molecules

MDPI

Review

Dietary Advanced Glycation End-Products (AGEs) in Pediatric Nutrition: Chemical and Biochemical Stability and Long-Term Implications for Insulin Resistance

Paweł Kołaczyk, Antoni Kuczyński, Emilia Leśniak, Joanna Lemanowicz * and Anetta Siwik-Ziomek

Division of Biochemistry, Faculty of Medicine, Bydgoszcz University of Science and Technology, Bernardyńska 6 St., 85-029 Bydgoszcz, Poland; pawel.kolaczyk@pbs.edu.pl (P.K.); antkuc000@pbs.edu.pl (A.K.); emiles001@pbs.edu.pl (E.L.); anetta.siwik-ziomek@pbs.edu.pl (A.S.-Z.)
* Correspondence: joanna.lemanowicz@pbs.edu.pl

Abstract

The rising prevalence of pediatric obesity has increased interest in dietary factors that may contribute to early metabolic dysfunction. Ultra-processed foods (UPFs) can contain substantial amounts of dietary advanced glycation end products (dAGEs) and advanced lipoxidation end products (ALEs), depending on food composition and processing conditions. This review examines dAGEs from their formation in the food matrix to their potential metabolic effects during childhood. We discuss the influence of industrial and domestic processing, including ultra-high-temperature treatment, extrusion, and air frying, on key glycation markers such as N^ε-(carboxymethyl)lysine (CML) and methylglyoxal-derived hydroimidazolone-1 (MG-H1). Food composition and processing conditions are considered important determinants of dAGE and ALE formation and dietary exposure. The bioavailability of dAGEs depends on gastrointestinal digestion, intestinal absorption of glycated peptides, and interactions with the gut microbiota. At the cellular level, dAGEs may promote oxidative stress and activate AGE–RAGE signaling, triggering inflammatory responses that impair IRS-1 signaling and GLUT4 translocation. These mechanisms may contribute to peripheral insulin resistance. Potential long-term consequences include endothelial dysfunction, adipose tissue fibrosis, and metabolic dysfunction-associated steatotic liver disease (MASLD). Particular attention is given to bioactive food components with antiglycative and antioxidant properties that may limit dAGE formation and their biological effects. Further research is needed to establish dietary exposure thresholds and assess regulatory approaches to dAGE content in foods intended for children.

Keywords: dietary AGEs (dAGEs); enzymes; Maillard reaction products; pediatric obesity; insulin resistance; RAGE receptor; ultra-processed foods; bioactive components of food; infant formula

Check for updates

Academic Editors: Aldona Sobota and Grażyna Cacak-Pietrzak

Received: 27 October 2026
Revised: 20 November 2026
Accepted: 25 November 2026
Published: 27 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

1.1. The Pediatric Obesity Epidemic and the Shift in Dietary Patterns

The increasing prevalence of obesity among children and adolescents represents a major public health challenge. According to the World Health Organization (WHO), approximately 400 million children and adolescents aged 5–19 years were overweight in 2024, including 170 million living with obesity. The global prevalence of overweight, including obesity, in this age group increased from 8% in 1990 to 20% in 2024 [1]. Global epidemiological studies further document substantial changes in the prevalence of obesity among

pediatric populations over recent decades [2]. Obesity tracking, defined as the persistence of obesity from childhood into adulthood, is a particular concern. Children with excess body weight not only experience early metabolic complications but also face a substantially increased risk of developing full-blown metabolic syndrome, type 2 diabetes, and premature cardiovascular disease later in life [3].

This trend has coincided with substantial changes in dietary patterns, including increased consumption of ultra-processed foods (UPFs) among children and adolescents. In many high-income countries, ultra-processed products currently account for more than half of the daily caloric intake of children and adolescents [4]. These products are often energy-dense and rich in refined carbohydrates and fats, while providing relatively little dietary fiber and few micronutrients. They have become a major component of children's diets, frequently displacing minimally processed foods. Thermal processing can influence both the sensory properties and chemical composition of foods. In particular, Maillard reactions contribute to the development of desirable flavors, aromas, and browning, while certain processing conditions may also promote the formation of dietary advanced glycation end-products (dAGEs). The extent of dAGE formation depends on food composition and processing conditions.

1.2. Definition, Chemical Heterogeneity, and Dual Origins of AGEs and ALEs

Advanced glycation end-products (AGEs) constitute a heterogeneous group of chemical compounds formed through the non-enzymatic modification of proteins, lipids, and nucleic acids by reducing sugars and their reactive derivatives [5]. In human physiology, two sources of AGEs can be distinguished: endogenous formation and exogenous exposure through the diet (dietary AGEs, or dAGEs). Endogenous AGEs are continuously formed within the body as a natural component of physiological tissue aging. Their formation is markedly accelerated under conditions of chronic hyperglycemia and oxidative stress, as documented in studies of adults with type 2 diabetes or renal failure [6].

Another source of AGEs is dietary exposure, particularly through thermally processed foods. These compounds form during the thermal processing of food matrices in industrial and culinary settings, where reactive dicarbonyls, including methylglyoxal and glyoxal, modify amino acid residues in proteins, particularly lysine and arginine, giving rise to mature adducts such as Nε-(carboxymethyl)lysine (CML) and pentosidine [7]. Concurrently with protein glycation, lipid peroxidation occurs in foods rich in polyunsaturated fatty acids, leading to the formation of advanced lipoxidation end-products (ALEs), which exhibit comparable tissue toxicity [8].

Whereas the endogenous AGE pool is physiologically low in children because they have not yet undergone decades of age-related degenerative changes, dietary exposure to exogenous dAGEs and ALEs in contemporary pediatric diets may reach substantial levels. The contrast between endogenous AGE formation and dietary exposure to dAGEs and ALEs provides a rationale for investigating the potential health effects of these compounds in children [9].

1.3. Early Nutritional Programming and "Metabolic Memory"

The Developmental Origins of Health and Disease (DOHaD) concept indicates infancy and early childhood as critical periods of phenotypic plasticity during which environmental exposures may have lasting physiological effects [10]. The potential consequences of consuming ultra-processed foods containing dAGEs and ALEs may extend beyond excess energy intake and adipose tissue accumulation. Following intestinal absorption, some dietary glycation products may enter the circulation as free adducts or protein-associated

compounds. Their presence may contribute to oxidative stress and inflammatory responses in peripheral tissues [7].

A diet rich in dAGEs may influence metabolic programming through biochemical and epigenetic mechanisms. This phenomenon may involve long-lived cell populations, including intestinal stem cells, preadipocytes, and immune progenitor cells in the bone marrow, rather than being restricted to short-lived differentiated cells [11]. Chronic stimulation of these cell populations by dAGEs may promote so-called trained immunity, reprogramming immune cells toward a sustained and exaggerated pro-inflammatory response [12].

A potential long-term consequence of this process is the early initiation of a pathophysiological cascade that may contribute to the development of specific diseases. Observational evidence from infants suggests associations between circulating AGE levels and selected metabolic markers, including insulin and HOMA indices [13]. However, these findings do not establish that dietary AGE exposure causes insulin resistance or other metabolic disorders in children. Concurrently, at the neurobiological and behavioral levels, persistent stimulation of metabolic pathways may contribute to disordered eating behaviors, including reduced sensitivity to peripheral satiety signals, potentially associated with leptin resistance, and a tendency toward compulsive consumption of ultra-processed foods, described as loss-of-control eating [14]. These potential metabolic and neurobehavioral changes may reinforce unhealthy dietary patterns and contribute to difficulties in modifying eating behaviors later in life [15].

1.4. Aim and Scope of the Review

Previous studies on the biological effects of advanced glycation end-products have predominantly focused on adults, particularly in relation to type 2 diabetes, renal failure, and aging [16]. Existing reviews have addressed different aspects of dietary AGEs, including their occurrence in foods and potential health effects [17], digestion, metabolism, and interactions with the gut microbiota [7], formation and analytical detection in food systems [18,19], and processing-related contaminants in infant formulas [20]. Building on these contributions, the present review integrates food chemistry, gastrointestinal transformations, and potential metabolic mechanisms, with particular emphasis on pediatric nutrition and the limitations of extrapolating experimental findings to children.

The primary aim of this review is to examine the molecular and enzymatic mechanisms through which dietary AGEs (dAGEs) and ALEs may contribute to metabolic disturbances in children, with particular emphasis on insulin resistance and subclinical inflammation. The review examines these compounds from their formation during food processing and their fate in the gastrointestinal tract to their potential cellular and organ-level effects in children. The review also discusses the potential use of dietary bioactive compounds, including polyphenols, as a nutritional strategy to help reduce dAGE formation and mitigate their pro-oxidative effects on the body.

A literature search was conducted in PubMed, Scopus, and Web of Science to identify studies addressing dietary advanced glycation end-products (dAGEs), their chemical properties, biological effects, and implications for pediatric health. Publications available up to November 2026 were included, with no restrictions on publication year. The search used combinations of the following keywords: “advanced glycation end products”, “dietary AGEs”, “food processing”, “pediatric nutrition”, “insulin resistance”, “oxidative stress”, “inflammation”, and “RAGE”. Original research articles, clinical and experimental studies, and relevant reviews were selected based on scientific quality and relevance to the scope of this review. Studies involving adults were also included when they provided relevant mechanistic insights. When interpreting the evidence, we distinguish between pediatric human studies, adult human studies, animal experiments, and in vitro investigations. Find-

ings from pediatric populations are considered most directly relevant, whereas evidence from adults and experimental models is treated as indirect support and does not establish causal effects of dietary AGEs in children.

2. Formation, Chemical Stability, and Dietary Sources of dAGEs in Pediatric Nutrition

2.1. Chemical Mechanisms: From the Maillard Reaction to Lipid Oxidation (AGEs and ALEs)

The Maillard reaction, a multistage process of non-enzymatic browning, is a major pathway of dietary AGE (dAGE) formation during food processing. In this process, the carbonyl groups of reducing sugars react with free amino groups of proteins, predominantly those of lysine and arginine residues [21].

This process can be divided into three main stages. It begins with an early condensation phase, during which an unstable Schiff base is formed and subsequently converted into more stable Amadori or Heyns products [5,7]. During the intermediate phase, these compounds undergo decomposition, generating highly reactive dicarbonyl compounds such as glyoxal (GO) and methylglyoxal (MGO) [22]. In the final stage, these reactive molecules form stable covalent modifications and cross-links in proteins, giving rise to advanced glycation end-products (AGEs). The most commonly quantified and best-studied markers of this group in processed foods are N^{ε}-(carboxymethyl) lysine (CML) and N^{ε}-(carboxyethyl) lysine (CEL) [23]. Methylglyoxal-derived compounds, such as the MG-H1 isomer, are also noteworthy, as their presence in the food matrix can serve as an indicator of the extent of glycation [24].

However, the Maillard reaction is not the only pathway contributing to the formation of processing-derived compounds relevant to pediatric nutrition. Foods such as infant formulas, popular snacks, and fast-food products contain not only carbohydrates and proteins but also substantial amounts of lipids. Polyunsaturated fatty acids (PUFAs), which contain two or more double bonds in their carbon chains, are particularly important in this context. Their chemical structure makes them highly susceptible to free-radical attack and oxidation [25]. This provides a basis for a second, equally important mechanism: lipid peroxidation.

During industrial processes involving elevated temperatures, such as spray drying of milk or frying, lipid oxidation can occur, generating reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), as well as glyoxal [26]. These compounds can react with proteins to form advanced lipoxidation end-products (ALEs). The pathways leading to AGE and ALE formation can overlap and share common reactive intermediates. For example, CML can be formed through two pathways: as a product of the Maillard reaction (AGE formation) and through interactions between oxidized lipids and proteins (ALE formation) [27].

From a chemical perspective, this means that food matrices rich in both reducing sugars and polyunsaturated fatty acids provide an environment in which AGE and ALE formation pathways may overlap. Consequently, the extent of protein and lipid modification in the final product may be greater than would be inferred from an analysis of the Maillard reaction alone.

2.2. Processing and Technological Determinants: At Home and in Industry

The formation and final concentrations of dAGEs and ALEs in food products are influenced by several interacting physicochemical factors. The most important include temperature, duration of thermal processing, environmental pH, and water activity (a_w) [28]. High temperatures combined with prolonged heating are major factors promoting dAGE formation, with reaction rates generally increasing substantially as temperature rises [29].

Environmental pH also plays an important role. Neutral or slightly alkaline conditions favor the deprotonation of free amino groups including those in lysine residues, thereby facilitating their initial condensation with sugar carbonyl groups. Conversely, acidic conditions tend to inhibit this process [30].

Water activity (a_w), which reflects the availability of water for chemical and physical processes within the food matrix, is another critical parameter. The relationship between water activity and the rate of the Maillard reaction is typically bell-shaped, with a maximum in the intermediate range ($a_w \approx 0.5$–0.8). In highly hydrated systems ($a_w > 0.8$), water dilutes the reactants and may favor the hydrolysis of reaction products. At very low water activity ($a_w < 0.2$), molecular mobility within the matrix is substantially restricted, limiting diffusion and molecular collisions [31].

These relationships help explain why certain industrial technologies used to manufacture foods for children may favor dAGE and ALE formation. The production of liquid infant and follow-on formulas may involve ultra-high-temperature (UHT) processing. Although brief heating at 135–150 °C for several seconds can limit vitamin losses and provide microbiological safety, this treatment may still initiate the formation of early Amadori products and CML in whey proteins and casein [32]. Extrusion, commonly used in the manufacture of breakfast cereals, corn snacks, and instant porridges, involves high pressure, shear forces, elevated temperatures that may exceed 150 °C, and low moisture content in the final product. These conditions can expose amino groups in denatured proteins and, in combination with reduced water activity, may promote dAGE formation in cereal-based products [33].

Air fryers use forced hot-air circulation, and the formation of Maillard reaction products during air frying depends on factors such as temperature, processing time, and humidity. In a study of fish cutlets, surface AGE content increased with heating time and was higher after deep-frying than after air frying. However, differences between the two methods were relatively small within the product [34]. In a study of chicken breast, air frying was associated with lower levels of the AGE precursors GO and MGO than deep-frying, although the findings concerning CML and CEL also depended on the use of grape seed extract [35]. Similarly, a study of French fries demonstrated that GO and MGO levels increased with air-frying temperature and duration [36]. These findings indicate that air frying cannot be considered a method that eliminates dAGE formation; its effects depend on processing parameters, particularly time and temperature. This is relevant to pediatric nutrition, in which protein-rich foods such as chicken nuggets are frequently prepared using this method.

Compared with conventional heating, microwave heating may reduce protein glycation in certain model systems. However, this effect depends on processing conditions and product composition, and the available evidence does not justify a general conclusion that microwave heating consistently reduces total dAGE content compared with baking [37]. Microwave heating can also produce a non-uniform temperature distribution within food, resulting in localized hot and cool spots [38]. Temperature heterogeneity during microwave heating may therefore contribute to uneven formation of Maillard reaction products within foods. However, this relationship has been demonstrated in model systems rather than directly in typical prepared meals [39].

The determination of AGEs in food requires analytical methods adapted to the target compounds and food matrix. Liquid chromatography coupled with mass spectrometry (LC-MS/MS or high-resolution MS) enables selective quantification of individual AGEs, including CML and CEL, in products such as infant formulas, dairy products, and processed foods [19,33]. However, sample preparation and hydrolysis conditions can affect analytical results. For example, Akıllıoğlu and Lund reported limits of detection of 1.4–60 ng/mL and

recoveries of 76–118% for their validated method, while demonstrating partial conversion of MG-H1 to MG-H3 during acid hydrolysis [33].

Enzyme-linked immunosorbent assays (ELISAs) provide a relatively rapid and inexpensive alternative, although their results depend on antibody specificity and may differ from those obtained by mass spectrometry. Fluorescence-based methods are useful for screening fluorescent glycation products but do not directly quantify non-fluorescent AGEs such as CML and CEL [18,19]. Therefore, method validation, including detection and quantification limits, recovery, precision, and matrix effects, is essential. Differences in sample preparation, analytical specificity, and reporting units should be considered when comparing AGE concentrations across food matrices and studies.

2.3. Sources of dAGE and ALE Exposure in the Pediatric Diet and Regulatory Challenges

In the European Union, specific regulatory measures have been introduced to reduce acrylamide levels in food. Commission Regulation (EU) 2017/2158 establishes mitigation measures and benchmark levels, including for selected products intended for infants and young children [40]. These benchmark levels should not, however, be confused with legally established maximum permissible limits. In the United States, the Food and Drug Administration (FDA) has issued non-binding guidance on acrylamide reduction without establishing a maximum recommended level or action level [41]. No analogous, specific legal limits for dAGEs or ALEs in food, including products intended for children, have been identified in the sources considered here. It is therefore more accurate to refer to the absence of specific limits for these compounds than to suggest that food regulation is entirely absent. The need for more explicit dietary guidance concerning dAGEs has also been highlighted in the scientific literature [18]. The lack of specific guidance is partly attributable to the difficulty of distinguishing the effects of exogenous dAGEs from those of the endogenous AGE pool, as well as to the complex influence of the food matrix on their absorption. Consequently, manufacturers of foods intended for children are not specifically required by dAGE- or ALE-related legislation to optimize processing conditions to reduce protein glycation and lipoxidation [42].

One of the earliest and potentially most significant sources of dietary dAGE exposure is infant formula, which may serve as an infant's sole source of nutrition during the first months of life. In this context, food technology must balance microbiological safety with the preservation of protein quality. To minimize the risk of infection by pathogens such as *Cronobacter sakazakii* and *Salmonella*, liquid and powdered formulas undergo thermal processing, including UHT treatment, pasteurization, and spray drying, depending on the product and manufacturing process [41,42]. Such processing can modify whey proteins and casein, resulting in the formation of compounds such as CML and CEL. Differences in feeding patterns and the composition of human milk and infant formula may contribute to differences in dietary AGE exposure. However, higher exposure to AGEs does not necessarily translate into impaired insulin sensitivity. In a study involving 166 healthy infants aged 3–14 months, Klenovics et al. [43] reported higher circulating CML concentrations in formula-fed infants than in breastfed infants in the younger age groups. Although formula-fed infants aged 3–6 months showed lower insulin sensitivity, no significant differences in insulin sensitivity were observed between infants receiving formulas with low and high CML contents. Moreover, circulating CML concentrations were not significantly associated with insulin sensitivity, suggesting that CML exposure did not explain the reduced insulin sensitivity observed in the younger formula-fed group. Given the observational design and the focus on CML as an AGE marker, these findings do not exclude potential effects of other dietary AGEs or longer-term metabolic consequences [44].

A recent study by Damasiewicz-Bodzek et al. [45] analyzed 20 commercial infant formulas in liquid and powdered forms, determining the concentrations of CML, CEL, furosine, GOLD, and MOLD using LC-MS/MS. Liquid formulas contained significantly higher CML concentrations than powdered formulas, whereas no significant differences in the analyzed compounds were observed between initial and follow-on formulas. These findings highlight the importance of product formulation and processing conditions in determining dietary exposure to glycation products during infancy.

During toddlerhood and early childhood (approximately 2–5 years), when food choices remain largely controlled by caregivers, commercial instant porridges, dairy desserts, and extruded corn or fruit snacks may contribute to dAGE intake. Although parents may perceive these products as safe and specifically formulated for young children, some undergo intensive thermomechanical processing under conditions of relatively low moisture, which can favor protein glycation [18]. During the school-age years (6–12 years), children gradually gain greater autonomy in food choices and may consume food outside the home more frequently. Extruded breakfast cereals, cereal bars, and packaged savory snacks may become important sources of dAGEs in this age group. Some of these products are formulated to achieve a so-called "bliss point," a balance of fats, sugars, and salt designed to maximize palatability and potentially encourage repeated consumption [4]. The presence of methylglyoxal (MGO), a reactive carbonyl compound and precursor of AGEs, has been demonstrated in ready-to-eat cereal products, including breakfast cereals, chips, and crackers [46]. Moreover, studies using simulated in vitro digestion suggest that MGO and GO concentrations in certain cereal products may change or increase under conditions mimicking gastrointestinal digestion [47]. Establishing appropriate dietary patterns at this stage is important for metabolic health and may help limit repeated exposure to high levels of dAGEs during adolescence. During adolescence (13–18 years), dietary behavior is increasingly influenced by social factors. Greater dietary autonomy and peer dynamics may contribute to the frequent consumption of ultra-processed foods. Social gatherings and eating outside the home can encourage the consumption of energy-dense foods rich in fat and sugar, including snacks and fast food. Studies in adolescents have reported higher consumption of such foods when eating in food-service establishments and in the presence of friends than when eating alone or at home [48]. Population-based studies have also indicated that ultra-processed foods make a substantial contribution to adolescent diets [49]. Nevertheless, dAGE and ALE concentrations depend on the type and composition of the product and the thermal processing conditions applied; a high degree of processing should therefore not automatically be equated with a high content of these compounds [50].

Fast-food products subjected to high-temperature processing, particularly deep-frying, may contain dAGEs, including N^{ε}-(carboxymethyl)lysine (CML) and N^{ε}-(carboxyethyl) lysine (CEL). Validated chromatographic methods coupled with mass spectrometry have enabled the quantification of these compounds in baked and fried foods, including French fries [51]. Furthermore, studies of French fries and poultry meat have demonstrated the transfer of malondialdehyde (MDA), a product of lipid peroxidation, from frying oil into the food matrix, indicating the possibility of simultaneous dietary exposure to products of glycation and lipid oxidation [52]. In a population-based study, higher dietary intake of advanced glycation end-products (dAGEs) among adolescents was associated with higher odds of metabolic syndrome [53]. Separately, research has indicated that greater consumption of ultra-processed foods may be associated with an increased risk of insulin resistance in overweight or obese adolescents [54]. These relationships warrant particular attention during puberty, a period characterized by a physiological and transient decline in insulin sensitivity [55]. Nevertheless, the available evidence does not establish that high

dAGE intake prolongs this physiological state or directly contributes to the development of insulin resistance in adolescents.

Evidence from human dietary intervention studies indicates that the relationship between dietary AGE intake and insulin resistance remains uncertain. A systematic review and meta-analysis of 13 randomized controlled trials by Sohouli et al. [56] found that low-AGE diets were associated with significant reductions in the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), an index estimating insulin resistance from fasting glucose and insulin concentrations, as well as in fasting insulin concentrations, compared with high-AGE diets. However, no significant overall effects were observed for fasting glucose or glycated hemoglobin (HbA1c), a marker of longer-term glycemic control. A more recent systematic review focusing specifically on adults with diabetes found no significant changes in HbA1c or HOMA-derived indices in the six and three trials assessing these outcomes, respectively [57]. Furthermore, Linkens et al. [58], in a four-week randomized controlled trial involving 73 adults with abdominal obesity, reported no significant differences in insulin sensitivity, insulin secretion, or insulin clearance between low- and high-AGE dietary groups, despite substantial differences in dietary AGE intake. These outcomes were assessed using metabolic clamp techniques, providing a different approach to evaluating insulin metabolism than HOMA-IR. Collectively, these findings indicate that the metabolic effects of dietary AGE restriction are not consistent across human studies. Differences in study populations, intervention duration, and assessment methods may contribute to this variability. Importantly, these intervention findings are derived from adult populations and cannot be directly extrapolated to children. Although pediatric observational studies provide some evidence of associations between dietary AGE exposure and metabolic outcomes, direct evidence of causality in children remains insufficient.

2.4. Chemical Stability of dAGEs in the Food Matrix and Their Bioaccessibility

Many dietary advanced glycation end-products (dAGEs) occur as stable covalent modifications of components within the food matrix. These compounds include N^{ε}-(carboxymethyl)lysine (CML) and N^{ε}-(carboxyethyl)lysine (CEL), which result from the modification of lysine residues, and pentosidine, which forms a cross-link between lysine and arginine residues [23]. Unlike relatively unstable and reversible Schiff bases, Amadori products are more stable intermediates of the Maillard reaction that can undergo further transformations leading to mature AGEs [55]. Similarly, advanced lipoxidation end-products (ALEs) comprise covalent adducts formed between reactive lipid oxidation products and macromolecules; their stability depends on the chemical structure and type of adduct formed [59].

CML and CEL may persist in powdered and dried foods during storage, although their concentrations can change over time. Studies of milk powder have shown that CML concentrations may increase during prolonged storage, with the rate of change depending on factors such as the drying method, temperature, and relative humidity [60]. In dried meat products, increases in both CML and CEL concentrations have also been observed during storage [61]. Both compounds have been quantified in powdered cereal products intended for infants and young children during a 28-day storage period, providing product-specific evidence of their behavior during storage [62]. Overall, analytical studies indicate that AGEs, including CML and CEL, can persist in powdered food products and may continue to form through ongoing Maillard reactions. In milk powder, the rate of CML formation has been shown to depend on temperature, relative humidity, and the drying method, among other factors [60]. Similar trends have been observed in infant formula stored after opening and in whole milk powder stored for 18 months, in which CML and CEL concentrations

increased [63,64]. These findings indicate that storage conditions can affect the final dAGE content of a product before consumption.

The presence of natural antioxidants in the food matrix, whether naturally occurring or deliberately added, may influence these processes during food processing and storage. Polyphenols can limit AGE formation during food processing by directly scavenging reactive α-dicarbonyl compounds, such as methylglyoxal (MGO) and glyoxal (GO). This mechanism has been described in studies of the Maillard reaction, and the direct trapping of MGO and GO by quercetin has been experimentally demonstrated in a model system [65,66]. The effectiveness of this process depends on the chemical structure of the polyphenols and the reaction conditions; it should therefore not be assumed to occur to the same extent in all food products [65]. Plant-derived bioactive compounds can also scavenge reactive carbonyl precursors and thereby reduce the formation of selected AGEs during thermal processing [67]. Nevertheless, in food matrices with limited antioxidant activity, such as some refined snacks or infant formulas, glycation may proceed and result in substantial protein modification.

Protein glycation and cross-linking can reduce susceptibility to enzymatic proteolysis, partly by blocking cleavage sites and restricting digestive enzyme access to polypeptide chains [68,69]. Studies using model proteins and dynamic gastrointestinal models indicate that some protein-bound dAGEs can persist through gastric and intestinal digestion, although the extent of this persistence depends on the type of protein modification and the food matrix [70]. This aspect is related to bioaccessibility, defined as the fraction of a compound released from the food matrix and made available in the gastrointestinal lumen during digestion. In vitro digestion models can be used to investigate this process by analyzing both free and protein-bound forms [70,71]. Understanding how protein cross-linking affects the digestion of dAGE-containing proteins may help clarify their subsequent metabolic fate, intestinal absorption, and potential effects on the intestinal barrier in children and adolescents.

2.5. Role of Dietary Bioactive Compounds in Inhibiting dAGE and ALE Formation During Food Processing

A major challenge in food processing is to minimize the formation of undesirable Maillard reaction and lipid peroxidation products while preserving sensory properties and overall product quality [72,73]. Polyphenols can inhibit AGE formation at various stages of the glycation process, including through the scavenging of reactive dicarbonyl compounds and free radicals [65,74]. Certain polyphenols have also been shown to inhibit lipid oxidation and secondary protein lipoxidation, potentially reducing the formation of selected ALEs [75].

One mechanism by which polyphenols may limit AGE formation is the direct scavenging of reactive α-dicarbonyl compounds, such as methylglyoxal. The rate of this reaction depends on the chemical structure of the polyphenol involved [76]. Certain polyphenols and polyphenol-rich plant extracts can reduce CML formation during thermal food processing. This effect has been demonstrated for blueberry extract in UHT-treated milk and grape seed extract in chicken meat, although the efficacy of these interventions depends on the food matrix and extract concentration [35,67]. Model studies and experiments involving coconut milk have also demonstrated a reduction in CML concentrations following the addition of catechins, including epicatechin and epigallocatechin gallate (EGCG) [77].

Another mechanism that may limit the later stages of the Maillard reaction involves the chelation of metal ions that catalyze the autoxidation of Amadori products. This mechanism has been described for pyridoxamine; however, its relevance to individual polyphenols requires separate confirmation [78,79]. Transition metal ions, particularly iron and copper,

can catalyze Fenton-type reactions and promote oxidative processes, including sugar glycoxidation and lipid peroxidation, thereby contributing to dAGE and ALE formation. Certain bioactive compounds may attenuate these processes by chelating metal ions and neutralizing reactive oxygen species. Such effects may reduce the formation of secondary lipid oxidation products, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [80,81].

Incorporating selected plant-derived ingredients may help reduce dAGE formation in processed foods. For example, blueberry polyphenol extract reduced CML formation in UHT-treated milk [67], while pectic oligosaccharides reduced the formation of selected AGEs in infant formula under experimental storage conditions [82]. However, these findings do not establish the effectiveness of such ingredients under routine manufacturing and storage conditions. The application of such ingredients in other foods intended for children, including extruded cereal products, warrants further investigation.

Experimental studies indicate that selected polyphenol-rich extracts and catechins can reduce CML and CEL formation in specific food matrices, although their effectiveness depends on concentration and processing conditions [35,67,77]. However, the sensory acceptability and safety of effective concentrations in foods intended for children have not been adequately established. Moreover, reductions in AGE formation during food processing do not necessarily translate into reduced systemic exposure or improved metabolic outcomes. Further research, including pediatric intervention studies, is needed before the practical benefits of these strategies can be confirmed.

2.6. Influence of the Food Matrix and Bioactive Compounds on dAGE Bioavailability

The gastrointestinal fate of dAGEs depends on their dietary concentration, chemical properties and the forms in which they occur within the food matrix. Distinguishing between free and protein-bound fractions is particularly important because these fractions may differ in their susceptibility to digestion, intestinal absorption, and excretion [83,84]. Food matrix composition and processing conditions can modulate these processes; however, the direct effects of polyphenols, dietary fiber, and lipophilic antioxidants on dAGE bioavailability require further investigation [8].

Certain polyphenols, including quercetin and catechins, can form adducts with reactive dicarbonyl compounds, such as methylglyoxal (MGO) and glyoxal (GO), thereby reducing their availability for subsequent glycation reactions [66,85]. However, the biological effects of polyphenol–dicarbonyl adducts require separate evaluation. Experimental evidence indicates that such adducts may retain biological activity, and their formation cannot automatically be regarded as a detoxification process [86]. Furthermore, their effects on intestinal absorption and systemic AGE exposure remain uncertain.

Plant-derived components, such as soluble dietary fiber fractions, may also increase the viscosity of gastrointestinal contents or form gel networks, potentially restricting digestive enzyme access to proteins and slowing the kinetics of proteolysis. Certain hydrocolloids have been shown to inhibit protein digestion in in vitro models, while glycation can further reduce protein susceptibility to enzymatic hydrolysis in the stomach and intestine [68,69,87]. These processes may affect the rate and extent of release of AGE-containing peptides. Nevertheless, the direct effects of dietary fiber and hydrocolloids on the digestion of glycated proteins and the release of low-molecular-weight AGE-containing peptides warrant further investigation.

Reducing dietary AGE intake may limit systemic AGE accumulation and attenuate certain oxidative processes. Animal studies have reported increased concentrations of reactive dicarbonyl compounds and protein carbonyl adducts following consumption of extensively heat-treated diets. Conversely, AGE-restricted diets have been associated with reduced systemic AGE accumulation and lower levels of selected oxidative stress markers [88,89]. These findings support the hypothesis that limiting dietary exposure to dAGEs may reduce

their contribution to the overall systemic carbonyl and oxidative burden. However, they do not demonstrate that slowing proteolysis through the use of dietary fiber or hydrocolloids directly reduces carbonyl stress in peripheral tissues, nor do they establish that such an effect preserves cellular proteostasis.

The amount and nature of dAGEs reaching different regions of the gastrointestinal tract may influence their subsequent interactions with the intestinal epithelium, gut microbiota, and local immune barrier. The implications of these relationships for dAGE bioavailability and long-term metabolic outcomes, particularly in children, require further investigation.

3. Enzymatic Kinetics and the Passage of Dietary AGEs as Determined by the Gastrointestinal Barrier

3.1. Enzymatic Kinetics and the Passage of Dietary AGEs

The dAGE content in food is not equivalent to its bioavailability [90]. Upon ingestion, these compounds are subjected to the gastric environment, proteolytic enzymes, and intestinal peptidases, followed by transport processes across the intestinal epithelium. Some AGEs may be released from proteins as free modified amino acids or short peptides. Others may remain bound to the high-molecular-weight protein fraction, limiting their availability for absorption [70,91,92]. When interpreting studies on the potential biological activity of dAGEs, it is important to distinguish between the amount of the compound ingested, its release during digestion, intestinal absorption, and the actual exposure of tissues to its metabolites. The human gastrointestinal tract is a dynamic system involving mixing via peristaltic movements and fluctuating pH levels. Furthermore, digestive fluids and meal components are cleared from the gastrointestinal tract through both passive and active absorption [93].

3.2. Proteolysis as the Initial Step Regulating Bioavailability

A significant proportion of dietary AGEs (dAGEs) present in food are bound to proteins. Consequently, their bioavailability depends primarily on the extent to which the modified protein is broken down by gastrointestinal enzymes [90]. In the stomach, proteins undergo denaturation in the acidic environment, followed by partial hydrolysis by pepsin. In the duodenum, this process continues through the action of pancreatic proteases—primarily trypsin and chymotrypsin—and subsequently intestinal peptidases. However, the course of this process for glycated proteins may differ from the proteolysis of unmodified proteins. Glycation can modify Lys and Arg residues, which serve as key recognition sites for proteases specific to these amino acids. Using glucose-glycated α-lactalbumin, Deng et al. [93] demonstrated that an increase in the degree of glycation reduced the protein's susceptibility to hydrolysis by trypsin. In the case of trypsin, the extent of hydrolysis decreased as the number of modified sites increased. The authors further showed that the impact of glycation depended on the protease's specificity and selectivity. From an enzymatic mechanism perspective, it is particularly significant that a modified Lys or Arg residue ceases to function as a valid recognition site for trypsin. Consequently, the glycation reaction can reduce the number of available cleavage sites without directly inhibiting the enzyme itself [93]. This implies that the reduced rate of proteolysis of glycated protein should be interpreted primarily as a change in substrate properties rather than as classic enzyme inhibition. In the later stages of the Maillard reaction, aggregation and the formation of cross-links between protein chains may also occur. Such structural changes can further restrict enzyme access to peptide bonds. Consequently, protein digestibility is simultaneously influenced by the degree of chemical modification, the location of modified residues, and changes in the protein's spatial structure [93]. Experimental evidence obtained with β-casein and β-lactoglobulin also indicates that the extent of these effects depends on the type of protein, the chemical

nature of the glycation products and the occurrence of cross-linking [69]. Glycation from α-dicarbonyl compounds reduced the in vitro digestibility of studied proteins in both the gastric and intestinal stages. Thus, the digestibility of glycated proteins is determined by the combined effects of modification degree, modification location, protein conformation and protease specificity.

3.3. Pepsin, Trypsin, and Chymotrypsin—The Significance of Protease Specificity

The interaction of glycation with specific proteases varies [94]. Trypsin exhibits high specificity for peptide bonds adjacent to Lys and Arg residues; consequently, the modification of these residues through glycation can directly reduce the number of effective cleavage sites. In a study by Deng et al. [93], the maximum degree of hydrolysis of glycated α-lactalbumin by trypsin decreased linearly with the increasing degree of glycation, reaching approximately 65% of the value observed for the unmodified protein at the highest glycation level. Chymotrypsin is characterized by different substrate specificity; therefore, its response to glycation may be primarily linked to the presence of modifications near its preferred cleavage sites. Deng et al. [93] demonstrated that the effect of glycation on proteolysis depends not only on the number of modified sites. The interpretation of pepsin-mediated proteolysis requires a different approach. Unlike trypsin, pepsin exhibits broad substrate specificity and preferentially hydrolyses peptide bonds involving hydrophobic and aromatic amino acid residues. Thus, glycation of lysine and arginine does not necessarily block its principal cleavage sites directly. Instead, the effects may involve changes in protein conformation, aggregation, solubility and the accessibility of peptide bonds. Protein structure and the physical organisation of the food matrix can also influence enzyme accessibility and the extent of hydrolysis [94]. Therefore, it would be inappropriate to attribute the effects of glycation on pepsin-mediated digestion exclusively to steric hindrance. The overall susceptibility of glycated proteins to proteolysis reflects the interaction between chemical modification, structural changes and the specificity of individual digestive enzymes.

3.4. Gastrointestinal Transformation of dAGEs

Experimental data indicate that a portion of protein-bound dAGEs can survive gastric and intestinal digestion [70]. Particularly significant are results obtained using the dynamic TIM-1 model (TNO gastroIntestinal Model—a dynamic in vitro model) that simulates conditions in the upper gastrointestinal tract [91]. The authors analyzed CML, CEL, MG-H1, and G-H1 in food products subjected to simulated digestion. The model accounted for dynamic pH changes, mixing of digesta, the addition of bile and pancreatic enzymes, and absorption. Vander Lugt et al. [70] demonstrated that protein-bound dAGEs can persist during gastrointestinal digestion and that their distribution between free and protein-bound forms changes during this process. Particularly striking was the increase in total MG-H1 recovery in ginger biscuits, reaching 494 ± 76% after gastric and small intestinal digestion relative to the initial content. Importantly, total MG-H1 represented the sum of free and protein-bound forms determined by analysing hydrolysed samples. The protein-bound fraction alone showed a recovery of 454 ± 73%. Thus, the observed increase cannot be explained solely by the redistribution of pre-existing MG-H1 between free and protein-bound fractions. The authors interpreted these findings as evidence of additional AGE formation during gastrointestinal digestion. Several mechanisms may contribute to the increased recovery of total MG-H1. First, proteolytic degradation of the protein matrix may facilitate the release and analytical recovery of previously inaccessible AGE-modified peptides and amino acid residues. Second, the gastrointestinal environment may promote chemical transformations of pre-existing glycation intermediates, leading to the formation of additional MG-H1. In particular, residual methylglyoxal and reactive arginine-containing

compounds may participate in further glycation reactions. These mechanisms are not mutually exclusive and may occur simultaneously. Direct experimental evidence supporting the possibility of additional MG-H1 formation was provided by Treibmann et al. [95], who demonstrated a recovery of 246 ± 29% for MG-H1 during digestion of ovalbumin in the TIM-1 model. The authors also showed that simultaneous digestion of methylglyoxal and ovalbumin resulted in the formation of additional MG-H1 and Nε-carboxyethyllysine (CEL). Interestingly, they proposed that the formation of MG-H1 may also involve the rearrangement of intermediate methylglyoxal-derived arginine adducts, including MG-H3 and Nε-carboxyethylarginine, although these intermediates were not directly quantified. However, additional AGE formation should not be assumed to occur to the same extent during the digestion of all AGE-containing foods. Yuan et al. [96] demonstrated that digestion of previously glycated proteins predominantly resulted in the gradual release of free AGE compounds without detectable additional AGE formation. In contrast, co-digestion of dietary proteins with reactive precursors, particularly fructose or glyoxal, promoted the formation of additional AGEs. These findings indicate that the availability of reactive carbonyl compounds and glycation intermediates is an important determinant of AGE formation during gastrointestinal digestion. The analytical interpretation of increased MG-H1 recovery also requires consideration of methodological limitations. In the study by van der Lugt et al. [97], potential co-elution of MG-H1 with its structural isomers, particularly MG-H2 and MG-H3, was identified as a possible source of analytical uncertainty. Therefore, although the recovery exceeding 400% provides evidence consistent with additional MG-H1 formation, the precise quantitative contribution of newly formed MG-H1 should be interpreted cautiously.

3.5. Kinetic Aspects of the Interaction Between Glycation Products and Enzymes

From the perspective of enzyme kinetics, the potential interaction between glycation products and enzymes can occur via several pathways. The first mechanism is competition for the active site; a compound structurally similar to the natural substrate may restrict the latter's access to the enzyme. The second is mixed inhibition, in which the compound can interact with both the free enzyme and the enzyme–substrate complex. The third mechanism involves the glycation product acting as an alternative substrate with a very low rate of hydrolysis. Schumacher and Kroh [98] demonstrated that certain Amadori products can cause reversible inhibition of α-amylase, glucoamylase, and α-glucosidase. These results indicate that Maillard reaction products can modify carbohydrate digestion kinetics, although they do not prove a similar effect for advanced glycation end-products (AGEs). In the classical Michaelis–Menten framework, the reaction velocity is described by the equation: $v = (Vmax \times [S])/(Km + [S])$ where Vmax represents the maximum reaction velocity, Km is the Michaelis constant, and [S] represents the substrate concentration. The catalytic turnover number (kcat) describes the number of substrate molecules converted per enzyme molecule per unit of time under substrate-saturating conditions. The ratio kcat/Km is commonly used to describe catalytic efficiency at relatively low substrate concentrations. When applied to glycated proteins, however, these parameters require careful interpretation. The total concentration of a protein substrate does not necessarily correspond to the concentration of peptide bonds accessible to a particular protease. Glycation may decrease the number of available cleavage sites without directly changing the intrinsic catalytic properties of the enzyme. Consequently, an apparent reduction in reaction velocity may arise from a decrease in effective substrate availability rather than from an increase in Km or a decrease in kcat. Moreover, AGE-modified proteins represent heterogeneous substrate populations that differ in the type, extent and location of chemical modifications, as well as in their conformational and aggregation states. Such substrates do not fulfil the assumptions of a

simple, homogeneous enzyme–substrate system. Therefore, classical Michaelis–Menten parameters may provide only an apparent description of the overall hydrolysis process and should not be interpreted as direct measures of intrinsic enzyme–substrate affinity or catalytic activity in these complex systems. An additional distinction concerns the direct effects of Maillard reaction products on digestive enzymes. Schumacher and Kroh [98] demonstrated that selected Amadori compounds could reversibly affect the activity of certain carbohydrate-digesting enzymes, including α-glucosidase and glucoamylase. However, these findings cannot be directly extrapolated to proteolytic enzymes or to the digestion of AGE-modified proteins. Thus, the potential inhibition of digestive enzymes by free Maillard reaction products should be considered separately from the reduced proteolytic susceptibility resulting from covalent modification of protein substrates.

3.6. Formation and Release of AGE-Peptides

Partial proteolysis of protein-bound dAGEs can lead to the formation of short glycated peptides. From the perspective of absorption, this is a critical step, as di- and tripeptides can be transported across enterocytes via the PEPT1 transporter. Consequently, limiting proteolysis does not necessarily result solely in reduced bioavailability; under certain conditions, it may also alter the molecular form of the available AGE.

This process can be illustrated as follows:

AGE-bound protein → partial proteolysis → AGE-oligopeptide → AGE-dipeptide → PEPT1 → enterocyte.

This is particularly relevant for CML, CEL, and MG-H1. Literature reviews indicate that glycated dipeptides can utilize PEPT1 as one of the mechanisms for uptake by enterocytes [99].

3.7. Transport of dAGEs by Enterocytes

Proteolysis and transport are functionally linked processes: the degree of protein hydrolysis determines the pool of AGEs made available to peptide transporters. Free, low-molecular-weight AGEs can be taken up by enterocytes via diffusion—a transport mechanism dependent on the physicochemical properties of the molecule. This mechanism is particularly significant for small, free AGEs that do not require prior breakdown into peptides. In contrast, the transport of di- and tripeptides is mediated by PEPT1 [SLC15A1], a transporter located on the apical membrane of enterocytes. Its potential relevance to dAGEs stems from the fact that products of the partial proteolysis of glycated proteins can retain the structure of short peptides containing modified amino acid residues [100]. Faist et al. [101] and Somoza et al. [102] concluded that MRPs are likely absorbed, though further research into absorption and the underlying mechanisms is needed to confirm this. In general, high-molecular-weight dAGEs are absorbed to a much lesser extent than low-molecular-weight dAGEs.

Hao et al. [103] investigated the absorption of CML bound to soy, gluten, and peanut proteins following in vitro digestion. The total absorption rates for CML were approximately 30.18%, 31.57%, and 29.50%, respectively. The authors noted that the CML fraction with a molecular weight >5 kDa was absorbed less efficiently and exhibited characteristics of active efflux. Importantly, the results suggested the involvement of paracellular transport, transcytosis, and the PEPT1-dependent pathway. This indicates that even protein-bound AGEs can be absorbed via multiple mechanisms. The intestinal epithelium acts as a selective barrier between the gastrointestinal lumen and the body's internal environment. In a properly functioning intestine, large protein molecules have very limited capacity to cross via the paracellular route. Therefore, high-molecular-weight dAGEs should not be considered compounds that easily traverse intact epithelium.

The potential impact of dAGEs on intestinal permeability is currently one of the most widely discussed aspects of their activity [90,92,97,104]. Impairment of intestinal barrier

function following exposure to dAGE-rich diets has been demonstrated in certain animal models. Meanwhile, in vitro studies have observed changes related to tight junction proteins, oxidative stress, and inflammatory responses. However, Jansen et al. [99] emphasize that these results should be interpreted with caution due to significant methodological limitations in some of the available studies—such as inadequate chemical characterization of the dAGEs used, a lack of appropriate experimental controls, and insufficient analysis of dose–response relationships. Jansen et al. [99] also point out that while barrier function impairment was observed in healthy rodent models, results in models of inflammatory bowel disease differed, even suggesting an anti-inflammatory effect. Experimental evidence suggests that dietary AGEs may modulate intestinal barrier function; however, the direction and magnitude of this effect remain dependent on AGE structure, dose, food matrix and physiological or pathological state of the intestinal epithelium.

3.8. Significance of the Non-Absorbed Fraction

A significant portion of dAGEs is not absorbed in the small intestine. This applies particularly to large, protein-bound, and aggregated glycation products. This fraction passes into the large intestine, where it can be utilized or modified by the microbiota [90]. Consequently, dAGEs can also interact with the body through mechanisms independent of direct absorption into the circulation [7].

This is particularly important when interpreting dAGE biomarkers. Low levels of a specific AGE in the circulation do not imply that the compound is biologically inactive; its non-absorbed fraction may interact locally with the epithelium or the microbiota [105].

3.9. Integrated dAGE Passage Model

Based on current knowledge, the following model regarding the fate of dAGEs can be proposed:

The model (Figure 1) indicates that the bioavailability of dAGEs is not a single parameter, but the result of subsequent processes dependent on many factors. The bioavailability of dAGEs can therefore be reduced to a function of chemical structure, degree of protein binding, proteolysis, molecular form, transport, barrier integrity, and organism metabolism.

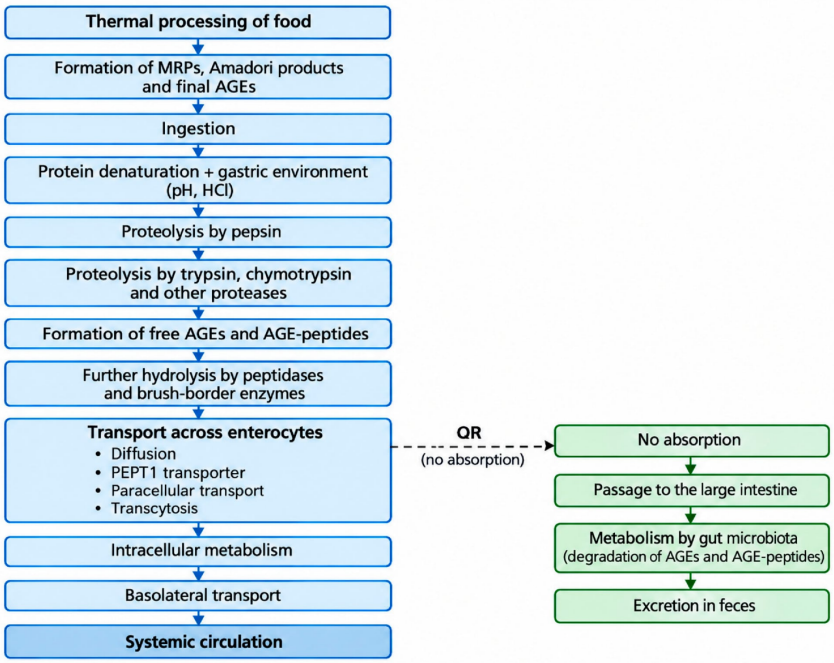


Figure 1. dAGE bioavailability model.

Despite significant progress in dAGE research, several important knowledge gaps remain. Jansen et al. [99] indicate, among others, the following research directions. First, many studies use mixtures of glycated proteins whose exact chemical profile is not sufficiently characterized. This is particularly important because "AGE" is not a single compound, but a very heterogeneous class of products [99]. Most studies of dAGE transport have been performed in in vitro models. The study by Hao et al. [103] provided important data indicating the involvement of PEPT1, paracellular transport and transcytosis, but validation of these mechanisms through in vivo studies is still necessary. Models more similar to the physiological conditions of the intestine are needed, including organoids, co-cultures of enterocytes with immune cells, and the influence of metabolites formed during the fermentation of dAGEs by the microbiota.

4. Molecular Mechanisms of Cellular Stress: AGE-Induced Impairment of Antioxidant Enzyme Systems

Circulating AGE levels reflect both endogenous formation and dietary exposure. Endogenous AGE production is promoted by hyperglycemia and oxidative stress, whereas dietary AGE restriction may reduce circulating CML concentrations. However, the relative contributions of these two sources remain unclear [57]. Experimental evidence suggests that AGE–RAGE signaling may promote oxidative stress by activating NADPH oxidase, increasing ROS production, and stimulating NF-κB-mediated inflammatory responses. Nevertheless, the extent to which dietary AGEs contribute to these mechanisms in children has not been established. Reactive carbonyl compounds may also directly modify antioxidant enzymes [106].

4.1. Direct Glycation of Antioxidant Enzymes

One proposed mechanism by which AGEs may affect the cellular antioxidant system involves the direct, nonenzymatic modification of antioxidant enzymes.

Dietary AGEs and endogenously formed AGEs may affect antioxidant defenses through distinct but interconnected mechanisms. Dietary AGEs may primarily promote systemic oxidative stress through AGE–RAGE signaling. Endogenous reactive carbonyl species can directly modify antioxidant enzymes through non-enzymatic glycation. Reactive dicarbonyl compounds, particularly methylglyoxal (MGO), glyoxal (GO), and 3-deoxyglucosone (3-DG), react with the ε-amino groups of Lys, the guanidino groups of Arg, and thiol groups of Cys residues (Figure 2).

These reactions generate stable AGE adducts and protein cross-links that alter protein conformation and, consequently, enzymatic function [55,107,108]. Such modifications may disrupt the architecture of the active site, restrict substrate accessibility, modify the local environment of catalytic residues, and interfere with cofactor binding. Collectively, these structural alterations can reduce the catalytic efficiency and activity of antioxidant enzymes, thereby weakening cellular antioxidant defenses [80,109]. From a nutritional perspective, bioactive food components, including polyphenols, carotenoids, vitamins, and chlorophyll derivatives, are of particular interest because of their antioxidant and potential antiglycative properties. These compounds may limit AGE formation during food processing while helping to preserve the nutritional quality of food. Therefore, strategies to reduce dietary AGE formation should consider not only lowering AGE levels but also maintaining the nutritional and sensory quality of food, including its taste, aroma, and color [110,111]. Enzymes involved in maintaining redox homeostasis, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are particularly susceptible to glycation. Reactive carbonyl compounds can modify Lys, Arg, and Cys residues, leading to conformational alterations, disruption of active-site architecture, and

reduced catalytic activity [108,112]. In SOD, glycation-induced structural modifications may impair the enzyme's capacity to scavenge superoxide anion radicals, thereby contributing to increased oxidative stress [113]. Moreover, AGE-mediated cross-linking can increase protein rigidity and promote aggregation, thereby limiting the efficient recognition and removal of damaged proteins. These changes may compromise cellular proteostasis by impairing both the ubiquitin–proteasome system and autophagic degradation. The resulting accumulation of dysfunctional proteins can further intensify oxidative stress, establishing a self-reinforcing cycle between carbonyl and oxidative stress [114].

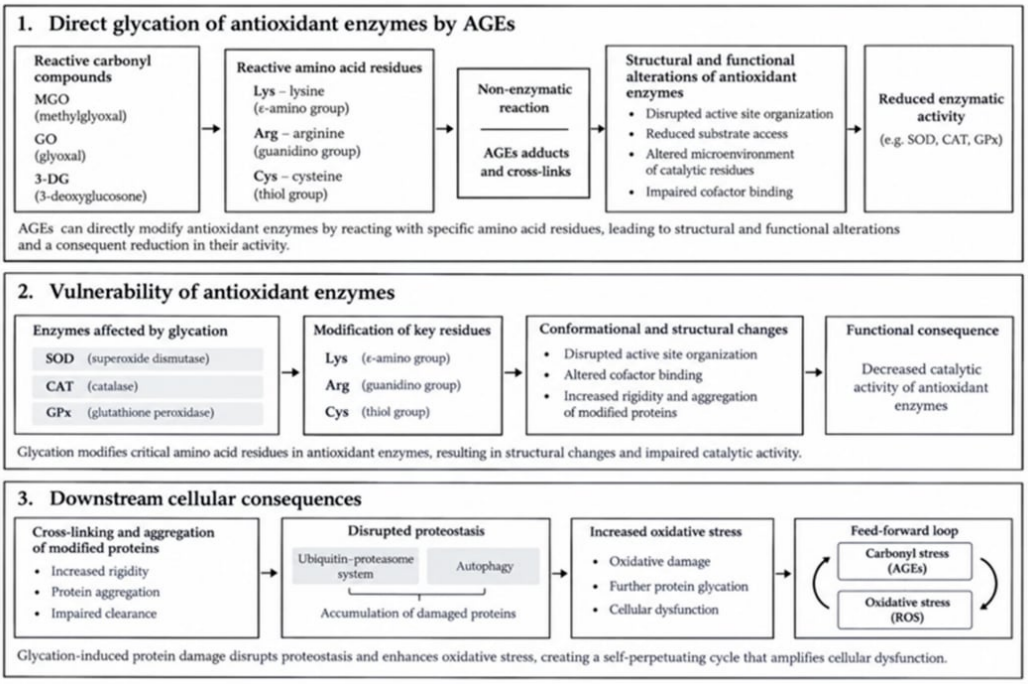


Figure 2. Molecular Mechanisms of AGE-Mediated Impairment of Antioxidant Enzymes.

4.1.1. Effects of Glycation on the Structure and Function of Superoxide Dismutases (SOD1 and SOD2)

Superoxide dismutases (SODs) constitute the first line of enzymatic antioxidant defense. They catalyze the dismutation of superoxide anion ($O_2^{\bullet -}$) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) [114,115]:

$$2O_2^{\bullet -} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

Cytoplasmic SOD1 (Cu/Zn-SOD) and mitochondrial SOD2 (Mn-SOD) are susceptible to nonenzymatic glycation by reactive carbonyl compounds and AGEs. Glycation of Lys and Arg residues can induce conformational changes and impair enzymatic activity. These modifications may increase carbonyl and oxidative stress and have been implicated in metabolic disturbances associated with insulin resistance in experimental models [109,116].

Reduced SOD1 and SOD2 activity limits the efficient dismutation of superoxide anions. This promotes ROS accumulation and increases oxidative damage to lipids, proteins, and DNA. Persistent oxidative stress may also interfere with insulin signaling through the IRS-1/PI3K/Akt pathway, particularly in pancreatic β-cells and insulin-sensitive tissues [108,117]. SOD activity also depends on the correct coordination of metal cofactors. SOD1 requires Cu^{2+} and Zn^{2+}, whereas SOD2 contains Mn^{2+} at its catalytic center. Glycation may reduce the affinity of SOD enzymes for their metal cofactors, thereby destabilizing their structure and impairing catalytic activity. It may also increase their susceptibility to

subsequent oxidative modifications. Persistent carbonyl stress can further aggravate mitochondrial dysfunction and impair insulin signaling [55,118]. Glycation may also promote partial unfolding of SOD1 and SOD2 and the formation of protein aggregates. In parallel, AGE-mediated cross-linking can hinder the recognition and degradation of modified proteins by the ubiquitin–proteasome system and autophagy. This may further reduce cellular antioxidant capacity. Together, these mechanisms may sustain oxidative stress and inflammation and could potentially contribute to insulin resistance; however, their direct relevance to dietary AGE exposure in children has not been established [117,119].

4.1.2. The Role of Catalase Glycation in H_2O_2 Accumulation and Redox Dysregulation

Catalase (CAT) is a heme-containing enzyme that catalyzes the decomposition of hydrogen peroxide (H_2O_2) into water and molecular oxygen. It plays a key role in maintaining redox homeostasis, particularly in tissues with high metabolic activity [115,120]:

$$2H_2O_2 \overset{CAT}{\rightarrow} 2H_2O + O_2$$

Experimental studies under chronic hyperglycemic conditions have demonstrated nonenzymatic glycation of CAT, primarily at Lys residues and, to a lesser extent, at Arg residues. These modifications contribute to the formation of Amadori products and, subsequently, AGEs [121]. Glycation can induce conformational changes, promote protein aggregation, and impair catalytic activity by altering the architecture of the active site [122]. Modification of residues located near the catalytic site may also disturb the microenvironment of the heme group, which is essential for H_2O_2 decomposition. Changes in the polarity and spatial organization of this microenvironment may restrict substrate access and reduce catalytic efficiency [121]. Moreover, CAT can undergo AGE-mediated modification during aging. This process may contribute to CAT inactivation and weaken antioxidant defense [123]. Glycation also increases CAT susceptibility to oxidation, partial unfolding, and proteolytic degradation [118]. Reduced CAT activity may contribute to H_2O_2 accumulation and oxidative stress in experimental models. This can increase oxidative damage to proteins, lipids, and nucleic acids and activate NF-κB-, MAPK-, and RAGE-dependent signaling pathways. In metabolically sensitive tissues, including the pancreas, liver, and skeletal muscle, persistent oxidative stress may impair insulin signaling and β-cell function. These changes may contribute to the progression of metabolic disorders associated with excessive AGE accumulation [121].

4.1.3. Disruption of the GSH–GPx Axis by Advanced Glycation End Products

Glutathione peroxidase (GPx) is a key component of the cellular antioxidant defense system [115]:

$$\text{for } H_2O_2: \; H_2O_2 + 2GSH \overset{GPx}{\rightarrow} 2H_2O + GSSG$$

for organic peroxides (ROOH):

$$ROOH + 2GSH \overset{GPx}{\rightarrow} ROH + H_2O + GSSG$$

GPx uses reduced glutathione (GSH) as a reducing substrate to detoxify H_2O_2, generating oxidized glutathione (GSSG). Excessive AGE exposure can increase oxidative stress and accelerate GSH depletion. This shifts the cellular GSH/GSSG redox balance toward the oxidized state:

$$2GSH + H_2O_2 \overset{GPx}{\rightarrow} GSSG + 2H_2O$$

GSH—reduced glutathione, GSSG—oxidized glutathione, and ROOH—organic peroxide, ROH—reduced alcohol.

The active site of GPx contains selenocysteine (Sec $C_3H_7NO_2Se$), which is essential for the reduction of H_2O_2 and lipid peroxides using GSH. The Sec residue undergoes reversible redox transitions during the catalytic cycle and is therefore critical for GPx antioxidant activity [119,124]. Experimental studies suggest that AGE-related oxidative stress may indirectly affect GPx function by increasing ROS generation and depleting the cellular GSH pool. Dietary AGE–RAGE signaling may increase ROS production and GSH consumption through NADPH oxidase activation. This may impair GPx activity by limiting GSH availability. A shift in the GSH/GSSG ratio toward the oxidized state further limits the capacity of GPx to detoxify peroxides [125]. Reduced GPx activity promotes the accumulation of H_2O_2 and lipid peroxides, thereby increasing membrane lipid peroxidation. Reactive aldehydes, including 4-hydroxynonenal (4-HNE) and methylglyoxal (MGO), may also modify amino acid residues within functionally important regions of GPx. Such modifications can impair GSH binding and further reduce enzyme activity [126]. Experimental evidence suggests that AGE exposure may impair antioxidant protection and contribute to metabolic disturbances associated with insulin resistance. In addition to direct effects on antioxidant enzymes, dietary AGEs can activate the receptor for advanced glycation end products (RAGE). AGE–RAGE interaction activates pro-inflammatory pathways, including nuclear factor kappa B (NF-κB), and increases ROS generation. This disrupts cellular redox homeostasis and accelerates GSH consumption, thereby weakening the GSH–GPx antioxidant system [115,119,125]. Reduced GSH availability limits the cellular capacity to detoxify peroxides and may further intensify oxidative stress. Thus, the AGE–RAGE axis represents a potential molecular link between AGE accumulation, oxidative stress, chronic inflammation, and metabolic dysfunction, although its specific contribution following dietary AGE exposure in children remains unclear. AGE binding to the receptor for advanced glycation end products (RAGE) activates NADPH oxidase, thereby increasing ROS generation. Elevated ROS levels activate the transcription factor nuclear factor kappa B (NF-κB), which promotes the expression of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [119]. These cytokines can further stimulate ROS-generating pathways and amplify oxidative stress. This creates a self-reinforcing cycle that links AGE–RAGE signaling to persistent oxidative stress and inflammation.

4.2. Generation of Reactive Oxygen Species

4.2.1. Disruption of Electron Transport

Mitochondria are a major source of cellular ROS [115]. Mitochondrial dysfunction is therefore an important mechanism underlying AGE-induced oxidative stress. Activation of the AGE–RAGE axis can increase ROS production and impair mitochondrial function. AGEs may disrupt the mitochondrial electron transport chain, resulting in inefficient electron transfer and increased electron leakage. Complexes I and III are particularly susceptible to functional impairment and can become important sites of ROS generation under conditions of mitochondrial stress [119]. Complex I (NADH oxidoreductase) and Complex III (ubiquinol c oxidoreductase) are key components of the mitochondrial electron transport chain. They mediate electron transfer and contribute to the generation of the proton gradient that drives ATP synthesis [126]. Impaired activity of these complexes can increase electron leakage from the respiratory chain. Leaked electrons may react with molecular oxygen (O_2), resulting in its one-electron reduction and the formation of superoxide anion ($O_2^{\bullet-}$). Complexes I and III are major sites of mitochondrial $O_2^{\bullet-}$ generation. Therefore, dysfunction of these complexes can substantially increase mitochondrial ROS production and contribute to oxidative stress [127]. Experimental studies suggest that AGE exposure may increase mitochondrial $O_2^{\bullet-}$ production, potentially exceeding the antioxidant capacity

of SOD2. This may promote ROS accumulation and mitochondrial damage. Such processes could contribute to insulin resistance, although their relevance to dietary AGE exposure in children remains to be established [128]. From a nutritional perspective, antioxidant-rich food components may help maintain cellular redox homeostasis under conditions of increased oxidative stress. Their antioxidant and antiglycative properties depend on the composition of the raw material and food processing conditions [110].

4.2.2. Singlet Oxygen and Its Role in Oxidative Reactions

Singlet oxygen ($^1O_2$) is an important non-radical reactive oxygen species that contributes to oxidative processes in biological and food systems. It is an electronically excited form of molecular oxygen, generated primarily through energy transfer from photoexcited sensitizers to ground-state oxygen. In food matrices, endogenous photosensitizers, including myoglobin and riboflavin, can promote $^1O_2$ formation upon light exposure, particularly in meat and dairy products [129,130]. $^1O_2$ readily reacts with polyunsaturated fatty acids through a non-radical oxidation mechanism, producing lipid hydroperoxides. Their subsequent decomposition generates secondary oxidation products, including aldehydes, which contribute to rancidity and deterioration of food quality. In addition, $^1O_2$ can oxidize susceptible amino acid residues, particularly histidine, methionine, tryptophan, and tyrosine, thereby altering protein structure and functionality [129,131]. These reactions may compromise the nutritional, sensory, and functional properties of food. Although the direct contribution of $^1O_2$ to AGE-associated oxidative stress remains insufficiently characterized, its potential involvement in oxidative damage should be considered alongside radical-mediated pathways.

4.2.3. Mitochondrial Dysfunction

Mitochondrial dysfunction is an important consequence of persistent oxidative stress. It disrupts cellular energy homeostasis and impairs mitochondrial function [115,132]. Oxidative damage to the inner mitochondrial membrane can reduce the mitochondrial membrane potential ($\Delta\Psi m$). This may promote the opening of the mitochondrial permeability transition pore (mPTP) and compromise mitochondrial membrane integrity [133]. Consequently, oxidative phosphorylation becomes impaired, ATP synthesis declines, and electron leakage from the respiratory chain may increase. This further enhances mitochondrial ROS generation and sustains oxidative stress [133]. Excessive ROS accumulation further damages mitochondrial proteins, lipids, and mitochondrial DNA (mtDNA), thereby aggravating mitochondrial dysfunction. Loss of $\Delta\Psi m$ prevents the import of PINK1 into mitochondria and promotes its accumulation on the outer mitochondrial membrane. PINK1 then recruits and activates the E3 ubiquitin ligase Parkin, initiating the ubiquitination of damaged mitochondrial components and their subsequent removal by mitophagy [134]. Under chronic oxidative stress, however, excessive mitochondrial damage may impair the efficiency of the PINK1/Parkin pathway. Reduced mitophagy can promote the accumulation of dysfunctional mitochondria, further compromising ATP production and increasing mitochondrial ROS generation [134,135]. This creates a self-reinforcing cycle in which oxidative stress promotes AGE formation, while AGE accumulation further impairs mitochondrial function. This interplay may contribute to insulin resistance, chronic inflammation, and age-related tissue damage [55,117].

4.2.4. Activation of NADPH Oxidase

NADPH oxidases (NOXs) are major extramitochondrial sources of ROS in eukaryotic cells [136]. The NOX family comprises seven isoforms: NOX1–NOX5, DUOX1, and DUOX2. Among them, NOX2 and NOX4 are particularly important in oxidative stress and cellular

damage [137,138]. NOX2 can be activated by pro-inflammatory cytokines, hyperglycemia, and AGEs. Its activation promotes the production of superoxide anion ($O_2^{\bullet-}$) [139]:

$$NADPH + 2O_2 \rightarrow NADP^+ + H^+ + 2O_2^{\bullet-}$$

In contrast, NOX4 exhibits relatively high constitutive activity and is highly expressed in endothelial, renal, and cardiac tissues. Unlike NOX2, NOX4 predominantly generates hydrogen peroxide (H_2O_2) [140,141]:

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2$$

The resulting $O_2^{\bullet-}$ undergoes dismutation to form H_2O_2. In the presence of transition metal ions, H_2O_2 can participate in the Fenton reaction and generate the highly reactive hydroxyl radical (•OH). Hydroxyl radicals readily oxidize proteins, lipids, and nucleic acids, thereby amplifying cellular damage [142]. Chronic activation of NOX2 and NOX4 can sustain elevated ROS levels, enhance pro-inflammatory signaling, and further impair mitochondrial function. These processes reinforce the interplay between oxidative stress and cellular damage [133,143].

4.2.5. The Fenton Reaction

The Fenton reaction is an important pathway for hydroxyl radical (•OH) generation under conditions of oxidative stress. In the presence of H_2O_2, ferrous iron (Fe^{2+}) catalyzes its conversion to the highly reactive •OH, as shown in the following equation [144]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$$

The resulting •OH radical is highly reactive and has a very short half-life. It therefore reacts rapidly and close to its site of formation with a broad range of biological molecules [145]. Hydroxyl radicals can initiate membrane lipid peroxidation, oxidize amino acid residues in proteins, and induce DNA strand breaks and nucleobase modifications. These reactions can cause extensive and often irreversible cellular damage [142]. Under chronic oxidative stress, excessive H_2O_2 production and increased availability of Fe^{2+} may enhance Fenton chemistry. This can further promote mitochondrial damage, pro-inflammatory signaling, and cell death [142]. The relevance of Fenton chemistry extends beyond biological systems to food matrices, particularly meat and meat products. These foods contain heme iron in myoglobin and hemoglobin, which can promote lipid oxidation. Thermal processing may induce the denaturation of iron-containing proteins, leading to the release of catalytically active non-heme iron. In the presence of H_2O_2 and lipid hydroperoxides, iron catalyzes radical formation and accelerates the oxidation of polyunsaturated fatty acids. Consequently, these reactions promote the formation of secondary oxidation products, reduce nutritional quality, and contribute to undesirable flavor development during meat processing and storage [146,147].

4.3. Structural Modifications of Proteins

4.3.1. Protein Carbonylation

Protein carbonylation is a common and largely irreversible oxidative modification induced by ROS. It involves the oxidation of susceptible amino acid residues, particularly Lys, Arg, Pro, and Thr, resulting in the formation of stable carbonyl groups within proteins [148]. The accumulation of carbonyl groups can alter protein conformation, impair folding, and reduce structural stability. These changes may compromise protein function and enzymatic activity [149]. Carbonylated proteins are also more prone to aggregation and are preferentially targeted by cellular protein quality-control systems, including the

ubiquitin–proteasome system and autophagy. Excessive carbonylation may exceed the capacity of these degradation pathways, resulting in the accumulation of damaged proteins and further cellular dysfunction [149,150].

4.3.2. Cross-Linking

A major consequence of advanced glycation is the formation of covalent cross-links between amino acid residues within and between proteins. Well-characterized AGE cross-links include pentosidine, glucosepane, glyoxal-lysine dimer (GOLD), and methylglyoxal-lysine dimer (MOLD). These compounds arise mainly from reactions of reactive dicarbonyls with Lys and Arg residues [116]. The accumulation of these cross-links increases protein stiffness, impairs mechanical properties, and reduces tissue elasticity. These effects are particularly relevant for long-lived structural proteins, such as collagen and elastin. Cross-link formation can also promote protein aggregation and reduce susceptibility to proteolytic degradation. This may impair tissue remodeling and regeneration and favor the accumulation of damaged macromolecules [116,151]. Among the best-characterized AGE cross-links, glucosepane is the most abundant in human tissues. It is considered an important contributor to age-related collagen stiffening and loss of extracellular matrix elasticity [151]. The formation of AGE cross-links begins with the reaction of a nucleophilic amino group, primarily from Lys or Arg, with the carbonyl group of a reducing sugar. This reaction initially forms a reversible Schiff base. Subsequent molecular rearrangement generates a more stable Amadori product. Further degradation and oxidation reactions can produce reactive dicarbonyl compounds that ultimately contribute to AGE formation.

4.3.3. Dysfunction of Enzymatic Proteins

ROS and reactive carbonyl species can modify multiple classes of proteins, altering their structure and function. In metabolic enzymes, oxidation of cysteine (Cys) and methionine (Met) residues, together with protein carbonylation, can reduce catalytic activity. This may disrupt metabolic pathways involved in cellular energy production [145,152]. Cytoskeletal proteins, including actin and tubulin, are also susceptible to oxidative modification. Such damage can alter cytoskeletal organization, impair intracellular transport, and disrupt cell migration. Oxidative modification of membrane receptors and ion channels may further affect protein conformation, ion conductance, and cellular signal transduction [153]. Mitochondrial proteins are particularly susceptible to oxidative damage because of the high local production of ROS. Their modification can impair respiratory chain complexes, reduce oxidative phosphorylation, and limit ATP synthesis. Impaired mitochondrial function may further increase ROS generation, thereby creating a self-reinforcing cycle that aggravates mitochondrial dysfunction [154]. Oxidative damage to proteins disrupts cellular proteostasis, promotes protein aggregation, and activates mechanisms for their degradation. Chronic oxidative stress, however, can overwhelm the capacity of protein quality control systems, leading to the accumulation of damaged macromolecules.

4.3.4. Impaired Protein Degradation

AGEs disrupt the functioning of cellular protein quality control systems. Glycation of Lys residues may compete with ubiquitination for the same modification sites, limiting the ubiquitination of target proteins and potentially disrupting their UPS-dependent degradation [155]. As a result, the efficiency of 26S proteasome-mediated degradation decreases, leading to the accumulation of damaged proteins. Excessive accumulation of AGE-modified proteins can also exceed the capacity of autophagic clearance, thereby limiting the removal of large protein aggregates. Persistent impairment of the functional interplay between the ubiquitin–proteasome system (UPS) and autophagy disrupts proteostasis and promotes the

formation of insoluble protein aggregates. These aggregates can further increase oxidative stress, impair cellular function, and contribute to neurodegenerative processes [108,116]. Recent studies indicate that AGEs impair antioxidant defenses not only through direct protein modification but also through the dysregulation of redox-sensitive signaling pathways. Activation of the RAGE receptor can enhance oxidative stress and interfere with the Nrf2/Keap1 pathway, thereby reducing the expression of antioxidant genes encoding SOD, CAT, and GPx [108,116,117]. In parallel, disruption of the SIRT1/FOXO3a axis may decrease the transcription of antioxidant enzymes and contribute to mitochondrial dysfunction [148]. Increasing attention has also been directed toward ferroptosis, a form of regulated cell death associated with impaired GPX4 activity, glutathione depletion, and excessive lipid peroxidation [116,156]. Furthermore, impairment of PINK1/Parkin-dependent mitophagy may promote the accumulation of damaged mitochondria and increase ROS production, thereby sustaining a vicious cycle of oxidative stress and glycoxidation [108,116,157]. These mechanisms highlight the potential importance of dietary sources of antioxidant compounds in the context of AGE-associated oxidative stress. Plant-based foods provide a broad spectrum of natural antioxidants, whose biological activity depends on their composition, interactions, bioavailability, and the properties of the food matrix [158].

Although experimental findings provide a biological rationale for the potential involvement of AGEs in oxidative stress and impaired insulin signaling, the available evidence does not establish that dietary AGE exposure directly induces these molecular changes in children. Most proposed mechanisms are derived from in vitro and animal studies, and pediatric findings remain limited and inconclusive. Therefore, these pathways should be interpreted as potential mechanisms rather than established causal effects of dietary AGEs [49].

The main molecular mechanisms through which AGEs impair antioxidant defense systems and promote oxidative stress, including their key molecular targets and biological consequences, are summarized in Table 1.

Table 1. Experimental and clinical evidence on the effects of advanced glycation end-products on antioxidant enzyme activity.

Mechanism/Pathway	Main Molecular Targets	Main Molecular Effects	Biological Consequences	References
Direct protein glycation	SOD1, SOD2, CAT, GPx	Modification of Lys, Arg and Cys residues; conformational changes and disruption of active sites	Reduced antioxidant enzyme activity and impaired ROS detoxification	[108,109,112,113,121]
AGE–RAGE signaling	RAGE, NADPH oxidase, NF-κB	Activation of pro-oxidant and pro-inflammatory signaling pathways	Increased ROS production and inflammation	[115,119,125]
Glutathione depletion	GSH–GPx system	Increased GSH consumption and altered GSH/GSSG ratio	Reduced detoxification of hydrogen peroxide and lipid peroxides	[119,124]
Mitochondrial dysfunction	Electron transport chain complexes I and III, SOD2	Increased electron leakage and mitochondrial ROS production	Mitochondrial damage, impaired ATP synthesis and sustained oxidative stress	[119,126–135]
NADPH oxidase activation	NOX2, NOX4	Increased production of superoxide anion and hydrogen peroxide	Amplification of oxidative stress and cellular damage	[136–143]

Table 1. *Cont.*

Mechanism/Pathway	Main Molecular Targets	Main Molecular Effects	Biological Consequences	References
Fenton reaction	Fe^{2+}, H_2O_2	Generation of highly reactive hydroxyl radicals (•OH)	Lipid peroxidation, protein oxidation and DNA damage	[142,144,145]
Protein carbonylation and cross-linking	Structural and enzymatic proteins	Oxidative modification, cross-link formation and altered protein conformation	Loss of protein function, aggregation and impaired tissue integrity	[116,148,154]
Impaired protein degradation	Ubiquitin–proteasome system (UPS), autophagy, PINK1/Parkin	Reduced degradation of AGE-modified proteins and impaired removal of damaged mitochondria	Accumulation of dysfunctional proteins and increased ROS production	[55,116,134,155,157]
Redox-sensitive signaling and ferroptosis	Nrf2/Keap1, SIRT1/FOXO3a, GPX4	Dysregulation of antioxidant gene expression, glutathione depletion and increased lipid peroxidation	Impaired antioxidant defense and increased susceptibility to ferroptosis	[55,116]

5. The RAGE Signaling Pathway and the Pathophysiology of AGE-Induced Insulin Resistance

5.1. Activation of the AGE–RAGE Axis, Oxidative Stress, and NF-κB-Dependent Inflammation

One proposed mechanism potentially linking dietary advanced glycation end products (dAGEs) with systemic metabolic effects involves their interaction with the receptor for advanced glycation end products (RAGE) [108]. RAGE is a multiligand membrane glycoprotein belonging to the immunoglobulin superfamily. Binding of AGEs to RAGE activates intracellular signaling cascades, including mitogen-activated protein kinase (MAPK) pathways such as extracellular signal-regulated kinases 1 and 2 (ERK1/2). These pathways promote reactive oxygen species (ROS) generation and activate NF-κB-dependent transcription of pro-inflammatory mediators, thereby sustaining chronic inflammation [159,160].

Experimental studies indicate that AGE–RAGE interactions may promote receptor oligomerization and recruitment of the adaptor protein DIAPH1 to the cytosolic domain of RAGE [161]. This interaction activates the small GTPase Rac1, which promotes assembly and activation of the NADPH oxidase 2 (NOX2) complex by facilitating the recruitment of cytosolic subunits, including p47phox, to the membrane [162]. Activated NOX2 generates superoxide ($O_2^{\bullet-}$), which is subsequently converted to H_2O_2, thereby increasing ROS levels and promoting oxidative stress [163,164]. In parallel with DIAPH1 recruitment, RAGE activation stimulates MAPK signaling, including the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. This signaling promotes activation of the IκB kinase (IKK) complex, leading to IκB phosphorylation, ubiquitination, and proteasomal degradation. The resulting release of NF-κB enables its translocation to the nucleus, where it binds regulatory DNA sequences and induces the expression of genes involved in inflammatory and oxidative responses [165,166]. A major consequence is increased production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), thereby contributing to sustained low-grade inflammation [167]. A second consequence is increased RAGE expression. NF-κB binds to regulatory regions of the AGER gene, which encodes RAGE, and promotes its transcription [168,169]. Increased RAGE expression may enhance cellular responsiveness to dAGEs and thereby reinforce a self-amplifying inflammatory loop.

Recent pediatric studies have reported lower circulating sRAGE concentrations in children and adolescents with obesity. However, Soylu Ustkoyuncu and Kocer found no significant differences in sRAGE levels according to insulin resistance or metabolic syndrome status [170], while Aradillas-García et al. observed associations with selected adiposity and lipid markers, but not with composite cardiometabolic risk indices [171]. These observational findings do not establish a causal relationship between dietary AGE exposure and metabolic dysfunction in children.

5.2. Molecular Mechanisms of Insulin Resistance: Aberrant Serine Phosphorylation of IRS-1 and Impaired GLUT4 Translocation

Insulin signaling in skeletal muscle and adipose tissue is initiated by insulin binding to the insulin receptor (IR). This interaction activates the receptor tyrosine kinase domain and induces autophosphorylation of tyrosine residues on the receptor and subsequent phosphorylation of adaptor proteins, including insulin receptor substrate 1 (IRS-1) [172–174]. Tyrosine-phosphorylated IRS-1 provides docking sites for Src homology 2 (SH2)-domain-containing proteins, enabling downstream activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway [175]. Phosphoinositide 3-kinase (PI3K) is a key component of insulin signaling. Following recruitment to tyrosine-phosphorylated IRS-1, PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). PIP_3 recruits phosphoinositide-dependent kinase 1 (PDK1), which phosphorylates and activates protein kinase B (Akt), thereby propagating downstream insulin signaling [172,176]. Experimental evidence suggests that AGE-related oxidative stress and inflammation may interfere with this signaling network. However, whether dietary AGE exposure induces these effects in children remains unclear. In experimental models, RAGE activation and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, have been associated with the activation of stress-responsive kinases, such as c-Jun N-terminal kinase (JNK) and IκB kinase β (IKKβ). These kinases may promote aberrant serine phosphorylation of IRS-1, including at Ser312, thereby impairing its function and subsequent tyrosine phosphorylation [177,178]. These kinases promote aberrant serine phosphorylation of IRS-1, including at Ser312, which impairs IRS-1 function and reduces its subsequent tyrosine phosphorylation [179,180]. Serine-phosphorylated IRS-1 can also undergo ubiquitination and proteasomal degradation, further reducing the cellular pool of functional IRS-1 [181]. In experimental models, impaired IRS-1 signaling has been associated with attenuation of the PI3K/Akt pathway and reduced GLUT4 translocation to the plasma membrane. These alterations may impair glucose uptake by skeletal muscle and adipose tissue and contribute to peripheral insulin resistance [182,183]. However, their direct association with dietary AGE exposure in children has not been demonstrated.

Figure 3 presents a proposed overview of the potential mechanisms linking dietary advanced glycation end-products (AGEs) with pathways involved in insulin resistance. It illustrates the formation of AGEs during high-temperature food processing, their digestion and intestinal absorption, and subsequent interaction with the receptor for AGEs (RAGE). This interaction may promote oxidative stress and inflammation, impair antioxidant defenses, and disrupt insulin signaling and GLUT4-mediated glucose uptake. These interconnected processes may contribute to the development of insulin resistance and metabolic dysfunction during childhood.

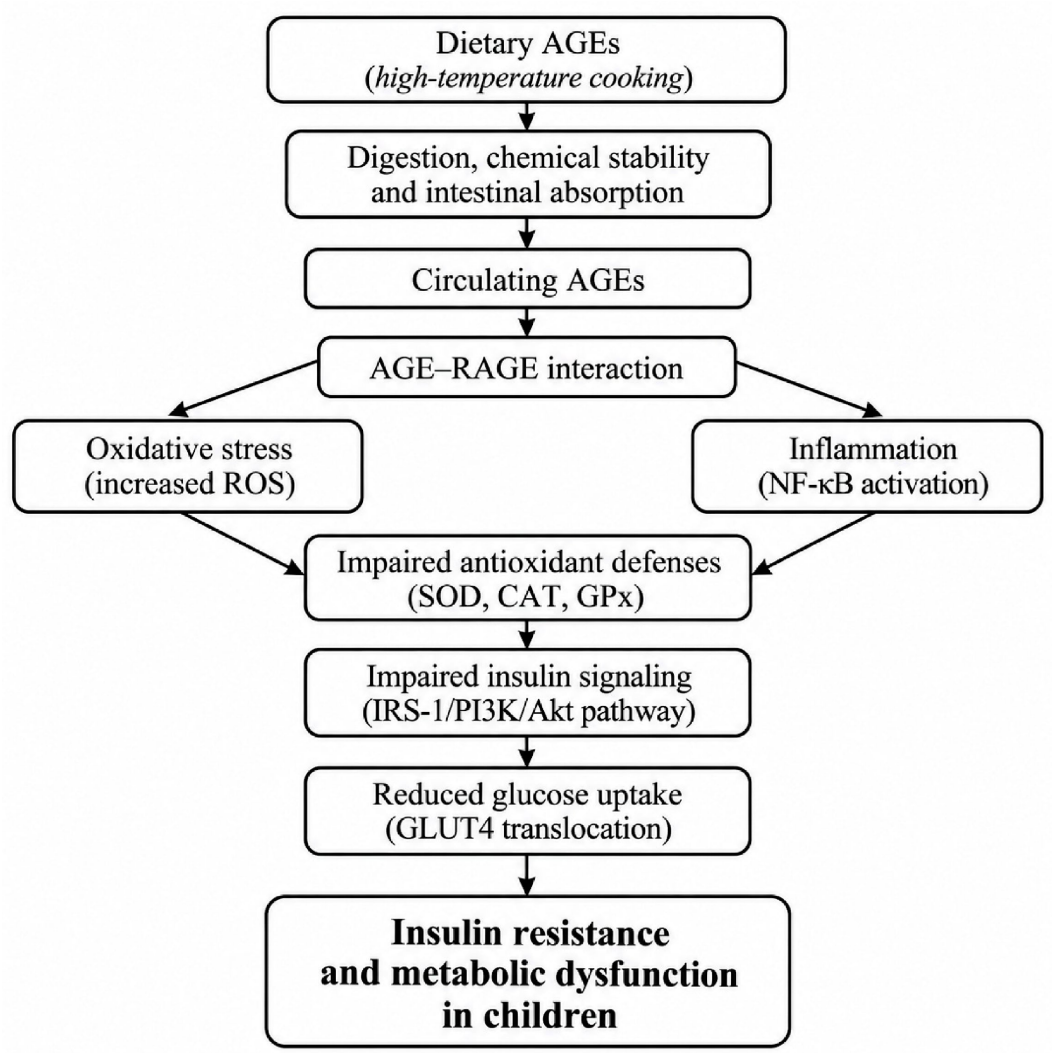


Figure 3. Proposed molecular pathways potentially linking dietary advanced glycation end-products (AGEs) with insulin resistance.

6. Long-Term Systemic Consequences of AGE Accumulation: From Childhood Obesity to Metabolic Dysfunction

6.1. Endothelial Dysfunction and Vascular Alterations

Normal vascular function depends on the structural and mechanical integrity of the vascular wall, which is largely determined by the organization and relative proportions of collagen and elastin fibers [184]. AGE accumulation promotes glycation and cross-linking of extracellular matrix proteins, altering the mechanical properties of the vascular wall and contributing to vascular stiffening and endothelial dysfunction [185,186]. The endothelium regulates vascular homeostasis by controlling leukocyte adhesion, platelet aggregation, vascular tone, and the balance between vasodilatory and vasoconstrictive signals. Nitric oxide (NO) is a key mediator of endothelium-dependent vasodilation. Endothelial dysfunction is associated with reduced NO bioavailability, impaired vasodilation, and loss of vascular homeostasis [185,187]. AGEs can further reduce NO bioavailability, thereby aggravating vascular dysfunction [188]. The AGE–RAGE axis further contributes to endothelial injury. Increased RAGE expression and activation impair endothelial repair and promote inflammatory signaling. These processes may accelerate atherogenesis through sustained inflammation, endothelial damage, and altered vascular smooth muscle cell function [189]. The proposed mechanisms are supported by evidence from pediatric studies. Children

with obesity have higher circulating concentrations of AGEs and markers of endothelial activation and inflammation than children with normal body weight. They also exhibit greater arterial stiffness. Positive associations have been reported between AGE concentrations and E-selectin, and between methylglyoxal concentrations and pulse wave velocity (PWV). These findings support an association between AGE accumulation and adverse vascular alterations in children with obesity [190].

6.2. Adipose Tissue Pathology

6.2.1. AGE Accumulation in Adipose Tissue

AGEs can accumulate in adipose tissue through local formation, promoted by increased glucose availability and oxidative stress, and through uptake from the circulation [189]. Individuals with obesity have higher levels of Nε-carboxymethyllysine (CML) in subcutaneous adipose tissue (SAT) than individuals with normal body weight. CML-modified proteins have been detected in adipocytes, with greater CML accumulation reported in visceral adipose tissue (VAT) than in SAT in individuals with severe obesity. Experimental evidence indicates that adipose tissue can take up circulating CML through a RAGE-dependent mechanism, potentially promoting its retention within the tissue [191,192]. AGE accumulation has also been detected in the adipose tissue extracellular matrix (ECM) [193].

6.2.2. Fibrosis of the Adipose Tissue Extracellular Matrix

AGE formation through protein glycation promotes intermolecular cross-linking, which alters protein structure and increases the stiffness of the adipose tissue microenvironment [194]. AGE accumulation and protein glycation promote extracellular matrix (ECM) remodeling in adipose tissue. Increased ECM mass and collagen content are associated with greater fiber density, tissue stiffness, and RAGE expression [195]. AGE-modified ECM and glycated type I collagen can impair insulin-stimulated glucose uptake by adipocytes, indicating that ECM glycation may directly interfere with adipocyte insulin responsiveness [196]. Consistent with these findings, enhanced glycation in animal models is associated with increased accumulation of Nε-carboxyethyllysine (CEL) and more pronounced adipose tissue fibrosis [197]. This fibrotic remodeling is characterized by excessive deposition of ECM components, particularly collagens, and increased tissue stiffness, which may further impair adipocyte function and contribute to metabolic dysfunction [198]. In a multicenter study of 461 children and adolescents with severe obesity, Galiniak et al. [199] reported marked hyperleptinemia, with higher leptin concentrations in girls than boys (64.40 vs. 49.66 ng mL^{-1}, $p < 0.001$). Leptin levels correlated positively with BMI ($r = 0.449$), waist circumference ($r = 0.248$), and body fat percentage ($r = 0.569$; all $p < 0.001$). These findings highlight the association between elevated leptin, adiposity, and metabolic disturbances in pediatric obesity.

6.2.3. Adipocyte Dysfunction and Dysregulated Adipokine Secretion

Adipose tissue is an active endocrine organ that secretes adipokines involved in the regulation of inflammation and insulin sensitivity. In obesity, including childhood obesity, adipose tissue dysfunction is accompanied by alterations in adipokine secretion, including increased leptin and reduced adiponectin levels [200,201]. AGE accumulation in adipose tissue may further contribute to adipocyte dysfunction by altering their secretory activity. Experimental studies have shown that CML-mediated RAGE activation reduces adiponectin secretion by human preadipocytes [193]. In adults, consumption of a low-AGE diet was associated with higher adiponectin and lower leptin concentrations compared with a high-AGE diet [202]. In prepubertal children, a higher leptin-to-adiponectin ratio was associated with greater insulin resistance, as reported in both earlier and more recent studies [13,203].

In the Project Viva prospective cohort (n = 468), lower adiponectin concentrations during mid-childhood ($\beta = -0.16$, 95% CI: −0.33 to 0.01), early adolescence ($\beta = -0.19$, 95% CI: −0.37 to −0.01), and late adolescence ($\beta = -0.40$, 95% CI: −0.57 to −0.23) were associated with higher HOMA-IR in late adolescence. These associations were attenuated after adjustment for BMI z-score and were more pronounced in males, suggesting a potential role of adiponectin in the development of insulin resistance. These findings suggest that alterations in adipokine secretion may represent an additional link between AGE accumulation, adipose tissue dysfunction, and impaired insulin sensitivity.

6.3. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by excessive ectopic lipid accumulation in hepatocytes and has become the most common chronic liver disease worldwide, with its prevalence increasing in parallel with the global rise in obesity [204]. Dietary patterns and associated metabolic disturbances may further influence the risk of MASLD development. Adipose tissue dysfunction and insulin resistance play an important role in this process. Impaired insulin signaling reduces the antilipolytic effect of insulin, resulting in increased release of free fatty acids (FFAs) from adipose tissue into the circulation [205]. Increased FFA delivery to the liver promotes their uptake and esterification into triglycerides, thereby contributing to hepatic lipid accumulation [206]. Hepatic steatosis is further promoted when lipid influx and de novo lipogenesis exceed the capacity for fatty acid oxidation and lipid export [207]. Excessive lipid accumulation can overwhelm hepatocyte metabolic capacity and promote lipotoxicity. This may trigger oxidative stress, inflammation, hepatocyte apoptosis, and fibrotic remodeling, contributing to disease progression [208]. Advanced glycation end products (AGEs) may also contribute to the development and progression of liver injury. Particular attention has been given to dietary AGEs (dAGEs), as increased exposure has been associated with hepatic steatosis and fibrosis in experimental models. One potential mechanism involves AGE–RAGE signaling, which can enhance oxidative stress and promote the activation of hepatic stellate cells, thereby contributing to fibrogenic processes [209,210]. In human studies involving adult populations, higher dietary AGE intake has been associated with a greater likelihood of nonalcoholic fatty liver disease, although these findings do not establish a causal relationship [211].

MASLD is increasingly recognized in children and adolescents, and fibrotic changes may already be detectable during adolescence [212]. Machado et al. [213] reported that children with hepatic steatosis had significantly lower adiponectin and higher fasting insulin and HOMA-IR than those without steatosis (all $p \leq 0.004$). Increased carotid intima-media thickness was also observed ($p = 0.013$). These findings link reduced adiponectin and insulin resistance with pediatric MASLD, independently of BMI z-score. Consistent with a potential role of AGEs in liver injury, elevated AGE-related markers have been reported in patients with nonalcoholic fatty liver disease, including increased AGE fluorescence and serum concentrations of Nε-carboxyethyllysine (CEL) [214]. Together, these findings support an association between AGE accumulation and hepatic steatosis and fibrotic remodeling, while the specific contribution of dietary AGEs to pediatric MASLD requires further investigation. In pediatric populations, lower circulating sRAGE concentrations have been reported in children with obesity and concomitant fatty liver disease, as well as in children with obesity compared with those who were overweight [215,216].

A clinical study by Medyńska et al. [190] involving 125 children with obesity and 33 normal-weight controls demonstrated significantly higher serum AGE (46.0 vs. 24.3 ng mL^{-1}), methylglyoxal (227.2 vs. 69.3 ng mL^{-1}), E-selectin (59.4 vs. 31.5 ng mL^{-1}), and hs-CRP levels in children with obesity (all $p = 0.0001$). They also exhibited increased

arterial stiffness (SDS-PWV, $p = 0.0106$). AGE levels correlated positively with E-selectin, while methylglyoxal correlated with SDS-PWV. These findings link AGE accumulation with endothelial activation, inflammation, and arterial stiffness in childhood.

7. Conclusions

Dietary advanced glycation end-products (dAGEs) and advanced lipoxidation end-products (ALEs) form during food processing. Their levels depend on food matrix composition and processing conditions. Key factors include temperature, heating time, water activity, and the availability of reactive compounds involved in glycation and lipid oxidation. Consequently, dAGEs and ALEs may occur in various food categories, including products intended for infants and children.

The biological significance of these compounds depends not only on their dietary levels but also on their fate during digestion. Protein modifications may alter susceptibility to proteolysis, resulting in proteins and peptides with different biochemical properties. The gastrointestinal fate of dAGEs may also involve interactions with the intestinal environment and gut microbiota. These processes highlight the need to consider both food composition and gastrointestinal transformations when evaluating the potential biological effects of dietary dAGEs.

The mechanisms discussed in this review suggest potential links between AGEs, oxidative stress, AGE–RAGE signaling, inflammatory responses, and impaired insulin signaling. These pathways provide a mechanistic basis for investigating the possible contribution of dAGEs to insulin resistance and other metabolic disturbances. However, their relevance to child health requires careful interpretation. The mechanisms described do not, in themselves, establish a direct causal relationship between dietary dAGE intake and metabolic disorders.

Food-processing strategies aimed at reducing dAGE and ALE formation may offer opportunities to limit dietary exposure to these compounds. Potential approaches include optimizing processing conditions and using compounds with antioxidant or antiglycation properties. Such strategies must be tailored to individual food matrices. They should also preserve nutritional value, food safety, and sensory quality.

Dietary AGEs and ALEs provide a link between food chemistry and processing, gastrointestinal transformations and cellular pathways associated with oxidative stress, inflammation, and insulin signaling. Their relevance to pediatric nutrition should be assessed through an integrated approach. This requires consideration of their dietary sources, gastrointestinal fate, and potential biological effects. Further research is needed to clarify their contribution to metabolic health during childhood.

Author Contributions: Conceptualization, P.K.; methodology, P.K., J.L. and A.S.-Z.; investigation, P.K., A.S.-Z., J.L., A.K. and E.L.; resources, P.K., E.L., A.K., A.S.-Z. and J.L.; writing—original draft preparation, P.K., A.K., E.L., J.L. and A.S.-Z.; writing—review and editing, P.K., J.L. and A.S.-Z.; visualization, A.S.-Z. and J.L.; supervision, J.L., A.S.-Z. and P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Bydgoszcz University of Science and Technology under Grant BN-WM-0.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. World Health Organization (WHO). Obesity and Overweight. Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 17 November 2026).
2. Phelps, N.H.; Singleton, R.K.; Zhou, B.; Heap, R.A.; Mishra, A.; Bennett, J.E.; Paciorek, C.J.; Lhoste, V.P.; Carrillo-Larco, R.M.; Stevens, G.A.; et al. Worldwide trends in underweight and obesity from 1990 to 2022: A Pooled Analysis of 3663 Population-Representative Studies with 222 Million Children, Adolescents, and Adults. *Lancet* **2024**, *403*, 1027–1050. [CrossRef]
3. Huang, J.-S.; Zhang, X.-Y.; Ramakrishnan, R.; Chu, J.-Q.; Lu, M.-S.; Shao, D.-T.; Qiu, X.; He, J.-R. Association of childhood obesity phenotypes with cardiometabolic outcomes in adulthood: A systematic review and meta-analysis. *Obes. Rev.* **2025**, *27*, 1–10. [CrossRef]
4. Wang, L.; Martínez Steele, E.; Du, M.; Pomeranz, J.L.; O'Connor, J.; Herrick, K.A.; Zhang, F.F. Trends in consumption of ultraprocessed foods among US youths aged 2–19 Years, 1999–2018. *JAMA* **2021**, *326*, 519–530. [CrossRef]
5. Chaudhuri, J.; Bains, Y.; Guha, S.; Kahn, A.; Hall, D.; Bose, N.; Gugliucci, A.; Kapahi, P. The role of advanced glycation end products in aging and metabolic diseases: Bridging association and causality. *Cell Metab.* **2018**, *28*, 337–352. [CrossRef]
6. Rabbani, N.; Thornalley, P.J. Advanced glycation end products in the pathogenesis of chronic kidney disease. *Kidney Int.* **2018**, *93*, 803–813. [CrossRef]
7. Snelson, M.; Coughlan, M.T. Dietary advanced glycation end products: Digestion, metabolism and modulation of gut microbial ecology. *Nutrients* **2019**, *11*, 215. [CrossRef]
8. Moldogazieva, N.T.; Mokhosoev, I.M.; Mel'nikova, T.I.; Porozov, Y.B.; Terentiev, A.A. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 3085756. [CrossRef]
9. Gupta, A.; Uribarri, J. Dietary advanced glycation end products and their potential role in cardiometabolic disease in children. *Horm. Res. Paediatr.* **2016**, *85*, 291–300. [CrossRef]
10. Hanson, M.A.; Gluckman, P.D. Developmental origins of health and disease—Global public health implications. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2015**, *29*, 24–31. [CrossRef]
11. Sharples, A.P.; Stewart, C.E.; Seaborne, R.A. Does skeletal muscle have an 'epi'-memory? The role of epigenetics in nutritional programming, metabolic disease, aging and exercise. *Aging Cell* **2016**, *15*, 603–616. [CrossRef]
12. Christ, A.; Günther, P.; Lauterbach, M.A.R.; Duewell, P.; Biswas, D.; Pelka, K.; Scholz, C.J.; Oosting, M.; Haendler, K.; Baßler, K.; et al. Western diet triggers NLRP3-dependent innate Immune reprogramming. *Cell* **2018**, *172*, 162–175. [CrossRef]
13. Mericq, V.; Piccardo, C.; Cai, W.; Chen, X.; Zhu, L.; Striker, G.E.; Vlassara, H.; Uribarri, J. Maternally transmitted and food-derived glycotoxins: A factor preconditioning the young to diabetes? *Diabetes Care* **2010**, *33*, 2232–2237. [CrossRef]
14. Sergi, D.; Boulestin, H.; Campbell, F.M.; Williams, L.M. The role of dietary advanced glycation end products in metabolic dysfunction. *Mol. Nutr. Food Res.* **2021**, *65*, e1900934. [CrossRef]
15. Vickers, M.H. Early life nutrition, epigenetics and programming of later life disease. *Nutrients* **2014**, *6*, 2165–2178. [CrossRef]
16. Uribarri, J.; Woodruff, S.; Goodman, S.; Cai, W.; Chen, X.; Pyzik, R.; Yong, A.; Striker, G.E.; Vlassara, H. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J. Am. Diet. Assoc.* **2010**, *110*, 911–916.e12. [CrossRef]
17. Poulsen, M.W.; Hedegaard, R.V.; Andersen, J.M.; de Courten, B.; Bügel, S.; Nielsen, J.; Skibsted, L.H.; Dragsted, L.O. Advanced glycation endproducts in food and their effects on health. *Food Chem. Toxicol.* **2013**, *60*, 10–37. [CrossRef]
18. Li, L.; Zhuang, Y.; Zou, X.; Chen, M.; Cui, B.; Jiao, Y.; Cheng, Y. Advanced glycation end products: A comprehensive review of their detection and occurrence in food. *Foods* **2023**, *12*, 2103. [CrossRef]
19. Wei, Q.; Liu, T.; Sun, D.-W. Advanced glycation end-products (ages) in foods and their detecting techniques and methods: A review. *Trends Food Sci. Technol.* **2018**, *82*, 32–45. [CrossRef]
20. Fardet, A.; Rock, E. Ultra-processed foods and food technical transformations: The main drivers of the metabolic syndrome epidemic. *Nutrients* **2020**, *12*, 3514. [CrossRef]
21. Inan-Eroglu, E.; Ayaz, A.; Buyuktuncer, Z. Formation of advanced glycation endproducts in foods during cooking process and underlying mechanisms: A comprehensive review of experimental studies. *Nutr. Res. Rev.* **2020**, *33*, 118–132. [CrossRef]
22. Bellier, J.; Nokin, M.-J.; Lardé, E.; Karoyan, P.; Peulen, O.; Castronovo, V.; Bellahcène, A. Methylglyoxal, a potent inducer of ages, connects between diabetes and cancer. *Diabetes Res. Clin. Pract.* **2019**, *148*, 200–211. [CrossRef]
23. Uribarri, J.; del Castillo, M.D.; de la Maza, M.P.; Filip, R.; Gugliucci, A.; Luevano-Contreras, C.; Macías-Cervantes, M.H.; Markowicz Bastos, D.H.; Medrano, A.; Menini, T.; et al. Dietary advanced glycation end products and their role in health and disease. *Adv. Nutr.* **2015**, *6*, 461–473. [CrossRef]
24. Domínguez, R.; Pateiro, M.; Gagaoua, M.; Barba, F.J.; Zhang, W.; Lorenzo, J.M. A comprehensive review on lipid oxidation in meat and meat products. *Antioxidants* **2019**, *8*, 429. [CrossRef]
25. Grootveld, M. Evidence-based challenges to the continued recommendation and use of peroxidatively-susceptible polyunsaturated fatty acid-rich culinary oils for high-temperature frying practises: Experimental revelations focused on toxic aldehydic lipid oxidation products. *Front. Nutr.* **2022**, *8*, 711640. [CrossRef]

26. Liu, R.; Du, X.; Li, Y.; Zhou, J.; Xia, X. Research progress on the formation, influencing factors, and mitigation strategies of advanced glycation end products in meat-based foods during frozen storage and processing. *Trends Food Sci. Technol.* **2025**, *163*, 105171. [CrossRef]
27. Nguyen, H.T.; van der Fels-Klerx, H.J.; van Boekel, M.A.J.S. Kinetics of N^{ε}-(Carboxymethyl)lysine formation in aqueous model systems of sugars and casein. *Food Chem.* **2016**, *192*, 125–133. [CrossRef]
28. Ajandouz, E.H.; Desseaux, V.; Tazi, S.; Puigserver, A. Effects of temperature and ph on the kinetics of caramelisation, protein cross-linking and maillard reactions in aqueous model Systems. *Food Chem.* **2008**, *107*, 1244–1252. [CrossRef]
29. Kutzli, I.; Weiss, J.; Gibis, M. Glycation of plant proteins via maillard reaction: Reaction chemistry, technofunctional properties, and potential food application. *Foods* **2021**, *10*, 376. [CrossRef]
30. Birlouez-Aragon, I.; Pischetsrieder, M.; Leclère, J.; Morales, F.J. Assessment of protein glycation markers in infant formulas. *Food Chem.* **2004**, *87*, 253–259. [CrossRef]
31. Akıllıoğlu, H.G.; Lund, M.N. Quantification of advanced glycation end products and amino acid cross-links in foods by high-resolution mass spectrometry: Applicability of acid hydrolysis. *Food Chem.* **2022**, *366*, 130601. [CrossRef]
32. Qin, R.; Wu, R.; Shi, H.; Jia, C.; Rong, J.; Liu, R. Formation of ages in fish cakes during air frying and other traditional heating methods. *Food Chem.* **2022**, *391*, 133213. [CrossRef]
33. Zhu, Z.; Fang, R.; Yang, J.; Khan, I.A.; Huang, J.; Huang, M. Air frying combined with grape seed extract inhibits nε-carboxymethyllysine and nε-carboxyethyllysine by controlling oxidation and glycosylation. *Poult. Sci.* **2021**, *100*, 1308–1318. [CrossRef]
34. Dong, L.; Qiu, C.; Wang, R.; Zhang, Y.; Wang, J.; Liu, J.; Yu, H.; Wang, S. Effects of air frying on french fries: The indication role of physicochemical properties on the formation of maillard hazards, and the changes of starch digestibility. *Front. Nutr.* **2022**, *9*, 889901. [CrossRef]
35. Wang, H.; Tu, Z.-C.; Liu, G.-X.; Liu, C.-M.; Huang, X.-Q.; Xiao, H. Comparison of glycation in conventionally and microwave-heated ovalbumin by high resolution mass spectrometry. *Food Chem.* **2013**, *141*, 985–991. [CrossRef]
36. Ohlsson, T.; Risman, P.O. Temperature distribution of microwave heating—Spheres and cylinders. *J. Microw. Power* **1978**, *13*, 302–309. [CrossRef]
37. Li, L.; Han, L.; Fu, Q.; Li, Y.; Liang, Z.; Su, J.; Li, B. Formation and inhibition of Nε-(Carboxymethyl)lysine in saccharide-lysine model systems during microwave heating. *Molecules* **2012**, *17*, 12758–12770. [CrossRef]
38. European Commission. Commission Regulation (EU) 2017/2158 of 20 November 2017 Establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food. *Off. J. Eur. Union* **2017**, *L 304*, 24–44. Available online: https://eur-lex.europa.eu/eli/reg/2017/2158/oj (accessed on 12 October 2026).
39. U.S. Food and Drug Administration. Acrylamide. Available online: https://www.fda.gov/food/process-contaminants-food/acrylamide (accessed on 12 October 2026).
40. Xie, Y.; van der Fels-Klerx, H.J.; van Leeuwen, S.P.J.; Fogliano, V. Dietary advanced glycation end-products, 2-monochloropropane-1,3-diol esters and 3-monochloropropane-1,2-diol esters and glycidyl esters in infant formulas: Occurrence, formulation and processing effects, mitigation strategies. *Compr. Rev. Food Sci. Food Saf.* **2021**, *20*, 5489–5515. [CrossRef]
41. Mousavi, Z.E.; Hunt, K.; Koolman, L.; Butler, F.; Fanning, S. cronobacter species in the built food production environment: A review on persistence, pathogenicity, regulation and detection methods. *Foods* **2023**, *12*, 2400. [CrossRef]
42. van Lieshout, G.A.A.; Lambers, T.T.; Bragt, M.C.E.; Hettinga, K.A. How processing may affect milk protein digestion and overall physiological outcomes: A systematic review. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 2422–2445. [CrossRef]
43. Klenovics, K.S.; Boor, P.; Somoza, V.; Celec, P.; Fogliano, V.; Šebeková, K. Advanced glycation end products in infant formulas do not contribute to insulin resistance associated with their consumption. *PLoS ONE* **2013**, *8*, e53056. [CrossRef]
44. Cengiz, S.; Kişmiroğlu, C.; Çebi, N.; Çatak, J.; Yaman, M. Determination of the most potent precursors of advanced glycation end products (ages) in chips, crackers, and breakfast cereals by high performance liquid chromatography (HPLC) using precolumn derivatization with 4-Nitro-1,2-phenlenediamine. *Microchem. J.* **2020**, *158*, 105170. [CrossRef]
45. Damasiewicz-Bodzek, A.; Szumska, M.; Nowak, A.; Waligóra, S.; Pastuszka, B.; Stopińska, K.; Janoszka, B. LC-Orbitrap-MS/MS analysis of chosen glycation products in infant formulas. *Molecules* **2025**, *30*, 2753. [CrossRef]
46. Yaman, M.; Demirci, M.; Ede-Cintesun, E.; Kurt, E.; Mızrak, Ö.F. Investigation of formation of well-known AGEs precursors in cookies using an in vitro simulated gastrointestinal digestive system. *Food Chem.* **2022**, *373*, 131451. [CrossRef]
47. Toumpakari, Z.; Tilling, K.; Haase, A.M.; Johnson, L. High-risk environments for eating foods surplus to requirements: A multilevel analysis of adolescents' non-core food intake in the national diet and nutrition survey (NDNS). *Public Health Nutr.* **2019**, *22*, 74–84. [CrossRef]
48. Chavez-Ugalde, I.Y.; de Vocht, F.; Jago, R.; Adams, J.; Ong, K.K.; Forouhi, N.G.; Colombet, Z.; Ricardo, L.I.C.; van Sluijs, E.; Toumpakari, Z. Ultra-processed food consumption in uk adolescents: Distribution, trends, and sociodemographic correlates using the national diet and nutrition survey 2008/09 to 2018/19. *Eur. J. Nutr.* **2024**, *63*, 2709–2723. [CrossRef]

49. Dello Russo, M.; Sirangelo, I.; Lauria, F.; Formisano, A.; Iannuzzi, C.; Hebestreit, A.; Pala, V.; Siani, A.; Russo, P. Dietary advanced glycation end products (AGEs) and urinary fluorescent AGEs in children and adolescents: Findings from the italian i.family project. *Nutrients* **2024**, *16*, 1831. [CrossRef]
50. Cheng, W.; Wang, X.; Zhang, Z.; Ma, L.; Liu, G.; Wang, Q.; Chen, F.; Cheng, K.-W. development of an isotope dilution UHPLC–QqQ-MS/MS-based method for simultaneous determination of typical advanced glycation end products and acrylamide in baked and fried foods. *J. Agric. Food Chem.* **2021**, *69*, 2611–2618. [CrossRef]
51. Ma, L.; He, Q.; Qiu, Y.; Liu, H.; Wu, J.; Liu, G.; Brennan, C.; Brennan, M.A.; Zhu, L. Food matrixes play a key role in the distribution of contaminants of lipid origin: A case study of malondialdehyde formation in vegetable oils during deep-frying. *Food Chem.* **2021**, *347*, 129080. [CrossRef]
52. Saha, A.; Poojary, P.; Chan, L.; Chauhan, K.; Nadkarni, G.; Coca, S.; Uribarri, J. Increased odds of metabolic syndrome with consumption of high dietary advanced glycation end products in adolescents. *Diabetes Metab.* **2017**, *43*, 469–471. [CrossRef]
53. Farzam, S.; Poursalehi, D.; Mirzaei, S.; Asadi, A.; Akhlaghi, M.; Saneei, P. Ultra-processed food intake in relation to metabolic health status in iranian adolescents with overweight and obesity. *Nutr. Metab.* **2024**, *21*, 111. [CrossRef]
54. Tagi, V.M.; Samvelyan, S.; Chiarelli, F. An update of the consensus statement on insulin resistance in children 2010. *Front. Endocrinol.* **2022**, *13*, 1061524. [CrossRef]
55. Uceda, A.B.; Mariño, L.; Casasnovas, R.; Adrover, M. An overview on glycation: Molecular mechanisms, impact on proteins, pathogenesis, and inhibition. *Biophys. Rev.* **2024**, *16*, 189–218. [CrossRef]
56. Sohouli, M.H.; Fatahi, S.; Sharifi-Zahabi, E.; Santos, H.O.; Tripathi, N.; Lari, A.; Pourrajab, B.; Kord-Varkaneh, H.; Găman, M.-A.; Shidfar, F. The impact of low advanced glycation end products diet on metabolic risk factors: A systematic review and meta-analysis of randomized controlled trials. *Adv. Nutr.* **2021**, *12*, 766–776. [CrossRef]
57. Detopoulou, P.; Voulgaridou, G.; Seva, V.; Kounetakis, O.; Desli, I.-I.; Tsoumana, D.; Dedes, V.; Papachristou, E.; Papadopoulou, S.; Panoutsopoulos, G. Dietary restriction of advanced glycation end-products (AGEs) in patients with diabetes: A systematic review of randomized controlled trials. *Int. J. Mol. Sci.* **2024**, *25*, 11407. [CrossRef]
58. Linkens, A.M.A.; Houben, A.J.H.M.; Niessen, P.M.; Wijckmans, N.E.G.; de Goei, E.E.C.; Van den Eynde, M.D.G.; Scheijen, J.L.J.M.; van den Waarenburg, M.P.H.; Mari, A.; Berendschot, T.T.J.M.; et al. A 4-week high-AGE diet does not impair glucose metabolism and vascular function in obese individuals. *JCI Insight* **2022**, *7*, e156950. [CrossRef]
59. Viedma-Poyatos, Á.; González-Jiménez, P.; Langlois, O.; Company-Marín, I.; Spickett, C.M.; Pérez-Sala, D. Protein lipoxidation: Basic concepts and emerging roles. *Antioxidants* **2021**, *10*, 295. [CrossRef]
60. Aalaei, K.; Sjöholm, I.; Rayner, M.; Tareke, E. The impact of different drying techniques and controlled storage on the development of advanced glycation end products in skim milk powders using isotope dilution ESI-LC-MS/MS. *Food Bioprocess Technol.* **2017**, *10*, 1704–1714. [CrossRef]
61. Yu, L.; Chai, M.; Zeng, M.; He, Z.; Chen, J. Effect of lipid oxidation on the formation of Nε-Carboxymethyl-Lysine and Nε-Carboxyethyl-Lysine in chinese-style sausage during storage. *Food Chem.* **2018**, *269*, 466–472. [CrossRef]
62. Plaza, M.; Östman, E.; Tareke, E. Maillard reaction products in powder based food for infants and toddlers. *Eur. J. Nutr. Food Saf.* **2016**, *6*, 65–74. [CrossRef]
63. Wang, S.; Wang, M.; Wang, Y.; Wu, Z.; Yang, J.; Li, H.; Li, H.; Yu, J. Control of the maillard reaction and secondary shelf-life prediction of infant formula during domestic use. *J. Food Sci.* **2023**, *88*, 681–695. [CrossRef]
64. Li, Y.; Quan, W.; Jia, X.; He, Z.; Wang, Z.; Zeng, M.; Chen, J. Profiles of initial, intermediate, and advanced stages of harmful maillard reaction products in whole-milk powders pre-treated with different heat loads during 18 months of storage. *Food Chem.* **2021**, *351*, 129361. [CrossRef]
65. Han, Z.; Zhu, M.; Wan, X.; Zhai, X.; Ho, C.-T.; Zhang, L. Food Polyphenols and maillard reaction: Regulation effect and chemical mechanism. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 4904–4920. [CrossRef]
66. Li, X.; Zheng, T.; Sang, S.; Lv, L. Quercetin inhibits advanced glycation end product formation by trapping methylglyoxal and glyoxal. *J. Agric. Food Chem.* **2014**, *62*, 12152–12158. [CrossRef]
67. Prestel, S.; de Falco, B.; Blidi, S.; Fiore, A.; Sturrock, K. Evaluation of the effect of berry extracts on carboxymethyllysine and lysine in ultra-high temperature treated milk. *Food Res. Int.* **2020**, *130*, 108923. [CrossRef]
68. Zhao, D.; Le, T.T.; Larsen, L.B.; Li, L.; Qin, D.; Su, G.; Li, B. Effect of glycation derived from α-dicarbonyl compounds on the in vitro digestibility of β-casein and β-lactoglobulin: A model study with glyoxal, methylglyoxal and butanedione. *Food Res. Int.* **2017**, *102*, 313–322. [CrossRef]
69. Zhao, D.; Li, L.; Le, T.T.; Larsen, L.B.; Su, G.; Liang, Y.; Li, B. digestibility of glyoxal-glycated β-casein and β-lactoglobulin and distribution of peptide-bound advanced glycation end products in gastrointestinal digests. *J. Agric. Food Chem.* **2017**, *65*, 5778–5788. [CrossRef]
70. van der Lugt, T.; Venema, K.; van Leeuwen, S.; Vrolijk, M.F.; Opperhuizen, A.; Bast, A. Gastrointestinal digestion of dietary advanced glycation end products using an in vitro model of the gastrointestinal tract (TIM-1). *Food Funct.* **2020**, *11*, 6297–6307. [CrossRef]

71. Grundy, M.M.-L.; Deglaire, A.; Le Feunteun, S.; Reboul, E.; Moughan, P.J.; Wilde, P.J.; McClements, D.J.; Marze, S. Bioaccessibility and associated concepts: Terminology in the context of in vitro food digestion studies. *Food Chem.* **2025**, *485*, 144424. [CrossRef]
72. Lund, M.N.; Ray, C.A. Control of maillard reactions in foods: Strategies and chemical mechanisms. *J. Agric. Food Chem.* **2017**, *65*, 4537–4552. [CrossRef]
73. Shi, B.; Guo, X.; Liu, H.; Jiang, K.; Liu, L.; Yan, N.; Farag, M.A.; Liu, L. Dissecting maillard reaction production in fried foods: Formation mechanisms, sensory characteristic attribution, control strategy, and gut homeostasis regulation. *Food Chem.* **2024**, *438*, 137994. [CrossRef]
74. Yeh, W.-J.; Hsia, S.-M.; Lee, W.-H.; Wu, C.-H. Polyphenols with antiglycation activity and mechanisms of action: A review of recent findings. *J. Food Drug Anal.* **2017**, *25*, 84–92. [CrossRef]
75. Lian, Z.; Han, J.; Cao, Y.; Yao, W.; Niu, X.; Xu, M.; Xu, J.; Zhu, Q. Epicatechin inhibited lipid oxidation and protein lipoxidation in a fish oil-fortified dairy mimicking system. *Foods* **2023**, *12*, 1559. [CrossRef]
76. Zhu, H.; Poojary, M.M.; Andersen, M.L.; Lund, M.N. The effect of molecular structure of polyphenols on the kinetics of the trapping reactions with methylglyoxal. *Food Chem.* **2020**, *319*, 126500. [CrossRef]
77. Li, Y.; Li, L.; Lund, M.N.; Li, B.; Hu, Y.; Zhang, X. Reduction of Nε-(Carboxymethyl) Lysine by (−)-Epicatechin and (−)-Epigallocatechin Gallate: The involvement of a possible trapping mechanism by catechin quinones. *Food Chem.* **2018**, *266*, 427–434. [CrossRef]
78. Adrover, M.; Vilanova, B.; Frau, J.; Muñoz, F.; Donoso, J. The pyridoxamine action on amadori compounds: A reexamination of its scavenging capacity and chelating effect. *Bioorg. Med. Chem.* **2008**, *16*, 5557–5569. [CrossRef]
79. Ramis, R.; Ortega-Castro, J.; Caballero, C.; Casasnovas, R.; Cerrillo, A.; Vilanova, B.; Adrover, M.; Frau, J. How does pyridoxamine inhibit the formation of advanced glycation end products? The role of its primary antioxidant activity. *Antioxidants* **2019**, *8*, 344. [CrossRef]
80. Reddy, V.P.; Aryal, P.; Darkwah, E.K. Advanced glycation end products in health and disease. *Microorganisms* **2022**, *10*, 1848. [CrossRef]
81. Vistoli, G.; De Maddis, D.; Cipak, A.; Zarkovic, N.; Carini, M.; Aldini, G. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): An overview of their mechanisms of formation. *Free Radic. Res.* **2013**, *47*, 3–27. [CrossRef]
82. Zhu, R.; Sun, X.; Zhang, Y.; Yang, T.; Wang, C.; Zhang, J.; Duan, Z.; Shang, F.; Fan, J.; Liu, Y.; et al. Effect of pectin oligosaccharides supplementation on infant formulas: The storage stability, formation and intestinal absorption of advanced glycation end products. *Food Chem.* **2022**, *373*, 131571. [CrossRef]
83. Zhang, Q.; Wang, Y.; Fu, L. Dietary advanced glycation end-products: Perspectives linking food processing with health implications. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 2559–2587. [CrossRef]
84. Zhao, D.; Sheng, B.; Wu, Y.; Li, H.; Xu, D.; Nian, Y.; Mao, S.; Li, C.; Xu, X.; Zhou, G. Comparison of free and bound advanced glycation end products in food: A review on the possible influence on human health. *J. Agric. Food Chem.* **2019**, *67*, 14007–14018. [CrossRef]
85. Lo, C.-Y.; Li, S.; Tan, D.; Pan, M.-H.; Sang, S.; Ho, C.-T. Trapping reactions of reactive carbonyl species with tea polyphenols in simulated physiological conditions. *Mol. Nutr. Food Res.* **2006**, *50*, 1118–1128. [CrossRef]
86. Liu, P.; Yin, Z.; Chen, M.; Huang, C.; Wu, Z.; Huang, J.; Ou, S.; Zheng, J. Cytotoxicity of adducts formed between quercetin and methylglyoxal in PC-12 Cells. *Food Chem.* **2021**, *352*, 129424. [CrossRef]
87. Yi, Y.; Jeon, H.-J.; Yoon, S.; Lee, S.-M. Hydrocolloids decrease the digestibility of corn starch, soy protein, and skim milk and the antioxidant capacity of grape juice. *Prev. Nutr. Food Sci.* **2015**, *20*, 276–283. [CrossRef]
88. Shangari, N.; Depeint, F.; Furrer, R.; Bruce, W.R.; Popovic, M.; Zheng, F.; O'Brien, P.J. A Thermolyzed diet increases oxidative stress, plasma α-aldehydes and colonic inflammation in the rat. *Chem.-Biol. Interact.* **2007**, *169*, 100–109. [CrossRef]
89. Cai, W.; He, J.C.; Zhu, L.; Chen, X.; Wallenstein, S.; Striker, G.E.; Vlassara, H. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: Association with Increased AGER1 Expression. *Am. J. Pathol.* **2007**, *170*, 1893–1902. [CrossRef]
90. Chen, J.H.; Lin, X.; Bu, C.; Zhang, X. Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. *Nutr. Metab.* **2018**, *15*, 72. [CrossRef]
91. van der Lugt, T.; Opperhuizen, A.; Bast, A.; Vrolijk, M.F. Dietary advanced glycation endproducts and the gastrointestinal tract. *Nutrients* **2020**, *12*, 2814. [CrossRef]
92. Guerra, A.; Etienne-Mesmin, L.; Livrelli, V.; Denis, S.; Blanquet-Diot, S.; Alric, M. Relevance and challenges in modeling human gastric and small intestinal digestion. *Trends Biotechnol.* **2012**, *30*, 591–600. [CrossRef]
93. Deng, Y.; Wierenga, P.A.; Schols, H.A.; Sforza, S.; Gruppen, H. Effect of maillard-induced glycation on protein hydrolysis by lysine/arginine and non-lysine/arginine specific proteases. *Food Hydrocoll.* **2017**, *69*, 210–219. [CrossRef]
94. Yang, M.; Yang, Z.; Everett, D.W.; Gilbert, E.P.; Singh, H.; Ye, A. Digestion of food proteins: The role of pepsin. *Crit. Rev. Food Sci. Nutr.* **2025**, *65*, 6919–6940. [CrossRef]
95. Treibmann, S.; Venema, K.; Henle, T. Glycation reactions of methylglyoxal during digestion in a dynamic, in vitro model of the upper gastrointestinal tract (TIM-1). *Food Sci. Nutr.* **2024**, *12*, 4702–4712. [CrossRef]

96. Yuan, X.; Feng, S.; Li, J.; Guo, R.; Nie, C.; Zhai, R.; Tu, A.; Cao, X.; Zhang, M.; Li, J. Generation of advanced glycation end products from glycated protein or fructose/glyoxal-protein adducts under in vitro simulated gastrointestinal digestion. *Food Chem.* **2025**, *463*, 141175. [CrossRef]
97. van der Lugt, T.; Vrolijk, M.F.; Bovee, T.F.H.; van Leeuwen, S.P.J.; Vonsovic, S.; Hamers, A.; Opperhuizen, A.; Bast, A. Gastrointestinal digestion of dietary advanced glycation endproducts increases their pro-inflammatory potential. *Food Funct.* **2021**, *12*, 6691–6696. [CrossRef]
98. Schumacher, D.; Kroh, L.W. The decomposition of maillard reaction products by amylolytic enzymes. 1. Reversible inhibition of alpha- and glucoamylase and alpha-glucosidase by oligosaccharide amadori compounds. *Z. Lebensm. Unters. Forsch.* **1994**, *199*, 270–274. [CrossRef]
99. Jansen, F.A.C.; Fogliano, V.; Rubert, J.; Hoppenbrouwers, T. Dietary advanced glycation end products interacting with the intestinal epithelium: What do we really know? *Mol. Metab.* **2023**, *73*, 101734. [CrossRef]
100. Rao, S.; Grover, M. Intestinal Proteases. *Curr. Opin. Gastroenterol.* **2023**, *39*, 472–478. [CrossRef]
101. Faist, V.; Erbersdobler, H.F. Metabolic Transit and in vivo effects of melanoidins and precursor compounds deriving from the maillard reaction. *Ann. Nutr. Metab.* **2001**, *45*, 1–12. [CrossRef]
102. Somoza, V. Five years of research on health risks and benefits of maillard reaction products: An update. *Mol. Nutr. Food Res.* **2005**, *49*, 663–672. [CrossRef]
103. Hao, S.; Ye, M.; Li, N.; Lu, Z.; Quan, W.; Xu, H.; Li, M. Comparison of intestinal absorption of soybean protein isolate-, glutenin- and peanut protein isolate-bound Nε-[carboxymethyl]lysine after in vitro gastrointestinal digestion. *Food Res. Int.* **2024**, *192*, 114811. [CrossRef]
104. Delgado-Andrade, C. Carboxymethyl-Lysine: Thirty years of investigation in the field of AGE formation. *Food Funct.* **2016**, *7*, 46–57. [CrossRef]
105. Martinez-Saez, N.; Fernandez-Gomez, B.; Cai, W.; Uribarri, J.; del Castillo, M.D. In Vitro formation of maillard reaction products during simulated digestion of meal-resembling systems. *Food Res. Int.* **2019**, *118*, 72–80. [CrossRef]
106. Martati, E.; Wang, H.; Rietjens, I.M.C.M.; Zheng, L. Advanced glycation end products (AGEs) and in vitro and in vivo approaches to study their mechanisms of action and the protective properties of natural compounds. *Phytomedicine* **2026**, *150*, 157772. [CrossRef]
107. Chen, C.; Zhang, J.-Q.; Li, L.; Guo, M.; He, Y.; Dong, Y.; Meng, H.; Yi, F. Advanced glycation end products in the skin: Molecular mechanisms, methods of measurement, and inhibitory pathways. *Front. Med.* **2022**, *11*, 837222. [CrossRef]
108. Twarda-Clapa, A.; Olczak, A.; Białkowska, A.M.; Koziołkiewicz, M. Advanced glycation end-products (AGEs): Formation, chemistry, classification, receptors, and diseases related to AGEs. *Cells* **2022**, *11*, 1312. [CrossRef]
109. Najjar, J.A.; Calvert, J.W. Effects of protein glycation and protective mechanisms against glycative stress. *Curr. Opin. Pharmacol.* **2024**, *76*, 102464. [CrossRef]
110. Hendrysiak, A.; Brzezowska, J.; Nicolet, N.; Bocquel, D.; Andlauer, W.; Michalska-Ciechanowska, A. Juice powders from rosehip (*Rosa canina* L.): Physical, chemical, and antiglycation properties. *Molecules* **2023**, *28*, 1674. [CrossRef]
111. Zhou, Q.; Liang, W.; Wan, J.; Wang, M. Spinach (Spinacia oleracea) microgreen prevents the formation of advanced glycation end products in model systems and breads. *Curr. Res. Food Sci.* **2023**, *6*, 100490. [CrossRef]
112. Schalkwijk, C.G.; Stehouwer, C.D.A. Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications, and other age-related diseases. *Physiol. Rev.* **2020**, *100*, 407–461. [CrossRef]
113. Khan, M.A.; Younus, H. Superoxide dismutase glycation: A contributor to disease and target for prevention. *Catalysts* **2025**, *15*, 247. [CrossRef]
114. Senavirathna, L.; Pan, S.; Chen, R. Protein advanced glycation end products and their implications in pancreatic cancer. *Cancer Prev. Res.* **2023**, *16*, 601–610. [CrossRef]
115. Lemanowicz, J.; Kloska, S.M.; Siwik-Ziomek, A.; Kołaczyk, P.; Wnuk Lipińska, U.; Kloska, A. Biochemical mechanisms of cellular stress adaptation in the pathogenesis of chronic diseases. *Molecules* **2026**, *31*, 1381. [CrossRef]
116. Yang, T.; Qi, F.; Guo, F.; Shao, M.; Song, Y.; Ren, G.; Linlin, Z.; Qin, G.; Zhao, Y. An update on chronic complications of diabetes mellitus: From molecular mechanisms to therapeutic strategies with a focus on metabolic memory. *Mol. Med.* **2024**, *30*, 71. [CrossRef]
117. Martin, M.S.; Jacob-Dolan, J.W.; Pham, V.T.T.; Sjoblom, N.M.; Scheck, R.A. The chemical language of protein glycation. *Nat. Chem. Biol.* **2025**, *21*, 324–336. [CrossRef]
118. Huang, M.; Liu, Y.U.; Yao, X.; Qin, D.; Su, H. Variability in SOD1-associated amyotrophic lateral sclerosis: Geographic patterns, clinical heterogeneity, molecular alterations, and therapeutic implications. *Transl. Neurodegener.* **2024**, *32*, 8. [CrossRef]
119. Rungratanawanich, W.; Qu, Y.; Wang, X.; Essa, M.M.; Song, B.-J. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. *Exp. Mol. Med.* **2021**, *53*, 168–188. [CrossRef]
120. Lemanowicz, J.; Gawlińska, K.; Jaskulska, I.; Leśniak, E.; Kuczyński, A. Enzymatic nanomotors integrated with plant extracts: Biochemical mechanisms, applications, and clinical perspectives. *Molecules* **2026**, *31*, 2344. [CrossRef]

121. Alhumaydhi, F.A.; Younus, H.; Khan, M.A. Catalase functions and glycation: Their central roles in oxidative stress, metabolic disorders, and neurodegeneration. *Catalysts* **2025**, *15*, 817. [CrossRef]
122. Bakala, H.; Hamelin, M.; Mary, J.; Borot-Laloi, C.; Friguet, B. Catalase, a target of glycation damage in rat liver mitochondria with aging. *Biochim. Biophys. Acta Mol. Basis Dis.* **2012**, *10*, 1527–1534. [CrossRef]
123. Najjar, F.M.; Taghavi, F.; Ghadari, R.; Sheibani, N.; Moosavi-Movahedi, A.A. Destructive effect of non-enzymatic glycation on catalase and remediation via curcumin. *Arch. Biochem. Biophys.* **2017**, *38*, 1–90. [CrossRef]
124. Pei, J.; Pan, X.; Wei, G.; Hua, Y. Research progress of glutathione peroxidase family (GPX) in redoxidation. *Front. Pharmacol.* **2023**, *31*, 147414. [CrossRef]
125. Averill-Bates, D.A. The antioxidant glutathione. *Vitam. Horm.* **2023**, *20121*, 109–141. [CrossRef]
126. Jentsch, L.; Ventura, N. Mitochondrial complex I deficiency-associated diseases and models. *Cell. Mol. Life Sci.* **2026**, *83*, 249. [CrossRef]
127. Casey, A.M.; Murphy, M.P. Uncovering the source of mitochondrial superoxide in pro-inflammatory macrophages: Insights from immunometabolism. *Biochim. Biophys. Acta Mol. Basis Dis.* **2022**, *10*, 166481. [CrossRef]
128. Cojocaru, K.-A.; Luchian, I.; Goriuc, A.; Antoci, L.-M.; Ciobanu, C.-G.; Popescu, R.; Vlad, C.-E.; Blaj, M.; Foia, L.G. Mitochondrial dysfunction, oxidative stress, and therapeutic strategies in diabetes, obesity, and cardiovascular disease. *Antioxidants* **2023**, *12*, 658. [CrossRef]
129. Xiao, L.; Zheng, S.; Lin, Z.; Zhang, C.; Zhang, H.; Chen, J.; Wang, L. Singlet oxygen in food: A review on its formation, oxidative damages, quenchers, and applications in preservation. *Antioxidants* **2025**, *14*, 865. [CrossRef]
130. Chen, Y.; Liu, L.; Bai, B.; Shen, Y. Mechanistic exploration of astaxanthin quenching singlet oxygen and inhibiting myoglobin-induced photooxidation. *Food Chem.* **2025**, *492*, 145463. [CrossRef]
131. Hajimohammadi, M.; Faraj, F.H.; Boghdachi, M.; Alwasiti, A.A.; Shnain, Z.Y. Sunlight-induced lipid oxidation and degradation of edible oil mediated by hemoglobin: Implications for food system sustainability. *Nutr. Food Sci.* **2026**, *14*, e72423. [CrossRef]
132. Connelly, E.M.; Frankel, K.S.; Shawm, G.S. Parkin and mitochondrial signalling. *Cell Signal.* **2023**, *106*, 110631. [CrossRef]
133. Yang, M.; Wei, X.; Yi, X.; Jiang, D.-S. Mitophagy-related regulated cell death: Molecular mechanisms and disease implications. *Cell Death Dis.* **2024**, *15*, 505. [CrossRef]
134. Narendra, D.P.; Youle, R.J. The role of PINK1–Parkin in mitochondrial quality control. *Nat. Cell Biol.* **2024**, *26*, 1639–1651. [CrossRef]
135. Lin, Y.; Alhaskawi, A.; Chen, L.; Moqbel, S.A.A. Recent advances in understanding oxidative stress in sepsis: Pathogenic roles and antioxidant therapeutic prospects—A narrative review. *Front. Pharmacol.* **2025**, *16*, 1695992. [CrossRef]
136. Vermot, A.; Petit-Härtlein, I.; Smith, S.M.E.; Fieschi, F. NADPH oxidases (NOX): An overview from discovery, molecular mechanisms to physiology and pathology. *Antioxidants* **2021**, *10*, 890. [CrossRef]
137. Eid, S.A.; Savelieff, M.G.; Eid, A.A.; Feldman, E.L. Nox, nox, are you there? The role of NADPH oxidases in the peripheral nervous system. *Antioxid. Redox Signal.* **2022**, *37*, 613–630. [CrossRef]
138. Matsushima, S.; Sadoshima, J. Yin and yang of NADPH oxidases in myocardial ischemia-reperfusion. *Antioxidants* **2022**, *31*, 1069. [CrossRef]
139. Ogboo, B.C.; Grabovyy, U.V.; Maini, A.; Scouten, S.; van der Vliet, A.; Mattevi, A.; Heppner, D.E. Architecture of the NADPH oxidase family of enzymes. *Redox Biol.* **2022**, *52*, 102298. [CrossRef]
140. Schiffer, T.A.; Carvalho, L.R.R.A.; Guimaraes, D.; Boeder, A.; Wikström, P.; Carlström, M. Specific NOX4 inhibition preserves mitochondrial function and dampens kidney dysfunction following ischemia–reperfusion-induced kidney injury. *Antioxidants* **2024**, *13*, 489. [CrossRef]
141. Camargo, L.L.; Rios, F.J.; Montezano, A.C.; Rouyz, R.M. Reactive oxygen species in hypertension. *Nat. Rev. Cardiol.* **2025**, *20*, 20–37. [CrossRef]
142. Chandimali, N.; Bak, S.G.; Park, E.H.; Lim, H.-J.; Won, Y.-S.; Kim, E.-K.; Park, S.-I.; Lee, S.J. Free radicals and their impact on health and antioxidant defenses: A review. *Cell Death Discov.* **2025**, *31*, 9. [CrossRef]
143. Altenhöfer, S.; Kleikers, P.W.; Radermacher, K.A.; Scheurer, P.; Hermans, J.J.; Schiffers, P.; Ho, H.; Wingler, K.; Schmidt, H.H. The NOX toolbox: Validating the role of NADPH oxidases in physiology and disease. *Cell. Mol. Life Sci.* **2012**, *69*, 2327–2343. [CrossRef]
144. Forman, H.J.; Zhang, H. Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. *Nat. Rev. Drug Discov.* **2021**, *20*, 689–709. [CrossRef]
145. Sies, H.; Jones, D.P. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 363–383. [CrossRef]
146. Dragoev, S.G. Lipid peroxidation in muscle foods: Impact on quality, safety and human health. *Foods* **2024**, *13*, 797. [CrossRef]
147. Luo, W.; Zhang, J.; Wu, H. Chapter one—Lipid oxidation in meat: From fundamental mechanisms to latest control solutions. *Adv. Food Nutr. Res.* **2025**, *116*, 1–66. [CrossRef]

148. Akagawa, M. Protein carbonylation: Molecular mechanisms, biological implications, and analytical approaches. *Free Radic. Res.* **2021**, *55*, 307–320. [CrossRef]
149. Estévez, M.; Díaz-Velasco, S.; Martínez, R. Protein carbonylation in food and nutrition: A concise update. *Amino Acids* **2022**, *54*, 559–573. [CrossRef]
150. Ling, A.; Schultz, K.R.; Knight, J.D.; Shearn, C.T.; Baumel-Alterzon, S. Scars of oxidative stress: Protein carbonylation and beta cell dysfunction in diabetes. *Front. Endocrinol.* **2025**, *16*, 1722623. [CrossRef]
151. Park, J.Y.C.; King, A.; Björk, V.; English, B.W.; Fedintsev, A.; Ewald, C.Y. Strategic outline of interventions targeting extracellular matrix for promoting healthy longevity. *Am. J. Physiol. Cell Physiol.* **2023**, *325*, C90–C128. [CrossRef]
152. Chahla, C.; Kovacic, H.; Ferhat, L.; Leloup, L. Pathological impact of redox post-translational modifications. *Antioxid. Redox Signal.* **2024**, *41*, 152–180. [CrossRef]
153. Orfali, R.; Alwatban, A.Z.; Orfali, R.S.; Lau, L.; Chea, N.; Alotaibi, A.M.; Nam, Y.-W.; Zhang, M. Oxidative stress and ion channels in neurodegenerative diseases. *Front. Physiol.* **2024**, *15*, 1320086. [CrossRef]
154. LeFort, K.R.; Rungratanawanich, W.; Song, B.J. Contributing roles of mitochondrial dysfunction and hepatocyte apoptosis in liver diseases through oxidative stress, post-translational modifications, inflammation, and intestinal barrier dysfunction. *Cell. Mol. Life Sci.* **2024**, *81*, 34. [CrossRef]
155. Gęgotek, A.; Brańska-Januszewska, J.; Samocik, P.; Kozłowski, R.; Koda, M.; Zarkovic, N.; Skrzydlewska, E.; Ostrowska, H. Protein modifications by advanced glycation end products (AGEs) in human clear cell renal cell carcinoma. *J. Transl. Med.* **2025**, *23*, 914. [CrossRef]
156. Guan, G.; Chen, Y.; Dong, Y. Unraveling the AMPK-SIRT1-FOXO pathway: The in-depth analysis and breakthrough prospects of oxidative stress-induced diseases. *Antioxidants* **2025**, *14*, 70. [CrossRef]
157. Ma, L.; Li, J.; Zhang, X.; Zhang, W.; Jiang, C.; Yang, B.; Yang, H. Chinese botanical drugs targeting mitophagy to alleviate diabetic kidney disease, a comprehensive review. *Front. Pharmacol.* **2024**, *15*, 1360179. [CrossRef]
158. Pinela, J.; Dias, M.I.; Pereira, C.; Alonso-Esteban, J.I. Antioxidant activity of foods and natural products. *Molecules* **2024**, *29*, 1814. [CrossRef]
159. Hudson, B.I.; Kalea, A.Z.; del Mar Arriero, M.; Harja, E.; Boulanger, E.; D'Agati, V.; Schmidt, A.M. Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42*. *J. Biol. Chem.* **2008**, *283*, 34457–34468. [CrossRef]
160. Cross, K.; Vetter, S.W.; Alam, Y.; Hasan, M.Z.; Nath, A.D.; Leclerc, E. Role of the receptor for advanced glycation end products (RAGE) and its ligands in inflammatory responses. *Biomolecules* **2024**, *14*, 1550. [CrossRef]
161. Dong, H.; Zhang, Y.; Huang, Y.; Deng, H. Pathophysiology of RAGE in inflammatory diseases. *Front. Immunol.* **2022**, *13*, 931473. [CrossRef]
162. Bhattacharya, R.; Alam, M.R.; Kamal, M.A.; Seo, K.J.; Singh, L.R. AGE-RAGE Axis culminates into multiple pathogenic processes: A central road to neurodegeneration. *Front. Mol. Neurosci.* **2023**, *16*, 1155175. [CrossRef]
163. Borchi, E.; Bargelli, V.; Guidotti, V.; Berti, A.; Stefani, M.; Nediani, C.; Rigacci, S. Mild exposure of RIN-5F β-Cells to human islet amyloid polypeptide aggregates upregulates antioxidant enzymes via NADPH oxidase-RAGE: An hormetic stimulus. *Redox Biol.* **2014**, *2*, 114–122. [CrossRef]
164. Gelain, D.P.; Bittencourt, R.R.; Bastos Mendes, L.F.; Moreira, J.C.F.; Outeiro, T.F. RAGE against the glycation machine in synucleinopathies: Time to explore new questions. *J. Park. Dis.* **2023**, *13*, 717–728. [CrossRef]
165. Khalid, M.; Petroianu, G.; Adem, A. Advanced glycation end products and diabetes mellitus: Mechanisms and perspectives. *Biomolecules* **2022**, *12*, 542. [CrossRef]
166. Wang, B.; Jiang, T.; Qi, Y.; Luo, S.; Xia, Y.; Lang, B.; Zhang, B.; Zheng, S. AGE-RAGE axis and cardiovascular diseases: Pathophysiologic mechanisms and prospects for clinical applications. *Cardiovasc. Drugs Ther.* **2025**, *39*, 1489–1506. [CrossRef]
167. Zhang, Q.; Lenardo, M.J.; Baltimore, D. 30 Years of NF-κB: A blossoming of relevance to human pathobiology. *Cell* **2017**, *168*, 37–57. [CrossRef]
168. Gelain, D.P.; Ojo, O.R.; Dorcas, A.O.; Ajeigbe, A.S.; Moreira, J.C.F. The modulation of RAGE by natural products and traditional medicines: Opening promising perspectives for inflammatory diseases. *J. Ethnopharmacol.* **2026**, *372*, 122144. [CrossRef]
169. Rojas, A.; Lindner, C.; Schneider, I.; Gonzalez, I.; Uribarri, J. The RAGE Axis: A relevant inflammatory hub in human diseases. *Biomolecules* **2024**, *14*, 412. [CrossRef]
170. Ustkoyuncu, P.S.; Kocer, D. Soluble receptor for advanced glycation end product (sRAGE) levels in adolescents with obesity, insulin resistance and metabolic syndrome: A case-control study and the review of the literature. *BMC Endocr. Disord.* **2025**, *25*, 209. [CrossRef]
171. Aradillas-García, C.; Vega-Cárdenas, M.; Vidal-Batres, M.; Portales-Pérez, D.P.; Gomez-Ojeda, A.; Luevano-Contreras, C. Soluble receptor of advanced glycation end products and cardiometabolic markers in children. *Cureus* **2025**, *17*, e81680. [CrossRef]
172. Dupont, J.; Scaramuzzi, R.J. Insulin signalling and glucose transport in the ovary and ovarian function during the ovarian cycle. *Biochem. J.* **2016**, *473*, 1483–1501. [CrossRef]

173. Choi, E.; Bai, X.C. The activation mechanism of the insulin receptor: A structural perspective. *Annu. Rev. Biochem.* **2023**, *92*, 247–272. [CrossRef]
174. Choi, E.; Duan, C.; Bai, X.C. Regulation and function of insulin and insulin-like growth factor receptor signalling. *Nat. Rev. Mol. Cell Biol.* **2025**, *26*, 558–580. [CrossRef]
175. Martínez, B.A.; Ayala, G.; Pedroza-Saavedra, A.; González-Sánchez, H.M.; Chihu Amparan, L. Phosphorylation codes in IRS-1 and IRS-2 are associated with the activation/inhibition of insulin canonical signaling pathways. *Curr. Issues Mol. Biol.* **2024**, *46*, 634–649. [CrossRef]
176. Tokarz, V.L.; MacDonald, P.E.; Klip, A. The cell biology of systemic insulin function. *J. Cell Biol.* **2018**, *217*, 2273–2289. [CrossRef]
177. Petersen, M.C.; Shulman, G.I. Mechanisms of insulin action and insulin resistance. *Physiol. Rev.* **2018**, *98*, 2133–2223. [CrossRef]
178. Zhang, Y.-X.; Ou, M.-Y.; Yang, Z.-H.; Sun, Y.; Li, Q.-F.; Zhou, S.-B. Adipose tissue aging is regulated by an altered immune system. *Front. Immunol.* **2023**, *14*, 1125395. [CrossRef]
179. Copps, K.D.; White, M.F. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia* **2012**, *55*, 2565–2582. [CrossRef]
180. Woo, J.R.; Bae, S.H.; Wales, T.E.; Engen, J.R.; Lee, J.; Jang, H.; Park, S. The serine phosphorylations in the IRS-1 PIR domain abrogate IRS-1 and IR interaction. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2401716121. [CrossRef]
181. Draznin, B. Molecular mechanisms of insulin resistance. In *Insulin Resistance: Childhood Precursors of Adult Disease*; Zeitler, P.S., Nadeau, K.J., Eds.; Springer International Publishing: Cham, Switzerland, 2020; pp. 55–66. [CrossRef]
182. Unoki, H.; Bujo, H.; Yamagishi, S.; Takeuchi, M.; Imaizumi, T.; Saito, Y. Advanced glycation end products attenuate cellular insulin sensitivity by increasing the generation of intracellular reactive oxygen species in adipocytes. *Diabetes Res. Clin. Pract.* **2007**, *76*, 236–244. [CrossRef]
183. Herman, R.; Kravos, N.A.; Jensterle, M.; Janež, A.; Dolžan, V. Metformin and insulin resistance: A review of the underlying mechanisms behind changes in GLUT4-mediated glucose transport. *Int. J. Mol. Sci.* **2022**, *23*, 1264. [CrossRef]
184. Herzog, M.J.; Müller, P.; Lechner, K.; Stiebler, M.; Arndt, P.; Kunz, M.; Ahrens, D.; Schmeißer, A.; Schreiber, S.; Braun-Dullaeus, R.C. Arterial stiffness and vascular aging: Mechanisms, prevention, and therapy. *Sig. Transduct. Target. Ther.* **2025**, *10*, 282. [CrossRef]
185. Zieman, S.J.; Melenovsky, V.; Clattenburg, L.; Corretti, M.; Capriotti, A.; Gerstenblith, G.; Kass, D.A. Advanced glycation endproduct crosslink Breaker (Alagebrium) improves endothelial function in patients with isolated systolic hypertension. *J. Hypertens.* **2007**, *25*, 577–583. [CrossRef]
186. Sud, N. Molecular regulators of diabetic endothelial dysfunction. *J. Diabetes Mellit.* **2026**, *16*, 82–95. [CrossRef]
187. Ajoolabady, A.; Pratico, D.; Ren, J. Endothelial dysfunction: Mechanisms and contribution to diseases. *Acta Pharmacol. Sin.* **2024**, *45*, 2023–2031. [CrossRef]
188. Wang, M.; Li, Y.; Li, S.; Lv, J. Endothelial dysfunction and diabetic cardiomyopathy. *Front. Endocrinol.* **2022**, *13*, 851941. [CrossRef]
189. Vianello, E.; Beltrami, A.P.; Aleksova, A.; Janjusevic, M.; Fluca, A.L.; Corsi Romanelli, M.M.; La Sala, L.; Dozio, E. Advanced glycation end products (AGEs)–receptor for advanced glycation end products (RAGE): An inflammatory pathway linking obesity to cardiovascular disease. *Int. J. Mol. Sci.* **2025**, *26*, 3707. [CrossRef]
190. Medyńska, A.; Noczyńska, A.; Zwolińska, D. Are advanced glycation end products and skin autofluorescence associated with e-selectin and pulse wave velocity as markers of atherosclerosis risk in children with obesity? *Int. J. Mol. Sci.* **2025**, *26*, 9966. [CrossRef]
191. Gaens, K.H.J.; Goossens, G.H.; Niessen, P.M.; van Greevenbroek, M.M.; van der Kallen, C.J.H.; Niessen, H.W.; Rensen, S.S.; Buurman, W.A.; Greve, J.W.M.; Blaak, E.E.; et al. Nε-(Carboxymethyl)lysine-receptor for advanced glycation end product axis is a key modulator of obesity-induced dysregulation of adipokine expression and insulin resistance. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 1199–1208. [CrossRef]
192. Ramasamy, R.; Shekhtman, A.; Schmidt, A.M. The RAGE/DIAPH1 axis and cardiometabolic disease: From nascent discoveries to therapeutic potential. *Arterioscler. Thromb. Vasc. Biol.* **2024**, *44*, 1497–1501. [CrossRef]
193. Gutowska, K.; Czajkowski, K.; Kuryłowicz, A. Receptor for advanced glycation end products (RAGE) in adipose tissue metabolism. *Int. J. Mol. Sci.* **2023**, *24*, 10982. [CrossRef]
194. Izgilov, R.; Naftaly, A.; Benayahu, D. Effects of advanced glycation end products on adipocyte niche stiffness and cell signaling. *Int. J. Mol. Sci.* **2023**, *24*, 2261. [CrossRef]
195. Naftaly, A.; Kislev, N.; Izgilov, R.; Adler, R.; Silber, M.; Shalgi, R.; Benayahu, D. Nutrition alters the stiffness of adipose tissue and cell signaling. *Int. J. Mol. Sci.* **2022**, *23*, 15237. [CrossRef]
196. Strieder-Barboza, C.; Baker, N.A.; Flesher, C.G.; Karmakar, M.; Neeley, C.K.; Polsinelli, D.; Dimick, J.B.; Finks, J.F.; Ghaferi, A.A.; Varban, O.A.; et al. Advanced glycation end-products regulate extracellular matrix-adipocyte metabolic crosstalk in diabetes. *Sci. Rep.* **2019**, *9*, 19748. [CrossRef]

197. Rodrigues, T.; Matafome, P.; Sereno, J.; Almeida, J.; Castelhano, J.; Gamas, L.; Neves, C.; Gonçalves, S.; Carvalho, C.; Arslanagic, A.; et al. Methylglyoxal-induced glycation changes adipose tissue vascular architecture, flow and expansion, leading to insulin resistance. *Sci. Rep.* **2017**, *7*, 1698. [CrossRef]
198. Sun, K.; Li, X.; Scherer, P.E. Extracellular matrix (ECM) and fibrosis in adipose tissue: Overview and perspectives. *Compr. Physiol.* **2023**, *13*, 4387–4407. [CrossRef]
199. Galiniak, S.; Biesiadecki, M.; Podgórski, R.; Dąbek, N.; Gramatyka-Drążek, E.; Gaweł, E.; Ranke, M.B.; Flehmig, B.; Wabitsch, M.; Brandt, S.; et al. Serum leptin and its relation to body composition, puberty, and metabolism in severe obesity. *Endocr. Connect.* **2025**, *14*, e250194. [CrossRef]
200. Murdolo, G.; Nowotny, B.; Celi, F.; Donati, M.; Bini, V.; Papi, F.; Gornitzka, G.; Castellani, S.; Roden, M.; Falorni, A.; et al. Inflammatory adipokines, high molecular weight adiponectin, and insulin resistance: A population-based survey in prepubertal schoolchildren. *PLoS ONE* **2011**, *6*, e17264. [CrossRef]
201. Vassilopoulou, E.; Giannopoulou, E.; Theodosiou, A.; Karaglani, E.; Manios, Y.; Moschonis, G. Adipokines and C-reactive protein as indicators of MetS presence in obese greek children: The healthy growth study. *Toxicol. Rep.* **2021**, *8*, 1645–1650. [CrossRef]
202. Sohouli, M.H.; Sharifi-Zahabi, E.; Lari, A.; Fatahi, S.; Shidfar, F. The impact of low advanced glycation end products diet on obesity and related hormones: A systematic review and meta-analysis. *Sci. Rep.* **2020**, *10*, 22194. [CrossRef]
203. Bravo, C.; Mericq, V.; Pereira, A.; Corvalán, C.; Tobar, H.E.; Miranda, J.P.; Santos, J.L. Association between plasma leptin/adiponectin ratio and insulin resistance indexes in prepubertal children. *Arch. Endocrinol. Metab.* **2024**, *68*, e220353. [CrossRef]
204. Chan, W.K.; Chuah, K.H.; Rajaram, R.B.; Lim, L.L.; Ratnasingam, J.; Vethakkan, S.R. Metabolic dysfunction-associated steatotic liver disease (MASLD): A state-of-the-art review. *J. Obes. Metab. Syndr.* **2023**, *32*, 197–213. [CrossRef]
205. Steinberg, G.R.; Valvano, C.M.; De Nardo, W.; Watt, M.J. Integrative metabolism in MASLD and MASH: Pathophysiology and emerging mechanisms. *J. Hepatol.* **2025**, *83*, 584–595. [CrossRef]
206. Bonet, J.; Weiss, R.; Galderisi, A.; Dalla Man, C.; Caprio, S.; Santoro, N. Adipose tissue insulin resistance in children and adolescents: Linking glucose and free fatty acid metabolism to markers of liver injury. *Am. J. Physiol. Endocrinol. Metab.* **2024**, *327*, E723–E728. [CrossRef]
207. Carli, F.; Della Pepa, G.; Sabatini, S.; Vidal Puig, A.; Gastaldelli, A. Lipid metabolism in MASLD and MASH: From mechanism to the clinic. *JHEP Rep.* **2024**, *6*, 101185. [CrossRef]
208. Accacha, S.; Barillas-Cerritos, J.; Srivastava, A.; Ross, F.; Drewes, W.; Gulkarov, S.; De Leon, J.; Reiss, A.B. From childhood obesity to metabolic dysfunction-associated steatotic liver disease (MASLD) and hyperlipidemia through oxidative stress in childhood. *Metabolites* **2025**, *15*, 287. [CrossRef]
209. Fernando, D.H.; Forbes, J.M.; Angus, P.W.; Herath, C.B. Progression and development of non-alcoholic fatty liver disease: The role of advanced glycation end products. *Int. J. Mol. Sci.* **2019**, *20*, 5037. [CrossRef]
210. Berdowska, I.; Matusiewicz, M.; Fecka, I. A Comprehensive review of metabolic dysfunction-associated steatotic liver disease: Its mechanistic development focusing on methylglyoxal and counterbalancing treatment strategies. *Int. J. Mol. Sci.* **2025**, *26*, 2394. [CrossRef]
211. Jahromi, M.K.; Tehrani, A.N.; Teymoori, F.; Daftari, G.; Ahmadirad, H.; Saber, N.; Salehi-Sahlabadi, A.; Farhadnejad, H.; Mirmiran, P. Dietary advanced glycation end products are associated with an increased risk of non-alcoholic fatty liver disease in iranian adults. *BMC Endocr. Disord.* **2023**, *23*, 111. [CrossRef]
212. Cao, W.; Feng, C.; Ye, J.; Zhou, J.; Wang, L.; Lian, Y. Longitudinal assessment of liver stiffness and risk factors for advanced fibrosis in adolescents with metabolic dysfunction-associated steatotic liver disease: A retrospective observational study. *Front. Med.* **2025**, *12*, 1657933. [CrossRef]
213. Machado, E.A.; Themistocles, B.L.C.; Teixeira, J.M.R.; Jannuzzi, F.M.G.; Tomaz, G.; Oliveira, C.; Madeira, I.R.; Terra, C.; Souza, M.D.G.C.; Monteiro, A.; et al. Metabolic dysfunction-associated steatotic liver disease, biomarkers, and cardiovascular risk factors in children with excess weight. *J. Pediatr.* **2026**, *102*, 101534. [CrossRef]
214. Litwinowicz, K.; Waszczuk, E.; Gamian, A. Advanced glycation end-products in common non-infectious liver diseases: Systematic review and meta-analysis. *Nutrients* **2021**, *13*, 3370. [CrossRef]
215. D'Adamo, E.; Giannini, C.; Chiavaroli, V.; de Giorgis, T.; Verrotti, A.; Chiarelli, F.; Mohn, A. What is the significance of soluble and endogenous secretory receptor for advanced glycation end products in liver steatosis in obese prepubertal children? *Antioxid. Redox Signal.* **2011**, *14*, 1167–1172. [CrossRef]
216. Vega-Cárdenas, M.; Vargas-Morales, J.M.; Portales-Pérez, D.P.; Gómez-Ojeda, A.; Luevano-Contreras, C.; Aradillas-García, C. Soluble receptor for advanced glycation end-products (sRAGE) in childhood obesity: Association with gene expression of RAGE and cardiometabolic markers. *Nutr. Hosp.* **2023**, *40*, 960–966. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.