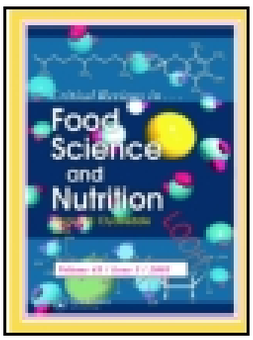

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Impact of Maillard Reaction products on Nutrition and Health: Current knowledge and need to understand their fate in the human digestive system

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Abstract

The Maillard Reaction (MR) is a non-enzymatic chemical reaction which results in the linkage between the amino group of amino acids and the carbonyl group of reduced sugars. MR products (MRPs) are common components of processed foods, mainly as a result of heating, especially in the Western diet. MRPs are classified as into three stages: initial, intermediate, and final stages, indicative of increased complexity and size, incurring different flavor, aroma, and texture. MRPs presence is known to reduce the nutritional quality of foods, particularly by reducing protein digestibility. Early reports have linked MRPs, especially advanced glycation end-products (AGEs) present in high concentration in the typical Western diet, to health conditions and diseases. However conflicting data has since been reported, and only a few (acrylamide, heterocyclic amines and 5-Hydroxymethylfurfural) MRPs have documented potential toxic or carcinogenic effects. High molecular weight MRPs are not available for direct absorption in the higher gastrointestinal tract, and are thus mostly metabolized by resident colonic microbes. MRPs have been the subject of sparse research interest in comparison with other non-digestible

dietary elements. In this review, we outline the state of knowledge on MRPs in nutrition and health, and highlight the need to develop the limited knowledge on their impact on the gut microbiota and which metabolites derive from MRPs fermentation.

Keywords

Maillard reaction products, Gut microbiota, Metabolomics, Advanced glycation end-products

1- Introduction

Western diet is becoming the dominant diet worldwide, and this trend is suspected to play an important role in the rise of western diseases. Western diet is characterized by higher intakes of red meat, fast foods, high-fat dairy products, fried and baked foods, high-sugar drinks, and a reduced intake of fibers and whole grains. While higher intake of simple sugars and fat are well known to increase disease and health conditions risks, there are also specific dietary elements that have been reported as detrimental. In this review, we will focus on Maillard Reaction Products (MRP), a relatively large class of molecules formed by linkage between carbohydrates and proteins/peptides. MRPs are known to occur in high levels in typical Western diet foodstuffs resulting from different food preparation methods, such as roasting, frying, and toasting. While early studies on MRPs have pointed to their role as biomarkers of Western diet consumption and potential correlation with diseases risk; there is currently no consensus on the role of MRPs in human health.

Although it has been known for decades that a symbiotic relationship exists between the host and microbiota, it is only recently that analytic tools have allowed for precise characterization of both microbiota members but also their metabolites. It is now well established that colonic microbes play an essential role in degrading undigested dietary elements and produce a vast array of metabolites. Diet-microbiota interactions are increasingly investigated in the context of health and disease (human and animal), with focus on cancer, inflammatory and metabolic diseases, obesity and more recently cognition and neurology. Surprisingly, MRPs and

MRPs-rich food interaction with the gut microbiota have received little attention from researchers in comparison with other dietary elements.

The purpose of this review is to outline the current knowledge on MRPs in the context of nutrition and health, and provide an overview of the scarce knowledge on metabolic impacts, microbiota interaction and metabolomics. We will conclude by summarizing the aspects for which extensive knowledge is available, and state the research directions that need to be undertaken to complete our knowledge of MRPs metabolic impacts.

2- The Chemistry of Maillard Reaction Products:

2-1 Maillard reaction in food

Maillard reaction (MR) was first described by Louis Camille Maillard in 1912, as the non-enzymatic chemical reaction between the carbonyl group of reducing sugar molecules with the amino group of amino acids occurring during processing and storage of foods. This reaction depends on physical parameters, such as heating, hydration, pH, and NH_2 requirements in order to form complex compounds that are not naturally in foods and are responsible for a range of colors, odors, flavors, and palatability. Thus, these molecules have positive or negative biological actions.

MR is divided into three stages: initial, intermediate, and final stage (HODGE. 1953) as described in Figure 1. In the initial stage, colorless products such as sugar-amine condensation and Amadori rearrangement products are produced. In the intermediate stage, yellow or colorless (with strong UV absorption) compounds are produced, including 5-Hydroxymethylfurfural,

reductone, and dicarbonyl compounds. In the final stage, brown color compounds are produced, such as melanoidins. The coloration occurs during heat pyrolysis of sugar, due to pH reaction on carbonyl group of sugar, while amino acids are not directly responsible for coloration (Adrian. 1974). The characteristic color in foodstuff, such as coffee, malt, bread, cocoa, and other roasted foods is the result of melanoidins, which are brown nitrogen-containing high molecular weight pigments (Bastos et al. 2012). In addition to desirable color, the intermediate and final stages are the most important to develop flavor and aroma, through Strecker degradation (Ames. 1990) (Somoza. 2007). MR can also affect the texture of food through protein cross-linking (Gerrard. 2002).

2-2 Generation of Maillard Reaction Products in vivo

In this review, we will focus on dietary MRPs. However, it is worth noting that MRPs have also been shown to be produced endogenously in humans. The knowledge on endogenous MR is reviewed extensively in (Tessier. 2010). The first report of MR in vivo was the glycation of aging proteins (MONNIER and CERAMI. 1981). In biological systems, this reaction is mainly implicated in protein modification, and divided into early and advance reaction stages. In the early stage, the formation of the Schiff base occurs, which is the interaction between the amine group of proteins with the reducing sugar, which generates α-dicarbonely compounds, or rearranges into the Amadori product. In the advance stage, the Amadori product undergoes rearrangements, which forms advanced glycation end products (AGEs) (BROWNLEE et al. 1984). The AGEs that have been detected in tissue protein are N^{ε}Carboxymethyllysine (CML), Pentosidins, and Glucosepane, and CML was the first AGEs isolated and characterized in vivo

(AHMED et al. 1986). The receptor of AGEs (RAGE) is a multi-ligand member of cell (Schmidt et al. 2000). Current studies demonstrated that CML/RAGE plays an important role in an induction the calcification cascade in diabetes (Wang et al. 2016). Thus, AGEs are known as metabolic products of glucose toxicity and play a significant role in the development of metabolic diseases (Wang et al. 2012).

2--3 Important Maillard Reaction Product Molecules

Evidence indicates that the most important Maillard reaction products in common diets are N^{ε}Fructoselysine (furosine), 5-Hydroxymethylfurfural (HMF), acrylamide, heterocyclic amines, advanced glycation end products (AGEs), and melanoidins. They all impact the nutritional quality of foodstuffs and biological systems either positively or negatively, as reviewed by (Tuohy et al. 2006). Table (1) summarizes the example of MRPs content of commonly consumed foods.

2-3-1 *N^{ε}Fructoselysine (Furosine) (FL)*:

The α-amino and Ɛ-amino group of lysine interact with reducing sugar, such as glucose, fructose, and maltose to form glycosylamine that undergo Amadori rearrangement products (ARP) in the early stage of Maillard reaction (HODGE. 1953). Amadori products are measured as N^{ε}fructoselysine because it was the first MRPs identified in foods, and is used as an indicator of the nutritional quality of foods. Moreover, FL amount is used to estimate protein damage caused by heating in the initial stage of MR in cereal products, such as pasta and bread (Erbersdobler and Somoza. 2007,Delgado-Andrade et al. 2005,Resmini et al. 1991). For example, low FL

values may indicate a decrease in pasta quality due to exposure low temperatures (Garcia-Banos et al. 2004). Temperature and time play an important role in the rise or decline of FL content in foods. For example, FL levels of soybean was high in extrusion treatments (66.55 µg/g) at 140 C° for 20--30s, followed by infrared heating (63.93 µg/g) at 110 C° for 50s, and microwave heating (56.07 µg/g) at 115C°for 5min (Zilic et al. 2014). Heating foods for a long time decreases the level of FL which gives rise to other products in the intermediate stage (Erbersdobler and Faist. 2001).

2-3-2 *5-Hydroxymethylfurfural (HMF)*:

5-Hydroxymethylfurfural (HMF) is produced in the intermediate stage of the Maillard reaction, and it forms in carbohydrate-rich food during acid-catalyzed dehydration of Schiff base of furfural (HODGE. 1953) (Figure 1). HMF is a widely used marker of nutritional quality of foods, such as baked diets and coffee, and it is not present in raw and fresh foods (Erbersdobler and Somoza. 2007). The concentration of HMF increases as thermal treatments or storage time of foodstuffs increase. Specifically, a positive correlation has been found between HMF content and the development of browning color so that reducing the heating period might be possible to reduce the concentration of HMF (Capuano et al. 2008). In addition to temperature, increasing pH plays an important role in decreasing the quantity of HMF in bakery products (Gokmen et al. 2007). Moreover, the type of sugar results in various quantities of HMF molecules. For example, hexose produce 4 to 5 times more HMF than pentose in baked foods. In addition to the type of sugars, the presence of certain amino acids, such as leucine, valine, and methionine can be linked to the concentration of HMF molecules in food products (Adrian. 1974). HMF is also formed

through the caramelization of sugars (Capuano and Fogliano. 2011). HMF has been found in different quantities in various foods. The concentration of HMF in dried fruits and caramel are high, but bakery foods and coffee are the major sources of HMF intake (Capuano and Fogliano. 2011,Murkovic and Pichler. 2006). It has been reported that coffee is the main source of HMF; the concentration of HMF in natural, blend, roasted and soluble coffee was 110, 625, 1734, 2480 mg HMF/kg, respectively (Arribas-Lorenzo and Morales. 2010).

2-3-3 *Acrylamide*:

Acrylamide, which is generated in intermediate stage of Maillard reaction, results from interaction between asparagine and reducing sugars such as fructose and glucose in heat treated bakery products and starchy foods (HODGE. 1953) (Figure 1). A diversity of chemical pathways lead to the formation of acrylamide in carbohydrate-rich foods (Granvogl and Schieberle. 2006,Granvogl and Schieberle. 2007). However, the major pathways are through Amadori products that degrade to form dicarbonyl compounds, which react with asparagine via Strecker degradation; or by the interaction of reducing sugar and asparagine to form the Schiff base without Amadori product (Granvogl and Schieberle. 2007,Granvogl and Schieberle. 2006). Like HMF, the formation of acrylamide is dependent on the type and concentrations of sugars, amino acids, temperature, and time. A positive correlation has been found between acrylamide levels and heating-time during baking of biscuits at 200 degrees C° and in potato chips that were fried at more than 248 °F (Nguyen et al. 2016,Tareke et al. 2002). Moreover, the interaction between glucose and asparagine generated the highest concentration of acrylamide, compared to fructose and asparagine (Capuano and Fogliano. 2011). Indeed, adding asparginase might control

acrylamide content in potato products (Zyzak et al. 2003). Unlike microwaved and boiled foods, the highest acrylamide concentration is formed through roasting, frying, and baking methods. The highest level of acrylamide was found in fried potato products. For instance, the average level of acrylamide found in potato crisps was 628 µg/kg, compared to biscuits, bread, and coffee, which were 317 µg/kg, 136 µg/kg, and 253 µg/kg, respectively (Capuano and Fogliano. 2011).

2-3-4 *Heterocyclic amines (HCAs)*:

Heterocyclic amines (HCAs), produced in the intermediate stage of Maillard reaction, result from the reaction between reducing sugar, amino acids, and their precursor creatine (a nitrogenous organic acid found naturally in muscles). To illustrate, the fragmentation of Amadori products can form various dicarbonyl compounds that can act with amino acids and creatine to form HCAs (JAGERSTAD et al. 1991,Tuohy et al. 2006) (Figure 1). Increasing temperature and time play an important role in generating HCAs, which are mainly found in muscles food, such as beef, pork, chicken, and fish. The most common of HCAs found and studied in foods are 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP), 2-amino-3-methyl-imidazo [4,5-f]quinoline (IQ), 2-amino-3-methylimidazo [4,5-f]quinoxaline (IQx), 2-amino-3,4-dimethylimidazo [4,5-f]quinoline (MeIQ), 2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline (MeIQx) and 2-amino-3,4,8-trimethyl-imidazo [4,5-f]quinoxaline (DiMeIQx) (Knize et al. 1994,Puangsombat et al. 2012).

The levels of HCAs in cooked meat depends on the type of meat and meat preparation methods. It has been reported that well done cooked beef had higher concentration of HCAs, compared to

medium cooked beef. Moreover, the highest level of total content of HCAs was quantified in fried bacon (17.59 ng/g), compared to fried pork (13.91 ng/g), fried beef (8.92 ng/g), or fried chicken (7.06 ng/g) (Puangsombat et al. 2012). In addition to total content of HCAs, high concentrations of PhIP were found in fried Tilapia (10.89 ng/g), followed by MeIQx (4.00 ng/g) and DiMeIQx (3.57 ng/g) in fried bacon, but IQ was not identified (Puangsombat et al. 2012). However, another study found the high levels of IQ was in well-done fried bacon (10.5 ng/g), which had high content of fat (Johansson and Jägerstad. 1994). It has also been reported that fried meat produced the highest concentration of HCAs, compared to baked meat (Puangsombat et al. 2012).

2-3-5 *Advanced Glycation End products (AGEs)*:

The interaction between glucose and protein or glucose and lipid generate advanced glycation end products (AGEs) that are also known as advanced Maillard reaction products (OBRIEN and MORRISSEY. 1989). AGEs are generated in the intermediate stage of the Maillard reaction. The degradation of Amadori products generate reactive dicarbonyl compounds that react further with amino acids to form irreversible and highly stable advance glycation end products (AGEs) (Tuohy et al. 2006,Cho et al. 2007) (Figure 1). AGEs are also produced endogenously through the glycation metabolic pathways (MONNIER and CERAMI. 1981). It has been found that Western diet is rich in AGEs, so this review concentrates on food-derived AGEs that have been detected and measured in more than 200 food items (Goldberg et al. 2004). The highest content of AGEs was found in fat food items, such as butter with, a mean of 100± 19 kilounits (kU)/g, compared to carbohydrate diet that contained the lowest levels of AGEs with a mean of

3.4±1.8kU/g (Goldberg et al. 2004). Moreover, the heating period and preparation methods appear to be more critical to form AGE. For example, the highest content of AGE was found in grilled foods at temperatures of 230°C for short time, compared to boiled foods at 100°C for long periods (Goldberg et al. 2004). There are many types of AGEs, and the most common studied are N^{ε}Carboxymethyllsine (CML) (non-cross-linking), pyrraline and pentosidine (cross-linking), which are most widely used as indicators of the nutritional quality of foodstuffs (Erbersdobler and Somoza. 2007).

N^{ε}Carboxymethyllsine (CML) is the most important bioactive markers of MRPs and a commonly measured AGE not only in food items (Goldberg et al. 2004) but also in biospecimens (Uribarri et al. 2003,Hofmann et al. 2002,Tessier et al. 2016). CML can be produced by the reaction of the carbonyl group of glyoxal from dicarbonyl componds with an epsilon-amino group of the lysine or by Amadori rearrangement products that act as a precursor of CML (HODGE. 1953,Tuohy et al. 2006). Besides furosine, CML was found to be a useful indicator of protein damage during the late stage of the Maillard reaction (Van Nguyen. 2006). Hull *et al* determined the CML content in 257 foods that are typically consumed in Western style diets (Hull et al. 2012).

2-3-6 *Melanoidins*:

Melanoidins, which are the final products of MR, are heterogeneous, insoluble, nitrogen-containing high molecular weight molecules that generate in the advanced stage of MR. Melanoidins are formed by dehydration, rearrangements, isomerization, and condensation of low molecules of MRPs formed in the intermediate stage (HODGE. 1953). To illustrate, during the

intermediate stage, dicarbonyl compounds, aldehydes, and furfural are generated, which react with each other to form aldol condensation products that react with amino acid to give rise to low molecular weights of MRPs, leading to the high molecular weights of melanoidins (HODGE. 1953) (Figure 1). Temperature and time appear to be significant factors affecting molecular weight, while pH plays an essential role in the chemical structure of melanoidins (Wang et al. 2011). The color of melanoidins that are found in coffee, malt, bread crust, cocoa, and honey, derive from the polymerization of MRPs (Hofmann. 1998,Hofmann. 1999). The highest amount of melanoidins was found in sourdough loaves (30 g per 100 g of crust), compared to soluble coffee (22.8 g per 100 g of coffee), but the quantity of melanoidins depends on the type of bread and the degree of roasting in coffee (Fogliano and Morales. 2011).

3-Maillard Reaction Products Impact on Nutrition and Health

3-1 Consequences of the Maillard Reaction in Nutrition:

Western diet, also known as the American standard diet, is characterized by higher intakes of red meat, high-fat dairy products, fried and baked foods, high-sugar drinks, and a reduced intake of fibers and whole grains. Maillard reaction products (MRPs), which are not naturally present in foods, are common in the Western diet (Hull et al. 2012). More than 200 staple food items of the typical Western diet contain measurable MRPs. These MRPs are the result of different food preparation methods, such as roasting, frying, and toasting, which are responsible for the aromas, colors, and tastes of foods (Goldberg et al. 2004,Hull et al. 2012,Zilic et al. 2014). For example, coffee and bread are the major source of Melanoidins (Fogliano and Morales. 2011), fried

chicken and broiled beef are rich in AGEs (Van Nguyen. 2006), and HCAs are found at the high concentration in cooked meat (Tamanna and Mahmood. 2015).

The typical exposure to several dietary MRPs has been reported by different survey-based studies. The estimation of dietary exposure to HMF from coffee was 5.26 mg HMF/day (Arribas-Lorenzo and Morales. 2010). The mean daily HCAs intake from meat products in a typical western diet was estimated at 450 ng per day^{-1}, including mainly PhIP, MeIQx and DiMeIQx (Keating et al. 1999). The average daily intake level of HCAs in Malaysia population was 553.7 ng per capita day^{-1}, and the highest level was PhIP followed by MeIQx and MeIQ (Jahurul et al. 2010). Based on the Spanish National consumption database, dietary exposure to acrylamide from potato crisps (based on a 3-day food record) was 0.053 µg/kg body weight for the adult population (17–60 years) and 0.142 µg/kg body weight for children (7–12 years), similar to other European countries (Arribas-Lorenzo and Morales. 2009). CML exposure from a MRP-high diet was shown to be 11.28 mg/day, while a MRP-low diet resulted in exposure of 5.36 mg/day in adolescents aged 11--14 years old (Delgado-Andrade et al. 2012). Dietary melanoidins represent the most abundant MRP the human diet and ranges between 10--12 g per day for individuals consuming a typical western diet (Fogliano and Morales. 2011,Pastoriza and Rufian-Henares. 2014). For example, the estimation of dietary melanoidins from coffee ranged between 0.5 to 2.0 g per day. The intake of bread and dry biscuits melanoidins ranged between 1.8-15 g and 3.2-8.5 g per day, respectively (Fogliano and Morales. 2011).

When foodstuffs undergo MR, the nutritional value of food is reduced, and some proteins are lost or become non-digestible, as reviewed by (Tuohy et al. 2006). For example, exposing

glucose and lysine to different heating periods caused loss of lysine (Adrian. 1974). Moreover, protein efficiency ratio (PER) decreases during MR, for example, the interaction between glycine and glucose reduced the PER by 22%, which reduced digestibility of nitrogen and metabolism of proteins measured in animals (Adrian. 1974). Increased amount of nitrogen in stool samples was also measured in young people who consumed MRPs-rich diet (Seiquer et al. 2006). MRPs presence also affects trace elements bioavailability. In an in-vitro study, the presence of MRPs in the diet (brown diet) reduced iron bioavailability (Mesias Garcia et al. 2009). MRPs decreased the digestion of magnesium in MRP-fed rats by 13%, compared to non-MRP-fed animals (Delgado-Andrade et al. 2007). Moreover, phosphorus bioavailability was linked to the consumption of a diet rich in MRPs (Delgado-Andrade et al. 2011). However, some reports indicate that melanoidins are likely to play a significant role in the binding of dietary metals thereby leading to antioxidant and antimicrobial properties (Morales et al. 2012). In particular, melanoidins that were prepared from glucose and glycine (GG) had a high chelating affinity towards copper (iron II) (32%), compared to melanoidins obtained from lactose and lysine (LL) and lactose N-acetyllysine (LLa) (Borrelli et al. 2002).

3-2 Effect of Maillard Reaction Products on Health**:**

The major concern arising from the Maillard reaction is the formation of compounds that are not naturally present in foodstuff. Time, high temperature, and other parameters generate products that may have detrimental health effects such as mutagenicity, carcinogenicity, cytotoxicity, and metabolic diseases, or beneficial impacts such as antioxidant, antimicrobial, and antihypertensive properties.

3-2-1 *Toxicity and Carcinogenicity*:

The MRPs that have been reported to possess toxic and carcinogenetic properties are HMF, Acrylamide, HCAs, and AGEs (Tuohy et al. 2006).

HMF is considered a toxicological compound because it can be converted into 5-sulphooxymethylfurfural (SMF) by sulfotransferase (SURH et al. 1994) and into 5-chloromethylfurfural (CMF) via allylic chlorination (SURH and TANNENBAUM. 1994). Both compounds are known to possess toxic and mutagenic compound. The highest daily exposure to dietary HMF was estimated as 8.57 mg HMF/day (Arribas-Lorenzo and Morales. 2010), and since the oral LD_{50} was found to be 3.1 g/kg body weight in rats (ULBRICHT et al. 1984), it can be considered that normal HMF intake may only represent a long term health risk. HMF was also shown to induce aberrant crypt foci of colon, in experimental animals (ARCHER et al. 1992). Skin papillomas caused by HMF have been reported in studies on rodents (SURH et al. 1994). Moreover, DNA damage, cytotoxicity of kidney, and mutagenicity of liver have been reported for HMF in mammalian cells (SCHOENTAL et al. 1971,Janzowski et al. 2000,Capuano and Fogliano. 2011,LEE et al. 1995). Specifically, HMF decreased the amount of glutathione, which is an important antioxidant that prevents damage to cellular components by reactive oxygen species (LEE et al. 1995).

Acrylamide was listed as a food-borne toxicant in 2002 by the Swedish National Food Administration, and it is considered a potentially carcinogenic and toxic compound (Tareke et al. 2002). As summarized in a review by Capuano *et al*, several studies demonstrated that acrylamide possesses cytotoxic, genotoxic, and tumorigenic activities (Capuano and Fogliano.

2011). In a study using rodents, the exposure of acrylamide in different amounts led to an increase in the risk of developing cancer in the lung, thyroid, skin, and pancreas (Beland et al. 2013). Previous studies indicated that the metabolism of acrylamide further converted to N-acetyl-S-(3-amino-3-oxopropyl)-cysteine (AAMA), and the oxidation of AAMA into AAMA-sulfoxide induced kidney and bladder toxicity (Ramu et al. 1995,Capuano and Fogliano. 2011). However, the actual mechanisms responsible for dietary acrylamide carcinogenicity are still not well documented (Capuano and Fogliano. 2011,Tuohy et al. 2006).

Because heterocyclic amines (HCAs) are known as mutagenic and carcinogenic compounds, several studies indicated that red meat might be a risk factor for colorectal cancer (Cross and Sinha. 2004). HCAs are converted into genotoxic compounds by hepatic cytochrome P-450 1A2 enzyme (CYP1A2), which is activated by many factors, such as HCAs-rich diet. Specifically, CYP1A2 converted dietary HCAs into MeIQx and PhIP that are found in human urine (Boobis et al. 1994). In 1993, MeIQ, MeIQx, and PhIP were categorized as carcinogenic compounds by the International Agency for Research on Cancer, and IQ might also be a human carcinogen. PhIP, but not IQ, has been shown to induce colon tumors in rodents (CANZIAN et al. 1994). Moreover, liver tumors were induced in mice fed 0.06% of MeIQx that was extracted from foods (Ohgaki et al. 1987), and 0.03% of MeIQ that was isolated from broiled sardines induced tumors in various organs, such as the Zymbal gland, oral cavity, colon, skin, and mammary gland of rat (Kato et al. 1989). Intestinal tumors were found in Nagase analbuminemic rats that were fed 0.04% to 0.01% of PhIP (Ochiai et al. 1991). Colonic aberrant crypt (AC) was found in the large intestine of rodents after 12 weeks of PhIP oral administration (Takahashi et al. 1991).

The potential role of endogenous AGEs and RAGE receptors in cancer risk has been extensively studies (Yamagishi et al. 2015). However, the pathological implications regarding the dietary AGEs and development of colorectal cancer risks have become more controversial. Elevated glyceraldehyde –AGEs levels were associated with the risk of rectal cancer but were not linked to the risk of colon cancer based on 1,055 colorectal cancer cases (Kong et al. 2015). Increased risk of pancreatic cancer was found to correlate with dietary CML-AGE consumption, particularly in male pancreatic cancer patients (Jiao et al. 2015). In contrast, melanoidins, mainly from coffee, have generally been reported as potentially protective against cancer (Vitaglione et al. 2012,Gasscht et al. 2015,Ludwig et al. 2014). In *vitro* studies have shown significant anti-proliferative effects of melanoidins from heated potato fiber (Langner et al. 2013,Langner et al. 2011), miso and soy sauce(Kamei et al. 1997) and coffee(Vitaglione et al. 2012). However, because melanoidins are likely to behave similarly to fiber in the colonic microbial ecosystem, it has been suggested that most anti-cancer properties may derive from microbial fermentation metabolites (Ludwig et al. 2014,Jaquet et al. 2009).

3-2-2 *Metabolic and Cardiovascular Diseases:*

The more common emerging evidence of MRPs in the pathogenesis of metabolic and cardiovascular diseases are dietary AGEs through their binding with the receptor for advanced glycation end products (RAGEs) (Goldin et al. 2006,Grillo and Colombatto. 2008,Hartog et al. 2007). The binding of AGE-RAGE in the endothelial cells activates the transcription nuclear factor-kappa B (NF-κB), which induces pro-inflammatory cytokines and up regulates inflammation, notably in association with the development of diabetes and cardiac dysfunction

(Hartog et al. 2007,Goldin et al. 2006). AGEs have been used as health biomarkers of several human diseases and conditions (Tessier and Birlouez-Aragon. 2012), such as inflammatory processes (Van Puyvelde et al. 2014), cardiovascular and metabolic diseases (Prasad et al. 2012,Yamagishi et al. 2017,de Vos et al. 2016) and aging (Wagner et al. 2016). Cai *et al* found that a high-AGE diet enhanced low-density lipoprotein (LDL) induces vascular toxicity through protein kinase stimulant in diabetic patients (Cai et al. 2004). In addition to heart failure, dietary AGEs were shown to induce Type 1 diabetes in non-obese-diabetic mice (Peppa et al. 2003). A diet high in AGEs induced inflammatory mediators such as TNF-α, which contributes to develop diabetes (Vlassara et al. 2003). In addition, a reduction in dietary AGE intake led to lower levels of circulating AGE and improved insulin sensitivity in db/db mice (Hofmann et al. 2002) and reduce possibly cardiovascular associated mortality in renal failure patients (Uribarri et al. 2003). AGEs were found to be involved in aging and in neurodegenerative pathways are reviewed by (Grillo and Colombatto. 2008).

CML has been identified in tissues (Wang et al. 2012), plasma (Teerlink et al. 2004), urine, and feces (Delgado-Andrade et al. 2012). Although, CML is produced within the organism endogenously (AHMED et al. 1986), several studies indicate that a significant correlation exists between dietary AGE content and CML serum in health people, as reviewed by (Uribarri et al. 2005). A recent study carried out by Tessier *et al* found that the accumulation of dietary CML-fed mice was high in the kidney, intestine, and lungs, compared to native CML-fed mice. (Tessier et al. 2016). Serum levels of CML were found significantly higher in patients with diabetes, compared to healthy subjects (Jara et al. 2012). Pyrraline was found in the extracellular matrix of glomerular and arteriolar renal tissues from both diabetic and aged nondiabetic people

(MONNIER et al. 1992). The highest level of pentosidine was found in lens proteins of diabetic and uremic patients (MONNIER et al. 1992).

3-2-3 *Antioxidant, Antimicrobial and Antihypertensive Activities*:

The beneficial effects of antioxidant properties of MRPs have been detected in some compounds, such as FL, HMF, and melanoidins. Amadori compounds might exert a moderate effect on the antioxidant activity of dehydrated onion and garlic during storage (Moreno et al. 2006). The pro-oxidant properties were observed in the early stages (FL) of pasta (Anese et al. 1999). Beside other wide range of products, HMF was found to play an important role of the antioxidant capacity of honey (Gheldof et al. 2002). Although the early and intermediate MRPs were shown to exert moderate antioxidant activity (Rufian-Henares and Delgado-Andrade. 2009), melanoidins are believed to be the major antioxidant MRPs (Rufian-Henares and Morales. 2007b).

Melanoidins are known as antioxidants, thus, several studies point out that food melanoidins could prevent gastrointestinal tract cancers (Morales et al. 2012). Melanoidins, extracted from different foods, such as roasted barley (malts) (MILIC et al. 1975), cocoa (Hofmann. 1999), bread crust, and coffee (Fogliano and Morales. 2011), have been shown to enhanced antioxidant capacity (Somoza et al. 2005). For example, a significant increase of antioxidant activity was reported in the plasma of healthy people after intake of 200 ml coffee (Natella et al. 2002). This result was in agreement with those reported by Vitaglione *et al*, demonstrating a decrease in liver damage in rodents fed melanoidins extracted from coffee (Vitaglione et al. 2010). In addition to coffee, malt and bread crust were found to increase the activity of chemopreventive enzymes of

the kidney and liver and to decrease oxidative stress levels in the plasma of rodents (Somoza et al. 2005). The beneficial effects of MRPs on the antimicrobial and antihypertensive properties have been studied with melanoidins (Rufian-Henares and Morales. 2007a,Wang et al. 2011). Coffee melanoidins demonstrasted higher antimicrobial activities towards *Geobacillus stearothermophylus var. calidolactis* (Rufian-Henares and Morales. 2006). Melanoidins fractions were shown to suppress *Helicobacter pylori* infection in vitro and in vivo studies (Hiramoto et al. 2004). Moreover, water-soluble melanoidins were shown to possess antimicrobial properties towards pathogenic *E.coli* strains by disrupting their membranes (Rufian-Henares and Morales. 2008). Data from vitro and vivo studies indicated that melanoidins fractions from bread crust and coffee have a prebiotic activity similar to that of dietary fiber (Wang et al. 2011,Jaquet et al. 2009). For example, bread crust stimulated growth of beneficial bacteria, such as *Bifidobacterium* spp (Borrelli and Fogliano. 2005). The antihypertensive activity of melanoidins isolated from coffee and beer has been investigated only through in vitro ACE-inhibitory activity (Rufian-Henares and Morales. 2007b).

4- MRPs and Gut Microbiome/Metabolome

4.1 Human Gut Microbiome and Metabolome

In the last decade, the human microbiome/microbiota has received extreme attention from basic and medical scientists, and it is now well established that the human body hosts up to 100 trillion (10^{14}) microbes. The vast majority of them are located in the human gastrointestinal tract (GIT), which has become the most investigated microbial ecosystem (Ley et al. 2006). While microbiota composition is subject to strong individuality, a core human gut microbiota can be

defined (Turnbaugh et al. 2009,Arumugam et al. 2011). The vast majority of colonic microorganisms depend on undigested dietary elements to support their metabolic needs, but some genera have also evolved to utilize other microbial by-products or host-derived compounds (Carbonero et al. 2012). The potential involvement of the gut microbiome has been extensively studied and reviewed for diseases such as intestinal cancer (Candela et al. 2014,O'Keefe et al. 2015), inflammatory bowel diseases (Wehkamp and Frick. 2017), diabetes and metabolic syndrome, obesity (Delzenne et al. 2015,Kahn and Flier. 2000) and more recently brain diseases (Fung et al. 2017).

Studies revealed a high level of variability in microbiota due to dietary habits, including short and long term dietary habits that impact the gut microbiome (Ley et al. 2006). For example, it has been reported that long-term diets were associated with the type of enterotypes of gut microbiota, but short-term diets were correlated with gut microbiota composition (Wu et al. 2011). Wu *et al* found that the prevalence of *Bacteroides* enterotype was strongly associated with the consumption of animal protein and saturated fats, but the dominance of the *Prevotella* enterotype was linked to a carbohydrate-based diet (Wu et al. 2011). Consequently, the interaction between diet and gut microbiome have been involved in both etiology and preservation from diseases (Louis et al. 2007,O'Keefe. 2016,O'Keefe. 2008).

Gut bacteria degrade undigested foods by two main metabolic pathways: saccharolytic and proteolytic. On the one hand, saccharolytic bacterial species, such as *Bacteroides* spp, *Bifidobacterium* spp, *Ruminococus* spp, *Peptostreptococcus* spp and *Roseburia intestinalis* hydrolyze non-digestable carbohydrates into monomeric sugars that convert to beneficial

products, such as short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate (GIBSON and ROBERFROID. 1995,Duncan et al. 2002). On the other hand, microbial metabolism of proteins, such as *Bacteroides* spp, *Propionbacterium* spp, *Eubacterium* spp, and *Peptococcus* spp degrade peptide and amino acids into a variety of products including short or branched-chain fatty acids, and other metabolites compounds, some of which are potentially toxic, such as uremic toxins (Evenepoel et al. 2009,Macfarlane et al. 1986), phenols and amines. While metabolites from these two pathways are arguably dominant in terms of abundance, the complete metabolome comprises at least tens of thousands of different molecules (42,003 in the most recent version of the Human Metabolome Database) (Wishart et al. 2016). Since MRPs are molecules with both carbohydrate and proteic structures, it is likely that there are less bacterial members able to degrade them, and that microbial consortia are probably needed to fully metabolize them to end-products.

4.2 Known Microbial Interactions between Microbes and MRPs

4.2.1 *Impact of MRPs on Food-Associated Microbes*

The impact of MRPs and associated environmental parameters on microorganisms has been studied mostly by culture-dependent studies, as reviewed in (Helou et al. 2014). The first study was by Hachisuka, describing the impact of heat treatments on germination spores of bacteria. The germination time of *Bacillus subtilis* spores decreased after exposing media to heat treatments (HACHISUKA et al. 1955). This finding was in agreement with the study reported by Viswanathan *et al*, describing an inhibitory growth of *Lactobacillus bulgaricus* in heated milk powders (VISWANATHAN and SARMA. 1957). On the contrary, Foster observed the growth

of lactic acid bacteria in heated milk (FOSTER. 1952). Lately, some studies have attempted to shed light on the effect of MRPs on microorganisms. For instance, Stecchini *et al* found that MRPs inhibited the growth of food-poisoning microorganism, such as *Staphylococcus aureus*, *Salmonella typhimurium*, and *Salmonella enteritidis* (STECCHINI et al. 1991). Several studies indicated microorganisms that were isolated from different environments were able to degrade and use MRPs from different stages as shown in Table (2).

FL was shown to be preferentially used as a carbon source by *Salmonella Typhimurium* in batch cultures, compared to AGEs and melanoidins (Chalova et al. 2012). Moreover, *Escherichia coli* were found to use FL as an energetic substrate. *Escherichia coli* has fructoselysine-6-phosphate deglycase enzyme that catalyzed the ATP-dependent phosphorylation of fructoselysine to fructoselysine 6-phosphate, and subsequently to lysine and glucose 6-phosphate. Thus, this enzyme reached high activity levels during fructoselysine utilization (Wiame et al. 2002). Another study identified glucoselysine-6-phosphate deglycase produced by *Enterococcus faecium* to convert fructoselysine into lysine and glucose 6-phosphate, which then used as an energy source (Wiame et al. 2005).

Among intermediate MRPs, it was found that SMF and CMF, which derived from HMF, had direct mutagenicity towards *Salmonella typhimurium* (Sommer et al. 2003). In addition to HMF, the formation of acrylamide during French fries deep-frying can be effectively lowered by prior lactic acid fermentation carried out by *Lactobacillus plantarum* (Baardseth et al. 2006). Moreover, a recent study described the reduction of acrylamide formation in wheat biscuits by lactic acid bacteria fermentation, including *Lactobacillus sakei, Pediococcus pentosaceus* and

Pediococcus acidilactici (Bartkiene et al. 2016). In a recent review, several studies indicated that acrylamide was catalyzed to ammonia and acrylic acid by some microorganisms, which produce amidases (an enzyme found in some microbes) (Duda-Chodak et al. 2016). In addition to above, data from microorganism studies found that some gram- positive and gram- negative bacteria could detoxify HCAs by binding of HCAs to the peptidoglycan layer and the outer membrane of microbes under physiologically conditions, which have been reviewed in details by (Knasmuller et al. 2001).

In the advanced products of MR, the reduction of AGEs and melanoidins levels were 37% and 15% respectively after incubating with *Salmonella Typhimurium* in batch cultures (Chalova et al. 2012). Inhibition of microbial growth by MRPs has been studied (EINARSSON et al. 1983). High molecular weight MRPs inhibited the growth of *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*, compared to low molecular weight MRPs (EINARSSON et al. 1983). These results are in agreement with studies by Rufian-Henares *et al,* demonstrating higher antimicrobial activity was found in high molecular weight of melanoidins, such as coffee (Rufian-Henares and Morales. 2006). This approach was successfully tested with darker coffee that exhibited high antimicrobial activity against *E.coli,* and report that melanoidins can damage both inner and outer membranes of the pathogenic bacteria strain (*E.coli*) (Rufian-Henares and Morales. 2008). Other studies showed that the antimicrobial activity of melanoidins were higher towards gram-positive microorganisms compared to gram-negative microbes (Rufian-Henares and Morales. 2006,Rufian-Henares and Morales. 2007a,Rufian-Henares and Morales. 2007b).

4.2.2 *Known Microbial Metabolites of MRPs*:

4.2.2.1 Metabolite of Amadori Products:

The available data for metabolism of early MRPs found that the urinary excretion of ingested fructolysine was 60--80% in rats and 3--10% in humans (Faist and Erbersdobler. 2001). It has been reported that the intestinal absorption rate of Ɛ-fructoselysine was higher than α-fructoselysine (Erbersdobler et al. 1981). Another study found that excretion of NƐFructoselysine in urine and feces was very low 3.68% in humans and 11.2%, rats (Erbersdobler and Faist. 2001). Thus, several studies indicated that the rest of NƐFructoselysine was more likely to be degraded by intestinal microorganisms or accumulate in different tissues, according to a review by Faist *et al* (Faist and Erbersdobler. 2001).

4.2.2.2 Metabolite of Advance MRPs (Pre-Melanoidins):

HMF is converted to 5-hydroxymethyl-2-furoic acid (HMFA), during its metabolism and is excreted through urine in mammals (Godfrey et al. 1999,Husoy et al. 2008). Acrylamide is converted into other substances, such as glycidamide or conjugated with glutathione (GSH). Both glycidamide and GSH are further converted into N-acetyl-S-(3-amino-3-oxopropyl)-cysteine (AAMA) and other substances that are excreted with urine (Boettcher et al. 2006). The excretion of CML in feces was high for rich-MRP 3.52 mg/day, compared to low-MRP1.23 mg/day. However, the elimination CML in urine was not significant difference between high and low MRPs (Delgado-Andrade et al. 2012). The large amounts of dietary CML recovered in urine (accounting for 26–29%) and in feces (accounting for 15–22%), but more than 50% of CML was not yet accounted for, which might be degraded by the intestinal microbiota (Ames. 1990).

4.2.2.3 Metabolites of Melanoidins:

The urinary excretion rate of melanoidins depends on molecular weight. To clarify, the rate of excretion of high molecular weight (HMW) melanoidins was 4.3%, compared to low molecular weight (LMW), which was 27% (FINOT and MAGNENAT. 1981). Importantly, several studies indicated that major dietary sources of melanoidins remain in the gastrointestinal tract where they have biological action, according to review by Tagliazucchi *et al* (Tagliazucchi and Bellesia. 2015).

4.2.3 *The Limited Knowledge on the Impact of MRPs on Gut Microbiota*

Most research focused on impact of dietary MRPs using in vitro assays using fermentation with human fecal samples or in vivo models by means of animal studies. In the early observation of the effect of MRPs on the gut microorganism in vitro study, Jemmali (1969) observed increase growth rates of three *Lactobacilli* strains, but no effect on *E.coli* growth in batch cultures of MRPs (Jemmali. 1969). Moreover, Horikoshi *et al* detected the impact of browning products, prepared from D-glucose and glycine, on the growth both aerobic and anaerobic *lactobacilli* in the microflora of rats (HORIKOSHI et al. 1981). From the small number of in vitro studies, it appears that MRPs stages influence the response of gut microbiota members (Table 3).

As stated previously, excretion of N^{ε}Fructoselysine (FL) in urine and feces is very low (Erbersdobler and Faist. 2001), and it has been shown that the human colonic microbiota can degrade FL after 4 hours of anaerobic incubation with human fecal samples (Hellwig et al. 2015). Moreover, gut bacteria related to *Intestinimonas AF211* were found to contain genes

coding for a butyrate-acetoacetyl-CoA transferase that can convert Amadori products into butyrate in the human intestine (Bui et al. 2015). A negative correlation between the fecal of *bifidobacteria* counts and Amadori product was found in study using human fecal samples, but no correlations were discovered between cecal *Bifidobacteria* numbers of rats and Amadori product (Seiquer et al. 2014).

Fecal suspensions of N^{ε}Carboxymethyllsine (CML) and pyrraline (PYR), the type of AGEs produce from the intermediate stage, were degraded by human gut microbiota after 24 hours (Hellwig et al. 2015). However, CML did not impact the growth rates of three strains of *E.coli* that were isolated from human and piglet feces, and there was no degradation of CML observed in the presence of *E.coli* (Helou et al. 2014). The number of *lactobacilli* and CML intake correlated negatively for both humans and animal studies (Seiquer et al. 2014). In addition to CML, negative correlations were found between Hydroxymethylfurfural (HMF) intake and *lactobacilli*, *Escherichia*, and *Shigella* counts both in vivo (animal) and vitro (human) studies (Seiquer et al. 2014). Moreover, HMF was converted into furfural alcohol, which is less toxic after it was incubated with enteric bacteria, such as *Klebsiella*, *Enterobacter*, and *Escherichia* in short time incubations. According to authors, these biotransformations might be valuable in the detoxification of furfural compounds (BOOPATHY et al. 1993). IQ, a known HCA as mutagenic compound, was converted into innocuous metabolites structure after incubation with human fecal samples (Bashir et al. 1987). Contrastingly, activation of IQ by *Eubacterium* and *Clostridium* into potentially mutagenic 7-hdroxy "IQ" compounds has also been shown in *Salmonella* (VANTASSELL et al. 1990).

Data from animal studies show that melanoidins escape digestion and pass into the lower gastrointestinal tract (FINOT and MAGNENAT. 1981). Subsequently, they are likely to be degraded by gut microorganisms (Faist and Erbersdobler. 2001). Indeed, melanoidins have been shown to have potential prebiotic activity (Wang et al. 2011). For instance, an increase in the number of gut bacteria was observed during fermentation with bread melanoidins, which could be used as sources of carbon and nitrogen, particularly *Bifidobacteria* strains, which had the highest growth among anaerobic bacteria (Borrelli and Fogliano. 2005). Moreover, because melanoidin fractions were found in coffee (Daglia et al. 2008), melanoidins might increase the proportion of *Bacteroides-prevotella*, compared to total cell counts after healthy human fecal samples were incubated with different roasted coffee (Reichardt et al. 2009). According to their findings, the composition of human fecal microbiota was changed during incubation with coffee. This result was in accordance with those studied by Jaquet *et al*, showing increase in *Bifidobacterium* spp and metabolic activity in healthy people after a three week test period of the consumption coffee (Jaquet et al. 2009).

5- Conclusions and perspectives:

The chemistry of dietary MRPs is relatively well known, but the biological impact of these molecules is less understood. While acrylamide, HCA and HMF have relatively well established detrimental health properties, the normal dietary exposure to these MRPs is arguably low, even in the case of Western diet. More in vitro or animal studies using relevant concentrations of MRPs, or actual MRP-rich food products are needed in order to better assess the status of MRPs towards different health conditions and diseases.

A significant fraction of dietary MRPs are large molecules that mostly escape digestion, but little is known about their fate in the gastrointestinal tract and their interaction with microbiota. In *vitro* models have been used most commonly to study the impact of MRPs on gut microbiota. However, it can be argued that in vitro models would actually be better suited to determine the metabolite profiles resulting from microbiota fermentation of MRPs. In *vivo* studies are greatly needed to track the impact of MRPs on gut microbiota as well as biomarkers of health.

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References

Adrian, J. (1974). Nutritional and physiological consequences of the Maillard reaction. *World review of nutrition and dietetics.* **19**: 71--122.

AHMED, M., THORPE, S., andBAYNES, J. (1986). Identification of N-Epsilon-Carboxymethyllysine as a Degradation Product of Fructoselysine in Glycated Protein. *J Biol Chem.* **261**: 4889--4894.

Ahmed, N., Mirshekar-Syahkal, B., Kennish, L., Karachalias, N., Babaei-Jadidi, R., andThornalley, P. (2005). Assay of advanced glycation endproducts in selected beverages and food by liquid chromatography with tandem mass spectrometric detection. *Molecular Nutrition & Food Research.* **49**: 691--699.

Ames, J. M. (1990). Control of the Maillard reaction in food systems. *Trends Food Sci Technol.* **1**: 150--154.

Anese, M., Nicoli, M., Massini, R., andLerici, C. (1999). Effects of drying processing on the Maillard reaction in pasta. *Food Res Int.* **32**: 193--199.

ARCHER, M., BRUCE, W., CHAN, C., CORPET, D., MEDLINE, A., RONCUCCI, L., STAMP, D., andZHANG, X. (1992). Aberrant Crypt Foci and Microadenoma as Markers for Colon Cancer. *Environ Health Perspect.* **98**: 195--197.

Arribas-Lorenzo, G. and Morales, F. J. (2009). Dietary exposure to acrylamide from potato crisps to the Spanish population. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* **26**: 289--297.

Arribas-Lorenzo, G. and Morales, F. J. (2010). Estimation of dietary intake of 5-hydroxymethylfurfural and related substances from coffee to Spanish population. *Food and Chemical Toxicology.* **48**: 644--649.

Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., Kurokawa, K., Leclerc, M., Levenez, F., Manichanh, C., Nielsen, H. B., Nielsen, T., Pons, N., Poulain, J., Qin, J., Sicheritz-Ponten, T., Tims, S., Torrents, D., Ugarte, E., Zoetendal, E. G., Wang, J., Guarner, F., Pedersen, O., de Vos, W. M., Brunak, S., Dore, J., Weissenbach, J., Ehrlich, S. D., Bork, P., andMetaHIT Consortium. (2011). Enterotypes of the human gut microbiome. *Nature.* **473**: 174--180.

Assar, S. H., Moloney, C., Lima, M., Magee, R., andAmes, J. M. (2009). Determination of N (E >)-(carboxymethyl)lysine in food systems by ultra performance liquid chromatography-mass spectrometry. *Amino Acids.* **36**: 317--326.

Baardseth, P., Blom, H., Skrede, G., Mydland, L., Skrede, A., andSlinde, E. (2006). Lactic acid fermentation reduces acrylamide formation and other Maillard reactions in French fries. *J Food Sci.* **71**: C28-C33.

Bartkiene, E., Jakobsone, I., Pugajeva, I., Bartkevics, V., Zadeike, D., andJuodeikiene, G. (2016). Reducing of acrylamide formation in wheat biscuits supplemented with flaxseed and lupine. *Lwt-Food Science and Technology.* **65**: 275--282.

Bashir, M., Kingston, D., Carman, R., Van Tassell, R., andWilkins, T. (1987). Anaerobic metabolism of 2-amino-3-methyl-3H-imidazo [4, 5-f] quinoline (IQ) by human fecal flora. *Mutation Research Letters.* **190**: 187--190.

Bastos, D. M., Monaro, É, Siguemoto, É, and Séfora, M. (2012). Maillard reaction products in processed food: Pros and Cons. INTECH Open Access Publisher.

Beland, F. A., Mellick, P. W., Olson, G. R., Mendoza, M. C. B., Marques, M. M., andDoerge, D. R. (2013). Carcinogenicity of acrylamide in B6C3F(1) mice and F344/N rats from a 2-year drinking water exposure. *Food and Chemical Toxicology.* **51**: 149--159.

Boettcher, M. I., Bolt, H. M., Drexler, H., andAngerer, J. (2006). Excretion of mercapturic acids of acrylamide and glycidamide in human urine after single oral administration of deuterium-labelled acrylamide. *Arch Toxicol.* **80**: 55--61.

Boobis, A. R., Lynch, A. M., Murray, S., de la Torre, R., Solans, A., Farre, M., Segura, J., Gooderham, N. J., andDavies, D. S. (1994). CYP1A2-catalyzed conversion of dietary heterocyclic amines to their proximate carcinogens is their major route of metabolism in humans. *Cancer Res.* **54**: 89--94.

BOOPATHY, R., BOKANG, H., andDANIELS, L. (1993). Biotransformation of Furfural and 5-Hydroxymethyl Furfural by Enteric Bacteria. *J Ind Microbiol.* **11**: 147--150.

Borrelli, R. and Fogliano, V. (2005). Bread crust melanoldins as potential prebiotic ingredients. *Molecular Nutrition & Food Research.* **49**: 673--678.

Borrelli, R., Fogliano, V., Monti, S., andAmes, J. (2002). Characterization of melanoidins from a glucose-glycine model system. *European Food Research and Technology.* **215**: 210--215.

BROWNLEE, M., VLASSARA, H., andCERAMI, A. (1984). Nonenzymatic Glycosylation and the Pathogenesis of Diabetic Complications. *Ann Intern Med.* **101**: 527--537.

Bui, T. P. N., Ritari, J., Boeren, S., de Waard, P., Plugge, C. M., andde Vos, W. M. (2015). Production of butyrate from lysine and the Amadori product fructoselysine by a human gut commensal. *Nature communications.* **6**.

Cai, W., He, J., Zhu, L., Peppa, M., Lu, C., Uribarri, J., andVlassara, H. (2004). High levels of dietary advanced glycation end products transform low-density lipoprotein into a potent redox-sensitive mitogen-activated protein kinase stimulant in diabetic patients. *Circulation.* **110**: 285--291.

Candela, M., Turroni, S., Biagi, E., Carbonero, F., Rampelli, S., Fiorentini, C., andBrigidi, P. (2014). Inflammation and colorectal cancer, when microbiota-host mutualism breaks. *World Journal of Gastroenterology.* **20**: 908--922.

CANZIAN, F., USHIJIMA, T., SERIKAWA, T., WAKABAYASHI, K., SUGIMURA, T., andNAGAO, M. (1994). Instability of Microsatellites in Rat Colon Tumors Induced by Heterocyclic Amines. *Cancer Res.* **54**: 6315--6317.

Capuano, E., Ferrigno, A., Acampa, I., Ait-Ameur, L., andFogliano, V. (2008). Characterization of the Maillard reaction in bread crisps. *European Food Research and Technology.* **228**: 311--319.

Capuano, E. and Fogliano, V. (2011). Acrylamide and 5-hydroxymethylfurfural (HMF): A review on metabolism, toxicity, occurrence in food and mitigation strategies. *Lwt-Food Science and Technology.* **44**: 793--810.

Carbonero, F., Benefiel, A. C., Alizadeh-Ghamsari, A. H., andGaskins, H. R. (2012). Microbial pathways in colonic sulfur metabolism and links with health and disease. *Frontiers in Physiology.* **3**: UNSP 448.

Chalova, V. I., Hernandez-Hernandez, O., Muthaiyan, A., Sirsat, S. A., Natesan, S., Luz Sanz, M., Javier Moreno, F., O'Bryan, C. A., Crandall, P. G., andRicke, S. C. (2012). Growth and transcriptional response of Salmonella Typhimurium LT2 to glucose-lysine-based Maillard reaction products generated under low water activity conditions. *Food Res Int.* **45**: 1044--1053.

Cho, S. -., Roman, G., Yeboah, F., andKonishi, Y. (2007). The road to advanced glycation end products: A mechanistic perspective. *Curr Med Chem.* **14**: 1653--1671.

Cross, A. J. and Sinha, R. (2004). Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen.* **44**: 44--55.

Daglia, M., Papetti, A., Aceti, C., Sordelli, B., Gregotti, C., andGazzani, G. (2008). Isolation of High Molecular Weight Components and Contribution to the Protective Activity of Coffee against Lipid Peroxidation in a Rat Liver Microsome System. *J Agric Food Chem.* **56**: 11653--11660.

de Vos, L. C., Lefrandt, J. D., Dullaart, R. P. F., Zeebregts, C. J., andSmit, A. J. (2016). Advanced glycation end products: An emerging biomarker for adverse outcome in patients with peripheral artery disease. *Atherosclerosis.* **254**: 291--299.

Delgado-Andrade, C., Rufian-Henares, J., andMorales, F. (2005). Fast method to determine furosine in breakfast cereals by capillary zone electrophoresis. *European Food Research and Technology.* **221**: 707--711.

Delgado-Andrade, C., Seiquer, I., andNavarro, M. P. (2007). Effects of consumption of Maillard reaction products on magnesium digestibility and tissue distribution in rats. *Food Sci Technol Int.* **13**: 109--115.

Delgado-Andrade, C., Seiquer, I., Mesias Garcia, M., Galdo, G., andPilar Navarro, M. (2011). Increased Maillard reaction products intake reduces phosphorus digestibility in male adolescent mice. *Nutrition.* **27**: 86--91.

Delgado-Andrade, C., Tessier, F. J., Niquet-Leridon, C., Seiquer, I., andPilar Navarro, M. (2012). Study of the urinary and faecal excretion of N (epsilon)-carboxymethyllysine in young human volunteers. *Amino Acids.* **43**: 595--602.

Delzenne, N. M., Cani, P. D., Everard, A., Neyrinck, A. M., andBindels, L. B. (2015). Gut microorganisms as promising targets for the management of type 2 diabetes. *Diabetologia.* **58**: 2206--2217.

Duda-Chodak, A., Wajda, L., Tarko, T., Sroka, P., andSatora, P. (2016). A review of the interactions between acrylamide, microorganisms and food components. *Food & Function.* **7**: 1282--1295.

Duncan, S., Hold, G., Barcenilla, A., Stewart, C., andFlint, H. (2002). Roseburia intestinalis sp nov., a novel saccharolytic, butyrate-producing bacterium from human faeces. *Int J Syst Evol Microbiol.* **52**: 1615--1620.

EINARSSON, H., SNYGG, B., andERIKSSON, C. (1983). Inhibition of Bacterial-Growth by Maillard Reaction-Products. *J Agric Food Chem.* **31**: 1043--1047.

Erbersdobler, H., Brandt, A., Scharrer, E., andVon Wangenheim, B. (1981). Transport and metabolism studies with fructose amino acids. *Progress in food and nutrition science.*

Erbersdobler, H. F. and Somoza, V. (2007). Forty years of furosine – Forty years of using Maillard reaction products as indicators of the nutritional quality of foods. *Molecular Nutrition & Food Research.* **51**: 423--430.

Erbersdobler, H. and Faist, V. (2001). Metabolic transit of Amadori products. *Nahrung-Food.* **45**: 177--181.

Evenepoel, P., Meijers, B. K. I., Bammens, B. R. M., andVerbeke, K. (2009). Uremic toxins originating from colonic microbial metabolism. *Kidney Int.* **76**: S12-S19.

Faist, V. and Erbersdobler, H. (2001). Metabolic transit and in vivo effects of melanoidins and precursor compounds deriving from the Maillard reaction. *Annals of Nutrition and Metabolism.* **45**: 1--12.

FINOT, P. and MAGNENAT, E. (1981). Metabolic Transit of Early and Advanced Maillard Products. *Progress in Food and Nutrition Science.* **5**: 193--207.

Fogliano, V. and Morales, F. J. (2011). Estimation of dietary intake of melanoidins from coffee and bread. *Food & Function.* **2**: 117--123.

FOSTER, E. (1952). The Effect of Heat on Milk as a Culture Medium for Lactic Acid Bacteria. *J Dairy Sci.* **35**: 988--997.

Fung, T. C., Olson, C. A., andHsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci.* **20**: 145--155.

Garcia-Banos, J., Corzo, N., Sanz, M., andOlano, A. (2004). Maltulose and furosine as indicators of quality of pasta products. *Food Chem.* **88**: 35--38.

Gasscht, F., Dicato, M., andDiederich, M. (2015). Coffee provides a natural multitarget pharmacopeia against the hallmarks of cancer. *Genes and Nutrition.* **10**: 51.

Gerrard, J. (2002). Protein-protein crosslinking in food: methods, consequences, applications. *Trends Food Sci Technol.* **13**: 391--399.

Gheldof, N., Wang, X., andEngeseth, N. (2002). Identification and quantification of antioxidant components of honeys from various floral sources. *J Agric Food Chem.* **50**: 5870--5877.

GIBSON, G. and ROBERFROID, M. (1995). Dietary Modulation of the Human Colonic Microbiota – Introducing the Concept of Prebiotics. *J Nutr.* **125**: 1401--1412.

Godfrey, V., Chen, L., Griffin, R., Lebetkin, E., andBurka, L. (1999). Distribution and metabolism of (5-hydroxymethyl)furfural in male F344 rats and B6C3F1 mice after oral administration. *Journal of Toxicology and Environmental Health-Part a.* **57**: 199--210.

Gokmen, V., Acar, O. C., Koksel, H., andAcar, J. (2007). Effects of dough formula and baking conditions on acrylamide and hydroxymethylfurfural formation in cookies. *Food Chem.* **104**: 1136--1142.

Goldberg, T., Cai, W., Peppa, M., Dardaine, V., Baliga, B., Uribarri, J., andVlassara, H. (2004). Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc.* **104**: 1287--1291.

Goldin, A., Beckman, J. A., Schmidt, A. M., andCreager, M. A. (2006). Advanced glycation end products – Sparking the development of diabetic vascular injury. *Circulation.* **114**: 597--605.

Granvogl, M. and Schieberle, P. (2007). Quantification of 3-aminopropionamide in cocoa, coffee and cereal products. *European Food Research and Technology.* **225**: 857--863.

Granvogl, M. and Schieberle, P. (2006). Thermally generated 3-aminopropionamide as a transient intermediate in the formation of acrylamide. *J Agric Food Chem.* **54**: 5933--5938.

Grillo, M. A. and Colombatto, S. (2008). Advanced glycation end-products (AGEs): involvement in aging and in neurodegenerative diseases. *Amino Acids.* **35**: 29--36.

HACHISUKA, Y., ASANO, N., KATO, N., OKAJIMA, M., KITAORI, M., andKUNO, T. (1955). Studies on spore germination. I. Effect of nitrogen sources on spore germination. *J Bacteriol.* **69**: 399--406.

Hartog, J. W. L., Voors, A. A., Bakker, S. J. L., Smit, A. J., andvan Veldhuisen, D. J. (2007). Advanced glycation end-products (AGES) and heart failure: Pathophysiology and clinical implications. *European Journal of Heart Failure.* **9**: 1146--1155.

Hellwig, M., Bunzel, D., Huch, M., Franz, C. M. A. P., Kulling, S. E., andHenle, T. (2015). Stability of Individual Maillard Reaction Products in the Presence of the Human Colonic Microbiota. *J Agric Food Chem.* **63**: 6723--6730.

Helou, C., Marier, D., Jacolot, P., Abdennebi-Najar, L., Niquet-Leridon, C., Tessier, F. J., andGadonna-Widehem, P. (2014). Microorganisms and Maillard reaction products: a review of the literature and recent findings. *Amino Acids.* **46**: 267--277.

Hiramoto, S., Itoh, K., Shizuuchi, S., Kawachi, Y., Morishita, Y., Nagase, M., Suzuki, Y., Nobuta, Y., Sudou, Y., Nakamura, O., Kagaya, I., Goshima, H., Kodama, Y., Icatro, F., Koizumi, W., Saigenji, K., Miura, S., Sugiyama, T., andKimura, N. (2004). Melanoidin, a food protein-derived advanced maillard reaction product, suppresses Helicobacter pylori in vitro and in vivo. *Helicobacter.* **9**: 429--435.

HODGE, J. (1953). Dehydrated Foods – Chemistry of Browning Reactions in Model Systems. *J Agric Food Chem.* **1**: 928--943.

Hofmann, S., Dong, H., Li, Z., Cai, W., Altomonte, J., Thung, S., Zeng, F., Fisher, E., andVlassara, H. (2002). Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. *Diabetes.* **51**: 2082--2089.

Hofmann, T. (1999). Structure, color, and formation of low- and high-molecular weight products formed by Maillard-type reactions. *Abstracts of Papers of the American Chemical Society.* **218**: U32-U32.

Hofmann, T. (1998). Studies on melanoidin-type colorants generated from the Maillard reaction of protein-bound lysine and furan-2-carboxaldehyde – chemical characterisation of a red coloured domaine. *Zeitschrift Fur Lebensmittel-Untersuchung Und-Forschung A-Food Research and Technology.* **206**: 251--258.

HORIKOSHI, M., OHMURA, M., GOMYO, T., KUWABARA, Y., andUEDA, S. (1981). Effects of Browning Products on the Intestinal Microflora of the Rat. *Progress in Food and Nutrition Science.* **5**: 223--228.

Hull, G. L. J., Woodside, J. V., Ames, J. M., andCuskelly, G. J. (2012). N-epsilon-(carboxymethyl)lysine content of foods commonly consumed in a Western style diet. *Food Chem.* **131**: 170--174.

Husoy, T., Haugen, M., Murkovic, M., Joebstl, D., Stolen, L. H., Bjellaas, T., Ronningborg, C., Glatt, H., andAlexander, J. (2008). Dietary exposure to 5-hydroxymethylfurfural from Norwegian food and correlations with urine metabolites of short-term exposure. *Food and Chemical Toxicology.* **46**: 3697--3702.

JAGERSTAD, M., SKOG, K., GRIVAS, S., andOLSSON, K. (1991). Formation of Heterocyclic Amines using Model Systems. *Mutat Res.* **259**: 219--233.

Jahurul, M. H. A., Jinap, S., Ang, S. J., Abdul-Hamid, A., Hajeb, P., Lioe, H. N., andZaidul, I. S. M. (2010). Dietary exposure to heterocyclic amines in high-temperature cooked meat and fish in Malaysia. *Food Additives and Contaminants Part A-Chemistry Analysis Control Exposure & Risk Assessment.* **27**: 1060--1071.

Janzowski, C., Glaab, V., Samimi, E., Schlatter, J., andEisenbrand, G. (2000). 5-hydroxymethylfurfural: assessment of mutagenicity, DNA-damaging potential and reactivity towards cellular glutathione. *Food and Chemical Toxicology.* **38**: 801--809.

Jaquet, M., Rochat, I., Moulin, J., Cavin, C., andBibiloni, R. (2009). Impact of coffee consumption on the gut microbiota: A human volunteer study. *Int J Food Microbiol.* **130**: 117--121.

Jara, N., Leal, M. J., Bunout, D., Hirsch, S., Barrera, G., Leiva, L., andde la Maza, M. P. (2012). Dietary intake increases serum levels of carboxymethil-lysine (CML) in diabetic patients. *Nutricion Hospitalaria.* **27**: 1272--1278.

Jemmali, M. (1969). Influence of the Maillard reaction products on some bacteria of the intestinal flora. *J Appl Bacteriol.* **32**: 151--155.

Jiao, L., Stolzenberg-Solomon, R., Zimmerman, T. P., Duan, Z., Chen, L., Kahle, L., Risch, A., Subar, A. F., Cross, A. J., Hollenbeck, A., Vlassara, H., Striker, G., andSinha, R. (2015). Dietary consumption of advanced glycation end products and pancreatic cancer in the prospective NIH-AARP Diet and Health Study. *Am J Clin Nutr.* **101**: 126--134.

Johansson, M. A. and Jägerstad, M. (1994). Occurrence of mutagenic/carcinogenic heterocyclic amines in meat and fish products, including pan residues, prepared under domestic conditions. *Carcinogenesis.* **15**: 1511--1518.

Kahn, B. and Flier, J. (2000). Obesity and insulin resistance. *J Clin Invest.* **106**: 473--481.

Kamei, H., Koide, T., Hashimoto, Y., Kojima, T., Umeda, T., andHasegawa, M. (1997). Tumor cell growth-inhibiting effect of melanoidins extracted from miso and soy sauce. *Cancer Biotherapy and Radiopharmaceuticals.* **12**: 405--409.

Kato, T., Migita, H., Ohgaki, H., Sato, S., Takayama, S., andSugimura, T. (1989). Induction of tumors in the Zymbal gland, oral cavity, colon, skin and mammary gland of F344 rats by a mutagenic compound, 2-amino-3,4-dimethylimidazo[4,5-f]quinoline. *Carcinogenesis.* **10**: 601--603.

Keating, G., Layton, D., andFelton, J. (1999). Factors determining dietary intakes of heterocyclic amines in cooked foods. *Mutat Res -Genet Toxicol Environ Mutag.* **443**: 149--156.

Knasmuller, S., Steinkellner, H., Hirschl, A., Rabot, S., Nobis, E., andKassie, F. (2001). Impact of bacteria in dairy products and of the intestinal microflora on the genotoxic and carcinogenic effects of heterocyclic aromatic amines. *Mutat Res -Fundam Mol Mech Mutag.* **480**: 129--138.

Knize, M., Dolbeare, F., Carroll, K., Moore, D. 2. n., andFelton, J. (1994). Effect of cooking time and temperature on the heterocyclic amine content of fried beef patties. *Food and Chemical Toxicology.* **32**: 595--603.

Kong, S. Y., Takeuchi, M., Hyogo, H., McKeown-Eyssen, G., Yamagishi, S., Chayama, K., O'Brien, P. J., Ferrari, P., Overvad, K., Olsen, A., Tjonneland, A., Boutron-Ruault, M., Bastide, N., Carbonnel, F., Kuehn, T., Kaaks, R., Boeing, H., Aleksandrova, K., Trichopoulou, A., Lagiou, P., Vasilopoulou, E., Masala, G., Pala, V., De Magistris, M. S., Tumino, R., Naccarati, A., Bueno-De-Mesquita, H. B., Peeters, P. H., Weiderpass, E., Quiros, J. R., Jakszyn, P., Sanchez, M., Dorronsoro, M., Gavrila, D., Ardanaz, E., Rutegard, M., Nystroem, H., Wareham, N. J., Khaw, K., Bradbury, K. E., Romieu, I., Freisling, H., Stavropoulou, F., Gunter, M. J., Cross, A. J., Riboli, E., Jenab, M., andBruce, W. R. (2015). The Association between Glyceraldehyde-Derived Advanced Glycation End-Products and Colorectal Cancer Risk. *Cancer Epidemiology Biomarkers & Prevention.* **24**: 1855--1863.

Langner, E., Nunes, F. M., Pozarowski, P., Kandefer-Szerszen, M., Pierzynowski, S. G., andRzeski, W. (2013). Melanoidins isolated from heated potato fiber (Potex) affect human colon cancer cells growth via modulation of cell cycle and proliferation regulatory proteins. *Food and Chemical Toxicology.* **57**: 246--255.

Langner, E., Nunes, F. M., Pozarowski, P., Kandefer-Szerszen, M., Pierzynowski, S. G., andRzeski, W. (2011). Antiproliferative Activity of Melanoidins Isolated from Heated Potato Fiber (Potex) in Glioma Cell Culture Model. *J Agric Food Chem.* **59**: 2708--2716.

LEE, Y., SHLYANKEVICH, M., JEONG, H., DOUGLAS, J., andSURH, Y. (1995). Bioactivation of 5-Hydroxymethyl-2-Furaldehyde to an Electrophilic and Mutagenic Allylic Sulfuric-Acid Ester. *Biochem Biophys Res Commun.* **209**: 996--1002.

Ley, R., Peterson, D., andGordon, J. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell.* **124**: 837--848.

Louis, P., Scott, K. P., Duncan, S. H., andFlint, H. J. (2007). Understanding the effects of diet on bacterial metabolism in the large intestine. *J Appl Microbiol.* **102**: 1197--1208.

Ludwig, I. A., Clifford, M. N., Lean, M. E. J., Ashihara, H., andCrozier, A. (2014). Coffee: biochemistry and potential impact on health. *Food & Function.* **5**: 1695--1717.

Macfarlane, G., Cummings, J., andAllison, C. (1986). Protein degradation by human intestinal bacteria. *Microbiology.* **132**: 1647--1656.

Mesias Garcia, M., Seiquer, I., Delgado-Andrade, C., Galdo, G., andPilar Navarro, M. (2009). Intake of Maillard reaction products reduces iron bioavailability in male adolescents. *Molecular Nutrition & Food Research.* **53**: 1551--1560.

MILIC, B., GRUJICINJAC, B., PILETIC, M., LAJSIC, S., andKOLAROV, L. (1975). Melanoidins and Carbohydrates in Roasted Barley. *J Agric Food Chem.* **23**: 960--963.

MONNIER, V. and CERAMI, A. (1981). Non-Enzymatic Browning Invivo – an Aging Process for Long-Lived Proteins. *Experientia.* **37**: 629--630.

MONNIER, V., SELL, D., NAGARAJ, R., MIYATA, S., GRANDHEE, S., ODETTI, P., andIBRAHIM, S. (1992). Maillard Reaction-Mediated Molecular Damage to Extracellular-Matrix and Other Tissue Proteins in Diabetes, Aging, and Uremia. *Diabetes.* **41**: 36--41.

Morales, F. J., Somoza, V., andFogliano, V. (2012). Physiological relevance of dietary melanoidins. *Amino Acids.* **42**: 1097--1109.

Moreno, F. J., Corzo-Martinez, M., del Castillo, M. D., andVillamiel, M. (2006). Changes in antioxidant activity of dehydrated onion and garlic during storage. *Food Res Int.* **39**: 891--897.

Murkovic, M. and Pichler, N. (2006). Analysis of 5-hydroxymethylfurfual in coffee, dried fruits and urine. *Molecular Nutrition & Food Research.* **50**: 842--846.

Natella, F., Nardini, M., Giannetti, I., Dattilo, C., andScaccini, C. (2002). Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem.* **50**: 6211--6216.

Nguyen, H. T., Van der Fels-Klerx, H. J. (., Peters, R. J. B., andVan Boekel, M. A. J. S. (2016). Acrylamide and 5-hydroxymethylfurfural formation during baking of biscuits: Part I: Effects of sugar type. *Food Chem.* **192**: 575--585.

OBRIEN, J. and MORRISSEY, P. (1989). Nutritional and Toxicological Aspects of the Maillard Browning Reaction in Foods. *Crit Rev Food Sci Nutr.* **28**: 211--248.

Ochiai, M., Ogawa, K., Wakabayashi, K., Sugimura, T., Nagase, S., Esumi, H., andNagao, M. (1991). Induction of Intestinal Adenocarcinomas by 2-Amino-l-methyl-6-phenylimidazo-[4, 5-b] pyridine in Nagase Analbuminemic Rats. *Jap J Cancer Res.* **82**: 363--366.

Ohgaki, H., Hasegawa, H., Suenaga, M., Sato, S., Takayama, S., andSugimura, T. (1987). Carcinogenicity in mice of a mutagenic compound, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) from cooked foods. *Carcinogenesis.* **8**: 665--668.

O'Keefe, S. J. D. (2016). Diet, microorganisms and their metabolites, and colon cancer. *Nature Reviews Gastroenterology & Hepatology.* **13**: 691--706.

O'Keefe, S. J. D. (2008). Nutrition and colonic health: the critical role of the microbiota. *Curr Opin Gastroenterol.* **24**: 51--58.

O'Keefe, S. J. D., Li, J. V., Lahti, L., Ou, J., Carbonero, F., Mohammed, K., Posma, J. M., Kinross, J., Wahl, E., Ruder, E., Vipperla, K., Naidoo, V., Mtshali, L., Tims, S., Puylaert, P. G. B., DeLany, J., Krasinskas, A., Benefiel, A. C., Kaseb, H. O., Newton, K., Nicholson, J. K., de Vos, W. M., Gaskins, H. R., andZoetendal, E. G. (2015). Fat, fibre and cancer risk in African Americans and rural Africans. *Nature Communications.* **6**: 6342.

Pastoriza, S. and Rufian-Henares, J. A. (2014). Contribution of melanoidins to the antioxidant capacity of the Spanish diet. *Food Chem.* **164**: 438--445.

Prasad, A., Bekker, P., andTsimikas, S. (2012). Advanced Glycation End Products and Diabetic Cardiovascular Disease. *Cardiol Rev.* **20**: 177--183.

Puangsombat, K., Gadgil, P., Houser, T. A., Hunt, M. C., andSmith, J. S. (2012). Occurrence of heterocyclic amines in cooked meat products. *Meat Sci.* **90**: 739--746.

Ramu, K., Fraiser, L. H., Mamiya, B., Ahmed, T., andKehrer, J. P. (1995). Acrolein mercapturates: synthesis, characterization, and assessment of their role in the bladder toxicity of cyclophosphamide. *Chem Res Toxicol.* **8**: 515--524.

Reichardt, N., Gniechwitz, D., Steinhart, H., Bunzel, M., andBlaut, M. (2009). Characterization of high molecular weight coffee fractions and their fermentation by human intestinal microbiota. *Molecular Nutrition & Food Research.* **53**: 287--299.

Resmini, P., Pagani, A., andPellegrino, L. (1991). Evaluation of the thermal damage to pasta by determination of epsilon-furoylmethyl-lysine (furosine) by HPLC. *Tecnica Molitoria.* **41**: 821--826.

Rufian-Henares, J. and Morales, F. (2006). A new application of a commercial microtiter plate-based assay for assessing the antimicrobial activity of Maillard reaction products. *Food Res Int.* **39**: 33--39.

Rufian-Henares, J. A. and Delgado-Andrade, C. (2009). Effect of digestive process on Maillard reaction indexes and antioxidant properties of breakfast cereals. *Food Res Int.* **42**: 394--400.

Rufian-Henares, J. A. and Morales, F. J. (2008). Antimicrobial activity of melanoidins against Escherichia coli is mediated by a membrane-damage mechanism. *J Agric Food Chem.* **56**: 2357--2362.

Rufian-Henares, J. A. and Morales, F. J. (2007a). Antimicrobial activity of melanoidins. *J Food Qual.* **30**: 160--168.

Rufian-Henares, J. A. and Morales, F. J. (2007b). Functional properties of melanoidins: In vitro antioxidant, antimicrobial and antihypertensive activities. *Food Res Int.* **40**: 995--1002.

Schmidt, A., Yan, S., Yan, S., andStern, D. (2000). The biology of the receptor for advanced glycation end products and its ligands. *Biochimica Et Biophysica Acta-Molecular Cell Research.* **1498**: 99--111.

SCHOENTAL, R., HARD, G., andGIBBARD, S. (1971). Histopathology of Renal Lipomatous Tumors in Rats Treated with Natural Products Pyrrolizidine Alkaloids and Alpha, Beta-Unsaturated Aldehydes. *Jnci-Journal of the National Cancer Institute.* **47**: 1037-+.

Seiquer, I., Diaz-Alguacil, J., Delgado-Andrade, C., Lopez-Frias, M., Hoyos, A., Galdo, G., andNavarro, M. (2006). Diets rich in Maillard reaction products affect protein digestibility in adolescent males aged 11--14 y. *Am J Clin Nutr.* **83**: 1082--1088.

Seiquer, I., Rubio, L. A., Jesus Peinado, M., Delgado-Andrade, C., andPilar Navarro, M. (2014). Maillard reaction products modulate gut microbiota composition in adolescents. *Molecular Nutrition & Food Research.* **58**: 1552--1560.

Sommer, Y., Hollnagel, H., Schneider, H., andGlatt, H. (2003). Metabolism of 5-hydroxymethyl-2-furfural (HMF) to the mutagen 5-sulfoxymethyl-2-furfural (SMF) by individual sulfotransferases. *Naunyn-Schmiedeberg's Arch Pharmacol.* **367**: R166-R166.

Somoza, V., Wenzel, E., Lindenmeier, M., Grothe, D., Erbersdobler, H., andHofmann, T. (2005). Influence of feeding malt,bread crust, and a pronylated protein on the activity of chemopreventive enzymes and antioxidative defense parameters in vivo. *J Agric Food Chem.* **53**: 8176--8182.

Somoza, V. (2007). The Maillard reaction in food and medicine. *Molecular Nutrition & Food Research.* **51**: 381--382.

STECCHINI, M., GIAVEDONI, P., SARAIS, I., andLERICI, C. (1991). Effect of Maillard Reaction-Products on the Growth of Selected Food-Poisoning Microorganisms. *Lett Appl Microbiol.* **13**: 93--96.

SURH, Y., LIEM, A., MILLER, J., andTANNENBAUM, S. (1994). 5-Sulfooxymethylfurfural as a Possible Ultimate Mutagenic and Carcinogenic Metabolite of the Maillard Reaction-Product, 5-Hydroxymethylfurfural. *Carcinogenesis.* **15**: 2375--2377.

SURH, Y. and TANNENBAUM, S. (1994). Activation of the Maillard Reaction-Product 5-(Hydroxymethyl)furfural to Strong Mutagens Via Allylic Sulfonation and Chlorination. *Chem Res Toxicol.* **7**: 313--318.

Tagliazucchi, D. and Bellesia, A. (2015). The gastro-intestinal tract as the major site of biological action of dietary melanoidins. *Amino Acids.* **47**: 1077--1089.

Takahashi, S., Ogawa, K., Ohshima, H., Esumi, H., Ito, N., andSugimura, T. (1991). Induction of Aberrant Crypt Foci in the Large Intestine of F344 Rats by Oral Administration of 2-Amino-l-methyl-6-phenylimidazo [4, 5-b] pyridine. *Jap J Cancer Res.* **82**: 135--137.

Tamanna, N. and Mahmood, N. (2015). Food Processing and Maillard Reaction Products: Effect on Human Health and Nutrition. *International Journal of Food Science.* **2015**: 1--6.

Tareke, E., Rydberg, P., Karlsson, P., Eriksson, S., andTornqvist, M. (2002). Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem.* **50**: 4998--5006.

Teerlink, T., Barto, R., Ten Brink, H., andSchalkwijk, C. (2004). Measurement of N-epsilon-(Carboxymethyl)lysine and N-epsilon-(Carboxyethyl)lysine in human plasma protein by stable-isotope-dilution tandem mass spectrometry. *Clin Chem.* **50**: 1222--1228.

Tessier, F. J. (2010). The Maillard reaction in the human body. The main discoveries and factors that affect glycation. *Pathologie Biologie.* **58**: 214--219.

Tessier, F. J. and Birlouez-Aragon, I. (2012). Health effects of dietary Maillard reaction products: the results of ICARE and other studies. *Amino Acids.* **42**: 1119--1131.

Tessier, F. J., Niquet-Leridon, C., Jacolot, P., Jouquand, C., Genin, M., Schmidt, A., Grossin, N., andBoulanger, E. (2016). Quantitative assessment of organ distribution of dietary protein-bound C-13-labeled N-epsilon-carboxymethyllysine after a chronic oral exposure in mice. *Molecular Nutrition & Food Research.* **60**: 2446--2456.

Tuohy, K. M., Hinton, D. J. S., Davies, S. J., Crabbe, M. J. C., Gibson, G. R., andAmes, J. M. (2006). Metabolism of Maillard reaction products by the human gut microbiota – implications for health. *Molecular Nutrition & Food Research.* **50**: 847--857.

Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., Sogin, M. L., Jones, W. J., Roe, B. A., Affourtit, J. P., Egholm, M., Henrissat, B., Heath, A. C., Knight, R., andGordon, J. I. (2009). A core gut microbiome in obese and lean twins. *Nature.* **457**: 480-U7.

ULBRICHT, R., NORTHUP, S., andTHOMAS, J. (1984). A Review of 5-Hydroxymethylfurfural (Hmf) in Parenteral Solutions. *Fundamental and Applied Toxicology.* **4**: 843--853.

Uribarri, J., Cai, W., Sandu, O., Peppa, M., Goldberg, T., andVlassara, H. (2005). Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. *Maillard Reaction: Chemistry at the Interface of Nutrition, Aging, and Disease.* **1043**: 461--466.

Uribarri, J., Peppa, M., Cai, W., Goldberg, T., Lu, M., He, C., andVlassara, H. (2003). Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. *Journal of the American Society of Nephrology.* **14**: 728--731.

Van Nguyen, C. (2006). Toxicity of the AGEs generated from the Maillard reaction: On the relationship of food-AGEs and biological-AGEs. *Molecular Nutrition & Food Research.* **50**: 1140--1149.

Van Puyvelde, K., Mets, T., Njemini, R., Beyer, I., andBautmans, I. (2014). Effect of advanced glycation end product intake on inflammation and aging: a systematic review. *Nutr Rev.* **72**: 638--650.

VANTASSELL, R., KINGSTON, D., andWILKINS, T. (1990). Metabolism of Dietary Genotoxins by the Human Colonic Microflora – the Fecapentaenes and Heterocyclic Amines. *Mutat Res.* **238**: 209--221.

VISWANATHAN, L. and SARMA, P. (1957). Growth Inhibitor of L-Bulgaricus-09. *Nature.* **180**: 1370--1371.

Vitaglione, P., Fogliano, V., andPellegrini, N. (2012). Coffee, colon function and colorectal cancer. *Food & Function.* **3**: 916--922.

Vitaglione, P., Morisco, F., Mazzone, G., Amoruso, D. C., Ribecco, M. T., Romano, A., Fogliano, V., Caporaso, N., andD'Argenio, G. (2010). Coffee Reduces Liver Damage in a Rat Model of Steatohepatitis: The Underlying Mechanisms and the Role of Polyphenols and Melanoidins. *Hepatology.* **52**: 1652--1661.

Wagner, K., Cameron-Smith, D., Wessner, B., andFranzke, B. (2016). Biomarkers of Aging: From Function to Molecular Biology. *Nutrients.* **8**: 338.

Wang, H., Qian, H., andYao, W. (2011). Melanoidins produced by the Mail lard reaction: Structure and biological activity. *Food Chem.* **128**: 573--584.

Wang, Z., Jiang, Y., Liu, N., Ren, L., Zhu, Y., An, Y., andChen, D. (2012). Advanced glycation end-product N-epsilon-carboxymethyl-Lysine accelerates progression of atherosclerotic calcification in diabetes. *Atherosclerosis.* **221**: 387--396.

Wang, Z., Li, L., Du, R., Yan, J., Liu, N., Yuan, W., Jiang, Y., Xu, S., Ye, F., Yuan, G., Zhang, B., andLiu, P. (2016). CML/RAGE signal induces calcification cascade in diabetes. *Diabetology & Metabolic Syndrome.* **8**: 83.

Wehkamp, J. and Frick, J. (2017). Microbiome and chronic inflammatory bowel diseases. *Journal of Molecular Medicine-Jmm.* **95**: 21--28.

Wenzel, E., Tasto, S., Erbersdobler, H., andFaist, V. (2002). Effect of heat-treated proteins on selected parameters of the biotransformation system in the rat. *Annals of Nutrition and Metabolism.* **46**: 9--16.

Wiame, E., Delpierre, G., Collard, F., andVan Schaftingen, E. (2002). Identification of a pathway for the utilization of the Amadori product fructoselysine in Escherichia coli. *J Biol Chem.* **277**: 42523--42529.

Wiame, E., Lamosa, P., Santos, H., andVan Schaftingen, E. (2005). Identification of glucoselysine-6-phosphate deglycase, an enzyme involved in the metabolism of the fructation product glucoselysine. *Biochem J.* **392**: 263--269.

Wishart, D. S., Mandal, R., Stanislaus, A., andRamirez-Gaona, M. (2016). Cancer Metabolomics and the Human Metabolome Database. *Metabolites.* **6**.

Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F. D., andLewis, J. D. (2011). Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. *Science.* **334**: 105--108.

Yamagishi, S., Matsui, T., andFukami, K. (2015). Role of Receptor for Advanced Glycation End Products (RAGE) and Its Ligands in Cancer Risk. *Rejuvenation Research.* **18**: 48--56.

Yamagishi, S., Nakamura, N., andMatsui, T. (2017). Glycation and cardiovascular disease in diabetes: A perspective on the concept of metabolic memory. *Journal of Diabetes.* **9**: 141--148.

Zilic, S., Mogol, B. A., Akillioglu, G., Serpen, A., Delic, N., andGokmen, V. (2014). Effects of extrusion, infrared and microwave processing on Maillard reaction products and phenolic compounds in soybean. *J Sci Food Agric.* **94**: 45--51.

Zyzak, D. V., Sanders, R. A., Stojanovic, M., Tallmadge, D. H., Eberhart, B. L., Ewald, D. K., Gruber, D. C., Morsch, T. R., Strothers, M. A., Rizzi, G. P., andVillagran, M. D. (2003). Acrylamide formation mechanism in heated foods. *J Agric Food Chem.* **51**: 4782--4787.

Table (1): Examples of MRPs content of commonly consumed foods

MRP type	Food item	Average MRP concentration	References
N^{ε}Fructoselysine (FL)	Soybean	66.55µg/g	(Zilic et al. 2014)
	Fresh Pasta	16-18.8 mg/100 g of protein	(Garcia-Banos et al. 2004)
	Dried Pasta	44.4-462 mg/100 g of protein	
5-Hydroxymethylfurfural (HMF)	Soluble Coffee	110 mg/kg	(Arribas-Lorenzo and Morales. 2010)
	Cookies (sucrose)	19 µg/g for 10 min at 230C°	(Gokmen et al. 2007)
	Cookies (glucose)	38 µg/g for 10 min at 230C°	
Acrylamide	Potato Chips	628 µg/kg	(Capuano and Fogliano. 2011)
	French Fries	350 µg/kg	
	Biscuits	317 µg/kg	
Heterocyclic amines (HCAs)	Fried Bacon	17 ng/g	(Puangsombat et al. 2012)
	Fried Tilapia	16.29 ng/g	
	Fried Pork	13.91 ng/g	
	Fried Beef	8.92 ng/g	
Advanced Glycation End products (AGEs)	Butter	100 KU/g	(Goldberg et al. 2004)
	Mayonnaise (fats)	265 KU/g	(Van Nguyen. 2006)
	American Cheese (proteins)	87 KU/g	
	Pancakes (carbohydrates)	10 KU/g	
N^{ε}Carboxymethyllsine (CML)	Sterilized Milk	2066 nM of protein	(Ahmed et al. 2005)
	Pasteurized Milk	887 nM of protein	
	Raw Milk	337 nM of protein	
	White Bread Crust	382 mg/kg of protein	(Assar et al. 2009)
	Wholemeal Bread Crust	329 mg/kg of protein	
	Doner Kebab	2357.87 mg/kg of	(Hull et al. 2012)

		protein	
Melanoidins	Sourdough Loaves	30 g/100g of crust	(Fogliano and Morales. 2011)
	Soluble Coffee	22 g/100 g	
	Roasted Barley	4.15% of 0.7 to1.0 kg	(MILIC et al. 1975)

Table (2): Previous reports on the impact of MRPs on microorganisms

MRP type	Microorganisms	The result of Study	References
FL	*Salmonella Typhimurium*	Utilization 95% of FL as carbon and energy sources	(Chalova et al. 2012)
	E.coli	Conversion FL into lysine and glucose 6 phosphate	(Wiame et al. 2002)
	Enterococcus faecium	Conversion FL into lysine and glucose 6 phosphate	
HMF (SMF)(CMF)	*Salmonella Typhimurium*	Mutagenicity in *Salmonella Typhimurium*	(Sommer et al. 2003)
Acrylamide	*Lactobacillus plantarum*	Reducing the levels of acrylamide	(Baardseth et al. 2006)
	Lactobacillus sakei, *Pediococcus pentosaceus* and *P. acidilactici*	Reducing the levels of acrylamide	(Bartkiene et al. 2016)
AGEs	*Salmonella Typhimurium*	Utilization 37% of AGEs as carbon and energy sources	(Chalova et al. 2012)
Melanoidins	*Salmonella Typhimurium*	Utilization 15% of Melanoidins as carbon and energy sources	(Chalova et al. 2012)
	E.coli	Inhibition the growth rates	(Rufian-Henares and Morales. 2008)

Table 3: Current available data of the effect of MRPs on colonic microbiota

The type of MRPs	The type of Gut bacteria	The results of study	References
FL	Viable microbiota (stability)	Use as carbon source after 4 hours	(Hellwig et al. 2015)
	Intestinimonas AF211	Conversion FL into butyrate	(Bui et al. 2015)
	Bifidobacteria counts	Decrease growth rates	(Seiquer et al. 2014)
CML/PYR	Viable microbiota (stability)	Use as carbon source for 24 hours	(Hellwig et al. 2015)
CML	*E.coli*	No effect on growth rates	(Helou et al. 2014)
CML	*Lactobacilli* counts	Decrease growth rates	(Seiquer et al. 2014)
HMF	*lactobacilli*, *Escherichia*, and *Shigella* counts	Decrease growth rates	(Seiquer et al. 2014)
HMF	*Klebsiella*, *Enterobacter*, and *Escherichia*	Conversion HMF into furfural alcohol	(BOOPATHY et al. 1993)
HCAs (IQ)	Gut microbiota	Conversion IQ into innocuous metabolites	(Bashir et al. 1987)
IQ	*Eubacterium* and *Clostridium*	Conversion IQ into7-hdroxy	(VANTASSELL et al. 1990)
Melanoidins	*Bifidobacteria*	Use as carbon source and increase growth rates	(Borrelli and Fogliano. 2005)
Melanoidins	*Bacteroides-prevotella*	Increase growth rates	(Reichardt et al. 2009)

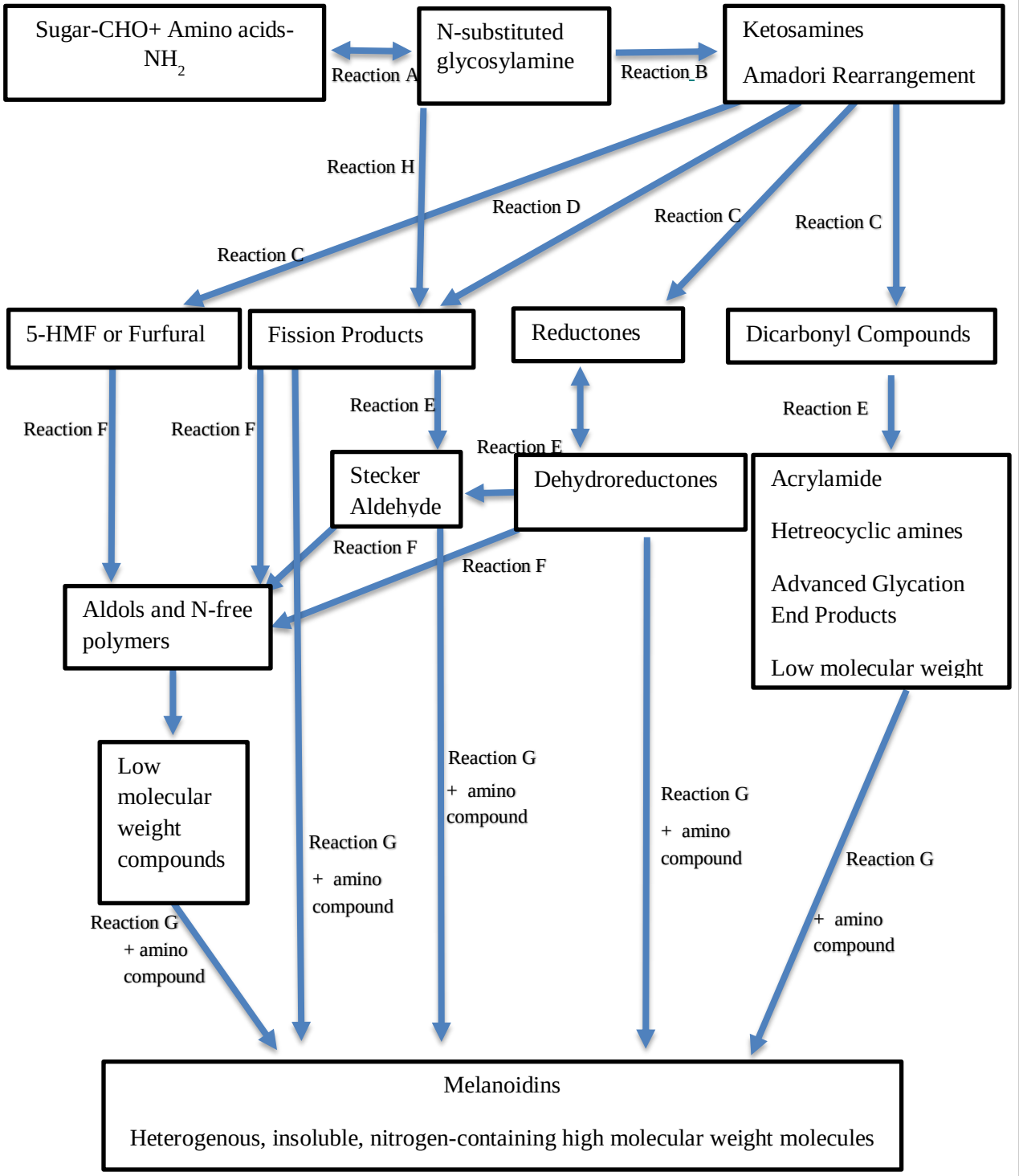

Figure 1.

Figure 1: Maillard Reaction Products stages (adapted from the initial description by Hodge in 1953 to reflect current knowledge). **1. Early stage:** condensation of the carbonyl group of reducing sugar with the amino group of amino acids (Reaction A), resulting in N-substituted glycosylamine and water. **2. Intermediate stages:** Conversion of glycosylamine through Amadori rearrangement to form ketosamines (Reaction B) and other products. Amadori products are dehydrated and hydrolyzed to form 5-Hydroxymethylfurfural (HMF) (Reaction C), which gives rise to either Aldose or N-free polymers (Reaction F). Reductones can be formed from either dehydration of sugars or Amadori product (Reaction C) leading to Aldose and N-free polymers (Reaction F) or Stecker Aldehydes (Reaction E). Stecker aldehydes are formed by fragmentation of amino acids, which enter browning reactions either by the aldehyde formed that can take part in aldol condensation which forms nitrogen-free polymers (Reaction F). Amadori product and N-substituted glycosylamines can be fragmented fission products (Reaction D and H). In addition, fragments of MRPs produce reactive dicarbonyl compounds that can act as precursors of acrylamide, heterocyclic amines, advanced glycation end products (AGEs), and low molecular weight compounds (Reaction C). **3. Advanced stages:** Melanoidins include a wide array of heterogeneous colored molecules Dehydroreductones, fission and dicarbonyl compounds, furfural and Aldose react with amino acids (Reaction G) to form melanoidins.