Enhancing and improving the extraction of omega-3 from fish oil

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ABSTRACT

Omega-3 fatty acids DHA and EPA derived from fish oil are widely marketed across the world as valued dietary supplements offering numerous health benefits to children and adults alike. Traditional extraction processes are energy intensive and use organic solvents. Green and sustainable alternatives are needed with the aim to significantly expand and improve the production of omega-3 extracts, especially with the aim to obtain these essential polyunsaturated fatty acids from fish processing waste available in > 20 million tonnes/year amount.

1. Introduction

Driven by increasing awareness and growing incidences of chronic diseases such as high blood pressure, cancer, depression, cardiovascular and Alzheimer’s disease, the global consumption of dietary supplements and nutraceutical products based on fish oil has rapidly expanded (Rizliya and Mendis, 2014). Fish oil, indeed, is the main source of omega-3 long-chain polyunsaturated fatty acids (PUFAs). Depending on the position of the first double bond from the methyl end group (ω end) of the fatty acid, long-chain PUFAs belong either to ω–6 (n-6) or to ω–3 (n-3) families (Fig. 1), with the position of the first double bond dictating much of the biological activity (Rustan and Drevon, 2005).

Fish oil derived from blue fish, in particular, is rich of both eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) which are the most investigated nutrients ever, (Landis, 2005) following the findings of two Danish medical doctors, Bang and Dyerberg, who analyzed blood samples from 61 male and 69 female Inuit living in a 1350 people village in northwest Greenland consuming a predominantly meat diet rich in PUFAs (Bang et al., 1971). They found lower levels of several types of lipids, including total cholesterol and plasma triglycerides, in comparison to the plasma lipids of healthy Danes; and made the hypothesis that this could explain the very low incidence of ischemic heart-disease and the complete absence of diabetes mellitus in Greenlandic Eskimos. Eight years later, the same scientists discovered that the Inuit had higher than normal amounts of two omega-3 fatty acids, DHA and EPA, in their plasma and platelet lipids, which led them to the hypothesis that these omega-3 fatty acids could protect the Inuit from the cardiovascular consequences of their high-fat diet (Dyerberg and Bang, 1979). Ever since, biochemical and biomedical research on these omega-3 fatty acids literally boomed, with over 31,000 peer-reviewed scientific articles published by January 2016. In brief, in what Lands has called the “complex food web” supporting human energy and health needs, the former C\textsubscript{20} and C\textsubscript{22} highly unsaturated fatty acids present in aquatic foodstuffs play a critical role (Lands, 2009). Ingestion of fats dominated by n-6 fatty acids can promote the pathogenesis of many diseases, (Simopoulos, 2008) including severe coronary heart disease (Bernstein et al., 2010). To the contrary ingestion of n-3 fatty acids contained in oily fish or fish oil, rich in both EPA and DHA, is critical for both physical and mental health, playing an important role in infant brain and eye development (EFSA J., 2014).

In 2010, the European Food Safety Authority recommended an adequate intake of 250 mg/day for EPA plus DHA (EFSA J., 2010). The World Health Organization, since 2008 recommends a daily intake of EPA plus DHA of 250 mg in primary prevention of coronary heart disease and 2 g in secondary prevention (FAO/WHO, 2008). The American Heart Association recommends a higher daily dosage (500 mg) for healthy adults, whereas the Linus Pauling Institute recommends that generally healthy adults increase their intake of omega-3 fats by eating fish twice weekly or, in case of lack of regular consumption of fish, a 2 g fish oil supplement several times a week (Linus Pauling Institute, 2014).

What happened in most countries, and especially in western countries, during the past century is that the dietary content of n-6 PUFAs mostly derived from the consumption of vegetable oils, as such or added in almost every commercially prepared food, dramatically increased, whereas the consumption of n-3 PUFAs correspondingly decreased, resulting in unbalanced n-6:n-3 PUFAs ratio of about 15–20:1 whereas the ideal ratio should be 1:1 (Simopoulos, 2002). In brief,
6.5 out of 7 billion people comprising the current world's population do not get sufficient intake of EPA and DHA (Micha et al., 2014). Considering a daily dosage of 250 mg, a daily production of 1625 t of EPA and DHA would be needed, not including the demand of fatty acids by hatcheries. Current yearly production of EPA and DHA enriched oils does not exceed 85,000 t which renders the scope of the effort needed to meet tomorrow’s demand.

This situation has led to the rapid rise of the marine oil omega-3 supplement industry. Today, fish oil is the most popular supplement both in Europe (taken by approximately 20% of adults) and in the US with sales more than doubled worldwide between 2005 and 2012 (O’Connor, 2015). In general, other sources than fish exist which can be advantageously extracted, including algal oil and microbial metabolism of yeast, fungi, or microalgae (de Oliveira Finco et al., 2016). The focus of this study on blue fish is due to the waste of valued oily fish by-products which continues in several fisheries across the world (see below). Only approximately 5% of world fish oil production is used to extract its omega-3 contents for use as food ingredients and food supplements, with the remainder fraction being instead used for fish farming (Lembke, 2013). Hence, increasing the production of omega-3 derived from fishery by-products (only in the process of filleting up to 60% of the fresh fish is cut off and generally treated as waste) by recovering and transferring these important nutrients from the sea to the human food chain is a relevant opportunity to promote economic growth, environmental protection and human health at large.

Investigating progress in fish oil omega-3 extraction, purification and stabilization methodologies, this study provides an overview of this sector of the emerging bioeconomy (Venkata Mohan et al., 2016).

2. New production methods and extract quality

Scheme 1 describes the conventional fish oil omega-3 concentrate production process. Once caught the small blue fish are cooked and pressed still on board the shipping vessel. The water-oil mixture is then separated from the protein by filtration and stored. The solid proteins will become fishmeal.

The omega-3 extraction process starts at industrial sites (Kolanowski, 2005). Here the water is removed from the oil with a 3-phase centrifuge. As mentioned above, most of this oil is then used in aquaculture to ensure that the farmed fish also contain a minimum amount of omega-3 fatty acids. The smaller portion of oil which goes to human consumption undergoes refinement in several consecutive steps including neutralization with alkalis to clear free fatty acids and decrease oil acidity, followed by bleaching to absorb pigments or contaminants, degumming (“winterization”) to separate phospholipids, and deodorization with steam at 160–200 °C to remove smelly compounds. The refined fish oil thereby obtained, known as “18/12TG” (where 18 stands for “18% EPA”, 12 stands for “12% DHA”, and TG stands for “triglyceride”), contains only about 30% omega-3 fatty acids, with the remaining 70% being a varying mixture of other components including cholesterol, omega-6 fatty acids, saturated fatty acids, oxidation products and contaminants (Fig. 2) (Garcia Solaesa et al., 2014).

In general, the fish oil omega-3 industry is increasingly paying attention to quality with efforts undertaken to assure purity and stability of its products. For example, since 2004, a Canada’s testing company manages a third party certification program for fish oils (International Fish Oil Standards) that in ten years has tested and certified more than 1500 fish oil products (from raw material to finished supplements) from 130 companies (Nutrasource Diagnostics, 2014). In 2010, Beltrán and co-workers in Spain, one of the world’s leading countries in fish oil manufacturing, published a thorough review on the production of omega-3 concentrates (generally in omega-3 ethyl ester oil) (Rubio-Rodríguez et al., 2010). Amongst the most researched advances, the team reported extraction with super-
critical carbon dioxide (scCO₂). Latest works identified therein were focusing on obtaining concentrates of omega-3 in their natural form rather than in their ethyl ester form, avoiding at the same time the use of high temperatures and organic solvent. In the following, we describe selected advances in production and stabilization of omega-3 extracts, including the first examples of companies using fish processing waste for the production of valued bioactive compounds.

2.1. Molecular distillation

A first progress occurred about a decade ago when the above mentioned “18/12TG” oil 30% in EPA+DHA was first replaced by 55% omega-3 ethyl ester oil. Triglycerides comprising natural fish oil usually contain one long-chain omega-3 PUFAs bound to one glycerol molecule. Hence, in order to produce extracts of high omega-3 concentration, the omega-3 fatty acids are usually converted into ethyl esters via reaction with ethanol catalyzed by base at 80–90 °C, followed by distillation under ultralow pressure (10⁻⁵ bar) at 140–160 °C.

This molecular distillation (MD) step produces omega-3 ethyl esters (EE) concentrates of about 55% concentration which still are those mostly found at retail stores. Further concentration beyond 55% using MD is possible, but requires special conditions, affording highly concentrated (“pharmaceutical”) fish oil providing 70% active ingredients. For example, the Chinese supplier Fenchem Biotech offers 70% DHA+EPA oil obtained via ultra short residence time during the distillation process carried out under nitrogen (Fenchem, 2011).

2.2. Supercritical fluid extraction and purification technology

A second major advance occurred when Lembke and co-workers at a pharmaceutical company in Spain developed on industrial scale the supercritical fluid extraction (SFE) technology combined with supercritical fluid chromatography (SFC) for the production of highly concentrated omega-3 extracts, in which the SFC step across long chromatographic columns packed with chromatographic silica xerogel eliminates the remaining smelly contaminants in the oil extracted with scCO₂ (Lembke, 2011). Indeed, along with the unoxidised fish oil, SFE involves the co-extraction of volatile compounds in the crude fish oil, such as amines or short chain organic acids, which reduce oil quality by increasing the fishy odor and the overall acidity (Pharma, 2016). The company at which Lembke’s team developed the technology currently operates in Germany one of the largest SFC plant for the production of concentrated omega-3 oils, in which, furthermore, the EPA/DHA composition of the final product can be finely tuned thanks to the unique versatility of the supercritical CO₂-based process. Several other companies in Europe and North America use carbon dioxide in its supercritical state to produce fish oils of high n-3 fatty acids purity, bioavailability and concentration.

2.3. Omega-3 supplements in triglyceride form

A third relevant advance in the field occurred when Kravolec, Barrow and co-workers at a omega-3 oil company based in Canada, developed enzyme-assisted concentration using immobilized Candida antarctica lipase B (CALB) in packed bed reactor for the conversion of the omega-3 ethyl esters back into triglyceride form (Kralovec et al., 2009). The process was industrialized at a new omega-3 plant in Nova Scotia, Canada, in the early 2000s.

The two-step reaction (Scheme 2), carried out at 50 °C, is driven forward by EtOH removal under vacuum. In the first step, the ethyl esters are converted to free fatty acids, followed by esterification with glycerol catalyzed by another immobilized lipase. Beyond being highly active and selective at low temperature, the immobilized lipases are extremely stable with over 80 reaction cycles possible without the need to replace the biocatalyst.

In 2010, Hahn and co-workers in Germany reported that omega-3 in triglyceride form lead to a faster and 70% higher increase in the omega-3 index when consumed as triacylglycerides than when consumed as ethyl esters (Neubronner et al., 2011). Omega-3 ethyl esters indeed are processed in the liver where they releasing ethanol and the free fatty acids. The latter are first converted back into a triglyceride, which is the only form in which they exist in fish and can be metabolized by the human body, and then split again into fatty acids and glycerol in an inefficient process that delays the omega-3 release to the bloodstream. Today, several manufacturers of fish oil supplements commercialize capsules containing the oil with high EPA and DHA concentration in triglyceride form, rather than derivatized as ethyl esters.

2.4. New stabilization methods

The highly unsaturated omega-3 molecules are rapidly oxidised by air’s oxygen in radical processes catalyzed by trace metals and favoured by high temperature and exposure to light. The hydroperoxides initially formed decompose into a variety of radicals which further react with unoxidised PUFAs to form additional hydroperoxides, eventually breaking the fatty acid molecular structure to form secondary oxidation products, such as volatile ketones and alcohols responsible for the bad smell and off-flavours of rancid oil (Cameron-Smith et al., 2015). Hence, the use of antioxidants as well as of protection techniques including microencapsulation is essential to preserve n-3 fatty acids from oxidation. When such protection from oxidation is insufficient, undesirable results are readily observed. For example, analyses carried out in North-America in 2015 on the oxidation levels of omega-3 supplements revealed that around 40% of 171 brands analyzed did not meet voluntary standards for oxidation (Jackowski et al., 2015). On the other hand, similar analyses carried out in 2014 on both percentage and also absolute content of EPA+DHA in a range of Australian products showed that most samples complied with label claim (Nichols et al., 2014).

In their 2010 study, (Rubio-Rodriguez et al., 2010) Beltrán and co-workers were reporting how in the previous decade, natural antioxidants (such as tocophersols, ascorbic acid and rosemary oil) were already used to prevent fish oil lipid peroxidation replacing synthetic (and toxic) phenol antioxidants such as such as butylated hydroxytoluene, butylated hydroxyanisole, tert-butylhydroquinone, and propyl gallate (Rajalakshmi and Narasimhan, 1996). Today, indeed, an increasing number of fish oil supplements are stabilized via addition of natural antioxidants, especially of rosemary extract whose bouquet of phenolic compounds exerts high antioxidant activity with little aroma imparted from the natural antioxidant. For example, menhaden oil protected with Duralox antioxidant (an enhanced rosemary extract comprised of rosemary extract, tocopherols and citric acid in vegetable oil) shows 4–8 times greater stability than the control using respectively 0.20% or 0.40% of antioxidant, when measured by oxidation stability index at 80 °C (Kalsec, 2013).

Microencapsulated fish oil and omega-3 fatty acids enriched foods are equalily efficient for providing these essential fatty acids as fish oil (Christophersen et al., 2016). In other words, long-term intake of food enriched with microencapsulated fish oil can be an efficient way to provide omega-3 fatty acids even with a low daily dose of omega-3 fatty acids, since the bioavailability of omega-3 fatty acids from food products enriched with microencapsulated fish oil is similar to that
of non encapsulated omega-3. Hence, encapsulation in gelatin or in whey gum via complex coacervation is widely used by industry to protect and deliver n-3 fatty acids in a wide range of products including bread, milk, fruit juices, chocolate, yogurt, spreads, peanut butter and even meat, affording high payload and low cost per dose of omega-3 (Kaushik et al., 2015).

State of the art companies use both innovative omega-3 concentration and microencapsulation such as in the case of a plant in Mulgrave, Nova Scotia, where omega-3 concentrates obtained from Peru’s sardines and Ecuador’s tuna oil are microencapsulated in protein-gum arabic (Kralovec et al., 2012).

3. Sustainability

The global production of refined omega-3 extracts from fish oil has gone from 20,000 t in 2001 to 85,000 t in 2009 (Rizliya and Mendis, 2014). Pointing to increasing awareness of the need to protect fish population and ensure bio-diversity, the number of companies certified to comply with sustainability standards which promote responsible and sustainable fishing practices (target stock to be not overexploited, low fishery discards, no bycatch of endangered species, no impact on the seabed, social accountability and gradual reduction of carbon footprint) is increasing.

However, the volume of EPA and DHA oils consumed in 2014 was 84,785 t (Bernasconi, 2014). In 2013, it was 86,208 t, with the decline mainly due to reduced availability of Peruvian anchovy after the Peruvian government in 2014 suspended one of two annual fishing seasons due to concerns about the number and size of the available anchovy. This fact alone reveals that sourcing omega-3 nutrients from fish stocks already endangered by non sustainable fishing may be unsustainable even at current production levels.

To solve the dilemma between increasing demand dictated by intake recommendations and availability of fish stocks, the omega-3 industry should rather start to use the vast amount of the blue fish and seafood industry waste whose leftovers such as head, skin, trimmings and bones are mostly thrown away back into the sea, even though the huge potential of marine processing byproducts for the production of bioactive compounds has been long recognized (Kim and Mendis, 2006). Noticeably, a few companies already collect and recycle fish and seafood leftovers, converting them into valued fish oil and fishmeal. In Japan, one company (Sanki Feed Industry) (See at the URL) collects some 700 t of leftovers per day (from 18,000 stores in Tokyo and 8 adjoining prefectures), which are then converted into fishmeal and fish oil. Another company (Lipromar) (See at the URL) in Germany’s second fishing port (Cuxhaven) buys the byproducts from local fish producers and produces fish oil and functional proteins for human consumption which are sold to omega-3 dietary supplement producers and to the pharmaceutical industry.

It should also be emphasized, as suggested by von Holten (2015) that fish industry by-products today are mostly obtained in factories meeting advanced food quality and safety legislation. This prevents rapid deterioration and adds to the relevance of fish processing waste as raw material of significant economic and health value. The picture in Fig. 3, on the other hand, displays the roads of a small urban centre in Sicily (where several companies process blue fish to produce salted sardines and salted anchovies), invaded by fish oil released as sewage after heavy rain in May 2016 (Rotolo, 2016).

Clearly, those who disposed of fish oil in this unwise manner did it because they are unaware of an existing, and flourishing, fish oil industry. Italy’s flourishing omega-3 industry has apparently been unable to reach out blue fish processing companies in Italy’s largest region to purchase the oily fish by-products and extract valued omega-3 concentrates. Rather than being of anecdotal value, a similar situation exists in most Mediterranean and, in practice, in all African countries.

From a sustainability viewpoint, furthermore, the extraction process based on molecular distillation at ultralow pressures and high temperatures needs to be replaced by milder extraction processes based on green solvents. Beyond the use of scCO2, today affording the best extracts in terms of purity and lack of degradation but requiring high pressures in dedicated plants, microwave-assisted extraction (MAE) with d-limonene, an excellent biosolvent for the extraction of fatty acids, (Virot et al., 2008) is proposed herein as an economically viable alternative. At the end of the extraction, non toxic and highly degreasing d-limonene solvent obtained from citrus peels, (Ciriminna et al., 2014) is fully recovered via hydrodistillation at 97.4 °C (rather than at 175 °C, boiling point of the biosolvent). Furthermore, the short duration of the MAE process (several minutes rather than several hours) today perfectly suited for industrial scale-up, (Ciriminna et al., 2016) minimizes the energy required.

4. Market and health aspects

The omega-3 market, worth € 28 billion in 2015, is expanding at about 5% yearly rate (to add € 5 billion by 2018) (Starling, 2015). Most companies supply omega-3 oil specifying the EPA and DHA percentage, generally in ethyl ester form but increasingly in triglyceride form, to the dietary supplement and functional food and beverage markets. According to 2014 figures provided by the main producer association (Table 1), most of this oil was obtained from anchovies.

The softgel capsule format leads the dietary supplements market both in terms of value and volume, with new formats including chews,

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<th>Fish</th>
<th>% EPA+DHA</th>
<th>Tons</th>
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<tr>
<td>Refined anchovy oils Concentrates</td>
<td>30% (18/12TG, for high level EPA concentrates)</td>
<td>41,600</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>30%</td>
<td>11,200</td>
</tr>
<tr>
<td>Menhaden oil</td>
<td>15–0%</td>
<td>8500</td>
</tr>
<tr>
<td>Salmon</td>
<td>20–24% (0.5/25TG) for high level EPA concentrates</td>
<td>2600</td>
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<td>Tuna</td>
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Fig. 3. Fish oil invading the roads of a small urban centre of Sicily, Aspra, where six companies produce blue fish salted fillets, after heavy rain in May 2016. (Photograph of Alessia Rotolo, reproduced from Rotolo (2016), with kind permission).
gummies and enhanced liquid products. The second product category consists of infant formulas, namely children’s milks and baby food, followed by functional food and beverage products, including margarines, breads, orange juice and even pizza. North America, the EU and Japan were the largest market for omega-3 PUFA in 2014, with India and China projected to be the fastest-growing markets.

To understand the relevance of this market, it is helpful to review the figures of a representative transaction occurred in 2012 when an international manufacturer of natural products based in Europe purchased the above mentioned Canada’s company for $540 million. The company bought had net sales of CAD 190 million (net income of CAD 55–60 million) having grown to about 20% annual rate between 2007 and 2012 DSM, (2012).

Currently more than 30 countries have recommended intakes (mg/day) and various health claims have been approved by different country’s food or health authorities around the world. Russia is the country where the highest intake is recommended (1300 mg/day), followed by France with 500 mg/day. Omega-3 PUFAs reduce the concentrations of prostaglandins 2-series PG, a potent mediator of inflammation and cell proliferation, and increase the synthesis of much less inflammatory 3-series PG (Bagga et al., 2003). In brief, omega-3 nutrients are fundamental hormone precursors which moderate the inherent propensity for arachidonic acid cascade overreactions when n-6 mediators dominate. The efficacy of the tissue to defend itself against oxidative stress depends upon its ω-6:ω-3 composition. High percentage of omega-6 leads to persistent inflammation reinforced by the action of free radical continuously generated. Eventually cells start to proliferate and early signs of chronic disease develop (De Meester, 2009). Being involved in this fundamental biochemical chain, the benefits of fish oil assumption extend to many pathologies, as recent research continues to show. For example, consuming for 6 months fish oil-derived n-3 PUFAs contained in commercial capsules is an effective therapeutic approach for preventing sarcopenia and maintaining physical independence in older adults as it slows the normal decline in muscle mass and function (Smith et al., 2015).

Similarly, a recent meta-analysis investigating the effects of omega-3 supplementation during pregnancy and youth on neurodevelopment and cognition in childhood, based on 15 standard randomized controlled trials (RCTs, Fig. 4) including data from 2525 children (with supplementation lasting 7.3 months on average and cognitive measures were taken around 16 months) led to the conclusions that both maternal and infant supplementation similarly improve child neurodevelopment (Shulkin et al., 2016).

As to the number of RCTs published up to 2015, only aspirin, penicillin, paclitaxel and prednisone have received more attention when compared to omega-3 fatty acids, with more than 81% of the 1863 studies on intervention trials published between 2006 and 2015 pointing to health benefits linked to omega-3 assumptions (Bernasconi, 2016).

The pioneering work of Bang et al. (1971), Dyerberg and Bang (1979), Lands (2005), Ackman (1989), Simopoulos (2002), Galli and Risé (2009) and several other scientists has shown the health relevance of marine oils, whose main omega-3 fatty acid EPA and DHA components provide significant and different benefits for cardiovascular, cognitive, prenatal and maternal health. Clinical research, in the meanwhile, actively continues across the world (Brigham and Women’s Hospital, VITAL: The VITamin D and OmegA-3 Trial, 2015).

5. Outlook and conclusions

Enhancing and improving the extraction, purification and stabilization methods of omega-3 from fish oil is of significant health, environmental and economic importance. First, better extracts and better supplements can be produced increasing the efficacy of the products, benefiting consumers and society. In Europe only, a daily intake of 1000 mg of EPA+DHA food supplementation could prevent 1.5 million cardiovascular disease-attributed hospital events over the subsequent five years (Frost and Sullivan, 2016).

In general, great room for improvement exists. Such progress, we argue, should focus on wide application of sustainability and green chemistry concepts across the industry. One may notice, for example, that improvements in extraction, purification and stabilization methods rely on green chemistry technologies such as supercritical carbon dioxide extraction and chromatography, or the use of immobilized enzymes. Similarly, the use of new (multipurpose) natural antioxidants of broad scope actively protects the PUFAs from oxidation while replacing toxic, synthetic antioxidants. Microwave-assisted extraction using green biosolvents such as d-limonene, we first argued in the study, will also find widespread commercial application.

Advocated since more than a decade, (Kim and Mendis, 2006) the use of fish industry by-products, so far disposed of as waste at high economic and environmental costs, is slowly but inevitably emerging. Again, the use of simple green chemistry processes and methods avoiding the use of toxic solvents, high temperatures and low pressure is poised to replace conventional extraction processes applied to fish processing waste. There are more than 20 million tonnes of fish by-products (discards) available every year from the world’s fisheries.

These advances are urgent, as new health benefits of omega-3 utilization are reported on a continuous base. For instance, researchers based in Island discovered in 2012 and are now industrializing the production of a new laxative formula based on omega-3 fish oil and free fatty acids, which offers parents and pediatricians a pain-free alternative to other pharmaceutical products (Ormarsson et al., 2016).

Companies, and Governments, should proactively act in building new extraction plants based on said sustainable chemistry technologies to extract all bioactive compounds, closing the materials cycle and putting an end to waste generation which creates also considerable environmental pressure when disposed of in landfills or discharged at sea. It is remarkable, in this respect, to learn that not only the German company now extracting bioactive products mentioned above is paying the leftovers suppliers for their raw material, but also that it pays the fish processing waste according to its sustainability profile, paying more if the waste is obtained from companies certified according to sustainability standards such as those managed by the Marine Stewardship Council (MSC) or Aquaculture Stewardship Council (ASC).

Finally, companies extracting omega-3 from fish oil will accompany improvements in sustainability along with advances in the ability to communicate the value of their products given that “linguistically” the industry was recently found “a bit like a street market with hundreds of brands shouting from all sides like someone who is feeling a bit unsure of themselves and overcompensating” (Ereaut, 2016). Altogether, we argue in conclusions, said improvements will make of the sustainable fish-oil based omega-3 sector a pillar of the emerging bioeconomy.

Fig. 4. Hierarchy of evidence in medicine. [Adapted from Bernasconi (2016), with kind permission].
Acknowledgments

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References

(Final Time Accessed 29 December 2016).
In the US For Example, The Large-Scale Randomized the Vitamin D and Omega-3 Trial due to end in 2018 is Currently following more than 25,000 Healthy Men and Women, Looking at the Effect of Both Omega-3 and Vitamin D in Healthy Adults by Taking Real or Placebo Pills over the Course of Five Years. See at the URL: ( vitalsstudy.org).
Linus Pauling Institute, 2014. Micronutrient Information Center, Essential Fatty Acids.
See at the URL: (www.sankishiyou.com).
See at the URL: (www.lipromar.com).