CHAPTER 7

AGE, ALE, RAGE, and Disease—A Food Perspective

Stig Bengmark

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7.1 MAILLARD PRODUCTS IMPROVE PALATABILITY, BUT ...

Humans have known for thousands of years that heating the food we eat to higher
temperatures will improve both its taste and smell. High temperature makes food
proteins change structure—coagulate, aggregate, and produce crusts—information
that modern food chemists, chefs, and cooks use every day to produce new delicious
foods. The French biochemist Louis-Camille Maillard explored and published in
1912 a description of the chemical processes that occur in foods during heating, an
achievement for which he received the distinguished prize of the French Medical
Academy in 1914. The process has ever since been referred to as the Maillard reaction and its products collectively named Maillard products. During the process, so-called reducing sugars; fructose, glucose, glyceraldehyde, lactose, arabinose, and maltose will bind to amino acids and nucleic acids, both DNA and RNA, peptides, and proteins, and produce compounds usually called Amadori products, which with time undergo complex changes: cyclization, dehydration, oxidation, condensation, cross-linking, and polymerization to form irreversible chemical products. In particular, reactive carbonyls such as glyoxal and methylglyoxal have been found to rapidly modify reactive side chains of proteins. Important amino acids such as lysine (essential amino acid) and histidine (essential for children) are often involved. During the heating process thousands of good-tasting and good-smelling volatile compounds are released in addition to significant amounts of pigments (melanoids) that often make the food or parts of the food brown or black, which is why sometimes the process is referred to as “browning.” Common browning products are bread crusts and the roasted surface of fried meat and fish. All sorts of broths, irrespective of vegetable or animal origin, Chinese soy, Balsamico products, smoked foods are rich in brown/black Maillard products. But not all Maillard products are dark in color. White Maillard products also exist; common examples are dairy products, especially cheese and powdered milk. It was early suggested that the Maillard process might be negative to health, at least when its products are consumed in larger amounts, as these products will accumulate in the body, sometimes for the rest of life, but also because the process might reduce the supply to the body of important and essential amino acids.

7.2 HEATING, REDUCTION OF ANTIOXIDANTS, AND ACCUMULATION OF MAILLARD PRODUCTS

Most of the well-known plant antioxidants are inactivated at temperatures between 30°C and 100°C. Antioxidants in common food oils such as olive and rapeseed oil will start disappearing at temperatures around 30°C. Heating to higher temperatures, as almost always occurs with microwaving, eliminates almost all antioxidants. The production of Maillard products occurs much in parallel to reduction of the content of antioxidants in foods, and accelerates dramatically, almost exponentially, as the temperatures are elevated above 100°C.

Maillard products based on association of carbonyl groups in sugars and proteins have in more recent years been collectively called advanced glycation end products (AGEs). Similar products are often formed between reactive fatty acids and proteins, referred to as advanced lipoxidation end products (ALEs). A long list of such synthetic products are identified, and two to three previously unknown such compounds are added to the list each year. Commonly studied AGEs/ALEs are pentosidine, \( \text{N}^\epsilon\text{-carboxymethyl} \)lysine (CML) and \( \text{N}^\epsilon\text{-carboxyethyl} \)lysine (CEL).

It is important to observe that the production of both AGEs and ALEs is not at all dependent on enzymes. The intensity in production increases, not only with the increase in temperature, but also with the length of storage at elevated temperatures,
and this already at room temperature. Other industrial processes commonly used by food industry, such as irradiation, ionization, microwaving, smoking, also significantly contribute to increased production of AGEs/ALEs. No foods seem to be excluded; industrial treatment of plant products (roasting, drying, “curing”) will contribute to increased amounts of AGEs/ALEs in foods to the same extent as animal products. Fresh tobacco leaves, fresh coffee beans, fresh peanuts are extremely rich in powerful antioxidants, which totally disappear during the industrial process (“curing,” roasting) and are replaced by larger amounts of AGEs/ALEs. As the temperature increases above 100°C, carcinogens, especially heterocyclic amines, are also produced, a production that also increases dramatically with higher temperatures.

AGEs/ALEs do not reach the body exclusively through the food we eat; these compounds are also produced spontaneously in the body, especially with elevated levels of sugars and fatty acids in body fluids and tissues. Accumulation in the body of late Maillard products—AGEs/ALEs—is generally regarded as irreversible; what is accumulated will stay more or less forever. The observation that these substances are found in larger amount has commonly been regarded as an expression of normal aging. However, it might not be so. Instead, it might depend mainly on lifestyle and thus in theory be preventable. Large to extreme increases in content of AGEs/ALEs are regularly observed in body fluids and tissues of patients with chronic diseases, particularly in diabetes and chronic renal diseases, especially so in those suffering complications such as patients with diabetes with reduced wound healing, nephropathy, and angiopathy. Advanced accumulation of AGEs/ALEs in tissues often occurs as amyloid, fibrillary tangles, or similar deposits. Such structures were long regarded as degenerative but biologically inert structures. However, increasing evidence supports the conclusion that these structures are foci with very strong proinflammatory potential, capable of maintaining chronic inflammation at high level in the tissues.

### 7.3 INTRODUCTION OF MOLECULAR BIOLOGY CHANGED THE VIEW OF AGES/ALES

Early on, Maillard had suggested that accumulation in the body of AGEs/ALEs could significantly contribute to progression in diseases such as diabetes and some chronic urogenital diseases, especially uremia. He created what he called “index of urogenital imperfection,” which he used to document an association between degree of accumulation in the body of Maillard products and severity of disease, especially chronic renal disease. However, the time was not yet ripe for such thinking and the concept was rejected by scientists and clinicians of that time and would remain so for several decades. With the introduction of modern molecular biology and particularly so with the identification of specific receptors in the body for these substances, human medicine became more seriously interested. Although identification by American Ann Marie Schmidt in 1992 of a specific receptor for AGEs/ALEs (RAGE) seems to be the turning point, it is only in the last few years that a wider interest in the concept has developed. Since the year 2000, several international
scientific organizations have demonstrated a significantly increased interest in the concept, and new societies have even been founded with the main goal to investigate the effects on health and well-being of AGEs/ALEs in foods. The New York Academy of Science appears to have taken the lead and a large number of scientific contributions about AGEs/ALEs are published each year in its annals. In excess of 5000 titles about AGE and ALE are registered on PubMed, in addition to another 14,000 titles about the glycated hemoglobin, HbA1c.

Several methods are available for measurement of content of AGEs/ALEs in body fluids and tissues: immunohistochemistry with polyclonal or monoclonal antibodies, high-performance liquid chromatography (HPLC), and mass spectrography. A large proportion, but not all, of these substances are autofluorescing, even if not visible to the human eye. Often studied substances such as CML and CEL have no fluorescing ability or any color. Despite that, measuring fluorescence is an excellent method especially for screening of individuals with suspected high levels of AGEs/ALEs in the body, but also for screening of foods suspected to be rich in these dysfunctioning proteins. The fluorescence has its maximum at wavelengths between 350 and 440 nm.

### 7.4 RAGE: A RECEPTOR AND MASTER SWITCH—A KEY ACTOR IN INFLAMMATION

RAGE is a prominent member of what has been called the immunoglobulin superfamily of cell surface molecules. It is described as a “master switch” with the ability to coordinate the inflammatory reaction in the body. RAGE induces a long-lasting activation of the proinflammatory transcription factor NF-κB and suppresses a series of endogenous autoregulatory functions. Increased deposition of AGEs/ALEs in tissues is suggested as a key element in the development of metabolic syndrome. AGE/ALE accumulation and subsequent activation of RAGE are reported to induce a significant downregulation of leptin in adipose cells. Pronounced effects of RAGE activation are often observed on endothelial cells, where increased expression of a long row of molecules such as VCAM-1, ICAM-1, E-selectin, eNOS, TGF-β, TNF-α, IL-6, PAI-1, and VEGF are induced. Strong RAGE-induced effects are often reported on immune cells, macrophages, and dendritic cells, as well as on smooth muscle, particularly in the walls of blood vessels, under the mucosa and in the skin, and associated with subsequent reduction in regenerative capacity and function of the cells, increased blood pressure, and with development of chronic diseases or exacerbation of complications to chronic diseases.

AGEs/ALEs accumulated in endothelial cells can be significantly reduced by control of intake of foods rich in these substances. The situation is different in tissues with low regenerative capacity and long life length such as myelin- and collagen-rich structures, where the substances risk staying forever: brain, peripheral nerves, skeleton muscles, tendons, joints, skin, and eye, especially the lens. More recent research has demonstrated the existence of an endogenous soluble form of RAGE called sRAGE, which acts as a decoy for RAGE and prevents accumulation of RAGE in
body tissues,27 and studies suggest that chronic diseases are associated not only with increased levels of RAGE in the body, but also, and probably as important, with low levels of sRAGE.

### 7.5 MANY ACTORS IN THE INFLAMMATION ORCHESTRA

The largest part of the immune system, in contrast to what was earlier believed, is to be found in the gastrointestinal system (Figure 7.1), which explains why the food we eat has such a dominating influence on our well-being and health.28 Apart from AGEs/ALEs, many other food-related factors influence the level of inflammation in the body and thus our health and well-being. Some evidence suggests that these factors are additive and that they collectively contribute to the sustained, long-lasting, but often discrete and unrecognized, exaggerated level of inflammation in the body, which is common to most chronic diseases. Among these factors are the following:

- **Low LEVEL of vitamin D in the body.** A strong correlation among the level of vitamin D in the body, the degree of inflammation, and the incidence of chronic diseases has been observed. Individuals living at higher latitudes, northern Scandinavia, Russia, and Canada, are reported to have generally lower levels of vitamin D in serum, especially during the winter season, which is associated with the observed higher incidence of coronary-vascular diseases in these regions and is suggested to contribute to the higher incidence of acute coronary events during the winter months in these countries.29,30

- **Low levels in the body of antioxidants such as folic acid and glutathione and increased levels of homocysteine.** Figure 7.2 illustrates the central role of folic acid and glutathione in prevention of accumulation of homocysteine in the body,31 a substance regularly associated with increased levels of systemic inflammation and chronic diseases.

![Figure 7.1](image)

**Figure 7.1** Distribution of the immune system within the body. (Adapted from Brandzaeg P. et al.28)
Impaired hormonal homeostasis. Aging, as well as chronic diseases, is often accompanied by hormonal disturbances, and aging was recently referred to as a state of “hormonal chaos.” Hormonal disturbances accompanied by increased oxidative stress/increased release of free radicals, intracellular accumulation of “waste products,” inhibition of apoptosis, disturbed repair mechanisms, reduced gene polymorphism, premature shortening of telomeres, reduced immune defense, and reduced resistance to disease are often observed in premature aging as well as in several chronic diseases. 17β-Estradiol has been shown to induce a strong activation of RAGE mRNA in endothelial cells, an effect that is abolished by supply of an antiestrogen such as 4-OH tamoxifen. An impaired hormonal homeostasis is suggested to explain why chronic diseases are often aggravated during pregnancy, especially vascular and eye complications to diabetes. Physical as well as mental stress contributes to activation of RAGE, and increased release of noradrenaline is reported to reduce immune defense and increase the susceptibility to acquire infections with up to 4 logs. Increased release of noradrenaline in the intestine will dramatically reduce the beneficial intestinal flora and increase the virulence of potentially pathogenic microorganisms, changes that most likely contribute to increased RAGE activation. Permanently increased levels of noradrenaline are also observed in a chronic disease such as Alzheimer’s disease and reported to correlate with the severity of disease. Parathyroid hormones constitute another example of hormones deeply involved in the inflammatory process, and significant elevations in IL-6s is observed in hyperparathyroidism (up to 16 times) but also in other conditions with a high level of systemic inflammation such as obesity.
• Angiotensin/rennin. It is well documented that release of angiotensin is significantly associated with oxidative stress, increased levels of free fatty acids in serum, and with reduction in beta cell function in diabetes. \(^{39-41}\) Recent studies demonstrate that blockage of the angiotensin receptor will reduce production and accumulation of AGE both \textit{in vitro} and \textit{in vivo}.\(^{41}\)

• Larger intake of glutenoids. Glutenoids are increasingly regarded as proinflammatory in the body (Tlaskalová-Hogenová H, personal communication), even in the absence of intestinal changes.\(^{42,43}\)

• Low intake of plant antioxidants

• High intake of carbohydrates

• High intake of saturated and trans-fatty acids. A strong association has repeatedly been documented between the average content of fat in food and the morbidity and/or mortality in chronic diseases in a country, as demonstrated for breast cancer in Figure 7.3,\(^{44}\) but also reported for various other cancers and chronic diseases such as coronary heart disease\(^{45,46}\) and diabetes.\(^{47}\) As more than three-fourths of the consumed saturated fat is of bovine origin, similar curves are also reported that correlate amount of intake of dairy products to incidence of various chronic diseases.\(^{48}\)

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure7.3.png}
\caption{Mortality in breast cancer in a country related to the mean intake of saturated fat in the same country. (Adapted from Carroll KK,\(^{44}\))}
\end{figure}
The incidence of most chronic diseases has dramatically increased during the last 150 years, much in parallel with a significantly altered intake of foods. The annual per person intake of saturated fat has doubled, the intake of omega-3 fatty acids has decreased by about 50 percent, and intake of omega-6 fatty acids more than doubled since the year 1850 (Figure 7.4). During the same time period, the intake of refined sugar has increased from 0.5 kg to almost 50 kg per person per year. To this shall be added a recent and fast increase in intake of high-fructose corn syrup, mainly used in carbonated drinks and fast foods, an intake which today in the United States exceeds that of sucrose. Much can be learned from studies in Japan, a country that has gone through identical changes in food habits in no more than 50 years and, during this time period, has seen a manifold increase in the incidence of several chronic diseases. The incidence of prostatic cancer, for example, has increased 25 times during this 50 year period, much in parallel with an increase in intake of industrially produced agricultural foods: egg 7 times, meat 9 times, and dairy products 20 times.

The annual per cow production of milk has in the Western world during the last 150 years increased up to 50 times. In addition, modern milk is today heated to high temperature before it is delivered to the consumer. Although consumption of drinking milk has decreased significantly during the last 50 years in Western countries (United States: from 144 L in 1950 to 92 L per person per year in 2000), the consumption of cheese has instead quadrupled (from 4 kg in 1950 to 15 kg in the United States and 19 kg in the European Union per person and year in 2000), to a large extent due to extensive use of cheese products in fast foods: pizza, tacos, nachos, salads, fast-food sandwiches, and sauces for potatoes and vegetables. But it is in intake of powdered milk that the largest increases has occurred; powdered milk

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**Figure 7.4** Changes in intake of fat in the Western world during the 40,000 years of human existence on Earth. (Adapted from Leaf A, Weber PC.)
is today used in most industrially produced foods as reconstituted milk, in bread and bakery products, chocolate, ice cream, and hundreds of other common foods, but also in baby formulas and clinical nutrition formulas.

Commonly, 10 to 20 percent, but sometimes up to 70 percent, of the amino acid lysine is reported to be modified during common industrial treatment of milk (sterilization, pasteurization, irradiation, etc.). Fructoselysine is the dominating modified molecule, but CML and pyrraline are also usually produced during processing of milk. The sugar content, level and time of elevated temperature, and storage time are the main factors behind increased production of AGEs/ALEs in milk products. Figure 7.5 demonstrates the influence of various industrial treatments on the content of the AGE furosine in various milk products including powdered milk.¹⁵¹

7.7 ANIMAL FEEDS HAVE CHANGED IN PARALLEL WITH HUMAN FOOD CHANGES

Not only human food but also animal feeds have undergone dramatic alterations during the twentieth century, from mainly forage-based feeds containing more starch-rich and fast-absorbed carbohydrates: corn, maize grains, barley, molasses,

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**Figure 7.5** Relative furosine content in various milk-based products. Key: a, powdered milk kept for 2 years at room temperature; b, powdered milk kept for 1 year at room temperature; c, DIF with whey plus casein; d, DIF with hydrolyzed whey; e, powdered milk kept for 1 year at 4°C; f, fresh milk powder; g, raw (whole) bovine milk. DIF, dietetic infant formulas; UHT, ultra heat treatment. (Adapted from Baptista JAB, Carvalho RCB.¹⁵¹)
and dextrose. Modern industry can produce a pig weighing 100 kg in less than half a year in contrast to about 2 years in the past and, as already mentioned, can drastically increase the cow’s production of milk. However, as in humans, such “force-feeding” will most likely induce insulin resistance in animals and, if the animals were allowed to live long enough, manifest diabetes. Insulin resistance is also reported in intensively milk- and lactose-fed calves. High levels of proinflammatory cytokines and various stress hormones are regularly registered in intensively fed animals. However, no information was found regarding whether or not such molecules can be transferred to humans by the food we eat. It is suggested that larger intake of hormone-rich foods, especially dairy products, might explain the reduced age of first menstruation in girls from approximately 17 years of age 200 years ago to the current about 12 years, and be responsible for shorter menstruation periods and later menopause among Western women. About 80 percent of milk consumed today, much in contrast to the old days, comes from pregnant cows, and is thus rich in various hormones, especially sex hormones. This is especially so for condensed products such as butter, cheese, and most likely also powdered milk. As this problem is increasingly observed, “hormone-free” milk has become available in such countries as the United States.

7.8 DISEASES ASSOCIATED WITH HIGH TISSUE LEVELS OF AGES/ALES

Increased levels of various AGE/ALE-substances in the body are reported in almost all chronic diseases, from allergy and Alzheimer’s disease to paradontosis, polycystic ovary syndrome, and various urogenital diseases, particularly uremia (Table 7.1). An association with dairy products is this far reported in significantly fewer such conditions, but is reported in allergy,84 coronary heart disease,85,86 and diabetes,87–89 Parkinson’s disease,90 and various cancers such as breast,48,91 prostatic,92,93 testicular,92 and ovarian84,95 malignancies. Increasing evidence also suggests that reduced bone density and osteoporosis are not, as believed in the past, dependent on deficiency in minerals, but instead are a result of increased inflammation in the body, which explains the high incidence of osteoporosis in patients with chronic diseases. High levels of AGE/ALE in the body are also reported in patients with osteoporosis.75,77 A recent American study reported reduced bone density in older women consuming more than three cola drinks per week compared to matched controls consuming similar amounts of other carbonated soft drinks.96 This becomes especially interesting when considering that cola drinks, much in contrast to other soft drinks, are rich in AGE. Increased AGE/ALE levels are also reported in other disease conditions with obscure etiology such as rupture of the Achilles’ tendon and fibromyalgia.54,72 The mouth reflects the health status of the body to a large extent, and paradontosis, frequently seen in patients with chronic diseases, is clearly associated with elevated inflammation in the body and elevated levels of AGE/ALE.77 It would not be a surprise if the lowest levels of AGE/ALE are to be found in the group referred to as raw eaters, but this group has
attracted few studies and none with regard to the content of AGEs/ALEs. However, it has been demonstrated that vegans, much in contrast to meat eaters and lacto vegetarians, have significantly lower levels of AGEs/ALEs in the body. As a matter of fact, it has been shown that lacto vegetarians have even higher levels of AGEs/ALEs in the body than meat eaters,97 which might be explained by a higher intake of dairy products, especially cheese, but might also be influenced by a higher intake of fructose. Significant health advantages are reported for vegans, when compared to the other groups: statistically significantly lower levels of proinflammatory molecules such as cytokines and acute phase proteins, lower systolic and diastolic blood pressure, lower total cholesterols, lower low-density lipoprotein (LDL)-cholesterols, lower fasting blood sugar and triglycerides, and lower incidence of chronic diseases, especially diabetes and complications to diabetes.

### 7.9 FOODS RICH IN AGES/ALES

This far, the information regarding AGE/ALE content in foods is incomplete. However, an international association has recently been formed with the goal of filling this gap. Leading universities around the world are building institutions for studies of nutragenomics, for example, how various food ingredients affect our health. However, from existing information it is clear that dysfunctioning proteins are especially rich in foods that have been subjected to industrial processing. Table 7.2 provides guidance on foods expected to contain larger amounts of AGEs/ALEs.
7.10 PREVENTION AND TREATMENT OF AGE/ALE ACCUMULATION

Several pharmaceuticals, especially those used for treatment of diabetes, are reported to reduce the content of AGES/ALEs in the body, at least in short-lived tissues, that is, tissues with high turnover. Significant reduction in body content of AGE/ALE in comparison to controls (eating standard Western food) is observed in individuals who practiced caloric restriction (CR, they eat only two-thirds of what they would like to) for more than 2 years, which is also accompanied by significant health advantages compared to matched controls: lower blood pressure (102/61 ± 7 vs. 131/83 mm Hg), and lower levels of markers of inflammation such as CRP (0.3 vs. 1.9 mg/L), TNF-α (0.8 vs. 1.5 pg/mL), and TGF-β (29.4 vs. 35.4 ng/mL). Elevated RAGE and low sRAGE is reported in patients with active rheumatoid arthritis (RA), but patients with RA practicing CR for about 2 months are reported to have lower levels of pentosidine (an often measured AGE) in urine, as well as lower disease activity.
Rich supply of vitamins such as A, B, especially B₆ and B₁₂, C, D, E, and K as well as glutathione and folic acid is often emphasized. A long line of plant antioxidants, particularly those collectively defined as polyphenols, with documented up to 10 times stronger oxidation-quenching properties than conventional vitamins have been shown to have strong chemopreventive abilities, strong ability to prevent accumulation in the body of AGEs/ALEs, significant ability to reduce inflammation in the body and to prevent reduction in organ function and premature aging. Such plant antioxidants exist in nature in many thousands of different compounds, most likely hundreds of thousands; of flavonoids alone, more than 4,000 have been identified and of carotenoids almost 1,000. Table 7.3 summarizes some of the most well-known and studied such plant antioxidants. Supplementing histidine, taurine, carnitine, and carnosine has also been reported to have AGE/ALE-protecting abilities. No vegetarian food with the exception of certain algae contains any taurine. This important amino acid is obtained only from eating animal-derived foods—meat, poultry, and fish.

### 7.11 Intestinal Flora and Probiotics of Great Importance

Most of the above-mentioned substances will need assistance from microbial enzymes for their release from foods and absorption into the body. A rich intestinal flora is regarded necessary for release and absorption of various important

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<tr>
<th>Table 7.3 Plant Antioxidants with Chemoprotective Effects on the Body; Reduction in Accumulation of Ages/Ales and Downregulation of the Rage Receptor Function</th>
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<tbody>
<tr>
<td>• Isothiocyanates in cruciferous vegetables</td>
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<td>• Anthocyanins and hydroxycinnamic acids in cherries</td>
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<td>• Epigallocatechin-3-gallate (EGCG) in green tea</td>
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<td>• Chlorogenic acid and caffeic acid in coffee beans and tobacco leaves</td>
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<td>• Capsaicin in hot chili peppers</td>
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<td>• Chalcones in apples</td>
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<td>• Eugenol in cloves</td>
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<td>• Gallic acid in rhubarb</td>
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<td>• Hisperitin in citrus fruits</td>
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<td>• Naringenin in citrus fruits</td>
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<td>• Kaempferol in white cabbage</td>
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<td>• Myricetin in berries</td>
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<td>• Rutin and quercetin in apples and onions</td>
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<tr>
<td>• Resveratrol and other procyanidin dimmers in red wine and virgin peanuts</td>
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<td>• Various curcumenoins in main yellow pigments in turmeric curry foods</td>
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<td>• Daidzein and genistein in soy beans</td>
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antioxidants. However, the increased intake of refined food and deficient intake of fresh fruits and vegetables among Westerners has led to a significant reduction in both density and diversity of the flora. This reduction is especially pronounced for strong fiber-fermenting lactic acid bacteria (LAB) such as *Lactobacillus plantarum* and *L. paracasei*; 75 percent of omnivorous Americans and 25 percent of vegetarians in the United States lack *L. plantarum*. A more recent Scandinavian study found *L. plantarum* in only 52 percent and *L. paracasei* in only 17 percent of healthy individuals. This information is particularly interesting as *L. plantarum* and *L. paracasei* belong to the small group of intestinal bacteria with ability to break down semiresistant fibers such as inulin, reduce inflammation, reduce infection, and eliminate pathogenic bacteria such as *Clostridium difficile*. Some LAB may well have the ability to eliminate AGEs/ALEs from foods, similar to what has been demonstrated for gluten and heterocyclic amines. In vitro studies have shown that fructoselysine, the dominating AGE in heated milk, can be effectively eliminated when incubated with fresh intestinal flora.

### 7.12 Future Aspects

Recent studies in the United States demonstrate an 83 percent reduction in rate of coronary heart disease, a 91 percent reduction in diabetes in women, and a 71 percent reduction in colon cancer in men in patients adhering to what today is regarded as an “healthy lifestyle”: no use of tobacco, moderate use of alcohol, regular physical exercise, and controlled eating. To this four factors should be added control of stress. Numerous studies demonstrate that both physical and mental stress increase the degree of inflammation in the body and activate RAGE. It is likely that control of both intake and endogenous production of AGEs/ALEs might further add to a healthy lifestyle and further improve health and well-being. It is unfortunate that only a small fraction of us will give priority to issues related to active control of health and prevention of disease. A recent study in the United States suggests that only a small minority of 3 percent adhere to the four principles mentioned above. Among these are mainly individuals who are otherwise fortunate in life, have a higher education, and a good financial status. Those who have low income and low level of education, including their children, are reported to be about 50 percent more unhealthy.

Too long have we ignored measures to control health by referring to the importance of genetic factors, which we thought we could not do much about. However, the message from numerous studies in monocygotic twins and in immigrants, especially Japanese and Italians, where one immigrated to the United States while the other remained in the home country is clear: lifestyle is significantly more important for health than genetic inheritance. The message from the winners of the 2006 Nobel prize in medicine and physiology is encouraging: it might well be possible to silence genes which might have a negative influence on health. Increasing evidence suggests that control of exaggerated systemic inflammation in the body is of the greatest importance for sustained health. For this, diet is a necessary, easily accessible, and most powerful tool.
REFERENCES


