

## Mini Review

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# Oxidation of Polyunsaturated Fatty Acids and its Impact on Food Quality and Human Health

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## ABSTRACT

For many years, both preclinical and clinical studies have provided evidences to support the beneficial effects of  $\omega$ -3 Polyunsaturated fatty acids (PUFAs), particularly Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) in the prevention of chronic diseases. However, recently, an increasing number of studies reported adverse or contradictory effects of  $\omega$ -3 PUFAs on human health. While dose and experimental condition need to be considered when evaluating these effects, oxidation of PUFAs also serves as an important factor contributing to the inconsistent results. In fact, oxidation of PUFAs happens frequently during food processing and storage, cooking and even after food ingestion. The free radicals and metabolites generated from PUFA oxidation may adversely affect food quality and shelf life by producing off-flavors and reducing nutritional values. The impact of PUFA oxidation in human health is more complicated, depending on the concentration of products, disease background and targets. This review will introduce different types of PUFA oxidation, discuss its impact on food quality and human health and provide some thoughts for the future research directions.

**KEYWORDS:** Polyunsaturated fatty acids; Oxidation; Food quality; Human health.

**ABBREVIATIONS:** ALA:  $\alpha$ -Linolenic acid; LOX: Lipoxygenase; COX: Cyclooxygenase; MaR: Maresin; CYP: Cytochromes P450; PD/NPD: Protectin/neuroprotectin; DHA: Docosahexaenoic acid; PL: Phospholipase; EPA: Eicosapentaenoic acid; PUFA: Polyunsaturated fatty acid; GST: Glutathione S-transferase; RvD: D-series resolvins; HHE: 4-Hydroxy-2-hexenal; RvE: E-series resolvins; HNE: 4-Hydroxy-2-nonenal; FAO: Food and Agriculture Organization; WHO: World Health Organization; AHA: American Heart Association.

## INTRODUCTION

Over the past few decades, chronic diseases including cardiovascular diseases, obesity, diabetes and cancer have increased rapidly in the USA and other countries of the world.<sup>1</sup> Diet and nutrition are important factors in the maintenance and promotion of good health throughout the entire life. By far, both preclinical and clinical studies have shown that  $\omega$ -3 Polyunsaturated fatty acids (PUFAs) in particular Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) exert health beneficial effects on cardiovascular diseases, diabetes, cancer and so on.<sup>2-5</sup> This leads to institutions worldwide publishing recommendations on the intake of EPA and DHA. For instance, Food and Agriculture Organization (FAO) and World Health Organization (WHO) recommend adults to take 0.25-2 g EPA+DHA per day.<sup>6</sup> American Heart Association (AHA) recommends daily intake of 0.5-1 g EPA+DHA per day per adult.<sup>7</sup>

However, as reviewed by Weylandt et al more recently, there are controversial results regarding to the health efficacy of  $\omega$ -3 PUFAs.<sup>8</sup> On one hand, the dose and experimental designs may contribute to the variation in results. On the other hand, with the nature of unsaturated bonds, PUFAs are prone to oxidation which generates various metabolites as well as reactive oxygen species. The extent of oxidation and the resulting metabolites may positively or negatively affect the efficacy of PUFAs. This review will introduce different types of PUFA

oxidation and discuss the effects of oxidation on food quality and human health.

#### ENZYMATIC AND NON-ENZYMATIC OXIDATION OF PUFAS

With multiple unsaturated bonds, PUFA is susceptible to oxidation, which is categorized into non-enzymatic oxidation and enzymatic oxidation. Non-enzymatic oxidation can be further divided into autoxidation (mediated by free radicals) and photooxidation (mediated by ultraviolet or singlet oxygen). In cells, several types of enzymes including Cyclooxygenases (COXs), Lipoxygenases (LOXs) and Cytochromes P450 (CYPs) are able to oxidize PUFAs and generate various metabolites.<sup>9</sup>

##### Non-Enzymatic Oxidation

In autoxidation, the reaction is mediated by free radicals, giving rise to a lipid hydroperoxide as the primary oxidation product.<sup>10</sup> In many cases, hydroperoxides can be further oxidized to ketones and ultimate malonaldehyde.<sup>11</sup> Hydroxy alkenals such as 4-Hydroxy-2-nonenal (HNE), generated by peroxidation of  $\omega$ -6 PUFAs,<sup>12-14</sup> and 4-Hydroxy-2-hexenal (HHE), a product from peroxidation of  $\omega$ -3 PUFAs<sup>15-17</sup> are also widely-studied autoxidative products of PUFAs. Apart from autoxidation, PUFAs are susceptible to light-induced photooxidation: photochemical oxidation and photosensitized oxidation.<sup>18</sup> The former one is initiated during exposure to ultraviolet irradiation. Photosensitized oxidation, instead, requires photosensitizers (*i.e.* chlorophyll, hemeprotein, riboflavin and synthetic dyes) and visible light.<sup>19</sup> The reaction can be categorized into two types: Type I reaction involves the production of free radicals by interaction of the excited sensitizer with a substrate; Type II reaction involves generation of singlet oxygen which further reacts with PUFAs to produce hydroperoxides.<sup>20,21</sup> In this case, vegetable oils with chlorophyll-like pigments are likely to undergo photooxidation during storage.

##### Enzymatic Oxidation

In enzymatic oxidation, Phospholipases A2 (PLA2) is the major phospholipase that cleaves phospholipids at the sn-2 position resulting in free PUFAs and lysophospholipids.<sup>22</sup> After freeing from membrane, PUFAs can be further catalyzed by COXs (COX1 or COX2) to form prostaglandin H2. It is unstable and can be converted into various prostanoids depending on the cellular prevalence of terminal prostanoid synthases.<sup>23,24</sup> In addition to COX, free fatty acids can be converted by LOXs to form hydroperoxides. LOXs belong to a family of dioxygenases which catalyze the insertion of molecular oxygen into PUFAs with at least one *cis*, *cis*-1,4-pentadiene in the structure.<sup>25</sup> Some of the LOX-catalyzed products have recently been discovered as potent lipid mediators. For example, enzymatic oxygenation of EPA yields new metabolites, named E-series Resolvins (RvEs), which were the first omega-3 lipid mediators reported to resolve inflammation *via* receptor-specific actions.<sup>26-28</sup> Likewise, DHA can form D-series Resolvins (RvDs),<sup>29,30</sup> Protectins/neuroprotec-

tins (PDs/NPDs)<sup>31-33</sup> and Maresins (MaRs)<sup>34-36</sup> through enzymes-mediated oxygenation. Those metabolites have been widely studied to dampen or resolve inflammation, protect from renal or brain dysfunctions, *etc.* COXs and LOXs can also convert  $\omega$ -3 and  $\omega$ -6 PUFAs into different series of prostaglandins, thromboxanes and leukotrienes.<sup>37</sup> CYPs are better known for their role in xenobiotic metabolism. However, they can also transform PUFAs to epoxy-, monohydroxylated-and dihydroxylated-metabolites. Recent work using recombinant human CYP enzymes has identified the predominant products from the epoxidation of EPA and DHA as 17,18-epoxyeicosatetraenoic acid and epoxy docosapentaenoic acid, respectively.<sup>38</sup>

#### IMPACT OF PUFA OXIDATION ON FOOD QUALITY

Plant oils and fish are known as major sources of  $\omega$ -3 PUFAs. Soybean oil, canola oil are commonly consumed oil and are rich in  $\alpha$ -Linolenic acid or Alpha-linolenic acid ((ALA), 7.8-9.2%), while some fatty fish including salmon, sardine, and menhaden contain abundant EPA and DHA (17%-27% of total fatty acids). Other dietary sources of  $\omega$ -3 PUFAs include nuts, seeds, egg yolk, *etc.*<sup>39,40</sup> With the recognition of the health beneficial effects of  $\omega$ -3 PUFAs, there is a growing industry providing novel sources of  $\omega$ -3 PUFAs such as fish oil capsules, algae products and food enriched with  $\omega$ -3 PUFAs.<sup>41</sup> Our lab recently used defatted green microalgal biomass to enrich  $\omega$ -3 PUFAs in chicken meat<sup>42</sup> and eggs (unpublished).

Susceptibility of lipid peroxidation in food depends on the lipid composition, the presence of prooxidants and antioxidants, oxygen levels, temperature, light and processing methods.<sup>43</sup> PUFA-rich foods are more susceptible for lipid oxidation. Likewise, presence of prooxidants such as redox active metals (Fe, Cu) and hemeproteins, exposure to high oxygen levels and high temperature may accelerate oxidation process. Lipid oxidation often brings problems in food processing and storage. First, it negatively affects food flavor due to the formation of aldehydes and ketones. Oxidation of PUFAs produces a complex mixture of volatile secondary oxidation products, and these cause particularly objectionable off-flavors.<sup>44</sup> For example, soybean oil can undergo "flavor reversion", a type of light-induced oxidation.<sup>45</sup> It has been suggested that the oxidation of ALA in soybean oil is responsible for the formation of 2-pentylfuran and its isomer, which may result in flavor reversion.<sup>46</sup> Butter enriched with unsaturated fatty acids or conjugated linoleic acid may be susceptible to off-flavor by generation of oxidized products including 3-methyl-1H-indole (mothball-like), pentanal (fatty), heptanal (green) and butanoic acid (cheesy).<sup>47</sup> Second, lipid oxidation may reduce the nutritional value by causing the destruction of essential fatty acids and the lipid-soluble vitamins A, D, E, and K as well as the decrease in caloric content.<sup>48</sup> Third, free radicals and metabolites formed during oxidation may exert adverse effects on human health.<sup>49</sup> More details of impact on human will be discussed in the next section.

Given lipid oxidation-triggered negative effects, mul-

multiple methods have been applied to reduce or prevent lipid oxidation so as to improve the food quality. The most commonly used method is addition of antioxidants. Since the 1940's, it is known that vitamin E is a major lipophilic chain-breaking antioxidant which protects tissue PUFAs against peroxidation<sup>50</sup> Serfert et al found a combination of tocopherols (rich in the  $\delta$ -derivative and low in the  $\alpha$ -derivative), ascorbyl palmitate and trace metal chelators (lecithin or citrem) efficiently stabilized the oil during microencapsulation. Addition of rosemary extract in the microencapsulated oil further retarded autoxidation during storage.<sup>51</sup> Besides vitamin E, other vitamins or precursors like ascorbic acid and  $\beta$ -carotene were shown antioxidant activity in food system.<sup>18,52</sup> Plant bioactive compounds particularly polyphenols have been widely reported to have antioxidant effects. For example, apple skin extracts prepared from "Northern Spy" cultivar were found effective in reducing the lipid oxidation induced by heat, Ultraviolet (UV) light and peroxy radicals.<sup>53</sup> Although it is plausible that natural polyphenols could prevent lipid oxidation, the approach of incorporating polyphenols into food and the effects of polyphenol additives on food flavor are not completely understood. In addition to the antioxidant supplementation, other methods are used to reduce lipid oxidation. Arruda et al reported that using nitrogen flushing to remove oxygen in the headspace of bottled soybean oil increased the sensory quality during storage. Shelf life can also be increased from 60 up to 180 days as the initial oxygen concentration is reduced from >15% to <3%.<sup>54</sup> Larsen et al found that cups with a high light barrier (incorporation of a black pigment into the packaging material) can sufficiently protect the sour cream from getting rancid due to photooxidation.<sup>55</sup>

#### IMPACT OF PUFA OXIDATION ON HUMAN HEALTH

In human body, PUFA is susceptible to oxidation under the exposure of free radicals and enzymes such as COXs, LOXs and CYPs. An increasing number of studies have been conducted to identify the oxidation pathway of PUFAs and related metabolites. However, the impact of PUFA oxidation on human health remains elusive.

HNE, a product from  $\omega$ -6 oxidation of PUFAs, has been found in many diseases including atherosclerosis,<sup>56,57</sup> neurodegenerative diseases,<sup>58,59</sup> cancer<sup>60,61</sup> and so on. Indeed, Uchida et al have recently found that HNE markedly induced intracellular ROS production in cultured rat hepatocytes RL34 cells.<sup>62</sup> This pro-oxidant effect of HNE was also observed in human neuroblastoma SH-SY5Y cells.<sup>63</sup> Awada et al reported that oxidized PUFAs (rich in HNE and HHE) induced oxidative stress and inflammation in mice and in human intestinal Caco-2/TC7 cells.<sup>64</sup> In human trials, Jenkinson et al also found that high PUFA diet (15% PUFA) significantly increased whole blood oxidized glutathione and urinary thiobarbituric acid reactive substances, indices of oxidative stress, in healthy male subjects.<sup>65</sup> Interestingly, PUFA oxidation products have also been reported to activate antioxidant pathways which detoxify cytotoxic xenobiotics. For instance, HNE has been shown to enhance the gene and protein

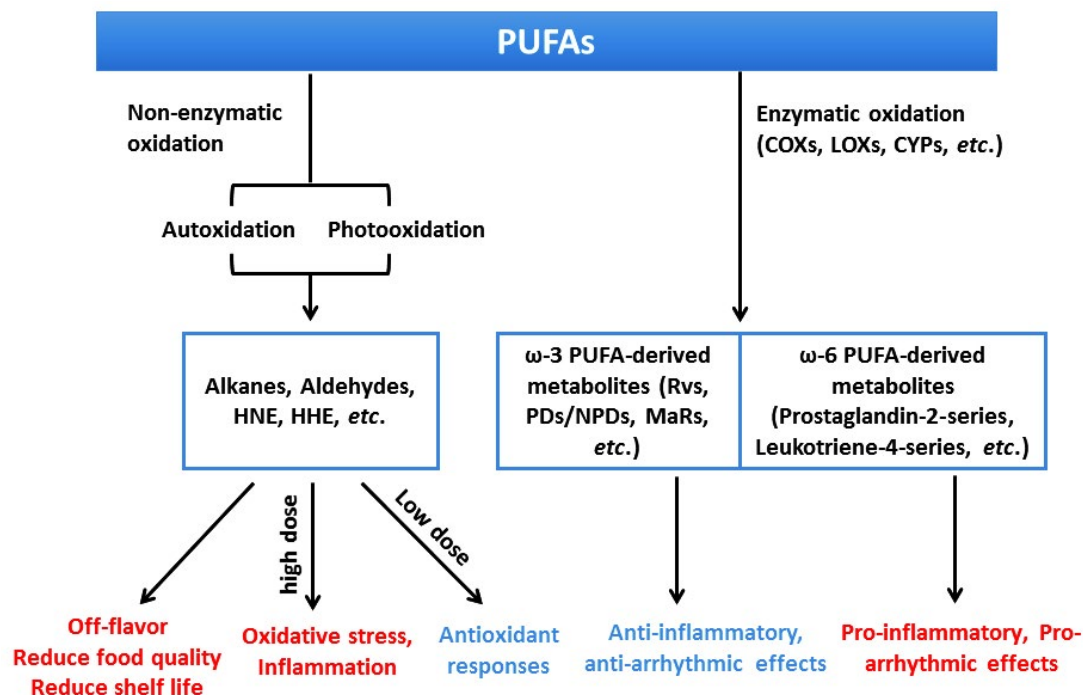
expression of class P Glutathione S-Transferase (GST-P) as well as the total GST activity in normal rat liver epithelial cells.<sup>66</sup> HNE can also activate antioxidant response element, leading to the induction of class A GST isozymes, such as GSTA1 and GSTA4, in rat clone 9 hepatoma cells.<sup>67</sup> In addition, HNE up-regulated nuclear factor, erythroid 2-like 2, an important regulator of antioxidant responses in the heart of high fat-fed mice.<sup>68</sup> The bi-directional effects of HNE or HHE are concentration dependent. HNE at concentration lower than 10  $\mu$ M tends to exert beneficial effects while higher concentrations may have toxic effects.<sup>69</sup> As supported by Zhang et al, treating cardiomyocytes with small, subtoxic doses (5  $\mu$ M) of HNE offered protection from subsequent exposure to toxic doses ( $>=20$   $\mu$ M).<sup>70</sup>

Over a decade, a growing number of PUFA metabolites have been discovered, including  $\omega$ -3 PUFAs-derived resolvins, protectins, maresins, prostaglandin-3-, thromboxane-3- and leukotriene-5-series as well as  $\omega$ -6 PUFA-derived prostaglandin-2-, thromboxane-2- and leukotriene-4-series.<sup>37,71</sup>  $\omega$ -3 PUFA-derived metabolites have shown potent anti-inflammatory, tissue protective and resolution-stimulating functions. For instance, RvDs and PD1/NPD1 inhibit neutrophil infiltration into injured kidneys, block toll-like receptor-mediated inflammatory activation of macrophages and mitigate renal dysfunctions.<sup>72</sup> Recently, Chiang et al demonstrated a previously unrecognized role of GPR18 as a receptor for RvD2 that stimulates efferocytosis and mediates the resolution of inflammation.<sup>73</sup> Another type of lipid mediator, MaR1 and MaR2 were identified to have potency at enhancing human macrophage phagocytosis and efferocytosis.<sup>34,74</sup>  $\omega$ -3 PUFAs-derived prostaglandin-3- and leukotriene-5-series have been found to exert anti-arrhythmic and anti-inflammatory effects, respectively. By contrast,  $\omega$ -6 PUFAs-derived prostaglandin-2-series have shown pro-arrhythmic effects and leukotriene-4-series from  $\omega$ -6 PUFAs have presented pro-inflammatory effects.<sup>37,75</sup> This indicates that enzymatic oxidation products of  $\omega$ -3 and  $\omega$ -6 PUFA may exert opposing effects on human health.

From current studies, we learnt that more PUFAs do not necessarily yield better effects as they may undergo oxidation and produce metabolites that exert adverse effects at high levels. Co-supplementation with antioxidants such as vitamin C and vitamin E may reduce autoxidation of PUFAs and potentially enhance the efficacy. In addition, increasing  $\omega$ -3 to  $\omega$ -6 ratio in the diet is likely to produce more beneficial metabolites, thereby enhancing efficacies of PUFAs. The optimal dose of PUFAs, antioxidant supplementation as well as  $\omega$ -3 to  $\omega$ -6 ratio, however, require additional research evidences.

#### CONCLUSION

As summarized in Figure 1, through non-enzymatic and enzymatic oxidation, PUFAs are transformed to various metabolites. In most cases, oxidation of PUFAs results in off-flavors and reduction of food quality and shelf life. The oxidation may induce oxidative stress and inflammation when the



COX: Cyclooxygenase; CYP: Cytochromes P450; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HHE: 4-Hydroxy-2-hexenal; HNE: 4-Hydroxy-2-nonenal; LOX: Lipoxygenase; MaR: Maresin; PD/NPD: Protectin/neuroprotectin; PUFA: Polyunsaturated fatty acid; Rv: Resolvin.

**Figure 1:** The oxidation of PUFAs and its impact on food quality and human health. With multiple unsaturated bonds, PUFAs can undergo both non-enzymatic and enzymatic oxidation and generate a variety of metabolites. Oxidation of PUFAs often brings adverse effects to food by producing off-flavors, reducing food quality and shelf life. The non-enzymatic oxidative products may induce oxidative stress and inflammation at high concentrations while exerting antioxidant effects at low concentrations. The enzymatic oxidative products of  $\omega$ -3 and  $\omega$ -6 PUFA may have opposing effects on inflammation and cardiac arrhythmicity.

metabolites are at high concentrations. At low concentrations, the metabolites may exert antioxidant effects. The enzymatic oxidative products of  $\omega$ -3 and  $\omega$ -6 PUFAs may have opposing effects on inflammation and cardiac arrhythmicity. At present, the functions and working mechanisms of PUFA metabolites are not completely understood. Moreover, whether PUFA itself or oxidized PUFA metabolites play more important roles in various disease context remains unclear. Herein, future studies are needed to tackle these problems.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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