCLC, Glutamate-cysteine ligase catalytic subunit; GPx, Glutathione peroxidase; GSH, Reduced glutathione; GSSG, Oxidized glutathione; HFD, High fat diet; HO-1, Heme oxygenase-1; Ikb- α , Inhibitor of kappa B-alpha; IL-1b, Interleukin-1b; IL-6, Interleukin-6; Nf-kb, Nuclear factor-kappa B Nrf2 (Nfe2l2), Nuclear factor-erythroid 2 related factor 2; NQO-1, NAD(P)H quinone dehydrogenase 1; qPCR, Quantitative-Polymerase chain reaction; PO, Palm olein; PUFA, Polyunsaturated fatty acids; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; ww, Wet weight

INTRODUCTION

Palm oil is the most produced (USAD, 2021) and consumed vegetable oil in the world (USAD, 2021). Although crude palm oil is known for its nutritional ben-

efits (Edem, 2002; Ong & Goh, 2002; Sen *et al.*, 2007), industry prefers deodorized and decoloured palm oil for which refining is mandatory. This refining can be based on chemical methods (treatment with alkalis or acids) (Cmolik & Pokorny, 2000; Dunford, 2012) or physical methods (steam refining, inert gas stripping, molecular distillation, etc.) (Dunford, 2012). This is followed by bleaching and deodorisation steps as well as other specific treatments depending on the first refining process applied. After refining, the product obtained will undergo fractionation to give derived fractions: palm olein or super-olein (a colourless, bland and stable oil, rich in oleic acid) and palm stearin (a fat, rich in saturated fatty acids) (Dunford, 2012; Lecerf, 2013). Refining results in a significant loss of carotenoids and a moderate loss of vitamin E (Tarmizi & Lin, 2008).

Palm olein is widely used in African, South American and Asian cuisines. Instead of partially hydrogenated oils that contain trans fatty acids, palm stearin is widely used by the food industry in the manufacture of many products such as sweets, cakes, cheese analogues, crisps, chocolates, confectionary fats, biscuits, doughnuts, frozen meals and products (pancakes, pies, pizzas, potatoes, etc.), instant meals, etc. (Mancini *et al.*, 2015; Mba *et al.*, 2015).

Olive oil (OO) is a vegetable oil known to be rich in polyphenols (Owen *et al.*, 2000). Numerous studies report the nutritional benefits of OO polyphenols (Perez-Jimenez *et al.*, 2005; Covas *et al.*, 2006; Assy *et al.*, 2009). PO, although naturally rich in phytonutrients (vitamin E, Coenzyme Q, etc.) considered beneficial for human health especially for their antioxidant properties (Ng *et al.*, 2012; Tiahou *et al.*, 2004; Rooyen *et al.*, 2008), is due to its high content of saturated fatty acids (50%) especially palmitic acid, accused of being potentially harmful to health (Fattore *et al.*, 2014; Odia *et al.*, 2015). Given this, it seemed appropriate to undertake this study to compare the effects of consuming diets rich in PO and OO on inflammation and antioxidant status in rats.

MATERIELS AND METHODS

Animals and diets

A total of twenty-four young male Wistar rats (Charles River, L'Arbresle, France) aged 6 weeks were used in the

present study. The rats were housed, two per cage, under conditions of constant temperature (20–22°C), humidity (45–50%), and a standard dark cycle (20.00–08.00 hours). The rats were randomised into four groups of eight animals and fed for 12 weeks with one of the following semi-purified diets: (1) control diet (Control), containing 5% lipid as soybean oil (11% energy from fat) this is sham control group, (2) high-fat diet (HFD) (55% energy from fat) rich in PO with 2.5% soybean oil and 30% PO or (3) HFD rich in OO with 2.5% soybean oil and 30% OO. PO was supplied by SANIA company (Côte d'Ivoire), and OO (virgin) was bought in a supermarket (these oils were chosen for their large current consumption). The detailed composition of these experimental diets is shown in Table 1. Rats were given free access to water and food during the whole experiment and body growth was determined weekly. Our institution guidelines for the care and use of laboratory animals were followed, and all the experimental procedures were approved by the local ethical committee in Montpellier, France (Reference CEEA-LR-12002).

Rat sacrifice and sampling

Blood was obtained from 16 h fasted rats anaesthetised with pentobarbital (Ceva Sante Animale, Libourne, France) by puncturing the abdominal vein with a heparinised syringe (Sodium heparinate, Panpharma SA Fougères, France). Blood was then distributed into a dry tube (3–4 ml) and a heparinised tube (5–6 ml), centrifuged at 1000×g for 10 min at 4°C, and serum and plasma were collected and stored at –80°C until analysis. The liver was perfused with 10 ml of 0.9% NaCl solution, quickly removed, weighed, and cut into different parts. One part was immediately frozen in liquid nitrogen and then kept at –80°C until analysis. Another part was fixed in 10% neutral buffered formalin and embedded in paraffin for histological analysis.

Inflammation and oxidative stress parameters in blood

Plasma interleukin-6 (IL-6) levels were quantified with ELISA kits (Fisher Scientific, France). The activity of an-

Table 1. Diet composition (g/kg) on the basis of the AIN-93M diet formulation.

Ingredients	Control	Palm Olein	Olive Oil
Casein	165	200	200
Cornstarch	443	234	234
Maltodextrine	144	80	80
Sucrose	100	53	53
Soybean oil	50	25	25
Palm olein	0	300	0
Olive oil	0	0	300
Cellulose	50	50	50
Mineral mix (AIN-93M)	35	42	42
Vitamin mix (AIN-93M)	10	12	12
L-Cystine	2	2.4	2.4
Choline chloride	1.5	1.8	1.8
TOTAL	1000	1000	1000

tiioxidant enzymes has been determined by spectrophotometric methods. Glutathione peroxidase (GPx) activity and total superoxide dismutase (SOD) were measured in blood according to the method of Flohe & Gunzler (1984) and Marklund (1976), respectively. Thiobarbituric acid-reactive substances (TBARS), was measured according to the method of Sunderman *et al.*, (1985). Protein oxidation was assessed by measurement of sulfhydryl groups (Faure & Lafond, 1995) in plasma.

Plasma 15-F_{2t}-isoprotanes, the more specific lipid peroxidation parameter, was also measured by mass spectrometry as described by Mas and others (Mas *et al.*, 2008). Briefly, aliquots of plasma samples were added with 15-F_{2t}-isoprostane D4 as an internal standard before extraction using an Agilent Bond Elut Certify II cartridges. Washes were performed with methanol 50% and ethyl acetate/hexane (1/3 v/v) and elution was performed with ethyl acetate/methanol (9/1 v/v). After esterification, samples were analyzed on a ThermoFinnigan Trace DSQ II interfaced with a Trace GC Ultra 2000 gas chromatograph, equipped with an AS 3000 automatic sampler (ThermoFinnigan).

Liver macrophage identification

Liver samples were fixed in a neutral 10% formalin buffer and then embedded in paraffin. Sections of 5 µm were made with a microtome (Leica RM 2145, Microsystems Nussloch GmbH, Germany). After staining with haematoxylin, macrophage infiltrations were detected by immuno-labelling with an anti - cluster of differentiation 68 (anti-CD68) antibody (Bio-Rad, France). Antibody distribution was visualized by a Vecstatin® ABC kit and an ImmPACT AEC substrate kit (Clinisciences, France). For CD68 determination, 10–20 fields per sample were analyzed and results were expressed as the average percentage of surface with positive staining to total surface of the field.

Inflammation and oxidative stress parameters in liver

Liver homogenates and supernatants from frozen liver were prepared as described by Coudray and others (Coudray *et al.*, 2016). Supernatant protein level was measured by Bradford's technique (Bradford, 1976). TBARS, thiol groups, reduced glutathione (GSH), oxidised glutathione (GSSG) levels and GPx, SOD and catalase activities were measured by spectrophotometric techniques as described previously (Djohan *et al.*, 2019). In addition, the gene expression of *Nrf2*, and some inflammation genes (*NF-κB*, *IκB-α*, *IL-1β*), and antioxidant genes (*NQO-1*, *HO-1*, *GCLC*) was also assessed (see Liver mRNA expression section).

Liver mRNA expression

Real-time quantitative PCR was used to measure the mRNA expression of the target genes in the tissues and was performed as described previously (Djohan *et al.*, 2019). The primer sequences used for real-time PCR are shown in the Supplemental Table (at <https://ojs.pt-bioch.edu.pl/index.php/abp/>). Results were normalized to *RPLPO* gene and were expressed as a percentage of the control. Liver genes analyzed include *GCLC*, *HO-1*, *IκB-α*, *IL-1β*, *NF-κB*, *NQO-1*, *Nrf2*.

Statistical analysis

Results were expressed as mean and standard deviations, n=7–8 animals per group. Statistical analysis was based on one-way ANOVA followed by a Tukey Kram-

Table 2. Blood and liver inflammation parameters

Rats were fed their respective diet for 12 weeks. Results were expressed as mean values \pm S.D., $n=7-8$ animals per group. Statistical analysis was based on one-way ANOVA followed by a Tukey Kramer multiple comparisons test. The limit of statistical significance was set at $p<0.05$. The group mean values with different letters (a, b, c) are significantly different.

	Control	PO	OO	<i>p</i>
Plasma				
IL-6(pg/mL)	14.67 \pm 2.7	13.98 \pm 2.6	14.48 \pm 4.1	NS
Liver				
<i>NF-kB</i> (qPCR)	1.00 \pm 0.07	0.96 \pm 0.04	1.07 \pm 0.02	NS
<i>IkB-α</i> (qPCR)	1.00 \pm 0.12 ^a	1.78 \pm 0.23 ^b	1.33 \pm 0.15 ^{ab}	0.027
<i>IL-1β</i> (qPCR)	1.00 \pm 0.12	0.92 \pm 0.07	1.00 \pm 0.05	NS

IkB- α , Inhibitor of kappa B-alpha; IL-1b, Interleukin-1b; IL-6, Interleukin-6; NF-kb, Nuclear factor-kappa B; qPCR, Quantitative-Polymerase chain reaction; OO, Olive oil; PO, palm olein

er multiple comparisons test. When statistical variances were unequal, a Welch test was performed. The limit of statistical significance was set at $p<0.05$. The group mean values with different letters (a, b, c) are significantly different. Statistical analyses were performed using the Stat-View program (SAS Institute, Cary, NC, USA).

RESULTS AND DISCUSSION

Effects of diet on inflammation

With regard to the inflammatory parameters studied (plasma IL-6, liver *IL-1 β* , *NF-kB* and *IkB-a* genes), no diet promoted inflammation (Table 2). In liver, PO diet promoted a significant increase ($p=0.027$) in the gene expression of *IkB-a* (+78%), compared to the control diet. OO diet has favoured a non-significant increase in the gene expression of *IkB-a* (+33%) compared to the control diet. The gene expression of *NF-kB* was decreased by 4% with PO diet and increased by 7% with OO diet compared to the control diet. On the other hand, OO diet induced a significant increase ($p<0.0001$) of macrophage density (+31% at least) in rat liver compared to PO and control diets. PO diet induced a significant decrease ($p<0.0001$) in macrophage density (-36% at least) in rat liver compared to OO and control diets (Table 2).

NF- κ B is the linchpin of phagocytic cells because it enables them to be activated. Consequently, an increase in NF- κ B and/or its activators is observed in acute or chronic inflammation (Monaco *et al.*, 2004; Song *et al.*, 2009; Hajishengallis & Chavakis, 2013). *IkB- α* inhibits NF- κ B by masking the nuclear localisation signals of NF- κ B proteins and sequestering them in an inactive state in the cytoplasm (Jacobs & Harrison, 1998; Hinz, 2012). In addition, *I κ B- α* blocks the ability of NF- κ B transcription factors to bind to deoxyribonucleic acid, which is necessary for the proper functioning of NF- κ B (Verma *et al.*, 1995; Huang, 2000; Birbach, 2002).

The significant increase in the gene expression of *IkB-a* by PO diet and the non-significant decrease in the gene expression of *NF- κ B* show that PO diet protects the liver better against inflammation. The actions of PO on *NF- κ B* and *IkB-a* genes could be explained by its high tocotrienol content (Sambanthamurthi *et al.*, 2000; Lecerf, 2013). Indeed, tocotrienols have anti-inflammatory properties (Reiter *et al.*, 2007; Yam *et al.*, 2009) due to their involvement in inhibiting NF- κ B activation pathway (Ahn *et al.*, 2007; Ng & Ko, 2012). *In-vitro* studies with palm oil tocotrienols have shown its anti-inflammatory effects (Wu *et al.*, 2008) and its ability to reduce cancer

cell proliferation by inhibiting NF- κ B activation pathway (Yap *et al.*, 2008; Ji *et al.*, 2015).

Studies in humans have shown that diets based on PO and OO do not promote inflammation at the plasma level (Teng *et al.*, 2011; Tholstrup *et al.*, 2011).

The search for macrophage infiltrations in liver with CD68 labeling (Fig. 1) showed a significant increase ($p<0.0001$) in macrophage density with the OO diet compared to other diets. The significant increase of macrophage density in liver of the rats that consumed OO suggests that OO promoted inflammation in liver. This action of OO on liver could be explained by its high content of ω -6 polyunsaturated fatty acids (PUFA). Indeed, according to many authors (Raphael & Sordillo, 2013; Marion-Letellier *et al.*, 2015) ω -6 PUFA promote inflammation.

Despite its richness in saturated fatty acids, particularly palmitic acid, which is considered pro-inflammatory because it activates the NF- κ B pathway (Ajuwon &

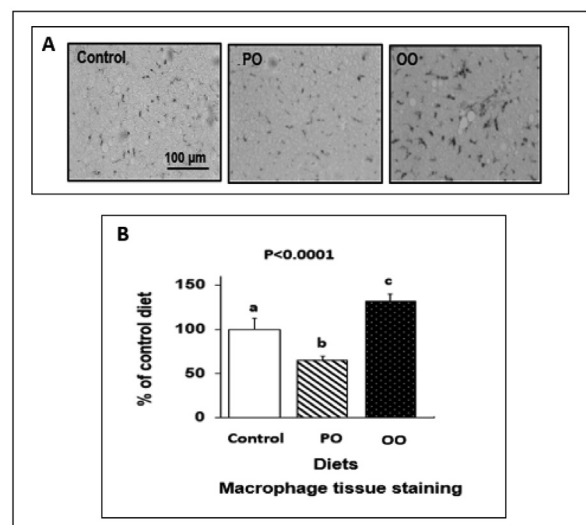


Figure 1. Effect of high dietary intake of palm olein and olive oil on hepatic macrophage infiltration.

(A) Histological section of liver ($n=10-20$ /rat) showing macrophage infiltrations after CD68 primary antibody marking (magnification $\times 200$). (B) Quantity of macrophages/ mm^2 of liver. Results were expressed as mean values \pm S.D., $n=7-8$ animals per group. Statistical analysis was based on one-way ANOVA followed by a Tukey Kramer multiple comparisons test. The limit of statistical significance was set at $p<0.05$. The group mean values with different letters (a, b, c) are significantly different. CD68, Cluster of differentiation 68; PO, Palm olein; OO, Olive oil.

Table 3. Blood oxidative stress parameters

Rats were fed their respective diet for 12 weeks. Results were expressed as mean values \pm S.D., $n=7-8$ animals per group. Statistical analysis was based on one-way ANOVA followed by a Tukey Kramer multiple comparisons test. The limit of statistical significance was set at $p<0.05$. The group mean values with different letters (a, b, c) are significantly different.

	Control	PO	OO	<i>p</i>
Antioxidant system				
SOD (IU/mL)	324 \pm 15 ^a	296 \pm 23 ^b	326 \pm 18 ^a	0.0108
GPx (IU/mL)	14.4 \pm 3.3	15.9 \pm 4.4	13.9 \pm 1.4	NS
Oxidation products				
Thiol groups (μ M)	112 \pm 52	124 \pm 49	111 \pm 44	NS
TBARS (μ M)	5.12 \pm 0.86	5.26 \pm 1.04	4.79 \pm 0.88	NS
15-F2t-isoprostane (AU)	53 \pm 16 ^a	44 \pm 06 ^{ab}	37 \pm 06 ^b	0.0167

AU, arbitrary Unit; GPx, Glutathione peroxidase; PO, Palm olein; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances.

Spurlock, 2005; Laine *et al.*, 2007), the results of this study and data from the literature show that PO has anti-inflammatory properties due to its high tocotrienol content.

Effects of diets on antioxidant status

In blood, SOD was significantly reduced ($p=0.0108$) with PO diet compared to other diets. None of the diets resulted in a significant increase in oxidation products (Table 3). Concerning oxidation products, compared to the control diet, PO diet resulted in a non-significant increase of thiol groups by 10% and a non-significant decrease of 15-F2t-isoprostane by 17%. Compared to the control diet, OO diet has favoured a decrease of 1% of thiol groups, a decrease of 7% of TBARS and a significant decrease ($p=0.0167$) of 15-F2t-isoprostane of 31% (Table 3).

In liver, no significant differences were observed between diets with regard to their effects on oxidative stress parameters (Table 4). Concerning oxidation products, the level of thiol groups showed a non-significant tendency to increase ($p=0.0779$) with PO (+11%) and

OO (+5%) compared to the control diet (Table 4). The study of the expression of genes involved in the anti-oxidant system showed a non-significant tendency to increase ($p=0.0696$) Nrf2 gene with OO diet (+35%) and PO diet (+9%) compared to the control diet. The gene expression of *NQO-1*, *HO-1* and *GCLC* was not modified in any diet (Table 4).

Thiols play a very important «buffer» role in the body. In the event of severe oxidative stress, thiols restore the «redox» balance (oxidation/reduction balance) by eliminating free radicals (Ferrer-Sueta *et al.*, 2011). PO diet effectively protects liver against free radicals because it promotes an increase in plasma and liver thiols. Moreover, no diet has led to a significant decrease in the level of plasma and liver thiol groups. This suggests that no diet has favoured oxidative stress, as only the collapsed thiol levels objectivise old and/or chronic oxidative stress (Musaogullari & Chai, 2020).

Lipoperoxidation was assessed by the determination of blood and liver TBARS and plasma 15-F2t-isoprostane. No diet resulted in a significant increase in these parameters compared to the control diet. Since only an

Table 4. Liver oxidative stress parameters

Rats were fed their respective diet for 12 weeks. Results were expressed as mean values \pm S.D., $n=7-8$ animals per group. Statistical analysis was based on one-way ANOVA followed by a Tukey Kramer multiple comparisons test. The limit of statistical significance was set at $p<0.05$. The group mean values with different letters (a, b, c) are significantly different.

	Control	PO	OO	<i>p</i>
Antioxidant system				
SOD (U/mg protein)	45.7 \pm 4.3	43.9 \pm 3.3	43.9 \pm 4.9	NS
GPx (U/mg protein)	6.69 \pm 0.51	6.96 \pm 0.75	6.52 \pm 0.72	NS
Catalase (U/mg protein)	725 \pm 57	791 \pm 125	787 \pm 53	NS
GSH (nmol/g ww)	126 \pm 16	140 \pm 16	122 \pm 18	NS
GSH/GSSG	4.91 \pm 0.34	5.02 \pm 0.18	4.96 \pm 0.46	NS
<i>Nrf2</i> (qPCR)	1.00 \pm 0.24 ^a	1.09 \pm 0.21 ^{ba}	1.35 \pm 0.39 ^b	0.0696
<i>NQO-1</i> (qPCR)	1.00 \pm 0.57	0.87 \pm 0.40	1.14 \pm 0.60	NS
<i>HO-1</i> (qPCR)	1.00 \pm 0.62	0.91 \pm 0.25	0.81 \pm 0.25	NS
<i>GCLC</i> (qPCR)	1.00 \pm 0.42	1.26 \pm 0.30	1.44 \pm 0.42	NS
Oxidation products				
Thiol groups (nmol/mg protein)	110 \pm 10 ^a	123 \pm 9 ^b	116 \pm 11 ^{ab}	0.0779
TBARS (nmol/mg protein)	99 \pm 20	90 \pm 18	83 \pm 12	NS

GCLC, Glutamate-cysteine ligase catalytic subunit; GPx, Glutathione peroxidase; GSH, Reduced glutathione; GSSG, Oxidized glutathione; HO-1, Heme oxygenase-1; Nrf2 (Nfe2l2), Nuclear factor-erythroid 2 related factor 2; NQO-1, NAD(P)H quinone dehydrogenase 1; qPCR, Quantitative-Polymerase chain reaction; PO, Palm olein; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; ww, Wet weight.

increase in these parameters indicates lipid oxidation by free radicals, we can say that PO and OO diets did not favour lipoperoxidation.

These results indicate that despite the significant decrease in SOD activity by PO diet compared to the control diet, PO diet does not favour oxidative stress compared to OO diet. This antioxidant power could be partly explained by the increase in the amount of thiols in the PO diet.

In addition, numerous studies argue in favour of the antioxidant power of palm oil. Selenium deficiency favours the reduction of GPx activity with the consequent occurrence of a significant oxidative stress, the source of many pathologies (Navarro-Alarcon & Lopez-Martinez, 2000; Rayman, 2000). A study carried out in Côte d'Ivoire showed that subjects deficient in selenium and GPx, regular consumers of palm oil (crude or olein) had a good antioxidant status and did not present oxidative stress (Tiahou *et al.*, 2004). In another study conducted on four varieties of palm oil from Côte d'Ivoire, Mondé and others (Mondé *et al.*, 2011) showed that antioxidants in these different variants reduce LDL oxidation *in vitro*.

Palm oil owes its nutritional benefits, linked to its antioxidant power, to its «minor» components. In animals, numerous studies (Suarna *et al.*, 1993; Azlina *et al.*, 2005; Suzana *et al.*, 2005) have highlighted the antioxidant effects of palm oil tocotrienols. Coenzyme Q10 (ubiquinone), a natural coenzyme of palm oil, is a powerful free radical scavenger (Niklowitz *et al.*, 2007) with ten times the antioxidant power of carotenoids and vitamin E (Ng *et al.*, 2006). Palm oil is the vegetable oil richest in tocotrienols (Sundram *et al.*, 2003; Sen *et al.*, 2010). Tocotrienols are powerful antiradical agents with a proven cardioprotective role (Rooyen *et al.*, 2008; Vasanthi *et al.*, 2012; Wong & Radhakrishnan, 2012).

Despite the loss of carotenoids (Lecerf, 2013) and micro-constituents such as flavonoids and phenolic acids during refining (Tan *et al.*, 2001), PO still retains its antioxidant properties, as the results of this study show. This may be due to the fact that during refining, PO is enriched with tocotrienols (Sambanthamurthi *et al.*, 2000; Lecerf, 2013), which are powerful free radical scavengers.

CONCLUSION

This study showed that PO decreases SOD activity compared to OO while OO increases macrophagic infiltration in the liver. PO consumption does not promote inflammation and oxidative stress.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding publication of this article.

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