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Unlocking the potential of olive residues for functional purposes: update on human intervention trials with health and cosmetic products

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Abstract

Olive mill waste (OMW) is a promising source of valuable compounds such as polyphenols, terpenes, sterols, and other bioactive compounds, which are of interest to the pharmaceuticals and cosmeceutical industries. This review examines the potential of OMW extracts for health and beauty applications based on evidence reports from human clinical trials. The results achieved to date indicate health-enhancing properties, but little is known about the underlying mechanisms of action, dose–response relationships, and long-term impacts. Therefore, while olive by-products, extracted using eco-friendly methods, present opportunities for the development of high-value health and cosmetic products, further studies are necessary to determine the full range of their effects and establish specific therapeutic strategies.

Keywords: bioactive compounds; olive oil by-products; waste reuse; circular economy; olive oil production; green technologies

INTRODUCTION

The production of olive oil contributes significantly to the economy of Mediterranean countries, which account for approximately 98% of global production. However, the cultivation of olive trees (*Olea europaea* L.) and the olive oil manufacturing process generate substantial volumes of solid waste and dark liquid by-products.[1-7]

The European Union Green Deal, a roadmap for achieving climate neutrality by 2050, promotes a transition to a circular economy. In this strategy, resource efficiency is maximized, and climate change, biodiversity loss, and pollution are addressed through principles of reduction, reuse, and recycling.[8] Despite growing interest in the circular economy, its implementation in the olive oil industry through waste valorization still faces barriers such as technological limitations, regulatory constraints, financial challenges, and managerial complexities.[9,10] Several new technologies have emerged to bolster the sustainability of olive oil production, aiming above all to reduce the generation of olive mill waste (OMW).[11] However, globally, around 12 million tons of non-environmental friendly residues (olive peels, pulp, stones, and wastewater) are still produced annually.[12-15]

The benefits of waste valorization through developments in the field of healthcare include a positive environmental impact, cost savings, and the creation of innovative, sustainable products that appeal to increasingly eco-conscious consumers. Due to its richness in nutrients and bioactive compounds, OMW can be perceived as a 'raw material' rather than a 'residue', representing a promising alternative source of natural antioxidants, recovered either as single compounds in pure form or antioxidant-rich

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extracts. Consequently, once extracted by green processes [e.g., ultrasonication, microwave, supercritical carbon dioxide (SCO_2), etc.], these by-products are transformed into added-value ingredients with the nutritional and cosmetic applications, in accordance with circular economy principles.

Nutritional supplements or functional ingredients from OMW can play a significant role in managing inflammation and associated chronic conditions, including autoimmune and cardiovascular diseases, and metabolic disorders. Used as functional ingredients, olive wastes and by-products such as olive pomace (OP) oil and olive leaf extract (OLE) may have beneficial cardiovascular and anti-inflammatory effects.[4-7,16,17] Another potential field of application is cosmetics, a steadily expanding industry predicted to maintain its growth momentum by around 6% annually. Among the factors responsible for the increase in the cosmetics market are technological advancements, and the rising demand for natural and organic beauty products.[18] As well as legal requirements, marketing strategies, and the ongoing innovations in technology, the successful development of a cosmetic product must be taken into account based on the consumers preferences. In this scenario, plant-based ingredients align perfectly with the current trend for eco-friendly and sustainable products.

Therefore, owing to the socio-economic significance, this review explores the potential pharmaceutical and cosmetic applications of olive oil by-products, focusing on the results of human intervention trials conducted in the last 5 years. The trials were drawn from electronic databases, including PubMed and Scopus, with extra trials identified manually reviewing the references. The following terms were used: olive mill waste, olive pomace, olive leaf, olive oil by-product, and trial.

NUTRITIONAL INTERVENTIONS IN HUMANS TO ASSESS THE POTENTIAL OF OLIVE RESIDUES FOR TREATING CARDIOMETABOLIC AND INFLAMMATORY DISEASES

In this section, we comprehensively review human studies performed in the last 5 years that highlight the value of different active components of OMW in the context of promoting cardiometabolic and inflammatory health (see Table 1).

Olive pomace oil

OP oil is obtained from the residues of the virgin olive oil extraction process, principally olive skins, pulp, and stones. Although OP oil contains fewer phenolic compounds than virgin olive oil, it is rich in bioactive components, including squalene, pentacyclic triterpenes, tocopherols, sterols, and aliphatic fatty alcohols, which are reported to benefit cardiometabolic health.[19] However, there is still limited research on the health effects of incorporating OP oil into the human diet.

In a randomized clinical trial (RCT) carried out by González-Rámila *et al*., the daily consumption of 45 g of OP oil consistently resulted in significant improvements in blood lipid profiles and adiposity in both normocholesterolemic and hypercholesterolemic participants, over a short (4 weeks) or longer (5 weeks) period. The improvements were characterized by significant reductions in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and the LDL-C/HDL-C (high-density lipoprotein cholesterol) ratio, as well as waist circumference and visceral fat.[4,6,20]

These findings suggest that OP oil is a valuable source of dietary fat, with potential benefits for cardiovascular health. In the same line, Antonopoulou *et al*. and Detopoulou *et al*. proposed that yoghurt enriched with a polar lipid extract of OP oil holds promise as a healthy functional food with anti-thrombotic and anti-inflammation properties.[3,21] Daily consumption of one serving of OP oil-enriched yogurt (150 g) for 4 or 8 weeks was found to reduce platelet-activating factor (PAF)-induced platelet aggregation, and levels of interleukin 6 (IL-6) and IL-10 in healthy adults. The reduction in IL-10 following OP oil-enriched yogurt intake may reflect a regulation of inflammation and/or platelet activity, with a lower secretion of immunomodulatory molecules, or the inhibition of IL-10 secretion by PAF activity.[3] In addition, the beneficial antithrombotic effect of OP oil-enriched yogurt is likely related to its ability to modulate the activity of the PAF enzyme, a proinflammatory lipid mediator, by reducing the biosynthesis of cytidine-5′-diphospho-choline:1-alkyl-2-acetyl-sn-glycerol choline-phosphotransferase and lipoprotein-associated phospholipase A2.[21] In another study, otherwise healthy subjects with hypercholesterolemia daily consumed 90 g of OP-enriched biscuits providing 17 mg/100 g of hydroxytyrosol for 9 weeks. The intervention was found to reduce oxidized LDL-C and increase bifidobacteria abundance, with a higher excretion of gut metabolites of hydroxytyrosol such as homovanillic acid and 3,4-dihydroxyphenylacetic acid, indicating an up-regulation of gut microbiota metabolism.[22]

Olive leaves

Olive leaves are a rich source of phenolic compounds with anti-inflammatory and antioxidant properties, including oleuropein, oleacein, verbascoside, and hydroxytyrosol, which animal and *in vitro* studies indicate are beneficial for cardiometabolic health and inflammation.[17] However, research into their potentially positive impact on human health is still an evolving field, with only a limited number of high-quality RCTs conducted to date.[7]

Angelopoulos *et al*.[22] demonstrated that a dietary supplement containing a low or high dose of monacolin K (3 and 10 mg, respectively), along with coenzyme Q10 (2 mg), grape seed extract (50 mg), and OLE (50 mg), reduced LDL-C in participants with mild hypercholesterolemia after 8 weeks.[23] However, the specific effects of OLE on the lipid profile could not be assessed as it was administered in combination with other bioactive components present in the dietary supplement. The effects of OLE supplementation alone were assessed in a systematic review and meta-analysis of 12 RCTs ($n = 819$ participants) by Razmpoosh *et al*.,[7] who found that it reduced the levels of triglycerides, total cholesterol (TC), and LDL-C in participants with hypertension and normal body weight. Interestingly, HDL-C levels decreased by 1.24 mg/dL in men after OLE supplementation. OLE supplementation is also associated with a positive effect on blood pressure, reducing systolic blood pressure (SBP) by 4.81 mmHg in individuals with hypertension, by 3.86 mmHg in those with a normal lipid profile, and by 7.05 mmHg in those with normal body weight. A significant reduction in diastolic blood pressure (DBP) of 2.45 mmHg was also observed in participants with hypertension.[7] Similar results were reported by Fatahian *et al*. in a meta-analysis of five human studies ($n = 145$ participants), SBP and DBP being found to decrease by 0.87 and 0.39 mmHg, respectively, after olive leaf consumption.[24] In contrast, another meta-analysis found a reduction only in SBP of 11.5 mmHg after daily supplementation with 500 mg of OLE, but no significant effect on either SBP or DBP was observed after administering higher

Table 1. Cardiometabolic and inflammatory effects of olive by-products in human intervention trials

Olive by-product	Study type	Participant	Dose	Main result	Reference
Olive pomace (OP)	Randomized, blinded, crossover, controlled clinical trial	64 healthy and hypercholesterolemic subjects aged 18–55 years with a body mass index (BMI) between 18 and 25 kg/m^2.	45 g/day of olive pomace oil (OPO), equivalent to 4–5 tablespoons, for 4 weeks	OPO reduced in LDL-C, Apo B, and the LDL-C/HDL-C ratio.	20
	Two randomized, blinded, cross-over controlled clinical trials	65 normocholesterolemic and 67 moderately hypercholesterolemic subjects aged 16–55 years, with a BMI less than 30 kg/m^2.	45 g/day of OPO (equivalent to 4–5 tablespoons) for two 4-week intervention phases	OPO consumption reduced TC and LDL-C levels. OPO consumption reduces waist circumference.	6
	Randomized, blinded, crossover, controlled clinical trial	68 normocholesterolemic and hypercholesterolemic subjects aged 19–59 years old, with a BMI between 19 and 32 kg/m^2.	45 g/day of OPO, equivalent to 4–5 tablespoons, for 4 weeks	OPO consumption decreased visceral fat. In hypercholesterolemic subjects, OPO increases leptin concentrations.	4
	A randomized, double-blind, placebo-controlled, three-arm parallel clinical trial	88 healthy subjects aged 35–65 years old, with normal BMI and overweight.	150 g/day of low-fat yogurt enriched with polar lipid extract of olive pomace for 8 weeks.	Enriched yogurt reduced platelet sensitivity against platelet-activating factor, and levels of IL-6 and IL-10.	3
	A randomized, double-blind, placebo-controlled, three-arm parallel clinical trial	88 healthy subjects aged 35–65 years old, with normal BMI and overweight.	150 g/day of low-fat yogurt enriched with polar lipid extract of olive pomace for 8 weeks.	Enriched yogurt reduced PAF-CPT and LpPLA2 activities.	21
	A randomized, double-blind, controlled, parallel clinical trial	62 healthy subjects aged between 30 and 65 years, with BMI between 20 and 29.9 kg/m^2.	One OP-enriched biscuit of 90 g daily for 8 weeks.	OP-enriched pomace reduced oxidation of LDL-C, and increased excretion of small phenolic acids in urine.	22
Olive leaf extract (OLE)	A prospective, multicentric, open-label, randomized controlled trial.	105 subjects with mild hypercholesterolemia and low CV risk aged 40–80 years.	A dietary supplement containing a low dose of monacolin K (10 and 3 mg) combined with coenzyme Q10 (2 mg), grape seed (50 mg), and OLE (50 mg) for 8 weeks.	Dietary supplements with 3 and 10 mg doses of monacolin reduced LDL-C. Higher 10 mg doses of monacolin reduced TG.	23
	Metanalysis based on 12 controlled trials.	819 subjects	OLE supplementation varied from 6 to 48 weeks, and 500 mg to 5 g daily, respectively.	OLE supplementation, reduced TG and SBP in overall subjects. OLE supplementation reduced SBP, DBP, TG, TC, and LDL-C in subjects with hypertension. OLE supplementation reduced TC, TG, and SBP in normal-weight subjects. No changes in glucose, liver and kidney, or inflammatory markers were observed.	7
	Metanalysis based on five randomized clinical trials.	145 subjects	Olive leaf supplementation varied from 1 to 12 weeks, and daily doses from 60 to 1600 mg.	Olive leaf consumption reduced SBP, DBP, TC, LDL-c, and TG levels.	24

Table 1. Continued

Olive by-product	Study type	Participant	Dose	Main result	Reference
				No changes in HDL-C, levels were observed.	
	Metanalysis based on 5 human trials.	325 subjects aged 18–80 years	Daily 500 mg or 1000 mg OLE supplementation for at least 8 weeks	OLE at 500 mg/day reduced SBP, and some inflammatory markers including IL-6 and TNF-α.	17
	A randomized, double-blinded, cross-over, placebo-controlled clinical trial.	13 subjects aged 18–38 years, BMI of 18 to 41 kg/m^2.	1 g of dried olive leaf tea diluted in 250 mL of water (mono dose)	Live-leaf tea delayed the glucose peak and increased glucose area under the curve.	25

Apo B, apoliprotein B; CPT, cytidine 5′-diphospho-choline:1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase; CV, cardiovascular; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; LpPLA2, lipoprotein associated phospholipase-A2; PAF, Platelet-activating factor; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TNF-α, tumour necrosis factor-alpha.

daily doses (1000 mg).[17] The possibility that OLE is more beneficial in hypertensive patients, as concluded by Razmpoosh *et al*.,[7] indicates a mechanism of action that affects blood pressure together with other cardiovascular risk factors.

Regarding glucose haemostasis, the results of studies on olive leaves are inconclusive. Meireles *et al*. showed that daily consumption of 250 mL of olive leaf tea delayed the postprandial glucose peak but increased the area under the curve in the glucose tolerance test after 2 h of ingestion compared to the placebo group, with no adverse effects observed.[25] Although the results did not support the intake of olive leaf infusion as a plausible dietary strategy to prevent diabetes, it was suggested that further research was warranted to investigate the effects of chronic consumption. Similarly, Razmpoosh *et al*. found no significant reduction in glucose levels after OLE supplementation based on a meta-analysis of six RCTs with a total of 442 adults, observing glucose reduction (−1.73 mg/dL) only in a subgroup analysis of participants without dyslipidemia. The authors concluded that this lack of effect may be due to the limited number of studies conducted.[7]

In summary, while reports suggest promising health benefits of OP oil and OLE in terms of improved lipid profiles and blood pressure, more robust human studies are needed to better understand these effects, and certain study limitations need to be addressed in future research. For example, some studies did not report the pure concentration of bioactive compounds isolated from olive by-products, such as oleuropein or its derivatives hydroxytyrosol and oleocanthal, which impedes the attribution of cardiometabolic and anti-inflammatory effects to these constituents. In addition, possible interactions between different bioactive compounds in the by-products have not been investigated. A further limitation, as highlighted by Razmpoosh *et al*. and Fatahian *et al*.,[7,24] is that most of the clinical trials covered in this review had short intervention periods, typically 4–8 weeks, which may not be sufficient to assess long-term effects on cardiometabolic and inflammatory markers, especially in healthy subjects. Nor did most studies consider potential confounding variables such as body mass index (BMI), dietary intake, physical activity, alcohol consumption, and smoking. Finally, the studies did not conduct gender-specific comparisons, which makes it difficult to differentiate the effects of olive by-product consumption on cardiometabolic and inflammatory outcomes between men and women.

OLIVE OIL BY-PRODUCTS IN COSMETICS

Olive oil residues are of great interest to the cosmetic industry, with versatile applications. They contain bioactive compounds with high antioxidant activity, especially oleuropein and hydroxytyrosol, and boast a distinctive fatty acid profile along with an attractive mineral composition.[26] These characteristics endow them with anti-ageing, anti-inflammatory, and hydrating properties, making them promising active ingredients for cosmetic products (see Fig. 1).

Atopic dermatitis is a chronic non-infectious inflammatory skin disorder characterized by intermittent flares, intense pruritus, and skin barrier disruption, which trigger scratching, lichenification, and increased transepidermal water loss.[27] Topical corticosteroids are the primary frontline treatment prescribed due to their anti-inflammatory, vasoconstrictive, immunosuppressive, and anti-proliferative properties. However, this therapy is associated with local side effects like striae, skin atrophy, and rosacea,

and risk of transcutaneous penetration, which can lead to hypertension, glaucoma, and other adverse ocular effects.[28] In this context, the *in vivo* tolerability and safety of cream for atopic dermatitis containing chitosan nanoparticles loaded with hydrocortisone and hydroxytyrosol (HC-HT CSNPs) were tested in a double-blind, vehicle-controlled study in humans.[29] Ten subjects were randomly assigned to receive either the test product or a vehicle sample cream on their arms for 28 days. No local irritation or toxicity was observed according to the measured transepidermal water loss, erythema, Draize scores, and skin biopsies. Blood analysis showed no significant changes in the serum cortisol levels, indicating non-systemic toxicity. A subsequent 6-week, randomized, double-blind, vehicle-controlled study was conducted to assess the safety and effectiveness of HC-HT CSNPs in the treatment of mild to moderate atopic dermatitis ($n = 9$).[30] The topical use of the HC-HT CSNP cream proved to be safe when administered twice daily to the affected region. Notable enhancements in the signs and symptoms of dermatitis were noted in individuals treated with the new cream compared to those treated with commercial (0.5% HC) and vehicle formulations. Importantly, there was no significant increase in liver enzymes, indicating that the drug did not enter the systemic circulation or affect the liver.

Another cream beneficial for skin health containing extracts from olive oil industry by-products was developed by Nunes *et al.*[31] OLE with a total phenolic content of approximately 5800 mg GAE/L was tested *in vitro* for cytotoxicity, skin enzyme inhibition, as well as antioxidant and photoprotection capacities, among other factors.[31] Subsequent safety studies such as ocular and skin irritation tests, ecotoxicity evaluation, and an *in vivo* human repeat insult patch test involving 51 volunteers were performed. Following the positive results, the OLE was integrated into cream formulations at a concentration of 5%, and their acceptability and antioxidant efficacy were assessed in ten healthy female volunteers aged 18–65 years. No adverse reactions were observed upon application of the formulations to the skin, and the cream with the highest phenolic concentrations demonstrated the greatest antioxidant efficiency.[31]

A prospective pilot study involving 36 participants with photoageing skin reported facial rejuvenation benefits of a 1% OLE-containing cream (SUPERHEAL™ O-Live Cream, USA Patent 6743449; PhytoCeuticals, Inc, New Jersey, USA).[32] All participants applied 0.6 g of the cream to their whole face twice daily for 2 months. The study assessed various biophysical skin properties, including melanin and erythema index, transepidermal water loss, hydration, pH, sebum level, texture, and wrinkles. Remarkable improvements in wrinkles were noticeable after just 1 month of treatment, while enhancements in skin barrier function, hydration, and texture were observed after 2 months. Despite the promising findings, the study has limitations, including its short duration and the absence of a control group. Moreover, the cream used in the study contained ceramide, which might have contributed to the observed effects. Distinctive disadvantages of the cream were its lack of perfume, resulting in an odour some might find unpleasant, and its colour, giving the skin a tan tone if applied in a significant amount.

Although only a few human studies have been published showcasing the application of OMW components in cosmetic products, several recent preliminary studies in this field have reported promising results. *In vitro* studies have demonstrated the cosmeceutical potential of hydroxytyrosol extracted from OMW, with protective effects for human dermal fibroblasts and keratocytes,

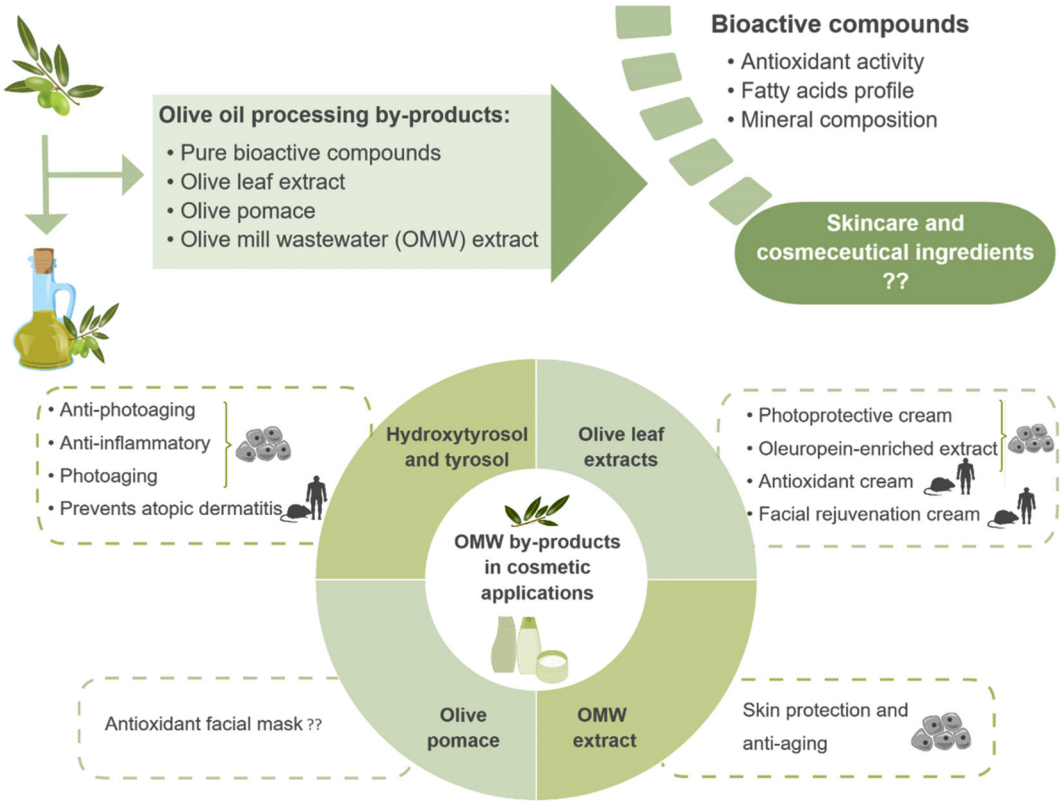

Figure 1. Potential use of olive oil processing by-products in cosmetics.

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due to skin anti-ageing and anti-inflammatory properties.[33-35] Additionally, Da Silva *et al*. demonstrated, in cell cultures, the photoprotective potential of OLE in sunscreen formulations, used in combination with organic ultraviolet (UV) filters.[36] More recently, the bioactivity of two oleuropein-enriched extracts from *O. europaea* fruits and leaves was comprehensively assessed by De la Cádiz-Gurrea *et al*. and remarkable antioxidant and antiradical activities were observed.[37] The effects of a phenol-rich olive mill wastewater extract (Patent 8815815) on skin cells were evaluated by Schlupp *et al*., who reported an inhibitory impact on cell proliferation as well as anti-inflammatory and anti-oxidative properties in a HaCaT model.[38]

As highlighted in this section, only a limited number of human studies have explored the effectiveness of olive oil by-products as bioactive ingredients in beauty products. Moreover, these studies lack robustness as they typically involve short treatment durations (1–2 months), small sample sizes, predominantly female participants, and some do not include a control group, rendering them preliminary. Consequently, despite the significant potential of olive oil processing by-products in cosmetic applications, more extensive investigation in this field is warranted.

MAIN REMARKS AND FUTURE PERSPECTIVES

The environmental impact of by-products generated by olive oil extraction is immense, due to their phytotoxicity, high organic content, and sheer volume. A strategy that can reduce the level of waste is the development of new applications that harness the health-giving properties of bioactive constituents found in these residues, above all phenolic compounds. Regarding health benefits, recent clinical trials in humans have demonstrated that olive oil by-products such as OP oil and OLE have the potential to improve cardiometabolic and inflammatory parameters. The consumption of OP oil has been associated with improvements in lipid profile and adiposity, while OLE is reported to reduce LDL-C and blood pressure. However, few high-quality RCTs in this field have been carried out to date, and further studies are needed to better understand the dose–response effects, underlying mechanisms of action, as well as long-term impacts. Future research should also explore optimal dosages, duration of intake, and potential side effects. Increased knowledge of the health benefits afforded by olive oil by-products could lead to the design of innovative dietary strategies and functional foods that can mitigate cardiometabolic disease and enhance wellbeing.

The cosmetics industry is booming, driven by technological advances and consumer desire for natural products. Olive oil residues have potential utility in the development of eco-friendly cosmetics as they are rich in antioxidants, notably oleuropein and hydroxytyrosol. However, their successful valorization hinges on additional research, particularly clinical trials to assess the safety and effectiveness of the resulting products. Additionally, more efforts are required to guarantee that all the technical challenges involved in the development of new beauty products containing OMW components are adequately resolved, including possible allergies, ingredient instability, malabsorption into the outermost layer of the skin, dispersion issues, interactions between the active ingredients and vehicle components, and concerns about the quality, safety, and efficacy of the final cosmetic product. Although various techniques for encapsulating olive oil by-products into microparticles or nanoparticles using freeze- or spray-drying methods have been developed, their application within the industry of cosmetics has not received thorough consideration. Nanoemulsions are promising alternatives for delivering these by-products; however, additional optimization studies are imperative to firmly establish its viability in this context.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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