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Biological effects of the olive tree and its derivatives on the skin

Lucía Melguizo-Rodríguez,†[a,b] Anabel González-Acedo,†[a] Rebeca Illescas-Montes,[a,b] Enrique García-Recio,[a,b] Javier Ramos-Torrecillas,[a,b] Victor J. Costela-Ruiz *[a,b] and Olga García-Martínez[a,b]

The olive tree and its derivatives are of great interest in the field of biomedicine due to their numerous health properties. The aim of the present study was to identify the effects of the use of olive products, extra virgin olive oil (EVOO) and products derived from its extraction, on the skin. Numerous studies have pointed out the protective effect of olive compounds on skin ageing, thanks to their role in the different mechanisms involved in the ageing process, such as reducing oxidative stress, increasing cell viability and decreasing histological alterations. With regard to their photoprotective effect, the olive tree and its fruit contain phenolic compounds which have a protective effect against radiation, such as low ultraviolet absorption and high antioxidant activity, acting as a protective factor against photocarcinogenesis. Similarly, the anti-tumour effects of olives have been studied at the level of the different compounds and extracts obtained from them, and their ability to selectively attack human melanoma cells has been observed. They have also shown antibacterial activity against microorganisms particularly implicated in skin infections, such as *Escherichia coli*, *Candida albicans*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus* spp. Likewise, on healthy tissue, they have shown the ability to stimulate growth, migration and the expression of genes involved in cell differentiation, which favours the regeneration of skin wounds. According to the results included in this review, the olive tree and its derivatives could be useful in the treatment of many skin conditions.

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Introduction

The olive tree (*Olea europaea*) and its derivatives are a fundamental element of the Mediterranean diet. Currently, the main producers of olives and extra virgin olive oil (EVOO) are Spain, Greece and Italy. The lipids present in the fruit and other components derived from olive by-products have been widely used for their numerous health-promoting properties, such as anti-inflammatory, antimicrobial and antioxidant activities.[1,2]

EVOO is the main derivative of olive oil. It consists mainly of triglyceride, monoglyceride and diglyceride fatty acids. The minor compounds of EVOO account for 2% of its total weight and include more than two hundred and thirty compounds, most notably hydrocarbons, sterols, aliphatic alcohols, tocopherols, pigments, volatile compounds and phenolic compounds, mainly flavonoids, lignans, phenolic acids, phenolic alcohols and secoiridoids.[3,4] Much of the health benefits of EVOO are related to the significant antioxidant potential of phenolic compounds. They act as chain breakers by donating hydrogen radicals to alkylperoxyl radicals, produced by lipid oxidation and the synthesis of stable derivatives during the reaction.[5,6] These properties have made them the focus of attention as nutraceutical targets for the food and pharmaceutical industries, as they represent potential preventive agents for chronic and degenerative diseases, and pathologies related to oxidative stress processes.[7–11]

The olive leaf is a by-product that represents up to 10% of the weight of the tree and is an excellent source of bioactive compounds, such as oleuropein (OLE), verbascoside (VerB), rutin (RU), tyrosol (Tyr) and hydroxytyrosol (Htyr), to which various biological properties have been attributed such as immunomodulatory, anti-inflammatory, antioxidant and other activities.[12–17]

The oil extraction process generates two types of products, olive pomace (OP) and olive mill wastewater (OMW). OP is a biomass by-product of EVOO production with a high content of pulp, skin, pits and water.[18] It is a rich source of phenolic compounds, sterols, pentacyclic triterpenes, carotenoids and mono- and polyunsaturated fatty acids[19] that confer it anti-

[a]*Biomedical Group (BIO277), Department of Nursing, Faculty of Health Sciences, University of Granada, Avda. Ilustración 60, 18016 Granada, Spain. E-mail: vircoss@ugr.es; Tel: +34647125104*
[b]*Institute of Biosanitary Research, ibs.Granada, Avda. de Madrid, 15 Pabellón de Consultas Externas, 2ª Planta 18012 Granada, Spain*
† These authors contributed equally to this work.

inflammatory, antioxidant, hepatoprotective, gastroprotective, anti-diabetic and lipid-lowering properties.[20–23] OMW is a liquid waste fraction with a high polluting power. Its components include heavy metals and a high content of phenolic compounds.[24]

Approximately 98% of the phenolic compounds in the olive remain in the OMW, with only 2% remaining in the oil itself.[25–27] Recent research has highlighted the potential therapeutic usefulness of OMW compounds, based on their biological properties, including dermatological applications.[28–33]

The skin is an organ of the integumentary system that acts as the first protective barrier against external agents and contributes to the maintenance of homeostasis. There are 3 different layers: epidermis, dermis and hypodermis and depending on functional needs, as an adaptation mechanism, this organ can alter some of its characteristics such as thickness, colour or texture.[34,35] This natural barrier can be altered by the influence of biological factors, such as age or immune status, or external agents such as chemical or physical elements or various traumas.[36] In this sense, olive and its derivatives have traditionally been used to treat dermatological disorders such as acne, psoriasis, rosacea and eczema.[37] Due to its skin moisturising power and the antioxidant capacity of the phenolic compounds it contains, it is of interest as an additive for topical hygiene and cosmetic products.[38]

Based on the biological properties mentioned above, the aim of this study was to identify the effects of the use of olive products, EVOO and products derived from its extraction, on the skin (Table 1).

Methods

A review of the literature was conducted using 4 biomedical databases: PubMed, Medline, Scopus and Cochrane. The search was updated in July 2022, including all possible terms for extra virgin olive oil, *Olea europaea*, olive tree, phenolic compounds, antimicrobial or antibacterial, skin cancer, skin ageing, wound healing or regeneration, using algorithms and search strategies that can be reproduced by any researcher. Search results were cross-checked to remove duplications, yielding a total of 73 articles. Two authors then reviewed the titles and abstracts of all reports yielded by the searches, selecting only articles in English that offer the highest level of scientific evidence for olive products, EVOO and products derived from its extraction, on the skin, not only in clinical research but also in "*in vitro*" studies. Articles were not restricted as a function of the method used. Articles were excluded if they contributed inadequate data on the patient selection, methodology or outcomes. Articles that did not address the issues of interest for our review were excluded. The review finally included 72 studies, which were classified according to the following content: effects on skin ageing, anti-inflammatory, antioxidant, antimicrobial and photoprotective effects, anticarcinogenic properties or biostimulant and regenerative effects.

Results

Effects on skin ageing

Skin ageing can be mediated by intrinsic or extrinsic factors and can be classified into chronological and premature ageing.[39] Chronological or intrinsic ageing is associated with a decrease in cell division in the different layers of the skin and an age-related deterioration in the collagen and elastin fibres that make up the extracellular matrix (ECM),[40] while premature or extrinsic ageing is caused by environmental factors such as solar radiation, air pollution, consumption of toxic substances such as alcohol or tobacco, and chronic psychological stress, among others.[41,42] At the histological level, both types of ageing are characterised by thinning and loss of elasticity resulting in the deterioration of the skin barrier.[43] These visible changes are related to an excessive presence of reactive oxygen species (ROS) that activate transcription factors such as AP-1 or ECM metalloproteases (MMP) which can lead to a degradation of the skin's collagen and excessive deterioration of the matrix.[43] In addition, following peroxidation of polyunsaturated lipids from the tissues, the skin synthesises lipofuscin, which results in an alteration of the pigmentation characteristic of skin ageing.[44]

Numerous studies have pointed out the protective effect of olive tree compounds on skin ageing, thanks to their role in the various mechanisms involved in the ageing process.[45–47] These compounds include squalene (Sq) from olives or their derivatives. In an *in vitro* test with HaCat keratinocytes, Kato *et al.*[45] observed a significant reduction in oxidative stress, an increase in cell viability, and a reduction in histological alterations in a 3D human skin model, which could translate into a protective effect against the appearance of signs of ageing. The same authors studied the antioxidant effect of Sq compared to a solution of Sq and C-60 fullerene in a clinical trial, analysing wrinkle formation and skin hydration. Both treatments reduced the area and depth of wrinkles, although not significantly, and increased skin hydration.[47] In terms of adverse effects, no cases of toxicity were reported, probably due to the fact that these products are not able to reach the dermal venous circulation.[48] In the same vein, Wanitphakdeedecha *et al.*[49] described that the use of a facial cream enriched with olive leaf extract promotes facial rejuvenation by decreasing transepidermal water loss and wrinkles and improving hydration.

Romana-Souza *et al.*[46] studied the protective effect of EVOO against epinephrine-induced stress in a model of human skin obtained from otoplasties, observing that EVOO attenuated the decrease in the thickness of the epidermis and dermis, decreasing the levels of ROS and malondialdehyde. Other authors have also described a decrease in MMP-9 expression and secretion in THP-1 cells treated with oleuropein aglycone. This could be due to impaired nuclear factor-kappaB signaling and could reflect in the decreased degradation of extracellular matrix components.[50]

However, the anti-ageing effect derived from the compounds present in the olive tree is not limited to its topical

Table 1 Different properties of the olive tree and its derivatives on the skin

Biological effect	Olive derivative	Main findings
Skin ageing properties	Sq	*In vitro* (human keratinocytes and human skin model): increased keratinocyte cell viability and suppression of wrinkle formation in a 3D artificial skin model after treatment with Sq.[45]
	Sq	*In vivo* (women from 38 to 40 years old): topically applied Sq cream improved skin moisture and prevented wrinkle formation. Significant improvement of the roughness–area ratio.[47]
	Sq	*In vitro* (fibroblast cells and human skin biopsy): Sq can penetrate the epidermis through the cornea but cannot penetrate the basement membrane, thus cannot reach the dermis. Non-toxicity of Sq is suggested.[48]
	Olive leaf extract-containing cream	*In vivo*: prospective pilot study with humans (women and men): after two months of applying the cream twice daily, transepidermal water loss was reduced, skin hydration was increased, wrinkles and skin texture improved.[49]
	Epinephrine and olive oil	*In vitro* (explants of human skin): olive oil treatment on *ex vivo* skin reverses epinephrine-induced reduction in epidermal and dermal thickness and reduction in collagen fibres. Moreover, reactive oxygen species production and malondialdehyde levels were attenuated.[46]
	OLE	*In vitro* (THP-1 cells): a decrease in MMP-9 expression and secretion in THP-1 cells treated with oleuropein aglycone.[50]
	Cross-sectional study on the consumption of monounsaturated fatty acids	*In vivo* cross sectional study (women and men): lower risk of photoageing in both sexes associated with the consumption of monounsaturated fatty acids from olive oil.[53]
	Olive oil	*In vivo* (male Wistar rats): decrease in DNA double chain breaks in the group that consumed extra virgin olive oil.[54]
Photoprotective properties	Phenols recovered from olive oil wastewater	*In vitro*: in the UVB and UVA regions, the absorption of synthetic UV filters increased as a function of olive phenol concentration. The relationship between the increase in the sun protection factor (SPF) and olive phenol concentration was linear. Improvement of water resistance in preparations with olive oil phenols.[66]
	Biophenols from olive leaves	*In vitro*: high absorption in the UV region of these compounds, showing high absorbance levels at different wavelengths.[68]
	UF-OMW	*In vitro* (human epidermal keratinocytes adult): all UF-OMW fractions administered together with UV radiation exerted significant *in vitro* antioxidant activity in keratinocyte cultures.[69]
	Oleo europaea leaf extract standardized to 20% OLE	*In vitro*: photoprotective, antimutagenic and antioxidant effects. In addition, a synergistic effect in association with UV filters, with an improvement of SPF values *in vitro* which reinforces the effect of oleuropein in sun protection formulations.[63]
	Tyr	*In vitro* (HaCaT cells): capacity of the polyphenol Tyr for *in vitro* reduction of apoptotic markers and protection of keratinocyte cell line HaCaT cells from UVB damage.[64]
	Phenolic compounds (melatonin, Cr monohydrate, Htyr, Tyr, hydroxytyrosyl laurate and hydroxytyrosyl myristate)	*In vitro* (HaCaT cells): following UV irradiation of keratinocytes, there was an evident decrease in ultrastructural apoptotic patterns and antioxidant activity after administration of the different phenolic compounds.[72]
	Olive leaf extract and its component OLE	*In vivo* (C57BL/6J mice): oral treatment with both components in C57BL/6J mice inhibited the increase in skin thickness produced by UVB radiation. In addition, they inhibited the increase in the number of Ki-67 and 8-hydroxy-2′-deoxyguanosine-positive cells, the area of melanin granules and the expression of matrix metalloproteinase-13 (MMP-13).[74]
	Htyr and OLE from OMW	*In vitro* (human corneal and conjunctival epithelial cells): in human corneal epithelial cells, the secretion of most of the proinflammatory interleukins measured was inhibited, showing anti-inflammatory effects. In human conjunctival epithelial cells, only the secretion of the biomolecule IP-10 was decreased. In both cell lines, Htyr and OLE showed strong dose-dependent antioxidant activity.[76]

Table 1 *(Contd.)*

Biological effect	Olive derivative	Main findings
	Olive oil	*In vivo* (male rats): reduction in the number of parotid acinar cells in groups of mice irradiated and treated with olive oil.[78]
	Olive oil	*In vivo* (human subjects with nasopharyngeal carcinoma): patients treated with olive oil applied topically during chemoradiotherapy sessions experienced significantly less severe radiodermatitis compared to patients in the control group.[79]
	Olive oil and calcium hydroxide emulsion	*In vivo* (women with post-mastectomy radiotherapy): less dermatitis in patients treated with olive oil and calcium hydroxide emulsion during post-mastectomy radiotherapy sessions.[80]
	Olive oil	*In vivo* (human volunteers): no significant increases or decreases in phototoxic dose values were shown for psoralen plus UVA after topical administration of olive oil.[81]
Anti-inflammatory and antioxidant effects	Htyr and OLE	*In vitro* (pre-senescence human lung and neonatal human dermal fibroblasts): both phenols reduced several senescence/inflammatory markers in pre-senescence human lung cells and neonatal human dermal fibroblasts.[57]
	HtyOle from olive oil, pomace and OMW	*In vitro* (human keratinocytes): antioxidant capacity of HtyOle in human keratinocytes.[59]
	Olive oil	*In vivo* (male Swiss mice): inhibition of inflammatory procedures and reduction of oxidation markers. *In vivo* (male Swiss mice) promotion of wound closure.[61]
Anticarcinogenic properties	OA, homovanillic alcohol and Htyr	*In vitro* (A375 melanoma cells and MNT1 melanoma cells): Htyr treatment significantly reduced the viability of A375 melanoma cells, but had no effect on the viability of MNT1 melanoma cells. OA and homovanillic alcohol altered the glycolytic rate of MNT1 by inhibiting extracellular signal-regulated kinase (ERK).[87]
	Htyr	*In vitro* (human melanoma cell line M14): protective effect of Htyr in preventing the increase of typical oxidative stress markers in human M14 melanoma cells. On the other hand, it prevents the increase of altered L-isoAsp residues induced by UVA radiation in M14 cells.[88]
	Htyr	*In vitro* (human keratinocytes): moderate radioprotective effects of Htyr at low doses in human keratinocytes. Positive up-regulation of certain antioxidant proteins and enzymes present in keratinocytes after Htyr treatment.[89]
	OC	*In vitro* (human malignant melanoma cells): OC had significant and selective activity in human melanoma cells *versus* human dermal fibroblast cells. Furthermore, significant inhibition of ERK1/2 and AKT phosphorylation and down-regulation of Bcl-2 expression were shown.[90]
	CA	*In vivo* (solar UV-induced skin carcinogenesis mouse model): significant inhibition of human skin cancer cell colony formation and neoplastic cell transformation upon treatment with CA. In addition, CA applied topically to the skin of mice significantly suppressed solar UV-induced skin tumour incidence and volume. The compound also acted directly on ERK1/2, inhibiting it *in vitro*.[91]
	OleaC	*In vitro* (human melanoma cells): cell growth induction in 501Mel melanoma cells after treatment with OleaC. This polyphenol induced G1/S phase arrest, DNA fragmentation and down-regulation of genes encoding anti-apoptotic and proliferative proteins in these cells. On the other hand, it increased the transcription levels of the proapoptotic protein BAX.[92]
	OC	*In vitro* (human melanoma cells): suppressed melanoma cell proliferation, migration and invasion, and induced melanoma cell apoptosis. *In vivo* produced potent tumour growth suppressor activity in a subcutaneous xenograft model.[93]
	OLE from olive leaves, olive stems and olive flowers	*In vitro*: antioxidant and antimelanogenic activities.[94]

Table 1 *(Contd.)*

Biological effect	Olive derivative	Main findings
	EA	*In vitro* (B16 melanoma cells): EA reacts specifically *in vitro* with copper located in the active centre of the tyrosinase molecule in B16 melanoma cells. *In vivo*, EA suppressed skin pigmentation in guinea pigs subjected to UV light.[95]
	Maslinic acid	*In vitro* (B16F10 melanoma cells): antiproliferative effects of maslinic acid on B16F10 murine melanoma cells, and its antioxidant effect.[96]
	Maslinic acid and oleanolic acid	*In vitro* (B16F10 melanoma cells): cytotoxic and antiproliferative effects of maslinic and oleanolic acids on B16F10 murine melanoma cells. Apoptosis levels of up to 90% were achieved in these cells.[97]
	Dry olive leaf extract	*In vitro* (B16F10 melanoma cells)/*in vivo* (mice): dry olive leaf extract significantly inhibited the proliferation of the B16 mouse melanoma line. It also restricted the clonogenicity of this cell line. In *in vivo* tests, it significantly reduced the tumour volume in mice.[98]
	Olive leaf extract enriched with OLE	*In vitro* (human melanoma cells): olive leaf extract enriched with OLE decreased the proliferation and motility of human melanoma cells. It was also able to reduce the rate of glycolysis in these cells without affecting oxidative phosphorylation.[99]
	Phenol enriched OMW	*In vitro* (HaCaT cell line): treatment with this compound inhibited A375 melanoma nodules in a melanoma skin model.[100]
	EVOO phytoextracts	*In vitro* (squamous cell carcinoma cells and human keratinocytes): OC and OleaC reduced cell viability and migration in epidermoid carcinoma skin cancer models. In addition, they prevented colony and spheroid formation.[101]
	Glycosylated and non-glycosylated plant polyphenols (verbascoside, resveratrol, polydatin, rutin, and quercetin)	*In vitro* (human epidermal keratinocytes): verbascoside interferes with multiple UV-sensitive cellular signals in human epidermal keratinocytes subjected to UVA and UVB; with a probable chemoprotective effect on skin cancer.[102]
	OLE	*In vivo* (male C57BL/6N mice): OLE inhibits melanoma progression induced by a high-fat diet in C57BL/6N mice, suppressing tumour progression and reducing the tumour cell expression of angiogenesis and lymphangiogenesis markers, among others.[103]
	EVOO	*In vivo* (mice): EVOO applied topically to mice delays the onset of EV-induced skin cancer. In addition, the compound reduces tumour-related skin damage once the tumour has appeared.[105]
Antimicrobial properties	Ethanolic extracts of olive leaves	*In vitro*: the extracts controlled the growth of the studied bacteria (*E. coli, P. aeruginosa, Salmonella sp, S. aureus, L. innocua*).[112]
	Different extracts from *Olea europaea* L.	*In vitro*: water MAE extract shows the strongest antimicrobial activity against *S. aureus, S. typhimurium, E. coli, L. monocytogenes* and *Y. enterocolitica.* The MIC range was between 2.5 and 60 mg mL^{-1}.[113]
	Olive leaf extract or OLE	*In vitro* (bacteria): OLE almost completely inhibited the growth of *L. monocytogenes, E. coli* and *S. enteritidis* at a concentration of 62.5 mg mL^{-1}. In addition, it decreased the cell motility of *L. monocytogenes* and prevented the biofilm formation in *L. monocytogenes* and *S. enteritidis.*[114]
	Olive leaf extract of Tanta	*In vitro* (bacteria)/*in vivo* (diabetic experimental rat models): this extract was the most active agent against methicillin-resistant *S. aureus* (MRSA) with a MIC value of 15.6 μg ml^{-1}.[115]
	OP extracts	*In vitro* (bacteria): these products with a higher Htyr content (220 mg/100 g) showed the best MIC against *S. aureus* and *E. coli*. No effects against *C. albicans* were observed.[116]
	OMW	*In vitro* (bacteria): OMW with high concentrations of Htyr, Tyr, FA and CA showed an antimicrobial affect against *S. aureus* and *P. aeruginosa* (MIC values of 0.13 and 0.25 mg mL^{-1}, respectively).[117]
	LU, API, FA, *p*-CA, and CA	*In vitro* (CCD-1064Sk fibroblast line) study using LU, API, *p*-CA and CA showed inhibition of halos against *S. aureus, S. epidermidis, E. coli, Proteus* spp. and *C. albicans* at the dose of 10^{-6}M.[119]

Table 1 *(Contd.)*

Biological effect	Olive derivative	Main findings
Biostimulant and regenerative properties	LU, API, FA, *p*-CA, and CA	*In vitro* (CCD-1064Sk fibroblast line): all compounds except for FA significantly stimulated the proliferative capacity of fibroblasts, increasing their migration, gene expression and differentiation.[119]
	3-Hydroxytyrosol	*In vitro* (epidermal keratinocyte cells): 3-hydroxytyrosol could induce cell proliferation in keratinocytes increasing the expression of CDK2 and CDK6. Moreover, it could improve the cell migration through the activation of some tissue remodeling factors.[121]
	Uvaol (natural pentacyclic triterpene found in olives and virgin olive oil)	*In vitro* (fibroblast and endothelial cells)/*in vivo* (mice): uvaol treatment increased fibroblast and endothelial cell migration through an increased synthesis of fibronectin and laminin proteins and increased tube formation, respectively. *In vivo* (mice): acceleration of skin wound closure in mice.[122]
	Sq	*In vitro* (M1 proinflammatory macrophages and TPH1 cell experimental model): Sq increased the synthesis of anti-inflammatory cytokines, such as IL-10, IL-13 and IL-4 in macrophages TPH1. Moreover, SQ decreased proinflammatory signals including TNF-α and NF-κB.[123]
	Olive oil rich in omega-3, omega-6 and omega-9 fatty acids	*In vivo* (rats): this product accelerated wound healing significantly, moderately improving the microvasculature and inducing the expression of growth factors.[124]
	OLE	*In vivo* (male Balb/c mice): 50 mg kg^{-1} of OLE accelerated skin wound healing in aged male Balb/c mice through increased collagen fiber deposition and higher VEGF expression, and decreased cellular infiltration.[125]
	Olea europaea leaf extracts (OLE)	*In vitro* (human dermal fibroblasts and keratinocytes): decreased H_2O_2-induced oxidative stress and increased viability in fibroblasts and keratinocytes. *In vivo*: protection against oxidative stress and improvement of the healing process in diabetic mice.[126]
	Olive leaf extracts (OLE) with microparticles of hyaluronic acid (MPHA-OLE) or chitosan (MPCs-OLE)	*In vitro* (human fibroblasts): both treatments significantly increased the percentage of wound closure on the scratch assay using fibroblasts; however, the free form extracts were less effective.[127]
	Olea europaea leaf extract hydrogel (EHO-85)	*In vivo* (human subjects/both sexes): this clinical trial observed that EHO-85 accelerated wound healing regardless of ulcer etiology by modulating reactive oxygen species and pH.[128]
	Aloe vera-olive oil combination cream	*In vivo* (human participants from both sexes): this clinical trial in patients with chronic wounds evidenced significant improvements in the wound size, depth, and edges. In addition, this treatment helped to reduce the pain associated with these lesions.[129]
	Olive oil and butter (BOB)	*In vivo* (rats): BOB treatment increased TGF-β1 and VEGF-α expressions in rats and improved the fibroblast activity and keratinization.[130]

Abbreviations: squalene (Sq); ultraviolet (UV); ultra-filtered olive mill wastewater (UF-OMW); oleuropein (OLE); sun protection factor (SPF); tyrosol (Tyr); hydroxytyrosol (Htyr); HtyOle (hydroxytyrosyl oleate); olive mill wastewater (OMW); oleic Acid (OA); oleocanthal (OC); caffeic acid (CA); oleacein (OleaC); ellagic acid (EA); luteolin (LU); apigenin (API); ferulic acid (FA); *p*-coumaric acid (*p*-CA); caffeic acid (CA); vascular endothelial growth factor (VEGF); transforming growth beta 1 (TGF-β1).

application, but benefits from the consumption of EVOO have also been reported.[51] The main reason why this element has been studied is its fat composition. The fat present in the diet can alter mitochondrial functions by modifying the biochemical parameters of its membranes and therefore the electron transport systems. Thus, a dietary pattern rich in monounsaturated fatty acids, such as those present in EVOO, could reduce oxidative stress, delaying ageing.[52] In this regard, Latreille *et al.*[53] showed that a higher intake of monounsaturated fatty acids from EVOO was associated with a lower risk of severe photoageing, a relationship that was not observed when the fatty acids were of animal origin. Finally, it is worth mentioning the protective role of EVOO against damage to the genetic material. Thus, Quiles *et al.*[54] have observed how EVOO consumption decreases DNA double-strand breaks associated with aging in Wistar rats compared to those consuming sunflower oil. This is of added value because DNA is particularly sensitive to oxidative damage and EVOO could prevent the amplification of this damage at the skin level.

Anti-inflammatory and antioxidant effects

Another effect attributed to the phenolic compounds in EVOO is their anti-inflammatory activity, due to their antioxidant activity or the regulation of signaling molecules involved in

inflammation, cell adhesion, cell growth, apoptosis and ageing.[55]

In this sense, the effect of different varieties of EVOO on the antioxidant action in the NIH-3T3 cell line has been demonstrated, showing that the increase in phenolic compounds depending on the variety of EVOO produces an increase in antioxidant action, due to the reduction of reactive oxygen species (ROS).[56]

Likewise, Menicacci *et al.*[57] evaluated the effect of Htyr and OLE on pre-senescent lung fibroblasts (MRC5 cell line) and neonatal human dermal fibroblasts (NHDF cell line) observing that they reduced senescence/inflammation markers such as β-galactosidase and p16 protein, and IL-6, metalloproteases, cyclooxygenase type 2 (COX-2) and α-actin. Furthermore, they reduced the level of the nuclear factor kappa-enhancer of activated B cell light chain kappa (NF-κB) protein, nuclear localization and COX-2 expression in NHDF cells, demonstrating that they are able to modulate the inflammatory process associated with senescence and could be used to prevent age-related diseases.

Robles-Almazán *et al.*[58] analyzed the participation of Htyr in different pathologies, identifying its antioxidant capacity by acting as a scavenger of ROS and as a prooxidant by inhibiting cyclin-dependent kinases (CDKs) and messengers involved in cell proliferation.

Benincasa *et al.*[59] found that hydroxytyrosyl esters such as hydroxytyrosyl oleate had high antioxidant activity on the human keratinocyte cell line HaCat: it decreased ROS and malondialdehyde (MDA) formation and glutathione-*S*-transferase (GST) and superoxide dismutase (SOD) activity; it also increased miRs involved in the redox state balance and skin regeneration potential (hsa-miR-21 and hsa-miR-29), observing that this compound controls the cellular redox state and the expression of microRNAs linked to skin. Similarly, OC has also shown anti-inflammatory and antioxidant actions, inhibiting the effect of COX-1 and COX-2, and thus the synthesis of prostaglandins, and the activity of human recombinant 5-lipoxygenase (5-LOX) and thus the synthesis of pro-inflammatory leukotrienes, while showing an inhibition of the action of nicotinamide adenine dinucleotide phosphate oxidase (NOX).[60]

In vivo studies have assessed the effect of EVOO on the healing of pressure ulcers in male Swiss mice, comparing treatment with soybean oil, EVOO or combinations of both, showing in the group treated with EVOO a reduction in the expression of neutrophils and COX-2 and an increased expression of nitric oxide synthase-2, protein and lipid oxidation, erythroid factor 2-related factor 2 protein expression and COL-I precursor protein, suggesting that a diet based on EVOO promotes pressure wound healing in mice by decreasing inflammation and promoting the redox balance.[61]

Photoprotective effects

Sunlight is the total spectrum of electromagnetic radiation coming from the Sun. It is composed of ultraviolet (UV) radiation of various types: UVC (100 to 280 nm), UVB (280 to 315 nm), and UVA (315 to 400 nm) as well as visible light (400 to 700 nm) and infrared radiation (700 nm to 1 mm). The atmosphere is capable of completely absorbing UVC radiation and most of the UVB radiation. Therefore, the only solar UV radiation relevant to health is the UVA and UVB wavelengths.[62] Exposure to radiation of these types is a very aggressive factor for human skin. In this sense, UV radiation generates chronic inflammation in the skin, which initially results in an alteration of the outermost superficial lipids, progressively reaching the viable layers of the epidermis and the underlying dermal compartments. In addition, UV rays induce dilation of dermal blood vessels, vascular hyperpermeability, cutaneous oedema, hyperplasia, infiltration of leukocytes, an increase in pro-inflammatory cytokines, and generation of ROS and other free radicals that end up producing direct damage to DNA, increasing the risk of suffering mutations that can lead to different types of skin cancer.[63,64] Melanin, a pigment capable of eliminating the products generated as a result of oxidative stress, is produced to defend against UV rays, thus preventing DNA damage.[65]

Research has identified a variety of products with the ability to block UV radiation and mitigate its effects on the skin, either through ingestion or topical application. The olive tree and its fruit contain certain phenolic compounds that exert a protective effect against UV radiation,[66] and are used as natural active ingredients in the formulation of sunscreens, as they have similar structures and mechanisms of action to chemical UV filters, synergistically enhance their action and improve their water resistance.[67]

In this sense, OLE and Htyr, present in olive leaves, show low UV absorption and high antioxidant activity, acting as protective factors against photocarcinogenesis. Olive leaf extract has greater antioxidant power than OLE alone due to its synergistic effects with other phenolic compounds present in the leaf.[68]

Compounds extracted from OMW have also shown photoprotective and antioxidant effects on UVA-treated keratinocytes and pro-oxidative and pro-apoptotic effects on keratinocytes with genetic damage.[69,70] These compounds also exert a photoprotective effect on some microorganisms, as reported by Da Silva *et al.*[71] They cultured *Saccharomyces cerevisiae* treated with sunlight in the presence of OLE, and observed photoprotective and antimutagenic effects on the colonies of this yeast.

On the other hand, both *in vitro* and *in vivo* studies have shown that phenolic compounds present in olives can also protect against UVB effects.[72,73] Some authors found that oral administration of both OLE and olive leaf extract prevented skin alterations associated with acute UVB exposure such as increased skin thickness, increased melanin granule size or increased expression of matrix MMPs.[74,75] Katsinas *et al.*[76] showed in an *in vitro* study with human corneal and conjunctival epithelial cells that treatment with OMW extract, Htyr or OLE significantly decreased ROS production in response to UVB exposure. There are also some commercial preparations of olive leaf extract which, when administered topically, are able to reduce lipid peroxidation caused by UV radiation.[77]

Some studies also suggest that the topical use of olive oil not only protects against the harmful effect of UV radiation, but may also be useful for cancer patients undergoing radiotherapy and radiochemotherapy, in order to delay the appearance of skin lesions associated with irradiation and reduce their severity, thus improving their quality of life.[78–80] In the same vein, Akarsu *et al.*[81] observed in patients treated with phototherapy and photochemotherapy that topical application of EVOO before a session increased the minimum phototoxic dose, *i.e.* the minimum dose of UVA at which noticeable erythema occurs.

Anticarcinogenic properties

Skin cancer represents the most common type of neoplasm in humans and includes non-melanoma tumours and malignant melanoma. The first type, whose incidence is higher, is represented by basal cell and squamous cell carcinomas which are characterised by their preventable and treatable nature.[82,83] Malignant melanoma, although less prevalent, is responsible for the majority of skin cancer deaths.[84,85] Although the anticancer properties of different olive extracts have been recognized, their role in skin cancer is little known.

The *in vitro* chemopreventive and anticancer actions of olive in melanoma skin cancer models have been described in the scientific literature. Thus, the anti-tumour effects of olives have been studied on the different compounds and extracts obtained from them. Many authors have focused on the study of the mechanisms of action by which olive compounds exert their antitumour effects on skin cancer. In this regard, the role of the Erk1/2-mediated signalling pathway, commonly referred to as the MAP kinase pathway or the MAPK/ERK pathway, which is essential for the development and progression of melanoma, should be highlighted. Most melanomas have genetic alterations that result in constitutive activation of Erk1/2 and proliferation of tumour cells.[86] In this line, Brito *et al.*[87] demonstrated the anticancer potential of oleic acid (OA), homovanillic alcohol and Htyr on A375 and MNT1 mutant melanoma lines. According to their results, Htyr reduced the cell viability of the A375 line, which could be related to a predominant glycolytic profile and activation of c-Jun N-terminal kinase (JNK); while the other compounds altered the glycolytic rate of MNT1 by inhibiting extracellular signal-regulated kinase (ERK). Htyr has also shown potential as a protective agent against UVA-induced damage in a melanoma cell model.[88,89] The ERK-mediated mechanism of action has also been discussed by other authors, who suggest that certain polyphenols such as oleocanthal (OC) or caffeic acid (CA) are able to selectively target human melanoma cells by inhibiting the ERK1/2 signalling pathway and a decrease in Bcl-2 expression.[90,91] Carpi *et al.*[92] proposed a mechanism of action based on the ability of compounds such as oleacein (OleaC) to modulate the expressions of certain genes and microRNAs relevant in the aetiopathogenesis of melanoma, such as BCL2, MCL1, c-KIT, K-RAS, PIK3R3, and mTOR and miR-193a-3p, miR-193a-5p, miR-34a-5p and miR-16-5p, respectively.

On the other hand, scientific evidence has demonstrated the protective activity against skin cancer of several polyphenols such as OC, which inhibited the proliferation, differentiation and induced apoptosis of melanoma cells;[93] or OLE and ellagic acid (EA) which disrupted the melanogenesis of the B16 tumour line by reacting with activated melanocytes and without damaging healthy cells.[94,95] Other authors have focused on the study of the anti-tumour effects of terpenes present in olives. The results suggest that molecules such as maslinic acid, oleanolic acid or other semi-synthetic derivatives of these are capable of inducing antiproliferative effects in cultures of murine B16f10 melanoma cells, while also improving intrinsic cellular tolerance to oxidative stress.[96,97] The same cell line was also used to describe the effects of extracts obtained from olive leaves. Assays have shown that they are able to reduce the glycolytic metabolism of the tumour, inhibit cell proliferation, stop the cycle in the G0/G1 phase and induce cell death.[98,99] These anti-proliferative effects in cultured human melanoma cells have also been observed with the use of phenol-rich OMW.[100]

However, although more detailed information is available for malignant melanoma, the effects of different olive extracts and compounds on non-melanoma skin cancer remain largely unknown. Polini *et al.*[101] described in their study the antitumour activity of different EVOO phytoextracts in an *in vitro* model with cutaneous squamous cell carcinoma cells. According to these authors, OC and OleaC are able to reduce the proliferation and migration of non-melanoma skin cancer cells, preventing colony formation by inhibiting Erk and Akt phosphorylation and suppressing B-Raf expression. Kostyuk *et al.*[102] demonstrated that VerB, a polyphenol also present in EVOO, is able to interfere with UV radiation, protecting against photo-oxidation and inhibiting pro-inflammatory signalling pathways in human epidermal keratinocytes, suggesting its chemopreventive potential against skin cancer.

Although *in vitro* tests provide encouraging data on the effectiveness of polyphenols in skin cancer, results obtained in *in vivo* studies are limited. Most of the work has been conducted in murine models using two main routes of administration: oral and topical. With regard to the first route, Song *et al.*[103] documented the antimelanogenic effects of OLE, which inhibited lipid and M2–MΦ accumulation in mice fed with a high-fat diet, while also inhibiting angiogenesis and lymphangiogenesis by decreasing the secretion of Vascular Endothelial Growth Factor (VEGF). The results obtained from the topical administration of EVOO or its derivatives have also shown its effectiveness in delaying the onset of skin cancer or even inhibiting melanogenesis without altering healthy skin cells.[95,104,105]

Antimicrobial effects

Bacterial infections are the cause of many skin problems. Some strains of *Staphylococcus* and *Streptococcus* are part of the saprophytic flora and can act as opportunistic infectious agents on certain occasions. In this regard, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Staphylococcus epidermidis* are

involved in the development of skin infections such as impetigo and pyoderma and infections of the nasal mucosa.[106,107]

Another common skin problem is bacterial colonisation of wounds, caused by a lack of oxygen or a hypoxic state that hinders wound healing. Among all the micro-organisms that are frequently isolated from chronic wounds are *Escherichia coli*, *Candida albicans*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus* spp.[108–110] In addition, the elevated presence of ROS in wounds that are difficult to heal promotes the destruction of the ECM that provides nutrition to pathogens.[111] Therefore, olive, with its antimicrobial and antioxidant capacities, could have a beneficial effect on the prevention and management of bacterial infections, allowing for normal wound healing progression.

Different studies have addressed the antimicrobial activity of olive leaf extracts against specific microorganisms such as *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. In this regard, different works found that ethanolic extracts of olive leaves were effective at controlling the growth of these microorganisms, with minimum inhibitory concentration (MIC) values of 2.5 to 60 mg mL^{-1} and minimum bactericidal concentration (MCB) values of 25 to 45 mg mL^{-1}.[112,113] In addition, authors such as Liu *et al.*[114] investigated the antimicrobial effect of OLE against *Listeria monocytogenes*, *Escherichia coli* and *Salmonella enteritidis*, showing that at a concentration of 62.5 mg ml^{-1}, it was able to almost completely inhibit the growth of these three pathogens. In addition, OLE also reduced the motility of *Listeria monocytogenes*, which correlated with the absence of flagella, inhibiting *Listeria monocytogenes* and *Salmonella enteritidis* biofilm formation. Similarly, Elnahas *et al.*[115] reported that Tanta olive leaf extract is particularly active against methicillin-resistant *Staphylococcus aureus*, with a MIC value of 15.6 μg ml^{-1}.

With respect to EVOO by-products, recent research has further investigated the antimicrobial activity of functional ingredients from different OP varieties against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, showing that these products with a higher Htyr content also showed the best MIC against the tested bacteria, except for *Candida albicans.*[116] On the other hand, several authors have identified that OMW extract, with high concentrations of Htyr, Tyr, ferulic acid (FA) and CA, also has antibacterial properties being effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, with MIC values of 0.13 and 0.25 mg mL^{-1}, respectively, and minimum bactericidal concentration values of 0.25 and 0.50 mg mL^{-1}, respectively.[117]

When using phenolic extracts of different origins, it is difficult to attribute their antimicrobial activity to a specific component. Several studies have focused on the evaluation of the antimicrobial activity of certain olive phenolic compounds. In this respect, benzaldehyde has been shown to possess antifungal, antibacterial and insecticidal activities.[118] Authors such as Melguizo-Rodríguez *et al.*[119] identified that 10^{-6} M doses of luteolin (LU), apigenin (API), coumaric acid (*p*-CA) and CA significantly inhibited the growth of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Proteus* spp. and *Candida Albicans*. The largest inhibition halos were obtained with CA and *p*-CA, with the effects being particularly marked against *Staphylococcus epidermidis*, *Proteus* spp. and *Candida albicans*.

With regard to the differences found in the sensitivity of microorganisms to the extracts or compounds analysed in the different studies, some authors argue that Gram-negative bacteria are considered more resistant due to the absence of a lipopolysaccharide layer in their wall, which is present in Gram-positive bacteria, making them more impermeable to antimicrobial compounds.[112,114]

Biostimulant and regenerative effects

The biological properties of the bioactive compounds of both leaf and EVOO make them of particular interest for use as biostimulants in wound treatment.[120] In this regard, the effect of different compounds present in EVOO, such as API, LU, CA, *p*-CA and FA, on the human fibroblast cell line CCD-1064Sk has been studied. All compounds except for FA significantly stimulated the proliferative capacity of fibroblasts, increasing their migration and their expression of genes related to cellular growth and differentiation.[119] Htyr, one of the main phenolic compounds in EVOO, has a direct effect on the wound healing process, although the molecular mechanisms responsible for this activity have not yet been elucidated. *In vitro* studies on HaCaT cells showed that Htyr treatment significantly increased cell viability, the expression of proteins involved in the cell cycle transition from the G1 to S phase such as cyclin D1 and D3, cyclin-dependent kinase 2 and cyclin-dependent kinase 6, and cell migration, decreasing the percentage of wound area. Similarly, the protective role of viability was observed in those cells pre-treated with Htyr to which H_2O_2 was subsequently added, significantly reducing cell apoptosis and showing antioxidant activity.[121]

Similar results have been found after treatment of fibroblasts and endothelial cells with uvaol, a natural terpenic alcohol found in EVOO and OP. Thus, Carmo *et al.*[122] observed increased migration of both cell lines, with a significant rate of wound closure between 22% and 40%, in those cells treated with uvaol, and an increased expression of Erk proteins such as fibronectin and laminin. Along these lines, Sánchez-Quesada *et al.*[123] identified the regenerative potential of Sq, a cyclic polyunsaturated hydrocarbon present in olives, in the treatment of wounds by studying its anti-inflammatory properties. Their results showed that Sq enhanced remodelling and repair signals and eosinophil and neutrophil recruitment, which are responsible for phagocytosis processes, suggesting that this molecule could promote wound healing by boosting macrophage responses in inflammation. Other *in vivo* trials have shown similar results with dermal application of other molecules present in EVOO such as omega-3, 6 and 9, or OLE.[124,125]

The therapeutic potential of *Olea europaea* leaf extracts for skin regeneration has also been studied, which showed antioxidant and protective effects against oxidative stress caused

by H_2O_2 administration in HaCaT cultures, showing a significant decrease in ROS and lipid peroxidation levels.[126] In the same vein, recent research has focused on the study of the effects of olive leaf extracts delivered by different microparticles based on hyaluronic acid or chitosan. Both preparations significantly increased the percentage of wound closure, while the free form extracts were less effective, possibly due to the rapid oxidation of OLE, the main compound of these extracts.[127] These results have been reproduced in wound models in Wistar rats treated with these extracts, showing a significant decrease in pH and lipid peroxidation in the wound bed, a higher percentage of wound closure and an increase in antioxidant capacity.[126]

The effects of the extracts have also been studied on chronic wounds in humans. Regardless of their aetiology, a greater number of patients achieved good results after application of the extracts in hydrogel form, with a significant reduction in the wound area and an acceleration of the healing process compared to that of the control.[128,129]

The benefits of olive oil and its derivatives are not only limited to the treatment of chronic wounds, but have also been used to treat other skin conditions such as burns. In this regard, Bayir *et al.*[130] evaluated the combined therapy of bandages impregnated with beeswax, olive oil and butter in a rat model of second-degree burns. The results showed that this treatment increased the expression of Transforming Growth Factor (TGF-β1) and VEGF-α compared to silver sulfadiazine gel, often used in these wounds. Moreover, it allowed a greater contraction of the wound tissues over 14 days of application.

Conclusions

Various studies have shown that the olive tree and its derivatives have beneficial effects in the treatment of skin ageing, solar radiation, oncogenic processes in the skin, and protection against infections caused by microorganisms. In addition, certain components of the olive tree have biostimulant, anti-inflammatory and regenerative effects at the tissue level. Thus, the use of these compounds may be a good therapeutic option or an alternative for the treatment of certain skin-related conditions, and for the improvement and homeostatic maintenance of the skin.

However, more research is needed on the design of dressings or products containing EVOO or its compounds, and on the development of protocols for use to enhance the preventive or regenerative effect in combination with the existing therapeutic options.

Author contributions

L. M. R.: investigation, methodology, conceptualization, visualization, writing – original draft, and writing – review & editing. A. G. A.: investigation, methodology, conceptualization, visualization, writing – original draft, and writing – review & editing. R. I. M.: investigation, methodology, and writing – original draft. E. G. R.: investigation, methodology, and writing – original draft. J. R. T.: investigation, methodology, and writing – original draft. V. J. C. R.: investigation, methodology, conceptualization, writing – original draft, and writing – review & editing. O. G. M.: investigation, methodology, conceptualization, supervision, writing – original draft, and writing – review & editing.

Conflicts of interest

The authors declare that they have no conflict of interest or competing financial interest.

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