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Review

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Protection by Polyphenols of Postprandial Human Plasma and Low-Density Lipoprotein Modification: The Stomach as a Bioreactor

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ABSTRACT: Recent studies dramatically showed that the removal of circulating modified low-density lipoprotein (LDL) results in complete prevention of atherosclerosis. The gastrointestinal tract is constantly exposed to food, some of it containing oxidized compounds. Lipid oxidation in the stomach was demonstrated by ingesting heated red meat in rats. Red wine polyphenols added to the rats' meat diet prevented lipid peroxidation in the stomach and absorption of malondialdehyde (MDA) in rat plasma. In humans, postprandial plasma MDA levels rose by 3-fold after a meal of red meat cutlets. MDA derived from meat consumption caused postprandial plasma LDL modification in human. The levels of plasma MDA showed a 75% reduction by consumption of red wine polyphenols during the meat meal. Locating the main biological site of action of polyphenols in the stomach led to a revision in the understanding of how antioxidants work in vivo and may help to elucidate the mechanism involved in the protective effects of polyphenols in human health.

KEYWORDS: *stomach, lipid oxidation, malondialdehyde, plasma, modified LDL, polyphenols, antioxidants*

INTRODUCTION

Postprandial oxidative stress is characterized by an increased susceptibility of the organism toward oxidative damage after consumption of a meal rich in lipids. The role of lipids in health and diseases has received increasing attention during the past decades and especially its connection with atherosclerosis. Atherosclerosis is the main cause of morbidity and mortality in Western countries. Several hypotheses have been articulated to explain the initiating events in atherosclerosis; however, its pathogenesis is still under debate; it seems to be a multifactor disease and, apart from genetic susceptibility, several risk factors are hypothesized to be involved. These include (a) response to injury and inflammation;[1] (b) lipoprotein oxidation or modification;[2] and (c) postprandial response to eating.[3,4] Atherogenesis may result at least partly from processes that occur after ingestion of high-fat foods that contain advanced lipid oxidation end-products (ALEs), some of which are cytotoxic and genotoxic compounds.[5] The aim of this review is to emphasize the effect of postprandial response to eating on low-density lipoprotein (LDL) modification and prevention of this phenomenon by plant polyphenols.

LIPID OXIDATION IN FOODS

Lipid oxidation in foods is one of the major degenerative processes responsible for decreased food quality, resulting in significant generation of cytotoxic and genotoxic compounds.[6] The free radicals generated during the process of lipid oxidation not only generate ALEs but also co-oxidize vitamins such A, E, and C, carotenoids, cholesterol, proteins, and many more compounds, thereby impairing the nutritional quality of foods.[6−9]

The direct oxidation of fatty acids by oxygen, which is in a triple state, is spin forbidden. In foods, ions of transition metals, and especially iron, in the presence of reducing agents are the driving force for activation of oxygen to free radicals and active oxygen species such as superoxide anion radical, perhydroxyl radical, hydrogen peroxide, ferryl, oxo-ferryl, and hydroxyl radical.[7] Hydroxyl and perhydroxyl radicals, ferryl, oxo-ferryl, singlet oxygen, and the enzymes lipoxygenase and cyclo-oxygenase are important initiators of lipid oxidation and generation of hydroperoxides in foods and biological systems.[7,10] Lipid hydroperoxides, in the presence of reduced metal ions or at high temperature, break down to lipid free radicals, which, in the presence of oxygen, form secondary oxidation products and ALEs such as aldehydes, ketones, epoxy and hydroxy fatty acids, furans, lactones, and many more.[11] The breakdown of hydroperoxides to small fragments, three to nine carbons in length, generates aldehydes such as 2-alkenals and 4-hydroxy-2-akenals.[12] Malondialdehyde (MDA), glyoxal, and acrolein are generated from peroxidation of fatty acids with three double bonds and more. MDA is in many instances the most abundant active carbonyl generated from lipid peroxidation in foods containing high unsaturated fatty acids and especially in red meat, in which its concentration could reach 300 μM.[13,14] Most recently results from two prospective cohort studies found that red meat consumption is associated with an increased risk of total cardiovascular diseases (CVD) and cancer mortality.[15]

POLYPHENOLS AS ANTIOXIDANTS

The antioxidant potency of polyphenols and especially flavonoids was one of the earliest functions proposed for

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these compounds, because they were identified to stabilize foodstuffs by retardation of rancidity and extension of shelf life.[16,17] Free radical scavenging capacity is primarily attributed to the high reactivity of the hydroxyl groups that participate in the reaction

$$PhOH + ROO^{\bullet} \rightarrow PhO^{\bullet} + ROOH \quad (1)$$

where PhOH = polyphenol, $ROO^{\bullet}$ = peroxyl radical, $PhO^{\bullet}$ = phenoxyl radical, and ROOH = hydroperoxide.

The oxygen of the hydroxyl undergoes an sp^3 hybridization, forming an electronic configuration of four orbitals. Two orbitals contain electrons forming the sigma bonding between oxygen and carbon and hydrogen atoms, and the other two orbitals are full with two pairs of nonbonded electrons. The benzene rings, which affect the hydrophobicity of the polyphenols, contain three π bonds of mobile reactive electrons, of high electron density and unsaturation, at which addition reactions could take place. The high electron density at the benzene ring and the high electron density around the oxygen allow one of the benzene π electrons to interact with one unbound electron, from the oxygen, to form a π bond between oxygen and the benzene carbon.

The displacement generates a mesomeric effect with a resonance stabilization, which very much decreases the activation energy for removing the hydrogen or the electron around hydrogen. This creates a state by which the hydroxyl group of the phenol donates easily hydrogen or an electron, forming a very good antioxidant.

The hydroxyl group acts also as a weak acid. The pH affects very much the activation energy needed for the displacement of the electron from the phenol group. This activation energy decreases by increasing the pH, forming a phenolate, which better donates the electron.

The electronic configuration of the hydroxyls, attached to the benzene ring, affected very much the functionality of the polyphenols as (a) electron/hydrogen donors, (b) metal chelators, and (c) reactive hydrogen bonders.

The scavenging of a free radical by the polyphenol gave rise to a phenoxyl radical. The resulting phenoxyl radical must be sufficiently stable or in a redox potential which does not initiate a new chain reaction. One of the features that stabilized the phenoxyl radical is the aromatic structure of the benzene ring that allows the formation of aroxyl radicals by resonance. This effect is easily adjusted when polyphenols are in a very broad mixture such as in plant material, by the reaction

$$PhO^{\bullet} + ArOH \rightarrow PhOH + ArO^{\bullet} \quad (2)$$

where ArOH = aroxyl and $ArO^{\bullet}$ = aroxyl radical.

Reaction 2 is much more rapid than reaction 1 and allows the stabilization of the phenoxyl radical.[18] The optimal antioxidant activity of polyphenols and flavonoids is governed by three criteria originally proposed by Bors and associates:[19] (1) The presence of an *o*-diphenol structure at the B-ring, (2) the presence of the 2,3 double bond in conjugation with a 4-carbonyl group at ring C, and (3) the presence of hydroxyls at positions 3 and 5 of rings C and A, respectively. These criteria were found to be correct also determining the antioxidant activity at pH 3.0 at simulated stomach condition by polyphenols such as protocatechuic acid, caffeic acid, catechin, kaempferol, quercetin, myricetin, apigenin, luteolin, eriodictol, cyanidin, malvidin, and malvidin 3-glucoside.[20] Quercetin represents a structure of such optimal antioxidant. Polyphenols and especially flavanoids with a structure similar to that of quercetin possess a high affinity for transition metal ions, acting as chelators. Sequestration of iron or other metal ions to prevent metal catalysis of lipid peroxidation and free radical generation is an antioxidant strategy.[21] With regard to the radical scavenging properties, polyphenols scavenge $O_2^{\bullet -}$, [22] $HO^{\bullet}$ radical,[23] $ROO^{\bullet}$ radical,[24] $RO^{\bullet}$ radical,[19] oxo-ferryl radical,[25,26] and $NO^{\bullet}$ radical[27] and quench singlet oxygen.[28] Polyphenols at a critical high concentration and in much excess to the metal ions or iron heme proteins act together by a peroxidase-like activity to catalyze the breakdown of H_2O_2 or ROOH to water or hydroxy fatty acids, inducing a stabilization of the system toward lipid peroxidation, without formation of cytotoxic ALEs.[29] However, kinetic aspects should be considered for the antioxidant effects of polyphenols because oxidation and antioxidation in biological systems are very much affected by metal or enzyme catalysis, membrane structure, molecule solubility and polarity, water activity, pH, dissociation of molecules, and, of course, bioavailability and metabolism. For these reasons determination of polyphenol antioxidant activity or the antioxidant activity of any molecule should be not only a test but a thorough study.[30−34]

■ POSTPRANDIAL OXIDATIVE STRESS

Postprandial oxidative stress is characterized by an increase in susceptibility of the organism toward oxidative damage after consumption of a meal especially rich in lipids. The gastrointestinal tract is constantly exposed to foods, some of it containing oxidized compounds. The Western diet contains large quantities of oxidized fatty acids and cholesterol, cytotoxic carbonyls, and other ALEs, because a large portion of the foods in the diet are often consumed in a fried, heated, or processed form.[5] More than 30 years ago Zilversmit[3] hypothesized that atherogenesis might result from phenomena that occur immediately after eating, and this concept seems to gain momentum. The human studies of Naruszewiez et al.[35] were among the first to demonstrate that oral administration of heated oil could cause a specific increase in plasma levels of oxidized lipids. Using HPLC chemiluminescence techniques, levels of plasma phospholipid hydroperoxides in healthy people have been reported to be about undetectable or to lie in the range of 10−500 nM.[36] By contrast, techniques that measure total lipid hydroperoxides in human plasma suggest higher and consistent values of hydroperoxides, which were estimated to be about 3 μM.[4,37] LDL was found to be the major carrier of lipid hydroperoxides in human plasma.[38] Absorption of lymphatic transport of peroxidized lipids by rats and humans in vivo was demonstrated.[39−42] However, evidence for transport of dietary peroxides into the circulation is controversial. A few studies documented the presence of LOOH in chylomicrons of rat[42,43] and human blood[41] after administration of lipid peroxide containing diets. Others were unable to record absorption of hydroperoxides.[44,45] Most recently, the same authors[46] using a method that determines lipid-conjugated dienes found that a meal of red meat hamburger induced incorporation of LOOH into plasma lipoproteins. Measurement of conjugated dienes as a method to determine lipid hydroperoxides should be considered as a method to determine many hydroperoxide breakdown products including hydroxyl fatty acids, which retain the conjugation double bonds.[11] After ingestion of oxidized foods, animals and humans have been shown to excrete increased amounts of MDA and lipophilic carbonyls.[47−49]

Absorption of active carbonyl compounds from a consumed meal that contained advanced glycation end-products (AGEs) was found in humans.[50−52] Oxidized cholesterol in the diet was also found to be a source of oxidized lipoprotein in human serum, whereas LDL exhibited the highest levels, presumably because of a transfer reaction by cholesterol ester transfer protein.[42]

Postprandial hyperlipidaemia and hyperglycemia affected by meals induce relative oxidative stress, which is typically accompanied by postprandial inflammation, which impaired endothelial function.[53−55] Inflammation as a process integral to atherosclerosis was suggested many years back by Ross and most recently by Heine et al.,[1,56] who argue that postprandial hyperlipidemia related oxidation products may be equally important to the development of CVD. We believe that postprandial ALEs are among the main factors which affect the postprandial atherogenesis process, affecting in part the development of CVD[32,57] (Gorelik et al., in publication process, 2012).

THE STOMACH AS A BIOREACTOR: PRO-OXIDATION AND ANTIOXIDATION

The stomach, which receives the masticated food and from time to time is open to the air, acts at least during the meal time in an aerobic environment. The stomach acts as a bioreactor and is an excellent medium for enhancing lipid oxidation and co-oxidation.[32,57] Lipid oxidation end-products are formed during digestion in the gastric fluid. To simulate the stomach bioreactor capability for further lipid oxidation, we have developed three model systems: (a) simulated stomach conditions containing human gastric fluid and heated red turkey meat (bioactivity and mechanism of action, in vitro); (b) rats fed homogenized heated red turkey meat (animal, in vivo); and (c) humans fed red turkey meat (in vivo).

Simulated Human Stomach Conditions (in Vitro). We investigated reactions that seem to occur in the acidic pH of the stomach and accelerate the generation of lipid peroxidation and co-oxidation of important dietary constituents. To estimate the oxygen content in the stomach after food consumption, oxygen released from masticated bread (20 g) into deoxygenated water (100 mL) was measured. Under these conditions, the oxygen concentration rose by 250 μM and reached full saturation. Heated red turkey meat incubated in human gastric fluid at pH 3 and 37 °C generated ROOH and MDA, enhancing accumulation of these compounds by 6−10-fold to 1200−2000 and 110 −180 μM, respectively.[20,32] The heated red turkey meat incubated for 3 h in gastric conditions could attain concentrations of ROOH and MDA that were 100-fold higher than in fresh meat. The cross-reaction between free radicals generated during this reaction in the gastric fluid co-oxidized vitamin E and β-carotene in a few minutes and has the capability to oxidize other vitamins, cholesterol, amino acids, and many other molecules that are important to maintain good health.[14]

The ability of dietary polyphenols to invert catalysis from pro-oxidation to antioxidation was examined in stomach conditions using soybean oil, metmyoglobin, or free iron ions as catalysts or plain red turkey meat. Metmyoglobin, one of the catalysts found in red meat, increased soybean oil peroxidation, resulting in an 8-fold rise of ROOH and MDA concentrations. However, in the presence of catechin or red wine polyphenols, metmyoglobin catalyzed the breakdown of hydroperoxides to zero, totally preventing propagation of lipid peroxidation, accumulation of MDA or other carbonyls, or co-oxidation of β-carotene. Both lipid peroxidation and co-oxidation of vitamin E and β-carotene by red meat at pH 3 were inhibited by red wine polyphenols at a critical high concentration possibly by the reactions[20,29,32]

$$Mb^{3+} + LOOH \rightarrow Mb^{4+}OH + LO^{\bullet} \quad (3)$$

$$Mb^{4+}OH + LOOH \rightarrow Mb^{3+} + LOO^{\bullet} + H_2O \quad (4)$$

$$Mb^{3+} + LOOH \rightarrow Mb^{2+} + LOO^{\bullet} + H^{+} \quad (5)$$

$$Mb^{2+} + LOOH \rightarrow Mb^{3+} + LO^{\bullet} + {}^{-}OH \quad (6)$$

$$PhOH + LOO^{\bullet}/LO^{\bullet} \rightarrow PhO^{\bullet} + LOOH/LOH \quad (7)$$

$$PhO^{\bullet} + LOO^{\bullet}/LO^{\bullet} \rightarrow LOOPhO/LOPhO \quad (8)$$

$$PhOH + Prot^{\bullet} \rightarrow PhO^{\bullet} + ProtH \quad (9)$$

where Mb^{3+} = metmyoglobin, Mb^{2+} = myoglobin, LOOH = hydroperoxide, $LO^{\bullet}$ = alkoxyl radical, $LOO^{\bullet}$ = peroxyl radical, PhOH = polyphenol, $PhO^{\bullet}$ = phenoxyl radical, $Prot^{\bullet}$ = protein radical, and LOOPhO/LOPhO = adducts between free radicals.

If lipid peroxidation was catalyzed by free iron ions, polyphenols at a critical high concentration inhibited lipid peroxidation by the reactions[20,29]

$$Fe^{3+} + PhOH \rightarrow Fe^{2+} + PhO^{\bullet} \quad (10)$$

$$Fe^{2+} + LOOH \rightarrow Fe^{3+} + LO^{\bullet} + {}^{-}OH \quad (11)$$

$$PhOH + LO^{\bullet} \rightarrow LOH + PhO^{\bullet} \quad (12)$$

Polyphenols from different groups were determined for the antioxidant activity at stomach conditions. The results show a high antioxidant activity of polyphenols from different classes such as phenolic acids, flavanols, flavonols, flavones, flavanones, anthocyanidins, and especially flavonoids with ortho-dihydroxylated groups at the B ring, unsaturation, and the presence of a 4-oxo group in the heterocyclic ring as demonstrated by quercetin.[20] Cooked red meat and heated frying oils are prone to oxidation in the gastric medium, by endogenous catalysts found in red muscle tissues. Our studies in in vitro model systems simulated stomach conditions and addressed the pro-oxidative activity of metmyoglobin and free iron ions and its activity inversion to antioxidation in the presence of polyphenols at a critical high concentration.[20,29,32] Recently,[58] by using a model of heme inducing lipid peroxidation in gastric conditions, it was shown that polyphenols are better antioxidants than α-tocopherol.

Rat Model System (Animal, in Vivo). Stomach bioreactor capability for oxidation or antioxidation was determined in rats fed by gavage 2 mL of heated red turkey meat homogenate (containing 1 g of meat with 3 volumes of water). After pyloric ligation, the stomach content of the rats showed >2-fold increases in LOOH and MDA accumulation. The effects of red wine polyphenols on red turkey meat lipid peroxidation in rat stomach affecting plasma MDA was estimated by feeding rats with meat cutlets without (meal A) or with red wine concentrate polyphenols (0.924 mg catechin equiv/g meat) (meal B). The amounts of meat consumed by the rats in the two groups were similar, about 2.2 g. The postprandial plasma MDA level increased significantly by 50% following meal A and fell by 34% below basal level following meal B, which contained the red wine polyphenols.[57] An interesting paper was published[59] in which it was found that by the addition of

polyphenols to rats the concentration of α-tocopherol in blood plasma and liver cells increased significantly. The authors' conclusion was that polyphenols prevent the vitamin E oxidation on LDL, which could explain the remaining high vitamin in LDL. However, we believe that polyphenols prevented the co-oxidation of the vitamin in the stomach lumen and, by this, its amount that remained to be absorbed in the gastrointestinal tract increased significantly.

Human Studies (in Vivo). In a randomized crossover study, in humans, the effect of red wine polyphenols on postprandial levels of plasma and urine MDA was investigated. Three meals of 250 g of turkey red meat cutlets supplemented by water (A), soaked in red wine after heating plus 200 mL of red wine (B), or soaked in red wine prior to heating plus 200 mL of red wine (C) were administered to 10 volunteers. Subject baseline plasma levels of MDA were 50 nM. After a meal of meat cutlets, plasma MDA levels rose by 160 nM; after meal B, there was a 75% reduction in the absorption of MDA. However, after meal C, the elevation of plasma MDA was completely prevented. Interestingly, in 50% of the volunteers the levels of plasma MDA fell significantly below the baseline, very similar to the results obtained in the rat experiment.[33,57]

We hypothesized that MDA derived from meat consumption could cause postprandial LDL modification, in vivo. To make sure, healthy volunteers consumed for four sequential days (A) frozen stored−heated turkey meat cutlets, (B) the same and red wine, (C) fresh heated turkey meat cutlets, and (D) the same and red wine, and the postprandial modification of LDL (MDA m-LDL) was determined. Postprandial plasma MDA levels, 3 h after meal A, increased by 106 nM, after meal B, by 57 nM, and after meal C, by 57 nM; after meal D, postprandial plasma MDA levels decreased by 9 nM from the baseline. Postprandial MDA m-LDL 3 h after meal A increased by 30% and following 4 days on the same meal, increased by 96% from the baseline. However, no changes in LDL were measured, 3 h postprandial or after 4 days on the same meal and red wine polyphenols (meal B). Modification of LDL by MDA was found to be directly dependent on the increase of plasma MDA level following a meal. The accumulation of MDA in the stomach model system, after 1.5 h of incubation (in vitro), affected by four different meals correlates with the postprandial increase in volunteers' plasma MDA levels, 6 h (in vivo) after consuming the same meals, $r^2 = 0.90$, $P = 0.05$ (Gorelik et al., in press).

Recently, other studies adopted red meat or hamburger for increasing lipid peroxidation end-products in the blood system. Humans consumed a double cheeseburger with 300 mL of water or red wine. The meal containing the meat and water at postprandial induced a significant increase in the plasma concentration of lipid hydroperoxides and cholesterol oxidation products. The postprandial increases in ALEs were fully prevented by consuming during the meal red wine.[60] Another study, by adding spices containing polyphenols to hamburger meat before cooking, showed a reduction in MDA concentration in meat and after ingestion in plasma and urine.[61]

Healthy volunteers consumed a meal containing a standard hamburger rich in lipid peroxides. After ingestion of the hamburger, the authors found that ALEs were incorporated into the volunteer's serum triglyceride-rich lipoproteins and LDL.[46]

POSTPRANDIAL MODIFICATION OF PLASMA LDL BY REACTIVE CARBONYLS: PREVENTION BY POLYPHENOLS

Circulating modified LDL is elevated in patients with advanced atherosclerosis. The association between modified LDL and atherogenesis is now firmly established.[62] The general opinion suggests that LDL oxidation occurs in the artery intima.[63,64] Data support the involvement of modified LDL in atherogenesis,[62] although confirmation that oxidation is the requisite modification for LDL is not complete and the cause of such oxidation in plasma in vivo is uncertain.[65,66]

Animals and humans, after ingestion of peroxidized foods, have been shown to excrete an increased amount of MDA and other carbonyls in urine.[48,64] Absorption of reactive carbonyls from a consumed meal that contained AGEs was found in humans.[51] However, most of the AGEs of selected popular foods in the United States are derived from muscle foods and high-fat foods.[67]

Reactive carbonyls seem to play a critical role in the pathogenesis of atherosclerosis.[68,69] The structural and functional changes associated with in vivo modification of apoB-LDL were simulated by direct interaction of MDA with LDL.[70,71] Monoclonal antibodies raised against MDA-modified LDL bind to epitopes in plasma and atherosclerosis lesions.[70,71] Most recently it was found that complement factor H binds MDA epitopes and protects vascular blood system from oxidative stress. This factor was found to block the uptake of MDA-modified LDL by macrophages and MDA-induced pro-inflammatory effects in vivo in mice.[72] The pathological effects of reactive carbonyls are related to their ability to modify reactive molecules by cross-linking and to bind to several cellular receptors.[68,73−75] Such interactions with proteins and receptors could promote inflammatory mediators and result in cellular oxidative stress.[68,74]

We assume that absorption of the MDA is after its digestion from proteins through N^{ε}-(2-propenal) lysine adducts. This adduct transforms the dicarbonyl MDA to a more active α,β-carbonyl, which retains its ability to modify proteins by generating a Schiff base with basic amino acids, especially lysine.[68,76] Evaluation of MDA−lysine bioavailability in rats showed incorporation mostly in the liver, small intestine, and plasma.[77] However, we assumed that other reactive carbonyls would exhibit a similar pattern. Our most recent data demonstrated that the amount of MDA generated in the stomach seems to be critical to the MDA transferred and absorbed into the blood system. The MDA transferred from the gut to the blood system seems to interact with the LDL protein, modifying apo-B-100. It was dramatically shown that the removal of circulating modified LDL results in complete prevention of atherosclerosis progression.[78,79] The interaction between reactive carbonyls in plasma seems not to be specific for only LDL. Other plasma lipoproteins as well as other particles could be modified by reactive carbonyls. Interactions between MDA−lysine and lysine residues at specific sites on apo-A-1, the major HDL protein, were demonstrated.[80] Such modification may facilitate the formation of macrophage foam cells by impairing cholesterol efflux by the ATP-binding cassette transporter A 1.[81,82] This modification of HDL should decrease the cardioprotective effects of this particle, which generally operate to reverse cholesterol to the liver for excretion in the bile. We hypothesized that MDA−lysine could modify apo-B-48 of chylomicron remnants, decreasing its transport to

the liver, and by this increase its concentration (triglycerides) in the blood system. MDA−lysine could also induce an oxidant stress and expression of inflammatory cytokines, chemokines, and adhesion molecules by monocytes[83] or by endothelial cells and by this affect athrogenesis.[84] Our data demonstrated unequivocally that daily and cumulative exposure of the human body (e.g., its arteries) to high levels of cytotoxins can explain the potentially harmful effects of intake of oxidized fats found in foods, and especially red meat (see Figures 1−3).

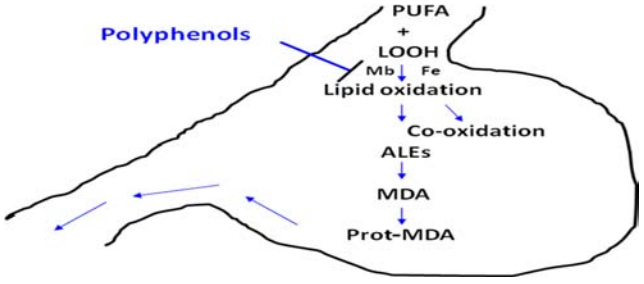

Figure 1. Lipid peroxidation of foods and polyphenols acting as antioxidants within the stomach lumen.

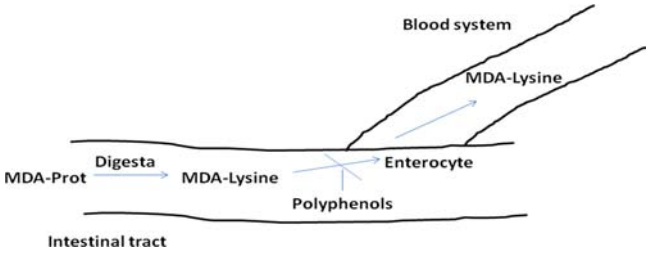

Figure 2. Intestinal tract digestion of MDA proteins and absorption of MDA lysine into the blood system.

The harmful results of the consumption of high-fat and high-iron potentially pro-oxidant foods such as red meat on plasma ALEs could be prevented by the consumption of food- or beverage-derived polyphenols with the meal, as was clearly demonstrated by our results and also by others.[60,61,85,86]

In the light of the present results, it can be assumed that the most important site of polyphenol action is in the digestive system, and especially in the stomach, before absorption. We suggest that the main benefit of consuming plant polyphenols in the human diet, as an integral part of the meal, arises from the ability to prevent during digestion the generation and absorption of cytotoxic ALEs, such as reactive carbonyls or other reactive compounds commonly found in our foods. Diets high in fats or red meat are contributory risk factors to our health. Consumption of polyphenol-rich fruits, vegetables, and their derived beverages during the meal reduces these risk factors and provides important protective benefits for our health.

Locating the main biological site of action of polyphenols in the stomach led to a revision in our understanding of how antioxidants work in vivo and may help to elucidate the mechanism involved in the "French paradox" phenomenon and the protective effect of the Mediterranean diet.

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Notes

The authors declare no competing financial interest.

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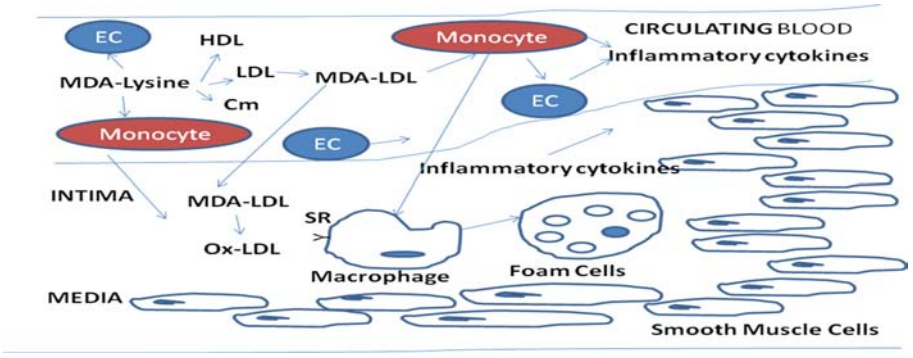

Figure 3. Postprandial atherogenesis affected by absorption of MDA lysine and other active carbonyls, and interaction with lipoproteins such as apo-B-100 of LDL, apo-A-1 of HDL, and apo-B-48 of chylomicrons, activating endothelial and monocyte cells, producing inflammatory factors, chemokines, and adhesion molecules in the blood system. CR, receptor for modified MDA-LDL; EC, endothelial cells; CM, chylomicon particles.

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