Conjugated linoleic acids modulate UVR-induced IL-8 and PGE2 in human skin cells: potential of CLA isomers in nutritional photoprotection

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Introduction

Conjugated linoleic acids (CLA), derivatives of linoleic acid found in food products, inhibit chemically induced skin cancers in mice. However, their potential photoprotective properties remain unexplored. We examined whether CLA may modulate ultraviolet radiation (UVR)-induced secretion of interleukin (IL)-8 and prostaglandin E2 (PGE2), mediators implicated in UVR-induced inflammation and carcinogenesis, in human skin cells. Since tumour necrosis factor (TNF)-α is an early mediator of UVR effects, we also examined influence of CLA on TNF-α-induced mediator release. HaCaT keratinocytes were supplemented with CLA isomers cis-9-trans-11 (c9,t11-CLA; >90%), trans-10-cis-12 (t10,c12-CLA; >90%) or all trans-trans isomers (t-t-CLA; 23.7%) in tetrahydrofuran/fetal calf serum (THF/FCS) or THF/FCS control. Supplementation of keratinocytes with c9,t11-CLA reduced Ultraviolet B(UVB)-induced IL-8 from 37 113 ± 2903 pg/mg protein to 14 167 ± 2063 pg/mg protein (P < 0.001). Similarly, t10,c12-CLA reduced UVB-induced IL-8 to 9786 ± 1291.5 pg/mg protein (P < 0.001). Additionally, t10,c12-CLA and t-t-CLA inhibited TNF-α-induced IL-8 from 11 669 ± 1692 pg/mg protein to 5540 ± 191 (P < 0.001) and 8082 ± 1298 pg/mg (P < 0.01) protein, respectively, UVB-induced PGE2 release was reduced by t-t-CLA supplementation, from 4.8 ± 1.2 to 1.6 ± 0.8 pg/mg protein (P < 0.01), but increased by t10,c12-CLA to 8.8 ± 1 pg/mg protein (P < 0.001). Influence of CLA on UVB-induced PGE2 release was further explored in CCl922SK dermal fibroblasts. CLA isomers reduced UVB-induced PGE2 in fibroblasts, reaching significance with c9,t11-CLA (98 ± 5 falling to 0 pg/mg protein, P < 0.05). Hence, CLA isomers differentially modulate UBV effects on skin cells in vitro. CLA-containing foods have potential in photoprotection; the cutaneous effects of individual isomers warrant clinical study.

Abbreviations: CLA, conjugated linoleic acid; c9,t11, cis-9-trans-11; FA, fatty acids; FCS, fetal calf serum; IL, interleukin; LA, linoleic acid; OA, oleic acid; PGE2, prostaglandin E2; t10,c12, trans-10-cis-12; THF, tetrahydrofuran; TNF, tumour necrosis factor; t-t, trans; UVR, ultraviolet radiation.

Properties of conjugated linoleic acids have been confirmed in several other models of cancer, including the mammary gland, stomach, colon and prostate (14). Furthermore, it has been suggested that the anti-carcinogenic properties of CLA may stem from their anti-inflammatory properties (15). However, their effects on ultraviolet radiation (UVR)-induced skin damage are currently unexplored.

The negative effects of UVR on human skin include the acute effects of sunburn (inflammation), photosensitivity rashes and immunosuppression and the longer term damage of photocarcinogenesis and photoaging (16). UVR is a complete carcinogen, both initiating the DNA damage that if unrepaired can lead to mutagenesis and promoting carcinogenesis principally through immunosuppression (17,18). Skin cancer is a major clinical problem continuing to rise in incidence and now presenting as the commonest cancer in white populations (19). Topical photoprotection has a number of drawbacks, and is often inadequately applied; hence, a dietary means for protection could provide a useful adjunctive measure, with potential application both to susceptible patients and the healthy population (16). As far as we are aware, we now report the first study designed to examine whether CLA may modulate UVR-induced effects and hence their potential activity as photoprotective agents.

Interleukin (IL)-8, an inflammatory cytokine and potent chemokine, is up-regulated in human skin following UVR exposure (20). It plays a pivotal role in the acute response of the skin to UBV, attracting neutrophils into the dermis where they mediate inflammation and cause tissue damage secondary to the release of reactive oxygen species. Prostaglandin E2 (PGE2) is another mediator important in the acute inflammatory response to UBV, responsible for the clinical erythema evident in the sunburn response (21,22), and capable of mediating the release of other inflammatory mediators including IL-6 and IL-8 in some, but not all, experimental models (23,24). The sunburn response and UBV-induced carcinogenesis are closely linked, and both IL-8 and PGE2 are also implicated in the latter. Whereas IL-8 is a mediator of angiogenesis, and is associated with tumour growth including development of malignant melanoma (25,26), PGE2 is a mediator of UBV-induced immunosuppression (27) and promotes skin carcinogenesis in mouse models (28). Furthermore, cyclooxygenase-2 inhibitors partially block photocarcinogenesis and this is believed to be mediated principally through reduction of PGE2 production (29).

The aims of this study were to examine the effects of purified forms of the two principal dietary CLA isomers, i.e. c9,t11-CLA and t10,c12-CLA, and a mixture of all t-t-CLA isomers on UVR-induced secretion of IL-8 and PGE2. Since tumour necrosis factor (TNF)-α shows early up-regulation by UBV and is a key mediator in the orchestration of the acute UVR response, the effects of CLA isomers on TNF-α-induced IL-8 secretion were also examined. Studies were performed in human skin cells, principally keratinocytes, while the influence of CLA on UVB-induced PGE2 was further examined in fibroblasts.

Materials and methods

Cell culture

HaCaT keratinocytes [derived from the periphery of a melanoma on the non-extensively sun-exposed back of a 62-year-old male donor, considered immortal but not tumorigenic, obtained from Dr Petra Boukamp, German Cancer Research Centre, Heidelberg, Germany (30)] and CCl922SK fibroblasts [derived from normal human breast skin of a 22-year-old female donor, American Type Culture Collection, No. CRL 1828, MD] were cultured in Dulbecco’s Modified Eagle Medium containing 10% fetal calf serum (FCS), 2 mM glutamine and 40 μg/ml penicillin and 40 μg/ml streptomycin.

Supplementation of fatty acids to cells

Twenty-four hours prior to experimental use, FCS-containing medium was aspirated from subconfluent cells and the cells were washed twice with...
phosphate-buffered saline and re-immersed in defined serum-free media, AIMV® (Gibco BRL™ Life Technologies Ltd, Paisley, Scotland) containing 2 mM glutamine. Free fatty acid (FA) (5 μl) was dissolved in 235 μl of FCS, vortexed thoroughly to ensure complete emulsion and then 10 μl of tetrahydroluran (THF) was added. The final mixture consisted of 2/4/94% FA/THF/ FCS (v/v/v). Stock solutions were then diluted with 4/96% THF/FCS (v/v) to produce stock solutions of 5 mM. This was diluted 1:100 with FCS-free culture media and supplemented to cells, providing a final dietary oil concentration of 50 μM. FAs used were e9,t11-CLA (18:2n-7; 93.8% purity), t10,c12-CLA (98% purity, 18:2n-6), t-CLA (23.7% purity; all CLA isomers were provided by Unilever Research Laboratories, Bedford, UK) and oleic acid (OA, 18:1n-9; 95% purity; Sigma, Poole, UK). Cell cultures were supplemented with FAs or THF/FCS vehicle control for 4.5 days before UVB exposure.

**UVB exposure**
Cells were exposed to single doses of UVB using a filtered broadband source emitting predominantly UVB (Phillips TL12, emission 270–400 nm, peak 311 nm, 61% UVB, 32% ultraviolet A and 7% ultraviolet C). The spectral transmission through the tissue culture plastic was <0.1% ultraviolet C (<290 nm). The irradiance (mW/cm²) of the lamps was measured using an IL 1400 A radiometer calibrated for use with this light source (International Light Ltd, Newburyport, MA) and the irradiation time was varied to provide doses of 25–100 mJ/cm² UVB. Prior to irradiation, cells were washed twice and re-immersed in phosphate-buffered saline. Post-UVB, cells were re-immersed in culture media and incubated for 48 h prior to experimental use.

**Cell viability and protein analysis**
Cell viability was determined using the trypan blue exclusion assay. There was no effect of UVB on HaCaT cell viability at doses of 25, 50 or 75 mJ/cm² but after an exposure of 100 mJ/cm² there was a significant decrease to 86.7%, *P < 0.05*. There was no significant difference in cell viability after supplementation of any of the FAs in HaCaT cells. Protein content, determined by the biocinchoninic acid method, was used to standardize IL-8 measurements (31).

**Bioavailability of FAs**
Cellular FA content was analyzed by gas chromatography. Lipid was extracted from cells using chloroform:methanol:0.9% aqueous NaCl, 2:1:0.9 (v/v/v), with a 20:1 (v/v) solvent to cellular extract ratio. Butylated hydroxytoluene was added as an antioxidant to a final concentration of 0.005%. FA methyl esters were produced by acid-catalyzed methylation and analyzed on a low-resolution, non-polar capillary column (Thames Restek UK Ltd, Saunderton, Buckinghamshire, UK), using 0.2 μl injection volumes, or a high-resolution, polar capillary column (Chrompack), using 0.5 μl injection volumes with split ratios adjusted for optimum column loading (32). Purified oils of known composition were used as reference standards for peak identification by retention time, including standards for CLA isomers e9,t11-CLA, t10,c12-CLA and t-CLA. To check the source of FAs, AIMV® medium and FCS were profiled.

**IL-8 measurement**
Supernatants were harvested 4.5 days after FA supplementation or 48 h after irradiation. IL-8 was quantified by enzyme-linked immunosorbent assay. Monoclonal and biotinylated anti-human IL-8 antibodies (R&D Systems Europe Ltd, Abingdon, UK) produced an assay with a typical sensitivity of 2.8 pg/ml. Recombinant IL-8 standards ranged from 7.81 to 1000 pg/ml. Data are presented as mean ± standard error of mean, *P < 0.05*.

**PGE2 radioimmunoassay**
Cells were grown until confluency in six-well plates. Supernatants were harvested 24 h after irradiation and PGE2 release was measured by RIA (125I)-RIA kit NEN Life Science Products, Hounslow, UK). Since cell supernatants from serum-free medium-cultured cells contain much less PGE2 than cells cultured in serum-containing medium, the NEN [125I]-RIA assay was adapted to measure lower levels of PGE2. Serum may be a source of PGE2 and/or contain agents that facilitate PGE2 synthesis. Briefly, cells were cultured in 0.5 ml media after irradiation. The PGE2 standard curve range was extended to include 0.5–100 pg/ml. The reaction mixture was aliquoted into duplicate polypropylene microtubes, antibody-antigen complexes were precipitated from free, unbound antibody and centrifuged at 22 000g for 30 min at 4°C and the pellet counted for 1 min in a gamma counter. The sensitivity limit for the PGE2 assay was <0.44 pg/0.1 ml; cross-reactivity was 30% with PGE1 and ≤1% with other prostaglandins.

**Statistical analysis**
Data are expressed as the mean ± standard error of mean and analyzed for significance using one-way analysis of variance and Bonferroni’s modified t-test at the 95% confidence interval.

**Results**

**Cellular incorporation of CLA isomers**
In keratinocytes, e9,r11-CLA supplementation caused a significant increase in incorporation of e9.r11-CLA from 0 to 2.2 ± 0.2% total FAs (*n = 4, P < 0.001* compared with THF/FCS vehicle control; Table I). Following exposure to UVB, the percentage content of e9.r11-CLA fell significantly from 2.2 ± 0.2 to 1.3 ± 0.2% (*P < 0.001* compared with unexposed e9,r11-CLA-supplemented cells; Table I), presumably reflecting the release and subsequent utilization of this FA. t10,c12-CLA was successfully incorporated into the cell membranes of three of four keratinocyte samples, but only two of the three samples could be accurately analyzed due to the presence of a gas chromatography contaminant; the mean increase in these cells was from 0 to 0.3 ± 0.1% total FAs. In the fibroblasts, t10,c12-CLA supplementation resulted in significant incorporation of t10,c12-CLA, with an increase from 0 to 3.5 ± 0.7% (*P < 0.001*) compared with the THF/FCS vehicle control cells, while e9,r11-CLA isomer was undetectable with or without e9,r11-CLA supplement. t-CLA was not detected in either cell line, possibly reflecting the lower concentration used in supplementation.

Supplementation with CLA was not accompanied by significant change in content of other cellular FAs, including LA, arachidonic acid and OA, in either cell line. OA supplements had no significant impact on keratinocyte content of other cellular FAs other than a lowering of LA in unexposed cells relative to THF/FCS control cells, with 10.5 ± 0.4 and 8.3 ± 0.4%, respectively, *P < 0.01*. This may be attributable to displacement of membrane FAs and indicates that OA cannot generally be assumed to be an inactive control supplemental FA.

**Effect of CLA isomers on keratinocyte IL-8 production in basal and UVB-exposed cells**
UVB exposure of keratinocytes at doses ranging from 25 to 100 ml/cm² produced a UVB dose-related increase in supernatant IL-8 level, *P < 0.001*, with optimal induction at 48 h after exposure. Hence, IL-8 was assayed at 48 h following a single dose of 100 ml/cm² UVB in subsequent experiments. It was found that basal, i.e. non-UVB exposed, levels of IL-8 were not significantly altered by the CLA isomers. UVB significantly induced IL-8 in the THF/FCS control group, levels increasing from 7279±4 ± 1088.7 to 37 113.0 ± 29033 pg/ng protein (*P < 0.001*), and the findings were similar in the OA-supplemented cells. Both e9,r11-CLA and t10,c12-CLA isomers significantly reduced UVB-induced IL-8, from 37 113.0 ± 2903 to 14 167.1 ± 2063.2 pg/ng protein (*P < 0.001*) by e9,r11-CLA and to 4470.5 ± 1291.5 pg/ng protein (*P < 0.001*) by t10,c12-CLA, at 48 h following 100 ml/cm² UVB (Figure 1). t10,c12-CLA quenched IL-8

**Table I. Effect of supplements on the e9,r11-CLA, t10,c12-CLA and OA content of unexposed and UVB-exposed HaCaT keratinocytes**

<table>
<thead>
<tr>
<th>FA</th>
<th>THF/FCS</th>
<th>OA</th>
<th>e9,r11-CLA</th>
<th>t10,c12-CLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ml/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>45.2 ± 1.9</td>
<td>46.7 ± 3.4</td>
<td>45.7 ± 1.3</td>
<td>34.4 ± 2.4</td>
</tr>
<tr>
<td>C9t11</td>
<td>0</td>
<td>0</td>
<td>2.2 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>T10c12</td>
<td>0</td>
<td>0</td>
<td>0.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>100 ml/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>37.6 ± 1.6</td>
<td>40.1 ± 1.9</td>
<td>43.6 ± 3.3</td>
<td>34.0 ± 4.1</td>
</tr>
<tr>
<td>C9t11</td>
<td>0</td>
<td>0</td>
<td>1.3 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>T10c12</td>
<td>0</td>
<td>0</td>
<td>0.5 ± 0.5</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error of mean, *n = 4* (except for t10,c12-CLA supplements, where *n = 2*); *++P < 0.01* and *+++P < 0.001* comparing supplemented groups with THF/FCS vehicle control; *+P < 0.01* and *++P < 0.001* comparing UVB-irradiated with non-irradiated cells.

*%FA* is the % FA/total cellular FAs.
levels so effectively that the UVB-induced IL-8 level was no longer significantly different from the basal IL-8 levels.

**Effect of CLA isomers on TNF-α-induced IL-8 production by keratinocytes**

Figure 2 illustrates that 20 ng/ml TNF-α induced a significant increase in IL-8 production in the THF/FCS control cells. r10,c12-CLA and t-t-CLA supplements significantly reduced TNF-α-induced IL-8 compared with the THF/FCS vehicle control group. Levels decreased from 11 669.3 ± 1692.1 pg/ng protein in control cells to 5540.5 ± 191.2 pg/ng protein (P < 0.001) after t10,c12-CLA and to 8082.2 ± 1297.9 pg/ng protein (P < 0.01) after t-t-CLA. OA and c9,t11-CLA supplements did not reduce cytokine-stimulated IL-8 production and similar levels were seen as in vehicle control cells.

**Effect of CLA isomers on basal and UVB-induced PGE2 release by keratinocytes**

Figure 3 shows the effect of the FAs on PGE2 production by HaCaT cells in unexposed cells (open bars) and 48 h following 100 ml/cm² UVB (shaded bars), all n = 4. **P < 0.01 and ***P < 0.001 comparing irradiated with non-irradiated cells, ++P < 0.01 comparing the FA-supplemented groups with the THF/FCS vehicle control.

**Effect of CLA isomers on basal and UVB-induced PGE2 release by fibroblasts**

In CCD922SK cells, there was a significant increase in PGE2 synthesis after exposure to 100 ml/cm² UVB in the unsupplemented group. There was an increase in PGE2 following UVB in the THF/FCS-treated cells, significant at the P < 0.05 level by paired t-test, but significance was lost when subjected to more multiple comparison (analysis of variance) analysis (Figure 4). Levels secreted by THF/FCS-supplemented control cells were not significantly different from unsupplemented cells. c9,t11-CLA and t-t-CLA supplements decreased basal PGE2 synthesis so effectively that values were below the levels of detection. c9,t11-CLA also inhibited UVB-induced PGE2 synthesis from 97.5 ± 5.1 pg/mg protein to a value that was below the level of detection.

**Discussion**

This study makes the novel observation that CLA isomers modulate UVR-induced IL-8 and PGE2 in human skin cells. CLA modulate UVR-induced IL-8 and PGE2 in human skin cells.
the growth of a range of tumours, including malignant melanoma (25,26,34,35). Thus, inhibition of IL-8 is anticipated to convey significant protection against UVB-induced skin inflammation and the longer term complication of skin cancer. Keratinocyte exposure to the pro-inflammatory cytokine TNF-\( \alpha \) also augmented IL-8 secretion, although not to the degree seen following UVB. While the \( \alpha \),\( \delta \)-CLA isomer, and also the \( \tau \)-CLA isomers, significantly inhibited TNF-\( \alpha \)-induced IL-8 (\( P < 0.001 \) and \( P < 0.01 \), respectively), revealing a secondary route for photoprotection by CLA as well as potential protection of skin cells from other injurious stimuli, no effect was seen with the \( \epsilon \),\( \tau \)-CLA isomer. This highlights that individual CLA isomers may convey differential effects, and consequently the importance of examining the activities of the isomeric forms. In this study, however, the two common CLA isomers were seen to convey a comparable degree of protection against UVB-induced IL-8 secretion.

Examination of the influence of the CLA isomers on UVB-induced PGE\(_2\) secretion by keratinocytes did not show the consistent pattern observed with UVB-induced IL-8. While \( \epsilon \),\( \tau \)-CLA had no impact on PGE\(_2\) levels, the \( \alpha \),\( \delta \)-CLA significantly increased the UVB-induced level, and only the \( \tau \)-CLA reduced the UVB-induced PGE\(_2\). Additionally, both the \( \alpha \),\( \delta \)-CLA and the \( \tau \)-CLA elevated the basal (non-UVB exposed) PGE\(_2\) level. This effect of \( \alpha \),\( \delta \)-CLA is consistent with reports that this isomer may increase PGE\(_2\) secretion in other cell culture models (36). Interestingly, where detrimental effects of CLA are observed in animal studies, these have been reported to be associated with the \( \alpha \),\( \delta \)-CLA isomer, including pro-carcinogenic effects in some cancer models. Few previous studies have examined the molecular effects of \( \tau \)-CLA, with which to compare our experimental results. However, while they are generally less prevalent in foods, \( \tau \)-CLA can represent a substantial component of some food products, and our data indicate they should not be completely overlooked since they clearly can have significant effects on UVB-induced mediator production. In 12-\( \delta \)-tetradeconyphlorobol-13-acetate-stimulated keratinocytes of the cell line HEL-30, pre-treatment with CLA reduced the resultant PGE\(_2\) levels (37), and in an animal model of 12-\( \delta \)-tetradeconyphlorobol-13-acetate-induce skin tumour promotion, dietary CLA reduced PGE\(_2\) synthesis in the epidermis (38). In view of the disparate effects of CLA observed in keratinocytes, we further examined their effects on UVB-induced PGE\(_2\) in cultured skin fibroblasts. Here, in contrast, we found that both the \( \epsilon \),\( \tau \)-CLA and \( \alpha \),\( \delta \)-CLA markedly reduced the UVB-induced PGE\(_2\) levels in basal cells. Hence, the modulatory effects of the CLA appear specific to cell type as well as isomer. Since a range of other dermal and epidermal skin cells, both resident cells e.g. endothelial cells and melanocytes, and infiltrating leucocytes may secrete PGE\(_2\) in response to UVB, the overall impact of CLA supplementation on skin production of this mediator requires examination in vivo (39).

In our studies, we removed cells from serum-containing media prior to experimentation since serum is an endogenous source of CLA. In keeping with other reports of analysis of PGE\(_2\) in serum-free media (39,40), however, we found that the increases in this mediator induced by UVB were not of high magnitude, and this should be taken into consideration in the interpretation of these experiments. The mechanism of the effects of \( \epsilon \),\( \tau \)-CLA and \( \alpha \),\( \delta \)-CLA isomers in fibroblasts and all \( \tau \)-CLA in keratinocytes on PGE\(_2\) secretion has not been elucidated in the present study, but could be similar to those proposed for another family of dietary FAs, the omega-3 FAs, which reduce UVB-induced PGE\(_2\) levels in vitro and in vivo (41,42). Hence, they may be capable of competing with the omega-6 polyunsaturated FAs LA and arachidonic acid for incorporation into cell membranes, and/or release by phospholipases, and possibly for metabolism and subsequent eicosanoid synthesis (6,37,43). Potent omega-6 polyunsaturated FA metabolites might be replaced by less active CLA-derived products, although the ability of CLA to act in this manner has been questioned. Since cyclooxygenase requires a methylene group at carbon 13 in the hydrocarbon chain, it is thought to be unlikely to act on either of the 20-carbon products of CLA isomers (5). Moreover, as our experimental data indicate, the mechanisms of action of the CLA isomers and \( \tau \) forms cannot be assumed to be uniform, with both anti- and pro-inflammatory activities being seen with respect to PGE\(_2\) synthesis.

The concurrent protection conveyed by the CLA isomers against UVB-induced IL-8 production suggests that protection against the release of both IL-8 and PGE\(_2\) might occur upstream, such as at the level of transcription factor activation. Although PGE\(_2\) has been reported to release IL-8, this was not replicated in skin cells (23,24). UVR activates nuclear factor-kappa beta, and this may be mediated via UVR generation of reactive oxygen species or pro-inflammatory cytokines such as TNF-\( \alpha \). The up-regulation of a wide range of genes responsible for pro-inflammatory cytokines and enzymes such as cyclooxygenase results. CLA are capable of inhibiting nuclear factor-kappa beta activity (10), and this may occur through their antioxidant activity reported in some (32,44), although not all studies (45). Again, parallels exist with omega-3 FAs, which are similarly effective in reducing UVB-induced IL-8 secretion in vitro (46), and appear effective in reducing aspects of oxidative damage in human studies (47). Interestingly, CLA inhibition of the growth of human cancer cells can occur in a PGE\(_2\)-independent manner (48) and in association with a reduction in oxidative stress (1). There is also evidence that CLA may convey anti-carcinogenic properties through wide-ranging activities including modulation of the nuclear hormone receptor peroxisome proliferator-activated receptor gamma, inhibition of angiogenesis, inhibition of cell proliferation and induction of apoptosis (49–53).

In summary, both CLA isomers \( \epsilon \),\( \tau \)-CLA and \( \alpha \),\( \delta \)-CLA significantly protect against UVB-induced IL-8 secretion by human keratinocytes, suggesting their potential in nutritional photoprotection. Moreover, the distinct action of \( \alpha \),\( \delta \)-CLA in suppressing TNF-\( \alpha \)-induced IL-8 suggests its potential for protection against other forms of cellular stress. The effects of CLA on UVB-induced PGE\(_2\) secretion appear isomer and cell type specific; evidence of protection by the more prevalent \( \epsilon \),\( \tau \)-CLA and augmentation by \( \alpha \),\( \delta \)-CLA implies a protective effect in the proportions found in common foodstuffs, and is in keeping with the generally stronger evidence for the anti-carcinogenic properties of the \( \epsilon \),\( \tau \)-CLA isomer (4). Studies should be performed to examine the differential effects of these isomers in human skin in vivo, with a view to optimizing the composition of CLA supplements for use in human photoprotection trials.

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Conflict of Interest Statement: None declared.

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CLA modulate UVR-induced IL-8 and PGE2 in human skin cells

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