Argan (Argania spinosa) oil lowers blood pressure and improves endothelial dysfunction in spontaneously hypertensive rats

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Traditionally hand-pressed argan oil, obtained from Argania spinosa seeds, is eaten raw in south-west Morocco; its rich composition of tocopherols, MUFA and PUFA make a study of its actions on risk factors for CVD, such as hypertension, interesting. The effects of 7 weeks of treatment with argan oil (10 ml/kg) on the blood pressure and endothelial function of spontaneously hypertensive rats (SHR) and normotensive Wistar–Kyoto rats were investigated. Systolic blood pressure and heart rate were measured every week by the tail-cuff method and endothelial function was assessed by carbachol (10⁻³ to 10⁻⁴ M)-induced relaxations of aortic rings and small mesenteric arteries pre-contracted with phenylephrine. Argan-oil administration reduced the mean blood pressure of SHR after the fifth week of treatment (P<0.05) and increased (P<0.01) the endothelial responses of arteries from SHR. The NO synthase inhibitor, L-Nω-nitroarginine (5 x 10⁻⁴ M) revealed a greater participation of NO in the relaxant effect after the treatment. When cyclooxygenase (COX) was blocked with indomethacin (10⁻⁵ M), an involvement of COX products in the endothelium-dependent response was characterized. Enzyme immunoassay of thromboxane B₂ showed a significant decrease (P<0.05) in the release of thromboxane A₂ in both aorta and small mesenteric artery after argan-oil treatment of SHR. Experiments in the presence of the thromboxane A₂–prostaglandin H₂ receptor antagonist ICI 192,605 (10⁻⁵ M) confirmed this result. Results after incubation with the antioxidants superoxide dismutase and catalase suggested that a decreased oxidative stress might contribute to explain the beneficial effects of argan-oil treatment.

Argan oil: Hypertension: Endothelium: Cyclooxygenase products: Spontaneously hypertensive rats

There is strong evidence for an association between a Mediterranean-style diet and protection from CVD (De Lorgeril et al. 1999). Such a diet lower total cholesterol and LDL-cholesterol compared with a diet very rich in saturated fatty acids, thus reducing a dominant risk factor for the development of atherosclerosis (Williams, 2001). Additional mechanisms have favourable effects on other CVD risk factors, such as hypertension (Simon et al. 1996) and diabetes (Hannah & Howard, 1994; Griffin et al. 1996). This style of diet, consumed by several different populations, has a common characteristic, namely the high proportion of olive oil (rich in MUFA, mainly oleic acid; Keys, 1995).

As well as olive oil, there are other vegetable oils that are sources of dietary unsaturated fatty acids. Argan oil is traditionally used particularly in Morocco for nutritional purposes. Traditionally hand-pressed argan oil, obtained from Argania spinosa seeds, is eaten raw in south-west Morocco, where it represents 25% of dietary fat intake and 9% of annual production. Argan oil and its preparations have been used in traditional Moroccan medicine for centuries to cure skin diseases topically. In addition, argan oil is used orally in rheumatology and is traditionally prescribed as a choleretic, hepatoprotective agent, and in cases of hypercholesterolaemia and atherosclerosis (Charrouf & Guillaume, 1999). However, its potential biological relevance in cosmetic, pharmaceutical or phytoprotective fields has yet not been established.

Argan oil is rich in MUFA and PUFA, whereas saturated fatty acids are present in lower proportions (Charrouf & Guillaume, 1999). Several studies have suggested that hypertension and CVD are related to a deficiency in PUFA, especially of linoleic acid (Das, 1995; Horrobin, 1995), so that an increase in the linoleic acid content of diet was associated with a decrease in systolic blood pressure (Aguila & Mandarin-de-Lacerda, 2000; Yoshioka et al. 2000). Argan oil is also rich in the antioxidant α-tocopherol (Charrouf & Guillaume, 1999), which reduced...
blood pressure in an experimental model of hypertension (Chen et al. 2001). Although a previous report showed a decrease in blood pressure after ingestion of argan oil (Berrada et al. 2000), the mechanism involved remains unknown. Because of the composition of argan oil and its antihypertensive action, it was of interest to carry out a deeper study of its cardiovascular effects, focusing on endothelial function. We have investigated the effect of chronic treatment with argan oil for 7 weeks on blood pressure and endothelial dysfunction in spontaneously hypertensive rats (SHR) compared with normotensive Wistar–Kyoto rats (WKY).

**Methods**

**Argan oil extraction**

Argan oil was extracted by a traditional hand-pressed method (Charrouf & Guillaume, 1999) from fresh seeds collected in the same year in order to prevent auto-oxidative reactions. The extraction was carried out in Essaouira (south-west Morocco).

**Animals**

Four-week-old male hypertensive SHR (n=12) and normotensive control WKY (n=12) rats, weighing 100–120 g, were purchased from Harlan Iberica (Barcelona, Spain). All experiments were performed according to guidelines for the ethical treatment of animals of the European Union (86/609/EEC). Both SHR and WKY were divided randomly into two groups of six animals each: the first group was fed with standard rat chow (control group; Panlab SRL, Barcelona, Spain). The second group was treated with 10 ml argan oil/kg body weight per d intragastrically for 7 weeks in addition to the standard diet. This dose has been shown to have hypolipidaemic and hypocholesterolaemic effects (Berrougui et al. 2003). All the animals were maintained in a temperature-controlled room (22 ± 2°C) with a 12 h light–dark cycle and with free access to standard rat chow and drinking water. The blood pressure and heart rate of conscious animals were measured indirectly each week by the tail-cuff method with a digital pressure meter (Niprem 645; Cibertec, Madrid, Spain).

**Arterial preparation and mounting**

The animals were anaesthetized with pentobarbitone sodium (50 mg/kg intraperitoneally) and exsanguinated. The thoracic aorta and branch II or III of the small mesenteric artery (SMA) were carefully removed and cleaned of fat and connective tissue. Then, artery segments (2–3 mm or 1.6–2.0 mm long for the aorta and the SMA respectively) were mounted on myographs filled with physiological salt solution of the following compositions (mM) for the aorta and SMA respectively: NaCl 119 and 119, KCl 47 and 47, MgSO4 1.17 and 1.17, KH2PO4 1.18 and 0.40, NaHCO3 25.0 and 14.9, CaCl2 1.8 and 2.5, glucose 11.0 and 5.5. The physiological salt solution was kept continuously at 37°C and gassed with 95% O2–5% CO2 at pH 7.4. Resting tension was adjusted to 2 g for the aorta and 200 mg for the SMA. Mechanical activity was recorded isometrically by a force transducer (Pioden UF-1 (Canterbury, Kent, UK) for the aorta and Multi Myograph System-610M (Aarhus, Denmark) for the SMA) coupled to a Powerlab® data acquisition system (AD-Instruments, Castle Hill, Victoria, Australia). After setting the vessel to its working length, challenges with 10^{-5} M phenylephrine (Phen)/l or 10^{-5} M noradrenaline/l were performed in aorta and SMA respectively to test their maximal contractile capacity and to elicit a reproducible contracting response.

**Relaxation experiments**

Arteries were pre-contracted with Phen: 3 × 10^{-7} M for the aorta and 3 × 10^{-5} M for the SMA. For each preparation, it was ensured that Phen-induced contractions were stable during all the experiments. When the contraction reached a plateau, cumulative addition of carbachol (10^{-8}–10^{-4} M) was performed. In order to analyse the involvement of endothelial factors, concentration–response curves were constructed in the absence or in the presence of the indicated inhibitor(s): the NO synthase inhibitor, l-Nω-nitroarginine (l-NOARG; 3 × 10^{-5} M), the cyclooxygenase (COX) inhibitor, indomethacin (10^{-5} M), the thromboxane A2–prostaglandin H2 receptor antagonist ICI 192,605 (10^{-5} M), the superoxide anion (O2-) scavenger superoxide dismutase (SOD; 1.5 × 10^{5} U/l), and catalase (10^{6} U/l). All the inhibitors were used at a maximally active concentration and were incubated with the tissue for 20 min before the pre-contraction with Phen except for SOD + catalase (i.e. 10 min before pre-contraction with Phen). The concentration of Phen after inhibitors was adjusted in order to obtain similar pre-contraction levels.

**Thromboxane A2 production**

Thromboxane (TX) A2 is unstable and is quickly converted to TXB2. Intact aortas and mesenteric bed from control and argan oil-treated SHR were incubated in physiological salt solution at 37°C and bubbled with 95% O2–5% CO2 gas mixture and stimulated with Phen (10^{-6} M for aorta and 10^{-5} M for SMA) and carbachol (10^{-6} M) to liberate to the medium vasoactive products. The concentration of TXB2 was assessed by competitive enzyme immunoassay kits (Cayman Chemical Company, Ann Arbor, MI, USA). TXB2 production was expressed as pg/mg dry tissue.

**Chemical reagents and drugs**

Acetylcholine chloride, indomethacin, l-NOARG, phenylephrine hydrochloride, carbachol chloride, catalase and SOD were purchased from Sigma Chemical Co. (St Louis, MO, USA). ICI 192,605 was purchased from Tocris (Biogen Cientifica S.L., Madrid, Spain). The drugs were dissolved in distilled and deionized water except for indomethacin and ICI 192,605, which were dissolved in dimethylsulfoxide. The final concentration of dimethylsulfoxide in the tissue bath was 0.1 g/l, which was shown to...
have no effect on the basal tonus of the preparation. All concentrations of the drugs used are expressed as final concentration in the organ chamber.

Statistical analysis

Results were expressed as a percentage from the initial pre-contraction level and as mean values with their standard errors for six determinations obtained from different animals. The pre-contraction levels of the arteries from the four groups of animals are summarized in Table 1. Areas under concentration–response to carbachol curves were calculated in the absence of inhibitors and in the presence of indoelmethacin or l-NOARG. In order to evaluate the approximate participation of COX products and NO, the subtraction area under control curve minus area in the presence of indomethacin or l-NOARG was calculated. A positive sign (+) in the result was interpreted as the prevalence of a relaxant factor and the negative (−) sign as a greater involvement of contracting products. ANOVA followed by Tukey’s multiple comparisons test was used for statistical analysis. P values <0.05 were considered to show a significant difference. Statview software package (version 5.0; SAS Institute Inc., Cary, NY, USA) was used to carry out statistical analysis.

Results

Blood pressure

Daily argan-oil administration induced a progressive reduction in mean blood pressure in SHR; this reduction was significant from the fifth week of treatment (P<0.05; Fig. 1). However, no change was observed in blood pressure of normotensive WKY during the 7 weeks of treatment with argan oil. Despite the decrease in blood pressure in SHR, the heart rate was not affected by treatment in either group (377.4 (SEM 11.6) and 388.8 (SEM 14.5) beats per min in WKY control and treated groups respectively; 429.6 (SEM 10.9) beats per min after treatment). Although animals were treated with 1 ml fatty compound/d, body weight was not affected (303.7 (SEM 6.8) and 284.7 (SEM 18.2) g for WKY control and treated groups respectively; 276.2 (SEM 6.8) and 258.7 (SEM 18.2) g for control and treated SHR groups respectively).

Endothelium-dependent relaxation

Endothelial function was assessed in two different vascular beds by relaxation induced by carbachol in arteries pre-contracted by Phen. After the 7-week treatment with argan oil, the concentration–response curves to carbachol of aortas and SMA from normotensive WKY were not significantly affected (Fig. 2(A and B)). In contrast, the endothelium-dependent relaxation of aortic rings from argan oil-treated SHR was significantly increased (P<0.01) compared with that of the SHR control group (Fig. 2(C)). The maximal relaxant response reached in SHR after treatment (83.7 (SEM 2.8) %) was even greater than that obtained in normotensive WKY (65.7 (SEM 8.6) %, P<0.001).

In SMA from SHR, the relaxation–response curve to carbachol had a biphasic profile with contraction induced by carbachol at concentration >10−6 M. Although maximal relaxation to carbachol was significantly increased by argan-oil treatment, this biphasic profile of the curve was not altered (Fig. 2(D)).

Characterization of endothelial factors involved

The effect of the NO-synthase inhibitor l-NOARG was studied in order to find out whether NO was involved in the improvement of endothelial relaxation in aortae and SMA. In both types of arteries l-NOARG (3×10−5 M) produced a statistically significant blockade of the relaxation in non-treated rats (Fig. 3(A and C), aorta; Fig. 4(A and C), SMA) and argan oil-treated rats (Fig. 3(B and D), aorta; Fig. 4(B and D), SMA).
Fig. 2. Endothelial function assessed by relaxant response to carbachol (CCh; $10^{-8}$ to $10^{-4}$ M) of isolated rat aortic rings (A and C) and small mesenteric artery (B and D) from normotensive Wistar–Kyoto rats (A and B) and spontaneously hypertensive rats (C and D). Results obtained from argan (Argania spinosa) oil-treated animals (†) were compared with age- and strain-matched animals (W). For details of treatments and procedures, see p. 922. Values are means with their standard errors shown by vertical bars. Mean values for argan-oil treated animals were significantly different from those of the control group: *$P<0.05$, **$P<0.01$.

Fig. 3. Characterization of endothelial factors released after stimulation with carbachol (CCh; $10^{-8}$ to $10^{-4}$ M) of aortic rings from non-treated Wistar–Kyoto rats (WKY) (A), argan (Argania spinosa) oil-treated WKY (B), non-treated spontaneously hypertensive rats (SHR) (C) and argan oil-treated SHR (D). Concentration–response curves constructed in the absence of inhibitors were considered as control curves (W) and compared with those made in the presence of L-Nω-nitroarginine (L-NOARG; $3 \times 10^{-5}$ M) (●), indomethacin ($10^{-5}$ M) (▲) or indomethacin plus L-NOARG (△). For details of treatments and procedures, see p. 922. Values are means with their standard errors shown by vertical bars. Mean values were significantly different from those of the control curve: *$P<0.05$, **$P<0.01$. Mean values for SHR were significantly different from those of WKY: †††$P<0.001$. Mean values for L-NOARG were significantly different from those of L-NOARG plus indomethacin: ‡$P<0.05$. 

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In order to study the involvement of COX products in endothelial relaxation, arteries were incubated in the presence of a non-selective COX inhibitor, indomethacin (10^{-5} M). This drug did not modify carbachol-induced relaxation of aortic rings from WKY. In aortas from control SHR, indomethacin increased the relaxant response, although this effect was not significant. With regard to SHR treated with argan oil, the presence of indomethacin did not affect the concentration–response curve of aortic rings. In resistance arteries from SHR, indomethacin significantly increased carbachol-induced relaxation (P<0.01) and abolished the biphasic profile of the control curve (Fig. 4(C and D)).

Exposure to indomethacin (10^{-5} M) plus L-NOARG (3 x 10^{-5} M) completely abolished (P<0.01) the carbachol-induced relaxation curve in rat aorta and SMA (Figs 3 and 4). In aortic rings from treated SHR, the inhibition obtained after incubation with indomethacin plus L-NOARG was significantly greater than that achieved in the presence of L-NOARG (P<0.05; Fig. 3(D)). The presence of a relaxant COX-product in aortic rings after argan-oil administration could well explain this result. However, in SMA from non-treated SHR, the greater relaxation in the presence of L-NOARG plus indomethacin than in the presence of L-NOARG (P<0.05; Fig. 4(C)) could be attributed to the presence of COX-derived contracting products in hypertensive rats.

In order to illustrate better the contribution of endothelium-derived factors in the relaxation induced by carbachol, areas under concentration–response curves were calculated in the absence and in the presence of L-NOARG and indomethacin, representing NO and COX products respectively. The calculated participation of NO in the carbachol-induced relaxation of isolated aorta from argan oil-treated rats was greater (P<0.05 in WKY; P<0.001 in SHR) than in aortic rings from untreated rats. With regard to the COX products released in isolated aorta, the resulting contracting effect was found in SHR, but not in WKY, where relaxant factors derived from COX had a greater involvement (Fig. 5(A)). The treatment with argan oil decreased the participation of COX products in aortic rings from SHR (P<0.05) without affecting the sign of the calculated value (Fig. 5(A)).

In SMA, the participation of NO was significantly greater after argan-oil treatment in SHR (P<0.01) but not in normotensive WKY. According to the results observed in the aorta, the involvement of contracting COX products was also decreased in SMA from SHR after treatment (P<0.05). However, the prevalence of contracting COX products was found in SMA from treated WKY (P<0.05; Fig. 5(B)).

To verify the nature of endothelial vasoconstrictor products from the COX involved, the effect of the TXA_{2}–prostaglandin H_{2} receptor antagonist, ICI 192,605 (10^{-5} M) on carbachol-induced relaxation in arteries from SHR was investigated. Though the relaxation of arteries from non-treated SHR was enhanced by incubation with ICI 192,605 (Fig. 6(A and C)), this increase was not statistically different. In aortic rings from argan-oil treated SHR, the presence of ICI 192,605 did not affect the relaxant response to carbachol. This antagonist significantly inhibited the relaxation in SMA from treated SHR (P<0.05; Fig. 6(D)).
were significantly different from those of the non-treated group of errors shown by vertical bars. Mean values for argan oil-treated rats procedures, see p. 922. Values are means with their standard error. Values are means with their standard error. (92·84 (SEM 2·34) pg/mg (9). Argan oil on endothelial function

**Thromboxane B2 production**

The TXB2 levels released by stimulated aortic rings and mesenteric bed from non-treated SHR were 312·66 (SEM 39·47) (n 4) and 157·49 (SEM 22·93) (n 4) pg/mg respectively. After 7-weeks treatment with argan oil, the release of TXB2 decreased significantly in aortic rings (193·61 (SEM 22·10) pg/mg (n 4), P<0·05) and mesenteric bed (92·84 (SEM 2·34) pg/mg (n 4), P<0·05).

**Involvement of oxygen free radicals in the effect of argan oil on endothelial function**

Finally, to investigate whether an augmented production of O2⁻ was involved, the effect of SOD was studied in SHR. In both isolated rat aorta and SMA the presence of SOD plus catalase significantly increased (P<0·05) the carbachol-induced relaxation in untreated rats, since SHR are rich in free radicals derived from O2. After argan oil administration, the endothelium-dependent relaxation of aortic ring was not increased by the presence of antioxidant enzymes (Fig. 7(B)). When the same experiment was carried out on SMA from treated animals, the presence of SOD plus catalase increased the contraction phase of the concentration–response curve (Fig. 7(D); P<0·01).

**Discussion**

Dietary fatty acids have been reported to influence the development of hypertension and vascular reactivity of both resistance and large conductance arteries (Schmidt, 1997; Angerer & Von Shackly, 2000). The preventive effects of PUFA such as linoleic and γ-linolenic acid on hypertension are well known, whereas saturated fatty acids have been shown to promote hypertension (Aguiña & Mandarín-de-Lascarra, 2000; Yoshioka et al. 2000). Changes in lipid metabolism caused by a diet rich in mono-unsaturated oleic acid that could be favourable in the prevention of atherosclerosis and thrombosis have been observed (Williams, 2001). In the present study, the effects of argan-oil ingestion on blood pressure and endothelial function were evaluated.

In relation to the chemical composition of argan oil, unsaturated fatty acids are the major components (oleic plus linoleic acids constitute 80 g/100 g total fatty acids) and linolenic acid is only present as a trace (Charrouf & Guillaume, 1999). Argan oil is about twice as rich in mono-unsaturated oleic acid that could be favourable in the prevention of atherosclerosis and thrombosis have been observed (Williams, 2001). In the present study, the effects of argan-oil ingestion on blood pressure and endothelial function were evaluated.

We have shown that chronic treatment with argan oil prevented the development of hypertension in this animal model (SHR), substantially modifying mean blood pressure from the fifth week of treatment without altering heart rate and body weight. Taking into account the composition of argan oil, two hypotheses could be put forward. First, the high proportion of the PUFA linoleic acid present in argan oil could play a role in blood pressure regulation. It has been demonstrated that plasma concentration of linoleic acid is inversely associated with blood pressure (Grimsgaard et al. 1999) and that diets enriched with linoleic or γ-linolenic acid attenuated the development of hypertension in SHR (Abeywardena & Head, 2001; Frenoux et al. 2001). The second hypothesis to consider is that the high proportion of α-tocopherol present in argan oil could be related to the antihypertensive effect observed. Thus, the dose of α-tocopherol administered in the argan oil to rats (3·8 mg/kg per d) was similar to the dose that has previously demonstrated prevention of high blood pressure in SHR (Newaz & Nawal, 1998; Newaz et al. 1999).

Regarding the improvement of endothelial dysfunction of SHR, pharmacological tools were used to evaluate the...
relative contribution of different endothelial factors to this effect. The presence of a NO synthase inhibitor revealed an increased participation of NO in relaxation induced by carbachol. In order to explain this increase of NO-dependent relaxation, the antioxidant properties of argan oil due to a high concentration of the antioxidant vitamin α-tocopherol should be noted. It has been shown previously that the oxidative stress in SHR could be decreased after treatment with vitamin E (Newaz & Nawal, 1998). Those animals receiving α-tocopherol elicited a lower release of
arteries, the TXA2–prostaglandin H2 Tp receptor antagonists present in argan oil could improve bioavailability of NO by both decreasing its breakdown and increasing its synthesis. To confirm this hypothesis experiments in the presence of antioxidant enzymes were carried out. The endothelial relaxation of both aortic rings and SMA after incubation with SOD plus catalase was improved in control animals. This increase in endothelial response after incubation with the antioxidant enzymes was due to an improved oxidant status, as previously demonstrated by our research group (Carneado et al. 2002). However, the presence of SOD plus catalase did not alter the concentration–response curve in aorta from treated animals, probably because of a lower release of superoxide or an increase in antioxidant defence after treatment with the oil. In SMA, the presence of SOD plus catalase even inhibited relaxation. This inhibitory effect on endothelium-dependent relaxation could be related to a high concentration of SOD that blunted endothelial NO. However, it is possible that reactive oxygen species were playing a role in the increase of endothelium-dependent relaxation of SMA after treatment with argan oil. In this way, it has been shown previously that O2\textsuperscript{-} could enhance Ca\textsuperscript{2+}–NO signalling in endothelial cells (Graier et al. 1996) and even stimulate those cells to produce NO (Dreher et al. 1995; Hu et al. 1998).

In addition to NO, the participation of COX-derived products in the effect of argan oil was studied. The presence of the COX inhibitor, indomethacin, revealed a decrease in the resulting COX contracting component. To explain this result, the minor involvement of vasoconstrictor TXA2 and prostaglandin H2 and/or an increase in vasodilator prostaglandin I2 should be noted. The enzyme immunoassay confirmed that after treatment with argan oil the TXA2 released by either aortic rings or SMA was significantly reduced. This result agrees with those shown in other studies (Newaz et al. 1995; Hu et al. 1998). The endothelial relaxation of both aortic rings and SMA after incubation with SOD plus catalase was improved in control animals. The enzyme immunoassay confirmed that after treatment with argan oil the TXA2 released by either aortic rings or SMA was significantly reduced. This result agrees with those shown in other studies (Newaz et al. 1995; Hu et al. 1998).

Another relevant fact was that involvement of COX products turned into a greater contracting component in SMA from treated WKY without increase in blood pressure. It has been reported that the two strains of rat differ in their fatty acid metabolism (Mills et al. 1990) and their vascular responses after diets enriched in PUFA were altered in different ways (Engler et al. 1992). Those differences in metabolism between the strains may help to explain the opposing endothelial response after COX inhibition. In addition to the previously discussed antioxidant properties of argan oil, its richness in linoleic acid could be related to the effect on endothelial COX products. Some studies suggest that linoleic acid could both increase synthesis of vasoactive prostaglandins (Calder, 1997) and decrease TX production (Engler, 1996).

In conclusion, treatment of hypertensive animals with argan oil not only prevented the increase in blood pressure, but also improved endothelial function. A high concentration of linoleic acid and \( \alpha \)-tocopherol could contribute to explaining this effect that was dependent on both COX products and NO. However, further studies should be done in order to identify the mechanisms of the effects of argan oil on endothelium as well as its mechanism of action. Although the present study supports the use of this oil in the diet and as a dietary supplement, the concentration used in the present study was higher than normal human consumption. Clinical research should be done before validating its use to improve endothelial dysfunction and hypertension.

References
Effect of argan oil on blood pressure


