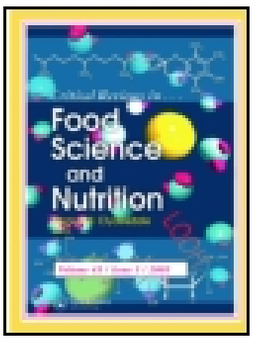

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Rinkesh Kumar Gupta, Kriti Gupta, Akanksha Sharma, Mukul Das, Irfan Ahmad Ansari & Premendra D Dwivedi (2016): Maillard reaction in food allergy: Pros and Cons, Critical Reviews in Food Science and Nutrition

To link to this article: http://dx.doi.org/10.1080/10408398.2016.1152949

Accepted author version posted online: 15 Mar 2016.

Title page:

Maillard reaction in food allergy: Pros and Cons

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Running Title: Impact of Maillard Reaction in food allergy

Abstract-

Food allergens have a notable potential to induce various health concerns in susceptible individuals. The majority of allergenic foods is usually subjected to thermal processing prior to their consumption. However, during thermal processing and long storage of foods, Maillard reaction (MR) often takes place. The MR is a non enzymatic glycation reaction between the carbonyl group of reducing sugars and compounds having free amino groups. MR may sometimes be beneficial by damaging epitope of allergens and reducing allergenic potential, while exacerbation in allergic reactions may also occur due to changes in the motifs of epitopes or neoallergen generation. Apart from these modulations, non enzymatic glycation can also modify the food protein(s) with various type of advance glycation end products (AGEs) such as Nε-(carboxymethyl-)lysine (CML), pentosidine, pyrraline and methylglyoxal-H1 derived from MR. These Maillard products may act as immunogen by inducing the activation and proliferation of various immune cells. Literature is available to understand pathogenesis of glycation in the context of various diseases but there is hardly any review that can provide a thorough insight on

the impact of glycation in food allergy. Therefore, present review explores the pathogenesis with special reference to food allergy caused by non enzymatic glycation as well as AGEs.

Keywords: Allergenicity; Food allergy; Neoallergen; Maillard reactions; AGEs

Introduction:

Food allergy (FA) is an adverse reaction of foods or food components and accounts for 6-8% in children and 3-4% of adults (Boyce et al., 2010). The determination of accurate prevalence of FA is a critical issue as it is very tough to predict the criterion behind the susceptibility of some individuals towards some foods rather than others. However, some genetic and environmental factors may influence prevalence rate and development of FA. The symptoms of FA may be mild to fatal including diarrhea, abdominal pain, vomiting, asthma, anaphylaxis and in extreme cases death (Hugh 2003). Serious steps should be taken in this regard as it is raising health concern in developed and developing countries. Modern lifestyle and lack of awareness about FA are major threats in gobal increase of FA and its pathogenesis. FA is the most prevalent type of allergy triggered by food components known as food allergens in susceptible individuals. The majority of food allergies occurs due to eight foods also known as “big eight” that includes milk (casein, whey), egg, wheat (gluten), soy, peanut, tree nut and shellfish allergens. These allergens are mainly proteinaceous in nature and reflect resistant to heat or acidic denaturation, remain intact even after processing, storage, cooking and digestion (Verma et al., 2012). FA is a Type-I immediate hypersensitivity reaction mainly induced by allergen-specific immunoglobulin E (IgE) antibody. Exposure to food allergens stimulates B-cells directly via IgD/IgM antibody present on their surface and leads to production of allergen-specific IgE antibodies by plasma cells in the susceptible individuals. During sensitization phase allergen-specific IgE binds to the FCϵRI receptor present on the surface of mast cells as well as basophils. Generally, during sensitization phase allergic symptoms are not very commonly occur, but once this phase is

completed individual become susceptible to reacting against offending allergens. Upon subsequent exposure to the same allergenic food, allergen cross-linked to IgE molecules already present on the surface of either mast cell or basophil and trigger these cells to release various allergic mediators into the bloodstream and tissues. Also, food allergens are internalized by antigen presenting cells (APCs) through various endocytic processes, which resulted into APCs activation (Morelli et al., 2004). Activated APCs display allergen epitopes through major histo-compatibility (MHC) molecules that are recognized by T-lymphocyte and results in B cell activation as well as IgE class switching (Kremer et al., 2007).

Allergenicity of food allergens in the susceptible individual is a complex immune event wherein the severity is dependent on two important factors. The first factor is associated with individuals immune susceptibility to certain food/s while the second factor is allergenicity potential of food/s. Usually, FA occurs due to the inappropriate immune response of the body, but it is not clearly known what makes food protein/s more or less allergenic (Siemasko et al., 1998; Bublin et al., 2014). That is why it is highly important to explore how allergenicity of certain foods are altered following various processing procedures.

In the past few years consumption of thermally processed food has increased drastically, which can induce multiple nonenzymatic and biochemical reactions in food. Among them one predominant reaction that occurs during thermal processing is Maillard Reaction causing glycation of certain food allergens. Processing of food is carried out to improve flavor, texture, taste, color, preservation, safety, convenience, variety, and to increase marketability as well as revenue (Sathe et al., 2009). Significant alteration in protein structure may occur during processing. The nature and extent of such changes are highly influenced by temperature, duration

of thermal processing, surrounding food matrix, the conditions of its environment including, pH as well as intrinsic characteristics of the protein. During thermal processing, loss of tertiary and secondary structure along with disulphide bond breakage and formation of aggregates may occur (Davis et al., 2001). Besides these physical alterations, chemical modification of protein may also occur at high temperature that may lead to the formation of covalent bonds between free amino groups and other constituents of food matrix (e. g. reducing sugars). This process of chemical modification is known as non enzymatic glycation or Maillard Reaction (MR). The MR may further lead to the formation of various adducts of protein with various types of glycated structures such as Nε-(carboxymethyl-) lysine (CML), pentosidine, pyrraline and methylglyoxal-H1. These Maillard products are collectively known as advance glycation end products (AGEs) (Toda et al., 2014). The modern diet is a large source of AGEs, which has been found in different foods as reviewed by Arena et al., (2013). The AGEs may have potential to induce the immune response by various immune cells when conjugated with a food allergen. Some recent studies have shown that AGEs may function as potent epitope and increase the risk of FA (Toda et al., 2014). Production of AGEs is more in foods that are exposed to dry heat such as grilling, roasting, baking etc. Besides the contribution in FA, ingestion of foodstuffs containing high amount of AGEs may also lead to significant cellular dysfunction that may include alteration of protein structure, interference with lipid metabolism together with oxidative stress, vascular inflammation and thrombogenesis (Barlovic et al., 2010; Yamagishi et al., 2007).

In addition to these consequences caused by AGEs, MR may influence the variability in the composition of allergen in the whole food, thermodynamics of allergens, food matrix structure, an increment in the allergen number, biochemical properties and conformation as well as linear

type of IgE epitopes. Epitopes are short fragment of allergenic protein/s that can recognize IgE antibodies. In the context of food allergen, conjugation with other protein, fat and sugar that are present in food matrix is complex and poorly understood. Thus, impact of food matrix ingredients on food allergy has become a subject of research, recently. Food allergens display two type's epitopes known as sequential (linear) and conformational epitopes. Sequential epitope consist of linear amino acid sequence, whereas conformational epitope comprise amino acid residues from different regions of allergen brought together by folding of protein. Conformational epitopes are more vulnerable to food processing than linear epitopes (Sathe et al., 2009; Teodorowicz et al., 2013). Conformational epitopes are altered by thermal treatment, whereas linear epitopes appeared with alteration upon hydrolysis (Nakamura S et al., 2008). However, thermal treatment can not abolish the allergenicity of food allergens as it modifies the conformational epitopes only, but linear epitopes still pose for antibody binding. The major food allergens like an egg (ovomucoid) and cherry (Pru v 3) remain immunogenic because of IgE reactivity remains intact even after thermal processing (Jimenez et al., 2011; Gruber et al., 2004). Food processing activities may pose either positive or negative impact on the allergenic potential of food borne allergens (Mills et al., 2009). Few published reports have demonstrated that allergenic proteins may change their behavior upon glycation (Toda et al., 2014). Sometimes food protein modification occurs due to glycation of allergens, leading to the formation of neo allergens after heating. The allergic reactions induced by Pecan nut and wheat flour have been reported in patients after cooking, long storage or heating. It is one of the best examples of the neo-allergen formation (Malanin, 1995).

Glycation of allergens during MR may have an impact on allergenicity but there is no defined rule on how these modifications alter their allergenic property. The realistic situation for MR in allergenic food have been presented in this review and the observation will be more applicable in the understanding of pathogenesis caused by non enzymatic glycation as well as advance glycation end products (AGEs). This review discusses an approach designed to develop a better understanding regarding the impact of MR in food allergy.

The Maillard reaction (MR):

The "Maillard reaction (MR)" was described for the first time by Louis C. Maillard in 1912. The MR is a non enzymatic glycation reaction that takes place between reducing sugars and compounds having free amino groups, leading to the glycation of food proteins. This event occurs during the thermal processing of foods. Although, MR reaction can start at room temperature, but may get elevated by various factors including pH, high temperature, light, presence of metals and alkaline conditions. The MR is a cascade of subsequent and multiple analogous reaction steps. MR encompasses a complex network of transient steps instead of a simple organic reaction, commencing from the initial attachment of glucose or its auto-oxidation products with amines, amino acids and proteins. The MR reaction leads to the formation of linear and cross linking adducts known as AGEs. Cross linking and other non cross linking (linear) modification of food proteins may have different immunological consequences. The MR progression can be divided into three main stages as summarized in figure 1. The first/early stage is characterized by the formation of a Schiff base and Amadori product. During this stage, carbonyl group of reducing sugar condenses with the free amine group via either N terminus of protein or the ϵ-amino group of Lys residues (Step A) that result in the formation of a Schiff base

such as aldamine (Step B, C). This thermodynamically unstable transient compound rearranges into Amadori (Ketoamine) product through an enaminol intermediate (Step H). For instance, Ne-(1-deoxy-D-fructose-1-yl) - Lys (also known as Ne-fructosyl-Lys, FL), Ne-(1-deoxy-Dlactulos-1-yl) -Lys, and Ne-(1-deoxy-D-maltulos-1-yl) -Lys, are the corresponding Amadori products of fructose, lactose and maltose, respectively. These intermediates are unstable in excessive heat and prolonged storage, thus undergo further degradation process. In the second step, Amadori products may get degraded into furfurals, reductones and fragmentation derivatives such as carbonyl and hydroxycarbonyl compounds (Step C, D) depending on participating reducing sugar and the surrounding pH (Ames, 1992; 2003). Another alternative pathway of this reaction followed by intra-molecular enolization and dehydration may also precede the formation of transient intermediate containing an alpha-dicarbonyl moiety bound with protein-glycan adduct, such as, Nϵ- (5,6-dihydroxy-2,3-dioxohexyl)-Lys, Nϵ-(2,3-dihydroxy-5,6-dioxohexyl)-Lys and Nϵ-(2-hydroxy-4,5-dioxopentyl)-Lys (Biemel et al., 2002a; Biemel et al., 2003). Subsequently, these early MR products may convert into stable, irreversible cross linked food protein structures probably because of dicarbonyl compounds working as linker capacity between lysine and arginine residues (Biemel et al., 2002b; Nemet et al., 2011). Sugar degradation is generally accompanied by retro-aldolization, generating several stable dicarbonyl compounds such as glyoxal (GO), methylglyoxal (MGO), glycolaldehyde, 1-deoxyglucosone (1-DG), 3-deoxyglucosone (3-DG), butanedione and other derivatives (Baker et al., 1994; Wells-Knecht et al., 1995; Thornalley et al., 1999, Martins et al., 2003). All the above mentioned alpha dicarbonyl reactive compounds may further react to protein via Strecker degradation process resulting in the formation of Strecker aldehydes of the amino acids and aminoketones (Step E, H)

which may later condense into pyrazine derivatives causing aroma in foods. The final and third stage of MR involves aldol condensation of furfurals, reductones and aldehydes, leading to the generation of small and/or large polymeric compounds (Step G) that generally contribute to color and/or fluorescence in food materials (Ledl et al., 1990; Hofmann, 1998). Interestingly, the reaction between the same intermediates leads to the generation of melanoidins brown pigment in foods and food products. These above mentioned intermediates and final MR products may have potential to alter the structure and biological activity of certain food proteins. Thus, each and every step of MR has raised the keen interest of scientist in food research.

AGEs are the final products of MR that may lead to the modification of food proteins with various glycated structures such as Nε-(carboxymethyl-) lysine (CML), Nε-(carboxyethyl-) lysine (CEL), pentosidine, pyrraline and methylglyoxal-H1. Recently, glycated structures of AGEs are considered as pathogenesis related factors in FA (Ilchmann et al., 2010). Till today, more than 20 AGEs have been characterized and most of them have been reported in baked or roasted food including, peanut (Henle, 2005, Ilchmann et al., 2010). Molecular structures of common food derived AGEs are given in Figure 2. Recent evidences suggest that some glycated structures of AGEs provoke various immune responses by triggering key immune cells. Thus, more attention is needed towards the role of AGEs in food allergenicity risk assessment.

Development of Neo-allergen during Maillard Reaction:

The glycation of food protein via MR may lead to conversion of nonallergenic profile of food into allergenic profile. MR contributes to the generation of new immunogenic structure known as neo-allergens with additional IgE binding property (Sathe et al., 2005; Nakamura 2005). During MR, neoallergens may be formed either due to aggregation of proteins/smaller peptides or

breakdown of a larger protein into smaller ones. Formation of neoallergen or neoantigen may increase the severity of allergic reaction in sensitive individuals. After food processing, development of novel allergenic epitope(s) on existing normal protein has been recognized for at least three decades that define why some people can not tolerate processed foods whereas the same people can easliy consume same unprocessed foods without any awful immune responses (Spies 1974). The introduction of neoantigens causes an enhancement in the allergic potential of several allergenic foods. For instance, scallop tropomyosin allergy was increased by structural changes induced by MR. These structural changes lead to protein cross linking that introduced novel epitopes having IgE binding property (Nakamura 2005; Maleki et al., 2000; Pastorello et al., 2002). The development of novel allergenic epitopes may occur during long storage and thermal processing of foods. The increased IgE reactivity was found in stored and heated soyabean and explanation for this increase may be defined by the appearance of 2 new allergens in stored soyabeen due to high temperature and long storage (Codina et al., 1998). Thus, appropriate storage conditions and processing temperature should be mentained to reduce the risk of allergy development in certain foods. Futhermore, allergens Ara h1, Ara h2 and Ara h3 from roasted peanut have been shown to have greater IgE binding property than boiled or fried peanuts, demonstrate that certain methods of food processing can introduce new IgE binding epitopes (Beyer et al., 2001; Maleki et al., 2000). Similarly, neoallergens have also been generated in pecan nut and wheat flour during food processing (Malanin et al., 1995; Leduc et al., 2003). It is reported that boiling of lentil proteins results into formation of neoantigens in the range of 12-16 kDa, however a major allergen Len C1 get eliminated within 30 min. after boiling (Cuadrado et al., 2009). More recently, stronger allergic reaction caused by neoallergens during

MR have been reported in soy sensitive patients, also (Teodorowicz et al. 2015). Conclusively, MR posses a severe risk to exacerbate allergic potential by the introduction of novel allergenic epitopes in a wide range of food proteins. Thus, formation of neoallergens during MR needs a through exploration with identification of the fate of allergens as they might be recongnized differently by the immune system. Further, avoidance of inappropriate storage for a long time and implying of certain processing methods should be considered for the offending foods.

Participating amino acids and sugars in Maillard Reaction

MR has both deleterious and beneficial health effects, thus a better comparison is needed among the MR variables like participating sugar and amino acids. A varied range of glycated adducts have been characterized that clearly state the pathophysiological connection between participating amino acids and reducing sugars (Muttucumaru et al., 20014; Bunn et al., 1981). Long ago, it was suggested that only certain basic amino acids such as lysine residue participate in the glycation of food allergens. However, apart from lysine, arginine (as they posses free ϵ-amino group) and occasionally histidine residue of proteins was also found to participate in the glycation process (Arena et al., 2014; Rabbani et al., 2012). The epitope without having lysine or arginine amino acid residues showed higher IgE binding affinity, indicating that other than basic amino acid residues may be also considered as a target for MR. For instance, sometime cysteine modification may also occurs, leading to the formation of a unique product (Zeng et al., 2005). As we have discussed that basic amino acid residues having free amino group of food allergens such as lysine and arginine are participatants during glycation of allergens, primarily. Thus, removal, inactivation or modification of particular these amino acid residues/free amino groups from food allergens may be considered as an efficacious aaproach to combat the food allergy

caused by corresponding glycated allergens. Further, amadori products of aspartic acid were found in freeze in dried mango pulp and orange juice after long storage. Similarly, amadori products of proline and serine were also detected in orange juice and tomato pulp, respectively (del Castillo et al., 2002). Moreover, tryptophan residues from β-lactoglobulin is also involved in glycation with lactose sugar (Moreaux, V., & Birlouez-Aragon, I. 1997). Epitopes are stretches of amino acids that may undergo MR and change their conformation as well as immunogenicity (either enhance or reduce). If the epitope consists of particular amino acids that are more prone to MR, such residues can be modified using different approaches to reduce the immunogenicity of food allergens containing such epitopes. But through studies are needed in this regard to understand the behavior of food allergens during glycation reaction. MR is also responsible for destruction and loss of essential amino acids including lysine and arginine and therefore MR may cause the production of some toxic and antinutritive compounds that needs to be investigated. In addition to this, it may reduce the bioavailability of participating amino acids by modification and consequently may impair the body growth and development.

The extant of MR depends upon number of open chain concentration present in participating sugar and its pH. Number of open chain form increases with increase in pH and it has been found that the acyclic forms are more in pentose sugars than hexoses and therefore the former is more reactive. The rate of AGEs production during MR depends upon different types of participating reducing sugars such as glucose, fructose and ribose. Compared to glucose, fructose and ribose sugar have greater capability (ribose > fructose >glucose) to modify BSA with AGE (Valencia et al., 2004). Similarly, D-ribose was found as a better modifier over fructose and lactose when cystatin purified from almond was glycated with these sugars (Siddiqui et al, 2015). Higher

activity of ribose was due to presence of more open chain (Bunn et al., 1981; Gary et al., 1982). In addition to these three sugars, BSA modification by glycolaldehyde has shown a higher binding affinity for the receptor for advance glycation end product (RAGE) than glyoxylic acid-modified BSA. Ribose and glycolaldehyde are the best modifiers causing fast and reproducible generation of AGEs induced modification (Valencia JV et al., 2004). As obvious, sucrose does not take part in browning reaction due to absence of free reducing groups. Thus amount of reducing sugars especially pentose present in either food matrix or its surrounding during processing should be avoided to prevent the glycation reaction, effectively.

During MR, formation of some undesirable compound such as acrylamide may also occur. Such contaminant formation correlates with sugar concentration and the presence of asparagine amino acid. Amino acid asparagines undergo MR and leads to the formation of acrylamide. An amide group of asparagines attached to chain of 2 carbon atoms makes it suitable reactant of MR. Recently, glucose and fructose showed the best correlation with acrylamide forming potential in both crisps and heated flour produced from different varieties of potatoes (Halford et al., 2012). Apart from these reducing sugars, free asparagine concentration also determines acrylamide formation in different varieties of potato (Muttucumaru N et al., 2014). Conclusively, free asparagine as well as reducing sugar concentration could be the most likely target to prevent the acrylamide formation in potato products.

Receptors for AGEs derived from Maillard Reaction:

Glyco-conjugation of food proteins during MR, enhances the allergic potential by production of AGEs, an interest towards the study of receptors, which mediate the interaction of immune cells to either AGEs or glycated allergens have been observed. Several receptors have shown binding

affinity with MR derived AGEs as showing in figure 3. Following receptors have been identified for AGEs: the receptor for advanced glycation end product (RAGE) (Schmidt et al., 1992; Neeper et al., 1992), AGEs receptor complex (AGE-R1/OST-48, AGE-R2/80K-H, AGE-R3/galactin-3) (Vlassara et al., 1995; Li et al., 1996) and several receptors belonging to the scavenger family; scavenger receptor class A type I and II (SR-AI/II) (Suzuki et al., 1997; Araki et al., 1995), scavenger receptor class B type I (SR-BI) and CD36 (Ohgami et al., 2001a; 2001b). Followings are brief details on various AGEs receptors:

Receptor for advance glycation end products (RAGE)

The RAGE a 45 kDa trans-membrane protein belongs to the IgG super family and acts as a key factor in the induction of immunological response induced by AGEs (Hofmann et al., 1999; Vlassara et al., 1988; Miyata et al., 1996; Schmidt et al. 1994). The RAGE is a multiligand domain containing structure, made up of N-terminal extracellular domain containing a V-region and two C-region like domains, one trans membrane domain and an intracellular C terminal domain. The V-region like domain is involved in ligand binding, while the C-terminus is important for signal transduction (Schmidt et al., 2000; Neeper et al., 1992; Huntington et al., 2001). RAGE belongs to pattern recongnition receptor (PRRs) family and its expression is found in several types of immune cells, including mast cell, DCs, macrophages/monocytes, T lymphocytes and B lymphocytes, suggesting its critical role in the induction of immune response caused by food derived AGEs (Lin et al., 2009; Cataldegirmen et al., 2005, Demling et al. 2006; Buckley et al. 2010). RAGE may act as receptor for integrins (present on leucocytes) and responsible for recruitment of inflammatory cells, activation of various cellular responses and upregulation of proinflammatory factors resulting in cytokine production and chronic

inflammation (Chavakis et al., 2003). RAGE is found in two forms within a cell, as a cell surface bound form and a secretory form termed as endogenous form. Membrane bound RAGE strongly interacts with glycated form of protein rather than its native form, whereas secretory RAGE captures its ligand to protect from injury caused by AGEs (Yonekura et al., 2003). Recent data suggested that AGEs-modified food allergen may provoke the cellular immune response triggered by RAGE activation. The RAGE receptor recognizes the three-dimensional structure of protein such as β-sheets and fibrils which represent the conformation of glycated allergen (Bucciarelli et al., 2008; Schmidt et al., 2001). RAGE binding affinity for food derived AGEs depends upon free amine groups of participating amino acids. However, its affinity kinetics strongly correlate with participating sugars and it differed among the three reducing sugars, including ribose, fructose and glucose (Valencia et al., 2004). The observed differences among them may be most probably due to ribose and fructose having the higher concentration of open chain that makes them more reactive. There are several new lines of evidence supporting the hypothesis that protein modified with AGEs can induce an immunogenic response. The RAGE receptor recognizes protein modified with AGEs as it was found by a study in Caco-2 cells (model for intestinal epithelia) that RAGE activation by AGEs induced inflammatory response following MAP-kinase pathway (Zill et al 2001). The recent immunological finding has shown RAGE receptor expressed on DCs preferentially recognize OVA modified with AGEs rather than its unmodified form and consequently a Th2 biased immune response was shifted towards allergy. In another recent study Arah1 and Ara h3 modified with CML preferentially recognized by membrane bound RAGE, whereas un-modified Ara h2 allergen did not show binding affinity to RAGE receptor (Mueller et al., 2013). These findings suggest that activation of RAGE

receptor through glycated food allergens may have contributed in allergic sensitization. Glycated structure other than CML may also have binding affinity to RAGE receptor but it is still unknown and need to be identified. Mast cells play a key role in provoking the immune response induced by food allergens. Till date, no study has been carried out to illustrate the AGEs induced mast cell mechanism related to pathogenesis of food allergy. However, AGEs activate mast cells by interacting RAGE receptor suggesting its role in the pathogenesis of MR derived AGEs in FA. BSA modified with AGEs has shown ability to stimulate the production of histamine following the release of intracellular calcium ions in mast cell (Sick et al., 2010). Therefore, a wide spectrum of mechanistic future aspects to be elucidated regarding diverse signaling kinases in mast cell that include phosphatidyl inositol 3-kinase (PI3K), extracellular signal regulated kinase (ERK), protein kinase C (PKC), c-Jun N terminal kinase (JNK), and of NF-kB. Here, we would also mention that there may be some connection between FcεRI and RAGE receptor mediated immune response.

The RAGE receptor can activate multiple cellular signaling pathways induced by food derived AGEs as well as non AGEs products. Downstream signaling through RAGE activation upon homodimerization may include ERK1/2 (p44/p42), p38 and SAPK/JNK MAP kinases with the production of Th2 cytokines (Oczypok et al., 2015, Zong et al., 2010; Zill et al., 2003; Sorci et al., 2004; Cortizo et al., 2003; Shanmugam et al., 2003). Furthermore, rho-GTPases, phosphoinositol-3-kinase (PI-3K) and JAK/STAT pathway have been also implicated in RAGE signaling. All the above mentioned cellular signaling cascades induce an immune response through the activation of downstream effector transcription factor NF-κB as described in figure 3 (Bierhaus et al., 2005). Although, possible downstream signaling pathway triggered by RAGE

activation have been studied in various other diseases, but in case of pathogenesis related to food derived AGEs are remains to be identified. RAGE receptor does not contribute in food allergy caused by native or unmodified alleregen, but do have an important role in pathogenesis related to FA caused by AGEs modified food allergens. Till date, littile is known regarding RAGE receptor mediated cell singnaling in the context of food allergy, however few recent studies have suggested that RAGE receptor has a significant contribution in the pathogenesis related to glycated food. Thus, future studies are needed to illustrate the mechanism induced by activated RAGE receptor in various immune cells that are actively involved in food allergic sensitization.

Scavenger receptor (SR) family:

The SR are described as a group of receptors expressed on the surface of macrophages, DCs, and mast cells (Faigerc et al., 2012). Macrophages and DCs may have a pivotal role in food allergic reaction as they act as principal APCs, whereas mast cells are considered as a main effector cells in FA as they secrete various Th2 cytokines and allergic mediators that are in involved in many complications related to allergy. Thus, receptors belonging to SR family have attracted concern towards the pathogenesis of food allergy caused by AGEs, recently. The SR family is basically endocytic receptor that performs endocytosis and presentation of antigens by APCs (Burgdorf et al., 2008). The common feature of SR family receptor is the internalization of extracellular components followed by lysosomal degradation which may have multifarious consequences, since they are linked to induce diverse specific signaling pathways. Scavenger receptors present on APCs facilitate the internalization and epitope presentation of native and glycated food allergens to T-cells. Subsequently, T-lymphocyte differentiates into Th2 cells and enhances the immunogenicity by producing several cytokines. It has been found that human cord blood mast

cells express scavenger receptor that are upregulated by low density lipoprotein particle. Thus, a study of scavenger receptor in FA is important. The SR receptor may binds with a broad spectrum of endogenous and exogenous poly anionic ligands that include modified protein, lipid, carbohydrate and nucleic acid (Plüddemann et al., 2007). Family of SR receptor is categorized into class A scavenger receptor (SR-A) and class B scavenger receptors (like CD36 and SR-BI) (Miyazaki et al., 2002).

The scavenger receptor class A (SR-A):

The SR-A receptor is a highly conserved receptor and found in several species, including human and mice (Ashkenas et al., 1993;, Matsumoto et al., 1990; Tomokiyo et al., 2002). SR-A binds with a variety of polyanionic ligands derived from artificial, microbial and endogenous origin, including polyribonucleotides, polysaccharides along with exogenous glycated proteins. It is restricted to the myeloid lineage and is expressed only on mature tissue macrophages and DCs derived from both bone marrow as well as spleen (Neyen et al., 2013). The SR-A is found in three isofoms, namely SR-AI, SR-AII and SR-AIII which are produced by alternative splicing of a single gene. SR AI/ II is a trimetric structure made up of three 80 kDa type II transmembrane proteins having an intracellular N-terminal domain, transmembrane domain, a spacer region, a helical coiled coil domain, a ligand binding collagenous domain and a shorter c-terminal cysteine rich domain than SR AI receptor. The SR-AIII is not known with any functional activity and remains trapped in the endoplasmic reticulum. Ligand binding specificity of both SR-AI and SR-AII is considered to be similar. The SR AI/ II play important role in the antigen uptake, degradation and subsequently antigen presentation by APCs (Horvai et al., 1995; Hughes et al., 1995; Gough et al., 1998; Nicoletti et al., 1999; Araki et al., 1995). The SR AI/II receptor

interacts with various glycated form of antigens (AGEs). Binding affinity for AGE to SR-AI/II was confirmed in peritoneal macrophages from SR-AI/II knockout mice, where degradation of AGE-BSA was significantly reduced compared to wild type macrophages (Suzuki et al., 1997). In another experiment conjugate of BSA-glycoaldehyde was recognized by SR-AI/II receptor (Nagai et al., 2000). In addition to BSA, food allergen modified with sugar was also captured and internalized by receptor from class A scavenger family. Further, SR-AI/II was found to be involved in the glycated allergen uptake as AGE-OVA was captured and presented through MHC class-II loading pathway by DCs (Ilchmann et al., 2010; Hilmenyuk et al., 2010). Till date, it is still unknown which glycation structures interact with SR-AI/II receptor as CML has been suggested as a major ligand structure for RAGE receptor. In addition to this, the receptors that mediate the uptake of other food derived AGEs by macrophages remain to be identified.

The Scavenger receptors class B (SR-B)

The SR-B is a group of two members, namely CD36 and SR-BI. Both receptors are glycoprotein having an extracellular loop with glycosylation sites (may act as ligand binding site), two transmembrane domains and two short intracellular tails (Greenwalt et al., 1992; Puente et al., 1996). CD36 is found on macrophages, platelets, adipocytes and some epithelial as well as endothelial cells whereas SR-BI is expressed on monocytes, macrophages and DCs as well as on hepatocytes (Terpstra et al., 2000). Studies have revealed that both members of SR-B family receptors capture and endocytose the AGEs in APCs (Ohgami et al., 2001b Ohgami et al., 2001a). Antigenic AGEs taken up by DCs via SR-B receptor is presented through MHC class I loading pathway, while those taken up by CD 36 are targeted to both MHC class I and class II

loading pathway (Barth et al., 2008; Fioravanti et al., 2011, Tagliani et al., 2008). From these studies, it may be concluded that class B Scavenger receptors also facilitate the AGEs uptake, processing and their presentation to T-cells via both MHC I and II antigen loading pathway. Thus, both CD36 and SR-BI receptor located on DCs and macrophages should be considered in future research design related to food allergy.

Mannose receptor (M receptor)

Similar to SR receptor family, mannose receptor uptake native and glycated food allergen by various immune cells. It is a c-type transmembrane lectin receptor having highly conserved domain, which participates in the carbohydrate recognition. The mannose receptor is expressed on the plasma membrane of macrophages, DCs, monocytes, dermal microvascular and liver endothelial cells (Harris et al., 1992; Figdor et al. 2002). The mannose receptor is made up of an intracellular domain, a transmembrane domain, eight carbohydrate recognition domain (CRD), a fibronectin type II repeat domain and an N-terminal cysteine rich domain (Ezekowitz et al., 1990). The conserved sequence of CRDs has binding affinity for terminal fucose, mannose or glucose residue of glycated protein, while the sulfated sugar moieties of glycoprotein are recognized by the extracellular cysteine rich domain (Largent et al., 1984). Native OVA consist of natural mannose residues, and its uptake is known to be facilitated by the mannose receptor (Huntington 2001; Burgdorf 2006; Autenrith et al., 2007). Modified OVA with AGEs also captured and endocytosed by this particular receptor but the exact glycated structure that binds with the M receptor is yet to be identified. Similar to OVA, other food allergens containing mannose residues may also get internalized by M receptor. It has also been found that allergen from dust mite (Derp1 & Derp2), dog (Cant 1), cockroach (Blag 2) and peanut (Ara h2) were

internalized by DCs through M receptor that recognizes carbohydrate moieties of these allergens as they bind to C-type lectin like CRDs domain 4-7 of M receptor (Royer et al., 2010). Evidence has suggested that both M receptor and SR receptor family may facilitate the allergen uptake in a synergestic manner and induce an immense immune response after food allergen exposure. Presently, sufficient amount of data is not available regarding food related pathogenesis mediated by mannose receptor, but some clue suggesting its involvement in certain cases of food allergy is given as under. Cat allergen Feld 1 is found to be recognized by cysteine rich domain of MR present on DCs and play an important role in allergic sensitization (Emara et al., 2011). Therefore, a careful consideration is required to evaluate the contribution of mannose receptor in AGEs related pathogenesis.

The AGE-receptor complex (AGE-R)

The AGE-R complex having three different components is associated with endocytic uptake of AGE-modified proteins along with AGEs related signaling. The first component of AGE-R also known as OST-48 as well as AGE-R1 is an integral plasma membrane protein with a single trans membrane domain and a long extracellular domain (Li et al., 1996). It is known to be active in binding of AGEs modified proteins on the surface of various cells that include macrophages, T-lymphocytes, endothelial cells, mesanglial cells, fibroblasts, smooth muscle and neuronal cells. The activated AGE-R1/OST-48 prevent the generation of oxidative stress by inhibiting the RAGE signaling (Lu et al., 2004; Cai et al., 2008). Similar to AGE-R1/OST-48, the second component of the AGE-R complex is also linked to intracellular trafficking of AGEs, termed as AGE-R2/80K-H. It is located in the cytosol as well as membrane without having a trans membrane domain (Hirai et al., 1990). Although, its biological role is poorly understood, it was

suggested that activated AGE-R2 after tyrosine phosphorylation by the protein kinase C (PKC) can induce intracellular receptor signaling like FGF receptor signaling (Goh et al., 1996; Kanai et al., 1997). The third component of the AGE-R complex is a member of lectin family known as AGE-R3/Galectin-3 that usually binds with lactose or galactose (Barondes et al., 1994). Lectins are carbohydrate binding proteins which can bind to both soluble carbohydrate and glyco-conjugate of any protein. Firstly, the Galectin-3 receptor was identified in activated macrophage as a cell surface marker (Ho et al., 1982). Later studies revealed that it is also expressed on monocytes, natural killer cells, the eosinophils, activated T and B lymphocytes and DCs (Dumic et al., 2006; Sato et al., 2004). Likely, RAGE receptor AGE-R complex is also not involved in food allergy caused by native allergens. But it is clear that AGE-R complex mediate the AGE derivatives (other than food) uptake by immune cells, therefore attention is needed to explore the food derived AGEs internalization by AGE-R receptor complex. Although, galactin-3 receptor is investigated but not found to be involved in the AGE-OVA uptake in DCs even it poses high binding affinity for AGE-BSA (Ilchmann et al., 2010; Hilmenyuk et al., 2010). Thus, it may concluded that interaction of galactin-3 receptor with its ligand depends upon either AGEs structure or its conjugated protein counterpart. Regarding glycated food allergen, no experimental data are available to show their binding affinity but it may hypothesized that AGE-R complex can mediate the immune response caused by food derived AGEs as it recognizes the AGEs derivatives other than food.

However, there should be some link in the signaling cascade via different AGEs receptor. As we discussed before RAGE receptor after binding with AGEs modified food allergens may trigger various signaling pathways including MAPKs (ERK, JNK& p38), PI3K and sometimes also

follow JAK/STAT pathway. These pathway comes to effect via NFk B activation and transcription/translation of various inflammatory cytokines. In contrst to RAGE receptor, SR family receptor endocytose their ligands such as food derived AGEs and food allergen in clathrin coated vescicles lead to endosome formation and recycling of receptor to the pasma membrane via trans-golgi network. Apart from this SR family receptors (SR-A) lead to the activation of PLCγ1, PI3K, PKC, MAPKs, production of caspases and cytokines (Hsu et al., 2001). SR-B can activate Lyn, Fyn p44/42 MAP kinase & upregulation of TNF-α (Murphy et al., 2005). Regarding mannose receptor, CD 206 (a MR c-type letin) present on APCs (DCs and macrophages) mediate the uptake of native and glycated allergens and consequently allergen induced T-cell polarization that may lead into the onset of allergic sensitization. These events take place via a series of signaling pathways, including activation of MAPKs, upregulation of NFkB & cytokine production are crucial and common events. Thus, it may predict that either all these AGEs receptors may act in a synergistic manner or each receptor alone triggers the signaling cascades after glycated allergen exposure. Through, studies are needed to explore the association and link of various foods derived AGEs receptors to each other, their downstream signaling pathways and subsequent cellular responses with regard to food allergy.

Impact of glycation on both innate and acquired immunity:

The impact of MR on food allergens is not bound to affect the IgE binding property and allergic mediator release potency. Recent studies have shown that glycation products influence both innate and adaptive immune responses in several ways. Glycation of food allergens may alter the way in which they are taken up by APCs across the gut mucosal barrier and presented to immune

cells. Before going to discuss, we must recall here, the FA is characterized by Th2 and Th17 type immune responses, whereas Th1 skewed response associated with T-regulatory cells are known to diminish the risk of FA development in sensitive individuals. The Maillard products have been found to be involved in the activation of antigen presenting cells (APCs) and induction of T-cell responses. There are three primary subsets of T-cells, namely CD8+ T-cells, CD4+ T-cells and T-reg cells. The majority of non IgE mediated food allergic reactions are mediated by CD4+ T-cells. The regulatory T-cells (T-regs) also known as CD4+CD25+Foxp3 cells actively participate in the development of oral tolerance and have been associated with reduced risk of food allergy via the modulation of IL-17 response and an increase in the Th-1 type immune response (Kumar et al., 2012; Rupa et al., 2014a). The constitutive CD4+ CD25+ T-reg cells alleviate immediate hypersensitivity to food allergen by modulating the priming of allergen-specific T and B cells during oral sensitization (Kanjarawi et al., 2011). Recently, enhanced number of circulating CD25+ FoxP3+ cells were found when mice were treated either with mannosylated egg white or various glycated forms of OVA with mannose and glucomannon (Rupa et al., 2014a; 2014b). Consequently, this may lead in the development of oral tolerance against OVA allergen. Thus, it may hypothesize that such modified allergens glycated with specific sugar could be used in clinically successful allergen immunotherapy because T-reg cells might play a pivotal role in specific allergen immunotherapy for FA. Such studies will also help us to understand the mechanism of development of tolerance to glycated food allergens and suggest an immunological way to overcome the food related pathogenesis using glycation approach. Besides acquired immunity, innate immune responses also have an important role in the food allergy progression. Our understanding regarding the contribution of innate immune system in

sensing the food allergens is limited in comparison to respiratory allergens mediated innate immunostimulation, although in certain cases direct activation of innate immune cells by food allergens has been also observed. The innate immunity involved in FA encompasses several cells, including DCs, macrophages, epithelial cells, basophils, nuocytes and NK cells. Innate immune response during FA commences from encounter of an allergen to APCs especially DCs of lamina propria in the intestine (Li et al., 2007). The allergens are internalized by DCs via endocytosis where they are processed into peptides and presented by major histocompatibility complex class-II (MHC-II) molecule to naïve CD4+ T cells. The T helper cells (CD4+ T cells) are differentiated into three classes named as Th1, Th2 and Th17 christened upon the type of cytokines they produce. After activation by allergens, the Th2 subset of CD4+T-cells produce a broad spectrum of cytokines like IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 whereas Th1 cell produces IFN-γ, TNF-α and IL-2 cytokines (Zill et al., 2003; Sorci et al., 2004; Cortizo et al., 2003). Recently discovered Th-17 cells producing subtype IL-17E but not IL-17A have also been found to be involved in allergic sensitization. The cytokine IL-17A is involved in inflammation while IL-17E is able to induce Th2 cytokine production and causes eosinophils expansion (Herberth et al., 2010). Diminished production of Th2 alongwith Th17 cytokines and elevated levels of Th1 and IL-10 cytokines are characteristics of reduced immune response in IgE mediated food allergic reactions that are considered as suppression of FA. This concept is corroboreted by several recent *In vitro* and *In vivo* studies using glycation approach. Stimulation of co-culture of T cells and DCs with OVA-mannose revealed decreased Th2 (IL-4) and increased Th1 (IL-12) cytokine production along with diminished T-cell activation via reduced IL-2 cytokine production (Rupa et al., 2014a). Similarly, preventative effects were observed in

mice treated orally with mannosylated egg white where decreased level of IL-4 and increased level of IL-10 cytokines were found in mice sera (Rupa et al., 2014b).

The IL-4 produced by Th2 cells is a key factor in FA which triggers the IgE production by B-cells and consequently, onset of allergic reaction occur. Several studies have suggested that glycation of food allergens may enhance their allergenicity by the same mechanism. The pyrraline a type of MR product enhances the CD4+ T-cells immunogenicity of the OVA food allergen by producing of higher level of IL-4 alongwith IL-17A cytokines (Heilmann et al., 2014). Furthermore, glyco-conjugates of OVA induce higher production of IgE antibody as activated Th2 cells that in turn induce class switching to IgE production *In vivo* (Yang et al., 2013). The ovalbumin modified with other AGEs have shown more potency than unmodified OVA towards the stimulation of specific T-cells, whereas CD8+ T-cell activation was comparable between AGEs-OVA and native OVA (Ilchmann et al., 2010, Hilmenyuk et al., 2010). The explaination behind the enhanced allergenicity of food allergen may be that glycation of allergens reduce the threshold amount of required allergen for allergic sensitization (figure 4). Till date, studies on the mechanistic aspects of glycated food allergens are still limited to DCs only and therefore the role of other immune cells, including mast cells and macrophages causing pathology of FA must be investigated in response to glycated food allergens.

The Maillard reaction in food allergy:

In the past few decades, consumption of thermally processed foods has increased significantly around the globe (Seo et al., 2014). Usually it is believed that thermal treatment should decrease the allergenicity of food as heating/cooking leads to the disruption of food allergens. During

thermal processing and prolonged storage, it is possible that foods typically experience MR. The MR has played an important role in improving the flavor and color of foods. Of late, it has been recently a major challenge in food research, since the MR is found to be associated with modulation in food allergy (FA). Few food allergic patients suffer from anaphylactic reaction only when they ingest food after either prolong storage or heated foods indicating towards a possible involvement of food derived AGEs in the pathogenesis of FA (Berrens 1996; Malanin et al., 1995). Apart from the AGEs generation, these effects may be due to the formation of stable neoantigens during food processing. But at the same time it should also be appreciated that some conformation epitopes are destroyed at the same time. There are no definite rules regarding the impact of MR/food processing in different foods. In some cases, it can promote their net allergenicity while in other it may decrese or has no effect in term of allergenicity. Therefore, a proper understanding about the impact of MR in FA is important to develop a better strategy to tackle FA related health issues. MR in food induced allergy has been a very interesting topic because of its vague impact on allergenicity. A wide spectrum of research is needed to understand that what(s) and how(s) we can explore impact of MR on the food allergen during food processing and prolong storage. The MR significantly affects the allergic potential of foods in several ways depending upon participating carbohydrate moieties and the nature of food proteins. Here, it is necessary to consider that the presentation of modified allergens to gut immune system is a major factor that affects the allergic potential. Recent, literatures suggest that structurally different glycated form of OVA altered with glucose, mannose, glucomannan and galactomannan demonstrate a differential impact on the allergenicity profile followed by multiple mechanism. The allergenic potential of any allergen is determined by their IgE binding

property that trigger the mast cells to release various allergic mediators such as histamine, MCPT-1 etc. leading to consequences of allergy. For example, OVA-mannan and OVA-glucomannan conjugates have shown their ability in the induction of allergic response (Yang et al., 2013). Also, potato protein has shown more immunoreactivity in the term of IgE binding property when glycated with galactose and galacto-oligosaccharide (Ma et al., 2013). However, modification with galactan to patatin showed decrease in immunoreactivity by showing hindrances in the binding of IgE to epitopes (Ma et al., 2013). Considering these facts, the fate of allergic response after glycation may depend upon the participating food protein as well as the glycating agent. Mannosylated egg white and glycated buckwheat allergen (Fag t 3) have shown prevention of FA caused by fag t-3 and egg white allergens suggesting that glycation with a particular type of sugar could be an approach to treat a particular type of food allergy (Hansen et al., 2003, Gruber et al., 2004). These results raised a positive side of MR and given a possibility that apart from exerbation in allergenicity potential, MR may also reduce allergic potential of some food proteins by altering the confirmation of allergenic proteins. For instance, glycation of OVA and squid tropomyosin proteins diminish allergic property by altering the secondary and tertiary conformation (Nakamura A et al., 2006). Similarly, glycation of Ara h2 and Ara h6 reduces the allergenicity due to lowered T-cell immunogenicity and decreased IgE antibody production (Davis et al., 1998, Vissers et al., 2011).

The MR has been found to be safe in many cases as listed in Table no. 2, but at the same time aggregation of proteins may have contribution towards allergenicity modulation and provide resistance to gastric digestion and bind to IgE antibody more effective. Simonato et al., (2001) has stated that Maillard products can induce cross linking of food proteins, leading to the

formation of protein aggregates where the IgE reactive protein of wheat was found extensively cross linked structure. Usually, protein aggregates affect their ability to sensitize by generally enhancing their immunogenicity but in case of food allergens, such aggregates of allergic proteins may increase or decrease their allergenicity by affecting their IgE binding property. Aggregation of glycated hazelnut allergen Cor a 11 causes a decrease in IgE production as well as IgG binding, while in the case of Ara h1 glycation, such aggregation leads to enhanced allergenicity (Burks et al., 1992; Ehn et al., 2004). The observed dual biological nature of protein aggregates may be probably due to the unpredicted conformation of crosslinked food allergen which might affect the uptake and processing of food allergen in the gastrointestinal tract. The majority of glycated fruit allergens do not cause enhanced allergenicity like other food allergens. Thus, glycation of Bet v 1 homologous to cherry and Pru av 1 considerably reduced the IgE binding property when glycated with ribose and fructose **(**Verma et al., 2013)**.** Similarly, conjugation of tropomyosin with ribose induces a strong inhibitory effect on IgE binding affinity **(**Burks et al., 1992)**.** More recently, glycation of almond cystatin protein lead to conformational changes and altered its biological and immunological activity (Siddiqui et al., 2015). Thus, MR may modulate FA by either masking of allergenic epitope recognized by IgE antibody or contributing in neo-allergen development. Taken together, glycation of allergens can significantly modify their immunogenicity and allergenicity as it can either promote or suppress allergenicity by altering the immunodominant epitopes. Considering the adverse health effects of non enzymatic glycation, there is also a safe and efficacious approach to combat food allergy. Glycation of food allergens may be a promising way to achieve certain food products with lower

allergenicity but before this hypothesis each and every food allergen has to be assessed for their allergenicity after glycation with various types of reducing sugars.

In foodstuffs, glycation reaction is not only limited to affecting the biological structure and function of proteins, it can also cause modification in phospholipids (PLs) creating various other health hazards in addition to allergy. Among food derived PLs, only phosphatidylethanolamines and phosphatidylserines,can be modified during MR because they posses a free amino group. Like food proteins, PLs can also form adducts with reducing sugar as called advanced glycation end-products. To date, glycated lipid products have been less characterized in comparison to proteins. Glycated aminophospholipids along with their derivatives have been reported in biological samples (Pamplona et al., 1995; Pamplona et al., 1998; Ravandi et al., 1995; 1996, Lertsiri et al., 1998 Fountain et al., 1999). Further, various PLs derived Amadori products have been also structurally determined in the egg yolk powders and lecithin products (Utzmann et al., 2000). Recently, phospholipid glycation and oxidation products have been found in various foodstuffs, including milk powders, pasteurized milk, ultra-high-temperature milk and soy flour (Calvano et al., 2014). All the above discussed Amadori products are considered useful as a marker of nutritional quality of foods as their higher concentration may affect the nutritional value (Erbersdobler et al., 2007). Accumulation of these products in processed foods generally reduces the essential amino acid content and consequently may impair cellular metabolism and body growth. Thus, similar to protein, PLs derived Amadori product concentration in food and food products should be determined carefully to mantain the nutritional value of foods.

Potentially inhibiting substances to glycation reaction

Inspite of several helth benefits, MR has also deleterious effects on health in the context of food allergy. Thus, more attention is needed towards the finding of such compounds that can potentially inhibit the MR during food processing. Researchers have suggested that non-enzymatic glycation of proteins either during food processing or due to hyperglycemic environment affect its biological properties (Rebecca et al., 2008). Such preventive efforts may lead to the preservation of biological functions of food proteins and may limit the pathogenesis related to food derived AGEs by their reduced production. Although, MR progresson during food processing can be controlled by some key factors such as pH, temperature, concentration of reducing sugars, transition metals and the presence of other redox-active compounds but it can be efficiently prevented by the using of some potent inhibitors. Various dicarbonyl compounds generated during MR cause formation of protein aggregates in different allergenic foods, leading to their undigestible forms with more IgE binding affinity. Several varities of MR inhibitors such as aminoguanodine, cysteines thiol group, pyridoxamine and sulphate containing compounds have been identified as they inhibit the advance glycation steps during MR between different sugars and food allergens. These compounds inhibit the production of more reactive dicarbonyl compounds leading to inhibition of food protein crosslinking and AGEs generation (Seo & Karboune 2014). In addition to targeting the dicarbonyl compounds, pyridoxamine (derivative of Vit B_6) reduce the rate of glycation reaction by targeting to some other intermediates of MR. For instance, it delayed the Amadori compounds and Nε- (carboxymethyl) lysine formation during MR between β-lactoglobulin and galactose/tagatose and blocks the protein cabonylation also (Corzo-Martínez et al., 2010; , Booth et al., 1997; Villaverde & Estévez 2013). Thus, regulation

of MR is not limited to targeting of a single step by a particular inhibitory compound as it may be controlled by various highly reactive intermediates during the MR progression.

Further identification of such rate limiting factors and stpes in glycation reaction is required and may be an efficacious approach towards lowering the risk of many health complications related to food allergy caused by MR. Recently, numerous phenolic compounds having antioxidant property have been identified as potent inhibitors in MR progression by inhibiting the reactive carbonyl species and AGEs formation. The polyphenols from green tea namly catechins, epicatechin or epigallocatechin gallate inhibit the formation of highly reactive intermediates during MR (Yin et al., 2014). The inhibitory action of such antioxidant polyphenols in MR progression may follow several mechanism as they exert their inhibitory effects either by an interference with sugar fragmentation or scavenging of intermediary radicals. In addition to this they can also react with amino acid residues directly, hence making them unavailable for MR. The more activated ring structure present in the certain phenolic compounds may also make them suitable to suppress the MR during food processing. Thus, the exploration of precise mechanism used by MR inhibitors and exact target intermediates further have to be investigated. Flavonoids are well known for their important biological and pharmacological properties due to their antioxidative potential. Among them, flavonoids demonstrated inhibitory potential in the AGEs generation. The glycation inhibitory potential is found among various flavonoids in the order of luteolin (84.4%) > rutin (77.9%) > qucertin (71.0%) > kaempferol (64.3%) > EGCG (52.3%) > ECG (32.5%) > naringenin (31.8%) at 100μM concentration. Ashraf et al., (2015) reported a comparative study between quercetin and aminoguanidine and concluded that quercetin as a better and the potent antiglycating agent than aminoguanidine at all stages of glycation reaction.

A comparative analysis of inhibiting potential of various MR inhibitors is needed in order to develop a better understanding of the use of inhibitors as food ingredients. Such natural inhibitory compounds without adverse effect may be better agents with more potential for the prevention in glycation of food proteins and in AGEs generation. Some natural compounds such as curcumin or glutamine modulates the immunogenicity of AGEs by affecting their transport across the intestinal membrane. Usually, AGEs transport across the intestinal membrane is very low and can play a critical role in immune response caused by food derived AGEs (Vanderhoof 2008). The dietary addition of glutamine or curcumin increase the intestinal permeability (IP) of AGEs and may overcome the pathology related to AGEs (Rapin & Wiernsperger 2010). However, the precise mechanism of action of both compounds either alone or in a synergestic manner regarding IP of food derived AGEs must be evaluated. The presence of a diverse range of compounds that can attenuate generation of Maillard products as well AGEs encourage scientific fraternity to explore its implication in preventive aspects of food allergy.

Conclusion and future prospective

Literature is flooded with the studies exploring the pathogenesis of glycation in the context of various diseases but any systemic review on food allergy and glycation is rare. Due to increasing demand of processes foods in the global market, understanding of basic and current knowledge behind the role of glycation in food allergy is highly important. Investigation of impact of food processing on food allergy is not a new concept, but inspite of a lot of knowledge, our attention regarding the contribution of MR take place during food processing to towards the allergic potential of food allergens has just begun. As in the past few years, consumption of highly processed foods has increased drastically that also indicate an enormous elevated exposure of

Maillard products or AGEs products generated by food processing. Therefore, Maillard products or AGEs have received tremendous attention since last decades. The MR modulates the allergic potential of different foods depending upon several key factors involved in processing environment (such as high temperature and pH). Therefore, such critical factors should be considered as target to combat the allergenicity. The major question affiliated with Maillard products and AGEs whether they participate in allergic events or not? On context basis literatures are divided in two different opinions, in first opinion generation of these products due to food processing especially MR may present an induced potential of allergic reactions compare to native food/s. In the second opinion, food processing may lead to attenuated allergenicity in food. The overall main fact is MR possesses positive as well as negative impact on the allergenicity of foods. Due to increased food demand and various life styles, it will be a tough job to eliminate processed foods from our dietary stuffs, therefore there is an urgent need to assess a wide range of processes foods for their allergenicity potential. MR reactions have shown its positive role in various food/s where allergenicity was down-regulated, those foods should be welcome. On the other hand, MR reactions causes up-regulated allergenicity potential in certain food/s, those foods should be excluded. Importantly, the individual allergic to certain food/s should take care of this. In developed countries foods are marked with the details related to the presence of any major allergens within the food/s. But, details regarding elevated allergenicity due to processing are rare. Thus, the food industry should pay more attention to this health concern. Although, this will cost a huge amount of investment, but we all know health is wealth.

For the scientific fraternity too, understanding the basic mechanisms behind how different allergenic foods respond to MR during thermal processing is an interesting and potential topic.

For instance, receptors that may be involved in the pathogenesis of food derived AGEs posses a broad mode of action, but detailed mechanistic insight is yet to be explored. Currently, there is hardly any study on signaling pathway in mast cell and macrophage triggered by glycated allergens that may have contribution in majority of the food allergic reactions. Therefore, future studies related to multiple cellular signaling cascade induced by food derived AGEs should be designed. Like food allergens, AGEs cross the intestinal epithelium poorly causing immunogenic response in human body because lower intestinal permeability is considered as a risk factor in food allergy. Thus a pharmacokinetic study related to food allergen modified with AGEs should be carried out to develop a better understanding about intestinal permeability of glycated food allergens. As reviewed here, glycation of OVA food allergen with either specific sugars such as mannose and glucomannon or MR product (pyralline) causes decrease in allergenicity by producing of T-regulatory cells (T-reg). The generation and surviaval of T-reg cells are key events for allergen specific immunotherapy (SIT) and oral immunotherapy (OIT) that are considered as prevention techniques in food allergy. Thus, such glycated food allergens inducing the production of T-reg cells may be used in both the SIT and OIT against specific food allergens. Further, utilization of various natural inhibitors of glycation reaction and AGEs generation may open a new dimension toward attenuated allergenicity of processed foods. Several antiglycating agents including, flavonoids and phenolic compounds can be utilized as food ingredients to limit or prevent the food protein aggregation and AGEs production associated with intermediate and advance stages of glycation reaction during food processing and its long storage.

Recently, information regarding the impact of MR in FA is still limited and identifying the glycation structures in thermally processed or stored allergenic foods may provide future insight towards the potential allergenicity of processed food allergens. The present attempt may be beneficial towards the knowledge regarding the consideration or elimination of food processing to overcome the corresponding allergy. Available reports on impact of MR in FA clearly indicate that not only MR, any type of glycation reaction in foods needs to be carefully considered in the allergenicity assessment of food allergens.

Acknowledgments

We are grateful to the Director of the Institute for his keen interest in this study. This work was financially supported by In-Depth Project (BSC-0111) of Council of Scientific and Industrial Research (CSIR), New Delhi. Thanks are also due to pathway builder tool version 2.0.

Conflict of interest

Authors have declared that there is no conflict of interest.

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Table.1 Impact of Miallard Reaction with enhanced allergenicity in food allergens

The Food	Major Allergen	Participating Sugar	Increased allergic parameters by Glycation	Reference
Egg	Ovalbumin	3-deoxyglucosone (1, 2 or 4 hrs at 70 °C)	T-cell immunogenicity along with IgE production	Heilmann et al., 2014
	Ovomucoid	Glucose (96 hrs at 50 °C)	Immunoreactivity	Jimenez-Saiz et al., 2011
Peanut	Ara h1	Glucose (60 min at 100 °C)	IgE reactivity	Maleki et a., 2000
	Ara h2	Maltose, Mannose, , Xylose (60 min at 100 °C)	IgE reactivity	Maleki et a., 2000
	rAra h2	Ribose (90 min at 100 °C)	IgE reactivity	Gruber et al., 2005
	Ara h2/Ara h6	Glucose (20 min at 145 °C)	IgE reactivity	Vissers et al., 2011
Apple	Mal d3	Glucose (120 min at 100 °C)	IgE reactivity	Sancho et al., 2005
Potato	Patatin	Galactose, Galactosaccharide (1-3 dyas at 48 °C)	Immunoreactivity	Seo et al., 2014

Codfish	Parvalbumin	Glucose (5, 12, 24, 48 hrs at 60 °C)	IgE binding Property	de Jongh et al., 2013
Shellfish	Tropomyosin	Glucose (180 min at 60 °C)	IgE reactivity	Nakamura et al., 2005

Table.2 Impact of Miallard Reaction with decreased allergenicity in food allergens.

The Food	Major Allergen(s)	Participating Sugar(s)	Decreased allergic parameters by Glycation	Reference
Egg	Ovalbumin	Mannose/ Glucomannon (55°C for 72 hrs)	Clinical signs and Specific IgE production	Rupa et al., 2014b
	Egg White	Mannose (55°C for 72 hrs)	Histamine, MMCP and Cytokines production	Rupa et al., 2014a
Peanut	Ara h1	Glucose (20 min at 145°C)	IgE reactivity	Vissers et al., 2011
	Ara h1/Ara h3	Glucose (20 min at 145 °C)	IgE reactivity	Kroghsbo et al., 2011, Mueller et al., 2013
Milk	β-Lactoglobulin	Ribose (72 h at 60°C)	IgE reactivity	Taheri-Kafrani et al., 2009
Soyabean	β-conglycinin	Glucose, Galactose, Maltose, Lactose, and Dextran (60°C from 0 to 72 hrs)	IgE Binding property	Guanhao et al., 2015

Potato	Patatin	Galactan (48 °C for 1 to 3 days)	Immunoreactivity	Seo et al., 2014
Buckwheat	Fag t 3	Plant Polysaccharide (3 days at 70 °C or for 15 min. at 160 °C)	IgE/IgG binding property	Yang et al., 2013
	Protein fraction	Dextran	IgE reactivity	Tazawa et al., 2014
Hazelnut	Cor a 11	Glucose (20 min at 145 °C)	IgE reactivity and mediator release capacity	Iwan et al., 2011
Grass carp	Parvalbumin	Maltose	IgE Binding Property	Zheng et al., 2014
Squid	Tropomyosin	Ribose (180 min at 60°C)	IgE reactivity	Nakamura et al., 2006
Fish	Fish Protein	Ribose (at 121 °C for 72 hrs)	Hexosaninidase and Histamine release capacity	Yanga et al., 2015

Fig. 1

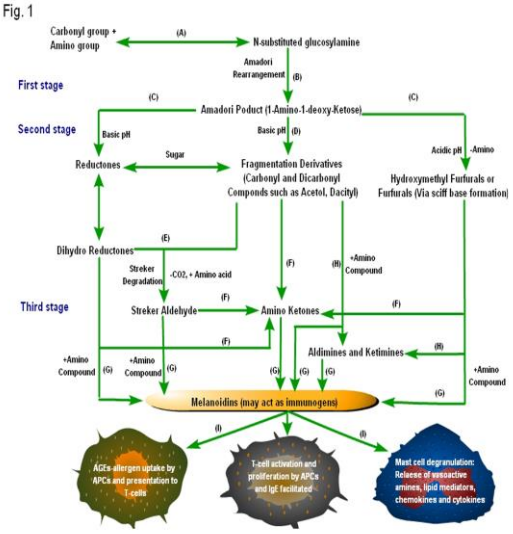

Fig. 2

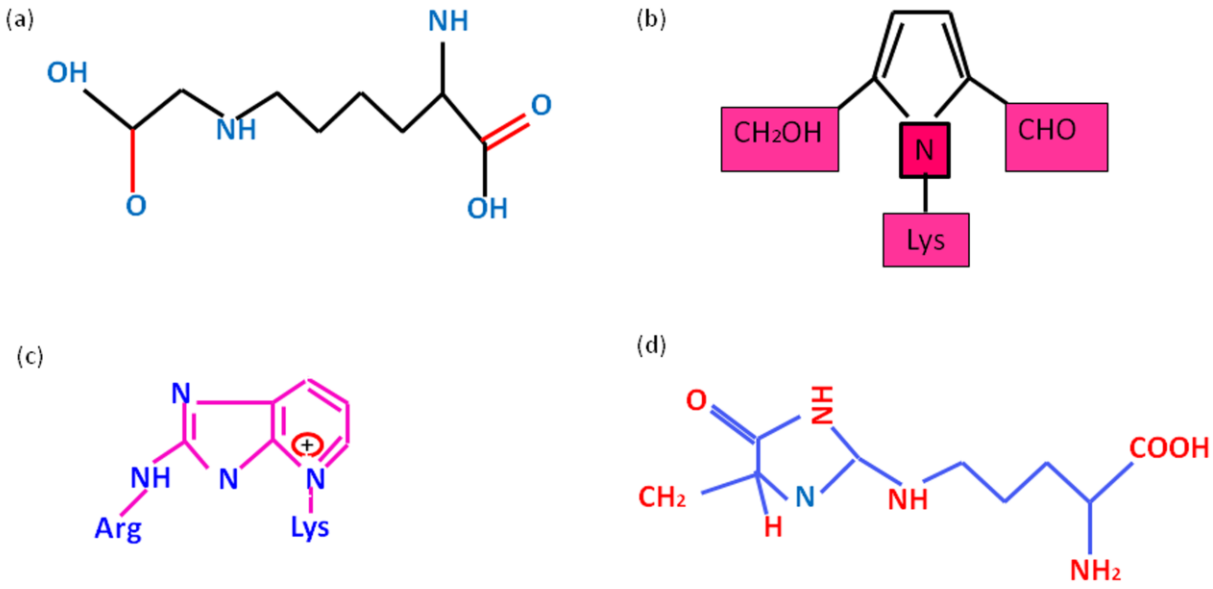

Fig. 3