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Review

Membrane composition and dynamics: A target of bioactive virgin olive oil constituents☆

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ABSTRACT

The endogenous synthesis of lipids, which requires suitable dietary raw materials, is critical for the formation of membrane bilayers. In eukaryotic cells, phospholipids are the predominant membrane lipids and consist of hydrophobic acyl chains attached to a hydrophilic head group. The relative balance between saturated, monounsaturated, and polyunsaturated acyl chains is required for the organization and normal function of membranes. Virgin olive oil is the richest natural dietary source of the monounsaturated lipid oleic acid and is one of the key components of the healthy Mediterranean diet. Virgin olive oil also contains a unique constellation of many other lipophilic and amphipathic constituents whose health benefits are still being discovered. The focus of this review is the latest evidence regarding the impact of oleic acid and the minor constituents of virgin olive oil on the arrangement and behavior of lipid bilayers. We highlight the relevance of these interactions to the potential use of virgin olive oil in preserving the functional properties of membranes to maintain health and in modulating membrane functions that can be altered in several pathologies. This article is part of a Special Issue entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

Contents

Abbreviations: ABCA1, ATP-binding cassette sub-family A member 1; AD, Alzheimer's disease; apoB48, apolipoprotein B-48; APP, amyloid precursor protein; BCMO1, β-carotene 15,15′-monooxygenase; BLAOA, bovine α-lactalbumin complexed with oleic acid; CD36, cluster of differentiation 36; ER, endoplasmic reticulum; FABPpm, plasma membrane fatty acid-binding protein; FAs, fatty acids; FAT, fatty acid translocase; FATP, fatty acid transport protein; GAP43, growth associated protein-43; GH, growth hormone; GHSR, GH secretagogue receptor; GLUT, glucose transporter; GPCRs, G-protein-coupled receptors; HAMLET, human α-lactalbumin made lethal to tumor cells; HDLs, high-density lipoproteins; HER2, human epidermal growth factor receptor 2; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; 5-HT_{7A}, 5-hydroxytryptamine 7A; INSIG1, insulin-induced gene 1; InsP3, inositol 1,4,5-triphosphate; LDLs, low-density lipoproteins; MAP2, microtubule-associated protein-2; MUFAs, monounsaturated fatty acids; NF-κB, nuclear factor-κB; NeuroD2, neuronal differentiation protein-2; NPC1L1, Niemann–Pick C1-Like1; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PLCβ1α/β, phospholipase Cβ1; ROS, reactive oxygen species; SCAP, SREBP cleavage-activating protein; SFAs, saturated fatty acids; SLC2, solute carrier member 2; SREBPs, sterol regulatory element-binding proteins; StARD3, StAR-related lipid transfer domain protein 3; PUFAs, polyunsaturated fatty acids; SCD1, stearoyl-CoA desaturase 1; TRPA1, transient receptor potential A1; UBX, ubiquitin-like; UBXD8, UBX-domain-containing protein 8; VLDLs, very-low-density lipoproteins

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1. Introduction

Virgin olive oil plays a pivotal role as the main source of fat in the Mediterranean diet, a diet that has traditionally been linked to longevity in Mediterranean populations and is associated with a significant improvement in health status, as measured by reduced mortality from several chronic diseases [1–8].

More than 90% of olive oil is formed in the mesocarp of the drupe from the fruit of the olive tree (*Olea europaea* L.). Virgin olive oil (for olive oil classification and definitions see Ref. [9]) is obtained exclusively from fresh and healthy olives by physical procedures under low thermal conditions (<27 °C) and is the only edible fat that can be consumed as a natural fruit product with no additives or preservatives. Spain is by far the largest producer of virgin olive oil in the world, accounting for approximately 50% (~1,600,000 tons) of total global production in 2012 [10]. More recently, due to the increasing recognition of the unique health properties of virgin olive oil, interest in virgin olive oil production has extended to countries outside the Mediterranean region, such as western Africa, Argentina, Australia, Azerbaijan, Brazil, China, India, Japan, Mexico, New Zealand, South Africa, and the USA.

The main bioactive constituents of virgin olive oil include monounsaturated oleic acid and a variety of compounds present in lower quantities ("minor constituents") [3,4,9,11–15; and references within the manuscript]. Almost all fatty acids (FAs) exist as a complex in the form of triacylglycerol, an ester derived from glycerol and 3 FAs (saponifiable fraction, >98%). The triacylglycerol content of virgin olive oil is responsible for its hydrophobicity. The minor constituents (unsaponifiable fraction, up to 1.5%) contribute to the specific properties of virgin olive oil, including its oxidative stability and unique flavor, as well as its color (the pigments in virgin olive oil include carotenoids and chlorophylls).

Cells can simultaneously acquire or import a spectrum of precursors through endocytosis of circulating lipoproteins of endogenous or exogenous (dietary) origin, which affects the biogenesis and remodeling of membranes. In this review, we will address the impact of the bioactive constituents of virgin olive oil on the modulation of membrane composition and function in the context of health and disease, as well as the potential therapeutic applications of these bioactive constituents.

2. Virgin olive oil: major and minor bioactive constituents

2.1. Oleic acid

FAs are carboxylic acids and often contain a long, unbranched aliphatic chain. FAs are categorized as saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA), based on their structural and chemical properties. SFAs do not contain any double bonds or other functional groups along the chain, which is fully saturated with hydrogen atoms. The principal dietary SFAs are palmitic (16:0) and stearic (18:0) acids, which are composed of 16 and 18 carbon atoms, respectively. MUFAs contain one pair of carbon atoms linked by a *cis* double bond. Oleic acid (18:1n − 9), which contains 18 carbon atoms with a double bond at the 9th carbon from the methyl end of the FA molecule, is the major dietary MUFA and represents 55 to 83% of the total FAs in virgin olive oil (Table 1). Carbon chains containing 2 or more *cis* double bonds, with the first double bond located between either the 3rd and 4th or the 6th and 7th carbon atoms from the methyl end of the FA molecule, belong to the n − 3 or n − 6, respectively, PUFA families. These families cannot be synthesized by the human body (double bonds can be introduced into all positions of the FA chain with the exception of the n − 3 and n − 6 positions) and therefore must be obtained from the diet as α-linolenic acid (18:3n − 3) and linoleic acid (18:2n − 6) or their long-chain PUFA derivatives. Of these FAs, eicosapentaenoic acid (20:5n − 3), docosahexaenoic acid (22:6n − 3), dihomo-γ-linolenic acid (20:3n − 6), and arachidonic acid (20:4n − 6) are the most metabolically significant. The concentrations of SFAs (palmitic + stearic acids) and PUFAs (α-linolenic + linoleic acids) in virgin olive oil range from 8 to 25% and from 3 to 21% of the total FAs, respectively. Some parameters, such as the area of production, altitude, climate, fruit variety, and stage of maturity of the fruit can greatly affect the FA composition of virgin olive oil [16].

Oleic acid is the primary component of virgin olive oil (~83% oleic acid in position *sn* − 2 of the triacylglycerols) and is also found in peanut oil (~59% oleic acid in position *sn* − 2 of the triacylglycerols) and canola oil (~37% oleic acid in position *sn* − 2 of the triacylglycerols). However, stearoyl-CoA desaturase 1 (SCD1, similar to the mouse orthologue *mScd1*), which is anchored in the endoplasmic reticulum (ER) of hepatocytes and adipose tissue cells [17], plays a central role in partitioning endogenous and exogenous (dietary) FAs into metabolically active or inactive pools and is the rate-limiting enzyme for the biosynthesis of MUFAs (mainly oleic acid) from SFAs. SCD1 catalyzes the insertion of a *cis* double bond into the 9th carbon atom of palmitic and stearic acids. Oleic acid is a key component of triacylglycerols and membrane lipids [18]. Importantly, oleic acid is the most common FA in nature, as well as in our diet (generally, oleic acid supplies an amount of calories equivalent or greater than the amount provided by SFAs and

Table 1
Chemical structure and range of major fatty acids in virgin olive oil.

Fatty acid	Regulations[a] (%)
16:0, palmitic acid	7.5–20.0
16:1n − 7, palmitoleic acid	0.3–3.5
18:0, stearic acid	0.5–5.0
18:1n − 9, oleic acid	55.0–83.0
18:2n − 6, linoleic acid	3.5–21.0
18:3n − 3, α-linolenic acid	≤1.0
MUFAs, monounsaturated fatty acids	53–87
SFAs, saturated fatty acids	8–26
PUFAs, polyunsaturated fatty acids	3–22

[a] International Olive Oil Council (www.internationaloliveoil.org).