CHAPTER

Fatty acids

12

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Chapter outline

1 Introduction

Fatty acids are essential compounds of our diet, and their esterification with glycerol molecules gives rise to the main constituents of fats and oils (Ahmad, 2017). These compounds have been used by humans for thousands of years, not only in the field of the food industry but also in the cleaning industry, through the manufacturing of soap. There is evidence that this was already used by the Babylonian people in 2500 BC for cleaning utensils (List, Kenar, & Moser, 2017). Some time ago, Western society has changed its eating habits, with an increase in the consumption of called fast and convenient foods. These products are high in energy and low in dietary fiber. Since the human gut has been adapting to the consumption of indigestible plant material for several millennia, this

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new modern diet might jeopardize our health (Waisundara, 2018). Western foods, particularly high in sugars, saturated and *trans* fats, together with sedentary behavior, are associated with an increase in obesity and overweight, which in turn are risk factors for the development of cardiovascular disease (CVD), hypertension, stroke, and coronary artery disease (CAD) (Chauhan, Singh, Ozimek, Singh, & Basu, 2016). In the United States, the epicenter of Western society, fast food represents a significant percentage of the daily energy consumed. In 1977, only 4% of the daily energy was represented by this type of diet. However, between 2003 and 2004 an increase of 11% was observed, and in 2010, the 50 most important fast-food chains in this country exceeded 141 billion dollars in turnover. Therefore, the consequences of unhealthy dietary guidelines are becoming a global issue (Bauer et al., 2012). Globalization has caused the expansion of major fast-food chains around the world, promoting inappropriate eating habits and increasing the rate of obesity (de Vogli, Kouvonen, & Gimeno, 2011). For this reason, based on randomized trials and prospective cohort studies, the scientific community is claiming for a reevaluation of classic dietary guidelines. Food and Agriculture Organization of United Nations (FAO)/World Health Organization (WHO) recommends a daily fat intake equivalent to 20%–35% of total daily energy (Eilander, Harika, & Zock, 2015). On the other hand, this recommendation would not be useful without attending to the chemical characteristics of fatty acids that make up the food. Structural differences between them will determine their biological properties. Based on scientific evidence, FAO estimates that the replacement of saturated fatty acids (SFAs) (lauric acid; C12:0, palmitic acid; C16:0) by polyunsaturated fatty acids (PUFAs) decreases LDL (low-density lipoprotein) cholesterol levels and total cholesterol/HDL (high-density lipoprotein) cholesterol ratio. It asserts that in general, a PUFA-rich diet decreases the risk of coronary heart disease (CHD) (FAO, 2010). Extensive research has suggested that adherence to a typical plant-rich diet, monounsaturated fatty acids (MUFAs) such as olive oil, moderate volumes of alcohol, and little consumption of saturated fats, known as the Mediterranean diet (MedDiet), may protect against CVD incidence (Rosato et al., 2019; Salas-Salvadó, Becerra-Tomás, García-Gavilán, Bulló, & Barrubés, 2018; Widmer, Flammer, Lerman, & Lerman, 2015). This diet can be defined as a series of eating habits observed in communities that lived in the Mediterranean area in the 1950–1960s of the last century. At that time, these communities based their diet on abundant consumption of vegetables, fruits, nuts, legumes, cereals, and olive oil, moderate consumption of fish, shellfish, and alcohol, represented by red wine, and very limited or zero of red meat and processed meats and whole-fat dairy products, only those fermented, such as cheese or yogurt (Martínez-González, Gea, & Ruiz-Canela, 2019).

In short, an intense effort is being made to increasingly understand the effects of fatty acids on health. This will help to develop optimized fat consumption guidelines that reduce the risk of any disease associated with their consumption and to improve the quality of life of people. This chapter intended to offer an updated summary of the most recent research concerning the effect of fatty acids on human health in an easily understandable way for the reader. A description of the concepts related to the chemical structure of fatty acids is also provided aiming to facilitate the understanding of the presented material throughout the writing.

2 Fatty acids present in nature

2.1 Chemical structure and differentiation of different fatty acids

Fatty acids are considered the primary components of lipids or fats (Calder, 2015). It could be said that they are the framework or skeleton of fat (Waisundara, 2018), being an essential part of more complex compounds, such as phospholipids, cholesterol esters, and triglycerides (TGs) (groups of three fatty acids) (Hashimoto, 2018). Precisely, the latter is the resulting molecule once fatty acids are absorbed by the body (Waisundara, 2018). Fatty acids are formed by a nonpolar aliphatic chain (CH) attached to a polar head consisting of a carboxylic group (COOH) (Waisundara, 2018). The chain length, whose number of carbon atoms can vary from 8 to over 80 (Kenar, Moser, & List, 2017), is usually used to classify fatty acids. According to this way of classification, fatty acids are divided into short-chain fatty acids (SCFA), with less than 5 carbon atoms; medium-chain fatty acids (MCFA), among 6 and 12 carbon atoms; long-chain fatty acids (LCFA), from 13 to 21 carbon atoms; and finally, very-long-chain fatty acids (VLCFA), which have more than 21 carbon atoms (Waisundara, 2018). This classification is fairly used in the field of food and health science, but others are possible. Among all of them, the most used is the one that differentiates fatty acids according to the number of double bonds ($C=C$) of the carbon chain. In this case, fatty acids are divided into SFAs, whose chains do not present any double bonds, and unsaturated fatty acids (UFAs), which present at least one double bond. The latter is in turn divided into MUFAs and PUFAs, depending on whether they contain a single double bond or more, respectively (Hashimoto, 2018). Within the UFAs, there are other classifications. One of them divides the fatty acids according to the arrangement of the carbon chains into *cis* and *trans* fatty acids (TFAs). In the former, the double bond is arranged so that the carbon chain is bent, while in the latter, the double bond does not generate any kind of bend in the chain, remaining linear (Marchand et al., 2010). In another not less important classification, the UFAs are distinguished according to the position of some of their double bonds. This differentiation is especially useful in the food scope because it allows UFAs to be grouped according to their properties or health effects. This classification is based on the position of the final double bond in the carbon chain, taking as a reference the terminal methyl end thereof, also called "omega" (Wiktorowska-Owczarek, Berezińska, & Nowak, 2015). In this way, four main types of UFAs are identified, omega-3 (final double bond between third and fourth carbon position counting from the terminal methyl end), omega-6 (final double bond between 6th and 7th carbon position), omega-7 (double bond between 7th and 8th carbon position), and omega-9 (double bond between ninth and tenth carbon position) (Hashimoto, 2018).

2.2 Natural sources of fatty acids

There are more than 1000 fatty acids known in nature. However, only a few (20–25) are widely distributed in food with a higher commercial importance given their influence on the diet by being constituents of major commodity plant oils and animal fats

(Kenar et al., 2017). SFAs are primarily present in animal fat, both in meat and in derived products (e.g., butter, cow's milk, and egg yolk), in fish such as salmon, and some plant products, such as chocolate, cocoa butter, coconut, and palm kernel oils (De Souza et al., 2015). Palmitic (C16:0), stearic (C18:0), myristic (C14:0), and lauric (C12:0) fatty acids are widely consumed. The first two are generally found in natural fats, and lauric acid is very abundant in coconut and palm kernel oils. Regarding myristic acid, it is primarily found in these oils and the butter (Ruiz-Núñez, Dijck-Brouwer, & Muskiet, 2016). The European Food Safety Authority (EFSA) and the WHO recommends a maximum SFA intake of 10% of the total energy ingested in the diet (Karam, Del Mar Bibiloni, Pons, & Tur, 2020). In France, a country with a long tradition in the consumption of animal fat products, such as pâté or dairy products, a study carried out in adults showed a consumption value of SFAs higher than 14%. This percentage was attributed to an excessive consumption of cheese and butter (Tressou et al., 2016). In contrast, further south, on the island of Mallorca (Spain), a significantly lower percentage was found in adults aged between 55 and 80 years. In this region, high consumption of MUFAs was observed, possibly associated with the follow-up of a MedDiet, which caused a reduction in the percentage of SFA intake below 10%. However, it is striking that the SFA intake in the United States become a part of the food culture associated with the intake of animal fat, where 35% of adults affirm to consume fast food at least twice a week (Janssen, Davies, Richardson, & Stevenson, 2018), approximates to that recommended by EFSA and WHO, with an average value of 10%. Myristic, palmitic, and stearic (Fig. 12.1) acids were the SFAs most commonly consumed by the American population (De Souza et al., 2015).

The perception of the population regarding MUFAs and PUFAs differs completely from that of SFAs. This is due to the extensive information existing about their beneficial effects on the body as a result of a periodic intake. MUFA consumption is related to a reduction in cholesterol levels, thus preventing CVD (Senila et al., 2020). It was found that these fatty acids may reduce the amount of LDL in the blood serum, popularly known as "bad cholesterol", and it is believed that it might even increase the amount of HDL, known as "good cholesterol." Red meat, dairy products made with whole milk, nuts, and fatty fruits, such as olives and avocados, are some of the natural sources of MUFAs (Orsavova, Misurcova, Vavra Ambrozova, Vicha, & Mlcek, 2015). Probably the food most associated with this group of fatty acids is olive oil, and oleic acid (C18:1*n*-9c), its most representative and recognized fatty acid worldwide. Traditionally, the beneficial properties of the extravirgin olive oil (EVOO) consumption were attributed to its high content of MUFAs, and specifically to that of oleic acid, whose concentration is ranging among 55% and 83% of the total fatty acids (Mazzocchi, Leone, Agostoni, & Pali-Schöll, 2019). Oleic acid (Fig. 12.1) can be also found in large amounts in other vegetable oils different from olive oil, such as peanut, palm, canola/rapeseed, and high-oleic sunflower (Kenar et al., 2017). On the other hand, PUFAs, which are divided into the omega-3 and omega-6 series, are even more relevant than MUFAs, since two fatty acids from these series, α-linolenic acid (C18:3*n*-3, ALA) (omega-3) and linoleic acid (C18:2*n*-6c, LA) (omega-6), are considered essential fatty acids (Das, 2006). This means that they must be incorporated through the diet since the body is not able to synthesize them (Fig. 12.2).

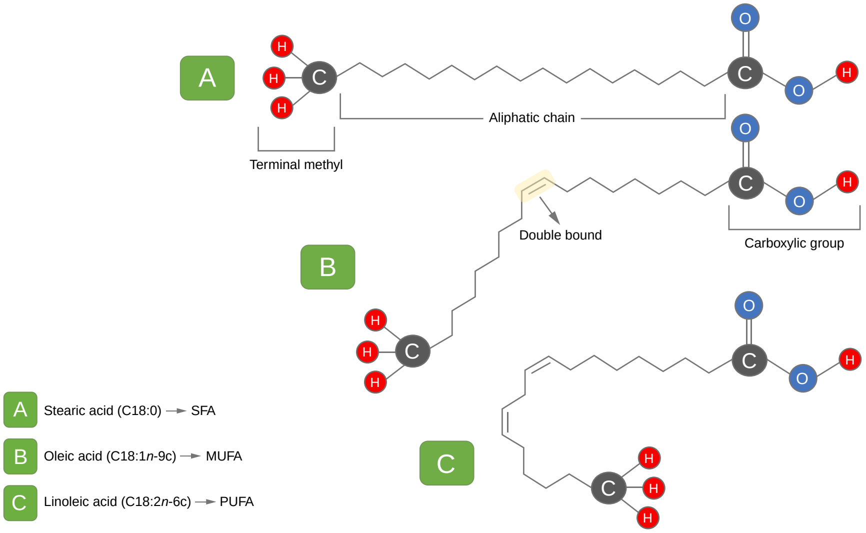

FIG. 12.1

Chemical structure of stearic, oleic, and linoleic fatty acids.-Three of the main fatty acids in the human diet.

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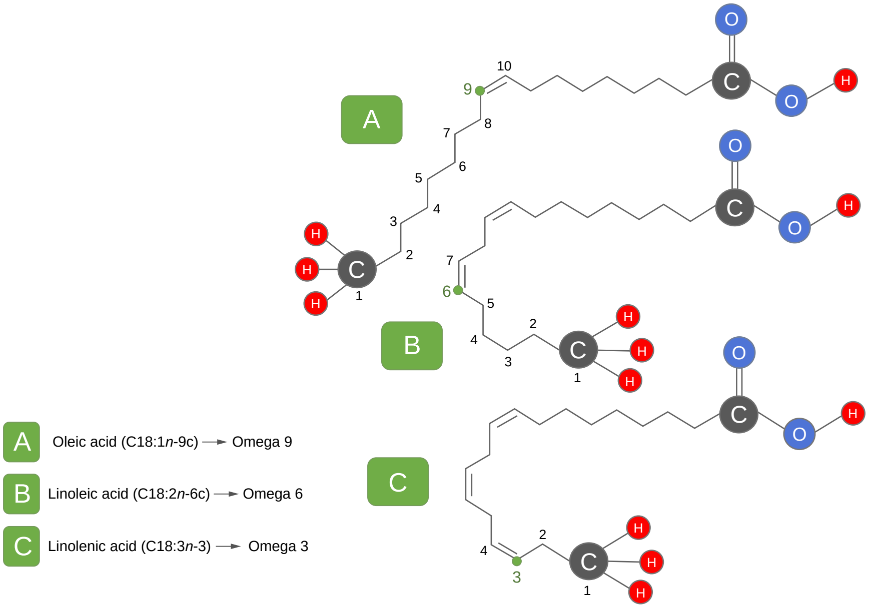

FIG. 12.2

Inclusion of oleic, linoleic, and linolenic fatty acids in omega-9, -6, and -3 groups, respectively.

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Fatty acids from the omega-6 series can be found in large amounts in most of the seeds and vegetable oils (e.g., canola, soybean, corn, and sunflower). Green leafy vegetables are also important sources of omega-6 (Saini & Keum, 2018). Regarding fatty acids from the omega-3 series, these are found disseminated between products of animal and vegetable origin. Flaxseed, walnuts, and their respective oils, as well as canola oil, are rich in ALA. Oily fish is source of eicosapentaenoic acid (C20:5*n*-3, EPA) and docosahexaenoic acid (C22:6*n*-3, DHA) (Tur, Bibiloni, Sureda, & Pons, 2012). These fatty acids can be also found in marine algae (Wells et al., 2017). The introduction of poultry meat into the diet is also known to contribute to slightly increased the level of these acids (Tur et al., 2012). The consumption of these PUFAs is linked to positive effects in the treatment of certain pathologies, such as CVD and inflammatory processes, and it was also found an improvement in neurocognitive health (Calder, 2018; Swanson, Block, & Mousa, 2012). The main food sources of fatty acids in the human diet are shown in Table 12.1.

3 Relationship between saturated fatty acid (SFA) intake and health status

SFAs have specific functions in the human body, such as participating in the construction of structural components, in the modification of proteins, in the regulation of gene transcription, and, of course, as an energy source. The human body can synthesize de novo and store SFAs from carbohydrates. These fatty acids are fundamentally the same that are ingested with the diet, such as C18:0, C14:0, C12:0, and especially C16:0 (Ruiz-Núñez et al., 2016). For this reason, experts advise against excessive consumption of animal fat, otherwise our health may be at risk. Different studies in both animals and humans have reported a relationship between the consumption of SFAs and the increase in the concentration of cholesterol in plasma and the risk of CVD (Hammad, Pu, & Jones, 2016). Still, the association between the consumption of SFA and CVD remains a matter of debate. Recent studies have questioned that excessive consumption of saturated fat increases the risk of CVD since it simply has not been possible to demonstrate (Bier, 2016). The current dietary recommendation guidelines in this regard are based on the direct relationship between the consumption of saturated fat and a possible increase in the levels of total serum cholesterol. However, it is more important to pay attention to the levels and size of LDL particles than to the global level of cholesterol. It has been observed that depending on the fatty acids ingested, the effect on these lipoproteins is different. Hence, the risk of developing CHD not is associated with the type of fat consumed and more specifically with the type of SFAs that it contains (DiNicolantonio, Lucan, & O'Keefe, 2016). The longer the hydrocarbon chain, the lower the increase in LDL cholesterol in the blood and vice versa. Thus, C12:0 increases more LDL levels than C14:0, and the latter more than C16:0. Nevertheless, C12:0 has been found to significantly increase the concentration of HDL cholesterol regarding other SFAs (Siri-Tarino, Chiu, Bergeron, & Krauss, 2015). This type of cholesterol participates in the return of excess cholesterol in the

Table 12.1 Food sources of fatty acids in the human diet.

Fatty acid		Food	Reference
SFAs	Butyric acid Caproic acid Caprylic acid Capric acid	Dairy products	Astrup et al. (2020)
	Pentadecanoic acid Heptadecanoic acid	Dairy products, red meat	
	Myristic acid	Coconut oil	Moigradean, Poiana, Alda, and Gogoasa (2013)
		Milk Yogurt Butter Meat and processed meats	O'Sullivan, Hafekost, Mitrou, and Lawrence (2013)
	Palmitic acid	Walnut oil	Moigradean et al. (2013)
		Linseed oil	Kostik, Memeti, and Bauer (2013) and Popa et al. (2012)
		Canola oil, soybean oil	Kostik et al. (2013) and Thandapilly et al. (2017)
		Corn oil, olive oil, peanut oil	Kostik et al. (2013)
		Milk Yogurt Butter Meat and processed meats	O'Sullivan et al. (2013)
	Stearic acid	Walnut oil	Moigradean et al. (2013)
		Linseed oil	Kostik et al. (2013) and Popa et al. (2012)
		Corn oil, soybean oil, peanut oil, canola oil	Kostik et al. (2013)
		Milk Yogurt Butter Meat and processed meats	O'Sullivan et al. (2013)
		Chocolate	Astrup et al. (2020)

Continued

Table 12.1 Food sources of fatty acids in the human diet—cont'd

Fatty acid		Food	Reference
MUFAs	Oleic acid	Olive oil	Sales-Campos, Reis De Souza, Peghini, Santana Da Silva, and Cardoso (2013)
		Walnut oil, coconut oil	Moigradean et al. (2013)
		Sunflower oil	Premnath, Narayana, Ramakrishnan, Kuppusamy, and Chockalingam (2016)
		Canola oil	Agregán et al. (2017) and Thandapilly et al. (2017)
		Soybean oil, safflower oil	Thandapilly et al. (2017)
		Pork	Kasprzyk, Tyra, and Babicz (2015)
	Erucic acid	Rapeseed	Knutsen et al. (2016) and Schwingshackl and Hoffmann (2012)
		Mustard seed, kale seed, cabbage seed, turnip seed	Knutsen et al. (2016)
	Vaccenic acid	Dairy products	Jacome-Sosa et al. (2014)
		Beef	
		Lamb	
PUFAs	Linoleic acid	Walnut oil, coconut oil	Moigradean et al. (2013)
		Linseed oil	Popa et al. (2012)
		Sunflower oil	Premnath et al. (2016)
		Canola oil	Agregán et al. (2017) and Thandapilly et al. (2017)
		Soybean oil, safflower oil	Thandapilly et al. (2017)
		Nuts	Whelan and Fritsche (2013)
		Eggs	
		Meat	
	Linolenic acid	Linseed oil	Popa et al. (2012)
		Canola oil, soybean oil	Rajaram (2014) and Thandapilly et al. (2017)
		Flaxseed oil, walnut oil	Rajaram (2014)
		Flax, chia seeds	
		Kale	
		Spinach	
	Arachidonic acid	Eggs	Forsyth, Gautier, and Salem (2016)
		Milk	
		Beef	
		Poultry	
	EPA and DHA	Fish	Forsyth et al. (2016) and Mohanty et al. (2016)

blood to the liver (März et al., 2017). Therefore, the consumption of C12:0 reduces the total cholesterol: HDL cholesterol ratio (Siri-Tarino et al., 2015). Regarding C16:0, the main SFA in palm oil, surprisingly it does not appear to negatively affect the lipid profile in the blood. This, together with other considerations related to the structure of palm oil lead us to consider whether the consumption of this product is harmful for cardiovascular health. Indeed, it was found that the consumption of palm olein as cooking oil in Malaysian population was found to have no detrimental effects on plasma lipid profiles (Bier, 2016). However, a study carried out with a total of 115,782 individuals free of chronic diseases at the beginning concluded that frequent intake of C16:0, as well as C12:0, C14:0, and C18:0 (the average intake of SFAs represented among 9.0% and 11.3% of the total energy intake in the diet of the participants) was related to an increased risk of CHD (Zong et al., 2016).

As commented above, the longer the SFA hydrocarbon chain, the lower the production of LDL and, therefore, its incidence in possible CVD. Malik et al. (2015) reached positive results by studying the effect on the body of the consumption of 3 very-long-chain saturated fatty acids (VLCSFAs) (arachidic acid, C20:0; behenic acid, C22:0, and lignoceric acid, C24:0). These authors found that VLCSFAs were correlated with healthy profiles of blood lipids. In addition, the total set of these acids in plasma represented a lower risk of CHD, specifically, the risk was reduced by 52% according to the authors. These results agree with those reported by Lemaitre et al. (2018), who linked the consumption of these same fatty acids with a lower risk of heart failure. The benefits of a VLCSFA-rich diet go even further. Fretts et al. (2019) investigated the association between the circulation of C20:0, C22:0, and C24:0 with type 2 diabetes incidence. The authors reported that of all the participants in the study (51,431) only 14,276 had diabetes, concluding that the people ingesting high amounts of the above fatty acids are less likely to develop this disease. Lemaitre et al. (2015) reached the same conclusion after studying the effect of these fatty acids in older adults of a mean age of 75. The analysis of the results showed an association between the consumption of C22:0 and C24:0, and a 47%, 33%, and 53% less probability of suffering from diabetes. Furthermore, each one of these fatty acids caused a lower circulation of TGs and C16:0. According to the authors of the work, both findings might be related. On the contrary, a diet rich in shorter chain SFAs may have the opposite effect. Koska et al. (2016) found that a SFA-rich diet (C16:0 comprised 42% of total SFAs) induced whole-body insulin resistance, a metabolic abnormality underlying the development of type 2 diabetes. The authors observed that after a day with a healthy diet this resistance was attenuated.

SFA intake has been linked to inflammatory processes in the brain. SFAs such as C16:0 induce activation of TLR4 receptors in hypothalamic microglia and stimulate cytokine release. Specifically, variations in the levels of the IL-1b, IL-6, and TNF-α cytokines can alter the normal functioning of the hippocampus, a region involved in learning, memory, as well as in depressive states and the effect of antidepressants. The mentioned cytokines play important roles in synaptic plasticity and may inhibit neurogenesis. Aggressive behavior and cognitive impairment have been reported in rodents after being subjected to a high-fat diet, and both phenomena have been linked to brain inflammation (Melo, Santos, & Ferreira, 2019).

SFAs have a negative impact on some types of cancer. After performing a meta-analysis of a total of 15 studies where fat intake (total fat and/or saturated fat) was related to mortality from breast cancer, Brennan, Woodside, Lunny, Cardwell, and Cantwell (2017) concluded that patients with breast cancer had a worse prognosis if their eating habits include high amounts of SFAs. Conversely, lower intakes of both saturated and total fats could improve survival after diagnosis. Even before being diagnosed, studies have linked the appearance of certain types of cancer, such as ovarian (Qiu, Lu, Qi, & Wang, 2016), stomach (Hu et al., 2015), and lung (Yang et al., 2017), with SFA-rich diets.

4 The role of unsaturated fatty acids (UFAs) in health

4.1 Monounsaturated fatty acids (MUFAs)

The results of different clinical trials have suggested the importance of maintaining a MUFA-rich diet to preserve a good health status. The American Heart Association (AHA) advises a maximum MUFA intake of 20% of total daily energy, meanwhile, the American Diabetes Association (ADA) and Dietitians of Canada (DC) set it to about 25%. These recommendations are based on studies demonstrating the positive effects of MUFA intake on the risk of CVD. In this regard, MUFA-rich diets have been found to increase HDL cholesterol more than PUFAs or carbohydrate-rich diets (Hammad et al., 2016). HDL cholesterol plays an important role in the transport of excess cholesterol from the periphery to the liver. Several epidemiologic studies have suggested that high levels of this cholesterol protect the healthy population from CHD. This has led to the belief that its presence is always positive. However, recent research has indicated that this might not always be the case (März et al., 2017). On the other hand, it was found that a high MUFA intake together with a reduction in SFA intake might reduce LDL cholesterol (associated with the development of atherosclerosis) and total cholesterol (Joris & Mensink, 2016). However, there is not yet enough evidence to link this fact with the prevention of CHD. In a study carried out with hypercholesterolemic rats, the addition of MUFAs to replace SFAs enhanced some of the alterations caused by an atherogenic diet, but the levels of cholesterol, body fat, and hepatic index remained high (Macri et al., 2015). In this regard, Zong et al. (2018) found that depending on the origin of MUFAs, CHD incidence and mortality may vary. Thus, the substitution of SFAs, *trans* fats, or refined carbohydrates by MUFAs of plant origin, such as vegetable oils, nuts, and related products, might significantly reduce the risk of suffering from CHD, but not MUFAs of animal origin. The consumption of olive oil is associated with a healthy lifestyle and many of its properties have been attributed to the high C18:1n-9 content such as the prevention of ischemic heart diseases (Karacor & Cam, 2015). The consumption of this oil as a part of the well-known MedDiet could be the reason for the low rate of cardiovascular mortality in Southern European Mediterranean populations (Fattore & Massa, 2018). It was observed that if an MedDiet is supplemented with EVOO (oil resulting from the first pressing of the ripe olives), there is a series of beneficial effects, including better regulation of blood pressure, glycemic control in diabetic patients, less oxidative stress, and improvement in the lipid profiles (Nocella et al., 2017). Guasch-Ferré et al. (2020) carried out a study with almost 10,000 CVD cases reported, of which more than 6000 and almost 4000 corresponded to CHD and stroke cases, respectively. They observed that those individuals who consumed more olive oil (> 1/2 tablespoon a day or more than 7 g) had a 14% lower risk of CVD and 18% lower risk of suffering from CHD. Replacing 5 g of saturated fat, such as butter or mayonnaise, with the equivalent amount of olive oil per day might reduce the risk of CVD and CHD by 5%–7%. Additionally, in some of the documented cases, olive oil intake was associated with a healthier lipid profile and antiinflammatory effect. In another study, Kouli et al. (2019) observed the efficiency of the continued consumption of olive oil in the prevention of CVD. The study called ATTICA was conducted in a healthy population of the metropolitan area of Athens. After about 10 years of evaluation, the results reported an inverse association between the partial or exclusive use of olive oil and CVD incidence, reinforcing the evidence of the beneficial effect of olive oil on cardiovascular health.

As frequently noted, the beneficial effects of olive oil are generally attributed to the high content of C18:1*n*-9. However, in an interesting review, Bernardini and Visioli (2017) stated that there is not enough scientific basis to attribute the healthy properties of olive oil to C18:1*n*-9. They argued that this fatty acid is not an essential fatty acid (EFA), since it can be synthesized by the body, and that there is also no evidence of deficiencies reported in the literature. On the other hand, the total amount of C18:1*n*-9 in Mediterranean countries (avid consumers of this oil) is not much different from that of other countries, such as the United States and United Kingdom, whose intake of C18:1*n*-9 is through the consumption of meats (e.g., pork and chicken). In this regard, the healthy actions of olive oil might be attributed to other minor components such as polyphenols. Gavahian et al. (2019) stated that bioactive compounds in olive oil, which include phenolic compounds (e.g., oleocanthal, tyrosol, hydroxytyrosol, oleuropein, and oleuropein aglycone) and carotenoids, such as A-and β-carotene, and lutein, can prevent CVD. This protection was found to be higher in EVOO. In addition, certain polyphenols found in this oil, with an attributed cardioprotective effect, are not present in refined olive oil. The release of bioactive compounds is intense in the first pressing of the olive, but the subsequent physical and chemical procedures may cause the loss of most of these bioactive compounds (Martínez-González et al., 2019).

Oleic acid is by far the most consumed *cis*-MUFA, although other *cis*-MUFA, also belonging to the omega-9 series, are also part of the diet. Delgado et al. (2017) assessed the individual effect of three MUFAs, gondoic acid (C20:1*n*-9), nervonic acid (C24:1*n*-9), and oleic acid, on the risk of cardiovascular mortality. They observed that the higher intake of these three fatty acids was associated with lower levels of LDL, HDL, and eGFR (glomerular filtration rate). In contrast, a low intake level presented a worse prognosis for heart failure, as well as a greater probability of suffering an inflammatory process. However, C24:1*n*-9 was associated with a higher probability of cardiovascular death in men, while in women, C20:1*n*-9 was the only fatty acid of those studied that presented any relationship with this fatality.

The consumption of MUFAs, especially olive oil, has been related to the prevention and/or a better prognosis of type 2 diabetes. Oleic acid produces higher levels of the endogenous lipid mediator oleoyl ethanolamide (OEA), which in turn decreases the intake capacity and slows down the bodyweight gain. In this regard, it was found that when the hypothalamus detects C18:1*n*-9, it sends a signal that causes a reduction in the food intake and lower glucose production. On the other hand, OEA is a strong endogenous agonist of GPR119, a G protein-coupled receptor expressed predominantly in the pancreas (β-cells), with the ability to increase insulin secretion. There are also three oleic acid derivatives capable of activating this endogenous lipid mediator. Nevertheless, some studies have shown conflicting results in this regard (Palomer, Pizarro-Delgado, Barroso, & Vázquez-Carrera, 2018). Schwingshackl et al. (2017) reviewed data reports from several studies in which olive oil was used and, through conducting a metaanalysis, concluded that this oil might effectively reduce the risk of type 2 diabetes, and being beneficial for the treatment of the disease. It should be noted that the reported results are not individually associated with C18:1*n*-9, but with olive oil as food. Despite this fact, there is enough scientific evidence to suggest the association of C18:1*n*-9 with the prevention and better prognosis of type 2 diabetes. Nemecz et al. (2019) showed that C18:1*n*-9 promotes the storage of natural lipids and insulin secretion. In addition, they found that the supplementation of C16:0 with C18:1*n*-9 reversed the negative effects of the former, regulating insulin secretion from pancreatic β-cells, and demonstrating the protective effect of this fatty acid against diabetes. Table 12.2 summarizes the main beneficial effects reported by the literature regarding oleic acid.

4.2 Polyunsaturated fatty acids (PUFAs)

PUFAs have a prominent place within the group of UFAs, due to the large number of healthy properties reported in the literature. Some of these properties are even indispensable for the body and are only produced by the intake of EFAs, which are irreplaceable and need to be supplied externally through the diet (Sokoła-Wysoczańska et al., 2018). Several important functions of PUFAs have been reported in the body. An improvement in the oxidation reactions of fatty acids occurs through the regulation of transcription factors. They also enhance the position, amount, and function of membrane proteins, in addition to increasing membrane fluidity. On the other hand, PUFAs can regulate inflammation, immunity, blood vessels, platelets, synaptic plasticity, cellular growth, pain, sleep, and other phenomena (Bentsen, 2017). Despite all these benefits, a daily intake of omega-6 PUFAs is associated with inflammation, constriction of blood vessels, and platelet aggregation (Saini & Keum, 2018). Arachidonic acid (C20:4*n*-6, ARA) and its precursor, LA, have been widely described as promoters of inflammatory processes since the first is a precursor of powerful proinflammatory mediators (e.g., prostaglandins

Table 12.2 Beneficial effects of oleic acid reported in original research papers.

Effect	Reference
Potential protection against myocardial injury	Singh et al. (2020)
Neuroprotection against global, transient and permanent focal cerebral ischemia	Song et al. (2019)
Protection of the cardiac mitochondria and improvement of adrenaline-induced mitochondrial dysfunction	Mishra et al. (2019)
Promotion of the storage of natural lipids and the insulin secretion	Nemecz et al. (2019)
Reduction of food intake and lower of glucose production	Palomer et al. (2018)
Increased insulin secretion	
Stimulation of mammary gland development	Meng et al. (2018)
Decreased production of proinflammatory cytokines	Medeiros-De-Moraes et al. (2018)
Increased IL-10 production	
Reduced neutrophil migration and accumulation in the site of infection	
Improved bacterial clearance	
Powerful anticancer effect in tongue squamous cell carcinoma by inducing apoptosis and autophagy	Jiang et al. (2017)
Cholesterol reduction	Ducheix et al. (2017)
Promotion LXR-dependent hepatic lipogenesis without harmful effects to the liver	
Lowering of LDL cholesterol	Delgado et al. (2017)
Decreased metabolic dysfunction and mortality in cases of sepsis	Gonçalves-de-Albuquerque et al. (2016)
Prevention of diabetic retinopathy	Alcubierre et al. (2016)
Protection against cardiovascular insulin resistance	Perdomo et al. (2015)
Improvement of endothelial dysfunction and reduction of inflammatory processes	
Possible contribution to the improvement of atherosclerosis and its stability	

and leukotrienes) (Innes & Calder, 2018). For example, in the case of a healing wound, ARA, which is the second most abundant fatty acid in this type of injury, is metabolized by cyclooxygenases and lipoxygenases, and eicosanoids are produced. These compounds include prostaglandins and thromboxanes of series 2, leukotrienes of series 4, lipoxins, and hydroxyeicosatetraenoic and epoxyeicosatrienoic acids. These metabolites from ARA are mainly proinflammatory by promoting chemotaxis of inflammatory cells, increasing the activity of the elastase enzyme (responsible for degrading extracellular proteins), and hindering the formation and regeneration of scar tissue (Silva et al., 2018). In any case, it should be emphasized that ARA concentrations are strictly regulated by the body and that there is no strong evidence that its levels increase after ingestion of LA, especially, in the human body (Poli & Visioli, 2015). Precisely, LA was found to have a beneficial effect by stimulating the release of proinflammatory mediators at the beginning of inflammation, reducing their production in the resolution phase (Silva et al., 2018).

The consumption of omega 6 PUFAs and the prevention of CVD has been discussed for decades and evidence from prospective studies suggests a direct relationship. The results of 30 prospective studies carried out with patients where the evaluation period lasted 2.5 and 31.9 years displayed an inverse relationship between high consumption of LA and CVD, associated mortality, and ischemic stroke. ARA did not show any relationship with cardiovascular events. Although at the highest levels found, a positive effect was reported (Marklund et al., 2019). These results are in the same line as those achieved by Yang et al. (2019), who found an inverse relationship between the omega-6 PUFA levels in the blood and the risk of CVD in a dose–response manner. The authors pointed out that 20.7% of the cardiovascular events that occurred during the study would have been prevented if the concentration of omega-6 PUFAs in plasma had been higher than 26% of the total fatty acids. Although there seems to be a consensus about the benefits of a omega-6 PUFA-rich diet for the prevention of cardiovascular accidents, there is some dissenting voice on the matter. Hooper et al. (2018) found a lack of evidence linking omega-6 fatty acids to a reduction in coronary events after a comprehensive evaluation of the data retrieved from various randomized trials, except for myocardial infarction, which might be prevented with increased consumption of these fatty acids. On the other hand, the results showed a reduction of LDL cholesterol levels in serum, but not from other blood fat fractions or adiposity when adding this polyunsaturated fat to the diet. Certain detrimental events for the body such as atherosclerosis have been associated with their consumption. In addition, LA is suspected to be one of the main factors associated with CHD (Dinicolantonio & O'Keefe, 2018). In fact, the association between omega-6 PUFAs of vegetables and seed oils and poor cardiovascular health has been indicated since the 1980s, when in vitro data of different trials showed problems related to their intakes, such as their oxidizability or proinflammatory potential, as previously discussed. However, recent research has shed some light on this controversy, and a revaluation of the cardioprotective effect of omega-6 PUFAs seems to indicate that an adequate intake could be very effective in reducing the risk of CHD (Poli & Visioli, 2015).

A group of isomers of LA, grouped under the generic name of conjugated LA (CLA) (Lehnen, da Silva, Camacho, Marcadenti, & Lehnen, 2015; Yang et al., 2015), has caught the attention of scientists, who have been interested in its biological properties. This group of PUFAs is naturally present in ruminant fat, which is introduced into the diet through the consumption of milk and dairy products from these animals and meats. The most consumed CLA are *cis*-9, *trans*-11 CLA (c9,t11-CLA) (it accounts for more than 80% of the total CLA provided by the diet) and *trans*-10, *cis*-12 CLA (t10,c12-CLA) (Bruen, Fitzsimons, & Belton, 2017). Research has linked CLA to the prevention of diseases, such as obesity or cancer. CLA seems to have positive effects in the reduction of body weight (den Hartigh, 2018; Kim, Kim, Kim, & Park, 2016) through a reduced energy intake, increased energy expenditure, and modulated metabolism in lipids, adipocytes, and skeletal muscle (Basak & Duttaroy, 2020). On the other hand, several studies in model animals, mainly rats, have suggested an anticancer effect. However, this effect has hardly been proved in humans. The mechanisms of action of CLA have been shown to vary for different types of tumors and different stages of tumor progression. Therefore, the body's response to different types of cancer is probably different (Shokryazdan et al., 2017).

4.2.1 Omega-3 polyunsaturated fatty acids (PUFAs), what makes them so special?

Omega-3 PUFAs are a heterogeneous group of fatty acids (Cholewski, Tomczykowa, & Tomczyk, 2018), divided into two main groups, long-chain omega-3, including EPA and DHA, mainly from marine foods, and ALA, found mostly in seeds, nuts, and their oils (Koh et al., 2015). EPA and DHA, together with another omega-3 fatty acid such as docosapentaenoic acid (C22:5*n*-3, DPA), can be synthesized from ALA (Shahidi & Ambigaipalan, 2018). Interest in these fatty acids has increased in recent years when it has found that they play an important role in welfare and disease prevention. A good number of scientific contributions provided results that support this assertion. The benefits of omega-3 PUFAs on cardiovascular health were first observed more than half a century ago. The consumption of fat from fish and Arctic mammals in large quantities by the Greenland Eskimo community and the low CVD incidence led researchers to suspect a dose-response relationship (Elagizi et al., 2018; Mori, 2017). This marine fat is rich in EPA and DHA, especially in oily fish. There are also significant levels of these acids in the fat and tissues of marine mammals, such as whales and seals (Innes & Calder, 2020). The inclusion of this LCFA in the diet throughout life is associated with improvement in the lipid profile leading to a reduction in the risk of suffering from CVD (Rangel-Huerta & Gil, 2018). This protection against diseases and conditions such as arterial hypertension, myocardial infarction, or cerebrovascular disease, is related to the ability of EPA and DHA to alter many physiological pathways and cardiovascular risk factors, including blood pressure, cardiac function, arterial compliance, vascular reactivity, and lipids. Additionally, antiplatelet, antiinflammatory, proresolving, and antioxidative activities have been reported (Mori, 2017). Alexander, Miller, Van Elswyk, Kuratko, and Bylsma (2017) carried out a comprehensive study of the effects of EPA and DHA intake on CHD incidence. Specifically, the authors assessed data from 18 randomized controlled trials and 16 prospective cohort studies published over a period of more than 50 years using metaanalysis. After carrying out this study methodology on the data extracted from randomized controlled trials, the results was not statistically significant, but a lower CHD risk can be inferred in participants who regularly consumed both EPA and DHA, including those with high levels of LDL cholesterol and TGs. On the other hand, the results of the analysis of data from prospective cohort studies also showed an inverse relationship between the consumption of both fatty acids and the CHD risk. Del Gobbo et al. (2016) found a similar result when addressing the analysis of a series of studies (a total of 19), in which were also intended to associate the intake of omega-3 PUFAs with CHD incidence. They indicated that the dietary intake of DPA helps to prevent this type of disease and reduce the risk of fatal outcomes. In contrast, other omega-3 PUFAs, such as ALA and DHA, were only shown to be effective in preventing a fatal outcome in the patients, but not in disease prevention. On the other hand, EPA and DHA were effective in preventing nonfatal myocardial infarction. The authors concluded that regular consumption of seafood and plant-based omega-3 PUFAs is associated with a lower risk of fatal CHD. However, Nestel et al. (2015) found no evidence either for or against the dietary intake of long-chain omega-3 PUFAs for the primary and secondary prevention of CHD. Other authors have also disagreed with the fact that omega-3 PUFAs have some beneficial effects on the cardiovascular system (Rizos & Elisaf, 2017; Walz, Barry, & Koshman, 2016).

This inconsistency of results may be due to intrinsic problems of the randomized and controlled trials performed. Indeed, these often have weaknesses in design, such as insufficient dose supplementation or lack of evaluation of long-chain omega-3 PUFAs before and during treatment (Maki & Dicklin, 2018). In an attempt to shed some light on this conflict, two trials have addressed many of these design limitations. One of these, called REDUCE-IT (Reduction of Cardiovascular Events with EPA Intervention Trial) reported positive results when supplementing with 4 g of icosapent ethyl (purified and stabilized ethyl ester of EPA) per day to patients with atherosclerotic cardiovascular disease (ASCVD) and elevated TG levels (≥ 150 mg/dL), who were receiving a stable dose of statin (a drug that inhibits the production of LDL cholesterol) at the beginning of the study. The treatment reduced the risk of the trial's primary atherosclerotic cardiovascular (CV) endpoint by 25%. Unlike all previously conducted trials, REDUCE-IT used patients with high TG levels (216 mg/dL on average) and a higher dose of omega-3 PUFA (4 g per day vs 850 mg per day in other large studies) (Baum & Scholz, 2019). Another similar trial called STRENGTH, completed in 2020, was conceived to assess whether the administration of a 4 g per day dose of a mix of omega-3 free fatty acids (75% EPA and DHA), called "epanova", can reduce TG levels in patients with hypertriglyceridemia and low levels of HDL cholesterol treated with statins (Nicholls et al., 2018). The investigators, however, concluded that this omega-3 fatty acid formulation did not affect the incidence of major adverse cardiovascular events in statin-treated patients at high cardiovascular risk but the findings also may raise broader issues of whether the high dose fish oil products might have benefits on the cardiovascular health.

It has been suggested that omega-3 PUFAs might have positive effects on cognition function, helping to prevent and ameliorate symptoms caused by neurodegenerative Alzheimer's disease (AD). The oxidative products of PUFAs might be involved in the reduction and resolution of inflammation caused by this disease, which would result in better neuronal health and increased neurogenesis and neuronal function. This would explain the lower AD incidence observed in populations with fish-rich diets, where the levels of DHA intake are higher. This fatty acid is abundant in fish oil and an essential component of membrane phospholipids in the brain (Devassy, Leng, Gabbs, Monirujjaman, & Aukema, 2016). In this regard, different prospective cohort studies and their metaanalysis seem to confirm that there is indeed a direct relationship between the periodic and prolonged consumption of fish and DHA and ALA fatty acids and a lower risk of dementia and AD (Cederholm, 2017). However, there is a certain disparity between the published data that suggests that more research is still necessary. After a systematic review, Wu et al. (2015) stated that high consumption of fish might reduce the risk of AD, but not dementia. In addition, they were not able to show either that such effects on the risk of AD were due to the intake of long-chain omega-3 acid. Similarly, Araya-Quintanilla et al. (2020) found no evidence of any relationship between omega-3 acid intake and progress in cognitive function in patients diagnosed with Alzheimer.

An inappropriate omega-6:omega-3 ratio has been shown to have detrimental consequences on body function. Historically, the relationship between these two PUFAs has been close to 1, which is considered essential for proper body development. However, the increase in agricultural production in the last 100–150 years has caused a change in this relationship. Livestock, which used to be grass-fed, is now fed with seeds, which also favors the production of vegetable oils rich in omega-6 PUFAs. The excessive introduction of these oils rich in fatty acids, such as LA or ARA, and the decrease in the consumption of omega-3-rich foods has led Western societies to increase the ratio omega-6:omega-3 from 1:1 to 20:1 (Simopoulos, 2016). This imbalance has generated a proinflammatory and proaggregatory state of health. Although LA helps to tackle high levels of LDL in plasma, it may cause an increase in the oxidation of these lipoproteins and thus increase the risk of CHD. In addition, metabolites generated during the oxidation of LA molecules may cause thrombosis and vasoconstriction (Dinicolantonio & Okeefe, 2019). Yang et al. (2016) showed that a diet with omega-6:omega-3 ratios of 1:1 and 1:5 had a cardioprotective effect in rats. Specifically, the authors found more favorable fatty acid profiles that produced antiinflammatory and antioxidant effects. In contrast, a high ratio (20:1) produced adverse effects. Despite these outcomes, the study emphasized the possible negative consequences of an excessively omega-3 PUFA-rich diet. Table 12.3 summarizes the main beneficial effects reported by the literature regarding omega-3 fatty acids.

5 The trans fatty acids (TFAs) and their health effects

As already commented at the beginning of this chapter, fatty acids with a *trans* configuration differ from those with a *cis* configuration in that the unsaturation does not generate any bends in the hydrocarbon chain and it remains linear (Fig. 12.3). *Trans* fats originate from natural or artificial sources. Some TFAs are produced by the bacteria in the rumen of ruminants and are found in foods, such as meat, milk, and dairy products. The consumption of these natural *trans* fats is minimal compared to those coming from artificial or industrial manufacture (Zupanič et al., 2018).

These are generated from oils through partial hydrogenation and because of their textural characteristics (solid consistency) and long shelf life, they are a reclaim for the food industry for the elaboration of many products, such as snacks and fast foods, becoming the most consumed *trans* fats (Mossoba, Srigley, McDonald, Azizian, &

Table 12.3 Beneficial effects of omega-3 fatty acids reported in original research papers.

Omega-3 fatty acid	Effect	Reference
Fish oil	Improvement of context- or auditory-dependent memory, anxiolytic, antidepressant, and antinociceptive effects in induced cognitive impairment	Nasehi, Mosavi-Nezhad, Khakpai, and Zarrindast (2018)
Fish oil + EPA + DHA	Promotion of posttraumatic brain injury restorative processes, including generation of immature neurons, microvessels, and oligodendrocytes	Pu et al. (2017)
Statin treatment (pitavastatin) + EPA	Reduction of plaque content in coronary arteries	Watanabe et al. (2017)
EPA + DHA	Attenuation of oxidative DNA damage and subsequent cell senescence	Sakai et al. (2017)
Seal oil (DPA, EPA, and DHA)	Supports early nerve regeneration in type 1 diabetic patients with nerve injury, favoring an increase in corneal nerve refiber length	Lewis et al. (2017)
EPA + DHA	Possible regulation of menstrual status in women with polycystic ovary syndrome by improving metabolic parameters: decrease in lipid profiles, waist circumference, and the interval between periods	Khani, Mardanian, and Fesharaki (2017)
DHA + EPA + vitamin D	Beneficial effects on fasting plasma glucose, serum insulin levels, insulin resistance, insulin sensitivity, triglycerides, and very-low-density lipoprotein (VLDL) cholesterol levels in gestational diabetes patients	Jamilian et al. (2017)
EPA, DHA, and ALA	Attenuation of breast cancer cell proliferation	Guo, Zhu, Wu., He, and Chen (2017)
Strong statin treatment (Atorvastatin, pitavastatin, rosuvastatin) + EPA	Reduction of plaque content in coronary arteries. Decrease in the production of inflammatory cytokines in patients with dyslipidemia	Niki et al. (2016)
EPA and DHA	Delayed cognitive impairment induced by vitamins of group B when they are above standard values	Oulhaj, Jernerén, Refsum, Smith, and De Jager (2016)
EPA + DHA	Increase in serum calcium level and high-density lipoprotein (HDL) cholesterol, and decrease in vascular cell adhesion molecule	Moeinzadeh et al. (2016)
EPA and DHA	Effects on the modulation of specific inflammation markers. Reduction in tumor necrosis factor-α. Reduction in triglyceride levels. Increase in low-density lipoprotein (LDL) cholesterol	Allaire et al. (2016)
DHA	Reduction in the production of interleukin-18 and 6 (IL-18, IL-6) and C-reactive protein.	
EPA + DHA	Reduction of fibrin generation in healthy patients. Reduction of peak thrombin production in healthy patients. Increased thrombin production time in a patient with cardiovascular disease (CVD). Short-term alteration of coagulation parameters	McEwen, Morel-Kopp, Tofler, and Ward (2015)

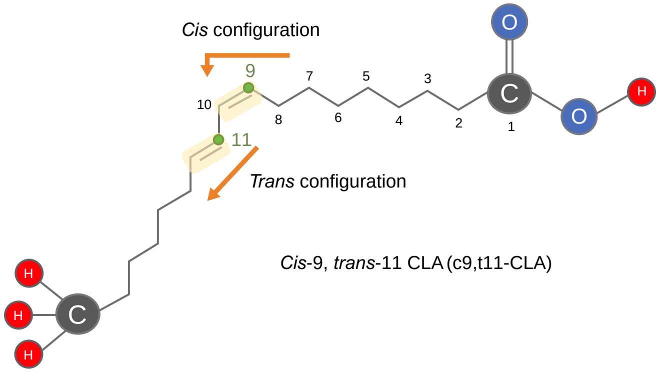

FIG. 12.3

Different spatial configurations (cis and trans) that double bounds can adopt in fatty acids.

No permission required.

Kramer, 2017). In the hydrogenation process, some double bonds of the fatty acid are saturated, decreasing the solidification point of the fat. However, this process is not 100% effective and some unsaturations may isomerize and change from *cis* to *trans* configuration (Hashempour-Baltork, Torbati, Azadmard-Damirchi, & Savage, 2016). Unfortunately, *trans* fats are in the spotlight for their possible harmful effects on health. A high concentration of TFAs in the blood would contribute to the promotion of inflammatory responses, and since their dietary intake corresponds to the levels found in plasma, limiting their consumption might be a way to prevent inflammation-related chronic diseases (Mazidi, Gao, & Kengne, 2017). The intake of TFAs has also been associated with deleterious effects on the cardiovascular system. Epidemiological studies have found a direct relationship between circulating LDL levels and the level of *trans* fat intake, with an increase in atherosclerosis incidence and CAD (Ganguly & Pierce, 2015). However, there appear to be no negative consequences at low concentrations. In fact, there could even be a positive effect. A study carried out in patients with chest pain or symptoms of possible myocardial ischemia [research framed within the Ludwigshafen Risk and Cardiovascular Health (LURIC) study] found that the highest concentrations of TFAs detected in the membrane of red blood cells (low compared to other population groups) corresponded to lower cholesterol and TG levels, lower fasting glucose, and lower blood pressure (Kleber, Delgado, Lorkowski, März, & Von Schacky, 2016). In addition, these authors have suggested that the consumption of *trans* fats of ruminants might be associated with a decrease in the risk of cardiovascular mortality and sudden cardiac death. Indeed, it seems that these TFAs may contribute to the maintenance of good cardiovascular health. The major ruminant TFA found in food is *trans*-11-vaccenic acid (C18:1*n*-7t) (De Souza et al., 2015; Ferlay, Bernard, Meynadier, & Malpuech-Brugère, 2017). The position of the *trans* bond at carbon 11 from the one that supports the acid functional group is associated with beneficial health effects. The few studies linking

TFAs from ruminants to health have not reported any adverse outcomes, and only diets with extremely high levels induce negative changes in blood lipids (Kuhnt, Degen, & Jahreis, 2016). On the other hand, it should be noted that the intake levels of these fatty acids are low. In European countries, the average daily intake of *trans*-11-vaccenic acid is 0.7–1.0 g. Amounts of this magnitude may not cause detectable changes in serum lipids (Dawczynski & Lorkowski, 2016).

6 Conclusions

The knowledge generated by the vast research carried out on the health effects of fat consumption suggests that an exacerbated consumption of SFA-rich food, such as animal fats and *trans* fats of artificial sources, has deleterious effects on the health and their replacement by MUFAs and PUFAs reverses this negative effect. However, this statement has implications that must be considered. It has been observed that the higher the number of carbons in the hydrocarbon chain of SFAs, the lower their harmful effect on health. The substitution of these fatty acids for other monounsaturated seems to have a positive effect on cardiovascular health. Olive oil stands as the largest source of this group of fatty acids in the diet, with oleic acid as the most representative compound. It is mostly considered responsible for the beneficial effects found in olive oil. However, there is still no general consensus on this issue among the scientific community. PUFAs have also been shown to be excellent candidates to replace SFAs in the diet due to multiple positive effects displayed in the body (e.g., regulation of inflammation and cellular growth, or pain). Nevertheless, an excess in the consumption of omega-6 PUFAs, such as LA and ARA, is associated with inflammatory processes and platelet aggregation. A greater intake of omega-3 fatty acids would reduce the proportion of omega-6 ingested and would alleviate these symptoms.

In general terms and based on the scientific findings to date, a diet limited in short-chain SFAs and abundant in MUFAs, especially C18:1*n*-9 from olive oil, and PUFAs, with an adequate proportion of omega-6 and omega-3 fatty acids might reduce the risk of certain food-related diseases.

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