Bioactive lipids: Chemistry, biochemistry, and biological properties

Ana Sofia Salsinha[a,b,1], Manuela Machado[a,1], Luís Miguel Rodríguez-Alcalá[a], Ana Maria Gomes[a], Manuela Pintado[a,*]

[a]Universidade Católica Portuguesa, CBQF - Centro de Biotecnologia e Química Fina – Laboratório Associado, Escola Superior de Biotecnologia, Rua de Diogo Botelho, 1327, 4169-005, Porto, Portugal

[b]Instituto de Investigação e Inovação em Saúde and Instituto de Biologia Molecular e Celular (IBMC), Rua Alfredo Allen, 208 4200-135, Porto, Portugal

[1]Both authors contributed equally.

*Corresponding author:

mpintado@ucp.pt

Escola Superior de Biotecnologia Universidade Católica Portuguesa | Porto

Rua de Diogo Botelho, 1327 12 4169-005 Porto, Portugal

Tel.: +351 225580097

Mobile: +351 9333095043

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Abbreviations

Alpha-linolenic acid (ALA); Conjugated Linoleic acid (CLA); Conjugated linolenic acid (CLNA); Docosahexaenoic acid (DHA); Docosapentaenoic acid (DPA); Eicosapentaenoic acid (EPA); High-density lipoprotein (HDL); histone deacetylase (HDAC); Linoleic acid (LA); Long-chain fatty acid (LCFA); Low-density lipoprotein (LDL); Medium-chain fatty acid (MCFA); Medium-chain triglyceride (MCT); Monounsaturated fatty acid (MUFA); Nuclear factor κB (NFκB); Polyunsaturated fatty acid (PUFA); Punicic acid (PUA); Short-chain fatty acid (SCFA)

1. Introduction: lipids' basic chemistry

Historically, during an extended period, lipids were only considered as a source of energy, and the basic component of cell membranes (W. Stillwell, 2016). Over the last years, many other functions have been studied and their importance in our health is now well established. From the chemical viewpoint, lipids are commonly defined as hydrophobic substances that are soluble in organic solvents but insoluble in water (Carrasco-Pancorbo et al., 2009; B. Chen et al., 2012). The main important lipid molecules include triglycerides and their metabolites (mono- and diglycerides and fatty acids), phospholipids, sphingolipids, ceramides and sterols.

Concerning the triglycerides and their derivatives, the chemical structure is mainly determined by the binding of fatty acids to glycerol by ester linkages (Valenzuela, 2012). The reaction of one hydroxyl group of glycerol, at any of its positions, with a fatty acid gives rise to a monoglyceride (Valenzuela, 2012). The linking of a second fatty acid, which may be similar or different from the existing fatty acid, gives rise to a diglyceride. Finally, when all three hydroxyl groups of glycerol are linked by fatty acids, the structure is identified as a triglyceride (Valenzuela, 2012). Phospholipids have different structural and functional properties. This is because the sn-1 and sn-2 positions of the glycerol fraction are occupied by fatty acids, most often polyunsaturated fatty acids, linked to glycerol by ester bonds. The sn-3 position of glycerol is linked to orthophosphoric acid (Fahy et al., 2005; Valenzuela, 2012).

1.1. Fatty acids

Fatty acids, as part of molecules, have diverse functions in cells that range from structural "building blocks" of cell membranes, to suppliers of energy and signaling molecules. The fatty acids in cells can either derive from exogenous sources or from *de novo* fatty acids synthesis. In some cases, organisms such as humans, require certain physiologically essential fatty acids compounds from the diet, namely linoleic and linolenic acids. Such designation derives from the fact that such polyunsaturated fatty acids cannot be synthesized *de novo* or cannot be synthesized in sufficient quantities to meet the organism demands for general metabolic functioning, somatic growth and reproduction (De Carvalho & Caramujo, 2018). Fatty acids are classified according to the presence or absence of double bonds: saturated (no double bonds), monounsaturated (one double bond), and polyunsaturated fatty acids, with two or more double bonds (Orsavova et al., 2015).

1.1.1. Short-chain fatty acids

Short-chain fatty acids (SCFAs) can be produced naturally through host metabolic pathways, being the colon the major site of production (Tan et al., 2014). Humans lack the necessary enzymes to degrade the bulk of dietary fibers. In consequence, the non-digestible carbohydrates go through the upper gastrointestinal tract and are fermented in the intestine by the anaerobic cecal and colonic microbiota. This fermentation process results in metabolites, of which SCFAs are the major group. The most general pathway of SCFA production in bacteria is via the glycolytic pathway, although other metabolic pathways can be used; for example the *Bifidobacterium* genus can use the pentose phosphate pathway instead (Tan et al., 2014). These fatty acids are necessary to the intestinal microbiota to balance redox equivalent production in the anaerobic environment of the gut (den Besten et al., 2013).

Chemically, SCFAs are carboxylic acids defined by the presence of an aliphatic tail of 2 to 6 carbons, being acetate (C2), propionate (C3) and butyrate (C4) the major (≥95%) SCFAs involved in mammalian physiology (Cook & Sellin, 1998).

1.1.2.Medium-chain fatty acids

Medium-chain fatty acids (MCFAs) are saturated or unsaturated fatty acids, which present 6 to 12 carbon atoms. Caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0) and lauric acid (C12:0) are examples of MCFAs.

MCFAs are commonly found in medium-chain triglycerides (MCTs) since the latter contain MCFAs esterified to the glycerol backbone. Those triglycerides are often completely hydrolyzed to yield free fatty acids by lipases that are present in the gastrointestinal tract. When absorbed directly, MCTs enter the blood circulation and are carried to the liver where they are oxidized to ketones (R. E. Aluko, 2012). Compared with the triglycerides containing long-chain fatty acids, MCTs have a lower melting point, smaller molecular size and provide slightly lower energy (8.4 versus 9.2 kcal/g) and are liquid at room temperature (Marten & Ã, 2006).

1.1.3.Long-chain fatty acids (Unsaturated fatty acids)

Long-chain fatty acids (LCFAs) are fatty acids with 14 or more linearly arranged carbon atoms, and may be saturated, having no double bonds, or unsaturated, having one or more double bonds.

Unsaturated fatty acids contain one or more carbon atom in a double bond, being the three major types: monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and *trans* fatty acids. The unsaturated fatty acids may exist in a *cis (c)* or *trans (t)* configuration. The *cis* configuration is found in most naturally unsaturated sources, the *trans* configuration results from technological processing, such as hydrogenation (Bozza & Viola, 2010; Orsavova et al., 2015).

1.1.3.1. Monounsaturated fatty acids

MUFAs include palmitoleic (C16:1 *c*9), oleic (C18:1 *c*9), elaidic (C18:1 *t*9) and vaccenic acids (C18:1 *c*11), being oleic acid (C18:1 *c*9) the most abundant MUFA in the diet (Assy et al., 2010). Considering that they can be synthesized in the body, they are not essential dietary lipids.

1.1.3.2. Polyunsaturated fatty acids

PUFAs are unsaturated fatty acids with two or more double bonds and their classification depend on the position of the first double bond relative to the methyl-end group. Therefore they can be subdivided into two groups: omega-6 (meaning that the double bound is 6 carbon atoms away from the terminal methyl group) and omega-3 fatty acids (meaning that the double bound is 3 carbon atoms away from the terminal methyl group). Omega-3 and omega-6 PUFAs are synthesized from the essential fatty acid alpha-linolenic acid (ALA) (C18:3 *c*9,*c*12,*c*15) and linoleic acid (LA) (C18:2 *c*9,*c*12), respectively. Humans and animals can metabolize these essential fatty acids to long-chain derivatives. Nevertheless, these precursors, ALA and LA, cannot be synthesized in the human body. Moreover, the human body cannot synthesize PUFAs with the first C3 and C6 double bonds from the methyl-end due to the lack of appropriate enzymes (Δ12 and Δ15 desaturases) (Brenna et al., 2009; Burdge & Wootton, 2002; Mišurcová et al., 2011; Orsavova et al., 2015; Proust et al., 2014). Therefore, they have to be obtained through dietary sources (Ander et al., 2003). In addition, omega-6 and omega-3 pathways compete with one another for enzyme activity. Therefore, considering these questions, the balance of omega-6 to omega-3 obtained through diet is very important to human health, since an overabundance of one type of fatty acids will interfere with the metabolic production of the other type and even limit it. Dietary recommendations toward a healthy lifestyle state a favourable omega-6:omega-3 ratio of 4:1.

The most important omega-6 fatty acids are LA, its conjugates, and arachidonic acid. Arachidonic acid can be synthesized by the conversion of LA after desaturation and elongation reactions (B. Chen et al., 2012).

In the case of conjugated linoleic acid isomers (CLA), this is a group of linoleic derivatives containing twenty-eight positional and geometric isomers (Pariza et al., 2001). It is normally found in dairy products and can be synthesized by partial hydrogenation or alkali isomerization of LA (B. Chen et al., 2012). Concerning CLA, the most studied isomers are *cis*-9, *trans*-11 (*c*9,*t*11 - rumenic acid), and *trans*-10, *cis*-12 (*t*10,*c*12), which belong to omega-7 and omega-6 PUFAs, respectively (Nornberg, 2016).

Arachidonic acid, for instance, is extremely important in brain and neural tissues, particularly up to two years of age (B. Chen et al., 2012). It is also an important signaling molecules precursor, including eicosanoids, prostaglandins, leukotrienes and lipoxins. Although it can be synthesized by the conversion of LA, its production rate from this fatty acid is low. Consequently, a daily intake of food rich in arachidonic acid has been recommended, especially in infants (B. Chen et al., 2012; Kelley et al., 1997).

ALA is important for cell membranes integrity, for energy production (in many cells and tissues), for adipose tissue and it is particularly important for conversion in long-chain omega-3 fatty acids (Baker et al., 2016). For instance, ALA is desaturated and elongated within the human body to yield Eicosapentaenoic acid (EPA) (C20:5 *c*5,*c*8,*c*11,*c*14,*c*17), Docosapentaenoic acid (DPA) (C22:5 *c*7,*c*10,c13,c16,c19) and Docosahexaenoic acid (DHA) (C22:6 *c*4,*c*7,*c*10,*c*13,*c*16,*c*19) (R. E. Aluko, 2012). EPA and DHA (as well as DPA) are metabolically related. Indeed, there is one pathway where EPA can be synthesized from ALA. The enzymes involved in such metabolic processes, regarding omega-3 fatty acid interconversion metabolism, are shared with the analogous omega-6 fatty acid pathway of conversion of LA to arachidonic acid (Calder, 2017).

1.2. Sterols

Sterols are derived from a common structural precursor, esterane or cyclopentanoperhydrophenanthrene, which consists of a four aromatic rings main structure, identified as rings A, B, C and D (Valenzuela, 2012). All sterols have at carbon 3 of the A ring a polar hydroxyl group, and the remaining structure is non-polar. Such structure confers them an amphiphilic nature. Sterols also present a double bond on carbons 5 and 6 of ring B (Fahy et al., 2005; Izar et al., 2011; Valenzuela, 2012). This double bond can be saturated (reduced), which leads to the formation of stanols. In carbon 17 (ring D), both sterols and stanols have attached an aliphatic group, consisting of a linear structure of 8, 9, or 10 carbon atoms, depending on whether the sterol is of animal origin (8 carbon atoms) or vegetable origin (9 or 10 carbon atoms) (Valenzuela, 2012). Sterols are an important constituent of all eukaryotic cells and play an important role in many cell functions, such as regulation and modulation of membrane-bound proteins (Jaramillo-Madrid et al., 2019).

2. Bioactive Lipids: biological properties and dietary sources

2.1. What are bioactive lipids?

Bioactive lipids are products of lipid metabolism which are involved in signalling processes in every cell of every organism. They are important in signal transduction and biological effects, playing, thus, active roles in regulating cellular functions such as homeostatic regulation of energy metabolism, of the cardiovascular system, strength, behavior, among other functions. These benefits come as a result of modification in tissue fatty acid composition or induction of cell signaling pathways. Nevertheless, variations in their levels can lead to pathophysiological consequences (Alhouayek & Muccioli, 2017; W. Stillwell, 2016). The term bioactive lipids can include fatty acids, phospholipids, sphingolipids, sterols and ceramides. This chapter will focus essentially on fatty acids and sterols. These compounds have important benefits in our health, including the reduction of cardiovascular diseases, the improvement of cognitive development and visual acuity, as well as anti-inflammatory and anti-atherosclerosis effects (Table 1).

[Table 1 near here]

In this chapter the most important bioactive lipids, such as MUFAs and PUFAs, SCFAs, namely butyric acid, and some MCFAs are going to be discussed. Their major dietary sources and biological role, focused on a human health perspective, are going to be presented. This first chapter intends to be an introduction to the themes that are going to be discussed throughout the book, thus the topics are going to be introduced and later deepened in the corresponding chapter.

2.2. Fatty acids

2.2.1. Short-chain fatty acids

It is well known that the development of the intestinal ecosystem is crucial for not only many gastrointestinal functions but to body health in general. In this context, SCFAs, which are produced by intestinal microbiota, present a significant role. The major products from the microbial fermentative activity in the gut are acetate (C2), propionate (C3) and butyrate (C4) (Cummings et al., 1987; Geisler et al., 2015; Morrison & Preston, 2016; Rowland et al., 2018). Those SFAs are mainly produced in the colon with a concentration of 60, 25 and 15%, respectively (R. E. Aluko, 2012). These SCFAs are involved in different processes in gastrointestinal digestion, such as electrolyte and water absorption (Vinolo et al., 2011). Cheese, butter, alcoholic beverages, pickles, sauerkraut, soy sauce and yoghurt are fermented foods made by bacterial fermentation, which makes them highly enriched in SCFAs. In fact, vinegar and alcoholic beverages contain acetate, cheese contains propionate and butyrate, and butter contains butyrate (Shimizu et al., 2019).

As mentioned, an important SCFA with relevant human health benefits is butyrate. Butyrate, commonly found in dairy fat, is one of the main by-products of fiber fermentation in the colon since it is synthesized from non-absorbed carbohydrates by colonic microbiota (Canani et al., 2011). The luminal pH value in the proximal colon is low, due to the increasing concentration of acidic fermentation products. This low pH value seems to perform an essential role in the formation of butyrate. The ability to produce butyrate is widely distributed among the Gram-positive anaerobic bacteria that are present in the human colon (Canani et al., 2011). The acidic pH values allow butyrate-producing bacteria to compete against Gram-negative carbohydrate-utilizing bacteria, such as *Bacteroides spp* (Guilloteau et al., 2010). The beneficial effects of butyrate are well characterized at the intestinal level since it plays a regulatory role on the transepithelial fluid transport: butyrate absorption has a significant impact on the absorption of NaCl and the electrolyte balance, in general (Kunzelmann & Mall, 2002). Besides, it shows stimulatory effects on normal colonic cell proliferation and has been used as a substrate used for both growth and regeneration of cells in the large and small intestine (R. Aluko, 2012; Rodríguez-

Alcalá et al., 2017; Rowland et al., 2018; Steliou et al., 2012). On the other hand, it can inhibit the growth and proliferation of colon cancer cell lines. As reviewed by Canani et al, (Canani et al., 2011), its role in the protection against colorectal cancer has been widely supported. Indeed, some *in vitro* studies with carcinoma cell lines, have suggested that the anti-colon cancer properties are achieved through enhanced apoptosis of mutant colonic cells and inhibition of proliferation (growth and migration) (Wenqi Wang et al., 2020).

Moreover, butyrate is known to ameliorate mucosal inflammation and oxidative status. This SCFA can reinforce the epithelial defense barrier and modulate visceral sensitivity and intestinal motility (Canani et al., 2011). The anti-inflammatory potential shown by butyrate has been primarily attributed to its ability to inhibit nuclear factor κB (NFκB) activation in human colonic epithelial cells (Inan et al., 2000). NFκB is a known regulator of several immune-inflammatory response genes. The importance of such anti-inflammatory role, associated with NFκB regulation (Canani et al., 2011), has been widely studied in several diseases, such as colon cancer (J. Chen & Vitetta, 2018; Pikarsky et al., 2004) and inflammatory diseases: inflammatory bowel disease (Aden et al., 2019), ulcerative colitis (C. Lee et al., 2017; Simeoli et al., 2017) and Crohn's disease (Di Sabatino et al., 2007).

At the extra-intestinal level, butyrate interest relies on its role in genetic metabolic diseases, hypercholesterolemia, insulin resistance and ischemic stroke. Many of butyrate's biological mechanisms rely on its potent regulatory effects on gene expression since it is an histone deacetylase (HDAC) inhibitor (Canani et al., 2011). In fact, it can directly activate G-coupled-receptors, therefore inhibiting HDACs and serve as energy substrate. HDAC can remove acetyl groups in histones. This is highly relevant since histone acetylation is thought to increase the accessibility of the transcriptional machinery to promote gene transcription. Besides butyrate, propionate is also known as a HDAC inhibitor. Indeed, HDAC inhibitors have been widely used for cancer therapy and present anti-inflammatory or immune-suppressive functions. Such inhibition results in the regulation of gene expression and the control of cell fate. Since some SCFAs present a potential to modulate gene expression, it is easily understood how they affect different physiological processes playing an important role in both health and disease (Koh et al., 2016).

Regarding hypercholesterolemia, after the liver, the intestine is the most important site of cholesterol biosynthesis since it accounts for 10% of the total amount of cholesterol biosynthesis per day. In hypercholesterolemia, when cholesterol biosynthesis is suppressed in most organs by fasting, the intestine becomes the major site of cholesterol biosynthesis and its contribution can increase up to 50%. Recent studies showed that butyrate can downregulate the expression of nine key genes that are involved in intestinal cholesterol biosynthesis inhibiting this pathway (Alvaro et al., 2008).

Furthermore, propionate and butyrate activate intestinal gluconeogenesis by the gut-brain neural circuit, thereby promoting benefits on body weight and glucose control (Kasubuchi et al., 2015). Acetate has a positive impact on the appetite reduction, explained by the changes in the expression profiles of the appetite regulatory neuropeptides through the activation of the tricarboxylic acid cycle (Frost et al., 2014; Kasubuchi et al., 2015). Also, dietary supplementation with butyrate was shown to prevent and ameliorate diet-induced obesity symptoms and insulin resistance in rodent models. Butyrate acts by promoting energy expenditure and by inducing mitochondrial function.

Several investigations showed promising beneficial effects of butyrate by oral administration. Indeed, there are some butyrate-based products commercially available, mostly pharmaceutical products. Such products are commercialized in capsules with micro-encapsulation of butyrate. In addition, ethyl butyrate and butyl butyrate, esters synthesized by reacting ethanol

and butanol, respectively, with butyrate, are used in food industry as artificial flavoring. However, the main problem is the availability of butyrate formulations that can be administered orally and the unpleasant taste and odor, which makes this route of administration more difficult, especially in children.

2.2.2.Medium-chain fatty acids

MCFAs are naturally found in coconut oil, with lauric acid (C12:0) representing on its own around 50% of coconut oil fat content (Xiang et al., 2019). High contents of lauric acid (41 to 55%) can also be found in palm kernel oil (Zentek et al., 2011) (table 3).

[Table 3 near here]

Abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein (HDL) cholesterol, hypertension and high fasting glucose levels are widespread and increasingly prevalent in industrialized countries, resulting in medical and socioeconomic problems. Such diseases are collectively defined as metabolic syndrome, which is in turn responsible for increasing cardiovascular morbidity and mortality. Although the exact details of metabolic syndrome are complex and not fully understood, besides lifestyle aspects, it has been widely suggested that the quality of dietary lipids are important modulators of this set of diseases (Nagao & Yanagita, 2010). As reviewed by Nagao and Yanagita, (2010) dietary MCFAs/MCTs suppress fat deposition through enhanced thermogenesis and fat oxidation in animal and human subjects, when compared to LCFAs rich-diets (Dong et al., 2011; Mumme & Stonehouse, 2015; St-Onge et al., 2003). Accordingly, MCTs have been suggested as important tools on weight management. A meta-analysis published by Karen Mumme and Welma Stonehouse (2015) compared the effect of MCTs and long-chain triglycerides in weight loss and concluded that MCTs have a positive effect on weight management and energy expenditure, although the mechanism of action is not sufficiently clear (Pgdipsc & Stonehouse, 2015). Among the possible mechanisms, in white adipose tissue, MCTs can activate the hormone-sensitive lipase and downregulate fatty acid synthase, which leads to lipolysis and reduced fat accumulation, respectively (R. Aluko, 2012). Other studies have demonstrated that MCTs reduced body mass index, hip circumference, waist-hip ratio, total abdominal, visceral and body fat mass, and waist circumference and increased the satiety (R. Aluko, 2012; Kurano et al., 2018; St-Onge & Jones, 2002). Besides, they can ameliorate insulin sensitivity in animal models and patients with type 2 diabetes (M.-E. Wang et al., 2017; Wein et al., 2009). Indeed, epidemiologic studies suggest that diets rich in MCFAs may prevent type 2 diabetes and cardiovascular disease (Airhart et al., 2016).

In addition to such health effects, studies with coconut oil have revealed that it possesses as much as 90 and 80% of antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, respectively (Khoramnia et al., 2013). This antimicrobial potential has been attributed to the high contents of lauric acid in this oil. Besides, a high antibacterial effect of MCFAs against *Enterococcus faecalis*, *Mycobacterium terrae*, *Streptococcus agalactiae* and *Listeria monocytogenes* was also described (Nagao & Yanagita, 2010; Vázquez et al., 2017). Indeed, among MCFAs lauric acid and its derivatives have been demonstrated as the most effective antimicrobial agents, for both food and cosmetic products. Such antimicrobial mechanism is suggested to be related with an increase of cell membrane fluidity by the MCFAs leading to its disruption (Anzaku et al., 2017; Sado-Kamdem et al., 2009).

Despite their promising results, MCT oils have limitations in their use as cooking oils. Due to the presence of MCFAs, these oils present lower smoke points than those containing LCFAs. This is highly relevant since the smoke point is a useful indicator of an oil or fat's suitability for frying. A general rule is that, fats with a higher smoke point are better suited for deep frying, whilst fats with a smoke point below 200 °C are not (Boateng et al., 2016). One

294 solution may be the development of oils with triglycerides combining MCFAs and LCFAs
295 esterified to the glycerol backbone: medium and long-chain triglycerides (R. E. Aluko, 2012).

2.2.3. Long-chain fatty acids (Unsaturated fatty acids)

2.2.3.1. Monounsaturated Fatty Acids

Dietary MUFAs are biologically active and have been claimed to have various health effects, for instance, anti-apoptotic, anti-inflammatory, hypocholesterolemic and atherogenesis risk reduction effects (B. Chen et al., 2012; Lopez-Huertas, 2010; Orsavova et al., 2015; Sales-Campos et al., 2013). This type of lipids are found in a variety of food (e.g. nuts and avocado) and oils (e.g. olive oil, safflower oil, peanut oil, and corn oil) (table 3) (Eshak et al., 2018). MUFAs have shown to reduce key risk factors for metabolic syndrome. They promote a healthy blood lipid profile, mediate blood pressure, and favorably modulate insulin sensitivity and glycemic control (Gillingham et al., 2011).

Oleic acid (C18:1 *c*9) is the most representative MUFA in the diet (≈90% of all MUFAs) and is found in various dietary products, for example, olive fruit, vegetable oils, and eggs (Kris-Etherton, 1999). Many health benefits are attributed to oleic acid, particularly the positive impact on the cardiovascular system, mainly the maintenance of LDL-cholesterol levels below risk levels and normal blood triglycerides and glucose concentrations (Kris-Etherton, 1999; Sikand et al., 2015; WHO, 2003). Moreover, many studies demonstrated the positive effect of this fatty acid in other pathologies, such as Alzheimer's and colorectal and breast cancers (R. Aluko, 2012; Y. S. Park et al., 2006).

As reviewed by Gillingham et al, (Gillingham et al., 2011) several randomized trials showed that when there is an isocaloric replacement of SFA for MUFA in the diet there are improvements in the total cholesterol to HDL cholesterol ratio, namely associated with a decrease in the serum low-density lipoprotein (LDL) cholesterol levels and preservation of HDL cholesterol levels. The preservation or even increasing of HDL cholesterol levels confer cardioprotective activities to MUFA (Ashton et al., 2001; Berglund et al., 2007; DiNicolantonio & O'Keefe, 2018; European Food Safety Authority (EFSA), 2010; Gillingham et al., 2011; Grundy, 1989). Besides, high MUFA diets showed significant reduction in triacylglycerol levels. Human clinical studies have shown that MUFA present either neutral or hypotensive effects when compared to diets rich in carbohydrates. Moreover, consistent reductions in blood pressure is seen when MUFA diets are compared to saturated fatty acid rich diets (Gillingham et al., 2011). In addition, the hypotensive effect provided by oleic acid from olive oil also alleviated the need of anti-hypertensive drug therapy by 48% (Alonso et al., 2006; Ferrara et al., 2000; H. Lee et al., 2019; Miura et al., 2013).

Type 2 diabetes is the main type of diabetes and is characterized as being a result of a high demand of insulin synthesis in pancreatic β-cells caused by hypercaloric diets and lifestyle conditions, such as the lack of physical activity which produces insulin resistance in the liver and insulin-dependent tissues, namely adipose tissue and muscle (Acosta-Montaño & García-González, 2018). Besides the detrimental effects that a hyperglycemic condition can generate and present in diabetes development, chronic exposure to high levels of free fatty acids leads to lipotoxicity (Harding et al., 2001). As reviewed by Acosta-Montaño and García-González, (Acosta-Montaño & García-González, 2018) high levels of free fatty acids have been proposed as a determinant factor in β-cells apoptosis in different models, since prolonged exposure of this cells to FFAs leads to inhibition of insulin biosynthesis, and secretion. Furthermore, palmitic exposure, more specifically, inhibits the expression of determinant factors in insulin pathway, such as the expression of transcription factors PDX-1, which plays a key role in pancreatic development and islet, and in key glucose transporters (e.g. GLUT2). In high-fat diets, adipose tissue storage capacity for triacylglycerols can be overloaded. Lipotoxicity describes the deleterious effects that lipid accumulation can cause in peripheral tissues. Such condition has been described as a contributing factor for the development of type 2 diabetes, characterized by the loss of β-cells functionality that eventually leads to cellular apoptosis – lipoapoptosis (Y. Yang et

al., 2016). Indeed, insulin resistance resulting from a high saturated fat diet leads to alterations in lipid cellular intake and accumulation which generate lipotoxic conditions, a key phenomenon in the metabolism of β-cells. Unsaturated fatty acids are generally related to protective effects, like preventing β-cells apoptosis, regulating plasmatic glucose concentrations and enhancing insulin sensitivity (Acosta-Montaño & García-González, 2018). Regarding type 2 diabetes, MUFA have been gaining attention due to their ability to regulate glycemic response and improve insulin sensitivity (Due et al., 2008; Juan A Paniagua et al., 2007; Shah et al., 2007) as well as their ability to decrease glucose plasma concentration in type 2 diabetes patients (López-Miranda et al., 2006). Recently, MUFA was shown to have a direct action on β-cell function and lower insulin resistance (Acosta-Montaño & García-González, 2018; López et al., 2008). The evaluation of different cell lines with different fatty acids showed that saturated fatty acids have pro-apoptotic properties, while unsaturated fatty acids maintain protective characteristics. Although, both MUFAs and PUFAs are equally effective in preventing apoptosis, MUFAs can be protective at low physiological levels (Eitel et al., 2002). Besides preventing apoptosis, palmitoleic and oleic acid, promote β-cells proliferation and prevents endoplasmic reticulum stress by inhibiting UPR over-activation (Acosta-Montaño & García-González, 2018; Maedler et al., 2001).

Dietary MUFA may be preferentially oxidized as compared to other dietary fatty acids, as the degree of fatty acid chain length and unsaturation may contribute to the partitioning of dietary fat to energy expenditure versus energy storage (DeLany et al., 2000; Jones et al., 2008). In fact, in double-masked trial, conducted in 43 healthy young adults, Kien et al, (2005) demonstrated that in contrast to palmitic acid (C18:0), increases in dietary oleic acid led to an increase in fat oxidation and daily energy expenditure. Thus, diets high in MUFA, such as the Mediterranean diet, are associated with maintenance of body weight and favorable shifts in reducing central body fat adiposity, potentially ameliorating overweight and obesity risks (M Bes-Rastrollo et al., 2006; Maira Bes-Rastrollo et al., 2007). Studies have shown that both healthy and insulin resistance subjects showed increased fat oxidation rates and decreased abdomen-to-leg adipose rations, as well as amelioration of weight gain after consumption of MUFA comparing to saturated fatty acids (Kaippert et al., 2015; Kien et al., 2005; J A Paniagua et al., 2007; L Schwingshackl et al., 2011).

Through prospective cohort studies dietary MUFA has been associated with a 20% reduced risk of coronary heart disease events (Mente et al., 2009). There is strong evidence that by replacing saturated fatty acids and carbohydrates with MUFA, various cardiovascular risk factors will be significantly improved. Although no detrimental side effects of MUFA-rich diets were reported in the literature, there still is no unanimous rationale for MUFA recommendations in a therapeutic regimen so long-term intervention studies are required (L Schwingshackl et al., 2011; Lukas Schwingshackl & Hoffmann, 2012).

2.2.3.2. Polyunsaturated Fatty Acids

Dietary PUFA are widely studied bioactive lipids since they are known to affect a great variety of physiological processes. For instance, ALA is found in, walnuts and vegetable oils such as canola, flaxseed, soybean, and rapeseed oil (table 4) (Baker et al., 2016). The beneficial effects of ALA are supported by several epidemiological studies and are particularly related to the prevention of cardiovascular diseases by the reduction of several cardiovascular biomarkers, such as cholesterol, triglycerides, and blood pressure. Some studies demonstrated that an increased intake of ALA reduces total and LDL cholesterol levels (Baker et al., 2016; Baxheinrich et al., 2012; Dittrich et al., 2015; Kontogianni et al., 2013; Kuhnt et al., 2014). On the other hand, the correlation between ALA intake and triglycerides levels is unclear. Patenaude et al (2009) described the effect of increased ALA consumption in two age groups (18-29 years and 45-69 years) and reported a 20% decrease in triglycerides concentration in younger people and a 3.5% increase in older people. In the case of blood pressure, studies demonstrated that 1% of ALA

content in adipose tissue, was associated with a 5 mm Hg decrease in systolic and diastolic blood pressures (Baker et al., 2016; Berry, 1986). Caligiuri et al demonstrated that the consumption of 7g/day of ALA during 6 months reduced systolic blood pressure by 10mmHg and by 7 mm Hg the diastolic pressure in the patients with hypertension (Caligiuri et al., 2014).

LA deserves special attention due to its impact on cardiovascular disease. The studies about its benefits in human health were started in 1950 when Ancel Keys and colleagues reported a relationship between the blood cholesterol level and the type of fatty acids that people ingested (Jandacek, 2017; Keys, 1997). More recently Ramsden and co-workers reviewed studies on the benefits of LA regarding the reduction of coronary diseases, and they found that the LA reduces blood cholesterol in the same way as predicted by the Keys and colleagues equation (Ramsden et al., 2013). Wu et al. analyzed the levels of LA in plasma phospholipids in 2792 participants and showed that higher levels of LA were associated with lower total mortality that was attributed to lower incidence of cardiovascular diseases (Wu et al., 2014).

[Table 4 near here]

The fatty acids EPA and DHA are essential nutrients to enhance life quality and lower the risk of premature death (Kidd, 2007). Fatty fish, such as mackerel, herring and salmon are important sources of ALA derivatives, EPA and DHA (table 4) (Ander et al., 2003). There are many biological effects of EPA and DHA including the reduction of triglycerides and cholesterol levels, normalization of blood pressure, and consequently the promotion of cardiovascular health (Bernstein et al., 2011; Dawczynski et al., 2010; Kris-etherton et al., 2000; P Bjerregaard, 2000; Rangel-Huerta & Gil, 2018). On the other hand, EPA and DHA have also a high anti-inflammatory effect, and an important role in the regulation of various metabolic processes such as β-oxidation, adipogenesis, lipogenesis, and glucose metabolism (Endo & Arita, 2016; Flachs et al., 2014; Gain et al., 2019; Jump et al., 2017; Kidd, 2007; Siscovick et al., 2017; Todorčević & Hodson, 2015). EPA and DHA have also an important effect on cognitive development, in the brain and visual development, particularly during the end of the first year of life (B. Chen et al., 2012; Kidd, 2007). Studies demonstrated that the changes in DHA content in the brain are positively associated with a better cognitive or behavioral performance (B. Chen et al., 2012), as well as a positive impact in visual acuity when compared with a placebo group (B. Chen et al., 2012)

Since most diets are mostly rich in omega-6 PUFAs, namely the western diet, greater focus has been placed in incorporating omega-3 PUFAs into the diet (Ander et al., 2003).

The main health benefits of PUFAs are summarized in table 2 and are going to be examined with greater detail in the corresponding chapters.

[Table 2 near here]

2.2.3.2.1. Conjugated Linoleic acid

Conjugated linoleic acid (CLA) occurs naturally and can be found at low levels in ruminant fats such as beef tallow and milk fat. Therefore, it is mostly found in the meat of ruminants, such as cows, sheep and goats, since they chew the cud containing linoleic acid. This happens because there are bacteria in the stomach of ruminants which convert linoleic acid to CLA, by biohydrogenation of linoleic acid to stearic acid. The products are then absorbed into the animal tissue. Besides, it can be synthesized from linoleic acid or vegetable oils that have high levels of linoleic acid such as corn, canola, soybean, safflower and sunflower. The principal bioactive dietary CLA isomer is *cis(c)*-9, *trans(t)*-11 (Rumenic acid), which is present at 73 to 94% content of the total CLA in milk, dairy products, meat and processed meat products of ruminant origin (Y. Park, 2009). The other predominant form in food products is the isomer *t*10, *c*12 (R. E. Aluko, 2012).

One of the most recognized and studied CLA abilities is its anti-carcinogenic effect, which has been studied both *in vitro* and *in vivo*, in rodent models. The anti-carcinogenic activity has been attributed to its potential of inhibiting tumor growth, enhancing apoptosis and inhibiting protein and nucleotide biosynthesis. As reviewed by Park et al, (Y. Park, 2009) CLA may also be involved in reducing eicosanoids production, interfering with cell signaling pathways, inhibiting DNA synthesis, as well as inhibiting angiogenesis as shown in reduced matrix metalloproteinases and vascular endothelial growth factors. By replacing arachidonic acid in the membrane phospholipids, CLA isomers alter the synthesis of eicosanoids that are involved in cell signaling (Rodríguez-Alcalá et al., 2017). Nevertheless, in the last years the role of CLA as an agonist of several peroxisome proliferator-activated receptor (PPAR) isoforms, has been uncovered. PPAR (α, β/δ and γ) are nuclear receptors that translate nutritional and/or pharmacologic stimuli into changes in gene expression. In several studies, PPARs were shown to be involved in the regulation of inflammation, immunity and epithelial cell differentiation (Bassaganya-riera et al., 2004; Cunard et al., 2002; R. A. Gupta et al., 2003; Jones et al., 2002; Natarajan & Bright, 2002; Y. L. Wang et al., 2002). Some *in vitro* studies concluded that dietary PUFA and their metabolites are endogenous PPAR γ ligands, for instance (Hwang, 2000). CLA has been demonstrated as being able to activate PPAR γ eliciting *in vivo* effects consistent with PPAR γ activation, namely on the reduction of the inflammatory response (Yang & Cook, 2003; Yu et al., 2002).

Since CLA were found to be PPARs ligands, their anti-inflammatory potential was hypothesized. In a study aimed at assessing the effect of CLA on ameliorating colitis, it was found that CLA exerted anti-inflammatory properties by repressing TNF-α expression and NFκB activation, while inducing the expression of the immunoregulatory cytokine transforming growth factor β1 (TGF-β1). The anti-inflammatory CLA action was reported to be mediated by PPAR γ and δ induction (Bassaganya-riera et al., 2004). *In vitro* studies have shown that CLA has the capacity to act as an anti-inflammatory modulator of monocytes and macrophages.

The beneficial effect of CLA on several peripheral tissues is well documented, namely on reducing body fat (Y. Park & Pariza, 2007; Whigham et al., 2007). In this case, several studies suggest that the mechanism for weight loss is related to the stimulatory effect of CLA in uncoupling protein expression in white and brown adipose tissue, and also in the liver, contributing toward a high metabolic rate (Salas-Salvadó, Márquez-Sandoval, & Bulló, 2006).

Such effect is thought to be a result of an interplay between different mechanisms: increasing energy expenditure, reducing lipid accumulation in adipose tissues and/or adipocytes differentiation, increasing adipocyte apoptosis, modulating adipokines and cytokines, such as leptin, TNF-a, adiponectin, or interleukins, and by increasing fatty acid β-oxidation in skeletal muscle (Y. Park, 2009; Y. Park & Pariza, 2007). CLA has also been associated with improving insulin resistance, which may present positive potential regarding both obesity and diabetes

treatment. Nevertheless, careful considerations have to be made and further studies are needed, since several investigations have been reporting contradictory results, suggesting that high doses of CLA mixtures (*c*9,*t*11 and *t*10,*c*12 isomers) may possess adverse effects on both glucose and insulin metabolism, ultimately leading to insulin resistance (Bezan et al., 2018; Moloney et al., 2004; Pang et al., 2019).

CLA has been shown to induce the regression of atherosclerosis in several animal models: mice, rabbits and hamsters. Considering the anti-inflammatory potential presented by CLA, it is easily understood that at least in part, CLA mediates its effects in atherosclerosis via inhibition of the inflammatory response. Other processes are also thought to be involved, such as CLA modulation of circulating cholesterol (Bruen et al., 2017b). Toomey et al, (2006) suggested that monocytes/macrophages are the cellular target through which CLA mediates its anti-atherosclerotic effects. Despite such promising results, Arbonés-Mainar et al., (2006) demonstrated that different CLA isomers could have different atherogenic effects. In fact, when the mice diet were supplemented with either *c*9,*t*11 or *t*10,*c*12 CLA isomers, different outcomes were observed. The development of atherosclerotic lesions was impaired in mice fed with *c*9,*t*11 isomer and in contrast pro-atherogenic effects were observed in the mice fed the *t*10,*c*12 isomer. Nevertheless, promising anti-atherogenic effects are well documented in both isomers in animal experimental models when administered in a blend (Toomey et al., 2006). Such results reinforce the need for more studies to understand the full spectrum of effects that such fatty acids, not only conjugated fatty acids, present in human health. Thus, giving a whole perspective of the involved physiological mechanisms.

Besides the known anti-inflammatory potential, other processes are also thought to be involved in CLA's anti-atherogenic potential, such as CLA modulation of circulating cholesterol (Bruen et al., 2017b). Indeed, the effects of CLA dietary supplementation in lowering cholesterol levels have been widely documented. Older studies have shown that in CLA fed groups, LDL concentrations are lowered and in consequence the signs of atherosclerosis are less evident (K. N. Lee et al., 1994). Other studies have shown, that besides lowering plasma total cholesterol, LDL also triglycerides are lowered in animal models fed with a supplemented CLA diet (Nicolosi et al., 1997). Some clinical trials have demonstrated such effect in healthy human patients (Wanders et al., 2010). Recent studies have suggested that the decrease of cholesterol resulting from dietary supplementation with CLA in both liver and egg of laying hens, might be mediated most likely by upregulation of hepatic low-density lipoprotein receptor (LDLR) expression and downregulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) and cholesterol 7 alpha hydroxylase 1 (CYP7A1) expression (S. Wang et al., 2019). Such molecules play crucial roles in the transport, synthesis, and secretion of cholesterol in the liver.

The anti-carcinogenic potential of CLA isomers has been associated, in part, to their antioxidant capacity. The antioxidant capacity of CLA was demonstrated both *in vivo*, in animal models, in combination with phytosterols (Marineli et al., 2012) and *in vitro* (Basiricò et al., 2017; Lalithadevi et al., 2018). When CLA was added to the diet or to the cells there was an improvement in antioxidant status and a reduction in lipid peroxidation. CLA presents antioxidant properties by direct scavenging free radicals, through inhibition of lipid peroxidation (Yu, 2001) and by upregulate vitamin E, which is a potent antioxidant (R. E. Aluko, 2012). By doing so, it protects membranes and tissues from the harmful oxidative stress since it maintains essential fatty acids integrity.

2.2.3.2.2. Conjugated Linolenic acid

Conjugated alpha linolenic acid (CLNA) isomers are naturally found in milk fat and meat of ruminants, but the higher concentrations are found in vegetable oils (table 4) (Mapiye et al., 2013; Nieuwenhove et al., 2012). As reviewed by Fontes et al. (2017) seven isomers are found in

plant seed oils: jacaric acid (C18:3 *c*8,*t*10,*c*12) is found mostly in the argentine native tree *Jacaranda mimosifolia*; α-eleostearic acid (α-ESA) (C18:3 *c*9,*t*11,*t*13) is described as the main compound of tung oil (*Aleurites fordii*), bitter melon (*Momordica charantia*), *Parinarium* spp. and in white mahlab (*Prunus mahaleb*); β-eleostearic acid (β-ESA) (C18:3 *t*9,*t*11,*t*13) can also be found in tung and bitter melon seed, although in lower concentrations than α-ESA; punicic acid (PUA) (C18:3 *c*9,*t*11,*c*13) is mostly found in pomegranate (*Punica granatum*) and balsam apple (*Momordica balsamina*); α- and β-calendic acid (C18:3 *t*8,*t*10,*c*12 and C18:3 *t*8,*t*10,*t*12, respectively) are found in pot marigold (*Calendula officinalis*); lastly catalpic acid (CPA) (C18:3 *t*9,*t*11,*c*13) is mainly found in *Catalpa ovata*. Only few of the mentioned CLNA sources are edible, being pomegranate one of them. Therefore, PUA and pomegranate seeds, as its source, are the most studied and used ones.

Indeed, due to similarities found between PUA and the mentioned *c*9, *t*11 CLA isomer similar biological activities to CLA have been attributed to CLNA. An anticarcinogenic effect was attributed to CLNA, since it shows a cytotoxic effect on different human tumor cell lines (Fontes, Pimentel, Simoes, et al., 2017). An increase of apoptosis rate (Shinohara et al., 2012), lipid peroxidation and antioxidant potential, induction of protein kinase C (PKC) that ultimately leads to inhibition of cell proliferation and activation of apoptosis (Grossmann et al., 2010) have been the mechanisms used to explain the anti-carcinogenic potential.

In agreement with what was previously discussed regarding CLA, CLNA isomers, specifically PUA, positive effects on body weight have been reported (Cao et al., 2007; Saha et al., 2012; Sengupta et al., 2015). Indeed, the beneficial effects of PUA in the peripheral tissues, namely adipose tissue (Miranda et al., 2011), are widely recognized.

Due to the similarities between both PUA and *c*9, *t*11 CLA, the possibility of PUA being also a PPAR activator was hypothesized. Indeed, PUA specifically activates PPAR α and γ in adipocyte cells in a dose-dependent manner (Hontecillas et al., 2009). Moreover, dietary PUA was found to decrease fasting plasma glucose concentrations, improve the glucose-normalizing ability, suppress NFκB activation. Moreover, PUA was found to ameliorate HFD induced obesity and insulin resistance in mice, by improving peripheral insulin sensitivity without affecting liver insulin (Vroegrijk et al., 2011).

The studies regarding PUA health effects on human subjects are scarce and the *in vivo* studies with animal models are sometimes contradictory. Indeed, despite promising results in body weight control, several studies have reported no alteration in total weight gain (de Melo et al., 2016). Thus, there is a great need to clarify the whole extent of CLNA isomers biological role, specifically in humans.

2.3. Phytosterols

Phytosterols comprising both plant sterols and stanols are compounds that naturally occur in all foods of plant origin such as vegetable oils, nuts, seeds, fruits and vegetables (table 5). A study published by Jiménez-Escrig et al. (2006) reveal that the concentration of phytosterols in vegetables range between 5-50 mg/100 g of fat. In relation to the vegetable oils, the content varies between 260 mg/100 g of fat for olive oil and 490 mg/100 g of fat for sunflower oil (Jiménez-Escrig et al., 2006; Phillips et al., 2002). According to the literature, the intake of naturally occurring phytosterols from the general diet is about 200–400 mg/day (Jiménez-Escrig et al., 2006; Klingberg et al., 2008; Ras et al., 2014; Sioen et al., 2011).

[Table 5 near here]

Epidemiological studies have pointed towards several benefits of phytosterols consumption in human health, such as, protection from cardiovascular diseases (Jones &

Abumweis, 2009; Marangoni & Poli, 2010), diabetes (Kurano et al., 2018; Misawa et al., 2012; Shahzad et al., 2017; Weicang Wang et al., 2017), cancer (Fernandes & Cabral, 2007; Jones & Abumweis, 2009; Jong et al., 2003; Shahzad et al., 2017), and the most studied the cholesterol-lowering effect (Jaramillo-Madrid et al., 2019; Jiménez-Escrig et al., 2006; Jong et al., 2003; Olkkonen et al., 2017; Ubeyitogullari & Ciftci, 2019; Vu et al., 2019).

Phytosterols and phytostanols inhibit food cholesterol absorption and cholesterol produced endogenously from the intestine (Gylling & Simonen, 2015). The exact mechanism of this inhibition is not yet clearly established. However, existing theories suggest that the principal mechanism of phytosterols cholesterol reduction is the competition between cholesterol molecules and phytosterols for incorporation into mixed micelles in the intestinal tract. A co-crystallization with cholesterol causes increased faecal excretion of cholesterol and consequently a decrease in their levels (Gylling & Simonen, 2015; Lagarda et al., 2006; Marangoni & Poli, 2010; Olkkonen et al., 2017). Several studies demonstrated a significant reduction of LDL-cholesterol levels in humans, the dose-effect relationship exhibits significant hypocholesterolaemia effects at intakes of about 500 mg/day. This effect increases for a daily intake range 500-2500 mg/day, for greater intakes the LDL-cholesterol levels seems to level off (AbuMweis et al., 2008; Andersson et al., 2004; Katan et al., 2003; Klingberg et al., 2008; Marangoni & Poli, 2010; Plat & Mensink, 2005). FDA and EFSA have reviewed the safety of plant sterols and stanols before and after approving their use in functional foods. EFSA declares the safety use of these compounds in functional foods with an intake of 3 g/day, in authorized matrices (yellow fat spreads, dairy products, mayonnaise and salad dressings). Besides EFSA recommend a consumption during two or three weeks for the effective effect on cholesterol levels (European Food Safety Authority, 2012).

3. Conclusion

Besides their role as a source of energy and in the cell membranes, lipids play an important role in our health and have been widely studied within such framework. Indeed, bioactive lipids have been associated with signalling processes playing active roles in regulating cellular functions, the cardiovascular system, behavioural actions, weight management, among others. Among the mentioned fatty acids (SCFAs, MCFAs, MUFAs, PUFAs and CLA and CLNA) and sterols, their importance in cardiovascular diseases, cognitive development, inflammation, reduction of cholesterol levels, insulin and glucose homeostasis and weight management was widely reported. Besides, antimicrobial activity was also attributed to some fatty acids.

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5. Conflicts of interest

The authors declare no conflict of interest.

List of Tables

Table 1 – Summarized bioactive fatty acid health effects

Bioactive fatty acid group	Principal Benefits	References
Short-chain fatty acids	Body weight management Food intake control Glucose homeostasis Insulin sensitivity	(Kasubuchi et al., 2015; Vinolo et al., 2011)
Medium-chain fatty acids	Body weight management Reduction of LDL cholesterol levels High antibacterial activity Increase the satiety	(R. Aluko, 2012; Kasubuchi et al., 2015; Nagao & Yanagita, 2008; Pgdipsc & Stonehouse, 2015; Tsuji et al., 2018; Vázquez et al., 2017)
Monounsaturated fatty acids	Anti-apoptotic Anti-inflammatory Reduction of atherogenesis risk Reduction of cholesterol levels Positive impact on Alzheimer and colorectal and breast cancer	(R. Aluko, 2012; B. Chen et al., 2012; Lopez-Huertas, 2010; Orsavova et al., 2015; Y. S. Park et al., 2006; Sales-Campos et al., 2013)
Polyunsaturated fatty acids	Maintenance of normal blood pressure Maintenance of normal heart function Reduction of cholesterol and triglycerides levels Normal brain development Visual acuity Body weight management Reduction of atherosclerosis development Stimulation of immune system Anti-inflammatory Better cognitive performance	(Bruen et al., 2017a; B. Chen et al., 2012; Flachs et al., 2014; Kidd, 2007; Lopez-Huertas, 2010; Mozaffarian & Wu, 2011; Nornberg, 2016; Orsavova et al., 2015; Siscovick et al., 2017)
Sterols	Protection against diabetes, cancer, and cardiovascular diseases Anti-inflammatory Reduction of cholesterol levels	(Jaramillo-Madrid et al., 2019; Jones & Abumweis, 2009; Kurano et al., 2018; Marangoni & Poli, 2010; Olkkonen et al., 2017; Shahzad et al., 2017; Ubeyitogullari & Ciftci, 2019; Vu et al., 2019; J. Wang et al., 2017)

Table 2a - Beneficial health effects attributed to Polyunsaturated fatty acids.

Health Condition	Polyunsaturated Fatty Acid (PUFA)	Main physiological processes involved	Reference
Cardiovascular Diseases (CVD)	Mostly omega-3 PUFAs	Combined effect on heart, vasculature and blood.	(Ander et al., 2003)
		Decrease on Apolipoprotein B lipoprotein levels – reduced production and increased catabolism. Providing protection against certain CVD resulting from excess levels of vascular cholesterol.	(R. E. Aluko, 2012)
		Reduction in circulating plasma level of triglycerides	(Abdelhamid AS & Hooper, 2018; R. E. Aluko, 2012)
Cholesterol	Linoleic and Linolenic acids;	Cholesterol lowering effects; Reduction on Apolipoprotein B lipoprotein levels – reduced production and increased catabolism	(R. E. Aluko, 2012)
	DHA	Formation of DHA-rich domains in the plasma membrane – highly disordered domains that serve as platforms for signaling proteins.	(Wassall & Stillwell, 2009)
Type 2 Diabetes	Mostly omega-3 PUFAs	Decrease blood levels of mediators of lipid-induced insulin resistance, increased insulin sensitivity and enhance leptin levels.	(R. E. Aluko, 2012; Jamilian et al., 2017; Rasic-Milutinovic et al., 2007)
	Unsaturated fatty acids in general	MUFA and PUFA are able to prevent β-cells apoptosis, regulate plasmatic glucose concentrations and enhance insulin sensitivity.	(Acosta-Montaño & García-González, 2018)
	Omega-3 fatty acids (flaxseed oil)	Diets containing ω3 fatty acids through GPR120 receptor can deaccelerate the retinopathy development associated with type 2 diabetes. GPR120 mediates anti-inflammatory and insulin-sensitizing responses.	(Dátilo et al., 2018)
Inflammatory diseases (asthma, lupus, diabetes, Chron's disease, rheumatoid arthritis, cystic fibrosis, Alzheimer´s, obesity and multiple sclerosis)	Mostly omega-3 PUFAs (fish oil)	Improve immune response. Reduce the level of proinflammatory compounds such as C-reactive proteins, interleukin-6 and 10, TNF-α and prostaglandins.	(R. E. Aluko, 2012; Gupta et al., 2012; Pimentel et al., 2013)
	EPA and DHA	Anti-inflammatory effects through inhibition of nuclear factor kappa-B (NFκB)	(Allam-Ndoul et al., 2016; Calder, 2013; Daak et al., 2015; Dang et al., 2017)

Table 2b - Beneficial health effects attributed to Polyunsaturated fatty acids.

Health Condition	Polyunsaturated Fatty Acid (PUFA)	Main physiological processes involved	Reference
Obesity	Mostly omega-3 PUFAs (EPA and DHA – fish oil)	Regulation of insulin and leptin levels; anti-inflammatory effect on hypothalamus (neuroinflammation); reduce body weight by affecting intra-abdominal and adipocyte size.	(Aluko, 2012; Cheng et al., 2020; Nascimento et al., 2016; Gustavo D Pimentel et al., 2012; Gustavo Duarte Pimentel et al., 2013; Tomé-carneiro et al., 2018)
Brain (cognitive function and neuroinflammatory diseases)	DHA	Neuroprotectins synthesis for therapeutic management of neurodegenerative diseases, e.g alzheimer's disease.	(Musto et al., 2011; Niemoller et al., 2009; Serhan et al., 2004)
	EPA and DHA (fish oil)	Anti-inflammatory effect may have an important in neuroinflammatory diseases.	(AlAmmar et al., 2019; Devassy et al., 2016; Joffre, 2019)
Hypertension	EPA and DHA	Decrease blood pressure, decrease blood viscosity by inhibition/decrease of angiotensin-converting enzyme (ACE) activity.	(Borghi & Cicero, 2006; Filipovic et al., 2018; Jayasooriya et al., 2008; Naini et al., 2015)
Cancer	EPA	Anti-proliferative effects of cancer cells in colorectal cancer. By reducing the level of proinflammatory eicosanoids in prostate cells, the omega-3 PUFAs have the potential to limit cellular damage and reduce the risk for carcinogenesis	(R. E. Aluko, 2012; Aucoin et al., 2017; Volpato et al., 2020; C. D. Williams et al., 2011)

Table 3 – Short-chain fatty acids, medium-chain fatty acids and monounsaturated fatty acids main dietary sources.

Lipid Class	Lipid ID	Main Dietary Sources			References
Short-chain fatty acids	Acetic acid	Vinegar		4-8% (w/w)	(Lim et al., 2016)
		Alcoholic beverages	Beer	12-155 mg/L	("Chemical composition of alcoholic beverages, additives and contaminants.," 1988)
			Wine	900-1200 mg/L	
			Rum	4.5-11.7 mg/L	
Medium-chain fatty acids	Caproic acid (C6)	Goat milk		9-20 g/100 g of fat	(Kompan & Komprej, 2012)
	Caprylic acid (C8)				
	Capric acid (C10)				
	Lauric Acid (C12)	Coconut oil fat		50 9-20 g/100 g of oil	(Xiang et al., 2019)
		Palm kernel oil		41-55 g/100 g of oil	(Tambun et al., 2019; Zentek et al., 2011)
		Goat milk		3.8-7.7 g/100 g of oil	(Kompan & Komprej, 2012)
Monounsaturated fatty acids	Oleic acid	Milk fat		25-26 g/100 g of fat total MUFA → 21-24 Oleic acid g/100 g of fat	(European Food Safety Authority (EFSA), 2010; Månsson, 2008)
		Olive oil		73-80 g/100 g of oil total MUFA → 71-74 g/100 g of oil Oleic acid	(Assy et al., 2010; Cheah et al., 2019; European Food Safety Authority (EFSA), 2010)
		Rapeseed oil		63.3 g/100 g of oil total MUFA → 61.7 g/100 g of oil Oleic acid	(European Food Safety Authority (EFSA), 2010)
		Palm oil		37 g/100 g of oil total MUFA → 36.6 g/100 g of oil Oleic acid	
		Corn oil		27.6 g/100 g of oil total MUFA → 27.3 g/100 g of oil Oleic acid	
	Total MUFA	Peanut oil		46-50 g/100 g of oil	(Hargrove et al., 2001)
		Nuts	Macadamia nuts	60 g/100 g	(Ros & Mataix, 2006)
			Hazelnuts	46 g/100 g	
			Pecans	41 g/100 g	
			Almonds	32 g/100 g	
		Hass avocado		71g/100 g of oil 9.8g/100g of fruit (edible portion)	(Dreher & Davenport, 2013; Weschenfelder et al., 2015)

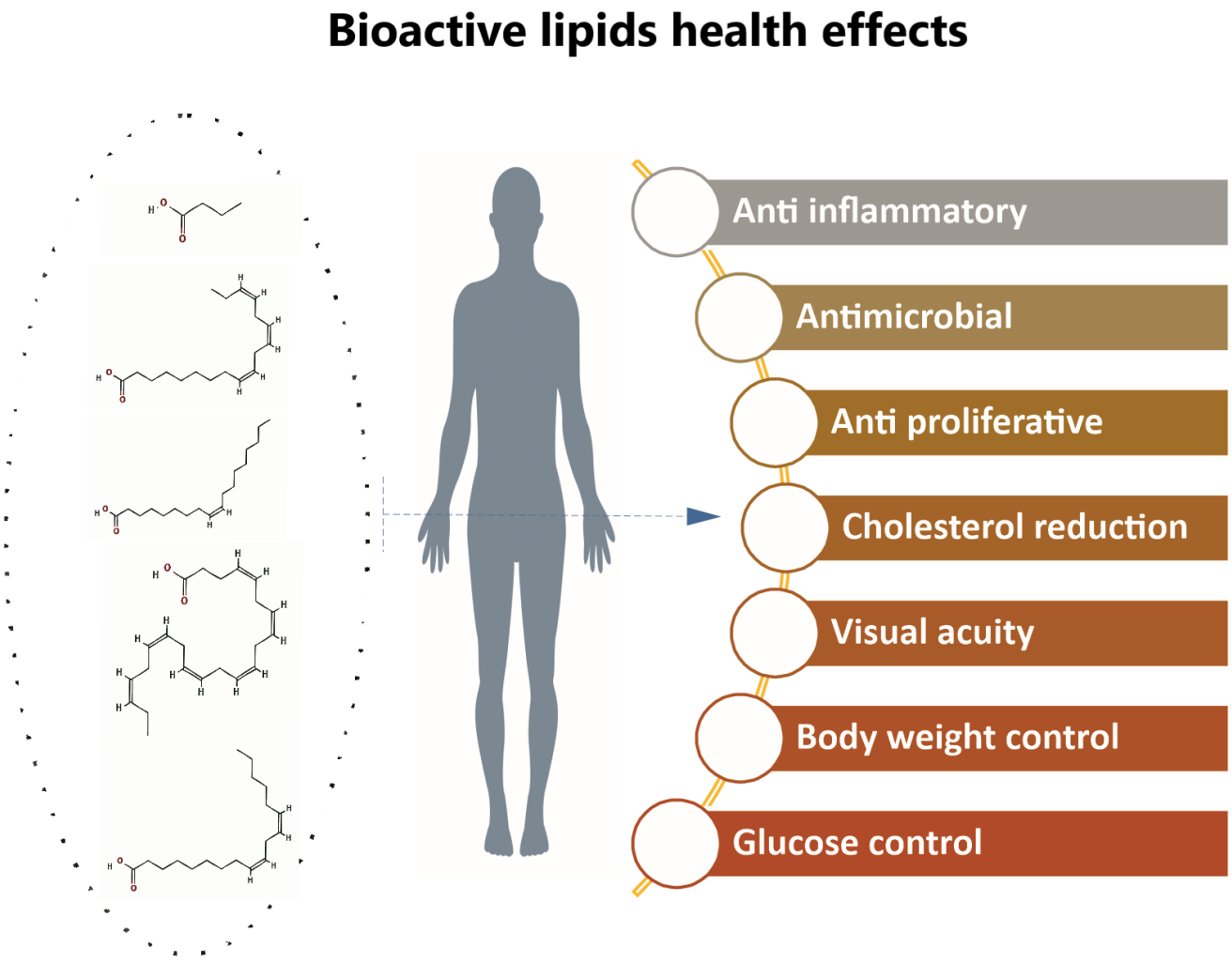
*Table 4 -Polyunsaturated fatty acids (PUFA) main dietary sources (mg of fatty acid/ 100 g of fat).*The fatty acid content of the mentioned fish and ruminant meat products greatly depends on the species, geographical location, food supply and time of the year, thus the values presented in this table intend to be demonstrative.*

Lipid ID	Main Dietary Sources (≈ g fatty acid/100 g fat)		References
Linoleic acid (LA - omega 6 fatty acid) and alpha-linolenic acid (ALA-omega 3 fatty acid)	Sunflower oil	54.6-65.7 total PUFA → 54.5-65.7 LA	(European Food Safety Authority (EFSA), 2010; Vingering & Ireland, 2010)
	Corn oil	54.7 total PUFA → 53.2 LA	(European Food Safety Authority (EFSA), 2010)
	Soybean oil	57.3 total PUFA → 50.1 LA +7.8 ALA	(Nill, 2016) (European Food Safety Authority (EFSA), 2010)
	Grapeseed	63.6 total PUFA → 63.3 LA	(Vingering & Ireland, 2010)
	Canola oil	26.9 total PUFA → 21 LA + 11 ALA	(Lin et al., 2013)
	Flaxseed oil	52 total PUFA → 39.9-53 ALA + 12.25-17 LA	(Guimarães et al., 2013)
	Walnut	68-69 total PUFA → 56-57.3 LA; 10.8-12.1 ALA	(Vingering & Ireland, 2010)v
	Rapeseed oil	35 total PUFA → 23.8 LA+ 11.3 ALA	(Vehovský et al., 2019)
Omega-3 PUFA (EPA+DHA)	Mackerel (12-20% fat)*	45.4-48.2 total PUFA → omega-3 PUFA 30.1-43.6 → 7.41% EPA+DHA	(Özogul et al., 2007; Regulska-Ilow et al., 2013)
	Herring-bloater (13.9-20% fat)*	40.8 total PUFA → omega-3 PUFA 30.2 → 8.63 EPA+13 DHA	(Regulska-Ilow et al., 2013)
	Sprat (≈17% fat)*	26-37 total PUFA → omega-3 PUFA 22-25.6 → 6.3 EPA+10 DHA	(Keinänen et al., 2017; Regulska-Ilow et al., 2013)
	Salmon (10-13% fat)*	13.5-24.2 total PUFA; n-3 PUFA 0.53-2.4 (0.65 EPA+ 1.8 DHA)	(Grahl-Nielsen & Glover, 2010; Linder et al., 2010; Strobel et al., 2012)
	Sardine (≈14% fat)*	30-49 total PUFA → n-3 PUFA 21-36 → 8.6-18.9 EPA+10.7-32.5 DHA	(Bimbo, 2013; De Leonardis & Macciola, 2004; Shirai, 2011)
	Anchovy (8-16% fat)*	29.6-36 total PUFA → omega-3 PUFA 25.7-31.2 → 9.2-11.6 EPA+ 14.7-19 DHA	(Kaya, 2008; ÖKsüz & Özyilmaz, 2010)
Conjugated linoleic acid (CLA)	Milk	0.7-1.03 total CLA → *c*9,*t*11 isomer 75-90% total CLA content	(M. Guo, 2009; Kumar et al., 2018; Mushtaq et al., 2010; Rodríguez-Alcalá et al., 2017)
	Ruminant meat*	0.07-2.97 total CLA	
	Cheese	0.06-1.42 total CLA → 0.14-0.73 *c*9,*t*11 isomer →78-84% total CLA content	
Conjugated linolenic acid (CLNA)	Pomegranate seed	≥70 of punicic acid isomer	(Fontes, Pimentel, Simões, et al., 2017)
	White mahaleb	40 of α-eleostearic acid isomer	
	Snake gourd (*Trichosanthes kirilowii*)	40 of PUA isomer	
	Milk (bovine)	0.03-0.39 rumelenic acid isomer (C18:3 *c*9,*t*11,*c*15) + 0.02-0.06 C18:3 *c*9,*t*11,*t*15 isomer	
	Ruminant meat	0.08-0.28 fat rumelenic isomer (C18:3 *c*9,*t*11,*c*15) + 0.02-0.03 C18:3 *c*9,*t*11,*t*15 isomer	

Table 5 – Phytosterols main dietary sources (mg of fatty acid/ 100 g of fat).

	Main Dietary Sources (≈ mg fatty acid/100 g fat)		References
Vegetables	Broccoli	36.7-49.4	(HAN et al., 2008; Kumar et al., 2018; Piironen et al., 2003)
	Cauliflower	18-43	
	Pea	17.9-53.7	
	Romaine lettuce	30.9	
	Brussel sprouts	37	
	Parsley	28.8	
	Onion	9.2-19.2	
Fruits	Passion fruit	44	
	Navel orange	32.6	
	Tangerine	25.5	
	Orange	22.8-24.2	
	Mango	24.4	
	Hawthorn	23.4	
	Apple	18.3	
	Corn	66-178	
Nuts	Peanuts	118-320	
	Almond	138-140	
	Avocado	75	
	Alfalfa seed	196	(Piironen et al., 2003)
Oils	Corn oil	686-991	(Kumar et al., 2018; R. Yang et al., 2019)
	Rapeseed oil	250-894	
	Sesame oil	640	
	Rice bran oil	858-1892	(Kumar et al., 2018; Sawadikiat & Hongsprabhas, 2014; R. Yang et al., 2019)
	Soybean oil	221-328	(Kumar et al., 2018)
	Sunflower oil	263-376	
	Olive oil	144-260	
	Palm oil	60-78	
Berries	Blueberry	26.4	(Piironen et al., 2003)
	Lingonberry	27.9	
	Raspberry	27.4	

Graphical Abstract



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