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Review article

Fatty acids from marine lipids: Biological activity, formulation and stability

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ABSTRACT

Cod-liver oil from Atlantic cod (*Gadus Morrhua* L.) and other fish oils are the main source of ω-3 polyunsaturated fatty acids (n-3 PUFAs) such as EPA and DHA that are known to possess numerous of health benefits and, thus, fish oils are commonly used as dietary supplements. Free unsaturated fatty acids (FAs) extracted from fish oils do also possess wide variety of biological effects. Free FAs extracted from cod-liver oil have been shown to possess antibacterial, antifungal and antiviral effect when formulated as water-free ointments and to possess laxative effect when given rectally in suppositories. The free FAs from cod-liver oil can also be used as enabling pharmaceutical excipients that enhance drug permeation through skin and the oral mucosa. Although in some cases these natural free FAs are less potent than many synthetic drugs they are also less likely to cause toxic side effects and this allows for administration of larger doses. Most often the potency of a given biologically active agent is not important per se but rather the therapeutic index of the agent, that is to say the ratio of the dose that causes toxic side effects and the dose producing the desired therapeutic effect.

Contents

1. Introduction

The health benefits of marine lipids containing polyunsaturated fatty acids (PUFAs), especially ω-3 polyunsaturated fatty acids (n-3 PUFAs), have been intensively studied over the past several decades. In general, *in vitro* experiments and studies in animals have consistently shown health benefits while studies in humans have

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; CD, cyclodextrin; PUFA, polyunsaturated fatty acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; MUFA, mono-unsaturated fatty acid; PhEur, European Pharmacopoeia, 8th Edition; SE, standard error; SFA, saturated fatty acids.

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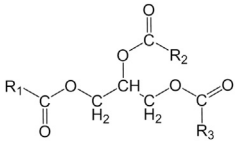
sometimes given mixed results [1–4]. Nevertheless, it is believed that PUFAs can have beneficial effects against wide variety of diseases including cardiovascular diseases [5,6], psychiatric disorders [7], age-related macular degeneration [8], cancer [9], arthritis [10], colitis [11] and pancreatitis [12], some of which are related to the anti-inflammatory effects of the long chain n-3 PUFAs [13–15]. But PUFAs are known to possess other biological effects such as antibacterial, antiviral and antifungal effects [16,17], and they have been shown to have laxative effect when given rectally [18], and to enhance drug permeation through skin [19] and mucosa [20]. These biological effects are frequently associated with specific PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The studies show that PUFAs can be used as enabling pharmaceutical excipients as well as active pharmaceutical ingredients. Following is a short review on the pharmaceutical applications of free fatty acid mixtures extracted from cod-liver oil, their composition, chemistry and biological activities.

2. Chemical stability and stabilization

Fatty acids (FAs) can exist in their free form and as esters in more complex lipids such as triglycerides, phospholipids and glycolipids as well as parts of complex structures such as lipoproteins and lipopolysaccharides. Fish oil mainly consists of mixed triglycerides (>90%) where three fatty acids, of which at least two are different, are bonded via ester linkage to a glycerol backbone. Other ingredients include other lipids (about 8%) such as monoglycerides, diglycerides and phospholipids, and unsaponifiable matter (1.5–2%) such as sterols, glyceryl ethers, fatty alcohols and vitamins A, D and E [19,21]. Cod-liver oil is purified fatty oil obtained from fresh livers of Atlantic cod (*Gadus Morrhua* L.). This is a pale yellowish clear liquid that mainly consists of mixed triglycerides of saturated and unsaturated fatty acids, including long-chain n-3 PUFAs such as EPA and DHA (Table 1). While vegetable oils such as corn oil may contain large amounts of linoleic acid (18:2 n-6) marine lipids such as cod-liver oil contain relatively high concentrations of EPA (20:5 n-3) and DHA (22:6 n-3) and are the major source of n-3 PUFAs. FA triglycerides are hydrolyzed in the small intestine to form free FAs and FA monoglycerides before being absorbed into the general blood circulation and reassembled again as triglycerides [22,23]. PUFAs such as EPA and DHA have somewhat higher oral bioavailability when given as triglycerides than when they are given as free FAs while ethyl esters of EPA and DHA, that are found in many nutritional supplements, have somewhat lower bioavailability [4].

Unsaturated FAs, and particularly PUFAs, are highly susceptible to oxidative degradation, especially in their free (i.e. unesterified) form. The main obstacle in the usage of unsaturated FA in pharmaceutical products is their chemical instability. Free and esterified unsaturated FAs undergo autoxidation, a complex oxidative degradation that proceeds through free radical chain reactions under formation of volatile secondary oxidation products. The radical chain process consists of three steps (Fig. 1) [24,25]. A free radical is formed in the initiation step, frequently through thermal or photochemical hemolytic cleavage of an R-H bond. Atmospheric oxygen is added to the free radical in the propagation step and the peroxyl radical formed extracts hydrogen atom from RH to form another R˙ radical. In the termination step the chain reaction is broken when two free radicals react to form non-radical products. The oxidative rancidity of fat is a form of autoxidation that is catalyzed by oxygen, heat, light and metal ions. The rancidification gives a distinct rancid smell and teste due to formation of volatile aldehydes, ketones and low molecular weight acids. The susceptibility of FA to oxidation increases with increasing degree of

Table 1
Relative amount of fatty acids in cod-liver oil and some vegetable oils. The oils consist mainly of mixed triglycerides where three fatty acids, of which at least two are different, are bonded via ester linkage to a glycerol backbone..



Trivial name of fatty acid (and nomenclature)	PhEur range for cod-liver oil (%)	Cod-liver oil (%) [19]	Portuguese extra virgin olive oil (%) [50]	Corn oil (%) [51]	Fatty acid extract from co-liver oil (%) [19]
Saturated fatty acids (SFAs):					
Myristic acid (14:0)	2.0–6.0	3.6	–	–	3.6
Palmitic acid (16:0)	7.0–14.0	10.5	11.3	11.6	10.4
Stearic acid (18:0)	1.0–4.0	2.6	3.3	1.8	2.6
Mono-unsaturated fatty acids (MUFAs):					
Palmitoleic acid (16:1 n-7)	4.5–11.5	6.5	1.0	–	6.5
cis-Vaccenic acid (18:1 n-7)	2.0–7.0	4.4	–	–	4.4
Oleic acid (18:1 n-9)	12.0–21.0	16.3	76.6	25.2	16.2
Gadoleic acid (20:1 n-11)	1.0–5.5	1.5	–	–	1.6
Gondoic acid (20:1 n-9)	5.0–17.0	9.6	–	–	9.4
Erucic acid (22:1 n-9)	0–1.5	0.6	–	–	0.6
Cetoleic acid (22:1 n-11 (+13))	5.0–12.0	7.7	–	–	7.8
Poly-unsaturated fatty acids (PUFAs):					
Linoleic acid (18:2 n-6)	0.5–3.0	1.6	6.6	59.7	1.5
α-Linolenic acid (18:3 n-3)	0–2.0	Not determined[a]	0.6	0.8	Not determined[a]
Moroctic acid (18:4 n-3)	0.5–4.5	2.4	–	–	2.4
Eicosapentaenoic acid (EPA) (20:5 n-3)[b]	7.0–16.0	9.6	–	–	9.3
Docosahexaenoic acid (DHA) (22:6 n-3)[c]	6.0–18.0	12.5	–	–	11.9

[a] Not determined but cod-liver oil usually contains less than 1% α-linolenic acid.
[b] Timnodonic acid (PhEur).
[c] Cervonic acid (PhEur).