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Review

Analysis and biological properties of amino acid derivates formed by Maillard reaction in foods

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Abstract

Maillard reaction products (MRPs), especially early stage MRPs and melanoidins, are currently gaining a lot of attention due to their reported health-promoting properties and their potential to be used as functional food ingredients. It is often not clear which specific biological function is assigned to which MRP, due to the large amount of MRPs formed during the reaction and difficulties in their purification and identification. This paper provides an overview of amino acid derivatives such as Amadori compounds, carboxymethyllysine, pyrraline, cross-linking products and melanoidins, which can be formed by Maillard reaction in foods, their biological properties and the analytical tools commonly employed for their determination.

Keywords: Maillard reaction products (MRPs); Biological functions; Analytical tools; Amino acid derivates; Melanoidins

Contents

1. Introduction

The phenomenon that foods turn progressively brown during thermal processing (e.g. baking, roasting and frying) or storage is the result of the well-known Maillard reaction [1]. This reaction, also called non-enzymatic browning or glycation, is of outstanding importance for the formation of colour, aroma and flavour precursors in foods. The majority of literature considers the Maillard reaction as a series of subsequent and parallel reactions, which can be divided into three stages: the early, advanced and final Maillard reaction steps. All these reactions can occur simultaneously, affected by each other as well as by reaction

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parameters [2,3]. The compounds involved in these reactions are carbonyl and amino compounds, which include reducing carbohydrates and the free amino groups of amino acids, peptides or proteins [4].

The Maillard reaction can cause both deterioration or enhancement of food quality [3,5–8]. In the past, many scientific works focused on the negative biological effects of the Maillard reaction. The formation of antinutritional and toxic Maillard reaction products (MRPs) has been reported frequently. In vitro studies revealed some harmful effects including mutagenic, carcinogenic [9,10] and cytotoxic effects [11]. Excessive glycation has also been stated to cause the destruction of essential amino acids, decreased digestibility, inactivation of enzymes, inhibition of regulatory molecule binding, cross-linking of the glycated extra-cellular matrix, decreased susceptibility to proteolysis, abnormalities of nucleic acid function, altered macromolecular recognition and endocytosis and increased immunogenicity [12].

The formation of beneficial compounds during the Maillard reaction has also been found and is currently gaining a lot of attention. MRPs containing antioxidant, antiallergenic, antimicrobial and cytotoxic properties are amongst others mostly detected [13–18]. Many studies focussed on the high antioxidant capacity of MRPs in model systems and foods such as beer [19], coffee [20] and bakery products [17]. In those studies it was shown that MRPs can contribute greatly to the shelf-life of heat-treated foods [21]. In vitro studies demonstrated that MRPs may offer substantial health-promoting activity as they can act as reducing agents [22], metal chelators [23] and radical scavengers [24]. It appears that especially low molecular weight MRPs exhibit antioxidant effects in the organism after they get absorbed by the small intestine [13,25,26].

Both consumers and regulatory organisations demand high quality, healthy and safe food (ingredients) while food scientists attempt to develop new processes to obtain these. In addition, there is a great interest in novel healthy food ingredients with a large number of works published in this area. Several papers indicate that the Maillard reaction can be a good means of producing functional food ingredients also since they can be obtained without the use of harmful chemicals and tedious purification procedures. The determination of MRPs with their beneficial or harmful properties is thus of key importance for the production of safe foods and for the development of novel functional food ingredients.

Most of the work focussing on the biological properties of MRPs demonstrate the formation of a large pool of compounds without knowing accurately which one is responsible for a particular biological activity. The analysis of known indicators, as described in this review, can help understand at what stage of the Maillard reaction the health-promoting compounds are produced. Those indicators may then be employed to control the industrial production of these health-promoting MRPs, which

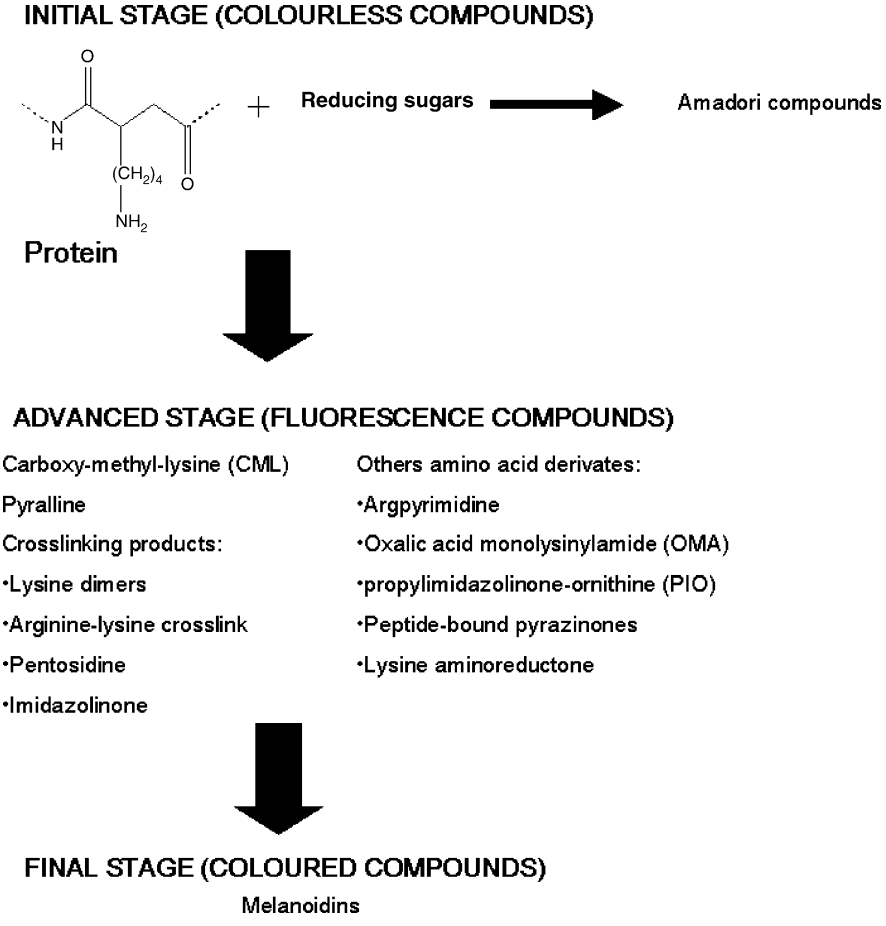

Fig. 1. General scheme of the MRPs formed during the Maillard reaction.

Table 1
Analytical tools for analysis of amino acid derivates formed by Maillard reaction in foods

Maillard reaction products (MRPs)	Analytical tool	Reference
Amadori compounds		
Direct analysis		
	Column chromatography	[35,39]
	HPLC differential refractometry detection	[29,40]
	HPLC involving derivatisation	[41,42]
	HPAEC coupled electrochimemical and/or DAD	[43,44]
	FAB–MS	[45]
	ESI coupled HPLC and EC	[46,47]
	EC coupled MS	[47]
	MALDI-TOF	[48]
	NMR	[48]
	LC–MS	[48]
	NBT	[50–52]
	ELISA	[53]
	Immunoblotting (lactosylated proteins)	[54–55]
Indirect analysis		
2-FM-AA	Ion-pair RP-HPLC	[63,65,67,69,74,76–79]
	CEC UV-detection	[64]
	HPLC–MS	[65,66]
Unreactive lysine	Colorimetric and fluorimetric methods	[81–83]
Advanced Maillard products		
General AGEs	FAST	[107,108]
	HPLC-DAD	[109]
CML	RP-HPLC	[115]
	RP-HPLC *o*-phthalaldehyde pre-column derivatisation	[110,111]
	GC–MS	[115]
	ELISA	[117]
	Immunoblotting	[117]
Pyrraline	Amino acid analysis with PAD	[121,123]
	RP-HPLC	[118,124–129]
Crosslinking products		
Lysine dimmers	LC–MS with ESI	[135]
Arginine–lysine	LC–MS with ESI	[135]
	Ion-exchange chromatography	[141]
	FAB–MS	[142]
Other amino acid derivates		
Argypirimidine	HPLC-coupled GC–MS	[145,146]
OMA	ELISA	[147–149]
PIO	RP-HPLC/LC–ESI–TOF–MS/NMR	[150]
Pyrazinones	HPLC with UV and fluorescence detection	[151]
Lysine aminoreductone	HPLC-DAD	[5,152]
Final stage MRP's		
General melanoidins	HPLC, NMR, MS, UV, IR spectrometry	[157,167]
	MALDI-TOF mass spectrometry	[26,168,169]
Pronyl-L-lysine	GC–MS chemical ionisation	[15,16]

are regarded as promising new functional food ingredients. Analysis of MRPs is also required for a better understanding of their structure and biological function. Furthermore, MRPs are excellent chemical indicators for the degree of glycation of a food or ingredient. Table 1 shows the different analytical tools for analysis of MRPs. In this article, we attempt to provide an overview of the analytical approaches used to characterise and quantify MRPs. The analytical techniques will be discussed according to the compounds produced during the three Maillard reaction stages as given in Fig. 1.

2. Techniques for the analysis of MRPs

2.1. Early stage MRPs

The first stable reaction products, which are formed during the early stages of the Maillard reaction, are the so-called Amadori compounds [2,27,28]. These are the result of the condensation between an amino group of amino acids, peptides or proteins and the carbonyl group of a reducing carbohydrate followed by a subsequent rearrangement. In the common case of

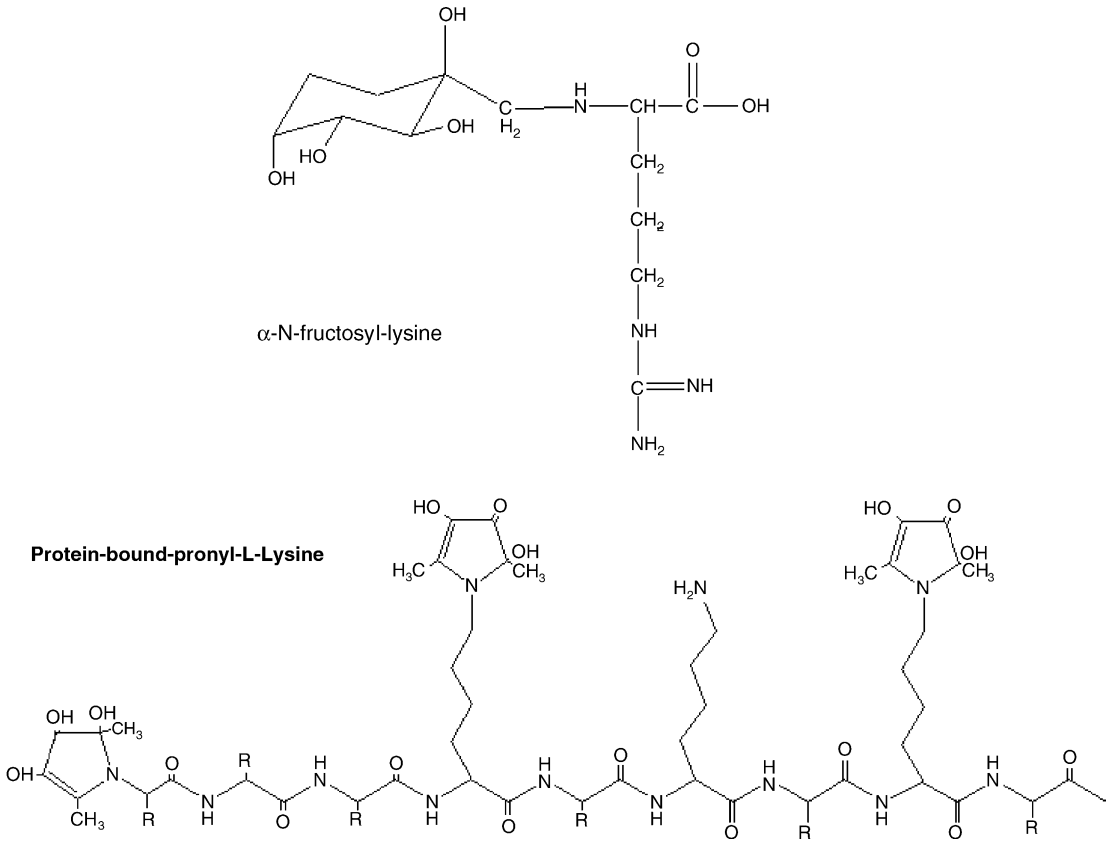

Fig. 2. MRPs with known structure and health-promoting properties.

foods containing proteins and glucose, the well-known Amadori compound ε-fructosyl-lysine (Fig. 2) is formed [29]. In heated milk samples, where the major carbohydrate is lactose, the formed Amadori compound is lactulosyl-lysine. This compound is often determined as processing indicator.

Amadori compounds are precursors of numerous products important in the formation of characteristic flavours, aromas and brown polymers. They are also responsible for the loss of nutritional value of amino acids and proteins because their biological availability is reduced in the formation of Amadori compounds. However, the antioxidant role of the Amadori rearrangement product, fructosyl arginine, in a concentrated aged garlic extract has been described [30,31]. Since they are formed before occurrence of sensory changes, their determination provide a very sensitive indicator for early detection of quality changes caused by Maillard reactions [29].

The quantification of Amadori compounds in foods or physiological samples is difficult since they are converted during the acid hydrolysis of the proteins, thus making it impossible to detect them with routine amino acid analysis [32–34]. Several direct and indirect methods, as described below, have been employed.

2.1.1. Direct analysis of Amadori compounds

Measurement of Amadori compounds was performed by column chromatography employing an automatic amino analyser and a post-column reaction with ninhydrine [35–39]. Alternatively, these compounds may be analysed by high-performance liquid chromatography (HPLC) with differential refractometry detection. However, the sensitivity of this method does not allow the detection of low Amadori compound concentrations [29,40]. To improve sensitivity, HPLC methods involving derivatisation have also been proposed [34,41,42]. A recent method using high-performance anion-exchange chromatography coupled with an electrochemical (ECD) and/or diode array detector (DAD) is regarded a powerful technique for the detection and monitoring of known Amadori compounds. Although gas chromatography (GC) shows better separation efficiency as compared to HPLC, the Amadori compounds need to be converted into volatile compounds prior to analysis. The necessity to derivatize and the ability of GC to separate tautomeric forms of Amadori compounds are the major drawbacks of this method [43,44].

The detection of Amadori compounds can also be achieved by fast atom bombardment (FAB) tandem mass spectrometry (MS) [45]. The particular advantage of this method is its simplicity as the samples are directly introduced into the ion source. However, the simultaneous analysis of several Amadori compounds is difficult with this method. FAB has been almost completely replaced by electrospray ionisation (ESI) since this technique offers the advantage of a very soft ionisation and easy coupling to on-line separation techniques like HPLC and capillary electrophoresis (CE). The last technique (CE) is complementary to HPLC, with the advantage of a higher resolving power for the

first dimension of the separation [46]. In addition, the consumption of solvents and chemicals is low. CE coupled to MS is an alternative and powerful analytical method and allows a rapid separation and identification [47].

Various analytical techniques have been developed for the analysis of lactulosyl-lysine in dairy products because of its usefulness as quality control indicator. Detection of lactulosyl-lysine has been conducted by spectroscopy techniques such as MALDI-TOF, electrospray and nuclear magnetic resonance (NMR) analysis. A selective liquid chromatography (LC)–MS procedure allowed the detection and quantification of lactulosyl-lysine after complete enzymatic hydrolysis in milk samples [48]. One of the main problems related to the direct quantification of lactulosyl-lysine and other Amadori compounds is the lack of a pure standard [35,49]. The synthetic strategies proposed so far are rather time-consuming and do not yield a consistent rate of pure Amadori compound.

A colorimetric method employed in foods for Amadori compounds direct detection is NBT [50], devised by Johnson et al. [51], is based on the reducing ability of fructosamines (glucose joined protein molecules) in alkaline solution, this procedure is fast, cheap and easily automated [52].

Recently, immunological approaches have been developed to directly detect lactosylated proteins without using an hydrolysis step. Both competitive enzyme-linked immunosorbent assay (ELISA) [53] and immunoblotting [54,55] methods using specific antibodies against lactosylated proteins were employed.

2.1.2. Indirect analysis of Amadori compounds

Peptide-bound Amadori compounds of lysine (fructosyl-lysine, lactulosyl-lysine or maltulosyl-lysine) are mainly quantified indirectly [56,57]. These indirect methods are either based on the quantification of reactive lysine [58] or involves an acid hydrolysis to give 2-furoylmethyl amino acids (2-FM-AA) [35,59–62]. The latter can be directly measured by ion-pair RP-HPLC [63] or cation-exchange chromatography (CEC) [64] both using UV-detection. HPLC–MS is a technique especially suitable for the identification of 2-FM-AA [65,66].

2-FM-AA are common indicators used to monitor the Maillard reaction during heat treatment [65,67–75] and storage [74,76–79] of foods (juices, dairy products, dehydrated foods, honey and tomato products). 2-Furoylmethyl-lysine, also called furosine is a well-known indicator used to express the extend of damage in processed foods or stored foods with a long shelf-life. Furosine is often determined by ion-pair RP-HPLC [8,63,65,67,69–74,76–79]. The main drawbacks of this procedure are the time of analysis and the fact that only part of Amadori compound (∼30%) is converted into 2-FM-AA [80].

The Amadori compounds can also be estimated indirectly by rapid colorimetric or fluorimetric methods. These methods are based on the analysis of unreactive lysine, which can be measured through the reaction of a dye reacting with the free NH_2 groups of lysine. Dyes such as *o*-phthalaldehyde [81], fluorescamine [82] and FDNB [83] are frequently employed. These methods have sometimes been criticized for their lack of specificity.

2.2. Advanced stage MRPs

Amadori compounds may undergo several degradation reactions during intense heating or prolonged storage. Depending on the incubation time and temperature, the initially formed Amadori compounds are degraded in the advanced stage to the highly reactive α-dicarbonyl compounds (e.g. glyoxal, methylglyoxal, 1-deoxyglucosulose or 3-deoxyglucosulose). The lysine and arginine side chains of proteins can react with these α-dicarbonyls to form stable peptide-bound amino acid derivates, the so-called advanced glycation end-products (AGEs) [12,84,85,86].

To date, most AGEs have been isolated from model mixtures and are less frequently quantified in foods or biological systems. These compounds are rather important in terms of nutritional and biological aspects, moreover since AGEs can also be produced during pathophysiological processes in vivo [85,87–100].Diet-derived AGE are major contributors to the total body AGE pool. Dietary AGEs may play an important role in the causation of chronic diseases associated with underlying inflammation. Excessive consumption of AGEs may represent an independent factor for inappropriate chronic oxidant stress and inflammatory factor surges during the healthy adult years, which over time may facilitate the emergence of complex diseases, such as diabetes and other disorders related to aging [101–106]. The large effects of AGEs on human health demonstrate there is a need for good detection methods.

2.2.1. General determination of AGEs

The fluorescence of advanced Maillard products and soluble tryptophan (FAST) method has been used to evaluate the formation of fluorescent advanced stage MRPs in milk [107,108]. This method gives a rapid evaluation of the nutritional quality of milk proteins and is compatible with industrial requirements, since the method is cheap and easy to use. In model reactions, lactose was heated with primary amines and more than 12 amine-free or amine containing Maillard AGEs were separated, identified and quantified by HPLC/DAD [109]. Most of these products were specific for lactose since they were not detected in Maillard mixtures containing monosaccharides such as glucose.

2.2.2. Analysis of carboxymethyllysine (CML)

The first lysine derivative of the advanced Maillard reaction detected in foods was *N*-α-carboxymethyllysine (CML) [110–113]. CML is formed from lysine and glyoxal during the oxidative degradation of the Amadori compounds [114]. This lysine derivate is a commonly used marker compound to evaluate the progress of the Maillard reaction in foods [112,115,116].

CML has been evaluated in dairy products by RP-HPLC [115] and modified RP-HPLC with *o*-phthalaldehyde pre-column-derivatisation [110,111], which gave a high sensitivity and very good reproducibility. GC–MS analysis of the trifluoroacetyl methyl ester of CML [115] or the silylated derivates has also been used to determine the CML content in foods. Derivatisation is required since CML is present in very low concentrations as compared to the native amino acids. Prior to GC analysis, samples are submitted to acid or enzymatic hydrolysis.

CML has also been determined by ELISA using an antibody specific for carboxymethylated protein [117]. This method is a fast, specific and easy-to-handle procedure to evaluate CML formation in heated food products, and does not require sample work up. However, for certain samples (e.g. milk) proper control determinations are required because of background signals in the ELISA. SDS-PAGE immunoblotting can also be helpful to detect CML in insoluble food proteins [117].

2.2.3. Pyrraline analysis

Another lysine derivate present in foods is pyrraline [118,119], which is formed from the α-amino group of lysine and 3-deoxyglucosulose, the degradation product of reducing sugars and Amadori compounds. Pyrraline can be found in food in either free [119,120] or protein-bound form [121,122] and can be a useful indicator to control the Maillard reaction in sterilised products that contain heat damage proteins. Pyrraline represents one of the dominating and few AGEs that have been quantified in foods such as milk, bakery products, enteral formulas and pasta. Its detection was done using either an amino acid analysis with photodiode array detection (PAD) [121,123] or RP-HPLC [118,124–129] after the total enzymatic hydrolysis of the proteins.

2.2.4. Analysis of cross-linking products

Lysine dimmers (imidazolium compounds) [130–133] result from the reaction between two lysine side chains and two molecules of glyoxal (GOLD), methylglyoxal (MOLD) or 3-deoxyglucosulose (DOLD) [134]. They were found in very low amounts in enzymatic hydrolysates of bakery products after analysis by LC–MS with ESI [135]. The low concentrations detected indicated a minor role of lysine dimmers in protein cross-linking in foodstuffs.

Arginine–lysine cross-links such as GODIC (lysine–arginine cross-link + glyoxal), MODIC (lysine–arginine cross-link + methylglyoxal), DODIC (lysine–arginine cross-link + 3-deoxyglucosulose), glucosepan [136–138], pentosidine [139] and imidazolinone [130,140] can also be formed during the Maillard reaction. MODIC, GODIC, DODIC and glucosepan were identified and quantified in several foodstuffs using LC–MS with ESI after enzymatic hydrolysis. Quantitative results showed that MODIC was the most important Maillard cross-link. The other amino acid derivates were present in far lower concentrations [135]. Pentosidine, resulting from the reaction of lysine, arginine and sugar derived carbonyl compounds, has been found in very low amounts in several processing foodstuffs (milk products, roasted coffee and bakery products) using ion-exchange chromatography with direct fluorescence detection and subsequent ninhydrin derivatisation [141]. This method not only allowed the quantification of pentosidine but also the determination of all other amino acids of the acid hydrolyzates. Imidazolinone is formed during the reaction between peptide-bound arginine and methylglyoxal and is regarded as one of the most abundant arginine cross-linking product in foods. This compound has been quantified in alkali-treated bakery products and roasted coffee by FAB–MS [142].

2.2.5. Analysis of other amino acid derivatives

Argpyrimidine [143,144] is formed from two molecules of methylglyoxal and the guanidino chain or arginine. It was identified and quantified as free acid in beer and malt by HPLC and coupled GC–MS [145,146].

Oxalic acid monolysinylamide (OMA), a MRP of L-ascorbic acid, was detected in heat-treated milk products and commercial infant formulas using ELISA [147–149]. In this qualitative assay, a polyclonal antibody, which binds with high specificity and affinity to OMA-modified proteins, was used.

Propylimidazolinone-ornithine (PIO), resulting from the reaction between arginine with C5-dicarbonyls [150], represents a new type of post-translational protein modification formed during food processing. It might be responsible for the major part of arginine derivatisation in disaccharide containing foods like milk. PIO was isolated by semi-preparative RP-HPLC and identified by liquid chromatography–electrospray–time of flight–mass spectroscopy (LC–ESI–TOF–MS) and NMR [150].

Peptide-bound pyrazinones are produced during the reaction between the N-terminal of peptides with glyoxal or methylglyoxal. These compounds form a new class of fluorescent AGEs that may have quantitative importance in heated peptide containing foods. Using HPLC with UV and fluorescence detection, a rapid derivatisation of the peptide and the concomitant formation of well-defined products were observed [151].

Lysine aminoreductone is another amino derivate which has been detected in heated or processed milk products by HPLC-DAD but has not yet been quantified [5,152].

2.3. Final stage MRPs

During the Maillard reaction brown-coloured high molecular weight peptide-bound MRPs known as melanoidins [2,153–156] are formed. Although not yet identified or quantified in browned foods, these compounds stand for a new class of MRPs. Melanoidins can be generated by a cross-linking reaction between a low molecular weight chromophore and a non-coloured high molecular weight biopolymer [157]. Their composition strongly depends on the food composition and the technological conditions. Melanoidins appear in several heat-treated foods and represent a significant part of our diet, with an average intake of grams per day. In spite of extensive studies, the exact chemical species responsible for this brown colouration still remains undefined.

From the technological point of view, melanoidin formation is essential for food flavour, colour and texture. Different studies have also demonstrated the high antioxidant capacity of melanoidins, which substantially contributes to the shelf-life of heat-treated foods [21] and physiological processes in vivo. Melanoidins demonstrated antioxidant capacity through a chain breaking, oxygen scavenging and metal chelating mechanism [158,159] without showing cytotoxic effects [17]. Currently unidentified melanoidins, present, e.g. in coffee beverages, are hypothesized to act as antioxidants [26] but also act in the activation of chemopreventive enzymes [160]. In addition, several Maillard compounds identified as constituents of melanoidins were found to inhibit tumour cell growth [161,162].

Several attempts have been undertaken to isolate and purify melanoidins from foods such as coffee [163], dark beer [164] and soya sauce [165,166]. However, owing to the complexity of the melanoidin fraction in foodstuffs, it has been difficult to characterise a pure melanoidin. Identification of coloured structures after careful hydrolysis of the protein skeleton provided useful information regarding the chromophores, which are linked to it. After complete enzymatic digestion of the protein skeleton, Hofmann [157] and Somoza et al. [167] could detect two intense red-coloured chromophore substructures by HPLC. These compounds were subsequently identified using several NMR techniques, MS, UV and IR spectroscopy. Melanoidins have also been analysed by MALDI-TOF mass spectrometry [26] after separation by gel filtration chromatography [168,169].

One melanoidin structure, called pronyl-L-lysine (Fig. 2) has been identified as a key antioxidant formed during heat treatment of Maillard-type reaction mixtures. This compound results from the reaction between lysine side chains and acetylformoin and has been detected and quantified in the crust and crumb of bread by high-resolution GC–MS in the chemical ionisation mode (CI) [15,16]. It was confirmed that pronyl-lysine modulates a chemopreventive phase II enzyme [170], the glutathione *S*-transferase (GST). The induction of this enzyme by pronyl-lysine represents a promising strategy for cancer prevention [171]. Recently, bread and coffee melanoidins have also been described as potential prebiotic ingredients [172,173].

The study of melanodins in health is gaining interest due to their molecular complexity, lack of stability and biological functions. More investigations and analytical tools are required in this field, especially to be able to assign a particular structure to a specific biological function. A group of European scientists are working on this through the EU-funded COST Action 927.

3. Conclusions

The Maillard reaction has great potential to become an effective industrial method to produce safe and healthy food (ingredients). This review has shown that especially the early stage MRPs and melanoidins have several health-promoting properties. However, the assignment of a specific biological function to a particular MRP is often difficult. This is caused by the large amount of products formed during this reaction and the difficulties encountered in their purification, identification and quantification of pure compounds. The methods here described can be of help to identify the reaction steps involved in the formation of biologically active MRPs. In addition, they may be employed in clinic as markers of pathophysiological processes such as diabetic retinopathy, nephropathy and neuropathy.

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