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Glycation of Animal Proteins Via Maillard Reaction and Their Bioactivity

Blanca Areli Mondaca-Navarro, Roberto Rodríguez Ramírez, Alma Guadalupe Villa Lerma, Luz Angelica Ávila Villa and Gabriel Davidov Pardo

Abstract

Nowadays there has been an increase in the need to incorporate foods in our diets that have optimal and palatable organoleptic characteristics as well as complex interaction in human biological processes that provide beneficial properties to human health. Animal foods and their by-products are an important source of macro- and micronutrients and also a great protein source; nevertheless the consumption of these products has been decreasing since they have been associated with the generation of chronic degenerative diseases; therefore the food industry has sought to innovate toward the generation of healthier foods. This chapter presents an overview of the glycation of proteins of animal origin via the Maillard reaction emphasizing on their posttranslational modifications and their possible uses in food, based on their bioactivity.

Keywords: glycation, Maillard reaction, bioactivity

1. Introduction

Nutritional and functional characteristics of proteins have been a subject of research for many years since they own catalytic, regulatory, and structural functions which are fundamental for several biological processes occurring in living beings. These macromolecules are formed by a combination of α -amino acids that are widely distributed in nature both from plant (legumes, cereal grains, nuts, fruits, and vegetables) and animal origin (dairy, meat, seafood, eggs) [1]. Each protein structure has a unique chain of amino acids linked together by a peptide bond providing bioactivities. The nutritional quality of a protein depends on its amino acid content and the physiological use of specific amino acids after digestion and absorption.

On the other hand, proteins give functional (structural-physicochemical) and bioactive (nutritional-health) properties to food products. These properties modify certain characteristics of foods that are industrially processed or used in households. Proteins modify the sensory properties as well as rheological behavior, stability, and nutritional value of such foods [2–4].

Previous research has questioned the safety of proteins that have been structurally modified to improve their functionality and bioactivity based on the dynamics of their environment [5]. In some case these modifications have resulted in the presence of genetic mutations, variation in the structure of the protein, as well as the generation of posttranslational modifications [6].

The importance of proteins in the health of humans is an opportunity for the development of new protein ingredients toward the improvement of separation processes and the exploitation of proteins obtained from different by-products considered as waste. During these processes, it is important to consider the functional properties of proteins in foods as well as their transformation during food processing and the metabolic behavior on the digestibility and bioavailability during gastrointestinal digestion [1].

Maillard reaction is one of the most common and important phenomena that takes place during the thermal processing both at an industrial and household levels or even during the storage of foods with high contents of reducing sugars and proteins [7]. Considering the fact that Maillard reaction occurs in several foods of common consumption and that it is generated spontaneously in foods under heat treatments, it is important to determine its safety and influence on the nutritional value of food products. Despite the ability of the Maillard reaction to affect color, taste, and texture of most foods, the compounds generated at different stages of this reaction can exert effects on the human body. In the past, Maillard reaction was mostly investigated for its negative effects, such as the loss of the nutritional value of the food. This is mainly attributed to inactivation or destruction of amino acids, decrease in the digestibility of nitrogen, and impaired absorption of brown compounds (melanoidins) in the intestine [8].

On the basis of this context, it is intended to show that, during the modification of proteins via Maillard reaction, the compounds that are formed do not have adverse effects, but actually have positive effects related to the bioactivity that they offer. Due to this reason in recent years investigations have been focused on the biological functionality of glycated protein resulting from the Maillard reaction from the point of view of the development of new foods or food additives.

2. Posttranslational modifications of proteins

Posttranslational modifications in proteins are defined as “covalent processing events that change the properties of a protein by proteolytic cleavage or by adding a modifying group to one or more amino acids” [9]. Knowing and analyzing these modifications of food proteins represents a challenge to understand their technological and biological function.

It is possible to find posttranslational modifications in animal proteins due to the action of different physical, enzymatic, and chemical treatments (acetylation, deamination, nitration, methylation, lipidation, carboxylation, formation of disulfide bonds, hydroxylation, sulfation, amidation, and glycosylation) [10–12]. A wide variety of posttranslational modifications have been characterized; some of them are formed mostly in intracellular proteins such as the phosphorylation mechanism, and conversely there are some other processes such as glycosylation, nonenzymatic glycation, formation of disulfide bonds, and carboxylation, which are formed in extracellular proteins [13].

Depending on the reaction mechanisms applied to them, protein modifications originate a wide range of characteristics (reaction, location, transformation) that could be studied through the science and technology of food products of animal origin. However, there is a limitation when using chemicals for the formation of

posttranslational modifications in proteins, since these could induce the production of toxic compounds resulting in the development of unfit food for human consumption [4, 13–15].

3. Maillard reaction

Maillard reaction is one of the most common, spontaneous, and important actions that are formed in the processing and storage of food. This set of chemical reactions give rise to the formation of brown pigments, odors, and flavors, as well as to alterations in the functionality, nutritional value, and shelf life of protein-rich foods. This reaction is also known as a nonenzymatic process that arises from the heat-catalyzed covalent condensation of a carbonyl-containing compound and a deprotonated amino group [7, 16]. This reaction was first discovered by Louis Camille Maillard in 1912, who established that this reaction alters the nutrients in food during cooking [17]. The first findings obtained from the Maillard reaction are briefly described below [18].

- Maillard reaction is universal, regardless of the nature of the amino group or the aldehyde/ketone group corresponding to reducing sugar.
- The reaction applies to nucleic acids, amino acids, peptides, and proteins.
- The aldehyde or the ketone group of sugar is essential for the reaction to take place.
- High temperatures are not essential. The reaction can be slowly carried out at 34°C and even at 15°C, as long as the mixture has been previously heated.
- Oxygen does not interfere with the reaction.
- During the reaction, the early products undergo extensive dehydration.
- In Maillard reaction there is a release of carbon dioxide, which comes from the amino acid.

3.1 Maillard reaction formation

Recently in 2017, Taghavi et al. [19] described Maillard reaction, as a series of complex reactions. Despite the advances in science and research related to this subject, Maillard reaction mechanism is not fully known, due to the reactivity and complexity of it. According to scientific literature, the most accepted route used as a reference to understand Maillard reaction is the one proposed by Hodge [20] which divided the process into three stages with seven different reactions (**Figure 1**):

1. Initial stage

A. Condensation: Schiff base formation

B. Amadori rearrangement

2. Intermediate stage

A. Dehydration of sugars

B. Fragmentation of sugars

C. Degradation of amino acids

3. Final stage

A. Polymerization and aldol condensation

B. Formation of heterocyclic nitrogen compounds and colored products

3.2 Description of Maillard reaction stages

Initial stage: Condensation (A) and rearrangement of Amadori or Heyns (B). At this stage the reaction consists of a simple condensation between a carbonyl group of a reducing sugar and a free amino group of an amino acid, protein, nucleic acid, or a low molecular weight amine, producing an N-substituted glycosylamine also called Schiff base. This step is considered a reversible reaction since in a strong acidic medium it can be protonated into the carbonyl of the reducing sugar and the free amino group from the amino acid. Schiff base is cyclized to form an N-substituted glycosylamine; an aldosome or ketosome can be formed depending on the type of reducing sugar that took part in the reaction, an aldose or a ketose, respectively. The molecule then forms an N-substituted-aldosome, and through the Amadori rearrangement, a 1-amine-1-deoxy-2-ketose is formed. However, when the molecule is an N-substituted-ketosome, a 2-amine-2-deoxy-2-aldose molecule is formed by means of the Heyns rearrangement [4].

The formation of Schiff bases and of the Amadori/Heyns rearrangements are the Maillard reaction stages where more research has been focused on; thus their structures have been precisely determined, as well as the properties of the first products

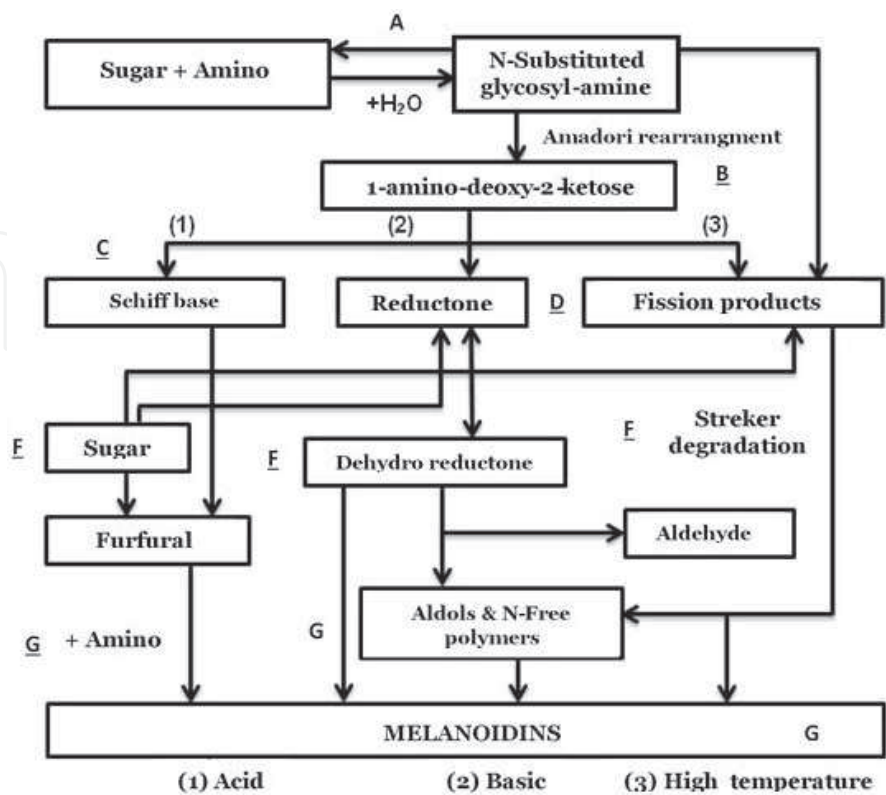


Figure 1. Maillard reaction depiction adapted from reference [20].

involved in this stage [21]. Amadori and Heyns products decompose depending on the pH and the temperature of the medium, resulting in the formation of different intermediate compounds. Specifically, the conditions or physical variables involved in the reaction are temperature and heating time, pH, water activity (A_w), as well as the type and availability of the reactants (amino acid and reducing sugar) [22], which directly affects the formation of glycoconjugates that are not naturally found in foods [23].

The intermediate stage includes dehydration of sugars (C), sugar fragmentation (D), and Strecker degradation (E) where a 1,2-enolization is formed at low pH, giving rise to the formation of dicarbonyl (precursors of brown compounds) and finally furfural or hydroxymethylfurfural (HMF). On the other hand, at basic pH 2,3-enolization is formed, and the final compounds are reductones, which can be dehydrated to form dehydro-reductones, forming polymers when reacting with amino groups [24]. Amadori compounds can be split into different products of low molecular weight such as glyceraldehyde, pyruvaldehyde, acetol, acetoin, and diacetyl [25]. All of them having a characteristic odor and high reactivity and being unsaturated substances, they follow various chemical routes depending on the pH, temperature, and A_w conditions [26].

Final stage: Hodge [27] described this stage as a sequence of reactions such as aldol condensation and polymerization (F) and formation of heterocyclic nitrogen compounds and colored products (G). These joint reactions show that amino compounds are effective catalysts for aldol condensation and polymerization, as well as oxidation and other spontaneous reactions, to produce a series of chemical compounds that are known as advanced glycation end products (AGEs). On the other hand, formation of nonvolatile colored and high molecular weight nitrogen compounds called melanoidins [28–30] is also carried out during the final stage. The structure of melanoidins is primarily made of aldehyde groups due to the degradation of sugars formed in the intermediate stage of Maillard reaction which are polymerized and bound to amino groups [31]. It is complicated to explain the progress of Maillard reaction in foods, due to the presence of different reactive groups mixed together (reducing amino acids and sugars) and to the dynamic conditions of food matrices that favor the formation of polymers. All this contributes to the difficulty of fully characterizing the later stages of the reaction due to their complicated chemical perspective [32].

4. Protein glycation via Maillard reaction

One of the technologies for the formation of posttranslational modifications in food proteins is nonenzymatic glycation, also known as glycation via Maillard reaction or simply glycation. This process is known as the chemical interaction between a reducing sugar with an amino group of peptides and proteins forming a covalent bond and leading to the formation of glycated proteins or glycoconjugates. Compared to other chemical methods used for protein modification, Maillard reaction glycation does not imply the use of reagents that may affect human health, which results in the creation of proteins with new technological and biological interest [2, 14].

In the early twentieth century, there was a very limited knowledge about glycoproteins, these were described as “Compounds of the protein molecule mixed with a substance containing a carbohydrate group that is not a nucleic acid” claiming that glycoproteins were those proteins containing a glycosyl bond [33]. However, years later the term glycation was defined as “All reactions that bind a sugar to a protein or a peptide, whether catalyzed or not by an enzyme” [19]; otherwise Lis and Sharon

in 1993 [34] theoretically differentiated the term enzymatic glycosylation and nonenzymatic glycation of sugar-bound proteins.

Regarding the process of modification of proteins by means of enzymatic glycosylation, there is the intervention of glycosyltransferases and nucleotides as sugar donors which form glycoproteins [35]. In the development of glycosylated proteins, nonreducing sugars cannot be used since the interaction of their aldehyde or ketone groups is not possible [34, 36, 37]. Glycoconjugates have the uniqueness of possessing bioactivity and functionalities that act to improve the native protein. Research have been focusing on the toxic effect of Maillard reaction on proteins due to the formation of the different intermediary compounds, which in consequence form amino acid derivatives (AGEs) [38–41]. It is convenient for the formation of glycoconjugates to avoid the advanced stages of the reaction, in the same way it is important to understand the complexity of the Maillard reaction for the development of new food products with added value [2, 4].

5. Bioactivity in glycoproteins of animal origin obtained via Maillard reaction

In recent years, and due to current global trends, consumers have demonstrated a potential interest and awareness about the importance of correlating health with food and achieving the combination of nutritional value, bioactivity, and improved organoleptic properties to those already existing in natural and processed foods, as well as their interaction with biological systems, which help to prevent pathological conditions. These changes in the food standards of consumers generate a field of opportunity for the formulation of new foods, so the search for bioactive properties in proteins of animal origin has been a challenge for food scientists and technologists, where research has been focused on the glycation of proteins with interest to the food industry.

5.1 Antioxidant capacity

The concept of antioxidant is defined as “any substance that, in presence of an oxidizable substrate, significantly delays or inhibits the oxidation of that substrate” [42–44]. The concept of antioxidant was first originated from chemistry and then adapted to biology, medicine, epidemiology, and nutrition. It describes the redox ability of molecules in food and biological systems and their interaction with free radicals [45].

In recent decades there has been a growing interest in the study of the antioxidant activity of food and diets of humans. The deficit of antioxidants in the body causes negative biological effects that lead to the presence of free radicals and as a consequence to the development and progress of chronic degenerative diseases related to oxidative stress. Based on scientific literature, oxidative stress is characterized by an increase in free radicals of reactive oxygen and nitrogen species, as well as by a decrease in the body’s antioxidant defenses [46]. This effect is associated with bad eating habits, generating an imbalance between antioxidant systems and the production of oxidizing agents that lead to the generation of several chronic degenerative pathologies that attain human health [47, 48].

Antioxidants in conjunction with the daily diet have great relevance since they have a determining role in human health, which help to reduce oxidative stress. In dietary matrices antioxidants are useful in delaying lipid peroxidation and therefore help in taste, texture, and in some cases color [49]. In the human body endogenous antioxidants help to protect, prevent, or delay cell death, tissue and organs lesions, as well as oxidative damage by reactive oxygen and nitrogen species [50].

Some of these studies are focused on giving an added value to the by-products of food industry, focusing on the analysis of antioxidant activity; an example of this is the use of pork blood as a protein source, which is an abundant by-product in the slaughter process. Porcine blood plasma contains a variety of bioactive compounds and high-quality proteins; for this reason there are several studies on the antioxidant capacity of glycoconjugates formed from proteins of pork serum with glucose, fructose, and galactose, which were glycated via Maillard reaction at 100°C, reporting that glycoconjugates formed with glucose showed the lowest antioxidant capacity, while the glycoconjugates formed with galactose were the ones showing the highest antioxidant capacity [51].

Following with the investigation on pork blood plasma proteins, different researchers determined the antioxidant capacity in glycoconjugates formed with 2% blood plasma and 2% glucose adjusted to several pH (8, 9, 10, 11, and 12) and 100°C at different heating times (0–8 h) reporting that glycoconjugates formed at higher pH (pH 12) showed a higher antioxidant activity than the ones obtained at lower pH levels, showing that pH was a factor in determining the antioxidant activity of glycoconjugates [52]. Years later, researchers reported that the glycation of hydrolyzed porcine serum plasma with glucose, fructose, or galactose heated at 95°C, for up to 6 h, yielded an antioxidant capacity of 45% [3].

A vast amount of research have been carried out on the milk protein glycation and its antioxidant action analyzed by different methodologies from which ABTS and DPPH techniques stand out. Most of the research have focused on dairy proteins such as lactoglobulins, caseins, and whey proteins. As an example glycoconjugates formed with hydrolyzed β -lactoglobulin with glucose heated to 90°C for a maximum of 18 h showed an antioxidant activity greater than 50% [53].

In another research Stanic-Vucinic et al. [54] tested high-intensity ultrasound in order to promote glycation of β -lactoglobulins with glucose, galactose, lactose, fructose, ribose, and arabinose via Maillard reaction at pH 6.5. As a result, an increased activity of DPPH radical inhibition was reported, with the glycoconjugates being the ones that showed the highest antioxidant activity with 42%. Similarly, glycoconjugates with ribose and milk proteins such as α -lactalbumin or β -lactoglobulin, heated at 95°C, for up to 5 h exhibited an increase in their antioxidant activity [55].

Different researchers formed glycoconjugates using casein and glucose, at pH 12 and at a temperature of 102°C for 130 min. Glycoconjugates were ultrafiltered in order to form fractions of different molecular weights (50 kDa, 30 kDa, 10 kDa, 5 kDa, 1 kDa) and to analyze the antioxidant activity by the DPPH method. It was shown that glycoconjugates with higher molecular weights were the ones with the best in vitro radical scavenging activity [56]. Jing and Kitts [57] formed glycoconjugates with glucose, fructose, and ribose at 55°C, pH 7.0 for 28 days. A concentration range of 0.1–0.5 mg/ml of sugar and casein was used, indicating that only the casein-ribose system showed antioxidant capacity with the DPPH radical inhibition technique (3–7%). On the other hand glucose-casein and fructose-casein systems showed no antioxidant activity in the concentrations and treatments tested.

There are only a few works related to glycated proteins of marine origin and their relationship with antioxidant capacity. Decourcelle et al. [58] evaluated the formation of glycoconjugates at 50°C for 48 hours between a shrimp hydrolyzate with xylose or dextran, reporting that the antioxidant capacity of the shrimp hydrolyzate mixed with xylose was 13.5 to 16 times higher than the shrimp hydrolyzate without the mixed carbohydrate.

Different researchers affirm that glycation via Maillard reaction could cause structural changes in protein molecules, which could generate a wide range of compounds or Maillard reaction products (MRP), which would lead to the

formation of conjugates and that these could contribute to the generation or increase of antioxidant capacity [59].

5.2 Chelating capacity

Transition metals are a systemic and determining part for the proper functioning of the structural and functional components of the organism; these metals have the ability to donate and accept electrons. Although they are also limited by the fact that transition metals can lead to toxicity that occurs when one or more of these metals are increased in the body, moreover the presence of transition metals favor the formation of free radicals [60]. Chelating agents are compounds capable of binding to metal ions leading to the formation of chelates; this metal-ion complex can carry a positive, negative charge, or in turn no charge [61].

Chelating agents have a “ligand” which binds the atoms that form the chelate with either two covalent bonds or a covalent bond and a coordinate bond or two coordinated bonds when bidentate chelates are formed. In biological systems the metal ions Na^+ , Mg^{2+} , Cu^{2+} , Zn^{2+} , and especially transition metals such as Mn^{2+} , Fe^{2+} , and Co are involved in the formation of chelates [62]. Of the aforementioned transition metals, iron and copper, despite being essential micronutrients for optimal organism functioning, have the peculiarity of transferring and gaining electrons from oxygen molecules and forming reactive oxygen species (ROS), which can quickly catalyze the superoxide radical and could generate oxidative stress [60].

There is scientific evidence proving that the molecules formed through the Maillard reaction have the ability to chelate metal ions giving them the characteristic of transforming metal behavior into physiological functions. Irving and Williams [63] were possibly the first researchers to confirm the formation of complexes involving the Maillard reaction and certain transition metal ions and describe the strength bond of chelates formed with metal ions following the order of $\text{Mn}^{2+} < \text{Fe}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+}$. Years later they confirmed the formation of these chelates in an order of $\text{Mg}^{2+} > \text{Cu}^{2+} = \text{Ca}^{2+} > \text{Zn}^{2+}$ [64]. This last order differs from that found in 1953, so they conclude that there could be due to the presence of more than one type of ligand [63].

References from previous research provide us with relevant information on the ability to chelate transition metals through glycated proteins via Maillard reaction. Gu et al. [56] formed casein glycoconjugates with glucose affirming that the glycoconjugates with greater molecular weight have greater chelating potential of ion Fe^{+2} than those of low molecular weight. Different researchers reported the formation of glycoconjugates with β -lactoglobulin hydrolyzate obtaining 64 and 61% iron chelation, for the glycoconjugate of β -lactoglobulin-glucose and β -lactoglobulin hydrolyzate, respectively. From the obtained results, they concluded that the increase in iron chelating activity was mainly related to the glucose caramelization reaction and not to the glycation process [53].

During the formation of β -lactoglobulin glycoconjugates with glucose, galactose, lactose, fructose, ribose, and arabinose via Maillard reaction, at pH 6.5, it was demonstrated that both native β -lactoglobulin and treated β -lactoglobulin possess chelating activity, in the same way the glycation of β -lactoglobulin in the presence of all sugars resulted in a significant increase in the ability of chelation of iron ($p < 0.05$), being the β -lactoglobulin-ribose system the one with the most prominent effect [54]. In the case of the model system consisting of glucose-asparagine-chitosan with different molecular weights of chitosan and a thermal treatment of 180°C for 30 min, a 60% ferrous ion chelation was obtained in all samples analyzed [65].

You et al. [66] tested the formation of glycoconjugates of silver carp hydrolyzate with glucose (w/w = 2:1, 1:1, 1:2, 1:4) at pH 7.5 and at 50 and 60°C for 24 h reporting

that the glycoconjugate with a protein-carbohydrate ratio of 2:1 showed a greater chelating effect (90%) than other ratios tested.

The effect of metal chelation has been related to the hydroxyl and pyroline groups, and also it has been attributed to the steric effects and the multiple interactions of the proteins in the Maillard reaction. However, other authors attribute the ability to chelate Fe^{2+} ions to the higher molecular weight MRPs such as melanoidins and hydroxyl groups formed in the final stage of the Maillard reaction [67, 68].

5.3 Prebiotic and antimicrobial effect

Significant amounts of compounds formed via Maillard reaction are consumed in the human diet, which interact in the body through the digestive system and the intestinal microflora itself; this microflora plays a crucial role for its proper functioning; therefore, maintaining a balance between beneficial and harmful microorganisms is of vital importance. Prebiotics are nondigestible or low digestible food ingredients that benefit the host organism selectively by stimulating the growth or activity of probiotic bacteria in the colon [69].

Different studies have found that products derived from the Maillard reaction can act as prebiotics by activating intestinal microflora, generating a positive effect on *Lactobacilli* and *Bifidobacteria*. This was observed in a study where intestinal bacteria were able to use the products formed in the different stages of the Maillard reaction, as a substrate, and transform them into energy [70]. Corzo-Martínez et al. [71] glycated dairy proteins specifically β -lactoglobulin and sodium caseinate with galactose and lactose evaluating the effect of hydrolyzed glycoconjugates on the growth of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* under simulated in vitro gastrointestinal digestion and reported that glycoconjugates formed with caseinate were rapidly fermented by some strains, promoting a greater growth rate than β -lactoglobulin complexes. Therefore, from the results obtained, they could conclude that the conjugation of both dairy proteins with galactose and lactose through the Maillard reaction could be an efficient method to obtain new food ingredients with a potential prebiotic character.

It has also been shown that the compounds formed by the Maillard reaction may be a solution for the infection of pathogenic bacteria such as *Helicobacter pylori*, *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*. The bacteriostatic power of these compounds was studied demonstrating that the action against the bacteria depended on the concentration of reactants, the pH, the temperature, as well as the molecular weight of the glycoconjugates. An example of this is a study performed for the inhibition of *Helicobacter pylori*, where casein-lactose glycoconjugates were given to infected subjects during 8 weeks, obtaining favorable results against *H. pylori* [72]. Similarly, a significant inhibition was observed in mice which received a 10-week treatment with the glycoconjugates [73].

Bacterial adhesion assays have been performed to assess if β -lactoglobulin protein glycated with chitin oligosaccharides (60°C for 6 and 12 h) can be recognized by bacterial adhesins from *Escherichia coli* K88 and *Salmonella choleraesuis*. Biorecognition analyses showed that glycoconjugates were in fact recognized by the adhesins of *E. coli* K88 and *S. choleraesuis*; both adhesins showed an effect similar to mucins (control) which are natural ligands for these microorganisms; that effect was not shown in the native or non-glycated protein concluding that the glycoconjugates formed could be used to investigate the interaction of protein-carbohydrate in biological systems as well as to look for alternatives to bacterial infections [74].

Research on this subject indicate that the antimicrobial activity of the compounds formed by Maillard reaction may be related to their anionic charges and

their ability to chelate transition metals such as Fe^{2+} , Zn^{2+} , and Cu^{2+} , which are essential for the proper functioning, survival, and growth of the pathogenic organism [75]. Chung et al. [76] reported the antimicrobial capacity of Maillard reaction products obtained by the condensation of chitosan and glucosamine, against *E. coli* and *Staphylococcus aureus*.

Cell membrane has been analyzed in different bacterial strains of both Gram-positive (*Staphylococcus aureus* and *Bacillus cereus*) and Gram-negative (*Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*) in order to correlate the antimicrobial effect by iron chelation, finding that at low concentrations of melanoidins, a bacteriostatic activity mediated by chelation of iron contained in the culture medium is exerted. Regarding bacterial strains capable of producing siderophores for iron acquisition, the compounds generated from the Maillard reaction chelate the Fe^{3+} siderophore, which could decrease the pathogenicity of the bacteria [67]. It suggests that foods which contain molecules formed by the Maillard reaction may be a beneficial alternative to the intestinal flora and digestive system.

5.4 Antihypertensive capacity

Angiotensin I enzyme (ACE) is also known as peptidyl dipeptidase A or Braquina II; since it eliminates carboxy-terminal dipeptides from a wide variety of peptide substrates [77], it is considered as the mechanism of action of food-derived antihypertensive activity. ACE is essential in the renin-angiotensin system, since it regulates blood pressure and water-salt balance in the human body. The activity of the ACE consists of the conversion of angiotensin I into angiotensin II, which is an effective vasoconstrictor, while degrading bradykinin, which is considered a potent vasodilator [78]. The importance of these mechanisms relies on the blocking of the renin-angiotensin-aldosterone system due to ACE inhibition, which has led to consider ACE inhibitors as first-line therapy against hypertension [79].

Synthetic ACE inhibitors own a mechanism of action consisting in occupying related and specific angiotensin I binding sites. There are commercial drugs such as captopril, enalapril, enalaprilat (active form of enalapril), and lisinopril, capable of inhibiting ACE and therefore decreasing blood pressure levels [80]. Although research has focused on natural origin peptides from different sources to inhibit ACE, it has been shown that some proteins modified via Maillard reaction are capable of presenting antihypertensive activity [81, 82] albeit studies on these kind of proteins is limited, because these research have been focused only on modified peptides [83].

The glycoconjugates formed by casein-xylose (110°C, 30 min) have shown an increase on ACE inhibitory activity when there was a prolonged reaction time of the Maillard reaction, under analyzed conditions [82]. Jiang et al. [84] reported a decrease in antihypertensive activity when analyzing a glycoconjugate formed of a tripeptide with ribose (98°C for a time range 0–8 h) found in the formed glycopeptide [82.] They also formulated glycoconjugates based on casein mixed with different carbohydrates (ribose, galactose, and lactose) showing a decreasing tendency of the ACE inhibitory activity and reporting that this tendency could be attributed to the consumption of casein peptides involved in polymerization during the different stages of the Maillard reaction; although they also confirm that some MRPs are involved in potentiating the ACE inhibitory activity [85]. This is similar to what was reported in a research performed in roasted coffee which demonstrated that melanoidins showed ACE inhibitory activity in vitro [86].

Jiang et al. [87] evaluated the effect of temperature and pH on the inhibitory activity of ACE, forming glycoconjugates with bovine casein and galactose peptides

in aqueous solution. Mixtures were heated at 70–120°C for 3 h, at pH 9.0, concluding that as the temperature increased, the ACE inhibitory activity of glycoconjugates gradually decreased.

The possible mechanism of action of ACE against PRM is unknown; however the inhibitory action may be related to chelation of transition metals or its antioxidant activity since ACE depends on metals such as Zn [88].

5.5 Cytotoxic effect

In previous years it was considered that compounds formed during the different stages of Maillard reaction were precursors of carcinogenic activity. This notion was due to the presence of acrylamide or heterocyclic amines that are formed by this reaction, which could have cytotoxic and antiproliferative properties. However, nowadays, there are some investigations that indicate that glycoconjugates obtained via Maillard reaction usually present inhibition of cancer cell proliferation; there it is important to study these compounds since they could bring certain health benefits.

The antimutagenic properties of the Maillard reaction have been widely investigated in in vitro model systems or in complex foods under controlled heat treatment conditions. This bioactive property has been attributed to the inhibition of the absorption of the mutagen or the inhibition of its activation [89]. An example of this has been the study of antiproliferative activity in model systems in 20 amino acids with glucose and fructose, in human colon cancer cells at concentrations of 0.35–1.5 mg/mL. The concentration that showed the highest antiproliferative activity in cancer cells was the fructose-methionine system (32.64%), while for tryptophan it was 15.01%, phenylalanine 30.73%, and tyrosine 21.52%. On the other hand, glycoconjugates derived from glucose mixed with the same amino acids also presented antiproliferative activity [88].

When mixtures of glucose with glycine have been studied, the results were different from those mentioned above since no antiproliferative activity was present [90]. However, when low and high molecular weight melanoidin fractions were isolated, low molecular weight fractions were found to be more reactive to genotoxicity and mutagenicity, although these compounds were considered not to be a health risk [91].

Some glycoproteins may have a non-cytotoxic action; this has been demonstrated through the use of carbohydrate protein model systems [92]. Jing and Kitts [57] tested sugars such as glucose, fructose, and ribose mixed with casein to form glycoproteins (55°C, pH 7, 28 days of incubation) and evaluated their toxicity against Caco-2 cells, concluding that there was no toxicity to the cell model using both low (0.5 mg/mL) and high (2.0 mg/mL) concentrations of analyzed glycoproteins. In agreement with these results, Wei et al. [93] performed an investigation with glycoconjugates formed by bovine albumin serum with galactose, ribose, and lactose showing a low toxicity in the inhibition of Caco-2 cells. Other glycoconjugates formed by ribose-casein peptide and lactose-casein peptides (95°C/5 h) have shown the same results, not presenting cytotoxicity in Caco-2 cells; however another system such as galactose-casein peptides showed a slight decrease in Caco-2 cells [85].

In general and regarding previous research, some of Maillard reaction products that have been synthesized and purified from different protein sources of animal origin can be considered to have an inhibition on the growth of human carcinoma cells in vitro [94].

6. Conclusions

The posttranslational modification of glycated proteins of animal origin has been shown to have or to potentiate specific bioactivity. Therefore, protein glycation of animal origin via Maillard reaction may represent an alternative for the use of by-products of the animal-based food industry. It could be possible to use glycoproteins as a food ingredient, or the incorporation of these bioactives into a technological process in the food industry could result in health benefits, as well as benefits to the environment.

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