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Review

Dietary advanced lipid oxidation endproducts are risk factors to human health

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Lipid oxidation in foods is one of the major degradative processes responsible for losses in food quality. The oxidation of unsaturated fatty acids results in significant generation of dietary advanced lipid oxidation endproducts (ALEs) which are in part cytotoxic and genotoxic compounds. The gastrointestinal tract is constantly exposed to dietary oxidized food compounds, after digestion a part of them are absorbed into the lymph or directly into the blood stream. After ingestion of oxidized fats animals and human have been shown to excrete in urine increase amounts of malondialdehyde but also lipophilic carbonyl compounds. Oxidized cholesterol in the diet was found to be a source of oxidized lipoproteins in human serum. Some of the dietary ALEs, which are absorbed from the gut to the circulatory system, seems to act as injurious chemicals that activate an inflammatory response which affects not only circulatory system but also organs such as liver, kidney, lung, and the gut itself. We believe that repeated consumption of oxidized fat in the diet poses a chronic threat to human health. High concentration of dietary antioxidants could prevent lipid oxidation and ALEs generation not only in foods but also in stomach condition and thereby potentially decrease absorption of ALEs from the gut. This could explains the health benefit of diets containing large amounts of dietary antioxidants such those present in fruits and vegetables, or products such as red-wine or tea consuming during the meal.

Keywords: ALEs / Diet / Lipid oxidation / Oxycholesterols / Reactive carbonyls

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This article focuses on pro arguments about "Dietary ALEs are a risk to human health".
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1 Introduction

For decades the role of lipids in health and disease has received increasing attention. Saturated fats and dietary cholesterol, because of their alleged role in the etiology of atherosclerosis and ischemic heart disease, have received an inordinate amount of attention in relation to public health [1–4]. Several epidemiological studies, as well as experimental data, suggest that populations on diets characterized by the Western pattern, with high intakes of high-fat red-meat, processed meat, butter, processed and fried foods, eggs and refined grains, but low in fruits and vegetables, are at a high risk for the development of atherosclerosis and of several kinds of cancers, especially colon cancer [5–9].

The association between low-density lipoprotein (LDL) cholesterol and atherogenesis is now firmly established, based, in part, on atherosclerotic complications, and the observation that cholesterol-lowering therapy greatly diminished the clinical manifestations of atherosclerosis. Despite the association between atherosclerosis and LDL cholesterol, LDL particles did not appear to be atherogenic in themselves, but became so only after minimal modification [10]. Oxidation, as a process which leads to a biological modification of LDL particles, that supports foam cell formation by macrophages, was proposed by Steinberg *et al.* [11]. Many data support LDL modification in atherogenesis, although confirmation that oxidation is the requisite LDL modification for atherogenesis is not complete and the origin of such modification *in vivo* is uncertain [12].

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Abbreviations: AGEs, advanced glycation endproducts; **ALEs,** advanced lipid oxidation endproducts; **GSH,** glutathione; **HNE,** 4-hydroxy-2-nonenal; **LDL,** low-density lipoprotein; **LOOH,** lipid hydroperoxide; **MDA,** malondialdehyde; **mm-LDL,** minimal modified LDL

Atherosclerosis may result, at least partly, from processes that occur following food ingestion. High-fat and high-cholesterol foods not only affect endogenous lipoprotein production and catabolism, but probably also lead to transient exposure of arteries to cytotoxic chylomicron remnants and advanced lipid oxidation endproducts (ALEs) [13]. The Western diet contains large quantities of oxidized fatty acids, oxidized cholesterol, cytotoxic aldehydes, and phospholipids, because a large proportion of the food in the diet is often consumed in a fried, heated, processed, and long-stored form.

The aim of the present review is to address some of the recent studies that demonstrated that dietary ALEs are risk factors to human health.

2 Lipid oxidation in foods

Lipid oxidation in foods in one of the major degradative processes responsible for changes in flavor, color, and texture; the oxidation of unsaturated lipids results in significant generation of cytotoxic and genotoxic compounds [1, 3] Furthermore, the free radicals generated by the process of lipid peroxidation not only generate cytotoxic compounds but also co-oxidize vitamins such as vitamin A and carotenoids, vitamin E and vitamin C, and thereby impair the nutritional quality of the foods [14, 15]. The process of lipid oxidation is initiated when a hydrogen atom is removed from a methylene group in the hydrocarbon chain of a lipid molecule, and especially from a dietary PUFA such as linoleate (18:2 *n* - 6) linolenate (18:3 *n* - 3) and arachidonic acid (20:4 *n* - 6), but also from eicosapetaenoic acid (20:5 *n* - 3) and docosahexaenoic acid (22:6 *n* - 3). The direct oxidation of PUFA by oxygen, which is in a triplet state, is spin forbidden. Ions of transition metals, and especially iron in the presence of reducing compounds are the driving force in forming high concentrations of ferrous ions, which are essential for the generation, in the presence of oxygen, of superoxide, hydrogen peroxide, and hydroxyl radicals. Hydroxyl radical is an important initiator of lipid oxidation in foods, but so are perhydroxyl radicals, hemeproteins activated to the ferryl state, and singlet oxygen [2]. These initiators are involved in the generation of lipid peroxides in foods. Lipid hydroperoxides (LOOH), in the presence of metal ions or at high temperature, breakdown to free radicals which, in the presence of oxygen, could form secondary oxidation products such as epoxyhydroperoxides, ketohydroperoxides, and cyclic peroxides, which could decompose to low-molecular-weight breakdown products or condense to polymers. The decomposition of LOOHs generates breakdown products such as aldehydes, ketones, alcohols, short fatty acids, esters, hydrocarbons, furans, and lactones [16]. Edible oils contain large amounts of hydroperoxides and hydrogen peroxide, which could reach 10 mM LOOH and 2 mM H_2O_2 [17, 18]. Hundreds of volatile and nonvolatile decomposition products have been identified in cooking oils subjected to commercial frying conditions; most of these are aldehydes [16, 19]. The breakdown of the hydroperoxides to small fragments, three to nine carbons in length, generates aldehydes such as 2-akenals and 4-hydroxy-2-alkenals [20] (Fig. 1). 4-Hydroxy-2-nonenal (HNE) is the most permanent aldehyde substance generated during lipid peroxidation of PUFA $n = 6$ such as linoleic acid and arachidonic acid [20]. It has been shown that HNE accumulates in membranes at concentrations of 5 – 10 μM in response to oxidation [20]. Lipid oxidation of PUFA from the $n = 3$ generates a closely related compound, 4-hydroxy-2-hexanal [21], whose concentration in several foods such as meat and fish products could reach 120 μM. Other important reactive aldehydes that originate from lipid peroxidation of linolenate and arachidonic acid are dialdehydes, including malondialdehyde (MDA), glyoxal, and acrolein. MDA is in many instances the most abundant individual aldehyde that results from lipid peroxidation in foods. Its concentration in meat and fish products could reach 300 μM or more [15, 21 – 23]. Glyoxal, a well-established intermediate in the glycoxidation reaction has been demonstrated also to be a product of lipid peroxidation of arachidonic acid [24].

Further complexity is introduced when one considers that dietary fatty acids and dietary cholesterol are co-oxidized. Cholesterol oxidation *via* lipid free radicals results in the formation of many oxidation byproducts such as 7α and 7β-hydroxy-cholesterol, 7-ketocholesterol, and 5α, 6α epoxy-cholesterol, and many of these oxycholesterols have been shown to have proatherogenic biological activities [25 – 28]. Oxycholesterols have been quantitated in cholesterol-rich processed foods [25, 26]. They are particularly prevalent in food products such as dried egg, milk powders, heated butter-ghee, but also in precooked meat and poultry products. The amount of oxycholesterols in these products could reach 10 to 100 μM; in ghee the amount of oxycholesterol exceed 12% of the cholesterol found in butter [29]. Those oxycholesterols and especially the 7-oxygenated species, revealed the highest cytotoxicity toward endothelial cell [30]. Interestingly, the interaction between various oxycholesterols regarding their proapoptotic action has been demonstrated [31].

3 The gastrointestinal tract: Chemistry and biochemistry

The gastrointestinal tract is constantly exposed to dietary oxidized food compounds produced during the reactions that occur during processing and storage of foods. The stomach is especially affected, primarily by these compounds, and we believe that the stomach acts as a "bioreactor". We hypothesized that the stomach and its gastric fluid could be a medium for further dietary lipid oxidation or

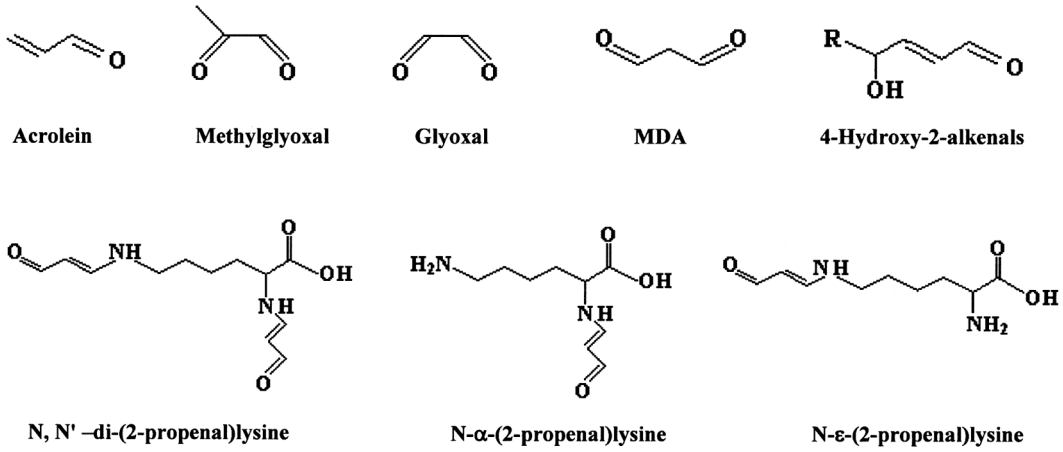


Figure 1. Reactive aldehydes generated from LOOHs and N-2 propenals derived by reaction of MDA with lysine.

antioxidation [15, 32]. The stomach, which receives the masticated food and from time to time is open to the atmosphere, acts, at least during the meal time, in an aerobic environment. Red meat, homogenized and incubated in human gastric fluid, exhibited an auto-oxidation process that generated LOOHs (2000 – 5000 μM after 180 min) and MDA (120 μM). As muscle tissue contains free iron ions and myoglobin, both catalysts affect lipid peroxidation in this system [33]. The crossreaction between free radicals produced during this reaction co-oxidized vitamin E, β-carotene, and vitamin C. However, both lipid peroxidation, generation of ALEs and co-oxidation of the vitamins in stomach medium could be inhibited by red-wine polyphenols [15]. Indeed, Halliwell *et al*. [34] proposed that antioxidant and other protective effects of phenolic compounds could occur within the gastrointestinal tract itself. Most recently we reported the dual role of saliva in lipid peroxidation under stomach conditions. It was found that lactoperoxidase increased lipid peroxidation, whereas thiocyanate and, especially nitrite, in the presence of reducing compound reduced it. We considered that the inhibitory effect of nitrite was due to nitric oxide. Elucidation of the antioxidant effect of saliva on co-oxidation of vitamin E in gastric fluid demonstrated that saliva alone could not protect against the co-oxidation, and the presence of polyphenol antioxidants was required [35]. The fate of pure linoleic hydroperoxides in the rat stomach was determined by Kamazawa and Ashida [36], who found that most of the hydroperoxides breakdown in the stomach to hydroxides, epoxy ketones, and aldehydes. Aldehydes were found to enter the small intestine and were partly absorbed into the body. More recently, Suomela and *et al.* [37], investigating the fate of triacylglycerol hydroperoxides in rats and pigs, obtained similar results; while also estimating the absorption of the breakdown products from oxidized sunflower seed oil in pig lipoproteins they found a significant amount of triglyceride molecules with a hydroxy, epoxy, and keto group as well as triglycerides with a core of aldehydes [37]. One should take into consideration that both studies were performed without prooxidant catalyzers such as those found in meat products. Nevertheless, the reactions that occur in the stomach seem to be of great importance because the breakdown products of hydroperoxides could lead to generation of not toxic or very toxic compounds [15, 32, 33]. Hemeproteins are known to decompose LOOHs catalytically to various aldehydes such as HNE, MDA, and other alkenals [38]. However, in the presence of high concentrations of polyphenol antioxidants hydroperoxides are decomposed mostly to hydroxy compounds and not to genotoxic and cytotoxic aldehydes [15, 32, 33]. In foods MDA is bound mainly to the lysine residues of proteins, from which it is released in the course of digestion, as *N*-ε-(2-propenal)lysine[39] (Fig. 1). A study conducted to investigate the bioavailability of lysine with radioactively labeled *N*-ε-(2-propenal)lysine found this compound to be absorbed from the gut into many organs [40]. *N*-ε-(2-propenal)lysine is an α-β-unsaturated aldehyde, and its residual aldehyde could further react with amino acids and proteins to give protein crosslinks and fluorescent products by Schiff base and Michael adducts.

Reactive aldehydes such HNE and MDA are known to react spontaneously with glutathione (GSH) [20]. The primary role of GSH is to protect cells from oxidative stress and to be a substrate for the GSH-peroxidases and GSH transferases [41]. GSH is abundant in the mucosal cells of the GI tract, and the exogenous introduction of GSH from foods affects its concentration [42]; it is usually ingested with foods, and its bioavailability depends on the intake of dietary proteins, especially sulfur amino acids. A standard human diet contains about 150 mg/d of GSH, but its concentration in the GI tract could be affected by oxidized reaction products derived from oxidized foods or reactive aldehydes [42]. Preadministration of parenteral GSH, cysteine, or antioxidant polyphenols such as quercetin in rats and humans was found to restore GSH levels in the gastric mucosa treated with ethanol [42 – 44]. MDA was found to decrease GSH in rat gastric mucosa while melatonin

restores GSH level [45]. The gastrointestinal GSH peroxidase isoenzyme (GI-Gpx) represents a first line of defense against ingested hydroperoxides. GSH reduced the amount of hydroperoxides transported from the rat or human gut into the lymph [41]. Other studies in rats demonstrated that inhibition of GI-GPx increased the absorption of LOOHs from the GI tract to the lymph and chylomicrons [46]. If reactive aldehydes could spontaneously deplete GSH and also inhibit GSH peroxidases [47], compounds such as *N*-ε-(2-propanal)lysine and other reactive aldehydes from potential ALEs, could weaken the mucosal and enterocyte first line of defense, with the result that more hydroperoxides and other toxic compound would be absorbed from the GI tract into the lymph or directly into the blood stream.

4 Absorption and plasma transport of LOOHs and ALEs

The dietary intakes of highly unsaturated fats and of several foods form an important contributor to LOOHs in the human stomach and intestines; an estimated daily intake of 1.4 mmol of LOOHs could occur in humans [42]. Absorption and lymphatic transport of peroxidized lipids by the rat small intestine *in vivo* was demonstrated by Aw *et al*. [48]; decreasing the intestinal GSH concentration resulted in increased absorption of the infused LOOHs.

Evidence for transport of dietary lipid peroxides into the circulation is controversial. A few studies documented the presence of LOOHs in the lymph of rats [49], in chylomicrons of rats and humans [50, 51], and in human blood plasma [52], after administration of lipid peroxide-containing diets. Others were unable to record absorption of hydroperoxides [36, 37]. Using a very sensitive kinetic chemiluminescence procedure Ursini *et al.* [52] detected a marked increase in plasma level of LOOHs in humans, during the postprandial phase after a high fat meal. Staprans *et al.* [50] examined whether oxidized fatty acids were incorporated into postprandial chylomicrons and chylomicron remnants in humans, following a meal that contained oxidized fatty acids derived from heated corn oil. They showed that the quantity of oxidized fatty acids found in chylomicrons, measured as conjugated dienes, was proportional to the amount of oxidized fatty acids in the test meal. The same researchers demonstrated that in diabetic subjects with poor glycemic control, dietary oxidized fatty acids induced an exaggerated and sustained increase in the level of oxidized fatty acids in chylomicrons, compared with the levels in controls or diabetic patients with good glycemic control [51]. Measurement of conjugated dienes, as a method to determine hydroperoxides, also should be considered as a means to determine many hydroperoxide breakdown products which retain the conjugated double bonds, such as aldehydes, ketones, ketoaldehydes, and epoxy compounds [16]. Suomela *et al*. [37] after ingestion of oxidized oil by pigs found a significant increase in the conjugated dienes compounds in chylomicrons, but only oxy, keto, epoxy fatty acids, and aldehydes were present, but no hydroperoxides. After ingestion of peroxidized foods animals and humans have been shown to excrete increased amounts of MDA [53 – 55] but also lipophilic aldehydes and related carbonyl compounds. During ingestion of cooked meat the urinary MDA increased from 2.1 to 23.1 μmol/day over a 7-day period [54]. Absorption of carbonyl compounds from a consumed meal that contained advanced glycation endproducts (AGEs) was also found in humans [56 – 58]. Interestingly, most of the AGE contents of selected popular foods in the USA are derived from muscle foods and foods high in fats [59].

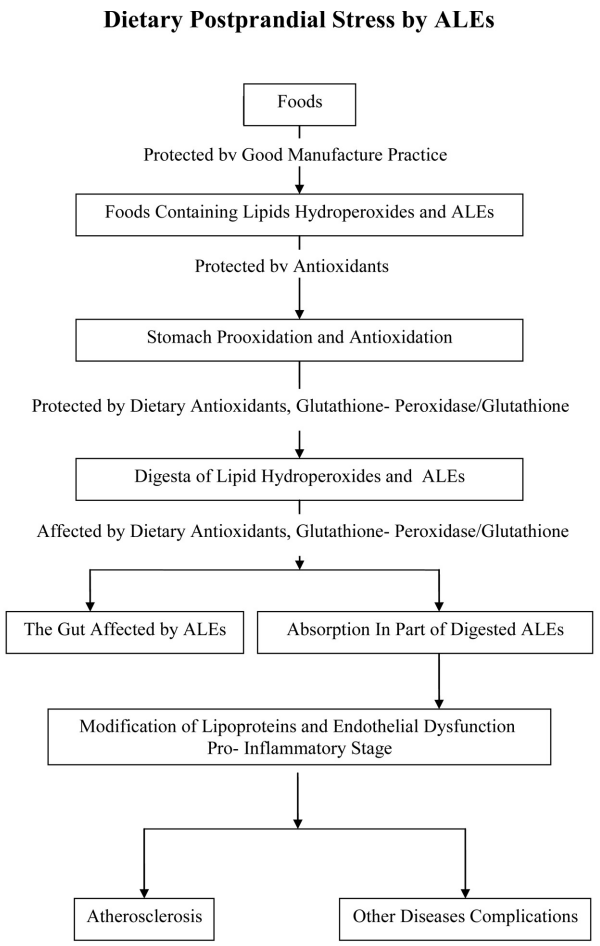
Oxidized cholesterol in the diet was found to be a source of oxidized lipoproteins in human serum [50]. Serum levels of α-epoxy cholesterol were found to correlate with the amount of α-epoxy cholesterol in the diet, and no α-epoxy cholesterol was detected in serum samples of subjects fed nonoxidized cholesterol. After the administration of the test meal, over a 10-h period epoxycholesterol was present in all lipoprotein fractions, with LDL exhibiting the highest levels, presumably because of a transfer reaction by cholesterol ester transfer protein [50]. A study that aimed to investigate the extent of oxycholesterol absorption in rat lymph chylomicrons was published by Vine *et al.* [60]. In rats given the oxidized cholesterol, 6% of the oxycholesterols load (which contained mostly 7 β-hydroxyl, 7-keto, 5α – 6α epoxy and 5β, 6β epoxy cholesterol) was absorbed and incorporated into lymph chylomicrons. Rats given pure cholesterol had no increase in oxycholesterols above baseline levels. Most recently, Larsson *et al*. [31] found that an oxycholesterol mixture containing 7β-hydroxy cholesterol and 7-keto-cholesterol mimicked the pathophysiological effects of oxycholesterols in arterial lesions of atherosclerotic patients. There are good evidences that oxidized cholesterol in the diet accelerates the development of aortic atherosclerosis [13, 27, 61, 62].

5 ALEs and risk factors in animal and human health

Oxidative stress is widely hypothesized to be a pathogenic mechanism for chronic diseases, especially atherosclerosis, but primary and secondary prevention trials based on antioxidant therapy failed to give satisfactory and conclusive results [63]. Regarding the lack of antioxidant efficacy in atherosclerosis, Stocker and Keaney [12], considered that oxidative events and atherosclerosis are not causally linked, and that the oxidative events represent a response to atherosclerosis but are not causative. It is generally believed that there is no “fully oxidized LDL” in the circulation, because blood is very rich in a variety of antioxidants. Even if oxidized LDL (ox-LDL) entered the circulation in minute

amounts, it would be rapidly cleared by the reticuloendothelial system, particularly in the liver [64]. In contrast, the presence of minimal modified LDL (mm-LDL) in the circulation was clearly described [65], and several groups reported evidence for the presence of specific epitopes such as modified MDA-LDL or other mm-LDLs [66, 67]. Food products contain protein bond MDA which in the course of digestion is broken down to *N*-ε-(2-propenal)lysine [39], a molecule found to be absorbed by the gut and to reach many organs [40]. As *N*-ε-(2-propenal)lysine is an α-β-unsaturated aldehyde, we hypothesize that its residual aldehyde group could further react with plasma proteins such as serum albumin, but also with apoB-48, apoB-100, and that it could modify these proteins to generate mm-LDL or mm-chylomicrons. These reactive aldehydes could also interact with receptors such as receptor-AGE (RAGE) that are expressed on the surface of endothelial [68] kidney [69] and colon [70] cells. Activation of RAGE induces generation of reactive oxygen species and activates the reactive oxygen species-mitogen activated protein kinase (ROS-MAPK) pathway, which activates and translocates nuclear factor kapa-B (NF-kB) [71]. Such inflammatory mediators were found in plasma after a diet rich on AGEs [56]. Induction of this pathway results in an inflammatory situation which seems to be the first trigger of atherogenesis. Inflammation as a process integral to atherosclerosis was suggested many years back by Ross [72]. Several observations have shown that the relationship between atherosclerosis risk factors and inflammation is close [73], and that modification of atherosclerosis risk factors reduces markers of inflammation in the circulation [74, 75].

There is now considerable evidence that apoB-48-containing lipoproteins (postprandial chylomicron remnants) may be atherogenic in their own right, especially if they include oxidized lipids. The arterial retention of chylomicron remnants could be consistent with atherogenesis and be a part of the postprandial phenomenon. Actually chylomicron remnants induce many reactions, such as foam cell formation in macrophage, apoptosis of endothelial cells, and formation of the monocyte chemoattractant protein-1, *via* p38 MAPK activation of vascular smooth muscle cells [76]. Postprandial chylomicrons contain lipid aldehydes, and oxy and epoxy fatty acids [37]; but they also contain oxycholesterol, which could induce cytotoxic responses that generate cytokines [50, 51] and activate inflammatory cells [73, 74]. Consumption of a meal with a high fat content, prepared after repeated deep frying and rich in lipid breakdown products, reduced endothelium dependent flow-mediated dilation by a factor of seven, whereas no effect was found following frying in the same amount of fresh cooking fat [77]. The data collected indicate that consumption of a fatty meal containing ALEs results in impaired vascular function [78] and increases the concentration of proinflammatory cytokines and soluble adhesion molecules [79]. Animal studies have shown that the toxicity of AGEs



Scheme 1.

in biological systems results in injurious impacts to vascular and kidney tissues [56, 80], and restriction of AGEs was associated with suppression of several immune defects, insulin resistance, and diabetic complications. Recent estimates of the AGEs levels in ~200 commonly consumed food found that the highest AGEs levels occurred in animal products with high fat and protein contents, a large proportion of which were ALEs [59].

Inflammation is the response of the organism's immune system to the damage caused to its cells and vascularized tissues by pathogens as well as by injurious chemicals or physical insults [73, 74, 81]. Some of the dietary ALEs, which are absorbed from the gut to the circulatory system, seem to act as injurious chemicals that activate an inflammation response which affects not only the circulatory system but also organs such as liver, kidney, lung, and the gut itself [81] (Scheme 1). More than 20 years ago Zilversmit [82] hypothesized that atherogenesis might results from phenomena that occur immediately after eating, and this concept seems gaining momentum. The populations of Western societies spend a large part of the day in a postpran-

dial state. We believe that repeated consumption of oxidized fat in the diet poses a chronic threat to human health.

Within the digestive tract, the stomach is a prime location for food digestion, and we believe that it acts as a bioreactor in which prooxidation and antioxidation reactions could occur. We demonstrated that high concentrations of polyphenolic antioxidants could prevent lipid peroxidation and the generation of ALEs under stomach conditions [33 – 35] and thereby potentially decrease absorption of ALEs from the gut. Most recently we discovered a novel function of red wine polyphenols, the prevention of absorption of the lipotoxin malondialdehyde in human [83]. Foods contain not only polyphenols but also other potential antioxidants such as carotenoids, ascorbic acid, GSH, and others provided a network protective system eliminating from the gastrointestinal tract injurious free radicals and other potential initiators. This may help to better explain the health effects of diets in which foods containing large amounts of antioxidants, such as those present in fruits and vegetables, or products such as red wine, tea, cocoa, or coffee are consumed during the meal.

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