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Review

Sustainably Sourced Olive Polyphenols and Omega-3 Marine Lipids: A Synergy Fostering Public Health

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ABSTRACT: Thanks to the pioneering studies of Østerud and co-workers, it is now increasingly understood that natural polyphenols present in marine oils play an essential role in protecting omega-3 lipids from oxidation and autoxidation, ensuring that no proinflammatory products are formed after intake as often happens with assumption of refined omega-3 concentrates. Strong antioxidants exerting multiple biological functions, olive biophenols are ideally suited to functionalize marine oils, creating a synergy that has the potential to improve public health across the world. This study identifies suitable avenues for advancing the sustainable production of health-beneficial formulations based on newly obtained natural marine oils and olive phenolic extracts. Important educational outcomes conclude the study.

KEYWORDS: *omega-3, olive, polyphenols, hydroxytyrosol, limonene, circular economy*

1. INTRODUCTION

The numerous health benefits of the biophenols found in *Olea europaea* include antiatherogenic, cardioprotective, anticancer, and neuroprotective activity.[1] Research in the field is flourishing, and book chapters[2] and review articles[3] regularly summarize newly discovered findings concerning the physiological role of these phenolic compounds, which include oleuropein, hydroxytyrosol, tyrosol, and oleocanthal.

Being powerful antioxidants (free radical scavengers),[4] olive phenolic extracts can be used as highly effective nontoxic replacements for toxic synthetic antioxidants used as preservative food additives.[5] These compounds also show significant anti-inflammatory activity. In the case of hydroxytyrosol [3,4-dihydroxyphenylethanol (HT)], quantum mechanical calculations and molecular docking simulations suggest that the anti-inflammatory activity may be due to binding and inhibition of the lipoxygenase and cyclooxygenase enzymes.[6] Another key relevant advantage in light of pharmaceutical applications of these phenolics is their lack of toxicity. For example, HT is not genotoxic or mutagenic, and its consumption is safe even in large doses.[7]

Several olive phenolic extracts have been commercialized as nutraceutical formulations with multiple health benefits,[3] ranging from prevention of cardiovascular disease to bone reinforcement, with the use of said formulations being at times supported by clinical evidence from randomized control trials.[8]

Similarly, docosahexaenoic acid (DHA, C22:6n-3) and eicosapentaenoic acid (EPA, C20:5n-3) omega-3 (or n-3) long chain polyunsaturated fatty acids (PUFA) abundant in oily blue fish exhibit anti-inflammatory, neuroprotective, and antithrombotic properties by lowering heart rate and blood pressure,[9] which makes consumption of fish and of blue fish in particular of fundamental relevance for the physical and mental health of adults and children.

Unfortunately, insufficient consumption of EPA and DHA is one of the main deficiencies in diets common to industrially developed countries, which led Harris to introduce a new index (EPA+DHA in red blood cells) directly related to changes in EPA+DHA intake,[10] to properly assess and evaluate this deficiency.

In brief, enhancing the amount of EPA+DHA essential fatty acids in the body requires either an increase in the frequency of consumption of blue fish and seafood or omega-3 supplementation. Growing at an annual rate of >10% (compound), the \$2.6 billion EPA/DHA ingredient global market in 2018 is estimated to almost triple by 2026,[11] further increasing overfishing pressure on anchovy and sardine stocks, because anchovy/sardine oils are the dominant raw materials used to produce food and dietary supplement products.[11]

The main production process employed to obtain fish oil omega-3 concentrate includes anchovy/sardine cooking and pressing on board the shipping vessel, followed by extensive chemical refining at omega-3 ingredient manufacturing sites.[12]

Recently, simple and effective methods for sustainably sourcing olive polyphenols from both olive and fish processing waste have been developed. In the case of olive phenolics, new processes include adsorption and subsequent release with an organic solvent of the polyphenol and lactone content in olive

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mill wastewater (OMWW) on a series of adsorbent resins,[13] or, more simply, employing citric acid to stabilize and progressively hydrolyze the polyphenolic glycosides in vegetation waters.[14] Extended to modern two-phase olive mills, the latter process affords olive phenolic aqueous extracts of unprecedented titer in hydroxytyrosol.[15]

In the case of anchovy fish oil, a new process starts from anchovy processing waste and uses citrus-derived *d*-limonene as the extraction solvent in a closed loop process in which the biobased solvent is fully recycled, affording an oil rich not only in EPA and DHA[16] but also in valued vitamin D_3.[17] When compared to the multistep conventional fish oil extraction and purification process, the new biobased circular process provides significant technical, economic, and environmental advantages.[18]

Following recent studies of Valenzuela and co-workers in which the benefits of consuming a mixture of extra virgin olive oil or hydroxytyrosol with *n*-3 PUFA (EPA + DHA or DHA) have been demonstrated in animal models (liver and adipose tissue),[19−22] in this study, we aim to show how combining sustainably sourced olive phenolic and omega-3 marine oil extracts may synergistically improve public health while providing substantial benefits to manufacturers of omega-3 and olive phenolic ingredients. Important educational outcomes for bioeconomy educators conclude the study.

2. THE CASE FOR SYNERGY BETWEEN OLIVE BIOPHENOLS AND OMEGA-3 LIPIDS

An immediate advantage of using olive polyphenols in combination with omega-3 lipids is the enhanced chemical stability to PUFA tryglycerides abundant in marine oils. This was shown by Spain's scholars in 2008 reporting that 90−95% pure hydroxytyrosol obtained by hydrothermal treatment of OMWW added at concentrations of 50 and 100 ppm to cod liver oil (40% of omega-3 lipids) was able to inhibit ω-3 lipid oxidation.[23] The higher level of oxidation inhibition was reached using 100 ppm of HT (Figure 1).

Exerting neuroprotective, anti-inflammatory, anticancer, and even antiviral (against several influenza A viruses)[24] activities,

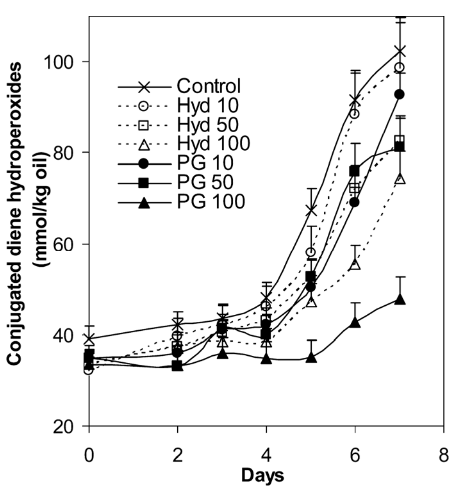

Figure 1. Effect of hydroxytyrosol (Hyd) and propyl gallate (PG) at different concentrations (10, 50, and 100 ppm) on the formation of conjugated diene hydroperoxides in fish oil during oxidation at 40 °C. Reproduced with permission from ref 23. Copyright 2008 American Chemical Society.

hydroxytyrosol, which is abundant in *O. europaea*, was recently found to be "the most actively investigated natural phenol".[25] The compound has limited antibacterial activity,[26] but its great pharmacological potential is widely recognized.[27] For example, in late 2020, Italy's scholars reported the human safety of an oral spray containing microencapsulated hydroxytyrosol developed with the aim of inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) endocytosis.[28]

Because of the evidence of industrial interest, a few months later a joint team including researchers from a large food company reported that OMWW is an excellent antioxidant for retarding lipid oxidation in fish oil-enriched food products.[29] Noting how the antioxidant properties of OMWW in fish bulk oil had not been previously reported, the team showed how it is enough to add lyophilized OMWW in 1 wt % amounts to tuna oil (5 wt % in medium chain triglyceride oil) to inhibit the formation of hydroperoxides, hexanal, and *t*,*t*-2,4-heptadienal throughout the storage period (14 days) by 94.2%, 96.5%, and 100%, respectively.[29] Volatile compounds hexanal and nonanal (oxidation products of *n*-6 PUFAs) and *t*,*t*-2,4-heptadienal (oxidation product of *n*-3 PUFAs) form during the storage of tuna oil, with hexanal being the main volatile formed during storage.

When compared to several antioxidants, including oregano and parsley, ethylenediaminetetraacetic acid (EDTA), and Trolox (a water-soluble α-tocopherol analogue), OMWW was found to be the best antioxidant (Table 1). Remarkably, the

Table 1. Percent Inhibition of the Formation of Oxidation Compounds at the End of the Storage Study (14 days) (adapted with permission from ref 29)

sample	% inhibition peroxide values	% inhibition hexanal/hexanal-d_{12}	% inhibition heptadienal/hexanal-d_{12}
control	NA[a]	NA[a]	NA[a]
EDTA	75.5	51.0	71.7
oregano	63.0	93.1	100
OMWW	94.2	96.5	100
parsley	78.4	75.0	90.8
Trolox	68.3	35.2	63.7

[a]Not applicable.

effectiveness of OMWW (as well as of parsley and oregano) as an antioxidant was found to relate to the total phenol content and oxygen radical absorbance capacity (ORAC) but not to the iron(II) chelating activity.

In a complementary and straightforward approach, a marine oil rich in omega-3 lipids such as algae oil (AO) is directly mixed with extra virgin olive oil (EVOO).[30] In detail, mixing a commercial AO with a high concentration of *n*-3 PUFAs [35% DHA, 20% EPA, and 5% docosapentaenoic acid (DPA, C22:5*n*-3)] with a shelf life of 1 month with EVOO with a minimum quantity of 60 mg/g of secoiridoids and 80% oleic acid decreased the extents of oxidation processes in a dose-dependent manner (Figure 2) throughout storage.

Eventually, after 10 weeks, the amount of *n*-3 PUFAs in the commercial oil was decreased by ~30%. It was enough to mix the AO oil with EVOO in a 50:50 ratio (mixture III) to decrease the reduction in the PUFA amount to 20%. Eventually, in an 83:17 EVOO/AO mixture, the PUFA content after 10 weeks was reduced by <10%. The team concluded that the addition of EVOO rich in polyphenols to

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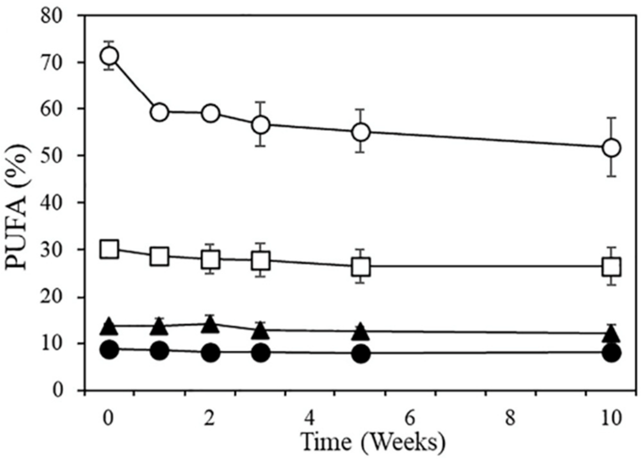

Figure 2. Changes in the concentrations of polyunsaturated fatty acids (PUFA; EPA + DHA + DPA) during accelerated storage conditions of EVOO, AO, and mixtures: (■) EVOO, (●) mixture I [17:83 (w/w) AO/EVOO], (▲) mixture II [25:75 (w/w) AO/EVOO], (□) mixture III [50:50 (w/w) AO/EVOO], and (○) AO. Each value is represented as the mean ± the standard deviation ($n = 3$ samples per oil). Reproduced with permission from ref 30. Copyright 2020 Elsevier.

marine oils is "a simple alternative for the stabilization of unstable oils rich in omega-3, facilitating their application in the industry".[30]

As mentioned above, the synergy between olive polyphenols and omega-3 lipids may extend well beyond the enhancement of omega-3 lipid oxidative stability.

For instance, as early as 2005, scholars in Brazil reported the outcomes of a clinical study showing that supplementation with olive oil in patients who had rheumatoid arthritis and were at the same time using fish oil supplements resulted in a more precocious and accentuated improvement when fish oil supplements were used in combination with olive oil.[31]

The conventional industrial processes used to extract and purify fish oil also remove the lipophilic polyphenols naturally present in the fish fat,[12] including the powerful antioxidant and anti-inflammatory phlorotannins obtained by fish eating brown algae.[32]

In 1986, studying the effect of 8 weeks of daily intake of omega-3 lipids in the form of fish oil or omega-3 capsules, Østerud found modest benefits in the activity of blood cells, suggesting that concentrated omega-3 lipids did not have the same health effects as marine oils in natural form. These preliminary findings were subsequently confirmed by numerous studies,[33−35] suggesting that a daily fish intake more effectively enhances the plasma concentration of n-3 PUFAs as compared with the intake of concentrated EPA and DHA ethyl esters in capsules.

Østerud and Elvevoll in Norway in the late 1990s first suggested that purification significantly weakens the health benefits of refined marine oils, freed of important natural antioxidants. In 2001, they reported at a congress held in Vienna the results of administering cold-pressed versus refined marine oils to healthy volunteers. Better results, seen as a consistent improvement in parameters related to the development of cardiovascular disease, were noted by supplementation with cold-pressed seal oil, despite a lower content of n-3 fatty acids in the unrefined oil.[34]

Three years earlier, studying the effect of the intake of various marine oils on the number and volume of platelets in 266 healthy volunteers, they reported that the combination of cod liver oil and olive oil produces better effects than the oils given separately.[36] A few years later, they were the first to recognize the commercial relevance of olive polyphenols to fish oil-based supplements, applying for a patent describing the combination of seal oil and cold-pressed virgin olive oil.[37] The trade name of the new combined oil was Olivita.

In a subsequent clinical study, healthy subjects were given 15 mL of combined cold-pressed olive oil per day with refined seal or fish oil for 10−14 weeks. The recombined oils regained the properties lost during refining with clear anti-inflammatory effects seen in reduction of MCP-1 (monocyte chomotactic protein-1), C-reactive protein (CRP), and thromboxane B_2 and leukotriene B_4 assuming the seal oil combined with olive oil, and reduction in cytokines when assuming the fish oil combined with olive oil.[38] In brief, the combination of EVOO and marine oils behaved like cold-pressed marine oils, while said changes were not observed in fish or seal oils without added EVOO.

In light of these and previous findings, scholars today associate the absence of diabetes and coronary heart disease in native Greenland Eskimos discovered by Bang and Dyerberg in the late 1960s and subsequently ascribed to high hematic levels of DHA and EPA abundant in seal and whale meat[39] also "at least partly ... to their co-ingestion of phlorotannins".[40]

Indeed, the use of brown algal phlorotannins to prevent refined fish oil from becoming rancid was proposed as early as 1996 when researchers in China reported that the antioxidant activity of 1% high-molecular weight phlorotannins extracted from *Sargassum kjellmanianum* was 2.6 times higher than that of 0.02% BHT (*tert*-butyl-4-hydroxytoluene), a commonly employed synthetic antioxidant.[41]

Today an omega-3 dietary supplement consisting of omega-3 from seal oil, extra virgin olive oil obtained from Spain, and vitamin D is produced in Norway and sold commercially across the world. The manufacturer recommends the intake of six capsules per day (not one or two as with omega-3 capsules using refined marine oils) because the omega-3 fatty acids are not concentrated.[42]

This suggests that newly developed olive biophenol extracts added to concentrated natural fish oil extracted with nontoxic and edible solvent limonene from, for example, anchovy leftovers[16] may reduce the number of needed capsules with respect to the latter formulation, while enhancing the amount of phenolic compounds whose benefits, as mentioned above, go well beyond simple antioxidant activity.

3. THE CASE FOR CONCENTRATED OLIVE BIOPHENOL EXTRACTS

Most routes of extraction of olive polyphenols from different sources such as olive leafs or olive mill wastewater afford extracts with phenolic concentrations of generally <20 wt %, and often <10 wt %.[3] A recently developed extraction and separation protocol for olive mill wastewater polyphenols, on the contrary, affords concentrated phenolic oils,[43] ideally suited to be mixed with marine oils.

In detail, raw OMWW obtained from olive mills undergoes centrifugation and simple filtration to remove all solid particles after which it is acidified to pH ≈2 with concentrated HCl and defatted in a separatory funnel using n-hexane. The resulting aqueous layers are extracted with EtOAc to retrieve the

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phenolic molecules, after which the EtOAc extract is dried over anhydrous Na_2SO_4 and evaporated under vacuum affording a yellowish-brown crude oil.

The crude extract is purified by dissolving it in EtOAc, followed by addition of powdered silica and solvent evaporation under reduced pressure. The oil adsorbed on silica is loaded onto a silica gel septum packed in *n*-hexane, which is first eluted with hexane to remove any residual apolar component and then with EtOAc to recover the biophenol fraction. The eluate is separated from the solvent via evaporation under reduced pressure, affording a yellowish oil comprised of olive phenolics [silica-purified polyphenol mixes (SPPM)].

The same crude samples obtained from liquid−liquid extraction were also purified through a C18 reversed phase silica column packed in a 9:1 acetonitrile/acidified water mixture [2.5% (w/w) formic acid]. The column was eluted with the latter eluent, and then the polarity was gradually increased to a 1:1 acetonitrile/acidified water mixture to recover a biophenol fraction obtained as a yellowish oil [C18-purified polyphenol mixes (CPPM)]. The oils (Figure 3) have a virtually identical phenolic profile, with tyrosol and hydroxytyrosol as the main components (Table 2).

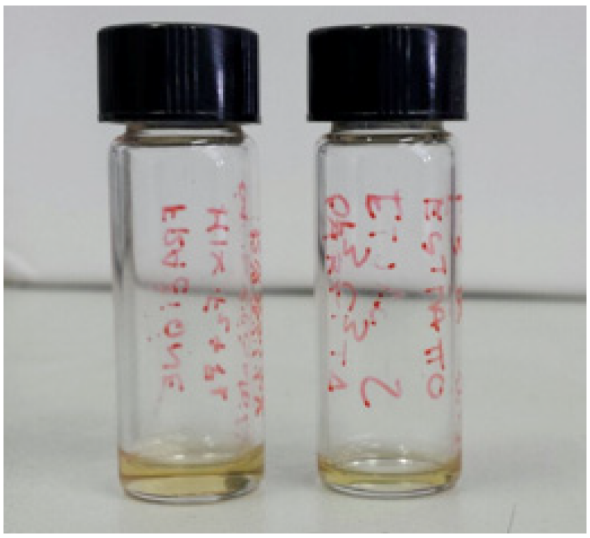

Figure 3. Typical olive biophenol extracts obtained via liquid−liquid extraction of OMWW followed by chromatographic purification through a silica-based column. Reproduced from ref 48. Creative Commons Attribution 4.0 International License.

Table 2. Amounts of Hydroxytyrosol and Tyrosol in the SPPM and CPPM Extracts (reproduced with permission from ref 43; copyright 2017 Elsevier)

sample	hydroxytyrosol (mg/L)	tyrosol (mg/L)
Biancolilla SPPM	65.90 ± 3.29	16.04 ± 0.81
Biancolilla CPPM	63.34 ± 3.16	18.25 ± 0.91
Cerasuola SPPM	125.43 ± 6.27	29.85 ± 1.49
Cerasuola CPPM	127.81 ± 6.37	28.12 ± 1.41

Aiming to avoid the use of harmful *n*-hexane, the industrial preparation of similar phenolic extracts will employ biobased limonene[44] to defat the raw OMWW and C18-reversed phase silica as the optimal stationary phase because it enables the use of water as a mobile phase combined with less polar solvents, including environmentally friendly ethyl lactate.[45]

Hydroxytyrosol is well known to have good solubility in oil and aqueous media, which allows useful application of hydroxytyrosol-rich extracts to protect from oxidation of multiple components and widely different foods such as lard[46] and foodstuffs rich in fish lipids.[47] OMWW is a virtually unlimited source of hydroxytyrosol and related valued olive biophenols. It is enough to quickly assess the amount of hydroxytyrosol and tyrosol contained therein and then to apply the aforementioned green commercial extraction process to OMWW batches with the largest amount of these polyphenols.[48]

Anchovy oil extracted with citrus-derived *d*-limonene from anchovy filleting waste affords a natural (nonrefined) oil rich in EPA and DHA,[16] vitamin D_3,[17] and zeaxanthin (Figure 4).

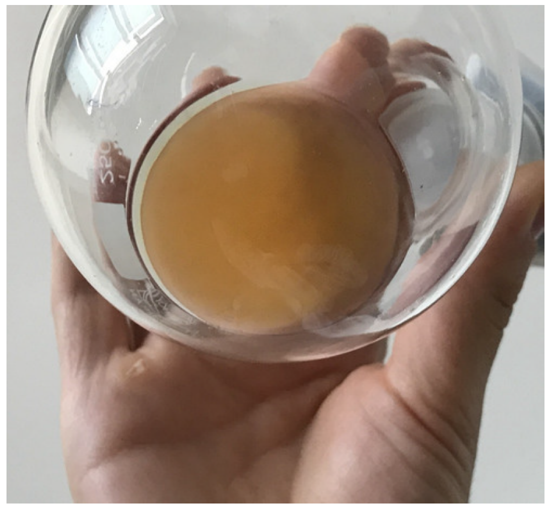

Figure 4. *AnchoisOil* obtained from anchovy fillet processing waste after extraction with limonene and solvent evaporation under reduced pressure. Reproduced with permission from ref 16. Copyright 2019 Wiley.

Found in several microalgae, fish, and seafood species, the latter carotenoid is a powerful antioxidant and an important neuroprotective agent.[49] Even for this newly developed marine oil, dubbed herein *AnchoisOil*, the addition of the new olive biophenol extracts described above would further protect the PUFA (and zeaxanthin) from oxidation.

At the same time, the intake of such a functionalized natural fish oil would result in cardoprotective action thanks to the olive biophenols integrated into the lipoproteins after they had entered the bloodstream protecting their lipid components from oxidation and exerting anti-inflammatory action at the artery walls.[40]

Clinical studies will be necessary to demonstrate the synergy between this new marine oil and concentrated olive biophenols in the prevention of diseases such as coronarial hearth disease or in the cure (relieving) of common morbidities such as atherosclerosis, joint and muscle pain, and psoriasis.

4. CONCLUSIONS AND PERSPECTIVES

Largely thanks to the pioneering studies of Østerud, it is now increasingly understood that supplementation of refined omega-3 polyunsaturated lipids in the form of ethyl esters may cause either a limited effect on human blood lipids, platelets, and coagulation[50] or even undesirable oxidative stress leading to an increase in the levels of proinflammatory products.[51] Østerud and Elevoll suggest that the lack of cardiovascular disease and type 2 diabetes observed in the late 1960s by Dyerbeg and Bang in native Greenlanders chiefly eating seal and whale blubber[39] has been due to the concomitant action of omega-3 lipids and the natural polyphenols contained in blubber protecting the unstable PUFAs from oxidation and autoxidation.[52]

Aware of the unique antioxidant power of olive polyphenols,[4] Norway's scholars in the mid 1990s started to study the clinical effects of mixing unrefined marine oils with extra virgin olive oil rich in phenolic compounds.[36]

Eventually, the combination of marine oils and EVOO was patented,[37] and new nutraceutical products protected against oxidative degradation and provided with further anti-inflammatory, anti-atherogenic, and cardioprotective activities due to synergy between olive biophenols and omega-3 lipids were commercialized.[42]

Subsequent advances in marine oil and olive biophenol extraction technologies have opened a route to the production of new nutraceutical and pharmacological products based on the combination of newly obtained natural marine oils and olive phenolic extracts.

In the case of marine oils, a new general strategy for obtaining highly valued marine oils in their natural form, namely as triglycerides containing plentiful natural antioxidants, including astaxanthin and zeaxanthin, was demonstrated for both anchovy[16] and shrimp[53] processing waste (rather than from anchovy and shrimp) using biobased and biocompatible citrus limonene as the extraction solvent.

In the case of olive phenolics, new green processes were used to readily obtain highly concentrated and pure phenolic extracts in two steps using liquid–liquid extraction followed by chromatography on hydrophobized silica.[43,48]

In the era of overfishing[54] and with the global population rapidly aging (22% of the world's projected population is expected to be >60 years of age by 2050, from just 12% in 2015),[55] these findings are of remarkable global relevance. Rather than mixing of olive and marine oils, the aforementioned natural marine oils obtained from overfished and mercury-free marine species such as anchovy and shrimp processing waste will be further functionalized with small amounts of olive oil waste extracts rich in pluripotent biophenols such as hydroxytyrosol, tyrosol, and oleocanthal.

Following clinical studies, the nutraceutical and pharmacological products based on the aforementioned combination of newly obtained natural marine oils and olive phenolics extracts will hopefully provide and improve the health benefits already observed via the combination of marine and olive oils.

Important educational consequences for green chemistry and bioeconomy educators using recent research achievements to foster student creativity[56] originate from the new green chemistry technologies summarized in this study for marine oils and olive phenolics. Students indeed find in this case study another example of how also in biochemistry and in the bioeconomy progress in science is far from being linear and requires the re-discovery of forgotten findings,[57] such as those concerning the unique role of antioxidants in marine oils and the dangers associated with their removal during the production of refined fish oil to manufacture food and nutraceutical supplements.[12,50–52] As the chemical industry evolves toward biobased productions carried out in distributed chemical plants using green chemistry technologies,[58] students learn how the production of marine oils and phenolic extracts at low cost enabled by the aforementioned green chemistry routes allows us to expand their commercial utilization of fishery and agricultural waste in low-income and middle-income countries, meeting a key requirement of the bioeconomy for which highly valued functional substances are sustainably derived from renewable resources.[59]

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Notes

The authors declare no competing financial interest.

■ DEDICATION

This work is dedicated to Professor Bjarne Østerud, University of Tromsø, for all he has done to elucidate the role of natural antioxidants in marine oils.

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