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Soybean Polyunsaturated Fatty Acids Exert Potential Effects on the Natural Course of Inflammatory Diseases

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1. Introduction

Soybean yields about 18.5% oil in weight (Soyatech, 2008), a characteristic that makes it an important source of vegetable oil. The majority of soybean oil production is used by food processors and food service operators as an ingredient for baked and fried food products, or it is packaged for sale as a cooking oil (Soyatech, 2008). The importance of soybean oil in human nutrition can be expressed in numbers; it accounts for about 50% of all the vegetable oil and for about 30% of all oils and fats produced around the world (USDA, 2010).

As the soybean oil is primarily used for human nutrition, constituting an important fraction of the lipids present in the diet of the majority of the population, it raises great economic and scientific interests. A quick search in the web for the keywords "soybean" and "oil" give out a list of about 30,000 articles published only in the last 10 years and the number of annual publications in this area is growing up about 10% per year. The aims of the majority of these scientific works are born in the lipid profile of this oil. But, what about the lipid profile of the soybean oil? It contains an impressive amount of PUFAs. Typically, it contains about 60% polyunsaturated fatty acids (PUFAs), 25% monounsaturated fatty acids (MUFAs) and 15% saturated fatty acids (SFAs). The high content of PUFAs in the soybean oil raises some questions which are the basis of the following discussion.

Lipids are not simply a source of energy in human nutrition as they do exert other important functions. They compose biological membranes, serve as precursors of inter/intracellular signaling molecules, carry hydrophobic molecules in the bloodstream, functionalize biomolecules such as enzymes and receptors, participate in the digestive process and are involved in several other aspects of the mammalian physiology. Particularly their hydrophobicity was intensively explored in biological evolution and the life as it is known would not be possible in the absence of lipids. Every cell in the human body contains lipids and is sensible for lipid-derived signaling molecules. The majority of the lipids required by the human cells are synthesized by the human body and, as expected for any physiological process, the control of the lipid metabolism is fine-tuned by feedback mechanisms. However, not every kind of lipids needed for the physiological processes to work properly is totally synthesized by the human cells.

Some lipids cannot be synthesized by the human cells by a *de novo* process, i.e., they are not synthesized by the cells from simple and freely available substrates. In this case, the dietary

intake of this kind of lipid is not only recommended but in fact essentially necessary. A nutrient that cannot be synthesized from simple substrates and then should be obtained by means of dietary intake is called "essential nutrient", a designation that summarizes the importance of including this nutrient in a diet. There are classical essential lipids, which are the ω3 and ω6 PUFAs. These fatty acids contain carbon-carbon double bonds (unsaturations) at the extremity of the acyl hydrocarbon chain – the first unsaturations at the third and at the sixth carbon atom counting from the methyl extremity, respectively – that cannot be achieved with the enzymes of the human cells. Although the human cells are not able to synthesize these lipids from simple substrates such as acetyl-CoA, they are necessary for several physiological processes, and this is the reason why these PUFAs are essential nutrients.

An example of a process dependent on essential lipids is the synthesis of the eicosanoids, a group of signaling molecules that participate in several physiological processes such as immunity, digestion, reproduction and neurotransmission. When the cell consumes the ω3 and ω6 PUFAs, restoration of the supply of these lipids must be done by means of the dietary intake. For example, when the synthesis of an eicosanoid is activated in a cell, the long chain ω3 and/or ω6 PUFAs are consumed. These lipids cannot be restored by the human cell by a *de novo* synthetic pathway. Instead, the cell must receive new ω3 or ω6 PUFAs from the diet. Therefore, if an individual consume little or no food containing all the essential lipids, the cell is not able to exert its proper function and this can lead to a physiological malfunction. Besides this, not only the quantity is important but also the dietary ω3-to-ω6 PUFAs ratio. These two kinds of lipids can be used in the same metabolic pathways but the products obtained may present quite different actions in some cases (James et al., 2000). Moreover, the human cells incorporate not only PUFAs but also MUFAs and SFAs, and the diet is an important determinant for the lipid composition of the cellular structures, which affect several cellular processes as discussed here.

Why the human organism is not able to *de novo* synthesize these kinds of lipids? The rational answer – and probably the right answer – is that the development of the biochemical machinery for producing them was not necessary because the human organism has evolved in an environment where the food itself offered a rich supply of these lipids. But nowadays a great part of the human population is living in an industrialized world. The food does not come directly from natural sources anymore but instead it is industrially processed before reaching the homes. Besides this, the great variety of nutrient sources for human nutrition available before agriculture was substituted by the large scale cultivation of some few very productive cultures (oligoculture), such as soybean. In this context, the arbitrary manipulation of the diet can give higher or lesser amounts of certain essential nutrients than the required by the organism (Bourre et al., 1989; Rapoport et al., 2007). Since the diet is the only source of these essential nutrients, this dietary imbalance can lead to physiological malfunction and exert health-deleterious effects.

As some lipids are provided only or mainly by the diet and cells are specialized in taking up these lipids, the diet profoundly affects the lipid profile of biological structures (James et al., 2000; Pan & Storlien, 1993). The relative excess intake of PUFAs – and not only the most discussed imbalanced intake of ω3 and ω6 PUFAs – can exert important health-deleterious effects in humans and this fact is closely related to both the essential nature of these lipids and to their higher susceptibility to oxidation. When PUFAs are oxidized, the pathogenesis and the natural course of an inflammatory disease can be affected. Therefore, this review shows that some facts point to the need of a rational consumption of the PUFAs-containing aliments, such as the soybean oil. Several inflammatory diseases can be influenced by

dietary PUFAs and the allergies are among them and are used in this chapter as a representative example. The dietary ω3-to-ω6 PUFAs ratio, which is another well discussed subject in the specific literature, will not be minutely discussed here. Above all, this text stresses the rational basis upon which new dietary studies and health-beneficial improvements in soybean products can be performed.

2. Changes in the dietary lipid profile in the industrialized world

The soybean oil has high contents of PUFAs and MUFAs, which are far known to exert several health-beneficial effects on the metabolism of lipids in the human body. This oil is one of the main sources of these fatty acids for the most of the population around the world and the importance of this food as a lipid source in human nutrition is increasing year after year.

Both the MUFAs and PUFAs are generally known as the "good fat" based on their health-beneficial effects in the context of the cardiovascular system. On the dark side of fatty acids are the bad fats, or the saturated fatty acids (SFAs) which, along with cholesterol, are known by most of the population to exert deleterious effects on human health when consumed in large amounts. This kind of judgment was based on the findings of several epidemiological and laboratory studies which have shown several correlations between lipids and cardiovascular diseases. These studies laid the basis for general recommendations for a healthy diet, which included a liberal intake of unsaturated fatty acids and a low SFAs dietary content.

These recommendations took effect mainly in the industrialized world, which includes both the western countries and some countries with westernized lifestyle. In these countries, the media-driven scientific discussions on health and the health-appeal in food marketing led to a quite interesting phenomenon: a fast rise on the dietary P/S ratio on the population living under the western lifestyle. Along with this health-appeal other factors such as some economic influences probably exerted an important role, but surely the first cited factor is one of the main events behind rise on the dietary P/S ratio.

Now it is worth analyzing the trend in fat consumption in the industrialized world. The data concerning the period between the years of 1966 and 2000 in the United Kingdom (UK) is shown in the graph below (Fig 1a). By analyzing this graph it is possible to see a markedly significant decrease in the SFAs consumption and a concomitant increase in the PUFAs consumption which taken together led to a significant rise in the dietary P/S ratio. The Fig 1 shows that in 2007 the P/S ratio was about 0.5, while at the middle 1960' it was about only 0.2, i.e., there was a increase of about 150 % in the P/S ratio in only four decades. The UK is a representative example for the industrialized countries in the context of the dietary lipids, as the trend in lipid consumption showed in the figures 1 and 2 was observed in other industrialized countries too.

The Fig 1a shows that, although the PUFAs consumption increased significantly, the rise in the dietary P/S ratio was mainly due to a decrease in the SFAs consumption. The trend of reduction on the dietary contribution of lipids for the total energy intake is the main responsible for the reduction in absolute SFAs consumption observed in the UK and in other industrialized countries. One of the strategies for reducing the intake of lipids was the substitution of fatty products by low-fat or fat-free products in the diet. In fact, over the last decades, SFA-rich products were substituted by low-fat or PUFAs-rich products and this trend is still observable in the last years (Bates et al., 2010). For example, in the beginning of the last century, butter (SFAs-rich) was the most consumed fat spread; nowadays,

margarines (PUFAs-rich) and low-fat spreads are the most common type of fat spread consumed (Bates et al., 2010). But the most important example of a decrease in SFAs consumption is related to the milk and milk products, which account for about 25 % SFA consumed by the UK population (fig 2). The consumption of milk was reduced in the period between 1997 and 2007 by 18 % in the UK population aged 11 to 18 years. For adults this decrease was larger, as the consumption fell by 32 % (Bates et al., 2010).

(a)   (b)
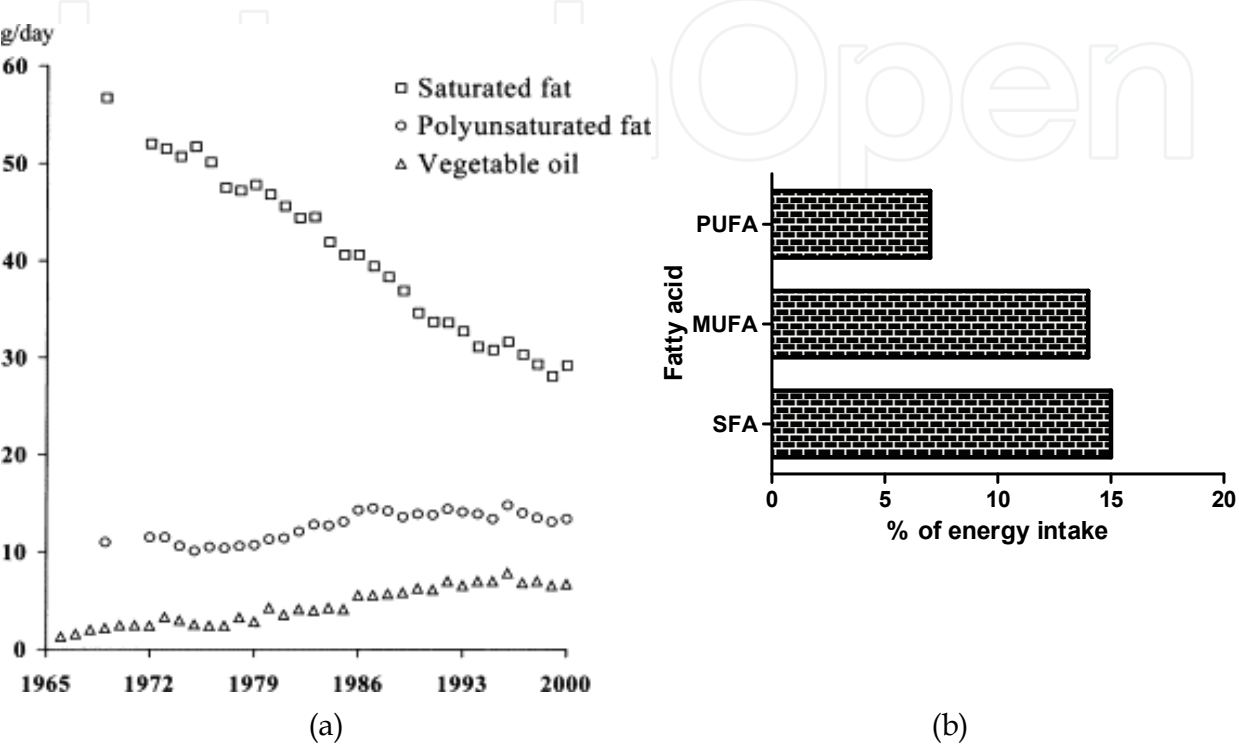
Fig. 1. a) Consumption of saturated fats, polyunsaturated fats and vegetable oils in the UK between 1966 and 2000 (DEFRA(UK), 2000; Devereux & Seaton, 2005); b) Dietary lipid profile in private UK households (Bates et al., 2010; DEFRA(UK), 2010).
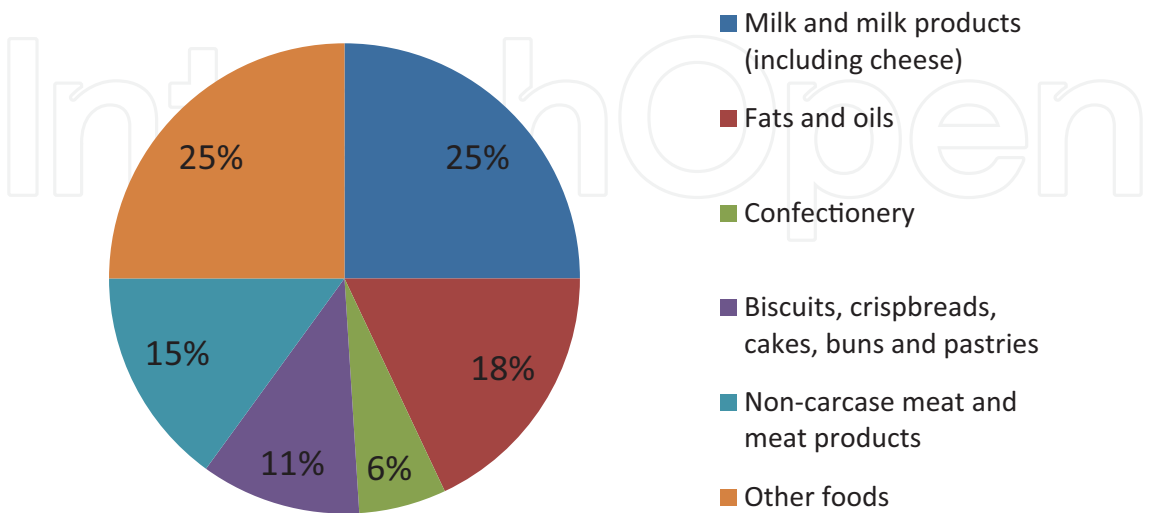

Fig. 2. Contributions of different sources of SFAs in household supplies in the United Kingdom in 2007 (DEFRA(UK), 2010).

Another interesting event concerning the change in dietary P/S ratio is that the rise in PUFAs consumption follows the rise in vegetable oil consumption (Fig 1a). This fact is easy to explain, as the vegetable oils are the main sources of PUFAs in human nutrition. The Fig 1a gives other relevant information about the PUFA consumption; the curves for both PUFAs and vegetable oils consumption are not perfectly parallel but instead they are convergent, evidencing that in the course of time the vegetable oils are contributing with an increasing fraction of the PUFAs in the westernized diet.

As soybean oil is increasingly the main vegetable oil used for human feeding purposes, its lipid profile is of great importance in human nutrition. For example, the linoleic acid (a ω6 PUFA) accounts for about 80% of the total PUFAs in soybean oil (Sanders, 2000). The linoleic acid is the main source of PUFAs in the diet of the UK population and the consumption of this fat increased about 50 % (from about 10g/day to 15g/day) between the 1970s and the 1990s in the UK (Sanders, 2000). The worldwide consumption of the soybean oil – as in the UK – has significantly increased over the last decades turning this oil one of the main responsible for the high content of linoleic acid in the diet of the population in the industrialized world (Sanders, 2000). These facts point to the important role played by soybean oil as a source of PUFAs (Sanders, 2000) in a population who is consuming more and more vegetable oils-derived PUFAs and less SFAs.

Now the discussion reaches a point where the trend in dietary lipid profile observed in the last decades should be paralleled to some events observed in the population under these drastic dietary changes. The increase in the dietary P/S ratio was accompanied by a concomitant decrease in the prevalence of several cardiovascular diseases, but could the dietary P/S ratio increase indefinitely with no deleterious effects on the human health? The next topics will stress why the optimal diet should include controlled amounts of PUFAs, MUFAs and SFAs instead of a higher as possible P/S ratio.

3. The western lifestyle-associated increase in allergy susceptibility

Several studies showed that, since the second half of the 20th century, the prevalence of allergic diseases is rising. This is not simply due to better diagnostic tools or to changes in diagnostic criteria. This could not also be due to a change in the genetic composition of the population, such as an increase in the percentage of the genetically susceptible individuals in the population. The common conclusion made by the authors at the time of the germinal studies in this area was that there should be an environmental change associated with allergy pathogenesis that could be responsible for the rise in allergy prevalence. It would not be so interesting if this effect was observable worldwide; instead, surprisingly, this increase had a geopolitical frontier! In 1993, the study by Nina and Russel showed that, between the years of 1964 and 1989, the prevalence of asthma and other allergies had doubled in Aberdeen, Scotland (Ninan & Russell, 1992). Still Another study in UK also showed that the prevalence of asthma had significantly risen over the same period (Burr et al., 1989). Similar results were found for different types of allergies and in different countries, like Australia, New Zealand, Finland, Sweden, United States and Canada (Seaton et al., 1994). On the other hand, other study showed an interesting finding regarding to asthma prevalence in Germany: the prevalence of this allergic disease was not the same in the areas of the two former German Republics; instead, it was significantly higher in West Germany in comparison to the East Germany (Magnussen et al., 1993). What was the difference between these two populations under the same flag? The population of the West Germany was under

a typical western lifestyle, which was very different from that found in the former eastern neighbor.

Further studies had shown similar results. The rise in the prevalence of allergies was restricted to the countries where the population was living under the western/westernized lifestyle. For example, the prevalence of asthma in three countries of the African region of Maghreb (Algeria, Morocco and Tunisia) is significantly lower than that found in industrialized countries, but in the urbanized regions (coastal cities) of these African countries this prevalence is higher than in the rural regions. Again, this event was associated with the westernized lifestyle adopted by the urban population (Bourdin et al., 2009). Therefore, there are plenty of solid evidences showing that the industrialized world shares its frontiers with the areas where the allergy prevalence has significantly increased.

Therefore, as the increase in allergy prevalence is somehow restricted to the industrialized countries (Devereux & Seaton, 2005; Grundy et al., 2002; Ramsey & Celedón, 2005), some issues can be raised. How could industrialization affect the susceptibility to allergy? What characteristics do the industrialized countries share that made its population more prone to develop allergy? Is the answer to this question a simple one or, alternatively, could this answer be complex, involving different and not necessarily correlated factors? Actually we do not know what the right answer is. Most probably a complex answer will be revealed as more studies are performed. Anyway, at the time these questions began to be raised, some hypotheses were formulated based on the knowledge on allergy pathogenesis and immune system available at that moment. These hypotheses did not ignore the fact that the rise in allergy prevalence was related to the westernized lifestyle, characteristic of the population of the industrialized world (Busse, 2000). The main first hypotheses presented below were based on the behavioral and environmental changes associated with the western lifestyle. Some of these hypotheses partially helped to explain the epidemiological data and opened new areas of interest in immunological researches.

3.1 Pollution?

The early industrial revolution increased the levels of airborne pollutants, including some environmental allergens. Therefore, a group of hypotheses was based on a supposed increase in the exposure of the population to allergens and other pollutants, which occurred mainly in the industrialized world. Indeed several air pollutants associated with the industrial activity characteristic of the developed world, such as sulphur dioxide and ozone, are known to increase the susceptibility to allergies and airway diseases. The logical basis of this kind of hypothesis is quite simple and therefore it initially raised some interest. However, it failed to explain why the allergy prevalence was increasing when the level of some important airborne pollutants (such as ozone) were stable (Seaton et al., 1994). Moreover, some pollutants (such as sulphur dioxide) had even decreasing atmospheric levels at the same period when the allergy prevalence was increasing (Seaton et al., 1994). If the airborne pollutants were the main responsible for the increased allergy prevalence in developed countries it would be expected that the increase in the level of these pollutants would parallel the increase in the prevalence of allergies; but this was not observed.

3.2 Hygiene?

Another hypothesis referred to a more complex characteristic of the westernized countries. This hypothesis proved to be solid as several evidences support it. This is the so called

"Hygiene Hypothesis", which was firstly proposed by Strachan who observed that the number of hay fever cases was inversely proportional to the household size (Okada et al., 2010; Strachan, 1989). This hypothesis proposes that the lower incidence of infections early in life due to better hygiene conditions, to the lower exposure of healthy individuals to infected ones (less siblings), and to the availability of new and better health care methods, – characteristics of the developed countries – could affect the whole development of the immune system, leading to an increased susceptibility to allergy. Indeed, the development of a proper immune response against antigens involves a complex network of cells and molecules, which are engaged in destroying harmful while tolerating innocuous molecules/cells. As allergy is related to an inadequate immune response to exogenous innocuous antigens, the inadequate development of the immune system early in life could in fact lead to an increased susceptibility to allergy. In this context, it is not surprising that the Hygiene Hypothesis is also applied to autoimmune diseases (Okada et al., 2010). The Hygiene Hypothesis is a good hypothesis for the purpose of explaining why the westernized lifestyle increases the susceptibility to allergies. However, it is very probable that this is just a partial and not the only explanation as other aspects of the westernized lifestyle have been associated to an increased susceptibility to allergy development. The dietary P/S ratio is one of them and it is minutely discussed below.

3.3 Dietary lipids?

There are plenty of evidences pointing to a correlation between diet and susceptibility to allergies (Devereux & Seaton, 2005). The changes in the westernized diet are increasingly being associated to the rise in the allergy prevalence seen in the industrialized world (Devereux & Seaton, 2005; McKeever & Britton, 2004). The dietary influence is not restricted to the most known sensitization to food allergens itself; it is notably related to the influence of some essential nutrients mainly on inflammation and on cell redox status. The investigation of the influence of vegetable oils consumption on the natural course of inflammation became increasingly important as epidemiological and laboratory studies showed some interesting facts linking the biosynthesis of proinflammatory mediators with the dietary lipid profile. Interestingly, dietary lipids can influence inflammation due to their interaction with oxidant species, which is closely related to the chemical characteristics of these lipids.

Since the association between oxidative stress and allergic inflammation was evidenced, some investigations focused on the potential effects of antioxidant nutrients on the asthmatic inflammation, as asthmatic patients are deficient in antioxidants such as vitamin C, vitamin E (Kalayci et al., 2000; Shanmugasundaram et al., 2001) β-carotene, α-carotene, lycopene, lutein e β- cryptoxanthin (Wood et al., 2005). The main rationale of these investigations was that the allergy-associated oxidative stress along with the deficiency in essential antioxidant nutrients could increase the risk of developing more intense allergy symptoms. Moreover, it was demonstrated that, in asthmatics, dietary supplementation with vitamin E attenuates the oxidative stress (Roberts, 2007), improves the pulmonary ventilation (Gilliland et al., 2003) and reduces both the production of IgE and the allergen sensitization (Fogarty et al., 2000). Besides these effects, the finding that the ratio between plasmatic oxidized/reduced tocopherol is directly proportional to the gravity of the asthmatic inflammation (Wood et al., 2008) is another evidence of the important role played by antioxidants in reducing the severity of allergic inflammation. Therefore, some authors suggest that the decreased intake of antioxidant nutrients due mainly to a decreased

consumption of fresh vegetables verified in the western diet in the last decades (Devereux & Seaton, 2005; Fogarty et al., 2000), increase the biological susceptibility to oxidative damage and lead to a higher susceptibility to allergy (Baker & Ayres, 2000). The influence of the oxidative stress in other inflammatory diseases is also very significant and the dietary intake of antioxidants can influence the inflammation in these cases.

Along with the antioxidants, the lipids figure among the nutrients which have been most extensively studied in the context of allergies. Black and Sharpe were the first authors to suggest that the dietary lipid profile could be associated to the increase in allergy prevalence in the industrialized world (Black & Sharpe, 1997). They noticed an apparent and interesting correlation between the trend in lipid consumption and the prevalence of allergies in developed countries (Black & Sharpe, 1997). According to these authors, the increase in dietary P/S ratio preceded and then accompanied the rise in the incidence of allergic diseases. This is a very interesting and intriguing conclusion, since it put a close correlation between dietary lipid profile and allergies.

Since the study by Black and Sharpe was published, several investigations support that the dietary lipid profile associated with the westernized lifestyle – high dietary P/S ratio – increase the susceptibility to allergies. In 2001, Bolte and cols demonstrated that the consumption of margarine – a source of vegetable PUFAs – was positively associated with allergic sensitization in children, as the allergy prevalence in this group was found to be significantly higher in comparison to the control group composed by children consuming butter – source of SFAs (Bolte et al., 2001). In a study published in 2003, Wijga and cols associated the consumption of milk and butter – again, important sources of SFAs – by almost 3000 children aged 2 years to a lower susceptibility to allergy when these children reached the age of 3 years (Wijga et al., 2003). In other study, in 2001, Haby and cols concluded that a PUFAs-rich diet is a significant risk factor for the development of asthma in children aged from 3 to 5 years (Haby et al., 2001). Interestingly, these authors even pointed that about 17 % of the asthma cases studied were directly associated only to a high intake of PUFAs and suggested that PUFAs consumption is a factor with a great potential to be modified in order to reduce the susceptibility to asthma in children [29].

Both the intake of antioxidant nutrients and the dietary lipid profile are behind the main mechanism by which the diet influences the natural course of inflammation, although the following discussion will be centered in the lipids themselves and in the potential effects of the soybean oil on allergy. Now it is worth discussing the reason why the lipids present in a tissue under oxidative stress – such as the lungs of an asthmatic individual – can be modified in such an extent that they can affect the inflammation and why the diet can influence the intensity of this event.

4. Mechanisms behind the influence of dietary lipids on allergies

Resuming the germinal study by Black and Sharpe, the mechanism pointed by these authors for the correlation between the dietary lipid profile and allergy risk was based mainly on a lower $\omega 3$ intake (Black & Sharpe, 1997). The main suggestion was that the dietary lipid profile in the western diet could favor the production of prostaglandin E_2 (PGE_2), a mediator of inflammation, which would then increase the susceptibility to allergic sensitization (Black & Sharpe, 1997). As the substrate for the PGE_2 synthesis is the arachidonic acid, a $\omega 6$ PUFA, the hypothesis suggested by Black and Sharpe was not simply based on an increase on the dietary P/S ratio, but it highlighted an increase of the $\omega 6$-to-$\omega 3$ PUFAs ratio – which was

also inferred by the authors based on the available data. In fact, by the time this study was published it was known that dietary ω6-to-ω3 PUFAs ratio significantly affects inflammation and there is a still growing huge mass of researches on this subject. Generally, these researches have focused on the anti-inflammatory effects of ω3 PUFAs which are mainly – but not fully – due to the competition of the ω3 with the ω6 PUFAs for the same enzymes in the eicosanoid biosynthesis pathways, leading to the production of a less pro-inflammatory mixture of eicosanoids in comparison to that generated by ω6 PUFAs.

There are studies on diet and allergy showing that the consumption of ω3 PUFAs, such as the docosahexaenoic acid (DHA) found in fish oil, reduces the risk for developing asthma (Hodge et al., 1996). However, a systematic review on the effects of the dietary supplementation of asthmatic patients with fish oil shows that this procedure is not associated with beneficial effects and furthermore there is a lack of evidences supporting this approach for helping controlling asthma (Woods et al., 2003). Therefore, the dietary ω6-to-ω3 PUFAs ratio is not the only factor behind the effects of dietary PUFAs on allergy (Devereux & Seaton, 2005).

4.1 PUFAs are better substrates for non-enzymatic oxidation reactions in comparison to MUFAs and SFAs

Dietary PUFAs are incorporated by cells and can affect several cell processes and characteristics (Nishiyama et al., 2000). These lipids can be used as substrates for enzymatic reactions which produce lipid-derived molecules that serve as messengers in several physiological processes, such as inflammation. In comparison to SFAs and MUFAs, the PUFAs have quite different chemical features and this fact must be stressed on a hypothesis linking dietary P/S ratio to allergy susceptibility. A characteristic of all the PUFAs (including ω6 and ω3) is their higher susceptibility to oxidation in comparison to both SFAs and MUFAs (Frankel, 1984). In biological systems, this characteristic is exploited by biosynthetic enzymatic pathways, such as those leading to eicosanoid production. However, in some situations, such as inflammation, this oxidation can be non-enzymatic and involves oxidant molecules such as free radicals that evade the antioxidant system.

Obviously, due to the potential deleterious effects following oxidation of biomolecules, biological evolution has led to the development of a complex and efficient antioxidant system in order to neutralize oxidant species. In healthy tissues, the antioxidant system is capable of neutralizing oxidant species, avoiding them to react with other important biological molecules. For example, the group of molecules generically named as vitamin E is an important component of the antioxidant system and is mainly found in biological lipid membranes, where it reacts with oxidant species, such as hydroxyl or lipid radicals (see "lipid radicals" in Figure 4), avoiding the continuation of the lipoperoxidation reaction (Matés et al., 2000). Another important component of the antioxidant system is the catalase, an enzyme responsible for degrading the hydrogen peroxide (Rahman et al., 2006), the main source of hydroxyl radical in biological cells.

It is just because of the existence of this antioxidant system that the non-enzymatic oxidation of PUFAs in healthy tissues is strictly limited and it has little or no biologically significant effects. But in some situations the antioxidant system is not capable of neutralizing all the oxidant species. This may occur when there is an increased production of oxidant species or when the antioxidant capacity itself is decreased. Anyway, when the level of oxidant species in a certain biological tissue or cell is high enough to surmount the antioxidant system, a phenomenon named "oxidative stress" occurs. Oxidative stress is often accompanied by

oxidative damage in biomolecules – non-enzymatic oxidation – leading to cell malfunction. As discussed below, the non-enzymatic radical-mediated oxidation of PUFAs that occur in tissues under oxidative stress can have deleterious consequences that significantly affect the pathogenesis of allergies, the inflammatory disease discussed here.

In the context of fatty acid oxidation the PUFAs are by far the preferential substrates compared with MUFAs and particularly with SFAs. The molecular structures presented in the figure 3 help understanding this characteristic. In this figure both the structure of a PUFA and of a bisallylic group are presented; the presence of two carbon-carbon cis-double bonds (unsaturations) spaced by a single carbon atom is the distinctive characteristic shared by the PUFAs and this type of unsaturated system is called the bisallylic group (figure 3b). This system is especially susceptible to radical attack and is present neither in MUFAs nor in SFAs. The reaction diagramed in the figure 3b is one of the possibilities for the production of a lipid radical, the main mechanism by which the lipids are non-enzymaticaly oxidized. In this reaction, the hydroxyl radical ($\cdot$OH) abstracts a hydrogen atom from the bisallylic group, producing a radical in which the unpaired electron is shared by 3 carbon atoms of the system. This phenomenon is called electronic resonance and the more the unpaired electron is dispersed in the resulting radical by resonance the more stable is the radical. This high stability renders this lipid radical sufficiently long-lived to react with other molecules – mainly with oxygen, as discussed ahead.

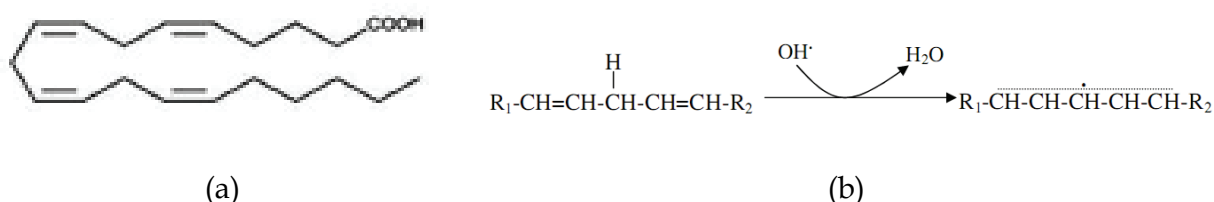

(a)　　　　　　　　　　　　　　　　　　　　　　(b)

Fig. 3. a) The structure of a polyunsaturated fatty acid (PUFA), the arachidonic acid; b) the bisallylic system is particularly prone to radical abstraction of a hydrogen atom from its central carbon due to the stabilization by resonance in the resulting radical.

The formation of the lipid radical is the key event for the initiation of the biologically relevant process known as lipoperoxidation (Frankel, 1984). In lipid membranes, the lipid radical is formed when the PUFA is esterified in the phosphatidic acid backbone of a phospholipid (Cracowski et al., 2002). It can then react with an oxygen molecule, generating another radical named the lipid peroxyl radical, which is able by its turn to react with another PUFA molecule (Frankel, 1984), producing another lipid radical (see figure 4). Therefore, when a peroxyl radical is generated in a PUFA-rich environment the lipoperoxidation can virtually continue indefinitely if the peroxyl radicals are not neutralized by some antioxidant. Such a PUFA-rich environment is found in biological lipid membranes and thus these structures are particularly prone to oxidative damage. When the cell is under oxidative stress the lipoperoxidation of PUFAs can persist sufficiently longer to produce deleterious effects.

4.2 Non-enzymatic oxidation of PUFAs can produce modified fatty acids with biological activity

Neither MUFAs nor SFAs present bisallylic systems. Due to this feature, MUFAs and SFAs are markedly less prone to the non-enzymatic radical-mediated oxidation in comparison to

PUFAs. Therefore, the higher the relative PUFA content of a certain biological structure – such as the cell membrane – the higher its susceptibility to the effects of oxidation. But does the higher dietary P/S ratio, observed in the westernized diet, affect the oxidability of biological structures? Several studies support an affirmative answer, indicating that the dietary lipid profile is the main variable behind the oxidability of biological structures (Aguilera et al., 2002; Berry et al., 1991; Cicero et al., 2008; Kratz et al., 2002; Mata et al., 1997; Muehlmann et al., 2009). However, how could the non-enzymatic oxidation of PUFAs affect the health? The answer for this question is as complex as the lipid metabolism itself. At one hand are the oxidation-mediated structural damages, on the other hand are the effects on the inter/intracellular signaling (Montuschi et al., 2004).

Regarding the cell signaling, several PUFA-derived molecules are produced by enzymatic pathways in normal physiology, which are under a fine-tuned feedback control. However, when an inflammatory disease generates the oxidative stress, the non-enzymatic radical-mediated fatty acid oxidation occurs in a significant extent (Talati et al., 2006) and, interestingly, this type of reaction is able to produce several molecules that mimic the physiological inflammatory mediators. Resuming the discussion on the allergy prevalence – the example used here in order to stress the health effects of a higher dietary P/S ratio – it is known that several PUFAs-derived molecules generated by enzymatic pathways are involved in allergy pathogenesis. It is not different when considering the inflammatory mediators generated by non-enzymatic oxidation of PUFAs. These mediators are produced after lipoperoxidation without the conventional feedback regulation (Marathe et al., 2000), having potential effects on the pathogenesis of allergies.

As some authors observed before, lipoperoxidation exerts deleterious effects in asthma (Wood et al., 2003), such as enhancement of airway hyperresponsiveness (Held & Uhlig, 2000; Talati et al., 2006), smooth muscle constriction (Fukunaga et al., 1993; Kawikova et al., 1996), airway obstruction, plasma exudation (Okazawa et al., 1997) and vascular constriction (Kromer & Tippins, 1996; Möbert et al., 1997). These references related these effects to the lipoperoxidation although these effects are classically known to be due to the activity of some proinflammatory mediators generated physiologically by enzymatic pathways in inflamed tissues. How could lipoperoxidation affect inflammation as it was due to the physiological pro-inflammatory mediators? The effect can be indirect, i.e., the lipoperoxidation damages the cells, an event that activates the production and release of pro-inflammatory mediators. But it also happens because some products of PUFAs lipoperoxidation possess biological activity analogous to that of the enzymatically-generated pro-inflammatory mediators. These biologically active PUFAs-derived molecules are named accordingly to the mediator molecule with which they share activity. In this context, two main types of inflammatory mediator-like molecules generated by peroxidation of PUFAs will be discussed: the isoeicosanoid and the PAF-like molecules, which have activity of eicosanoid and platelet-activating factor (PAF), respectively. These two kinds of non-enzymatically generated inflammatory mediators are known to exert biological actions that are important in several inflammatory diseases.

4.2.1 Isoeicosanoids: isoprostanes, isoleukotriene B4 e isotromboxanes

After lipoperoxidation (figure 4), the fatty acid peroxyl radical can undergo chemical rearrangements and the addition of further oxygen molecules. These modifications can produce molecules with prostaglandin, leukotriene B_4 or thromboxane-like activity
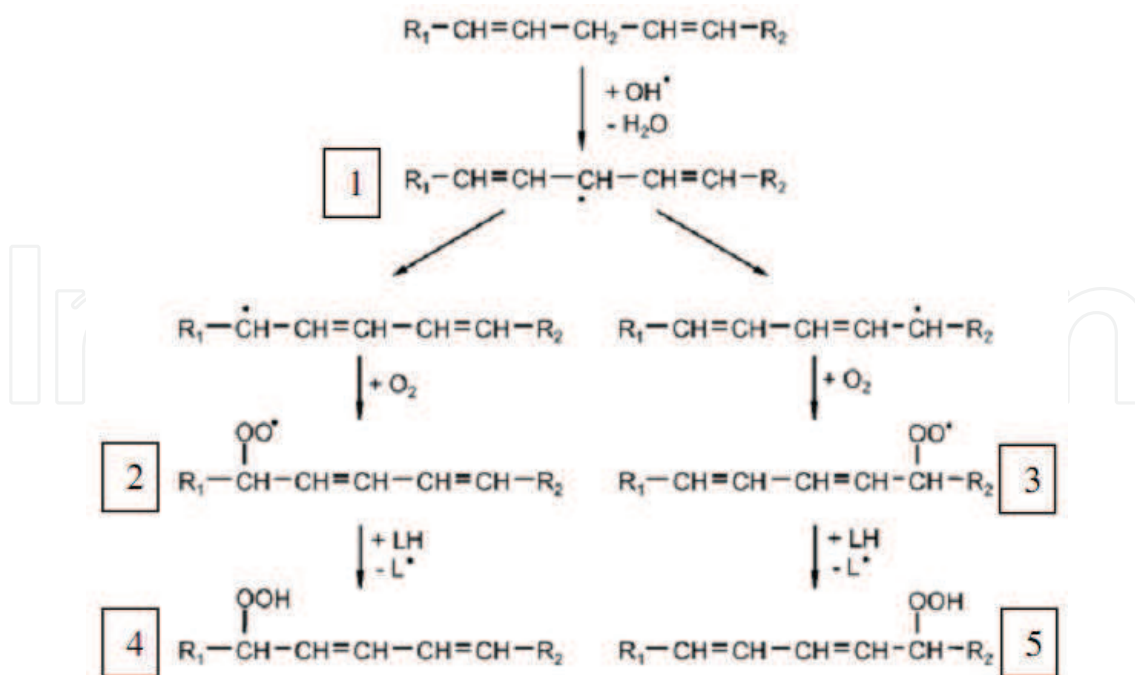
Fig. 4. The main steps involved in the formation of lipid hydroperoxides (4 and 5) from a lipid radical (1). Note that the lipid peroxyl radicals (2 and 3) are capable of producing additional lipid radicals (L·), leading to the continuation of the lipoperoxidation process. Adapted from Spitteler (2001) (Spiteller, 2001).

(Kayganich-Harrison et al., 1993; Wood et al., 2003) which are named, respectively, isoprostanes (iP), isoleukotriene B_4 (iL) and isothromboxane (iT) (Harrison & Murphy, 1995; Morrow & Roberts, 1996). The figure 5 schematically shows the reactions for the production of four types of iP-F_2 molecules. All the reactions presented in this diagram are initiated when a PUFA (arachidonic acid) is firstly converted into a radical by some oxidant species. Note the reaction where the PUFA radical is converted into a peroxyl radical; this radical is able to produce more PUFAs radicals by abstracting a hydrogen atom from the bisallylic system. In the sequence, further rearrangements and additions of oxygen molecules produce the molecular complexity necessary for conferring these molecules an iP activity. The rationale for the production of iL and iT is basically the same, with some differences in the steps after the formation of the peroxyl radical.

The iPs are the most studied isoeicosanoids. The generation of these molecules is strongly associated with oxidative stress, so that they are used as markers of both oxidative stress and lipoperoxidation (Cracowski et al., 2002). The iPs are formed by the peroxidation of the PUFA arachidonic acid (Morrow et al., 1990) generally esterified in phospholipids, from which they can be released by phospholipase-mediated hydrolysis (Cracowski et al., 2002; Morrow et al., 1990). Some iPs exert important roles in the asthma pathogenesis, such as bronchiolar (Cracowski et al., 2002) and vascular (Morrow et al., 1990) constriction, alveolar plasma exudation (Okazawa et al., 1997) and airways hyperresponsiveness (Sametz et al., 1999). These effects are related to the prostaglandin-like activity conferred to these oxidized PUFAs by the structural similarity with the prostaglandins. The structures of both the prostaglandin $F_{2\alpha}$ and the iP F_{2a} generated by the non-enzymatic PUFA oxidation can be observed in the figure 6; their structural similarities are reflected in their similar biological activities.
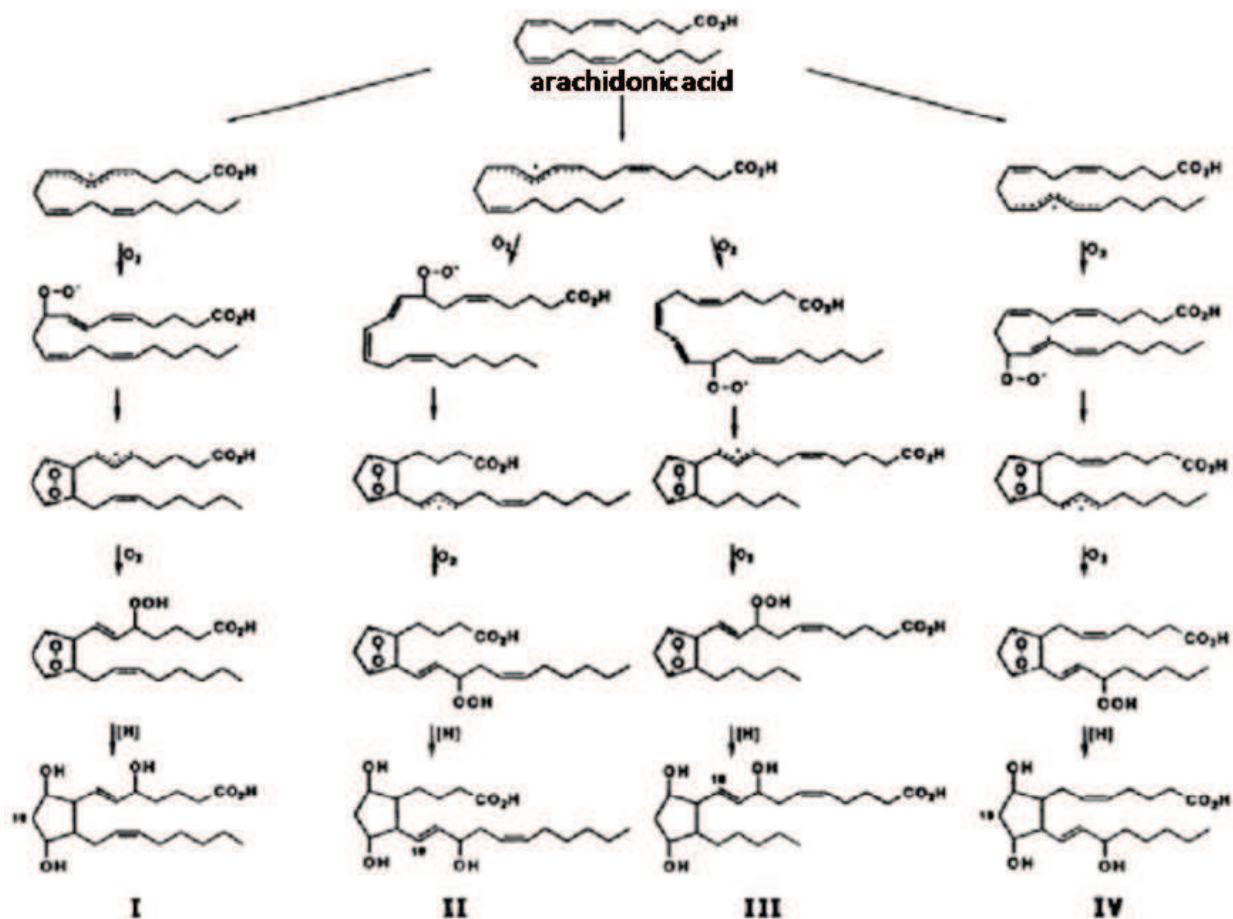
Fig. 5. Steps in the formation of isoprostanes by means of lipoperoxidation. Four possible isoprostane F_2 isomers are formed from arachidonic acid (Morrow et al., 1990).
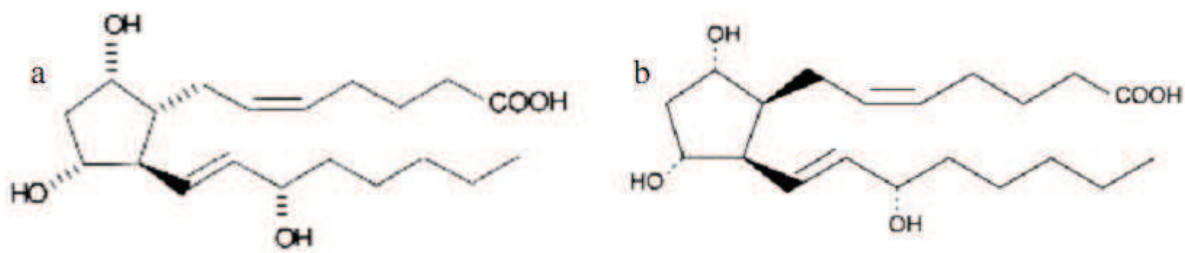
Fig. 6. a) Prostaglandin $F_{2\alpha}$ and b) one of its analogous molecules generated by means of lipoperoxidation, the isoprostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$).

PAF-like phospholipids

The molecules with biological activities shown in the precedent topic are generated by non-enzymatic oxidation and rearrangement occurring in PUFAs in an oxidant environment. Another important non-enzymatic oxidation reaction leading to the generation of some molecules with pronounced biological activity is the hydrocarbon chain cleavage that can occur in PUFAs. As in the formation of isoeicosanoids, the reactions leading to the formation of PAF-like lipids are initiated by lipoperoxidation. The schematic reaction steps are presented in the figure 7.

Both the PUFAs peroxyl (LOO·) and alkoxyl (LO·) radicals can undergo hydrocarbon chain cleavage (figure 7 and 8) producing shortened carbon-chains and aldehydes (Marathe et al., 2000). These radicals are easily formed by a reaction involving lipoperoxide and transition metallic cations (Coffey et al., 1995), such as the ferrous (figure 8).
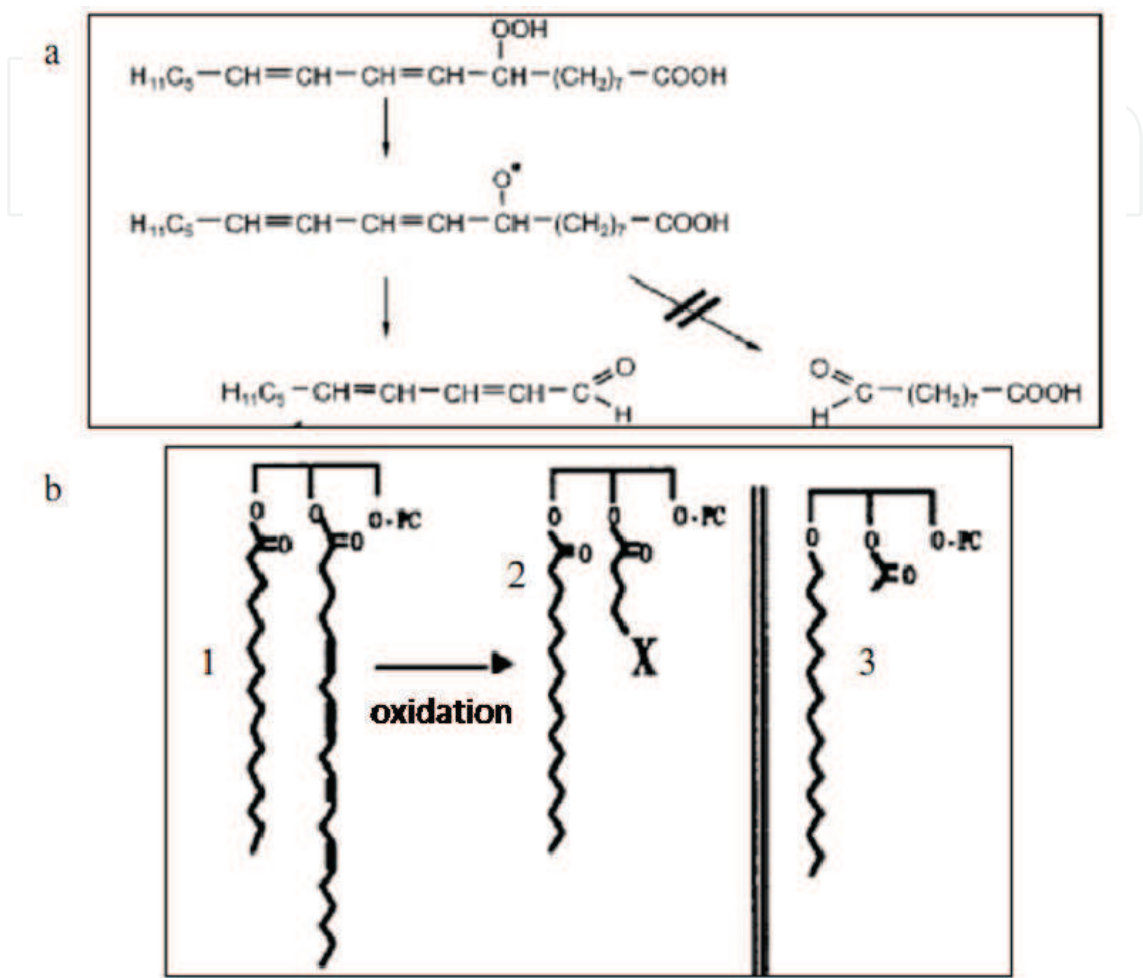

Fig. 7. a) Cleavage of a carbon-carbon bond in the hydrocarbon chain of a polyunsaturated fatty acid hydroperoxide; adapted from Spitteler (2001) (Spiteller, 2001). b) The shortening of the acyl hydrocarbon chain in the sn-2 position of a phosphatidylcholine (1) yields a PAF-like lipid (2), whose structure and activity resemble those of the authentic PAF; based on Zimmerman and cols (1995) (Zimmerman et al., 1995). The phosphatidylcholine precursor of a PAF-like molecule can have an acyl or an alkyl group in the sn-1 position (Stremler et al., 1991).
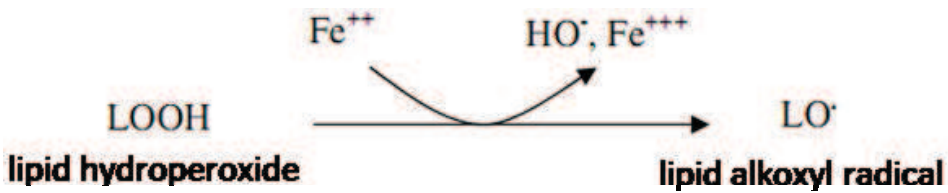

Fig. 8. Formation of a lipid alkoxyl radical by the cleavage of the peroxide bond in the presence of ferrous cation.

When a phosphatidylcholine contains a oxidatively shortened acyl group esterified in the sn-2 position, the resultant phospholipid can present PAF-like biological activity (Marathe et al., 2000). Once more, this phospholipid with a shortened sn-2 hydrocarbon chain has biological activity just because it has a close structural similarity to a biologic messenger, in this case the PAF (figure 7). It was shown that the formation of PAF-like phospholipids can take place in cell membranes (Patel et al., 1992), lipoprotein particles such as the LDL (Heery et al., 1995) and in synthetic phosphatidylcholines (Smiley et al., 1991).

Even if produced in low amounts, the PAF-like phospholipids derived from the non-enzymatic oxidation of PUFA-containing phospholipids exert several important actions in inflammatory diseases. The PAF is a highly potent and versatile proinflammatory mediator known to exert several effects in different cells (Uhlig et al., 2005). PAF is biosynthesized from the precursor sn-1 alkyl phosphatidylcholine and it is structurally named 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine (Marathe et al., 2001). Physiologically, PAF is produced by the transesterification of the sn-2 position of the lysophosphatidylcholine glycerol backbone, where an acetyl group substitutes the usual long-chain fatty acyl group in a fine-tuned enzymatic reaction (Marathe et al., 2001). The pathogenesis and the pathophysiology of several inflammatory diseases involve the PAF actions and several studies demonstrate that this pro-inflammatory mediator has important roles in the asthmatic inflammation, such as leukocyte chemotaxis and activation, increase in vascular permeability, vasoconstriction, and bronchial constriction and hyperresponsiveness (Chung, 1992; Hsieh & Ng, 1993; Uhlig et al., 2005; Zimmerman et al., 2002). The PAF-like phospholipids are about 10 times less potent than the PAF itself (figure 9) however, taking into account that PAF elicits proinflammatory effects even in subnanomolar concentrations

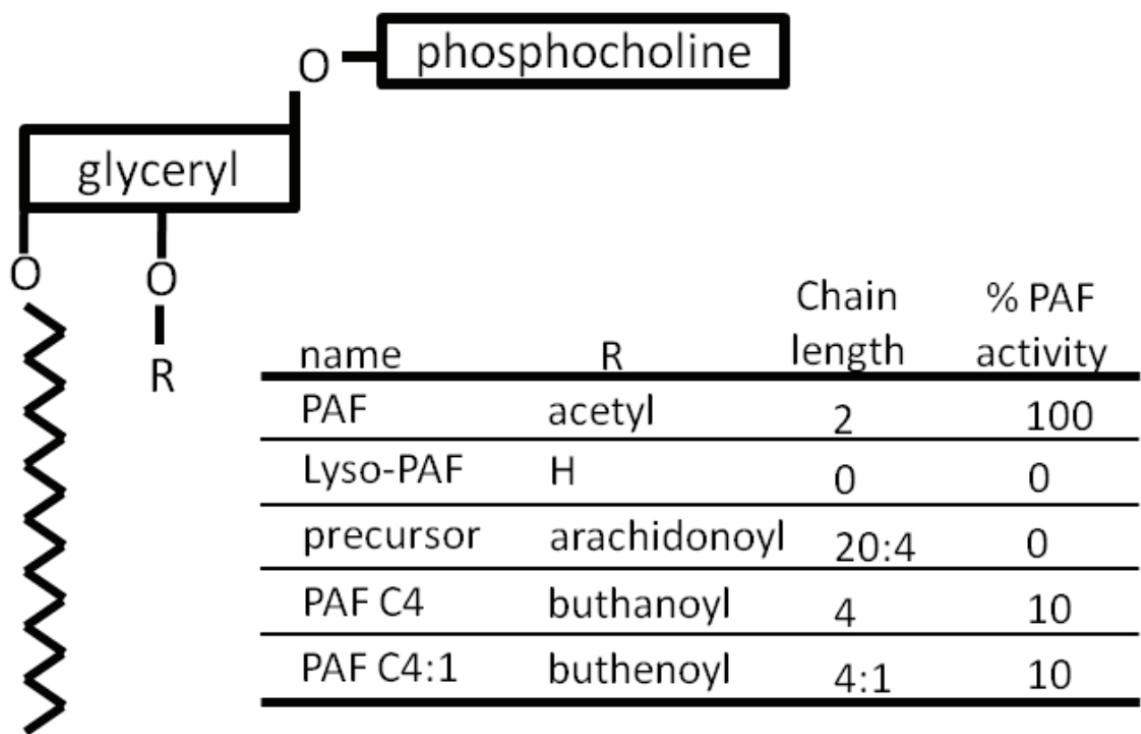| name	R	Chain length	% PAF activity
PAF	acetyl	2	100
Lyso-PAF	H	0	0
precursor	arachidonoyl	20:4	0
PAF C4	buthanoyl	4	10
PAF C4:1	buthenoyl	4:1	10

Fig. 9. PAF and its structural analogues. Phosphatidylcholine containing a shortened acyl group in the sn-2 position has PAF-like activity. Adapted from Marathe and cols (2001) (Marathe et al., 2001).

(Marathe et al., 2001), the non-enzymatic production of PAF-like phospholipids is an important event in inflammatory diseases (Marathe et al., 1999). In addition to the PAF-like phospholipids containing the fatty alkyl group in the sn-1 position, a characteristic of the PAF, it was shown that some PAF-like phospholipids can have a fatty acyl group in this position (Stremler et al., 1991), though these lipids are about 800 times less potent than their sn-1 alkyl analogs (Marathe et al., 1999).

5. The rational consumption of vegetable oils can help controlling inflammatory diseases

The PUFAs are essential nutrients and the consumption of these lipids is a necessary component in any healthy diet. However, there is a relative limit for PUFAs consumption. The arguments presented here lead to the conclusion that there is in fact a healthy limit for the dietary P/S ratio, especially when the subject is inflammatory diseases. The PUFAs are necessary for several physiological processes and the control of some cellular characteristics, such as the fluidity of cellular membranes, the functionality of membrane-associated proteins, the cell-cell communication (as messengers), the intracellular signaling, the neurotransmission, the fat metabolism, and so on. However, once the proportion of PUFAs in biological structures is above a certain limit, the oxidative damage that occurs in oxidative stress situations – such as during inflammation – can be very deleterious due to the high oxidability of these PUFAs-rich structures.

As the dietary PUFAs are incorporated in the cells, the oxidability of the cellular structures is affected by the dietary lipid profile. The great amount of PUFAs in soybean oil is an important feature of this widely consumed edible oil and the importance of this food as a lipid source is growing up as it is more and more used for human nutrition. PUFAs account for about 60% of the total fatty acids content in the soybean oil and linoleic acid, a ω6 PUFA, accounts for about 80% of the soybean PUFAs. The molecules derived from oxidized PUFAs – generated in inflamed tissues – can exert significant effects on the natural course of inflammation, an event that can be partially responsible for the worsening or for the developing of an inflammatory disease, such as allergy.

Indeed, a recent study showed that dietary supplementation with soybean lecithin (a soybean oil derivative) exerts deleterious effects on asthma by means of PAF-like molecules – a product of the oxidation of PUFAs-containing phosphatidylcholine, discussed above (Muehlmann et al., 2009). In this study, the diet of asthmatic rats was supplemented with soybean lecithin, increasing the dietary P/S ratio in comparison to the control group, receiving a conventional diet. The authors showed that both the PAF activity – which includes the activity of both PAF and PAF-like molecules – and lipoperoxidation were increased in the lungs of the group receiving soybean lecithin. Interestingly, these effects were totally reverted by the concomitant supplementation with vitamin E, evidencing that the dietary lipids and the cell redox status affect inflammation by means of the products of PUFAs oxidation possessing pro-inflammatory activity (Muehlmann et al., 2009).

There is a huge mass of data available in the literature on the association between dietary lipids and the risk of inflammatory diseases. The evidences and the rationale presented here can be used in order to improve the lipid profile of the soybean as well as for the design of diets with the optimal lipid profile. As the dietary SFAs increase the plasma LDL levels and

the risk of a cardiovascular disease, high MUFAs, instead of high SFAs, diet has already been recommended for reducing the oxidability of biological structures (Berry et al., 1991; Cicero et al., 2008). Anyway, it is becoming increasingly clear that the consumption of vegetable oils or even the lipid profile of the vegetable oils could be improved in order to help controlling the inflammatory diseases.

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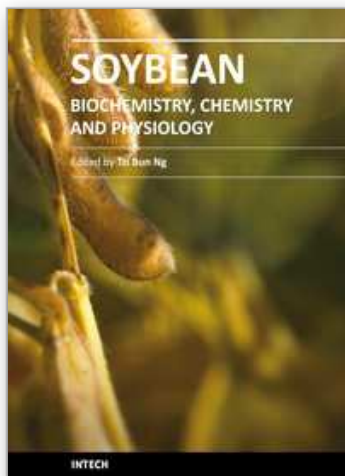
Soybean - Biochemistry, Chemistry and Physiology

Edited by Prof. Tzi-Bun Ng

Soybean is an agricultural crop of tremendous economic importance. Soybean and food items derived from it form dietary components of numerous people, especially those living in the Orient. The health benefits of soybean have attracted the attention of nutritionists as well as common people.

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