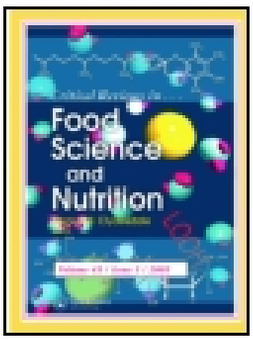

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REVIEW

Maillard reaction products derived from food protein-derived peptides: insights into flavor and bioactivity

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ABSTRACT

Food protein-derived peptides serve as food ingredients that can influence flavor and bioactivity of foods. The Maillard reaction plays a crucial role in food processing and storage, and generates a wide range of Maillard reaction products (MRPs) that contribute to flavor and bioactivity of foods. Even though the reactions between proteins and carbohydrates have been extensively investigated, the modifications of food protein-derived peptides and the subsequent impacts on flavor and bioactivity of foods have not been fully elucidated. In this review, the flavor and bioactive properties of food-derived peptides are reviewed. The formation mechanisms with respect to MRPs generated from food protein-derived peptides have been discussed. The state-of-the-art studies on impacts of the Maillard reaction on flavor and bioactivity of food protein-derived peptides are also discussed. In addition, some potential negative effects of MRPs are described.

KEYWORDS

Food protein-derived peptides; Maillard reaction products; flavor; bioactivity; reducing sugars

Introduction

The growing global population has led to increased demand for high-protein ingredients in the food industry (Henchion et al. 2017; Rao, Klaassen Kamdar, and Labuza 2016). The latest estimates suggest a global demand for protein ingredients of approximately 5.5 million tons in 2018 (Rao, Klaassen Kamdar, and Labuza 2016). Protein ingredients are normally categorized into either intact proteins or protein hydrolysates depending on the integrity of the primary structure of native protein molecules (Rao, Klaassen Kamdar, and Labuza 2016). Protein hydrolysates can be defined as a mixture of peptides and amino acids that are derived from proteolysis (destruction of native primary structure) of a variety of animal and plant proteins (Clemente 2000; Rao, Klaassen Kamdar, and Labuza 2016). They have been ubiquitously applied in the food industry as functional food ingredients, flavorings as well as a good source of amino acids (Martínez-Alvarez, Chamorro, and Brenes 2015). Furthermore, protein hydrolysates are more effectively absorbed by human body than intact proteins or free amino acids (Manninen 2009). Several excellent review articles concerning health-promoting effects of protein hydrolysate from various protein sources are available (Aluko 2015a; Fu, Therkildsen, et al. 2019; Li-Chan 2015; Nongonierma and FitzGerald 2017; Udenigwe and Aluko 2012).

The Maillard reaction is a non-enzymatic reaction between carbonyl groups of carbohydrates and amino groups from amino acids, peptides or proteins (Horvat and Roscic 2010). During this reaction, a complex array of compounds referred to as Maillard reaction products (MRPs) are produced (Yilmaz and Toledo 2005). In recent years, an increasing number of studies have demonstrated that MRPs derived from food protein-derived peptides contribute to flavor and color, in addition to the bioactive properties of foods (Jiang et al. 2013; Karnjanapratum et al. 2016; Song et al. 2017; Yu et al. 2018). Since food protein-derived peptides are widely employed as functional ingredients or included in processed foods, research on modifications of protein hydrolysates/peptides via the Maillard reaction deserves attention. Even though studies on the glycation reaction between amino acids or proteins and carbohydrate through Maillard reaction have been broadly reviewed (Akhtar and Ding 2017; de Oliveira et al. 2016; Liu, Ru, et al. 2012; Oliver, Melton, and Stanley 2006), information on glycation of protein hydrolysates/peptides through Maillard reaction is still scanty. Therefore, the present review outlines the flavor and bioactive characteristics of food-derived peptides in addition to the mechanisms involved in MRPs formation from these peptides. The state-of-the-art studies on impacts of Maillard reaction on flavor and bioactivity of food protein-derived peptides were subsequently summarized. Additionally, several negative aspects of MRPs from food protein-derived peptides are further discussed.

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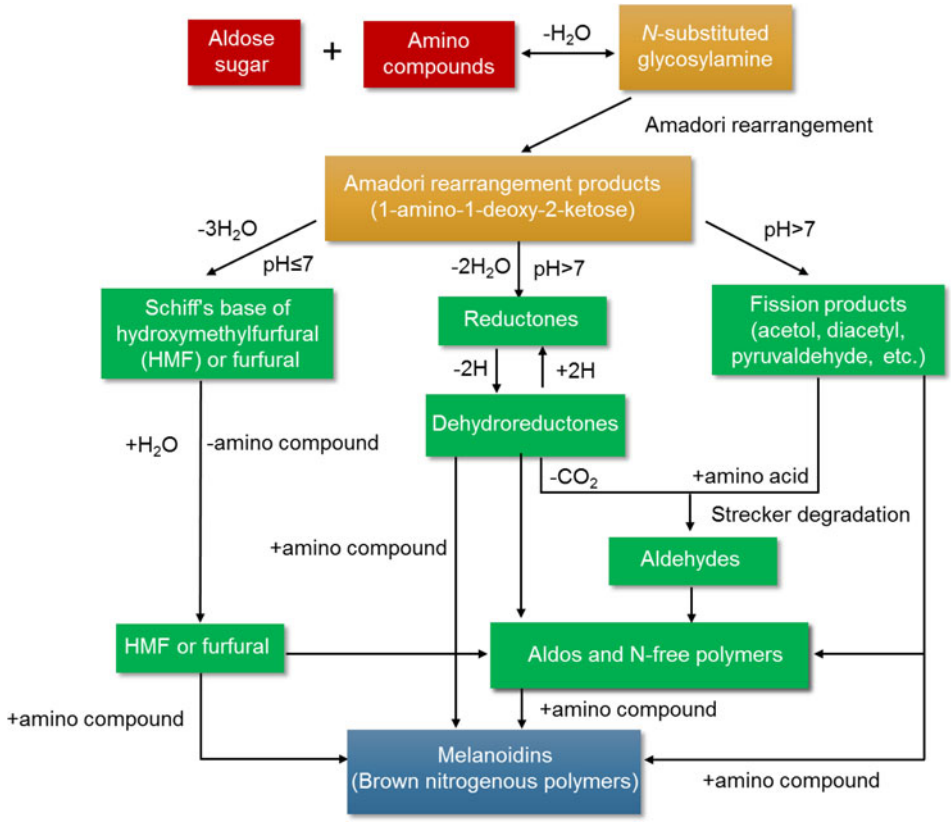

Figure 1. General pathway of the Maillard reaction. The MRPs in the text boxes with different colors correspond to reaction products of three stages. The yellow frames represent the products from early stage, the green frames represent the products from intermediate stage, and the blue frames represent the products from final stage. It should be noted that peptides cannot follow the typical Strecker degradation due to the absence of free carboxyl group at the α-carbon in relation to free amino group, resulting in failure of decarboxylation. Adapted with permission from (Hodge J. E. 1953. Dehydrated Foods, Chemistry of Browning Reactions in Model Systems. J Agric Food Chem. 1: 928–943). Copyright (1953) American Chemical Society.

Protein hydrolysates/peptides

Production of protein hydrolysates

A large number of animal and plant proteins has been exploited as precursors for production of protein hydrolysates (Udenigwe and Aluko 2012). Basically, protein hydrolysates can be produced through chemical hydrolysis, enzymatic hydrolysis and microbial fermentation of proteins (Neklyudov, Ivankin, and Berdutina 2000). However, chemical hydrolysis of proteins by strong acid and alkali is highly extreme such that considerable racemization and destruction of amino acids and peptides occur (Lieske and Konrad 1994). Therefore, enzymatic hydrolysis or microbial fermentation has been regarded as a major approach to generate desirable protein hydrolysates that can be safely used as functional food ingredients. Addition of protein hydrolysates to food systems can exert an impact on the quality of products thereof, including flavor and bioactive properties (Lafarga et al. 2016; Wouters et al. 2016).

Taste-active properties of food protein-derived peptides

Taste of protein hydrolysates/peptides is a vital aspect when considering functional food ingredients. Peptides can exhibit a wide range of tastes, such as sweet, bitter, umami, sour or salty taste (Temussi 2012). For instance, peptides have been reported to elicit umami taste, a broth-like or savory taste (Zhang et al. 2017). Apart from the umami taste, peptides can confer thickness, mouthfulness and richness taste to foods (Feng et al. 2016). This flavor, known as "kokumi", is characterized by taste-enhancing, complex and a long-lasting impression (Liu, Song, et al. 2015). However, bitterness of peptides is a main limiting factor, which may hinder their increasing application in the development of peptide-based food products (Li-Chan 2015). Reduction of peptide bitterness is a challenging task, though different approaches have been described in the literature (FitzGerald and O'Cuinn 2006; Saha and Hayashi 2001). A recent review on protein hydrolysates from animal by-products has summarized debittering methods of protein hydrolysates (Fu, Chen, et al. 2019). The most used approach is degradation of bitter peptides by different types of exopeptidases (Raksakulthai and Haard 2003; Cheung, Aluko, et al. 2015). Use of exopeptidase has been successful in reducing bitterness in many applications, especially hydrolysates derived from animal and plant proteins (Sujith and Hymavathi 2011; Cheung, Aluko, et al. 2015).

Bioactivity of food protein-derived peptides

In addition to taste-active properties of food-derived peptides, increasing attention has been paid to different bioactivity of peptides, such as antioxidant, angiotensin I-converting enzyme (ACE) inhibitory, antibacterial, antidiabetic,

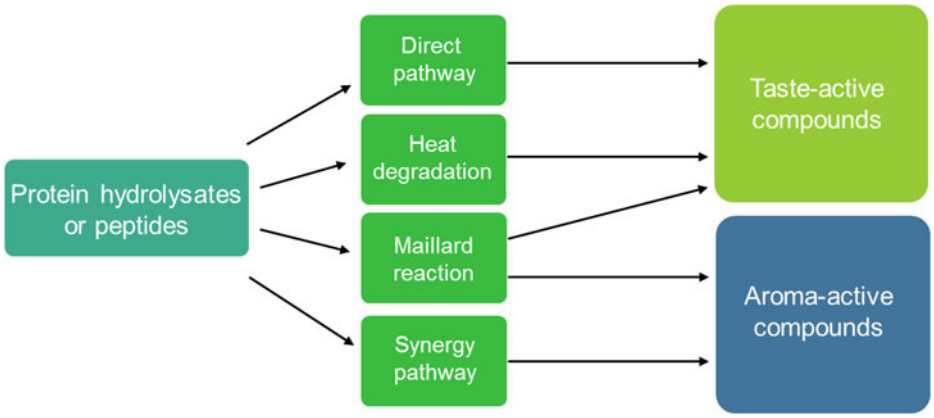

Figure 2. The contribution of protein hydrolysates/peptides to taste- and aroma-active compounds.

immunomodulation and mineral binding activities (Udenigwe and Aluko 2012). A large number of bioactive peptides derived from dairy, plant and animal muscle proteins has been well reviewed (Albenzio et al. 2017; Aluko 2015b; Cheung, Aluko, et al. 2015). Recently, protein hydrolysates/peptides derived from animal processing by-products, which can provide a good valorization opportunity to transform by-products into high value-added food ingredients, have been reported (Fu, Therkildsen, et al. 2019; Martínez-Alvarez, Chamorro, and Brenes 2015).

MRPs derived from food protein-derived peptides

The Maillard reaction

During food processing and storage, the Maillard reaction, a well-known non-enzymatic browning reaction, plays a pivotal role in influencing color, aroma, taste and nutritional properties of foods (Ames 1998; Martins, Jongen, and Van Boekel 2000). The Maillard reaction occurs between carbonyl (esp. reducing sugars) and primary amino groups of amino acids, peptides or proteins; however, the pathways and mechanisms underlying the Maillard reaction are extremely complicated. Maillard reaction can be influenced by several factors, such as participating reactants, temperature, pH, water activity, among others (Ames 1990). The changes in these factors can lead to alterations in reaction rate, reaction pathways and reaction end-products (Sumaya-Martinez et al. 2005).

The past few decades have witnessed remarkable advances in research on the chemistry and mechanisms of the Maillard reaction (Ames 1990; Ames 2005; Fay and Brevard 2005; Hodge 1953; Horvat and Roscic 2010). It is widely accepted that the Maillard reaction is mainly composed of three key stages (Fig. 1), including initial, intermediate and final stages (Hodge 1953). The initial stage involves interaction between sugar and amino compounds and formation of a Schiff base of free amino and carbonyl group, followed by Amadori rearrangement of Schiff base (Yaylayan 2003; Yaylayan, Huyghues-Despointes, and Feather 1994). The intermediate stage normally initiates from Amadori rearrangement products, which is characterized by several pathways, including enolization, dehydration, aldol condensation and Strecker degradation. The dicarbonyl compounds generated during intermediate stage of Maillard reaction can serve as main precursors for development of numerous heterocyclic compounds, polymers and flavor products (Martins, Jongen, and Van Boekel 2000; Mottram 2007). In addition, the reaction between Strecker aldehydes and Maillard intermediates is noticeably responsible for formation of aroma compounds in foods (Hofmann and Schieberle 2000). In the final stage, melanoidins or heterocyclic compounds, referred to as advanced glycation end-products (AGEs), are formed from active intermediate products (Henle 2005).

Preparation of MRPs

Food protein-derived peptides have been used as functional ingredients in an array of food systems (Hartmann and Meisel 2007). Although the Maillard reaction between amino acids or proteins and carbohydrates has been investigated in previous studies (Akhtar and Ding 2017; de Oliveira et al. 2016; Liu, Ru, et al. 2012; Oliver, Melton, and Stanley 2006), Maillard reaction between peptides and reducing sugar during food processing and storage remains to be fully understood. Preparation of MRPs can be implemented in either wet- or dry-heating treatment. Dry-heating is initiated by mixing powders of peptides and sugars, followed by heat treatment at certain temperature and relative humidity conditions (Kato, Minaki, and Kobayashi 1993). Maillard reaction in the dry state is relatively limited due to time-consuming procedure and uneven contact of raw materials (Qi et al. 2010). By contrast, wet-heating treatment involves a peptide-sugar mixture in aqueous-based solutions heated at a specific temperature (O'Mahony et al. 2017), which is extensively employed in modification of peptides via Maillard reaction. The Maillard reaction-induced modifications of food protein-derived peptides can play a crucial role in their flavor and bioactivity (Van Lancker, Adams, and De Kimpe 2011). The peptide chain length, peptide composition and sequence, and hydrolysis susceptibility of peptide bonds exert an influence on the ultimate flavor and bioactivity of MRPs (Izzo and Ho 1992).

Table 1. Summary of the recent studies on flavor properties of Maillard reaction products generated from various protein hydrolysates/peptides and carbohydrate sources.

Protein hydrolysates/ Peptides	Carbohydrate	Reaction conditions	Flavor properties	References
Smooth hound viscera protein hydrolysates	Sucrose	90 °C , 2 h	Reduced bitter taste	Abdelhedi et al. 2017
Rice bran protein hydrolysates	Sucrose, glucose or fructose	pH 7.0, 95 °C for 10 min	Higher sweet, cocoa-like and milk powder-like aroma intensities	Arsa and Theerakulkait 2015
Chinese shrimp waste hydrolysates	Xylose	0 - 180 min, 115 °C	Strong meaty and seafood aroma, umami and mouthfulness taste	Cai et al. 2016
Sunflower protein hydrolysates	Xylose	120 °C, 2.0 h, pH 7.4	Greater mouthfulness and continuity	Eric et al. 2013
Poultry proteins hydrolysates	Glucosamine	pH7.0, 37 or 50 °C for 3.5 h	Saltier taste and savoriness	
Sunflower, corn or soyabean peptides	Xylose	120 °C, 2.0 h, pH 7.4	Improved mouthfulness and continuity	Karangwa et al. 2016
Salmon hydrolysates	Xylose	45-50 °C, 4-6 h, pH 5.5-7.5	Masking fish odor	Kouakou et al. 2014
Chicken peptides	Xylose	pH 6.5, 80-140 °C, 0.5-2 h	Increased meaty aroma at high temperature (>100 °C). Umami and kokumi taste at mild temperature (80 °C).	Liu, Song, et al. 2015
Soybean protein hydrolysates	Xylose	pH 7.4, 120 °C, 2h	Improved mouthfulness, umami and meaty flavor	Song et al. 2013
Collichthys niveatus hydrolysate	Glucose and Xylose	pH 8.5, 120 °C, 1h	Toasty, nutty and sweet caramel-like aroma	Zhao et al. 2016

Flavor properties of MRPs generated from peptides

In general, protein hydrolysates/peptides can contribute to taste and aroma in foods (Temussi 2012; Zhang, Dorjpalam, and Ho 1992) through direct contribution, heat degradation, Maillard reaction or synergy with other food components (Fig. 2). Peptides are recognized as essential flavor potentiators and precursors of the Maillard reaction (Van Lancker, Adams, and De Kimpe 2011). Recently, an increasing number of studies has indicated that MRPs prepared from protein hydrolysates/peptides and carbohydrates can influence flavor properties of food products. The flavor properties of MRPs derived from diverse protein hydrolysates/peptides and carbohydrates are summarized in Table 1.

Taste-active MRPs

MRPs generated from peptides have been reported to exhibit an enhanced effect on taste of food products. Ogasawara, Katsumata, and Egi (2006) reported the taste-enhancing potential of MRPs generated from xylose and soybean peptides (1–5 kDa), indicating that Maillard reacted peptides can behave as a taste enhancer to increase the intensity of umami and "kokumi" sensations. It has been shown that peptide degradation and cross-linking simultaneously occur during Maillard reaction between soybean peptides and xylose (Lan et al. 2010). Formation of Maillard reacted peptides defined by molecular weight (1-5 kDa) was capable of masking bitterness (Lan et al. 2010; Liu, Liu, Song, et al. 2015). Similarly, Maillard reaction of xylose and chicken peptides at 80 °C and extended heating time generated low bitter and high broth-like taste (umami and kokumi) (Liu, Liu, Song, et al. 2015). An interesting study by Karangwa et al. (2016) revealed that the taste-enhancing properties of MRPs are not only attributed to Maillard reacted peptides, but also cross-linking products that can also contribute to "kokumi" effect. In addition to umami and "kokumi" taste, MRPs prepared from soybean peptides and different carbonyl compounds (galacturonic acid, glucosamine, xylose, fructose, or glucose) have been reported to exhibit a biphasic effect on human salt taste perception via enhancing or suppressing the NaCl response at low or high concentrations (Katsumata et al. 2008).

Enzymatic cross-linking via microbial transglutaminase (MTGase) has been employed to increase the yield of Maillard reacted peptides (1-5 kDa) in protein hydrolysates. Song et al. (2013) claimed that MTGase treatment of soybean peptides increased the amount of Maillard reacted peptides, which was responsible for improved mouthfulness as well as reduced bitterness. Recently, demonstrated that glucosamine-induced glycation of chicken protein hydrolysates in the presence of MTGase showed an improved salty and savory taste. 2,5-Diketopiperazines (2,5-DKPs) referred to as cyclic dipeptides are formed as thermal reaction by-products accompanying Maillard reaction, and is also a source of taste-active compounds in processed foods (Borthwick and Da Costa 2017). 2,5-DKPs have been shown to elicit astringent, salty, metallic, or bitter taste and detected in different food systems, such as beef, beer, bread, cocoa, chicken essence, roasted coffee, among others (Borthwick and Da Costa 2017). The research on Maillard reaction of peptide-xylose system has indicated that peptides can be degraded to cyclic peptides at the early stage of Maillard reaction (Xu et al. 2013). A nonapeptide (GVTVFEDLK) from beef protein hydrolysates was capable of splitting at the position of aspartic acid and leucine and the cyclic peptides were further formed from LK by dehydration and cyclization reactions (Xu et al. 2013).

Aroma-active MRPs

The Maillard reaction can produce numerous volatile compounds (van Boekel 2006). Compared with free amino acids, peptides contribute to formation of several specific aroma

compounds (Van Lancker, Adams, and De Kimpe 2011). MRPs of peptides and sugars possess a strong meaty-like flavor due to formation of specific aroma compounds, such as pyrazines, pyrazinones, thiazoles and thiophenes. Investigations on Maillard reaction using pure peptide models have revealed that peptides are involved in Maillard reaction in several pathways, including bond cleavage, cyclization and glycation (Liu, Liu, Song, et al. 2015; Yang, Wang, and Song 2012). In recent years, MRPs from protein hydrolysates derived from sunflower (Karangwa et al. 2017), chicken (Liu, Liu, Song, et al. 2015), shrimp waste (Cai et al. 2016) and soybean (Song et al. 2013) have been reported to improve the aroma as well as overall flavor of end products thereof. Formation of the specific volatile compounds during Maillard reaction is highly dependent on molecular weight distribution of hydrolysates as well as composition and configuration of peptides (Song et al. 2013). As protein hydrolysates contain a large number of peptides, it is reasonable that MRPs derived from protein hydrolysates can exhibit a wide variety of aroma.

Pyrazines, nitrogen-containing heterocyclic compounds, are representative volatile compounds identified in MRPs (Hwang et al. 1994). Pyrazines have been shown to elicit the nutty and roasted meat-like odorant (Mottram 1994). The formation mechanisms of pyrazines involve α-aminoketones produced from condensation of dicarbonyl compounds with amino compounds during Maillard reaction (Van Lancker, Adams, and De Kimpe 2010). Additionally, pyrazines can be generated via interaction between dicarbonyl compounds and ammonia from deamination of amino acids (e.g. glutamine and asparagine) (Hwang et al. 1994). Hence, it can be speculated that glutamine- or asparagine-abundant peptides can generate relatively high amounts of pyrazines. More pyrazines can be produced in the model system between glucose and dipeptides, compared with free amino acids (Van Lancker, Adams, and De Kimpe 2010). Moreover, peptides derived from whey protein isolate have been shown to make a significant contribution to an increased amount of pyrazines, while free amino acids originally occurring in whey protein hydrolysates could exert a minor effect. Van Lancker, Adams, and De Kimpe (2012) suggested that structural characteristics of N-terminal amino acid of peptides are determinant factors responsible for overall production of pyrazines. A recent study by Liu, Liu, Song, et al. (2015) have demonstrated that low molecular weight peptides (<500 Da) are considered the most important contributor for generation of pyrazines due to the high reaction activity of amidogen. Therefore, impacts of peptides on formation of pyrazines from the Maillard reaction are of great importance and remain to be further investigated.

Pyrazinones with unique toasted aroma are peptide-specific MRPs derived from the Maillard reaction of dicarbonyls (glyoxal or methylglyoxal) with glycine dipeptide, which cannot be formed in the free amino acid system (Izzo and Ho 1992; Oh, Shu, and Ho 1992). Pyrazinones can be identified in the reaction of glucose with dipeptides (GL and LG) or peptides with various peptide chain lengths (diglycine, triglycine, and tetraglycine) (Izzo and Ho 1992). It is interesting to note that pyrazinones generated from dipeptides (GL and LG) are qualitatively same, but slightly different in quantity (Oh, Shu, and Ho 1992). The underlying reason is that GL is in equilibrium with the LG (Oh, Shu, and Ho 1992). Keyhani and Yaylayan (1996) elucidated the formation mechanisms of pyrazinones based on a glycine dipeptide model using the labeled glucose and dicarbonyl compounds. Two possible pathways are involved in formation of pyrazinones. In pathway A, it requires glyoxal and pyruvaldehyde to produce dimethylpyrazinones and trimethylpyrazinones, respectively. Thereafter, it incorporates three glycine molecules in the structure of pyrazinones (Keyhani and Yaylayan 1996). In contrast, the number of glycine molecules incorporated in Pathway B mainly depends on whether pyruvaldehyde and 2,3-butanedione are derived from Amadori compounds or generated via transformation of glyoxal and pyruvaldehyde by glycine (Keyhani and Yaylayan 1996). In addition to pyrazines and pyrazinones, sulfur-containing heterocyclic compounds (e.g. thiophenes and thiazoles) formed during the Maillard reaction or Strecker degradations can serve as major volatile compounds with roasted and meaty aroma (Jayasena et al. 2013; Mottram 1998). During Maillard reaction, H_2S released from S-containing amino acids can react with MRPs, giving rise to formation of an array of S-containing compounds (Van Lancker, Adams, and De Kimpe 2011). Due to the relatively low odor thresholds, these compounds can significantly contribute to overall aroma of foods (Mottram 1998). Peptide-bound cysteine can generate S-containing compounds during Maillard reaction (Van Lancker, Adams, and De Kimpe 2011). In addition, comparison of volatiles generated from Maillard reaction of glucose with cysteine and glutathione revealed that more thiophenes and thiazoles were generated in the glucose/cysteine model system, compared with the glucose/glutathione model system (Zhang and Ho 1991). The difference in production of sulphur-containing compounds may be attributable to lack of aldehydes generated in the reaction of glucose and glutathione, as peptides cannot follow the typical Strecker degradation due to the absence of free carboxyl group at the α-carbon in relation to free amino group, resulting in failure of decarboxylation (van Boekel 2006).

A great many of studies have reported that MRPs derived from protein hydrolysates and reducing sugar exhibit a pleasant flavor. Apart from typical Maillard aroma compounds, Strecker degradation occurring between amino acids and dicarbonyl compounds can confer pungent, unpleasant and burnt aroma. In addition, a rich source of oxygen-containing heterocyclic compounds can be formed, including furans and furfurals that can provide characteristic flavor.

Bioactive properties of MRPs generated from peptides

In past years, a growing number of studies have demonstrated that MRPs derived from peptides can display various bioactivities, including antioxidant, antibacterial, antihypertensive, anti-inflammatory and bifidogenic properties

Table 2. Summary of the recent studies on antioxidant activity of Maillard reaction products generated from various protein hydrolysates/peptides and carbohydrate sources.

Protein hydrolysates/ Peptides	Carbohydrate	Reaction conditions	Antioxidant activity	References
Chicken bone hydrolysates	Galactose	100 °C, 1.5-7.5 h	DPPH and hydroxyl radical scavenging activity; reducing power assay	Nie et al. 2017
Smooth hound viscera protein hydrolysates	Sucrose	90 °C , 2 h	β-carotene bleaching assay; reducing power assay	Abdelhedi et al. 2017
Chicken peptides	Glucose	30–240 min, 100-150 °C	DPPH and hydroxyl radical scavenging activity; ferrous ion chelating activity	Bai et al. 2017
Sunflower protein hydrolysates	Xylose	pH 7.4, 120 °C , 2 h	DPPH radical scavenging activity; reducing power assay	Eric et al. 2013
Sea cucumber gut hydrolysates	Ribose	pH 7.0 or 8.0, 75-95 °C, 12 h	DPPH radical scavenging activity	Han et al. 2017
Tripeptide (Ile-Pro-Pro)	Ribose	pH 9.0, 98 °C , 0-8 h	DPPH radical scavenging activity; ferrous reducing power	Jiang et al. 2013
Sunflower free amino acid and peptides	Xylose	pH 7.4, 120 °C , 2 h	DPPH radical-scavenging activity; ferrous reducing power	
Unicorn leatherjacket gelatin hydrolysates	Galactose	65% water activity, 60 °C, 12-48 h	Ferric reducing power; ABTS radical scavenging activity	
Porcine plasma protein hydrolysates	Glucose, fructose or galactose	pH 7.0, 95 °C, 0-6 h	Ferric reducing power; ABTS and hydroxyl radical scavenging activity	
Whey protein hydrolysates	Lactose or lactulose	pH 6.0, 90 °C, 45 min	DPPH radical-scavenging activity	Nooshkam & Madadlou 2016
Shrimp by-product protein hydrolysates	Glucose	pH 6.5, 110 °C, 10 h	DPPH scavenging activity; oxygen radical absorbance capacity; intracellular ROS in HepG2 cells	Zha et al. 2015

(Somoza 2005; Van Lancker, Adams, and De Kimpe 2011). Furthermore, some bioactivities of MRPs have been confirmed using in vivo animal and human clinical trials. Recently, accumulative evidence has revealed antioxidant and some other biological activities of MRPs generated from the reaction between diverse sources of protein hydrolysates and carbohydrates, as summarized in Table 2 and Table 3, respectively.

Antioxidant activities of MRPs

MRPs can display potent antioxidant activities (Alfawaz, Smith, and Jeon 1994), which confers on them the potential as substitutes for synthetic antioxidants (Vhangani and Van Wyk 2016). The antioxidant activity of MRPs was first documented in the reaction model between glucose and glycine or sodium glutamate. It has been widely reported that MRPs generated from protein hydrolysates/peptides have been shown to possess antioxidant activities. They tend to exhibit considerably increased antioxidant activity, when compared with protein hydrolysate/peptides alone (Bai et al. 2017; Lingnert and Eriksson 1980; Zhang et al. 2018).

The antioxidant potencies of MRPs can be influenced by amino acid composition, sequence and chain length of peptides. Lingnert and Eriksson (1980) reported a higher antioxidant activity with MRPs derived from the Maillard reaction between reducing sugars (glucose and xylose) and Gly-His dipeptides compared to MRPs obtained through His-Gly dipeptides. This may suggest that antioxidant activity depends on not only amino acid composition of peptides but also their sequence (Lingnert and Eriksson 1980). Furthermore, peptide chain length and stability of peptide bond against heat treatment are also related to antioxidant activity of MRPs. Measured antioxidant activity of MRPs prepared from the model systems of glucose with glycine, diglycine, and triglycine. They observed that MRPs from diglycine model system showed the most potent antioxidant activity. In addition, antioxidant activity of MRPs was observed to increase as heating time was extended in those model systems (Kim and Lee 2009). However, the relationships between molecular weight of peptides and antioxidant activities of their corresponding MRPs have not been totally elucidated. The MRPs generated from xylose-soybean peptides (below 1 kDa) model system possessed stronger antioxidant activity (Liu, Huang, et al. 2012), compared with their counterpart (1–5 kDa). By contrast, Yu et al. (2018) reported that MRPs derived from xylose and a soybean peptide fraction (1–3 kDa) showed the highest DPPH radical-scavenging activity when compared to those from the other peptide fractions. Similarly, Nie et al. (2017) reported that the MRPs derived from the galactose-chicken bone peptides (1–3 kDa) model system showed more potent free radical scavenging activity when compared with other peptide fractions that were examined. In addition, peanut peptide fraction (1–3 kDa) also exhibited the highest antioxidant activity of MRPs among the different peptide fractions (Su et al. 2011).

Although the in vitro antioxidant activities of MRPs derived from peptides have been well recognized, their antioxidant mechanisms have not been fully understood. In view of the complexity of MRPs, a variety of compounds in MRPs can show antioxidant activity through different mechanisms, including reducing power ability, scavenging activity towards free radicals, metal ion chelating activity and

Table 3. Summary of the recent studies on other bioactivities of Maillard reaction products generated from various protein hydrolysates/peptides and carbohydrate sources.

Protein hydrolysates/ Peptides	Carbohydrate	Reaction conditions	Bioactivities	References
Half-fin anchovy hydrolysates	Glucose	pH 9.0, 120 °C, 100 min	Antibacterial activity	Song et al. 2017
Gluten hydrolysates	Glucosamine	pH 7.0, 25 or 37 °C, 3.5 h	Antimicrobial activity	Gottardi et al. 2014
Bovine casein hydrolysates	Xylose	pH 8.0, 110 °C, 16 h	ACE-inhibitory activity	Hong, Meng, and Lu 2015
Bovine casein peptides	Galactose	pH 5.0-12.0, 70-120 °C, 3 h	ACE-inhibitory activity	
Bovine casein peptides	Ribose, galactose and lactose	pH 8.0, 95 °C, 0-5 h	ACE-inhibitory activity	Jiang et al. 2013
Leatherjacket skin gelatin hydrolysates	Galactose	70 °C, 36 h, 55% water activity	*In vitro* immunomodulatory properties and anti-cancer activity	Karnjanapratum et al. 2016
Flatfish byproduct hydrolysate	Ribose	pH 8.26, 121 °C, 38.09 min	Anti-inflammatory activity	Choe et al. 2016
Anchovy protein hydrolysate	Ribose	pH 7.0, 110 °C, 30 min	Improved memory in mice	Su et al. 2016
Halibut protein hydrolysates	Ribose	pH 5.0-7.0, 121 °C, 30-60 min	Anti-allergy activity	
Fish protein hydrolysates	Galactooligosaccharide	pH 7.0, 80 °C, 120 min	Beneficial effects on rat gut	Jin et al. 2018

regulation of intracellular antioxidant enzymes in vivo (Vhangani and Van Wyk 2013, 2016). In an interesting study by Chuyen et al. (1998), researchers confirmed in vivo antioxidant activity of MRPs prepared from peptides–glucose mixtures. These MRPs possessed potent scavenging activity against reactive oxygen species (ROS), which plays a crucial role in the in vivo antioxidant effect of MRPs (Chuyen et al. 1998).

Melanoidins have been reported to be responsible for antioxidant activities of MRPs due to heterocyclic compounds and reductones generated from the Maillard reaction (Amarowicz 2009; Eichner 1980; Kanzler et al. 2016; Wagner et al. 2002). Melanoidins are defined as high molecular weight, nitrogen-containing and brown-colored compounds produced in the late stages of Maillard reaction (Mesías and Delgado-Andrade 2017). Currently, three major chemical structures of melanoidins have been proposed, including polymers composed of repeating units of furans and/or pyrroles, cross-linking products of low-molecular-weight colored substances, and sugar degradation products cross-linked by amino compounds (Cämmerer, Jalyschko, and Kroh 2002). Since structures of these polymers are still unclear, the exact mechanism underlying the antioxidant activity of melanoidins has not been fully clarified. It is assumed that antioxidant mechanisms of melanoidins can be ascribed to radical-scavenging activity (Delgado-Andrade and Morales 2005; Rufián-Henares and Morales 2007b). Another suggested that the main antioxidant mechanism of melanoidins is the metal chelating capacity caused by its anionic hydrophilic nature that can form stable complexes with metal cations (Morales, Fernández-Fraguas, and Jiménez-Pérez 2005).

Antioxidant activities of several major dicarbonyl compounds and heterocyclic intermediates have been confirmed based on different approaches (Kanzler, Haase, and Kroh 2014; Kanzler et al. 2016). Their potential antioxidant mechanisms can be attributed to their functions as electron donors (Eichner 1980; Kanzler, Haase, and Kroh 2014; Kanzler et al. 2016). Besides, reductones can be formed in the intermediate stage of the Maillard reaction (Garbe et al. 2008). A number of MRPs containing reductone-like structures and exhibiting reducing properties have been identified, including dicarbonyl compounds as well as heterocyclic intermediates (Kanzler et al. 2017; Pischetsrieder et al. 1998).

Some volatile compounds formed during the Maillard reaction, such as furans, pyrroles, thiophene and thiazoles, were discovered to possess antioxidant activity (Eiserich and Shibamoto 1994). The heterocyclic aromatic ring of these compounds has a high electron density of carbon atoms, which are capable of scavenging free radicals (Shaker, Ghazy, and Shibamoto 1995). It is hypothesized that addition of an electron-donating group (e.g. a methyl group) can enhance electron density at carbon atoms of the heterocyclic ring, which subsequently leads to increased scavenging capacity of free radicals (Yanagimoto et al. 2002a). In contrast, the presence of an electron-withdrawing group, e.g. an acetyl group, can decrease electron density in the heterocyclic ring, which can further reduce the ability to scavenge free radicals (Fuster et al. 2000). Aside from electron density of carbon atoms on the heterocyclic ring, antioxidant potency of these volatile compounds can be influenced by their polarity (Yanagimoto et al. 2002a, 2002b). Moreover, thiol-containing compounds can possess antioxidant activity through different mechanisms. The nucleophilic thiol group can either serve as the one-electron-reducing agent to scavenge peroxyl and alkoxy1 radicals or decompose hydroperoxides by two-electron reduction and subsequent disulfide formation (Eiserich and Shibamoto 1994; Shaker, Ghazy, and Shibamoto 1995).

Antibacterial activities of MRPs

The antimicrobial effect of MRPs against different strains of bacteria, such as *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Shigella dysenteriae* and *Salmonella typhimurium*, has been documented (Chung, Yeh, and Tsai 2011; Einarsson, Snygg, and Eriksson 1983; Hauser et al. 2014; Rufian-Henares and Morales 2007b). Hong et al. (2014) revealed that MRPs of fish gelatin hydrolysates displayed specificity towards inhibition of *Escherichia coli*. Recently, Song et al. (2016) reported that MRPs obtained from half-fin anchovy hydrolysates/glucose model system exhibited antibacterial activities against several microorganisms, including *Escherichia coli*, *Pseudomonas fluorescens*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus megaterium*, and *Sarcina lutea*. Furthermore, seven antibacterial peptide sequences were subsequently identified, including RVAPEEHPTL, WLPVVR, FFTQATDLLSR, VLLLWR,

VLLVLLR, VLLALWR and LLSWYDNEFGYSNR (Song et al. 2017). In addition, the antimicrobial activity of melanoidins has been confirmed (Rufián-Henares and de la Cueva 2009; Rurián-Henares and Morales 2008). Rufián-Henares and de la Cueva (2009) postulated that melanoidins formed in the final stage of Maillard reaction showed antibacterial activity through chelating metal ion from outer membrane and provoking irreversible cell membrane damage. Another possible mechanism proposed is that MRPs can generate hydrogen peroxide, which is regarded as a major antibacterial component agent formed during non-enzymatic browning (Hauser et al. 2014; Mueller et al. 2011). Nevertheless, the exact mechanism by which MRPs or melanoidins exhibit antibacterial effects remains to be investigated.

ACE-inhibitory activities of MRPs

In the renin-angiotensin system, ACE plays a pivotal role in regulation of blood pressure and electrolyte homeostasis (Perazella and Setaro 2003). Inhibition of ACE activity serves as a main approach for treatment of hypertension (Fu et al. 2016). The MRPs prepared from peptide-sugar model systems have been reported to display ACE-inhibitory activity (Hong, Meng, and Lu 2015; Hwang et al. 2011; Jiang et al. 2013). Moreover, melanoidins from coffee have been confirmed for their ACE inhibitory effects in vitro (Rufian-Henares and Morales 2007a). Hong, Meng, and Lu (2015) demonstrated that MRPs obtained from bovine casein hydrolysates and xylose exhibited significantly higher ACE-inhibitory activity after 2 h reaction, compared to the original casein hydrolysate, which was attributed to carbonyl ammonia condensation reaction in the MRPs. However, Jiang et al. (2013) investigated the ACE-inhibitory activity of MRPs derived from different reducing sugars (ribose, galactose and lactose) and bovine casein peptide systems. Interestingly, ACE-inhibitory activity of MRPs was significantly reduced after Maillard reaction, while antioxidant activity was accordingly increased, when compared with casein peptides (Jiang et al. 2013). The reason for this phenomenon could be excessive sugar used in the Maillard reaction, which might provoke drastic caramelization that impairs ACE-inhibitory activity (Hong, Meng, and Lu 2015; Jiang et al. 2013). A recent study by Li et al. (2016) indicated ACE-inhibitory activity of MRPs during the fermentation and ripening processes of soy paste, and authors suggested the significant contribution of ACE-inhibitory activity by MRPs with extended maturation.

In vitro bifidogenic effects of MRPs

Gut homeostasis is of great significance for maintaining gut health. Modification of protein hydrolysates/peptides by Maillard reaction can improve resistance towards digestive enzymes and reduce gastrointestinal digestibility, which provides more possibilities for gut microbiota to utilize and ferment these MRPs (Hernandez-Hernandez, Moreno, et al. 2011; Hernandez-Hernandez, Sanz, et al. 2011). Muthaiyan et al. (2012) showed that MRPs derived from hydrolyzed caseinomacropeptide conjugated with galactooligosaccharides could enhance growth and bile tolerance in *Lactobacillus* strains, including the increased production of acetate and lactate. Moreover, this glycoconjugate was able to reduce intestinal pathogen adhesion to mucin and affect the interaction of virulence factors of *Listeria monocytogenes* (Laparra et al. 2013). In vitro fermentation by human gut bacteria of MRPs derived from hydrolyzed caseinomacropeptide and prebiotic carbohydrates (lactulose, galacto-oligosaccharides and galacto-oligosaccharides) displayed excellent bifidogenic effects (Hernandez-Hernandez, Sanz, et al. 2011). The production of lactic acid and short-chain fatty acids (SCFA) by MRPs was comparable to those of free carbohydrates (Hernandez-Hernandez, Sanz, et al. 2011). Recently, Jin et al. (2018) revealed that grass carp fish hydrolysates glycated with galactooligosaccharide can significantly alter the pattern of SCFA production in the hindgut of rats with increased levels of total SCFA, butyrate and propionate in the proximal colon, and the butyrate levels (74%) in the distal colon of rats.

The anti-inflammatory effects of MRPs

Apart from the bioactivities described above, MRPs from peptides have been documented to exert anti-inflammatory effects. Glycation of caseinomacropeptide with lactulose via Maillard reaction can inhibit production of interleukin-1β in intestinal epithelial (Caco-2) cells stimulated by pathogens, such as *Salmonella enterica* CECT 443 and *Listeria monocytogenes* CECT 935 (Laparra et al. 2013). Choe et al. (2016) reported that MRPs derived from protein hydrolysates of flatfish by-product and ribose possessed anti-inflammatory effects by suppressing lipopolysaccharide (LPS)-induced production of nitric oxide and prostaglandin E2 as well as the expression of inducible nitric oxide synthase and cyclooxygenase-2 in RAW 264.7 mouse macrophage cells. It was suggested that the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPKs) signaling pathways were involved in anti-inflammatory effects of MRPs (Choe et al. 2016). Similarly, MRP prepared from unicorn leatherjacket gelatin hydrolysate and galactose showed anti-inflammatory activity by reducing the expression of pro-inflammatory cytokines (interleukin-6 and interleukin-1β) and production of nitric oxide in LPS-induced RAW 264.7 cells (Karnjanapratum et al. 2016).

Bioactivities of volatile MRPs

As discussed earlier, there is a wide range of aroma compounds in MRPs, which are contributors to overall flavor in foods (Arihara, Zhou, and Ohata 2017). However, information on the bioactivity of odor components generated by MRPs is limited. The impacts of odor produced from Maillard reaction between glucose and glycine on human mood and brainwaves were evaluated by Zhou, Ohata, and Arihara (2016) who demonstrated that odor generated from Maillard reaction could significantly decrease negative

moods in panelists, including depressed, tense, fatigue and restless moods. This might be due to the positive hedonic perceptions of panelists towards these odorants (Zhou, Ohata, and Arihara 2016). Meanwhile, the increased alpha brainwave distribution implied a relaxing effect on the mental state of panelists. 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) was identified as a putative agent for changes in alpha brainwave distribution (Zhou, Ohata, and Arihara 2016). More recently, the same research group has reported that odor derived from Maillard reaction of xylose with chicken protein hydrolysates can significantly reduce systolic blood pressure in Wistar rats (Zhou et al. 2018). DMHF and 5-methyl-2-pyrazinemethanol (MPM) were ascertained to be key components responsible for the decreased blood pressure. After exposure to DMHF, the improved gastric vagal nerve activity and decreased renal sympathetic nerve activity were observed. Therefore, it was suggested that DMHF might lower blood pressure through the autonomic nervous system (Zhou et al. 2018).

The negative aspects and future considerations

Although MRPs obtained from food protein-derived peptides and carbohydrate mixtures can exert positive effects on flavor and bioactivity of food, several negative aspects of the use of glycated peptides cannot be ignored. For example, non-enzymatic browning is a limiting factor that can shorten the shelf life of food products containing MRPs (Guerra-Hernandez et al. 2002; Guyomarc'h et al. 2000). Furthermore, glycation of protein hydrolysates/peptides by Maillard reaction may damage nutritional quality of foods due to loss of essential amino acids, especially Lys, Arg, Met and Trp (Hurrell 1990). The formed MRPs can destroy certain vitamins (e.g. Vitamin B1 and B6), which affects metabolism of trace elements in the human body (Hurrell 1990). As a consequence of structural changes, MRPs exhibit high resistance towards gastrointestinal digestive enzymes, which further decreases protein digestibility (Delgado-Andrade and Morales 2005; Oste et al. 1986). It has been confirmed that consumption of MRPs-rich diet can exert negative impacts on protein digestibility (Seiquer et al. 2006) and dietary phosphorus absorption (Delgado-Andrade et al. 2011) in adolescent males. In addition, some MRPs have been linked to the increased prevalence of several diseases, such as diabetes, aging, cardiovascular disease, atherosclerosis and Alzheimer's disease (Brownlee 1995; Colaco and Harrington 1996; Hegab et al. 2012; Robert and Labat-Robert 2014). A recent study has revealed that high levels of MRPs (e.g. CML and furosine) can be detected in hydrolyzed infant formula, and these MRPs could induce oxidative stress based on in vitro cell models, which may exert a negative effect on infants exposed to hydrolyzed infant formula (Chen et al. 2019). Besides, Maillard reaction-derived browning is another detrimental factor for sensory quality of food as well as the acceptability of consumers. An increasing number of researchers are working on development of light-colored Maillard flavor-enhancing peptides. It has been reported that addition of cysteine to Maillard reaction system can contribute to formation of light-colored Maillard flavor-enhancing peptides (Eric et al. 2013), which is mainly due to interaction between cysteine and Amadori compound as well as inhibition of dicarbonyl compounds generation (Zhai et al. 2019). A recent study by Fu et al. (2020) has revealed that glucosamine, a highly reactive amino sugar, can induce peptide glycation for high-temperature, short-time treatment to generate light-colored Maillard flavor-enhancing peptides.

Since both beneficial and adverse aspects of MRPs during food processing coexist, it is imperative to control processing conditions and limit progression of Maillard reaction to reach the advanced stages. Detection of early and intermediate MRPs through chemical (Aalaei, Rayner, and Sjöholm 2019), spectroscopic (Ioannou and Varotsis 2016; Lin and Lin 2016) or chromatographic and mass spectrometric techniques (Troise 2018) can contribute to monitoring progression of the Maillard reaction. As the detection and accurate quantification of MRPs is a major challenge, liquid chromatography/gas chromatography-mass spectrometry may be essential to elucidate the structural characteristics of MRPs responsible for their impacts on bioactivity and flavor. In addition, numerous different strategies, such as addition of functional ingredients and use of enzymatic intervention, have been used for controlling and tailoring the extent of the Maillard reaction (Lund and Ray 2017). Understanding of structure-function relationship of MRPs would enable the optimization of food processing conditions and further controlling the extent of Maillard reactions. The toxicological and physiological effects of MRPs remain to be thoroughly investigated in order to acquire more information on their practical effects in vivo, which can contribute to further application as food ingredients. Such efforts would open new opportunities for use of MRPs in the food industry.

Conclusions

In recent years, increasing attention has been paid to the Maillard reaction of food protein-derived peptides. This review demonstrates that Maillard reaction-induced modifications exert some beneficial impacts on the flavor and bioactive properties of food protein-derived peptides. Due to the unique molecular structures and formation mechanisms of peptide-specific MRPs, they contribute to unique flavor development during food processing and storage. Furthermore, these MRPs also possess diverse bioactivities, such as antioxidant, antibacterial, antihypertensive, anti-inflammatory and bifidogenic properties. Subsequent understanding of structure-function relationship of MRPs and the in vivo physiological aspects of MRPs will contribute to their development as functional food ingredients. However, in view of the potential negative effects of MRPs, further investigations in monitoring and controlling Maillard reaction are crucial in order to fully obtain the benefits of peptide-based MRPs.

Disclosure statement

No potential conflict of interest was reported by the authors.

Abbreviations

MRPs	Maillard reaction products
2,5-DKPs	2,5-Diketopiperazines
ACE	Angiotensin I-converting enzyme
LC-MS	Liquid chromatography-mass spectrometry
LPS	Lipopolysaccharide
NF-κB	nuclear factor kappa B
MAPKs	mitogen-activated protein kinase
DMHF	2,5-dimethyl-4-hydroxy-3(2H)-furanone
MPM	5-methyl-2-pyrazinemethanol

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