JOURNAL OF FOOD AND DRUG ANALYSIS 25 (2017) 84–92

Available online at www.sciencedirect.com

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journal homepage: www.jfda-online.com

Review Article

Polyphenols with antiglycation activity and mechanisms of action: A review of recent findings

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ARTICLE INFO

Article history:
Received 23 September 2016
Received in revised form
6 October 2016
Accepted 12 October 2016
Available online 5 December 2016

Keywords:
advanced glycation end products
antiglycation
flavonoid
phenolic acid
polyphenols

ABSTRACT

Advanced glycation end products (AGEs) are substances composed of amino groups of proteins and reducing sugars. The initial and propagation phases of the glycation process are accompanied by the production of a large amount of free radicals, carbonyl species, and reactive dicarbonyl species, of which, methylglyoxal (MG) is the most reactive and can cause dicarbonyl stress, influencing normal physiological functions. In the advanced phase, the production of AGEs and the interaction between AGEs and their receptor, RAGE, are also considered to be among the causes of chronic diseases, oxidative stress, and inflammatory reaction. Till date, multiple physiological activities of polyphenols have been confirmed. Recently, there have been many studies discussing the ability of polyphenols to suppress the MG and AGEs formation, which was also confirmed in some *in vivo* studies. This review article collects recent literatures concerning the effects of polyphenols on the generation of MG and AGEs through different pathways and discusses the feasibility of the inhibition of glycative stress and dicarbonyl stress by polyphenols.

1. Introduction

The spontaneous post-translational modification of proteins or amino acids through reducing sugars is called the Maillard reaction or nonenzymatic glycation, and the products resulting after the exposure to reducing sugars are called as advanced glycation end products (AGEs) [1]. In the course of food processing, heating, and storage, the Maillard reaction can enhance food flavor and color; however, excessive AGEs in food have been confirmed to cause many chronic diseases in organisms, including diabetes mellitus (DM) [2] and kidney diseases [3], and are among the causes of the development and malignancy of tumors [4]. Therefore, there have already been many studies investigating various factors in the application of the Maillard reaction in food chemistry, physiology, and toxicology.

The production of dicarbonyl compounds during the Maillard reaction is an important step in the production of AGEs [5], among which methylglyoxal (MG) is one of the

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http://dx.doi.org/10.1016/j.jfda.2016.10.017

most highly reactive carbonyl species (RCS) in the human body [6]. In addition to investigating the effects of AGEs, recent studies have also addressed the effects of MG on many chronic diseases and aging-related diseases in clinical practice [7]. The MG concentration in the blood of DM patients is reported to be significantly higher than that in non-DM patients, reaching 400μM [8]. Additionally, endogenous MG is produced in the bodies of organisms. Under pathological conditions, an even higher concentration of MG will be accumulated in the body, which might be associated with the imbalance of the antiglycation system, known as the glyoxalase system [9]. Therefore, the accumulation of RCS, such as MG, in organisms and the associated metabolic imbalance will result in the development of many human diseases.

Recently, antiglycation has been considered as an effective strategy to slow down human aging and disease development. The inhibition of glycation can suppress inflammasome activation to reduce the development of inflammatory reactions [3,10]. The antioxidant and anti-inflammation abilities of polyphenol substances have been extensively studied, and their antiglycation functions have been screened in many *in vitro* experimental platforms. The results show that polyphenols can inhibit the biosynthesis of AGEs through their antioxidant properties, metal-chelating ability, protein interaction, MG trapping, and/or blocking the receptor for advanced glycation end products (RAGE) [11,12]. Polyphenols were classified into four large groups in this article, phenolic acids, stilbenes, lignans, and flavonoids, and different antiglycation functions of polyphenols found in recent years were examined to evaluate the antiglycation potential of polyphenols.

2. AGEs formation

The Maillard reaction is a nonenzymatic glycation function. It involves many steps, and the reaction usually requires several days or even several weeks to complete (Figure 1).

2.1. *Initial phase*

In the initial phase of the Maillard reaction, reducing sugars, such as glucose, fructose, or ribose, will act on the terminal amino groups of proteins, nucleic acids, or phospholipids to form unstable Schiff bases, which will further become more stable keto-amines, also called Amadori products, after rearrangement. The reactions in this phase are all reversible, and depending on the substrate concentrations and reaction time, these reactions have different effects. In addition, Schiff bases are prone to oxidation to produce free radicals, resulting in the formation of active carbonyl intermediate products [13].

2.2. *Propagation phase*

During the process of Amadori rearrangement, the oxidation function induced by the catalytic function of metal ions or oxygen will produce many carbonyl compounds, including MG, glyoxal, and 3-deoxyglucosone. This stage is the intermediate phase of the Maillard reaction.

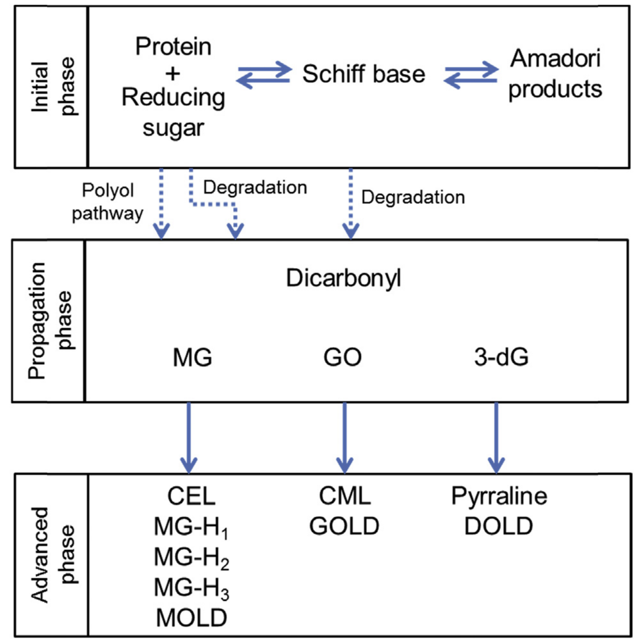

Figure 1 – Pathway for AGE formation. The N-terminal amino groups of protein and reducing sugar form dicarbonyls including methylglyoxal, glyoxal, and 3-deoxyglucosone through polyol pathway, glycolysis, or autoxidation of reducing sugar, leading to generation of pathological AGEs. AGE = advanced glycation end product; CEL = N $^{\varepsilon-}$carboxyethyllysine; CML = N $^{\varepsilon}$-carboxymethyl-lysine; 3-dG = 3-deoxyglucosone; DOLD = 3-deoxyglucosone lysine dimer; GO = glyoxal; GOLD = glyoxal-lysine dimer; MG = methylglyoxal; MG-H = MG-derived-hydroimidazalone; MOLD = methylglyoxal-lysine dimer.

2.3. *Advanced phase*

The advanced phase is the last phase of the Maillard reaction. In the advanced phase, dicarbonyl compounds form isomers with the arginine and lysine residues of proteins, called AGEs. They are characterized by thermal stability. The major AGEs are classified into 3 groups: (1) fluorescent crosslinking AGEs, such as crossline and pentosidine; (2) nonfluorescent crosslinking AGEs, such as imidazolium dilysine crosslinks; and (3) nonfluorescent non-crosslinking AGEs, such as $N^{\varepsilon-}$carboxyethyllysine (CEL) and N^{ε}-carboxymethyl-lysine (CML). Except for pyrraline and pentosidine, the production of AGEs is irreversible.

3. Carbonyl stress mediated by MG

The propagation phase of the glycation process produces RCS, which are considered as precursors for the formation of AGEs. MG is a highly reactive substance and is considered as one of the most reactive precursors of AGEs, which can be produced by endogenous enzymatic reactions or nonenzymatic reactions [14]. MG can produce many types of AGEs through the