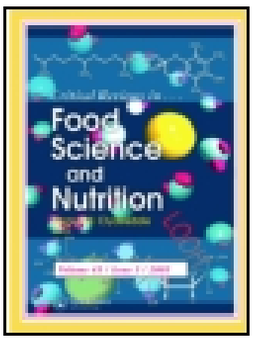

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REVIEW

Review of the formation and influencing factors of food-derived glycated lipids

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ABSTRACT

Glycated lipids are formed by a Maillard reaction between the aldehyde group of a reducing sugar with the free amino group of an amino-lipid. The formation and accumulation of glycated lipids are closely related to the prognosis of diabetes, vascular disease, and cancer. However, it is not clear whether food-derived glycated lipids pose a direct threat to the human body. In this review, potentially harmful effect, distribution, formation environment and mechanism, and determination and inhibitory methods of glycated lipids are presented. Future research directions for the study of food-derived glycated lipids include: (1) understanding their digestion, absorption, and metabolism in the human body; (2) expanding the available database for associated risk assessment; (3) relating their formation mechanism to food production processes; (4) revealing the formation mechanism of food-derived glycated lipids; (5) developing rapid, reliable, and inexpensive determination methods for the compounds in different foods; and (6) seeking effective inhibitors. This review will contribute to the final control of food-derived glycated lipids.

KEYWORDS

Diabetes; food-derived; glycated lipids; inhibitory methods; Maillard reaction

Introduction

The Maillard reaction is the chemical reaction between reducing sugars and amino compounds. Studies have shown that some Maillard reaction products have a nonnegligible hazardous impact on human health, including acrylamide produced in starch-rich processed foods, and advanced glycation end products occurred in protein-rich cooked foods. They are known to be mutagens and carcinogens (Teng et al. 2018). At present, most researchers focus on protein glycation (Batool et al. 2020; Hu et al. 2020; Li et al. 2020; Liang et al. 2020; Xu et al. 2020; Xu et al. 2019; Zhao et al. 2019, 2020; Zhu et al. 2021). However, scientists begin to focus on lipid glycation. Glycated lipids are a series of products formed by the Maillard reaction of the aldehyde group of a reducing sugar with the free amino group of a phospholipids such as phosphatidylethanolamine (PE) and phosphatidylserine (Colombo et al. 2019). Glycated lipids can be identified as Amadori-phospholipids and aldehyde-phospholipids based on their chemical structure. To date, numerous studies in clinical (Breitling-Utzmann et al. 2001; Colombo et al. 2019; Nakagawa, Oak, Higuchi, et al. 2005; Ravandi et al. 1996; Requena et al. 1997), animal (Bacot et al. 2007), and cellular trials (Eitsuka et al. 2012; Guo et al. 2012; Nakagawa, Oak and Miyazawa 2005; Oak, Nakagawa, and Miyazawa 2000; Simoes et al. 2013) have shown that the formation and accumulation of glycated lipids are related to the prognosis of many diseases such as diabetes, vascular disease and cancer.

In this review, potentially harmful effect, distribution, formation environment and mechanism, and determination and inhibitory methods of glycated lipids are presented. This review will contribute to the final control of food-derived glycated lipids.

Potentially harmful effect

Clinical, animal and cellular trials have shown that glycated lipids are harmful to human health (Bacot et al. 2007; Breitling-Utzmann et al. 2001; Colombo et al. 2019; Colombo et al. 2019; Eitsuka et al. 2012; Guo et al. 2012; Nakagawa, Oak, Higuchi, et al. 2005; Nakagawa, Oak, and Miyazawa 2005; Oak, Nakagawa, and Miyazawa 2000; Ravandi et al. 1996; Requena et al. 1997; Simoes et al. 2013).

In clinical trials, Ravandi et al. found that glycated lipids existed in the plasma of patients with diabetes. It made up 100–160 g kg^{-1} of the total PE in the plasma of patients with diabetes. Its content in healthy people was 10–20 g kg^{-1} (Ravandi et al. 1996). Breitling-Utzmann et al. found Amadori-PE in the blood of patients with diabetes and healthy people. The content of Amadori-PE in the blood of patients with diabetes (0.47–3.75 g kg^{-1}) was significantly higher than that in healthy people (0.18–0.55 g kg^{-1}) (Breitling-Utzmann et al. 2001). Nakagawa et al. found that the content of Amadori-PE in the plasma of patients with

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diabetes (1.5–2.9 g kg^{-1}) was significantly higher than that in healthy people (0.8 g kg^{-1}) (Nakagawa, Oak, Higuchi, et al. 2005). All these studies indicate that glycated lipids are related to the prognosis of diabetes, and they are identified as signaling molecules regulating cell death (Colombo et al. 2019). Requena et al. found carboxymethyl PE (CM-PE), a kind of aldehyde-phospholipid, in the blood of patients with diabetes. The content of CM-PE and PE were 0.146 and 0.135 g kg^{-1}, respectively in the red blood cell membranes of diabetic patients and control subjects (Requena et al. 1997).

In animal trials, Bacot et al. found 4-hydroxy-2-nonenal-PE, a kind of aldehyde-phospholipid, in the retinas of streptozotocin-induced diabetes rats. The content of 4-hydroxy-2-nonenal-PE in diabetes rat retinas was 6.3 times as much as that in controls. Their results suggested that 4-hydroxy-2-nonenal-PE could be used as specific markers of membrane disorders occurring in pathophysiological states (Bacot et al. 2007).

In cellular trials, Oak et al. reported that the accumulation of glycated lipids in vivo could cause membrane lipid oxidation and membrane protein glycation, which led to the destruction of cellular integrity and functionality (Oak, Nakagawa, and Miyazawa 2000). Eitsuka et al. reported that Amadori-PE could up-regulates telomerase activity in a time- and dose-dependent manner by up-regulating hTERT expression through induction of c-myc, which provided experimental evidence for a role of Amadori-PE in linking diabetes and cancer (Eitsuka et al. 2012). Nakagawa et al. found that Amadori-PE could significantly enhance proliferation, migration, and tube formation of cultured human umbilical vein endothelial cells, which resulted in secretion of matrix metalloproteinase 2, a pivotal enzyme in the initial step of angiogenesis. The results indicated that Amadori-PE could elicit vascular disease through angiogenic potency on endothelial cells, thereby playing an important role in the development and progression of diabetic microangiopathy (Nakagawa, Oak, and Miyazawa 2005). Simoes et al. used flow cytometry analysis to evaluate the effect of Amadori-PE on the expression of different cytokines in monocytes or myeloid dendritic cells. The results showed that Amadori-PE had the ability to stimulate monocytes and myeloid dendritic cells, and that Amadori-PE could be considered as a predictor of an inflammatory state (Simoes et al. 2013). Guo et al. evaluated the ability of CM-PE to induce endothelial dysfunction. The results indicated that CM-PE could induce inflammatory response, such as adhesion of monocytes, and could promote the development of atherosclerosis disease (Guo et al. 2012).

Glycated lipids can be identified into endogenous glycated lipids and food-derived glycated lipids based on their formation environment. Endogenous glycated lipids are formed in the human body, while food-derived glycated lipids are formed in food production process. The harmful effect of endogenous glycated lipids on human body is certain (Bacot et al. 2007; Eitsuka et al. 2012; Guo et al. 2012; Nakagawa, Oak, Higuchi, et al. 2005; Oak, Nakagawa, and Miyazawa 2000; Simoes et al. 2013), but there are few reports on the harmful effect of food-derived glycated lipids on human. The key point is related to the digestion and absorption of food-derived glycated lipids.

To the best of our knowledge, there is no quantitative pharmacokinetic data for the digestion, absorption, metabolism and excretion of food-derived glycated lipids. This might be explained by the fact that harmful effect of glycated lipids has not been thoroughly revealed in the biological and medical field at that time. With more in-depth researches on the potentially harmful effects of endogenous glycated lipids, it is necessary to investigate the digestion and absorption of food-derived glycated lipids.

Distribution in food

Although glycated lipids have been detected in the organs, blood and urine of patients with diabetes (Colombo et al. 2019), vascular disease patients and cancer patients (Eitsuka et al. 2018), only a few studies have focused on the existence of glycated lipids in commonly consumed foods.

Glycated lipids are widely distributed in food containing phospholipids. The normal dietary intake of phospholipids is 2–8 g/day (Cohn et al. 2010). Foods with a high phospholipids content include eggs, organ and lean meats, fish and cereal. The content of phospholipids in egg yolk, pig liver, chicken breast, soybean, squid, chicken breast, beef, and peanuts is 103.06, 29.01, 25.42, 23.08, 10.98, 7.82, 6.60, and 6.20 g kg^{-1}, respectively (Cohn et al. 2010). Phospholipids is widely used as food emulsifier to form stable emulsions. Although the allowed amount of phospholipids in foods is low (5 g kg^{-1}) (Cohn et al. 2010), their widespread in food may cause excessive food-derived glycated lipids. However, there is no direct data for the dietary intake of food-derived glycated lipids.

Utzmann and Lederer determined the content of glycated lipids in a PE and glucose model system with heating at 65 °C for 2 h and heating at 100 °C for 3 h. The results showed that higher temperatures and longer time heating promoted the formation of CM-PE. Analyses of spray-dried egg yolk powders showed that 110–155 g kg^{-1} of PE transformed Amadori-PE (Utzmann and Lederer 2000a). Oak et al. examined the presence of Amadori-PE in several food samples, which was 0.112, 0.004, and 0.012 g kg^{-1}, respectively in infant formula, chocolate and mayonnaise, respectively. In contrast, cream powder, yogurt, butter, margarine and tea contained less Amadori-PE, which was probably due to their low content of phospholipids, as well as low heating temperature (Oak, Nakagawa, and Miyazawa 2002). Hidalgo et al. studied the role of phospholipids in removing highly toxic oxygenated aldehydes (4-hydroxy-2-alkenals and 4,5-epoxy-2-alkenals) produced in foods. The results showed that PE could rapidly react with aldehydes, and produced aldehyde-phospholipids. However, Hidalgo et al. did not realize the potentially harmful effect of aldehyde-phospholipids (Hidalgo, Nogales, and Zamora 2008). Calvano et al. developed a matrix-assisted laser desorption/ionization-mass spectrometry method which could determine glycated PE in milk powders, pasteurized milk, ultra-high temperature milk

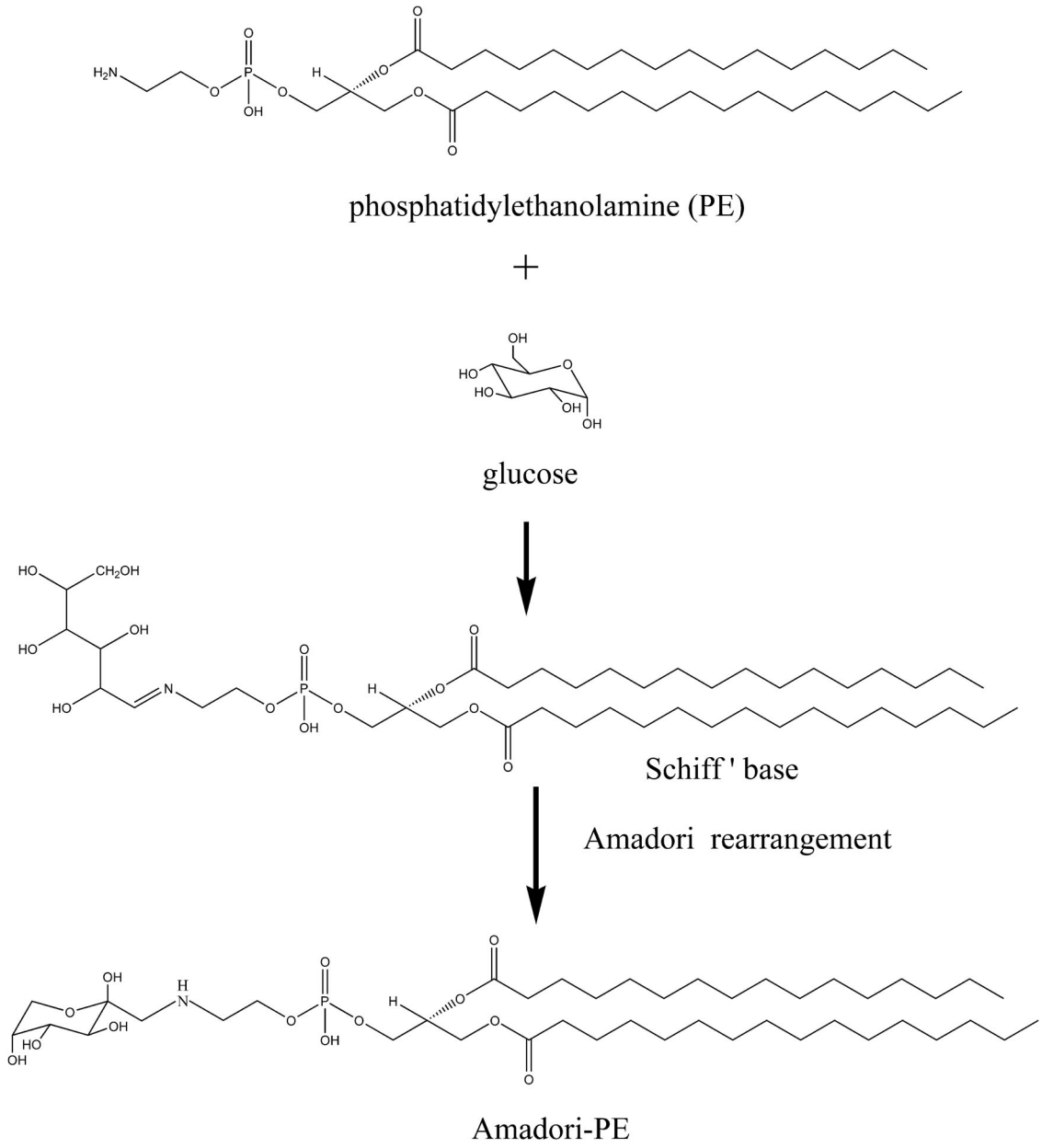

Figure 1. Formation pathway of Amadori-phospholipid.

and soy flour, but the data on glycated PE was not shown (Calvano, De Ceglie, and Zambonin 2014). Kodate et al. measured the Amadori-PE content of powdered milk in a range of 0.043 to 82.390 g kg^{-1} (Kodate et al. 2018).

Although all these studies did not show the evidence that food-derived glycated lipids directly contributed to the accumulation of glycated lipids in vivo, the limitation of the intake of heated processed foods rich in glycated lipids may reduce the risk of related diseases (Estevez 2011). For this purpose, it is necessary to expand the available glycated lipids database for risk assessment.

Formation environment

There are two main differences between the formation environments of endogenous glycated lipids and food-derived glycated lipids. First, endogenous glycated lipids are formed at a moderate temperature (37 °C) in body fluid and tissue (Zamora, Nogales, and Hidalgo 2005), while food-derived glycated lipids are formed at more severe temperatures (100–250 °C) during the thermal processing, such as boiling (Hernandez, Navarro, and Toldra 1999), frying (Tengilimoglu-Metin et al. 2017) and baking (Numanoglu et al. 2013). Second, the composition of body fluid and tissue is relatively simple and stable, mainly depending on the enzymatic action of metabolism. In contrast, the thermal processing may lead to many kinds of food-derived glycated lipids (Han et al. 2013). More research on the issues of glycated lipids formation relative to food processing is necessary in the future.

Formation mechanism

To date, understanding of the formation mechanism of glycated lipids mainly relies on research of endogenous

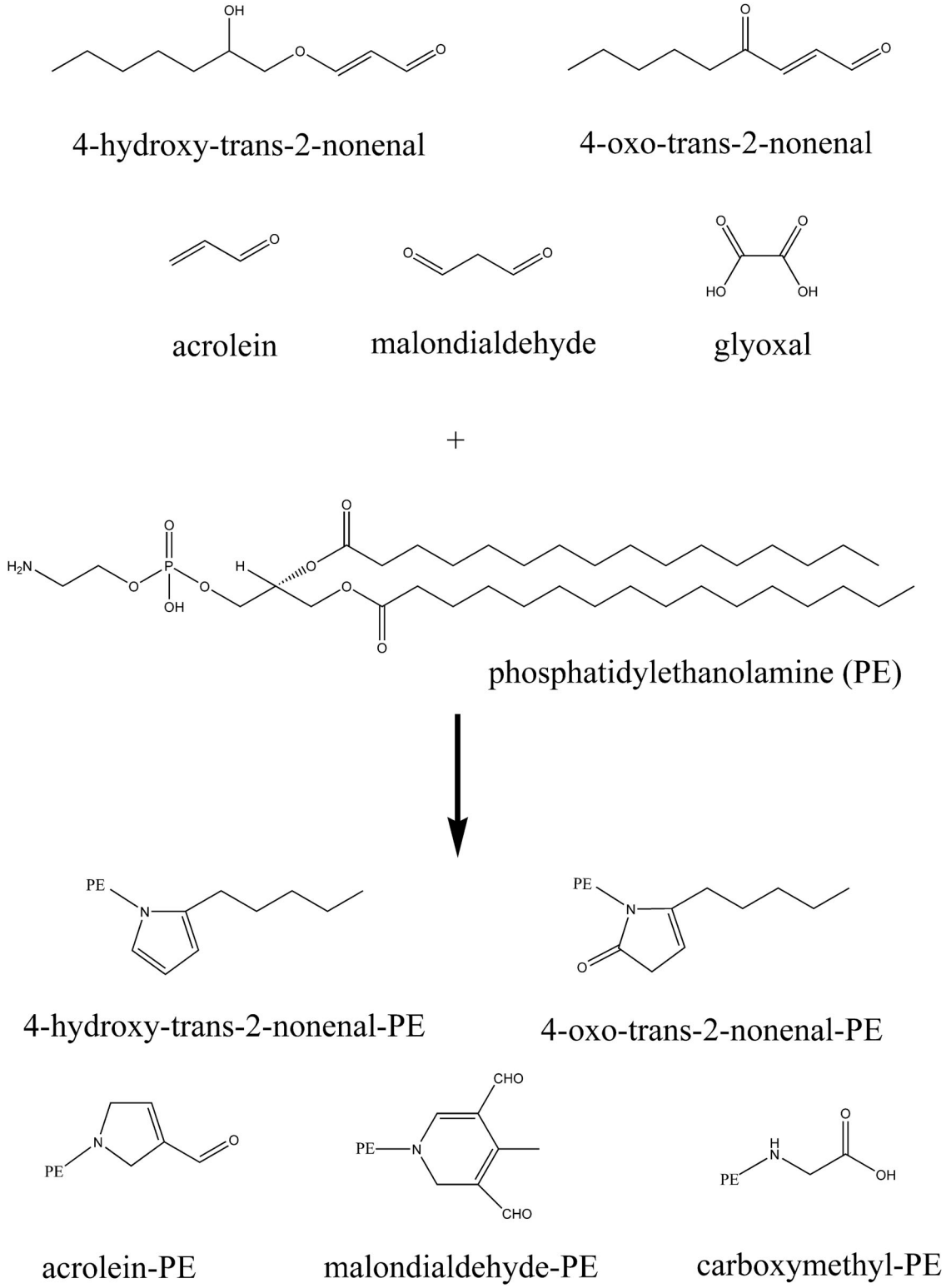

Figure 2. The reaction pathway for the formation of aldehyde-phospholipid.

glycated lipids (He, Chen, and Zhang 2019). The formation pathway of Amadori-phospholipids is shown in Figure 1. The free amino group of phospholipids, such as PE, reacts with the aldehyde group of a reducing sugar to produce a Schiff base. The reaction is reversible. The Schiff base then cyclizes into an unstable N-substituted glycosylamine (He and Zhang 2018).

Subsequently, the Schiff base goes through a further isomerization called an Amadori rearrangement to form a more stable Amadori-phospholipid such as Amadori-PE (Lederer, Dreisbusch, and Bundschuh 1997).

Aldehyde-phospholipid is formed through two pathways. The first pathway is through the further oxidation of Amadori-phospholipids. The second pathway is shown in

Table 1. Determination methods used for Amadori-PE and CM-PE in different samples.

Sample source	Object	Method	Detection limit	Precision	Accuracy	Analysis time	Reference
Endogenous glycated lipids							
Human plasma	Amadori-PE	LC-MS/MS	10 pmol/mL	—	—	10 min	Nakagawa, Oak, Higuchi, et al. (2005)
Human erythrocytes and blood plasma	CM-PE	LC-MS/MS	0.5 pmol/mL	—	—	8 min	Shoji et al. (2010)
Model system	CM-PE	LC-HRMS	—	—	—	16 min	Colombo et al. (2019)
Food-derived glycated lipids							
Egg yolk food	Amadori-PE CM-PE	LC-MS	97 pmol/mL 57 pmol/mL	— —	— —	24 min	Utzmann and Lederer (2000a)
Infant food, chocolate, mayonnaise and soy milk	Amadori-PE	HPLC-UV	500 pmol/mL	—	—	20 min	Oak, Nakagawa, and Miyazawa (2002)
Milk powders, pasteurized milk, ultra-high-temperature milk and soy flour	Amadori-PE	MALDI-MS	—	—	—	—	Calvano, De Ceglie, and Zambonin (2014)
Powdered milk and powdered buttermilk		LC-MS	5 pmol/mL	1.8%–8.0%	3.5%–4.3%	25 min	Kodate et al. (2018)

Note: LC-HRMS, liquid chromatography-high resolution tandem mass spectrometry; MALDI-MS, matrix-assisted laser desorption/ionization-mass spectrometry.

Figure 2. The aldehyde group reacts with the free amino group of a phospholipids such as PE. The aldehyde or ketone group comes from methylglyoxal, 4-hydroxy-2-nonenal (HNE), acrolein, glyoxal, 4-oxononenal (ONE), or malondialdehyde (MDA) formed by the oxidation of sugars or lipids (Pamplona et al. 1999).

There are only a few studies on the formation mechanism of food-derived glycated lipids. Our previous study indicated that Amadori-phospholipid was identified to generate carboxymethyl-phospholipid through oxidative cleavage of glycated polar head group under high temperature and extended incubation time. Additionally, during the thermal processing, retro-aldol reactions of glucose led to the formation of glyoxal. It reacted with amino group of phospholipids to form carboxymethyl-phospholipid (Lin et al. 2018). We also proved that lipids could promote the formation of glycated phospholipids by inducing hydroxyl radicals in Maillard reaction system (Han et al. 2019c).

Therefore, revealing the formation mechanism of food-derived glycated lipids will be a direction for future research.

Determination methods

To date, the distribution of glycated lipids in food has been gaining attention in the literature, which sets a demand for better determination methods. High performance liquid chromatography-mass spectrometry-ultraviolet spectroscopy (HPLC-UV) (Oak, Nakagawa, and Miyazawa 2002), high performance liquid chromatography-diode array detection (HPLC-DAD) (Lederer, Dreisbusch, and Bundschuh 1997; Lertsiri, Shiraishi, and Miyazawa 1998), gas chromatography-mass spectrometry (GC-MS) (Pamplona et al. 1995), HPLC-MS (Calvano, De Ceglie, and Zambonin 2014; Colombo et al. 2019; Kodate et al. 2018; Nakagawa, Oak, Higuchi, et al. 2005 Shoji et al. 2010; Utzmann and Lederer 2000a) and nuclear magnetic resonance (NMR) (Utzmann and Lederer 2000b) are the methods that have been developed for the determination of glycated lipids.

Among them, HPLC-UV and HPLC-DAD can only detect products that have UV absorption, which means that glycated lipids must react with derivatization reagent first. Nevertheless, the derivation procedure is significantly affected by temperature, pH conditions and the type of labeling reagents (van de Merbel et al. 2004).

The HPLC-MS/MS method is useful for structural analysis and quantification of glycated lipids in biological and food samples (He and Zhang 2018). Some of its advantages are as follows. The method is applicable for heat-sensitive glycated lipids and their intermediates in food heating processes. It has a detection limit of a nanogram per milliliter, which is lower than that of UV detectors. MS analysis relied on ion trap (Ehrlich et al. 2010), quadrupole-time of flight (Penndorf et al. 2008), and triple quadrupole (Beisswenger et al. 2014) mass analyzers, operated either in a full-MS (Ehrlich et al. 2009), or in a multiple reaction monitoring (MRM) modes. With MRM, it can simultaneously detect several parent ions and further reconfirm them by daughter ions, which allows the determination of glycated lipids from complex products even if the complex products are not isolated effectively by a chromatographic column (Kodate et al. 2018). MRM with stable isotope dilution or standard addition represents "a gold standard" for the quantification of glycated lipids (Soboleva et al. 2017). But the method is expensive and requires highly trained personnel.

Table 1 summarizes the determination methods for Amadori-PE and CM-PE in recent years, which are the representatives of Amadori-phospholipids and aldehyde-phospholipids, respectively. Table 1 suggests that most of the determination methods are LC-MS/MS. The samples are from limited foods such as infant food, chocolate, mayonnaise and soybean milk. Therefore, developing rapid,

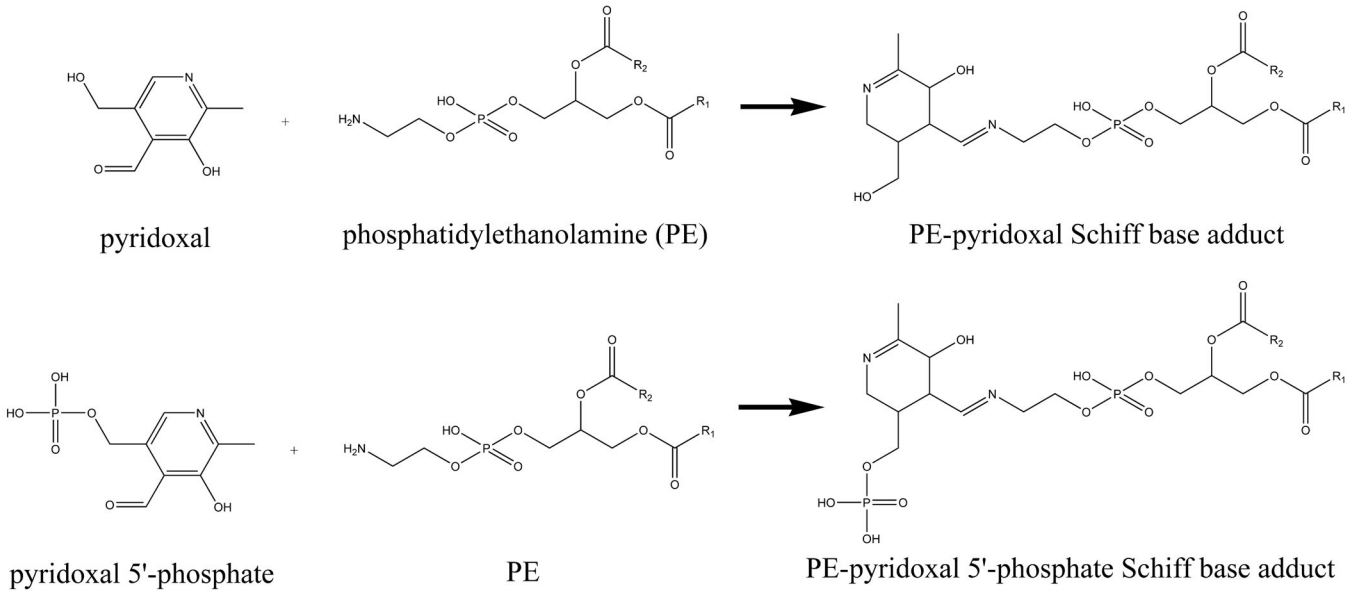

Figure 3. Scheme for the reaction of pyridoxal 5′-phosphate with phosphatidylethanolamine.

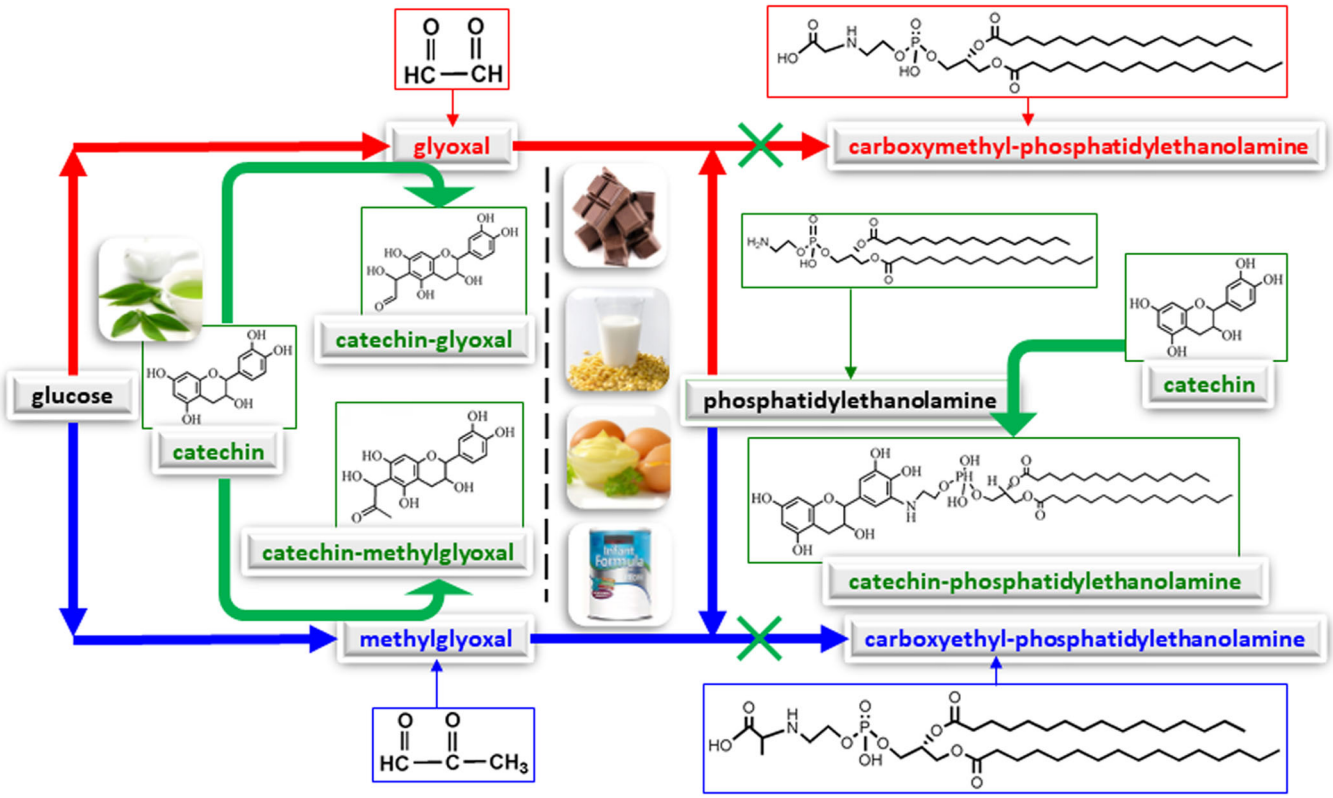

Figure 4. Inhibition mechanism of catechin on the formation of food-derived glycated lipids.

reliable, and inexpensive determination methods for glycated lipids in different food will be one of the future research directions.

Inhibition methods

Although there are few reports on the harmful effect of food-derived glycated lipids on human, it is necessary to study the methods of inhibiting the formation of these compounds. According to the formation mechanism, we suppose that there are at least two inhibitory mechanisms. One mechanism is to block the reaction between the aldehyde group of the glucose with the amino group of the phospholipid. The other mechanism is to trap intermediates such as aldehydes from glucose or lipid oxidation. Higuchi et al. set up a model system considering various conditions for the reaction between PE and glucose. The inhibitory effects of different inhibitors (carnosine, aminoguanidine, and pyridoxamine), antioxidants (rutin, quercetin,

tocopherol, and ascorbic acid), and other food compounds (pyridoxal 5′-phosphate, pyridoxal, lysine, and cysteine) on glycated lipids in the model system were compared. The result showed that pyridoxal 5′-phosphate was the most effective inhibitors for glycated lipids with inhibitory percentage of 38%. The pyridoxals could compete with glucoses to react with PE, as shown in Figure 3 (Higuchi et al. 2006). According to our previous work, the percentage inhibition of the four catechins (epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate) on the formation of CM-PE is 38.84%, 33.31%, 20.71%, and 22.66%, respectively. The inhibitory percentage of the four catechins on the formation of carboxyethyl carboxyethyl PE (CE-PE) is 42.04%, 41.99%, 31.70%, and 36.24%, respectively (Han et al. 2019a). We illuminated three inhibitory mechanisms of catechin for CM-PE: (1) catechin scavenges hydroxyl radical, which blocks the process of Amadori-PE to CM-PE; (2) catechin inhibits the formation of CM-PE by trapping reactive glyoxal or methylglyoxal; (3) catechin is oxidized to o-benzoquinone. O-Benzoquinone reacts with CM-PE or CE-PE through nucleophilic substitution, which competes with the reaction between glucose and PE (Han et al. 2019a, 2019b). As shown in Figure 4. All these researches provided theoretical basis for the use of natural products to inhibit the formation of food-derived glycated lipids. More research can be conducted in terms of seeking effective inhibitors for food production.

Conclusions and prospects

The effect of exogeneous glycated lipids on human health in the medical domain has been widely studied, while food-derived glycation lipid, have not received enough attention. With more focus on the potential chemical hazards produced in food production processes in recent years, it is necessary to conduct research on food-derived glycated lipids. Future research directions for the study of food-derived glycated lipids include: (1) understanding their digestion, absorption, and metabolism in the human body; (2) expanding the available database for associated risk assessment; (3) relating their formation mechanism to food production processes; (4) revealing the formation mechanism of food-derived glycated lipids; (5) developing rapid, reliable, and inexpensive determination methods for the compounds in different foods; and (6) seeking effective inhibitors.

Disclosure statement

The authors declare no conflict of interest

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