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Tomato paste rich in lycopene protects against cutaneous photodamage in humans *in vivo*: a randomized controlled trial

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Summary

Background Previous epidemiological, animal and human data report that lycopene has a protective effect against ultraviolet radiation (UVR)-induced erythema.

Objectives We examined whether tomato paste – rich in lycopene, a powerful antioxidant – can protect human skin against UVR-induced effects partially mediated by oxidative stress, i.e. erythema, matrix changes and mitochondrial DNA (mtDNA) damage.

Methods In a randomized controlled study, 20 healthy women (median age 33 years, range 21–47; phototype I/II) ingested 55 g tomato paste (16 mg lycopene) in olive oil, or olive oil alone, daily for 12 weeks. Pre- and postsupplementation, UVR erythemal sensitivity was assessed visually as the minimal erythema dose (MED) and quantified with a reflectance instrument. Biopsies were taken from unexposed and UVR-exposed (3 × MED 24 h earlier) buttock skin pre- and postsupplementation, and analysed immunohistochemically for procollagen (pC) I, fibrillin-1 and matrix metalloproteinase (MMP)-1, and by quantitative polymerase chain reaction for mtDNA 3895-bp deletion.

Results Mean ± SD erythemal D_{30} was significantly higher following tomato paste vs. control (baseline, 26·5 ± 7·5 mJ cm^{-2}; control, 23 ± 6·6 mJ cm^{-2}; tomato paste, 36·6 ± 14·7 mJ cm^{-2}; $P = 0·03$), while the MED was not significantly different between groups (baseline, 35·1 ± 9·9 mJ cm^{-2}; control, 32·6 ± 9·6 mJ cm^{-2}; tomato paste, 42·2 ± 11·3 mJ cm^{-2}). Presupplementation, UVR induced an increase in MMP-1 ($P = 0·01$) and a reduction in fibrillin-1 ($P = 0·03$). Postsupplementation, UVR-induced MMP-1 was reduced in the tomato paste vs. control group ($P = 0·04$), while the UVR-induced reduction in fibrillin-1 was similarly abrogated in both groups, and an increase in pCI deposition was seen following tomato paste ($P = 0·05$). mtDNA 3895-bp deletion following 3 × MED UVR was significantly reduced postsupplementation with tomato paste ($P = 0·01$).

Conclusions Tomato paste containing lycopene provides protection against acute and potentially longer-term aspects of photodamage.

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Conflicts of interest
None declared.

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Ultraviolet (UV) radiation (UVR) poses an increasing hazard to human health. Many of the adverse effects of UVR appear attributable, at least in part, to UVR-generated reactive oxygen species (ROS). These effects include the sunburn response (which can be reduced by high-dose combined antioxidants[1]), indirect DNA damage[2] and parameters of photodamage.[3–5] Lycopene is a lipophilic carotenoid antioxidant found in red fruits and vegetables and is a promising agent for oral photoprotection in humans.[6] Obtained particularly from tomatoes and tomato products, lycopene has been shown to be the most efficient singlet oxygen quencher of all the carotenoids.[7,8] The potential cancer-preventing properties of lycopene are under examination epidemiologically and in *in vitro* models, and it is reported that dietary lycopene intake corre-

lates with diminished prostate cancer risk.[9] It has been reported that following dietary supplementation, the concentration of lycopene is increased in human skin, where it provides protection from UVR-induced erythema;[10,11] its further potential in skin photoprotection remains unexplored. We have examined the ability of tomato paste, rich in lycopene, to convey protection against acute and longer-term indicators of photodamage.

Mitochondrial DNA (mtDNA) damage has been identified as a reliable marker of cumulative UVR exposure in human skin.[12–14] Unlike nuclear DNA, it lacks protective histones[15–17] resulting in a 10-fold higher mutation rate than nuclear DNA.[18] Additionally, a cell may contain several thousand copies of the mtDNA genome, so enabling it to tolerate very high levels of damaged mtDNA through complementation of the remaining wild-type, without compromise of cellular function.[19,20] Thus mtDNA damage has a greater propensity to accumulate than does nuclear DNA damage. There are a number of mtDNA deletions identified in UVR-exposed human skin,[21] the major deletions described being the 4977-bp 'common' deletion and the 3895-bp deletion.[12,22,23] These mtDNA deletions can also be induced in human skin by sublethal repetitive doses of UVR.[12] It has been proposed that generation of the mtDNA 'common' deletion involves an intragenomic recombination event facilitated by DNA bending in structurally labile 13-bp repeat DNA sequences, and a similar mechanism may underlie generation of the bp3895 deletion adjacent to 12-bp repeats.[24,25] As UVR-induced mtDNA damage can be caused by oxidative stress, we have used a documented quantitative polymerase chain reaction (PCR) assay to investigate whether dietary supplementation with tomato paste protects against its occurrence. The mtDNA 3895-bp deletion was selected for analysis as it is suggested that it is a highly sensitive mtDNA biomarker of UVR exposure when compared with other mtDNA biomarkers including the bp4977 'common' deletion.[22,26]

Chronic UVR exposure also leads to premature skin ageing (photodamage) characterized by loss of skin elasticity and the occurrence of coarse wrinkles and uneven pigmentation at sun-exposed sites. The mechanism of photodamage appears to involve changes to components of the dermal extracellular matrix (ECM), i.e. decreased synthesis of ECM proteins and increased ECM remodelling.[27] Biochemically, there is: (i) solar elastosis;[28] (ii) reduction in procollagen (pC) I and III;[29] (iii) reduction of fibrillin-rich microfibrils (oxytalan fibres) at the dermal–epidermal junction (DEJ)[30,31] and (iv) an upregulation of matrix metalloproteinases (MMPs).[32] Induction of MMP-1 by UVR-generated oxidative stress leads to degradation of dermal ECM proteins and has been shown to play a major role in the pathogenesis of photodamage.[12,33] Although damage to the ECM of skin is the hallmark of long-term exposure to UVR, it has been demonstrated that MMPs,[34] pCI[35] and fibrillin-1[36] may also act as early and sensitive markers of acute UVR-induced ECM changes.

The aim of the present study was to examine the potential for dietary photoprotection by a tomato product, rich in lycopene, against UVR-induced skin damage. In a randomized controlled trial we explored whether such an intervention produces measurable differences in UVR induction of skin erythema and in biochemical markers of mtDNA and ECM damage.

Materials and methods

Subjects and study design

The study design was single-blinded (i.e. the investigator assessing study outcomes was unaware of supplement allocation), randomized and controlled. The study was performed according to the Declaration of Helsinki. Ethical Approval was granted by the Salford & Trafford Local Research Ethics Committee and written informed consent was obtained. The subjects were 20 healthy white women, skin phototype I or II, median age 33 years (range 21–47) and nonsmokers. Exclusions were: photosensitivity; history of skin cancers; photosensitizing medication; and sunbed use or sunbathing in the previous 3 months. Subjects were randomly assigned to either tomato paste with olive oil (active) or olive oil alone (control) using a computer-generated randomization code (StatsDirect Ltd, Altrincham, U.K.) and these supplemental foods were distributed by a research nurse uninvolved in the study assessments. Subjects were asked to continue with their usual diets during the study. Compliance with supplement intake was assessed by monthly telephone calls. Subjects were assessed by the same physician (M.R.) at baseline (week 0) and end of the supplementation period (week 12) for erythema assessment and skin sampling.

Dietary supplements

Tomato paste, 55 g daily, providing approximately 16 mg daily of lycopene, was taken with olive oil 10 g daily on white bread in the active group, while olive oil 10 g daily alone on white bread was taken by the control group. Tomato paste contained 293 p.p.m. of lycopene, 13·97 p.p.m. β-carotene and 12·27 p.p.m. other carotenoids and was provided by Unilever Ltd (Colworth, U.K.).

Phototesting

The UVR source used was a Philips TL-12 fluorescent broadband UVR lamp (emission 270–400 nm, peak 311 nm). The irradiance at the skin surface was 30 mW cm^{-2} (IL 1400 Radiometer; International Light, Boston, MA, U.S.A.). Doses given were erythemally weighted UVR. The erythemal sensitivity of the subjects' skin was assessed at the beginning and end of supplementation by applying a geometric series of 10 UVR doses (1 cm diameter sites) to the skin of the upper buttock. At 24 h, sites were assessed visually to determine the minimal erythema dose (MED), i.e. the lowest dose of UVR that produced a perceptible erythema, and erythema measurements were taken as follows.

Ultraviolet radiation erythema dose response

Objective measurements of the intensity of erythema were made using a reflectance instrument (Erythema Meter; Diastron, Andover, U.K.) which gave an erythema index (EI) related to the blood content of the superficial dermis. Triplicate measurements were made at each irradiated site and the erythema due to the UVR exposure was expressed as the difference between the mean EI at each test site and the mean EI of adjacent unirradiated skin, i.e. the ΔE. UVR erythema dose–response modelling was performed using a dedicated data analysis package (Regional Medical Physics Department, Gateshead & Tyneside Health Authority, U.K.) to ascertain an individual's D_{30}, the UVR dose that would result in a ΔE of 30 arbitrary units. This objective threshold value approximates the individual's visually assessed MED.[37]

Skin sampling

Samples were taken from upper buttock skin under local anaesthesia (2% lignocaine without adrenaline) at week 0 and week 12 (four samples in total from each subject). These comprised 5-mm punch biopsies from both unexposed skin and from skin 24 h after receiving 3 × MED of UVR. MED at baseline was used for calculation of the UVR doses given pre- and postsupplementation. Samples were bisected and snap frozen at −70 °C. One half was assessed for mtDNA damage and the other was assessed immunohistochemically for expression of pCI, fibrillin-1 and MMP-1.

Immunohistochemical analysis

Immunohistochemistry was performed as previously described[31] to identify a panel of ECM molecules or remodelling enzymes in frozen sections. Primary antibodies were applied overnight at 4 °C. These were: rat antihuman pCI (clone M-58; Chemicon International, Inc., Temecula, CA, U.S.A.) diluted 1 : 1000; mouse antihuman fibrillin-1 (clone 11C1.3; Neomarkers, Union City, CA, U.S.A.) diluted 1 : 100 or mouse antihuman MMP-1 (Oncogene Research Products, Boston, MA, U.S.A.) diluted 1 : 100. Negative controls were by incubation of isotype sera at the appropriate concentration or omission of primary antibody. Sections were washed in Tris-buffered saline prior to incubation with the appropriate biotinylated secondary antibody for 30 min. Antibody staining was visualized using a well-characterized immunoperoxidase reaction (VectaStain® *Elite* ABC system; Vector Laboratories, Burlingame, CA, U.S.A.) utilizing Vector SG® as chromogen. Following light counterstaining with nuclear fast red (pCI and fibrillin-1 only), sections were serially dehydrated and permanently mounted.

Stained sections were randomized, blinded and examined on a Nikon OPTIPHOT microscope (Tokyo, Japan). The degree of immunostaining for pCI and fibrillin-1 was assessed as previously described.[31] In brief, a five-point semiquantitative scale was used where 0 = no staining and 4 = maximal staining within the experiment. The numbers of MMP-1-positive dermal cells were quantified per high-power field (×400). Four sections (including control) were examined per subject, per site, per treatment and the mean score calculated.

Mitochondrial DNA damage analysis

mtDNA damage was assessed by real-time TaqMan-PCR assay for quantification of the 3895-bp deletion using a previously described method.[22] In brief, DNA was extracted using a Qiagen DNeasy tissue extraction kit (Crawley, U.K.) and 200 ng of genomic DNA was amplified using Faststart universal mastermix (Roche, Burgess Hill, U.K.) in a 25-μL reaction using the primers and probes described in Table 1. The amount of mutation corresponds to the ratio of mtDNA with the 3895-bp deletion to wild-type mtDNA within each sample as previously described.[22]

Statistical analyses

Data were tested using either paired Student's *t*-test or repeated measures analysis of variance for multiple comparisons. Significance was taken at the 5% level. Analysis was performed using the SPSS package (SPSS Inc., Chicago, IL, U.S.A.). Data are shown as mean ± SD in the text unless otherwise specified, and presented graphically as mean ± SEM.

Results

Seventeen subjects completed the study; drop outs were for personal reasons and were not due to any adverse effects during the study. Of the 17 completions, nine individuals received the active treatment (tomato paste with olive oil) and eight individuals received the control (olive oil alone). Supple-

Table 1 Oligonucleotide primers used to detect the 3895-bp deletion in the real-time polymerase chain reaction assay

Name	Dye	Position	Sequence
ISF		16042–16066	5′-GAT TTG GGT ACC ACC CAA GTA TTG-3′
ISR		16125–16102	5′-AAT ATT CAT GGT GGC TGG CAG TA-3′
IS-probe	Fam	16069–16101	5′-CAC CCA TCA ACA ACC GCT ATG TAT TTC GTA CA-3′BHQ
3895F		491–508	5′-CAA CCC TCG CCC ATC CTA-3′
3895R		4516–4489	5′-CCT GCA AAG ATG GTA GAG TAG ATG AC-3′
3895-probe	Fam	527//4450	5′-TGC TAA CCC CAT ACC CCG AAA ATG TTG G-3′BHQ

ments were well tolerated by all subjects and there was no report of adverse events.

Erythema

Minimal erythema dose

The mean ± SD MED in the tomato paste group (n = 9) was 36·4 ± 11 mJ cm^{-2} at baseline and 42·2 ± 11·3 mJ cm^{-2} postsupplement, whereas the olive oil alone group (n = 8) showed a presupplement mean ± SD MED of 33·6 ± 8·8 mJ cm^{-2} and postsupplement value of 32·6 ± 9·6 mJ cm^{-2}. However, there was no statistically significant difference in this clinical endpoint between the groups postsupplementation (Fig. 1a).

Ultraviolet radiation erythema dose response

The D_{30} increased from a mean ± SD of 26·4 ± 8·1 mJ cm^{-2} at baseline to 36·6 ± 14·7 mJ cm^{-2} after 3 months of lycopene supplementation (n = 9) whereas there was no increase in response in the control group (presupplementation, mean ± SD 26·5 ± 7·3 mJ cm^{-2}; postsupplementation, 23 ± 6·6 mJ cm^{-2}; n = 8; Fig. 1b). While mean values at baseline were not significantly different for the active and control groups, postsupplementation there was a significant difference in D_{30} reading, identifying a significant effect of the supplement (P = 0·03).

The mean ± SD UVR erythema slope in both groups was 0·29 ± 0·05 at baseline. Postsupplement, mean ± SD slopes were 0·23 ± 0·06 for the active group and 0·21 ± 0·07 for the control group (P = 0·56). The postsupplement slope showed a significant shift to the right in the active group (P < 0·05) while there was a nonsignificant shift to the left in the control group, as compared with baseline (Fig. 1c).

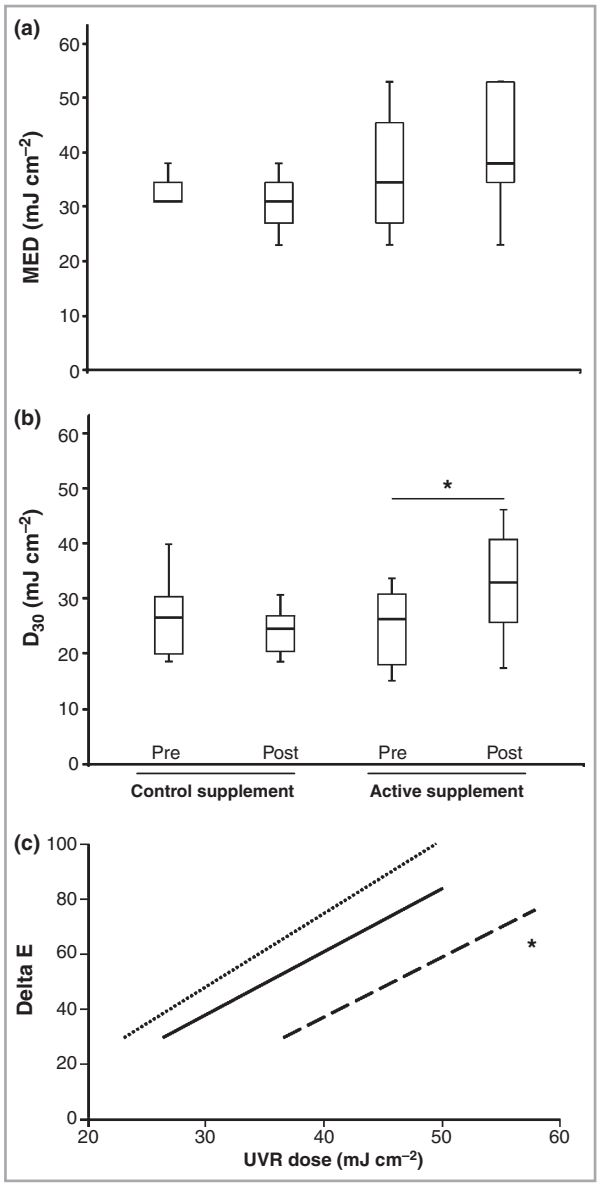

Fig 1. Ultraviolet radiation (UVR) erythema dose–response modelling reveals a protective effect of tomato paste supplementation. Visual assessment of the minimal erythema dose (MED) did not reveal a significant protective effect of oral supplementation (a), while objective erythemal measurement using an erythema meter (b) identified a significant protection against UVR following tomato paste supplementation, reflected in a significant shift to the right in the UVR erythema slope (c). Dotted line, control supplement (olive oil); dashed line, active supplement (tomato paste plus olive oil); solid line, presupplementation (both groups). The box and whisker plots show the median value (central line), interquartile range (box) and spread of the data (whiskers). *P < 0·05 compared with baseline.

Immunohistochemistry

Procollagen I

pCI staining was observed in the papillary dermis and did not significantly alter following UVR prior to supplementation (n = 17; mean ± SEM: baseline, 3·1 ± 0·11; UVR, 3·29 ± 0·15; Fig. 2a, b). Following 3 months of supplementation a small but significant increase in pCI was seen following UVR in the group receiving tomato paste as compared with the unirradiated baseline site (n = 9; mean ± SEM: baseline, 2·78 ± 0·18; UVR, 3·44 ± 0·13; P = 0·05; Fig. 2c, d) whereas this was unaltered in the control group (n = 8; mean ± SEM: baseline, 2·99 ± 0·23; UVR, 3·07 ± 0·29; Fig. 3a).

Fibrillin-1

UVR significantly reduced the occurrence of fibrillin-rich microfibrils as demonstrated by fibrillin-1 immunohistochemistry, compared with nonirradiated skin (n = 17; mean ± SEM: baseline, 3·42 ± 0·14; UVR, 3·02 ± 0·19; P = 0·03; Fig. 4a, b). This UVR-induced reduction in fibrillin was abolished postsupplementation in both groups (olive oil alone: baseline, 3·09 ± 0·23; UVR, 3·26 ± 0·23, P > 0·05; tomato paste plus olive oil: baseline, 2·81 ± 0·21; UVR, 2·77 ± 0·2, P > 0·05; Figs 3b and 4c–f).

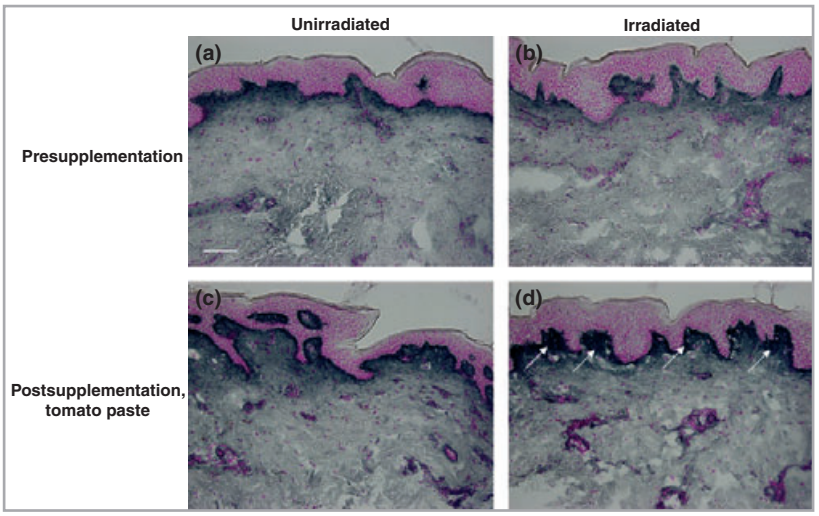

Fig 2. Tomato paste supplementation appears to enhance procollagen (pC) I deposition following acute ultraviolet radiation (UVR) exposure. Representative photomicrographs of pCI staining of presupplemented skin at baseline (unirradiated) (a) and 24 h post-UVR (b). While dietary supplementation with olive oil alone did not affect the deposition of pCI (data not shown), supplementation with tomato paste appeared to enhance deposition following the UVR insult (arrows): postsupplementation unirradiated (c); postsupplementation irradiated (d). Scale bar, 100 μm.

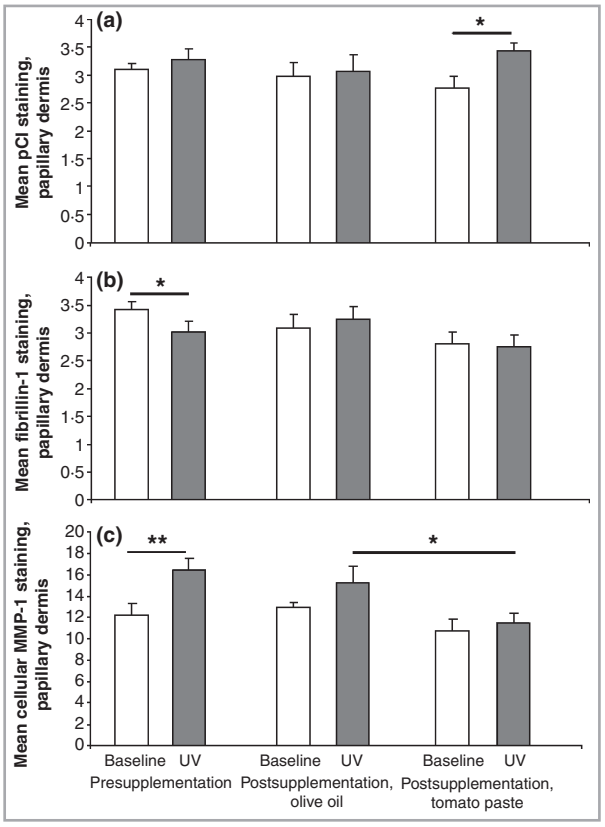

Fig 3. Quantification of immunohistochemical analyses of extracellular matrix molecules pre- and postultraviolet radiation (UVR) and dietary supplementation. (a) Procollagen (pC) I; (b) fibrillin-1 and (c) cellular matrix metalloproteinase (MMP)-1. Open bars represent UVR-unexposed values, closed bars represent values 24 h post-UVR. Data are shown as mean ± SEM. *$P < 0{\cdot}05$, **$P = 0{\cdot}01$.

Matrix metalloproteinase-1

Before supplementation, UVR induced a significant increase in dermal MMP-1 expression ($n = 17$; mean ± SEM: baseline, $12{\cdot}21 \pm 1{\cdot}06$; UVR, $16{\cdot}39 \pm 1{\cdot}12$; $P = 0{\cdot}01$; Fig. 5a, b). After 3 months supplementation, UVR-induced MMP-1 expression was reduced in the active group ($n = 9$; $11{\cdot}44 \pm 0{\cdot}91$; Figs 3c and 5c, d) compared with the control group ($n = 8$; $15{\cdot}28 \pm 1{\cdot}48$; $P = 0{\cdot}04$; Fig. 3c).

Mitochondrial DNA damage assay

Quantity of mtDNA damage in 3 × MED UVR-exposed skin varied presupplementation (Fig. 6). In those receiving active supplement, UVR-induced mtDNA damage reduced from a mean ± SD presupplement ratio of 3895-bp deletion: wild-type DNA of $0{\cdot}0291 \pm 0{\cdot}028$ to $0{\cdot}0019 \pm 0{\cdot}003$ postsupplement ($n = 9$; $P = 0{\cdot}01$), while in those receiving the control supplement the mean ± SD ratio changed from $0{\cdot}0459 \pm 0{\cdot}095$ to $0{\cdot}0058 \pm 0{\cdot}012$ (olive oil; $n = 8$; no statistically significant difference).

Discussion

This study indicates that tomato paste rich in lycopene conveys significant protective properties against the UVR-induced erythemal response and acute indicators of tissue photodamage in human skin. In the current study we used tomato paste mixed with olive oil as a carrier, as it has been shown that the bioavailability of this carotenoid is greater when derived from processed, rather than fresh, tomatoes[38] and has increased absorption in an oily medium.[39] We anticipate that a range of commonly consumed foods containing highly processed tomato could have similar effects if ingested in equivalent amounts, but this requires confirmation in further studies. Our data identify lycopene-rich tomato paste to have properties appropriate for its potential development in systemic photoprotection.[40]

The protective effect of lycopene against UVR-induced erythema is in agreement with previous studies.[10,11] We have shown that the D_{30} and erythema dose–response curve shift significantly following dietary supplementation with tomato paste. Our findings further indicate the greater sensitivity of

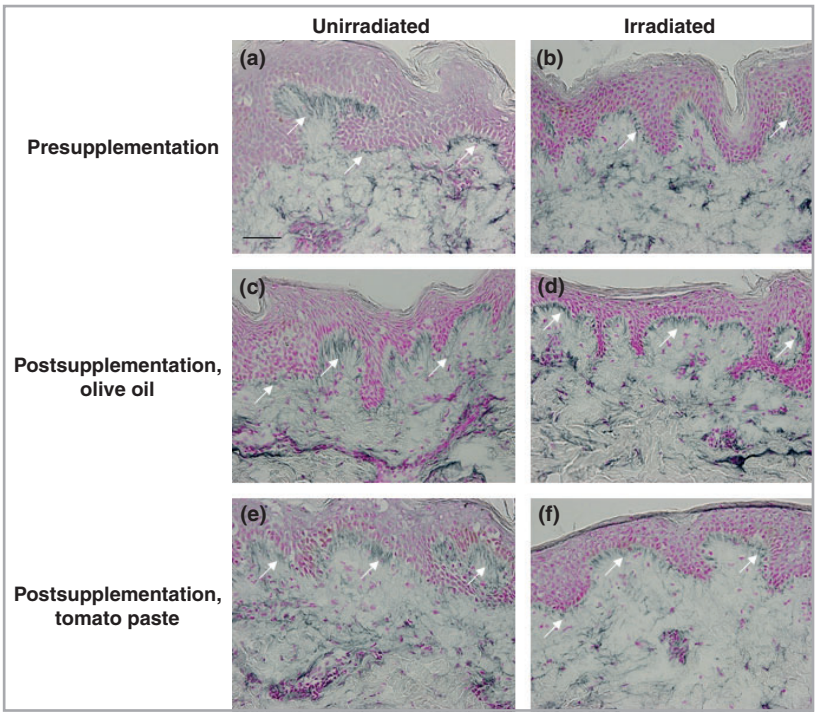

Fig 4. Acute ultraviolet radiation (UVR) causes disruption of the fibrillin-rich microfibrillar network and dietary supplementation gives partial protection. Representative photomicrographs of fibrillin-1 staining of presupplemented skin at baseline (unirradiated) (a) and 24 h post-UVR (b) showing a truncated fibrillin-rich microfibrillar network following UVR (arrows indicate the presence of microfibrils). This remodelling was offset by dietary supplementation with both olive oil [unirradiated (c), irradiated (d)] and tomato paste with olive oil [unirradiated (e), irradiated (f)]. Scale bar, 50 μm.

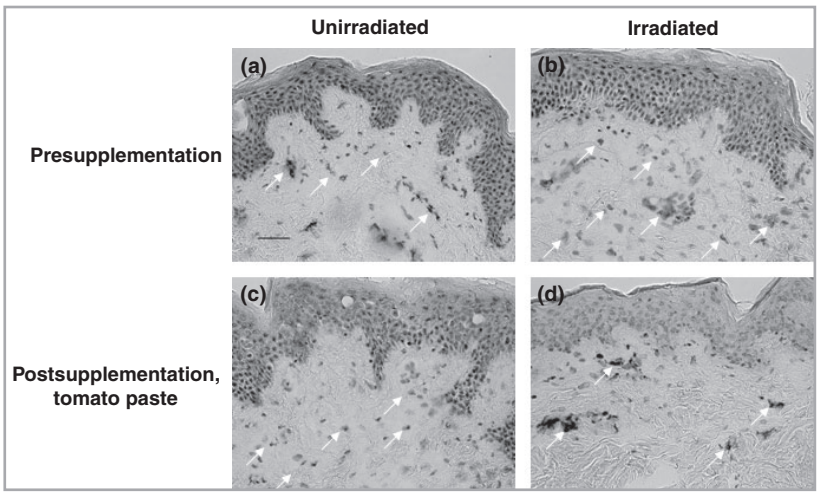

Fig 5. Acute ultraviolet radiation (UVR) induces matrix metalloproteinase (MMP)-1 expression and this is abrogated by dietary supplementation with tomato paste. Representative photomicrographs of MMP-1 staining of presupplemented skin at baseline (unirradiated) (a) and 24 h post-UVR (b) showing an induction of this enzyme. This induction was partially offset by dietary supplementation with tomato paste [unirradiated (c), irradiated (d)]. The arrows highlight positively stained cells. Scale bar, 50 μm.

objective erythemal measurements compared with the visual assessment of the MED. An MED is derived using an interval scale of UVR change, meaning that small alterations in erythemal sensitivity may go undetected, while erythema measurements provide a more sensitive tool in assessing the impact of potentially protective agents. The degree of protection observed would not provide clinically useful protection against sunburn erythema, but indicates some abrogation of UVR-induced effects on skin.

In an acute model of photoageing, we assessed the potential protective effects of tomato paste on a range of molecules implicated in mechanisms of photodamage. MMP-1, a major collagenolytic enzyme, is a key regulator in the photoageing process, mediated by modulation of collagen turnover and remodelling in the dermis. Induction of MMP-1 is mediated through transcription factor AP-1, which in turn is activated through UVR-induction of MAP kinase signalling pathways.[34] We have demonstrated that a single UVR dose increased MMP-1 expression in the dermis before supplementation, consistent with previous studies.[30] Following tomato paste supplementation there was inhibition of UVR-induced MMP-1 expression in the dermis, whereas the control (olive oil alone) did not effect change. This inhibitory effect of tomato paste on UVR induction of MMP-1 was accompanied by a small increase in the deposition of pCI in the papillary dermis. Hence, this infers a shift towards reduced collagenolytic activity and increased collagen synthesis. As well as increasing collagenolysis, UVR inhibits pCI synthesis and it has been reported that the photoprotective abilities of potential antiphotoageing substances might be tested by assessment of pCI synthesis.[41] In our study

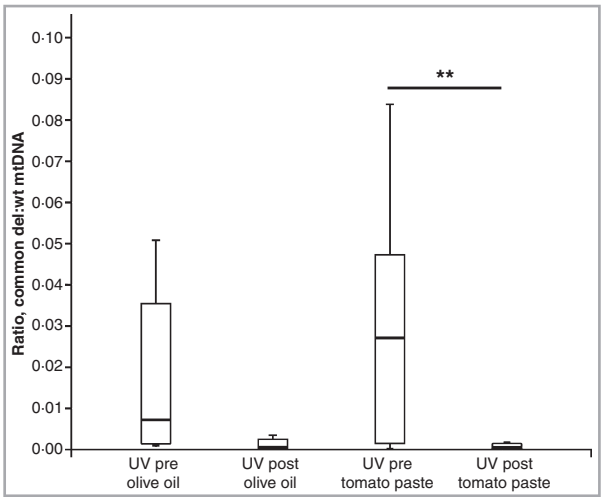

Fig 6. Tomato paste significantly reduces the ultraviolet (UV) radiation-induced mitochondrial DNA (mtDNA) 3895-bp deletion. Following supplementation with tomato paste, the ratio of mutated to wild-type mtDNA (common del:wt mtDNA) is significantly reduced compared with the presupplementation ratio. The box and whisker plots show the median value (central line), interquartile range (box) and spread of the data (whiskers). $^{**}P = 0{\cdot}01$.

the UVR dose applied appeared insufficient to alter pCI expression at baseline or in the olive oil group postsupplementation. However the post-UVR increase in pCI following lycopene intake potentially indicates a regenerative response to the UVR insult facilitated by this antioxidant.

Fibrillin-1 is the major glycoprotein component of fibrillin-rich microfibrils, or oxytalan fibres, situated in the papillary dermis proximal to the DEJ. Both chronic and acute photodamage are known to deplete these structures in human skin.[31,36] These structures were significantly reduced in UV-irradiated skin compared with nonirradiated samples at the beginning of the study. Following supplementation this UVR-induced reduction was abolished in both the active (tomato paste and olive oil) and control (olive oil) groups, indicating some degree of protection by both agents or perhaps occurring as a function of a lipid-rich carrier. Further studies are required to dissect out the characteristics of each agent in regard to their protective role.

A further aspect of our study was the examination of potential photoprotection against mtDNA damage by dietary agent. The relationship between mtDNA damage and nuclear DNA damage in such acute UVR insult models is currently unknown and requires further exploration. However, mtDNA damage may have a significant role in the mechanisms underlying photoageing, including generation of oxidative stress.[42] The sensitivity and reproducibility of mtDNA as a biomarker for cumulative UVR exposure is well established[22,43,44] and it is suggested that the bp3895 deletion is a more sensitive biomarker of UVR exposure than the 4977-bp 'common' deletion.[22,26] Previous data support bp3895 induction by UVR exposure in cultured skin cells *in vitro*,[26] while UVR-induced levels of bp4977 deletion were reduced *in vitro* following addition of the carotenoid β-carotene,[44] and a nonsignificant trend was found for photoprotection against bp4977 deletion in five volunteers administered extracts of the fern *Polypodium leucotomos*.[45] Our observed protective effect of tomato supplement on UVR-induced mtDNA deletion *in vivo* implicates the role of ROS in their formation. In addition, it indicates reduction of mtDNA damage, which may improve mitochondrial function and reduce oxidative stress. This also supports suggestions of a close association between the induction of MMP-1 and mtDNA damage, with increased oxidative stress following mtDNA damage potentially leading to increased MMP-1 induction.[42]

We propose the following sequence of events underlying the UVR-induced effects and dietary protection against induction of mtDNA deletion and MMP-1 observed in this study (Fig. 7). UVR-generated ROS trigger both the mtDNA deletion

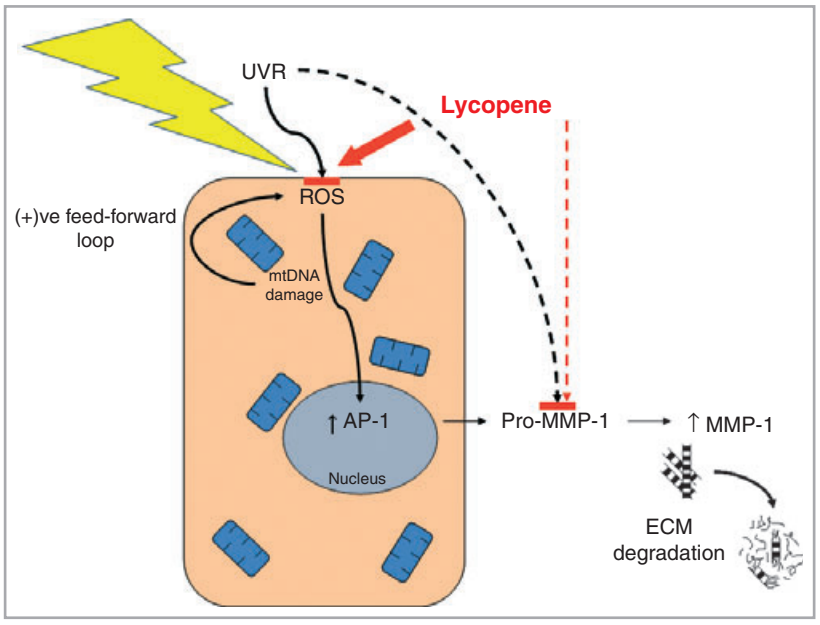

Fig 7. Schematic illustrating the proposed oxidative route (solid arrows) of ultraviolet radiation (UVR)-initiated photodamage and protection conveyed by lycopene. ROS, reactive oxygen species; mtDNA, mitochondrial DNA; MMP, matrix metalloproteinase; ECM, extracellular matrix.

and MMP-1 induction (the latter via AP-1 activation[34]), and this is exacerbated by a feed-forward loop involving the mitochondria. The damaged mtDNA is situated close to the 'power-house' of the cell, i.e. the mitochondrial respiratory chain, causing its dysfunction with the further release of ROS.[24,46] Lycopene, a powerful antioxidant and singlet oxygen-quenching agent, protects against the UVR-induction of mtDNA deletion and MMP-1 by combating the ROS and oxidative stress generated both initially by UVR and secondarily through the mitochondrial damage. Additionally, lycopene may convey protection through effects on cell signalling and the upregulation of antioxidant response element genes.[47] Other effects of UVR may also be operating, including via other cell signalling routes, direct as well as ROS-induced increase in frequency of mtDNA deletion,[24] and the release of active MMP-1 from its proenzyme, following which degradation of the ECM occurs, contributing to photodamage.

This study supports previous epidemiological, animal and human data reporting protective effects of lycopene and indicates that this agent also protects against UVR-induced tissue damage. Further, erythema dose–response modelling has been demonstrated to be a more sensitive instrument than the visual MED for assessing photoprotection. Moreover, mtDNA damage assessment is a novel tool awaiting further development for application in human photoprotection studies. Nutritional photoprotection with tomato products is a promising area for research, and further investigative and clinical studies are required to explore these novel findings.

What's already known about this topic?

- Lycopene is a powerful carotenoid antioxidant found in red fruits and vegetables.
- Lycopene reportedly protects against ultraviolet radiation (UVR)-induced erythema.
- Mitochondrial DNA (mtDNA) damage accumulates in skin following UVR exposure.

What does this study add?

- This study supports that tomato paste, rich in lycopene, protects skin against acute and potentially longer-term photodamage.
- mtDNA damage is a promising tool for development in the evaluation of dietary approaches to protection from UVR hazards.

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