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Maillard Browning Inhibition by Ellagic Acid via Its Adduct Formation with the Amadori Rearrangement Product

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ABSTRACT: The Maillard reaction performed under a stepwise increase of temperature was applied for researching the inhibition of Maillard browning caused by ellagic acid. Ellagic acid was found effective for the inhibition of melanoidin formation in the xylose−glycine Maillard reaction but depended on its dosage and the point of time it was added in the reaction system. The lightest color of the Maillard reaction products was observed when ellagic acid was added at the 90th min, which was the point of time when the Amadori rearrangement product (ARP) developed the most. LC-ESI-MS/MS analysis results showed a significant tendency of the ellagic acid hydrolysis product to react with the predominant intermediate ARP to yield an adduct. The adduct stabilized the ARP and delayed its decomposition and inhibited the downstream reactions toward browning. After the ARP was depleted, ellagic acid also showed an effect on scavenging some short-chain dicarbonyls which contributed to the inhibition of Maillard browning.

KEYWORDS: *ellagic acid, Maillard reaction, Amadori rearrangement products, nonenzymatic browning inhibition, adducts*

INTRODUCTION

Maillard reaction is a cascade of complex reactions which occurs in foods during storage and processing and accounts for the formation of food flavor and browning. The products of the initial stage of Maillard reaction, Amadori/Heyns rearrangement products (ARP/HRP) could undergo enolization and generate deoxyosones which can convert to short-chain α-dicarbonyls and α-hydroxycarbonyls through retro-aldolization or hydrolysis.[1] The α-hydroxycarbonyls could also generate α-dicarbonyls through oxidation. These α-dicarbonyl compounds such as glyoxal and methylglyoxal derived from deoxyosones are important precursors of browning products due to their unique role in cross-linking the amino acids containing the guanidine group or more amino groups,[2] which was proved by the evidence of significant pronyl-lysine formation in bread during baking.[3] In addition, glyoxal is an important precursor of the 1,4-bis(5-amino-5-carboxy1-pentyl)pyrazinium radical cation that leads to the cross-linking of amino acids and facilitates browning.[4] Glyoxal, deoxyosones, and ARPs showed great reactivity to construct molecular skeletons of the pigment compounds via dehydration and oxidation to form glycosidic bonds,[5] or successive dehydration with amino acids to yield the oligomer,[6] or even aldolization for carbon chain growth.[7] Different from glyoxal, methylglyoxal was found to be reactive for the development of the molecular skeleton of the pigment compounds because of its carbanion formation as a prerequisite for aldolization.[7]

The browning caused by the Maillard reaction is sometimes undesired due to the unsightly result of processed food. Browning inhibition shows its importance in the food industry, for obvious instance the light-colored Maillard flavorings as flavor supplements are especially crucial when applied in oriental steamed foods. Therefore, many researchers focused on the development of strategies and chemical mechanisms for the Maillard browning control.[8,9] Some vitamins, amino acids, and peptide derivatives were discovered to be effective for Maillard reaction inhibition by trapping the reactants, intermediates, or products.[10] The trapping compounds were reported including creatine, hydroxytyrosol, pyramine, and low molecular weight thiols such as cysteine, homocysteine, and glutathione.[8,11] Polyphenols are naturally occurring antioxidant compounds which are observed to effectively inhibit Maillard browning due to their capacity of scavenging α-dicarbonyl compounds.[12,13] These antioxidant compounds have great potential to improve the functionality of Maillard reaction products, such as color and health profiles.[14,15] During the Maillard reaction, methylglyoxal was found to be attached to unsubstituted carbons on the benzene ring of caffeic acid, a typical polyphenol compound.[12] One of the most important tea polyphenols, (−)-epigallocatechin gallate (EGCG), is regarded effective for scavenging reactive carbonyl species. A slightly alkaline pH usually improves the generation of two mono-methylglyoxal adducts and one di-methylglyoxal adduct of methylglyoxal with EGCG.[16] It was widely agreed that the highly active hydroxyl groups on the A ring of this flavonoid polyphenol tend to promote para- and ortho-directed electrophilic aromatic substitution.[8] Ellagic acid is a natural plant polyphenol found in many fruits or leaves such as grapes,[17] raspberries,[18] strawberries,[19] and tea.[20] Recently, various

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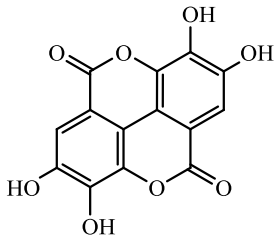
functions of ellagic acid like anti-inflammation,[21] anti-tumor,[22] anti-depression,[23] and potential Parkinson's disease management[24] were reported and it was regarded as a valuable lead compound with low cytotoxicity for pharmaceutical use, as well as an important ingredient of functional foods. On the other hand, as a dimeric form of gallic acid, a resorcinol structure of ellagic acid (Figure 1, compound **1**) creates high nucleophilic



Compound **1**

Figure 1. Structure of ellagic acid.

centers at the carbon with hydrogen, which could be directly associated with trapping the reactive carbonyl species generated during the Maillard reaction. Consequently, the activity of ellagic acid for controlling advanced glycation end-products was confirmed.[25,26] This indicates potential of ellagic acid to be used in the Maillard browning control.

Accordingly, this research focused on the involvement of ellagic acid in the Maillard reaction via the interaction with the carbonyl intermediates such as ARP, deoxyosones, glyoxal, and methylglyoxal crucial for the browning formation. The changes in intermediates caused by ellagic acid intervention during the Maillard reaction were investigated. The target intermediate whom the ellagic acid interacted with was sought, and the interaction mechanism, as well as its effects on the browning formation were revealed.

MATERIALS AND METHODS

Chemicals. D-Xylose (PubChem CID: 135191) and L-glycine (PubChem CID: 750) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Glyoxal and methylglyoxal were obtained from J&K Scientific (Shanghai, China). Diacetyl and *o*-phenylenediamine (OPD) were supplied by Rhawn Chemical Reagent Co., Ltd. (Shanghai, China). 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), diethylenetriaminepentacetic acid (DTPA), formic acid, methylglyoxal-q, and glyoxal-q were acquired from Aladdin Chemical Reagent Co. Ltd (Shanghai, China). Ellagic acid (PubChem CID: 5281855), acetonitrile, and methanol were provided by Oka Chemical Reagent Co. Ltd (Beijing, China). Ultrapure water was prepared with a Milli-Q Gradient A 10 system (Millipore, Schwalbach, Germany). The ARP derived from xylose–glycine (*N*-(1-deoxy-D-xylulos-1-yl)-glycine) was synthesized in our lab according to the method described below (purity 98.99%).

Maillard Reaction Performed under Stepwise Increase of Temperature. The effect of ellagic acid on the Maillard browning inhibition was evaluated through the Maillard reaction performed under a stepwise increase of temperature.[27] Xylose (0.2 mol/L) and glycine (0.1 mol/L) were dissolved in 50 mL of ultrapure water and then the pH was adjusted to 7.0 ± 0.1 with NaOH (6 mol/L). The solution was sealed and placed in a water bath at a constant temperature of 90 °C for different duration time, then immediately cooled in ice water. Ellagic acid was added into the reacted solution in solid state and the final concentration in the model system with Xyl/Gly was 5 mmol/L. The pH of the system was readjusted to 7.0 ± 0.1 with NaOH (6 mol/L). The mixture was transferred into a pressure-resistant hermetical glass tube (120 mL) and reacted in an oil bath at 140 °C for 60 min. Although the solubility of ellagic acid was less than 1 mg/mL at room temperature, the ellagic acid added to the Maillard reaction solution was dissolved well during the heat treatment. The control group was the samples prepared at 140 °C for 60 min without adding ellagic acid.

Browning Intensity Measurement. Browning intensity of the final Maillard reaction products was measured using an ultraviolet–visible (UV–vis) spectrophotometer (UV-1800, Shimadzu Co., Shanghai, China). The absorbance of Maillard reaction final products was measured at 420 nm (A_{420}).[28] To ensure the accuracy of the measurement, the sample was diluted 15-fold to ensure the absorbance between 0.2 and 0.8.

Preparation of ARP in Aqueous Medium. The ARP derived from xylose–glycine was prepared according to the method proposed by Cui et al.[29] The mixture of xylose (0.2 mol/L) and glycine (0.1 mol/L) was dissolved in 50 mL of ultrapure water, and then the pH of the mixtures was adjusted to 7.5 ± 0.1 with NaOH (6 mol/L). The mixture was placed in a water bath at a constant temperature of 90 °C for 70 min. Then, it was transferred into a round bottom flask fitted with a rotary evaporator and the atmospheric pressure was decreased to 5 mbar within 1.5 min in a water bath at 90 °C. The mixture was kept reacting for 10 min and then cooled to 0 °C in ice water, and then reconstituted to 50 mL with ultrapure water.

Purification of ARP. The Maillard reaction mixtures containing ARP were added to a column (2.6 cm × 30 cm) filled with Dowex 50WX4 200–400 mesh ion exchange resin (100 g) in H^+-form. At first, the column was eluted with ultrapure water (3 mL/min) to remove xylose from the mixture. 3,5-Dinitrosalicylic acid (DNS) was used to detect the presence of xylose. After that, ammonium hydroxide (0.2 mol/L) was used at a flow rate of 1 mL/min to separate the ARP and glycine. Then the eluate from the column was collected for high-performance liquid chromatography (HPLC) detection.

Characterization of ARP through UPLC-MS/MS. The purified ARP was identified by Q-TOF MS spectrometry (Waters, Synapt Q-TOF MS) using a BEH C_{18} column (1.7 μm, 2.1 mm × 50 mm, Waters).[30] An UPLC-ESI-MS system with an Acquity PDA detector was used to acquire the spectra and the mass spectrometer was in positive ESI mode. Mobile phase A was 100% acetonitrile and mobile phase B was water with 0.1% formic acid. The flow rate of LC-MS was 0.3 mL/min, the injection volume was 1 μL, and the column temperature is 45 °C. The gradient elution method of the sample was as follows: initial 98% B; 0–4 min, 98–90% B; 4–7 min, 90–85% B; 7–10 min, 85–65% B; 10–12 min, 65–0% B. The conditions of ionization were as follows: the capillary voltage, cone voltage, and extractor voltage were set at 3.5 kV, 20 V, and 7 V, respectively. The source block and the desolvation temperatures were 100 and 400 °C, respectively. The cone gas flow was set at 50 L/h. The purified ARP was analyzed by MS detection using a full-scan mode over the range of m/z 20–1000. The scanning time and the inter scanning delay were 1 and 0.1 s, respectively. MassLynx software (version 4.1, Waters, Milford, MA) was used to analyze the data, and the MS/MS spectrum (Figure S1a), as well as the fragmentation of the ARP molecular ions (Figure S1b), are illustrated in the Supporting Information.

Analysis of ARP, Xylose, and Glycine by HPLC. The quantitation of ARP, xylose, and glycine was done using an HPLC-ELSD system. An XBridge BEH Amide column (3.5 μm, 4.6 mm × 150 mm, Waters) was used for separation. ELSD evaporation tube temperature was set at 55 °C. The air compressor for the evaporation tube was set at 3.0 mL/min. Formic acid (0.01%) in water (A) and 100% acetonitrile (B) were used as mobile phases. The flow rate of the mobile phase was 0.7 mL/min, and the column temperature was set at 35 °C. The injection volume was 10 μL. The gradient elution method was as follows: initial, 80% B; 0–6 min, 75% B; 6–18 min, 70% B; 18–22 min, 80% B; 22–27 min, 80% B.

The calibration equation, limit of detection (LOD), and the limit of quantitation (LOQ) were as follows: xylose ($\log y = 1.010 \times \log x + 8.706$, LOD = 0.015 mmol/L, LOQ = 0.060 mmol/L); glycine ($\log y$

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= 1.293 × log x + 7.174, LOD = 0.018 mmol/L, LOQ = 0.065 mmol/L); and ARP (log y = 1.327 × log x + 6.632, LOD = 0.025 mmol/L, LOQ = 0.070 mmol/L). The x and y presented the concentration (mmol/L) and peak area of the corresponding compounds, respectively.

Analysis of 1-Deoxyosone, 3-Deoxyosone, Glyoxal, and Methylglyoxal by HPLC. The 1-deoxyosone (PubChem CID: 443434), 3-deoxyosone (PubChem CID: 277989), glyoxal (PubChem CID: 7860), and methylglyoxal (PubChem CID: 880) derived from ARP were analyzed through HPLC−DAD. The detection methods were similar as described by Yu et al.[13]

Analysis of the Ellagic Acid−ARP Adduct and Ellagic Acid−Dicarbonyl Adducts through UPLC/MS/MS. The ellagic acid−ARP, ellagic acid−glyoxal, and ellagic acid−methylglyoxal models were established to undergo the thermal reaction followed by the analysis of their respectively derived adducts. ARP (4.3 mmol/L) and ellagic acid (5 mmol/L) were dissolved in 10 mL of ultrapure water at their optimal concentrations in the system determined via the Maillard reaction performed under a stepwise increase of temperature, and then the pH was adjusted to 7.0 ± 0.1 with NaOH (0.1 mol/L). The mixtures were heated in a pressure-resistant hermetic glass tube at 140 °C for 10 min. Then the mixtures were immediately cooled in ice water. Similar conditions were applied for the preparation of ellagic acid−glyoxal and ellagic acid−methylglyoxal model reaction products. The mixtures were diluted appropriately for subsequent analysis.

The ellagic acid−ARP adduct and ellagic acid−dicarbonyl adducts formed during heat treatment of the models were measured through LC-TOF-MS (Synapt MALDI Q-TOF MS, Waters) using a BEH C18 column (1.7 μm, 2.1 mm × 50 mm, Waters). All of the adduct compounds were identified using the full-scan mode (m/z 50−1500) and selective reaction monitoring (SRM) analysis with UV detection at 280 nm. The capillary voltage, cone voltage, and extractor voltage of the ESI^- ion source were 3.5 kV, 15 eV, and 5 V, respectively. The source block temperature was 100 °C, the desolvation temperature was 400 °C, the cone gas flow was adjusted to 50 L/h, and the desolvation gas flow was subsequently adjusted to 700 L/h. Acetonitrile (100%) was used as mobile phase A and an aqueous solution of 0.1% formic acid was used as mobile phase B. The flow rate of the mobile phase was 0.3 mL/min. The gradient elution method of the sample was as follows: initial, 95% B; 80% B, 5 min; 65% B, 5−7 min; 20% B, 7−8 min; and 95% B, 8−12 min. The injection volume was 5 μL, and the column temperature was 45.0 °C. The MS/MS data were analyzed using MassLynx software (version 4.1, Milford, MA). Further identification of the ellagic acid−ARP adduct was accomplished by multiple reaction monitor (MRM) analysis using a Waters ACQUITY UPLC-TQD. The UPLC analysis conditions were similar to that of LC-TOF-MS described above.

Statistical Analysis. All of the measurements were carried out in triplicate for each sample. Data were assessed by the analysis of variance (ANOVA) using SPSS 19.0 (IBM, Armonk, NY). Significant differences were determined by Duncan's multiple comparison test, and $p < 0.05$ represented the significant differences.

RESULTS AND DISCUSSION

Inhibition Effect of Ellagic Acid on Xylose−Glycine Maillard Browning. Xylose and glycine were selected for the model Maillard reaction since they are with simpler structures of amino acid and sugar, respectively. The changes in the browning intensity of xylose−glycine aqueous solution during the Maillard reaction with and without the ellagic acid addition were investigated. It was assumed that ellagic acid would probably get involved in the Maillard reaction through interaction with some intermediates. Thus, the Maillard reaction performed under a stepwise increase of temperature was applied for improving the efficiency of ellagic acid participation in the reaction. In the first step of the heat treatment, a xylose−glycine mixture was reacted at a relatively lower temperature of 90 °C for accumulation of the intermediates which may interact with ellagic acid. Then, the reaction solution was heated at a higher temperature for 60 min after ellagic acid was added into the solution to accelerate the Maillard browning, which could be regarded as the second step of the heat treatment.

The results of browning intensity show that without ellagic acid addition, the final products of the Maillard reaction performed under the stepwise increase of temperature increased as the reaction time prolonged (Figure 2a). The addition of ellagic acid to the reaction solution positively or negatively affected the Maillard browning intensity depending on both its point of time of addition during the reaction and the dosage (Figure 2a). When 1 mmol/L ellagic acid was added into the system at the beginning, 30 and 60 min of the reaction, it facilitated the browning of the solution (Figure 2a, compared with no addition of ellagic acid). This result was probably caused by the oxidation and polymerization of ellagic acid itself during the heat treatment since a significant increase in the browning intensity of sole ellagic acid solution was also observed (Figure S2).[31] However, when ellagic acid was added after 60 min, the effect of ellagic acid on the Maillard browning inhibition became obvious, and the minimal browning value was observed at 90 min (Figure 2a). Similar time course characteristics of the browning intensity were found for the final Maillard reaction products prepared with different ellagic acid dosages, and the A_{420} went down with an increase in the ellagic acid dosage (Figure 2a). These results indicated an evidently effective inhibition effect of ellagic acid addition on the Maillard browning of xylose−glycine. Mildner-Szkudlarz et al.[32] also found the significant effect of polyphenolic compounds on the inhibition of the Maillard reaction that reduced N^{ε}-(carboxymethyl)lysine and pyrazine formation. Ellagic acid did get involved in the xylose−glycine Maillard reaction and suppressed melanoidin formation, and increasing amounts of ellagic acid reinforced its role in the Maillard reaction. Nonetheless, the browning inhibition effect of ellagic acid weakened when its dosage was above 5 mmol/L (Figure 2a). This phenomenon probably resulted from the oxidation and polymerization of excess ellagic acid as well.[31] However, with the ellagic acid dosage of 0−9 mmol/L, the lightest color of the final reaction solution was found when ellagic acid was added at the 90th minute of reaction, and it was also lighter than that of the control. These results revealed the fact that ellagic acid showed the optimal browning inhibition effect on xylose−glycine Maillard reaction system when it got involved at the 90th minute. Hence, it was speculated that there were some intermediates rather than the reactants which interacted with ellagic acid leading to browning inhibition. Subsequently, the reaction models of ellagic acid prepared by mixing it with different reactants and main intermediates were investigated for the determination of the target compound trapped by ellagic acid during the browning inhibition.

Determination of the Target Intermediate Trapped by Ellagic Acid during the Maillard Reaction. Xylose and glycine were mixed with ellagic acid at a concentration equal to that at the 90th minute of the first mild reaction step. The mixtures were heated at 140 °C and the concentration of xylose and glycine in the final solution is shown in Figure 2b,c. It could be found from Figure 2b,c that ellagic acid did not react with xylose to cause a decrease in the xylose concentration in the xylose−ellagic acid model during heat treatment at 140 °C, and a similar result was observed for the

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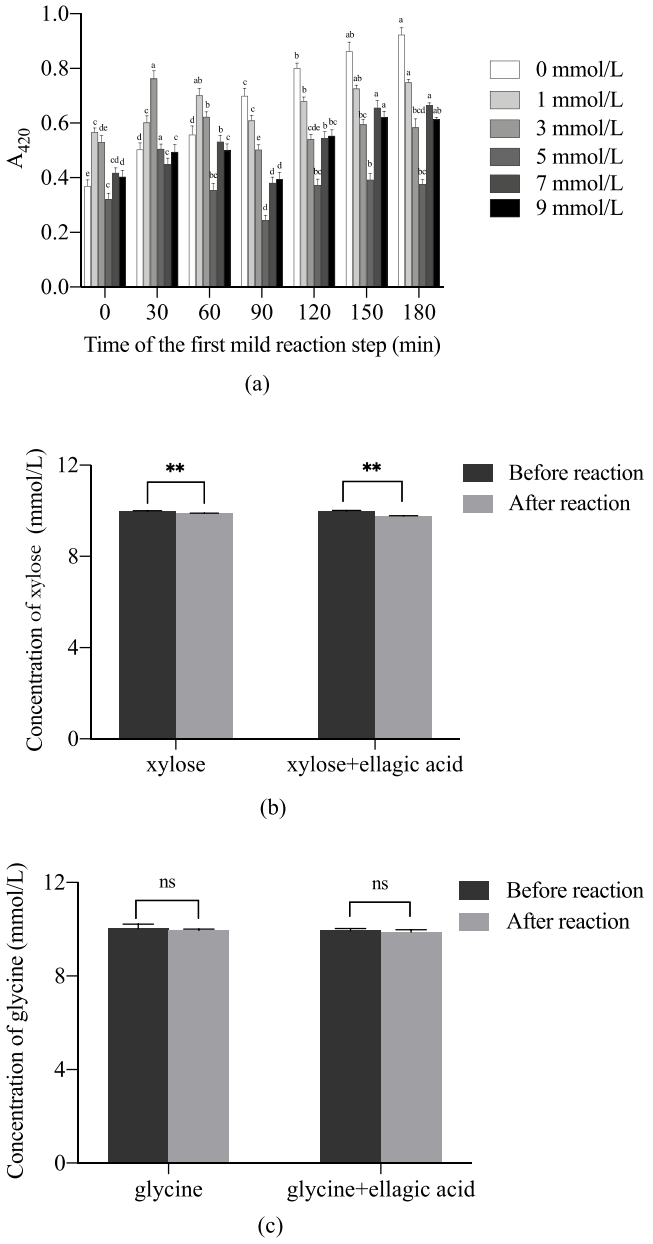

Figure 2. Browning intensity (A_{420}) of the final products of the Maillard reaction performed under a stepwise increase of temperature with ellagic acid addition at different points of time of the reaction at different dosages (relative molar ratio of xylose−glycine 2:1, initial pH 7.0; first mild reaction step: 90 °C, 0−180 min; elevated temperature reaction step: 140 °C, 60 min) (a). Effect of ellagic acid on the concentration of xylose (b) and glycine (c) in the model system during thermal treatment (the molar concentration of ellagic acid was 10 mmol/L, molar concentration of xylose or glycine was 10 mmol/L; initial pH was 7.0; the heat treatment was at 140 °C for 10 min). Two asterisks indicate significance ($0.01 < p < 0.05$), "ns" means no significant difference at the level $p > 0.10$.

glycine−ellagic acid model. Moreover, when ellagic acid was mixed with xylose and glycine, followed by heat treatment, the browning of the final reaction products was not optimally inhibited (Figure 2a, reaction time 0 min). These results showed that ellagic acid could not react with xylose or glycine directly for hindering the melanoidin formation. It was more likely that the Maillard reaction intermediates derived from xylose−glycine were trapped by ellagic acid and led to the browning inhibition.

From the time course for the concentrations of ARP, 3-deoxyosone, 1-deoxyosone, glyoxal, and methylglyoxal formed during the mild reaction of xylose−glycine without ellagic acid addition, it could be seen that these Maillard reaction intermediates were increased by heat treatment (Figure 3).

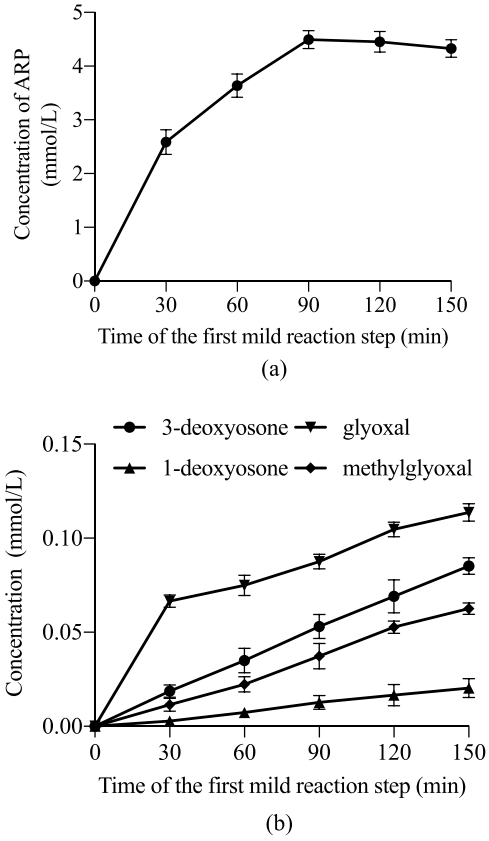

Figure 3. Time course for ARP (a) and α-dicarbonyl compound (b) in the first mild reaction step (the molar ratio of xylose to glycine was 2:1; initial pH was 7.0; the reaction was performed at 90 °C for 0−150 min).

The rate of increase in the ARP concentration was much higher than that of the dicarbonyl compounds since the ARP is the most important precursor of dicarbonyls (Figure 3). The concentration of 3-deoxyosone remained higher than that of 1-deoxyosone during the reaction because 1-deoxyosone with a structure of highly reactive reductone was not as stable as 3-deoxyosone (Figure 3b).[33] Glyoxal was mainly generated via the oxidation of glycolaldehyde that was the product of deoxyosone retroaldolization.[34] Methylglyoxal also formed through the retroaldolization of deoxyosones. However, the concentration of methylglyoxal was much lower than that of glyoxal. This is probably attributed to relatively higher reactivity of methylglyoxal that could give rise to carbanion formation as a prerequisite for aldolization.[7] Glyoxal was observed to be the most abundant among these dicarbonyls. Whereas, the content of ARP was higher compared to other intermediates (Figure 3). Additionally, the concentration of 3-deoxyosone, 1-deoxyosone, glyoxal, and methylglyoxal increased continually during the reaction for 150 min, while that of the ARP increased up to its peak concentration at the 90th min (Figure 3). The critical formation time of the ARP

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was identical to the optimal point of time of ellagic acid addition during the Maillard reaction performed under a stepwise increase of temperature. Ellagic acid showed the most effective inhibition of Maillard browning when it was added into the system at the point of time at which the ARP was developed the most. Therefore, it was inferred that ellagic acid trapped the ARP and altered the original reaction pathway of xylose−glycine, which suppressed the browning formation.

Subsequently, the ARP derived from xylose−glycine was collected and purified. Then, the ARP aqueous solution was heated at 140 °C with and without ellagic acid addition. Because the first step of ARP decomposition is mainly enolization followed by an immediate retro-Michael reaction with the loss of the original amino acid, the recovered glycine from the ARP was analyzed via HPLC. As shown in Figure 4a,

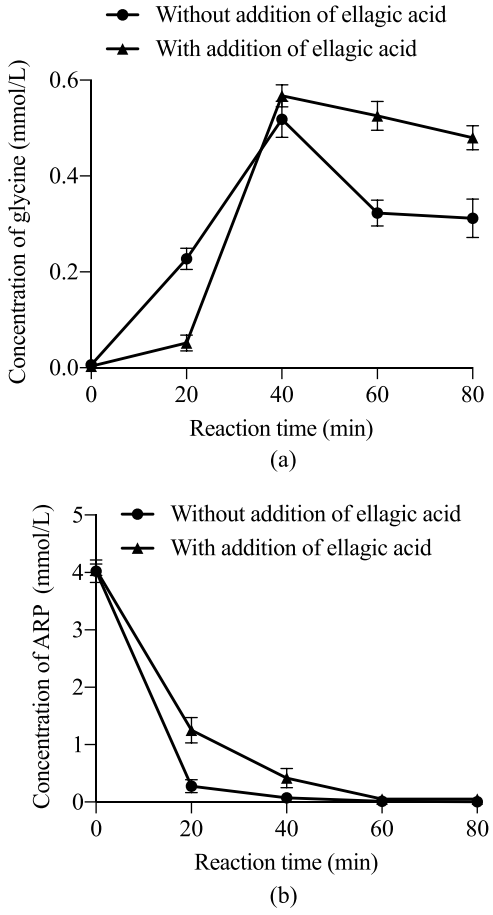

Figure 4. Effect of ellagic acid addition on the change in the concentration of recovered glycine (a) and ARP (b) during the thermal treatment of the ARP model (the concentration of ellagic acid was 5 mmol/L; the concentration of ARP was 4.3 mmol/L; initial pH was 7.0; the heat treatment was at 140 °C for 0−80 min).

the concentration of the recovered glycine increased up to the maximum at the 40th min before a slow decrease during the thermal treatment. This result indicated predominant glycine formation from ARP in the first 40 min and the predominant Strecker degradation after 40 min. However, the concentration of the recovered glycine was much higher after 40 min of reaction of ARP with ellagic acid (Figure 4a), confirming the fact that the interaction between the ARP and ellagic acid cause interference of the retro-Michael reaction of ARP giving rise to glycine. It should be noted that the concentration of the recovered glycine increased by 1000.13% with ellagic acid involving Maillard reaction when the heat treatment time was prolonged, and overtook that without ellagic acid involvement before the 40th min (Figure 4a). This result revealed that the effect of ellagic acid on the inhibition of ARP conversion to glycine was reversible and ARP decomposition was delayed, which was consistent with the results of the research on EGCG−ARP interaction reported by Yu et al.[13,14] This conclusion was clearly verified in the thermal reaction models of ARP with and without ellagic acid addition, as shown in Figure 4b, where an evident inhibition of ARP consumption by ellagic acid could be observed. During the latter heat treatment, the concentration of the recovered glycine from the Maillard reaction involving ellagic acid decreased only slightly, and remained higher than that of the concentration of recovered glycine without ellagic acid involvement (Figure 4b), indicating limited consumption of the recovered glycine through Strecker degradation or other reactions. Hence, during the Maillard reaction, the ellagic acid reacted with ARP inhibiting its decomposition at first and then inhibited the recovered glycine from involving in the subsequent reactions. The interaction between ellagic acid and ARP was subsequently further researched.

Analysis of the Interaction between Ellagic Acid and ARP. Monforte et al.[35] and Zhang et al.[36] had reported that, as a result of the nucleophilic addition reaction, polyphenolic compounds such as catechin and myricetin tended to trap dicarbonyls to form adducts. Their reactivity highly depends on the polyphenol structure. Due to the conjugate effect of the benzene ring, a polyphenol molecule readily converts into a stronger nucleophilic intermediate on deprotonation of the OH groups with more electrons rearranging to the ortho or para position of C_{-OH}, which consequently forms a carbanion.[16] Thus, the presence of ortho or para hydrogen of C_{-OH} on the benzene ring makes the polyphenolic compound more reactive as a nucleophile.[37] This structural characteristic can also be found for an ellagic acid molecule, which indicates a probable formation of ellagic acid−deoxyosone and ellagic acid−ARP via a nucleophilic addition reaction during the heat treatment of the ellagic acid−ARP model.[38]

Following the optimal conditions of the Maillard reaction performed under a stepwise increase of temperature for browning inhibition, ellagic acid was added at the 90th min of the first mild reaction step before subsequent heat treatment at a higher temperature. The final products were analyzed using LC-ESI-MS/MS. According to the MS/MS analysis results (Figure 5a), the adduct compounds of ellagic acid−ARP (m/z 527) were observed and presented as an opened lactone ring (Figure 5b), confirming the reaction of ellagic acid with ARP during the aqueous Maillard reaction and one of the depside bonds on ellagic acid was hydrolyzed simultaneously. This data is available at the NIH Metabolomics Workbench (http://www.metabolomicsworkbench.org) where it has been assigned Data ID 2800. The fragmentation pattern of the ellagic acid−ARP adduct is shown in Figure 5b. It was speculated that the proton tended to interact with the benzene ring to form a $\pi\cdots$H complex during ionization under the negative ESI mode due to the reactive circuit conjugate π bond of the ellagic acid moiety. The molecular anion of the complex with m/z 527 showed a tendency to undergo a loss of one molecule of water and generate an ion with a pyrrole ring which could successively lose molecules of water and acetic

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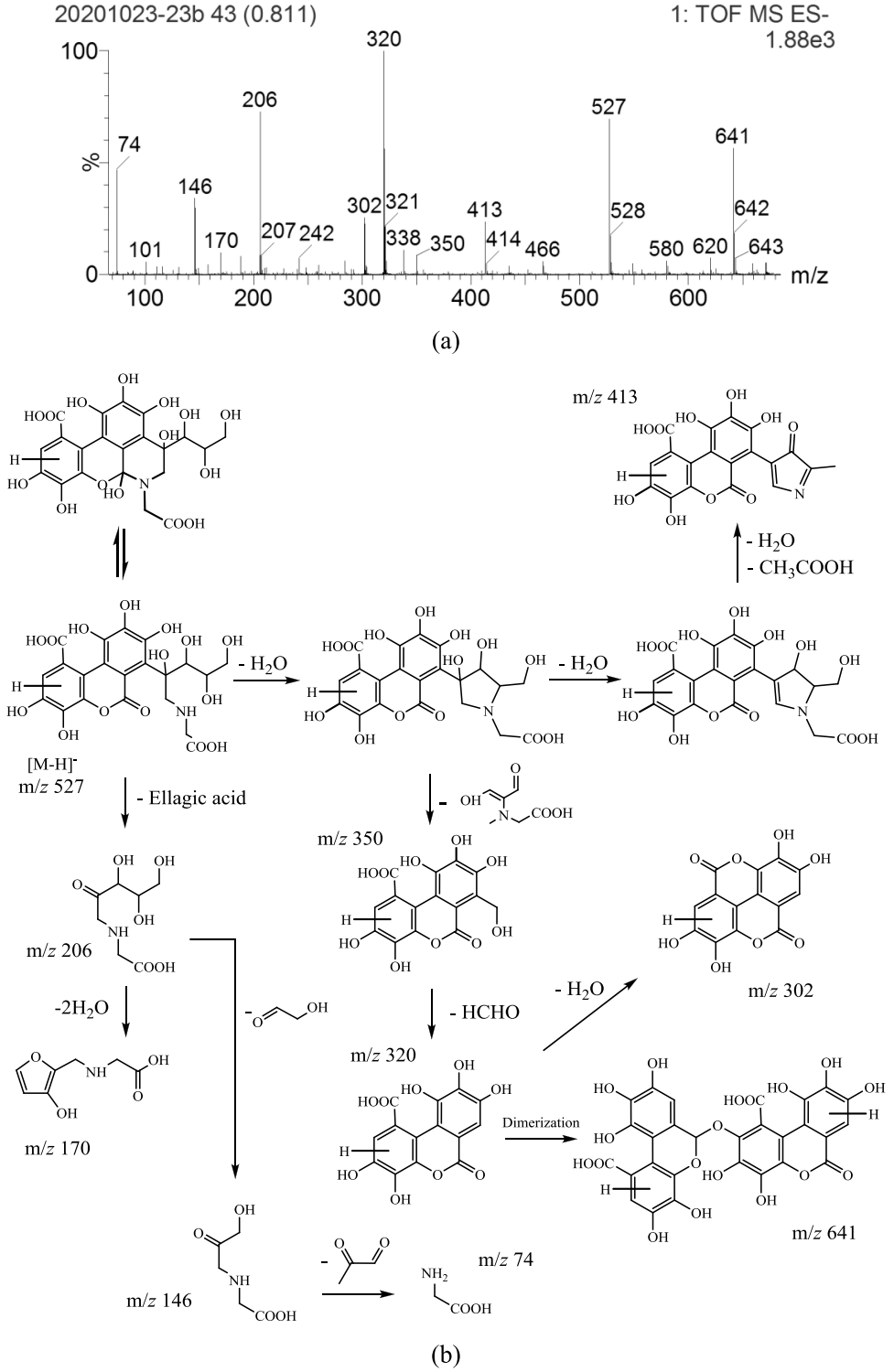

Figure 5. MS/MS spectrum of ellagic acid−ARP (a) and the fragmentation ions (b).

acid to yield the ion at m/z 413, or undergo cleavage of the pyrrole ring through a conjugate elimination reaction to yield the ion at m/z 350. The loss of a formaldehyde molecule through the disproportionation reaction on the ion at m/z 350 was observed to yield the ion at m/z 320 followed by either loss of a molecule of water with the recovery of the ellagic acid molecule or dimerization for generating the ion at m/z 641. The ARP ion (m/z 206) separated from the parent ion was also observed, which tended to undergo a successive loss of the molecules of glycolaldehyde and methylglyoxal yielding the ions at m/z 146 and m/z 74, respectively. A successive loss of 2 molecules of water from the ARP ion corresponded to the fragments with m/z 170. The chemical structure of ellagic acid−ARP adduct was further identified through MRM analysis, and the obtained MS spectra were similar to those recorded by ESI-MS/MS (Figure S3). The fragments at m/z 527 and m/z 413 were determined as characteristic ions for the quantitation of ellagic acid−ARP. The fragments at m/z 206

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and m/z 302 were determined as characteristic ions for the quantitation of ARP and ellagic acid, respectively.

Yu et al.[13,30] recently reported the occurrence of the adducts EGCG with Maillard reaction intermediates and proposed the formation pathway of both the EGCG−ARP adduct and EGCG−deoxyosone adducts. However, ellagic acid−deoxyosone adducts were not observed in this research. This difference probably came from the different nucleophilic addition reactivity of the polyphenols. The A benzene ring of EGCG with the electron-donating groups in a meta configuration was more reactive than the ortho configuration of the benzene ring of ellagic acid. On the other hand, the hydrolysis of ellagic acid during the aqueous thermal reaction gave rise to the carboxyl group formed on the benzene ring, which weakened the electron-donating effect of the ortho carbon of C_{-OH} on the benzene, resulting in a decrease of available reactive sites on the ellagic acid molecules. Besides, a relatively stronger steric-hindrance effect of ellagic acid might also account for its weaker trap of deoxyosones than that of EGCG.

Although ellagic acid could trap ARP through a nucleophilic addition with the carbonyl group during the Maillard reaction, it was verified that it cannot react with xylose (Figure 2c). These results might be attributed to the formation of a relatively stable pyridine ring with both carbonyl and amino groups on the ARP molecule participating in the reaction (Figure 5b), as thus, the polyhydroxyl structure of the xylose moiety could be available for interactions with the hydroxyl groups via hydrogen bonding.[39] On the other hand, the amino acid moiety of the ARP could also show a high binding affinity with ellagic acid via hydrogen-bonds at diverse sites, which greatly improved the reactivity of ellagic acid trapping the ARP during the Maillard reaction.[40,41]

Mechanism of Ellagic Acid−ARP Adduct Formation Inhibiting Maillard Browning. According to the discussion above, it is obvious that the decomposition of ARP into glycine and deoxyosones was interfered and delayed due to the formation of the ellagic acid−ARP adduct. Further research on the thermal reaction models of ARP with and without ellagic acid addition reflected more about the effect of ellagic acid−ARP interaction on the subsequent Maillard reaction starting from ARP decomposition. As shown in Figure 6a, during the ARP decomposition, the concentration of dicarbonyl compounds such as 3-deoxyosone, 1-deoxyosone, glyoxal, and methylglyoxal increased in the first 20 min followed by a decrease in the next 20 min because of the abundant yield of the recovered glycine that readily consumed the dicarbonyls via the Strecker reaction (Figure 4a). During the subsequent 20 min, the significant decline in the glycine concentration led to more accumulation of dicarbonyls (Figures 4a and 6a). Nevertheless, continued heat treatment depleted the ARP, thus the concentration of both glycine and dicarbonyls went back down (Figures 4a, b and 6a). However, with the involvement of ellagic acid, the concentrations of 3-deoxyosone, 1-deoxyosone, glyoxal, and methylglyoxal were much less than those without ellagic acid addition, especially after 40 min of heat treatment (Figure 6a,b). These results were important on account of the inhibition of ARP decomposition caused by the ellagic acid−ARP reaction. On the other hand, as a nucleophilic reagent, ellagic acid could also scavenge glyoxal and methylglyoxal.[42,43] Using LC-ESI-MS/MS, the ellagic acid−methylglyoxal adduct was also found in the reaction system despite its much lower content than ellagic acid−ARP

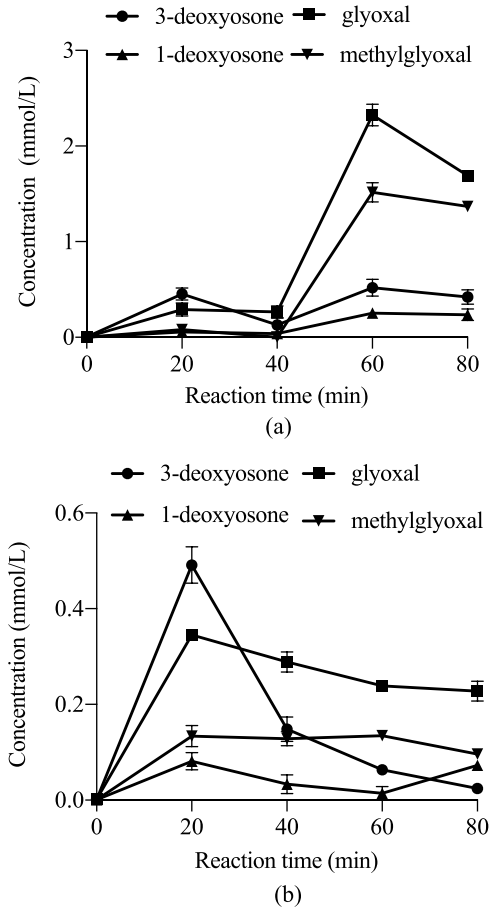

Figure 6. Time course for 1-deoxyosone, 3-deoxyosone, glyoxal, and methylglyoxal formation in the ARP model during the thermal treatment without (a) and with (b) ellagic acid addition (the concentration of ellagic acid was 5 mmol/L; the concentration of ARP was 4.3 mmol/L; initial pH was 7.0; the heat treatment was at 140 °C for 0−80 min).

and the MS/MS spectrum is shown in the Supporting Information (Figure S4). The molecular ion of the ellagic acid−methylglyoxal adduct was [ellagic acid+ methylglyoxal−H]$^-$ labeled as m/z 373. The fragment with m/z 249 was probably obtained from the molecular ion via loss of a pyrone molecule (Figure S4). Although the adduct between ellagic acid and glyoxal was not observed in the ellagic acid−glyoxal model system, some redox reactions between them were still believed to occur and affect the Maillard browning formation. According to Zheng et al.,[44] the antioxidant activity of the related groups on an ellagic acid molecule was influenced by its intramolecular hydrogen-bonds, and the stronger the hydrogen-bond was, the weaker the antioxidant activity of the proton donating group was. Thus, if the intramolecular hydrogen-bonds contributed a lot to the stabilization of the ellagic acid−ARP adduct at an earlier stage of the thermal treatment (Figure 4a), the recovered ellagic acid from the adduct decomposition would achieve higher antioxidant activity to scavenge glyoxal and methylglyoxal, leading to reduction of these short-chain dicarbonyl compounds. Zhu et al.[45] reported that other polyphenolic compounds such as kaempferol, resveratrol, apigenin, and fisetin also tended to undergo trapping reactions with methylglyoxal, and the trapping efficiency of MGO was found to be highly dependent on the molecular structure of polyphenols. As important browning precursors, the ARP was

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stabilized and the development of dicarbonyls was suppressed by ellagic acid, which contributed to a significant browning inhibition during the xylose−glycine Maillard reaction. Additionally, as another polyphenolic compound, catechin was observed to react with amino acids, sugars, or both at the para position of its B ring to form adducts while simultaneously inhibiting the formation of browning precursors. This reported result indicated the complexity of the involvement of polyphenols in the Maillard reaction.[46]

In conclusion, ellagic acid was found effective for the inhibition of melanoidin formation in the xylose−glycine Maillard reaction. Increasing amounts of ellagic acid reinforced this effect but an excess amount of ellagic acid resulted in facilitating browning through the self-oxidation and polymerization of ellagic acid. The effect of browning inhibition caused by ellagic acid was also dependent on the point of time it got involved in the Maillard reaction. The lightest color of the Maillard reaction products was observed when ellagic acid was added at the point of time when the ARP developed the most. The adduct between ARP and the hydrolysis product of ellagic acid was readily formed and it stabilized the ARP from decomposition to yield more browning precursors. Moreover, the antioxidant potential of ellagic acid through scavenging some short-chain dicarbonyls also contributed to the inhibition of Maillard browning. The involvement of polyphenols in the Maillard reaction was quite complicated. The matrix effect on the modulation of ellagic acid oxidation and browning inhibition is worth further research in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jafc.1c03481.

MS/MS spectra of the purified ARP derived from xylose−glycine (a) and the fragmentation of the molecular ion (b) (Figure S1); Browning intensity (A_{420}) of ellagic acid heated at 140 °C for 0−60 min (Figure S2); MS spectra of ellagic acid−ARP adduct recorded by multiple reaction monitor (MRM) (Figure S3); and MS/MS spectra of ellagic acid−MGO adduct (a) and the main fragmentation of the molecular ion (b) (Figure S4) (PDF)

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