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Investigating the inhibitory effect of pomegranate peel extract on the formation of advanced glycation end products (AGEs) in the model systems

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ABSTRACT

Advanced glycation end products (AGEs) are a group of compounds formed during the Maillard reaction, which can have adverse effects. This study aims to investigate the formation of fluorescent AGEs using the response surface method (RSM). Factors such as protein type ((whey protein, 2.0, 3.5, and 5.0% w/v) and casein (1.0, 2.0, and 3.0% w/v)), sugar type ((glucose and fructose (0.2, 0.6, and 1.0 M) and lactose (0.1, 0.3, and 0.5 M)), and pomegranate peel extract (PPE, 250.0, 500.0, and 750.0 ppm) along with their interactions are analyzed. The results of this study showed that, the type of protein, type of sugar, and concentration of phenolic extract from pomegranate peel were effective in preventing the formation of AGEs, and the pomegranate peel extract was able to effectively prevent glycation reaction (specially at 750.0 ppm). According to the results, protein type and concentration significantly influence AGEs formation. The inhibitory activity of the extract in the model system containing casein was lower than system containing whey protein, and overall, the inhibitory power decreased with an increase in protein concentration. By changing the type of sugar present in the model system, the inhibitory behavior of the pomegranate peel extract became complex, showing increased, decreased, or no effect in some cases. Further investigations can suggest the use of this extract, especially in the formulation of food products, including infant formulas.

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1-Introduction

With improving quality of life, there is an increasing demand for high-quality food, and consumers not only pay attention to the color, taste, and flavor of food but also to its nutritional composition, quality, and safety. In food processing, Maillard reaction often occurs to create a unique taste and appealing color (1). However, these processes often come with the risks of unintentional chemical compound formation. Advanced glycation end products (AGEs) are a family of harmful compounds that are produced through complex non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids (Maillard reaction). Various factors affect the formation of these compounds, including different food components (such as sugar, protein, fat, water, etc.), influential factors during storage (such as temperature, time, humidity, pH, etc.), and processing methods (such as steaming, boiling, frying, baking, grilling, etc.) [2]. The accumulation of these compounds in the body can lead to the development of chronic diseases such as type 2 diabetes, atherosclerosis, and Alzheimer's [3].

Based on their thermal stability, final products of glycation are mainly categorized into three groups: 1) Advanced glycation end products with a cross-link and fluorescent properties, such as pentosidine, 2) Advanced glycation end products with a cross-link but without fluorescent properties, such as imidazolium dityrosine, and 3) Advanced glycation end products without a cross-link and without fluorescent properties, such as N-carboxyethyllysine (CEL) and N-carboxymethyllysine (CML). Among these, CML and pentosidine are of particular importance in the body and are used as indicators of advanced glycation end product accumulation [4, 5]. Furthermore, the close relationship between potential chemical hazards in food processing and many chronic human diseases has gradually become evident. Recent studies have shown that the accumulation of advanced glycation end products in the body leads to oxidative reactions and damage to nerve cells, which can result in diseases such as neurological disorders, inflammatory reactions, kidney diseases, allergic reactions, cardiovascular diseases, cancer, and diabetes [6, 7]. Due to the wide range of these compounds and the complex composition of food and chemical reactions involved, the detection and determination of AGEs in food are challenging. Therefore, extensive research is being conducted on the detection and measurement of advanced glycation end products, the effects of various processes on them, and the development of methods to inhibit their formation in the food industry [8]. Additionally, numerous studies have investigated the relationship between the intake of AGEs and cancer and chronic metabolic diseases.

The Maillard reaction and glycation are of particular importance in the food industry. These reactions have an effect on sensory characteristics, color improvement, protein function and its biological value, and other nutritional properties of the product. Since glycation reactions are also responsible for creating the desired taste and color, reducing glycation in food products is a challenging issue. Heating foods leads to ease of digestion, good mouthfeel and microbial safety of food. But high temperature and long-term cooking can significantly increase the content of AGEs in food [9]. For example, in processes such as grilling and cooking meat, the production of fluorescence compounds increases exponentially [9]. Therefore, it is necessary to find a way to minimize the amount of AGEs in foods, while maintaining acceptable sensory properties and microbial safety. Factors affecting glycation such as reactive species, amount of available water, pH, and presence of oxygen can affect the progress of this reaction. Therefore, by changing and controlling these factors, glycation is reduced. On the other hand,

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many synthetic and natural substances have been proposed to inhibit the formation of advanced glycation end products. Although synthetic compounds have stronger inhibitory ability than natural types, they may have side effects. Compared to synthetic inhibitors, natural compounds may be a good choice for use in food to reduce the content of these harmful compounds [10, 11].

Polyphenols are the most natural compounds used in food systems as antiglycation agents. Their antiglycation effect is mostly related to antioxidant activities and trapping dicarbonyls (the main intermediate and important factor in the progress of the reaction). In fact, antioxidants prevent the continuation of the reaction and the formation of AGEs by chelating metal ions, absorbing free radical species, reducing oxidative stress, and also by trapping carbonyl compounds (in the middle stage of glycation) (12, 13).

In a research, the antilycation activity of olive leaf extract in biscuits was investigated. In this research, quercetin and gallic acid were used as standards with antiglycation activity. Thus, these two standards and olive leaf extract were added in the range of 0.25- 0.75% (w/w) to the biscuit samples and then baked at 180°C for 20 minutes. The results showed that the samples formulated with olive leaf extract have a positive antiglycation activity by reducing the amounts of pentosidine and N-carboxyethyl-lysine formation [14]. In another study, researchers evaluated the effect of mulberry leaf extract on the glycation reaction in the model system (bovine serum albumin-glucose); The results showed that this extract contains lutein and apigenin and has significant antiglycation properties [15].

In another study, the effect of 14 types of seasoning used in food on the glycation reaction of 1- bovine serum albumin-glucose and 2- bovine serum albumin-methylglyoxal was investigated. The results showed that in the second model system, the most inhibitory effect was related to fennel (88%), followed by cinnamon (85%), bell pepper (81%), and cloves (79%). Also, in the first model system, the inhibitory effect of oregano was the highest [16].

In another study in 2019, it was shown that the main pigments of tomatoes (lycopene, lutein and beta-carotene) affect the glycation reaction. By examining the amount of glyoxal, carboxymethyllysine and pentosidine through fluorescence spectroscopy, it was found that all three pigments have a good inhibitory effect on the glycation reaction. In another part of this research, the inhibitory effect of tomato pigment on the amount of AGEs and carboxymethyllysine in the formulated cookie was investigated and the results showed that tomato pigment at the level of 2.7% was able to reduce 46% and 26% of the AGEs and carboxymethyllysine, respectively [17].

In another study in 2020, the antiglycation effect of phenolic compounds of sage extract was investigated. The results showed that this extract had the same effects as aminoguanidine and caused a decrease in the intensity of fluorescence emission, so it was found that the damage to albumin in the presence of these two compounds, rosmarinic acid and resveratrol, was reduced by 53% and 50%, respectively. On the other hand, protection of protein thiol groups increased by 50 and 44%, respectively, and protein carbonyl accumulation decreased by 67 and 71%, respectively. Because sage extract is a rich source of polyphenol compounds, therefor it can prevent the formation of AGEs and leads to the reduction of cardiovascular complications and diabetic disorders caused by them [18].

Pomegranate (*Punica granatum* L.) is an important commercial fruit that is widely cultivated in regions of Asia, North Africa, Mediterranean and Middle East, and Iran is one of the most important producers and exporters of pomegranate in the world. A large part of the pomegranate fruit is its skin, which is usually used for animal feed or dyeing and is not used more usefully. Pomegranate skin is a rich source of phenolic compounds that have strong antioxidant properties, and many studies have been conducted in this field and the use of its skin extract [19, 20]. Also, pomegranate peel

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extract contains large amounts of phenolic compounds, including anthocyanins, ellagic acid, punicalin, punicalagin, pedoncolagin and flavanols [21]. It has also been determined that pomegranate peel extract is a stronger antioxidant than its pulp and seeds, and it has almost ten times higher antioxidant properties.

Although in recent years, many new technologies have been developed, such as hyperspectral spectroscopy and Raman spectroscopy to detect the quality and safety characteristics of food, but the existing diagnostic methods for AGEs are mainly divided into instrumental analysis and bioassay methods. To date, gas chromatography-mass spectrometry (GC-MS), HPLC (with various detectors including diode array and fluorescence), fingerprinting by fluorescence spectroscopy, mass spectrometry (MS), and MS/MS are powerful instrumental technologies for determining AGEs and ELISA is one of the bioassay method that has been used to determine the amount of AGEs [22]. Fluorescence spectroscopy is used to measure advanced fluorescent glycation end products (such as pentosidine). In this spectroscopy, the excitation wavelength of advanced glycation end products is selected between 300 and 420 nm and their emission wavelength between 350 and 600 nm [23].

Since the accumulation of these compounds in the body can lead to chronic diseases such as type 2 diabetes, atherosclerosis, and Alzheimer's, and pomegranate peel extract (PPEs) is an rich source of antioxidative compounds (such as tannins and phenolic compounds) it can be consider as a natural inhibitor of AGEs. Therefore, the aim of this study is to investigate the inhibitory effect of aqueous extract of pomegranate peel on the progress of glycation reaction in different conditions. In this research, the effect of this extract was investigated in model systems (two types of protein (casein and whey protein) and three types of sugar (glucose, lactose and fructose). For this purpose, the fluorescence intensities of the samples were measured as an index to evaluate the antiglycation activities of the extract on the advanced glycation end products formation (such as pentosidine).

2. Materials and Methods

2.1. Chemicals

Glucose, fructose, and lactose were purchased from Merck Chemical Co. (Germany). Casein was purchased from Sigma-Aldrich (USA) and whey protein was purchased from Karen Company (Yazd, Iran). All the chemicals used in this research were of the highest purity and were used without further purifications.

2.2. Preparation of pomegranate peel extract (PPE)

Burnt and damaged pomegranates were separated and pomegranates with healthy skin were peeled by hand. The pomegranate peels were dried in the shadow and at room temperature, and then they were crushed by a grinder, then passed through a sieve with 40 mesh and kept at -20 ^{o}C until extraction. Next, the distilled water was mixed with peel`s powder in a ratio of 4:1, and the extraction process was carried out for 8 h at room temperature. The extract was filtered by Whatman No. 41 paper to remove any particles. The extract was concentrated by a rotary evaporator (under vacuum and at a temperature of 45 ^{o}C).

2.3. Preparation of samples

The basis of all the glycation reactions was sugar and protein, and different treatments were designed using response surface method (central composite face-centered (CCF)). In general, for the design of model systems, there were three dependent variables at three levels: there sugars namely fructose and glucose (at concentration 0.2, 0.6 and 1.0 M) and lactose (at concentration 0.5-0.1 M), whey protein at concentration (0.2, 3.5 and 0.5% by w/v) and casein (at concentration 0.1, 0.2 and 0.3% w/v) and pomegranate peel extract at 0.250, 0.500 and 0.750 ppm (Table 1).

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Table 1. Designed models for investigating the inhibitory effect of studied extract on glycation reaction*.

Run No.	Protein	Sugar	Extract
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1
9	-1	0	0
10	1	0	0
11	0	-1	0
12	0	1	0
13	0	0	-1
14	0	0	1
15	0	0	0
16	0	0	0
17	0	0	0

* -1 , 0, and, 1 means lowest, central, and highest level of independent variables, respectively. Extract (PPE, 250.0, 500.0, and 750.0 ppm); Sugar Glucose (0.2, 0.6, and 1.0 M), Fructose (0.2, 0.6, and 1.0 M), and Lactose (0.1, 0.3, and 0.5 M); Protein (Whey, 2.0, 3.5, and 5.0 %w/v and Casein, 1.0, 2.0 and 3.0 % w/v).

2.4. Glycation reaction

500 µl of sugar and protein solutions with predetermined concentrations were mixed according to the specified treatment in Table 1. Then, 100 µl of extracts were added in their predetermined concentrations. Finally, 20 µl microliters of sodium azide was added to the mixtures to prevent the growth of mold and yeast. After that, samples were incubated for 7 days at 25 ºC. After this period, 100 µl of the reaction mixture was placed into a 384 microplate (Corning, USA) and fluorescent emission was measured by a Cytation 3 device (Bio Tek, USA). The excitation and emission wavelengths were340 nm and 430 nm, respectively. Finally, the percent of inhibition (or antiglycation activity) was calculated according to the eq. 1:

Inhibition (%)= $[(F_c - F_s)/F_c] \times 100$ (1)

where, F_c and F_s are the fluorescence of control and sample, respectively.

2.5. Statistical analysis

In this study, the response surface method (RSM, CCF design) was used, and a total of 17 formulas (Table 1) were prepared and tested for each type of protein. Experiments were carried out in triplicates and data was analysed using MODDE® 7 software of Sartreoz company (Italy).

3. Results and discussion

3.1. Antiglycation activity of PPE in whey protein + sugar model system

Table 2 shows the validation parameters of the RSM design for the model systems of whey protein + pomegranate peel extract + three studied sugars. The results showed that the fitted model for whey protein + fructose has 95% accuracy and also has high repeatability, which was 94% and 87% for systems containing glucose and lactose sugars, respectively. On the other hand, the validation of the model's predictive power shows that the predictive ability of the model by examining the difference between the predicted and actual inhibition activities of the optimal treatment.

Table 2. RSM model validation parameters of pomegranate peel extract + whey protein + sugar.

Model	R^2	R^2 Adj.	Q^2 [2]	RSD[1]	Repeatability

[1] Relative standard deviation (RSD)

[2] Q^2 is the median value in the set.

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Whey + Glucose	0.94	0.92	0.90	2.76	0.93
Whey + Fructose	0.95	0.94	0.92	0.95	0.95
Whey + Lactose	0.87	0.84	0.78	5.29	0.86

Table 3 shows the main and interaction of the effective parameters in the glycation reaction as well as the effect of the studied extract. The results showed that the concentration of whey protein has a negative effect on the inhibition activity of the extract and by increasing whey protein concentration, the glycation reaction progressed more intensively. The interaction of whey and fructose had the greatest effect and reduced the inhibition percentage, and the whey + lactose mixture had the least effect in reducing the inhibition percentage of the extract. Unlike the control samples, which glycation reaction rate increased by increasing the amount of sugar, in the presence of PPE, the progress of the glycation reaction decreased. There are three main reasons for this observation. In fact, in addition to the important effect of the type of sugar on the glycation reaction, the presence of sugar reduces the solubility of the oxygen in the aqueous medium, inhibits free oxygen and forms chelated metal ions, and as a result prevents the oxidation of phenolic compounds [24]. Therefore, due to its reactivity, besides participating in the browning reaction, sugar also protects the phenolic compounds in the extract and reduces the formation of advanced glycation products. The greatest effect of PPE was seen in the model system containing lactose, but in general, in all formulations containing whey protein, pomegranate peel extract could significantly prevent the glycation reaction, and on average its effect coefficient was 0.15-11.5.

Table Table 3. Regression coefficients of predicted quadratic polynomial models for the response of antiglycation activity of pomegranate peel extract (PPE) in model system containing whey protein

Independent variable	Glucose		Fructose		Lactose	
	Coeff. SC	*p*-value	Coeff. SC	*p*-value	Coeff. SC	*p*-value
Total constant	70.12	0.00	78.62	0.00	73.27	0.00
Protein	-4.03	0.00	-4.44	0.00	-2.83	0.00
Sugar	2.11	0.00	3.04	0.00	2.23	0.02
Extract	11.43	0.00	13.98	0.00	14.99	0.00
Protein × Protein	0.30	0.75*	-0.37	0.72*	4.78	0.01
Sugar × Sugar	-2.92	0.00	-3.75	0.00	-5.63	0.00
Extract × Extract	-3.38	0.00	-4.50	0.00	-6.26	0.00
Protein × Sugar	0.14	0.79*	-1.67	0.00	-1.77	0.10*
Extract × Protein	1.17	0.04	3.92	0.00	1.56	0.15*
Sugar × Extract	-2.53	0.00	-1.32	0.03	-0.45	0.67*

No significant difference observed ($p<0.05$).

In Fig. 1 shows the changes of inhibitory effect of pomegranate peel extract (at a concentration of 750 ppm) by varying protein and sugar concentrations. Also, PPE`s antiglycation acitivity can be predicted by these plots.

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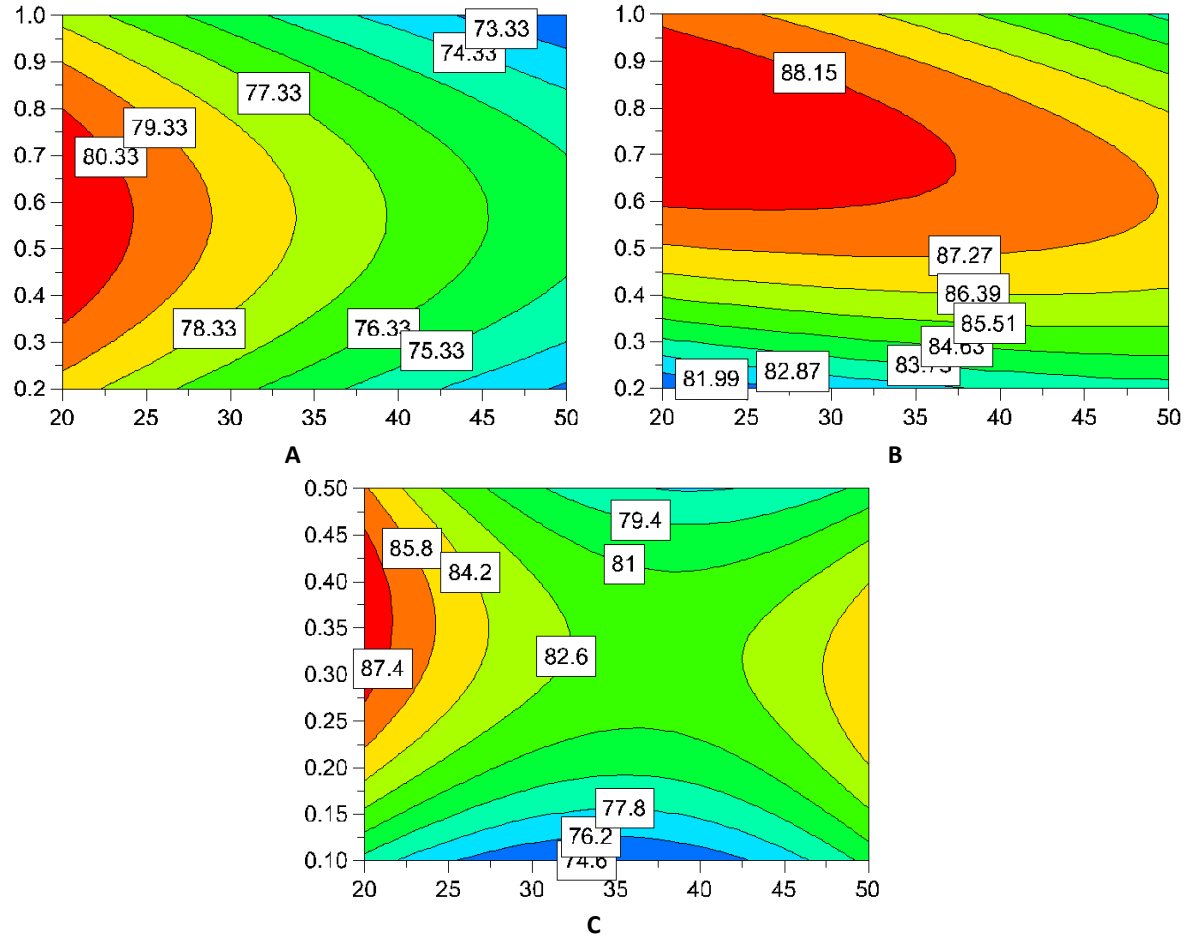

Fig. 1. The color map of antiglycation activity in the model system containing whey protein and pomegranate peel extract (750 ppm). A: containing glucose; B: containing fructose; C: containing lactose. The horizontal axis shows protein concentration (% w/v × 100) and the vertical axis shows sugar concentration (M).

3.2. Antiglycation activity of PPE in whey protein + sugar model system

The accuracy of the model containing casein and different sugars (glucose, fructose, and lactose) was 91.0, 89.0 and 90.0 %, respectively. Also, these models have acceptable reproducibility and validity (Table 4).

Table 4. RSM model validation parameters of pomegranate peel extract + casein + sugar.

Model	R^2	R^2 Adj.	Q^2	RSD	Repeatability
Casein + Glucose	0.91	0.89	0.86	5.35	0.90
Casein + Fructose	0.89	0.87	0.85	4.84	0.89
Casein + Lactose	0.90	0.88	0.84	4.33	0.87

Table 5 shows the main and interactions of the effective parameters in inhibiting the glycation reaction. Like the results of section 3.1, the effect of protein with a negative coefficient showed that the inhibitory effect of the extract decreases by increasing the casein concentration. By comparing the results of

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these two studied proteins, it can be seen that in the system containing casein, the inhibitory activity of the extract decreases compared to the system containing whey protein, probably due to the difference in the structure and amino acid composition of the studied proteins. The rate of glycation reaction and AGEs formation is higher in the model containing casein. The effect of sugar (and its positive coefficient) was similar to the results of section 3.1, and pomegranate peel extract reduced the glycation reaction rate. In addition, pomegranate peel extract was able to significantly prevent the glycation reaction.

Pomegranate peel extract contains large amounts of phenolic compounds, including anthocyanins, ellagic acid, punicalin, punicalagin, pedunculagin, and flavanols, which have high antioxidant properties [20]. As previously reported, these compounds inhibit the glycation reaction through antioxidant activities and trapping dicarbonyls. In addition, in the studied model systems, these antioxidants prevented the formation of advanced glycation end products by chelating metal ions, absorbing free radical species and reducing oxidative stress in the middle stage of glycation [25].

In the initial stage of glycation, the carbonyl group of the reducing carbohydrate condenses with the free amino group on the protein or amino acids and forms Amadori products, which also increases the mass of the proteins. In a previously published paper the effect of pomegranate extract compounds on the glycation reaction in the model system of bovine serum albumin and fructose was investigated. It was found that in the initial stage of glycation, phenolic compounds such as gallic acid (compared to punicalagin acid and ellagic acid, a very small amount of it present in pomegranate extract) which is usually present in many plant sources, does not have a significant inhibitory effect on the formation of early glycation products [25]. While punicalagin acid and ellagic acid played an important role in inhibition in the early stages of glycation. In addition, in the above study, effect of pomegranate extract on the intermediate stage of glycation reaction was studied. As it is known, in the intermediate stage of glycation, Amadori products are produced and eventually cause the production of fluorescent AGEs (such as pentosidine). After performing the glycation reaction, the fluorescence emission intensity of each sample was measured to detect the fluorescent AGEs formed in the intermediate stage [25]. The results of this study showed that the inhibitory power of punicalagin acid, ellagic acid, and gallic acid was 90.0, 70.0, and 60.0 %, respectively, which indicates the greater inhibitory power of punicalagin in this reaction [26].

In another study, the effect of different fruit extracts on the glycation reaction was investigated. The results showed that apple extract had no significant effect compared to the control sample. While strawberry, mulberry and peach extracts had a better effect than apple extract. But the most inhibitory effect was related to the samples with pomegranate extract [27].

Table 5. Regression coefficients of predicted quadratic polynomial models for the response of antiglycation activity of pomegranate peel extract (PPE) in model systems containing casein.

Independent variable	Glucose		Fructose		Lactose	
	Coeff. SC	*p*-value	Coeff. SC	*p*-value	Coeff. SC	*p*-value
Total constant	73.33	0.00	70.37	0.00	60.17	0.00
Protein	-11.66	0.00	-9.18	0.00	-8.83	0.00
Sugar	2.14	0.03	2.23	0.01	2.93	0.00
Extract	15.95	0.00	12.96	0.00	11.88	0.00
Protein × Protein	-1.87	0.32*	-3.34	0.06*	3.57	0.02
Sugar × Sugar	-5.07	0.01	-0.35	0.83*	-1.15	0.45*

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Extract × Extract	-1.57	0.40*	0.46	0.78*	02.15	0.16*
Protein × Sugar	2.06	0.06*	-1.51	0.13*	-2.45	0.00
Extract × Protein	-0.52	0.63*	0.35	0.72	2.92	0.00
Sugar × Extract	-1.53	0.16*	-4.09	0.00	-3.25	0.00

* No significant difference observed (p<0.05).

Fig. 2 shows the observed and predicted inhibitory effect of pomegranate peel extract (at a concentration of 750 ppm) by varing the protein and sugar concentrations. In fact, this map is a library of information related to the degree of inhibition of the extract in the glycation reaction.

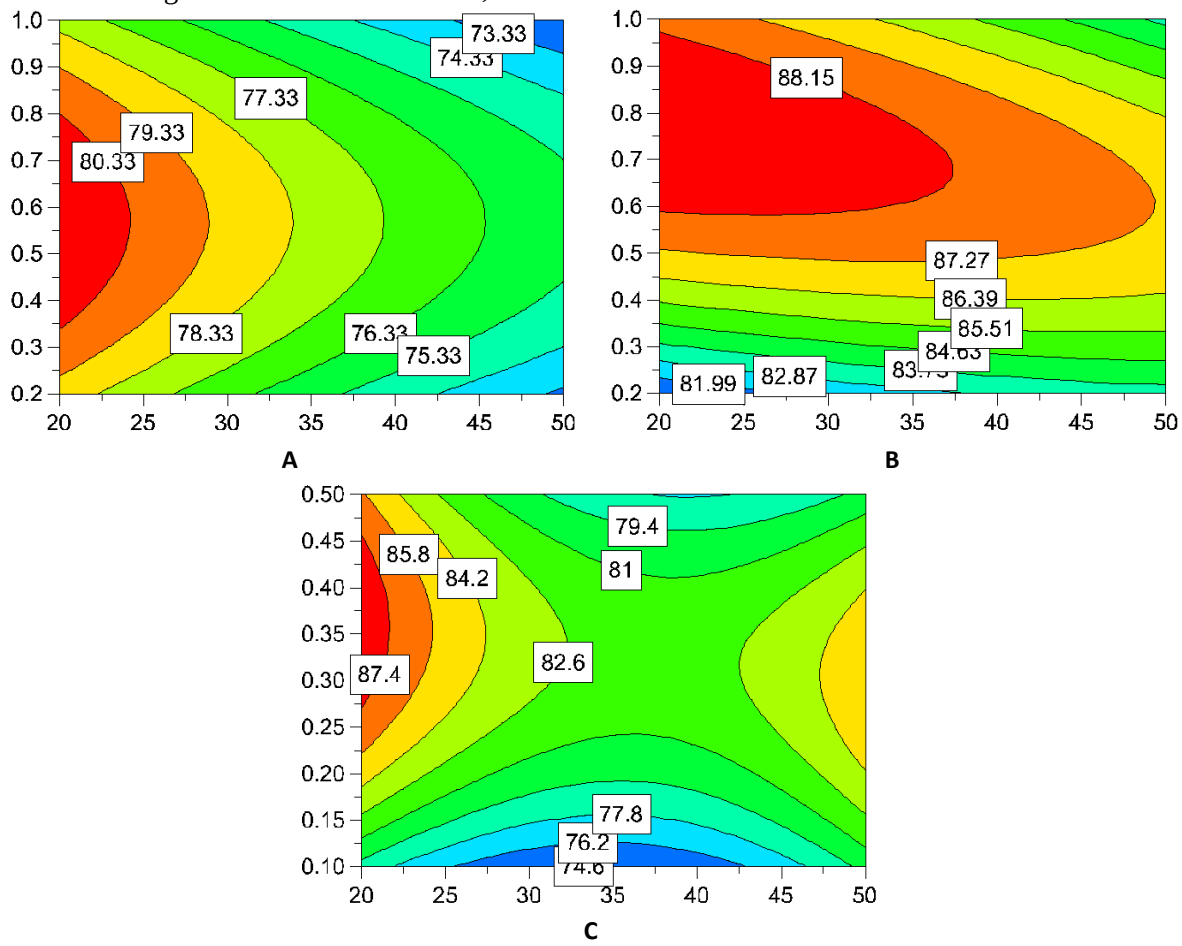

Fig. 2. The color map of antiglycation activity in the model system containing casein and pomegranate peel extract (750 ppm). A: containing glucose; B: containing fructose; C: containing lactose. The horizontal axis shows protein concentration (% w/v × 100) and the vertical axis shows sugar concentration (M).

4. Conclusion

In this study, the antiglycation activity of pomegranate peel extract on several model systems containing two types of proteins (whey and casein), three types of sugars (glucose, fructose and lactose) was examined. The results showed that by increasing the protein concentration, the rate of glycation reaction increases. In addition, the interaction between protein and sugar was negative, which indicates the increase of glycation reaction rate. In the presence of pomegranate peel extract, the progress of glycation reaction decreased by increasing the sugar concentration. The presence of sugar reduces the dissolution of

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oxygen in the aqueous media, inhibits free oxygen and chelates metal ions, and as a result prevents the oxidation of phenolic compounds. The greatest effect of pomegranate peel extract was observed in the model system containing lactose, but overall, in all models with whey protein, pomegranate peel extract could significantly prevent the glycation reaction. The use of casein compared to whey protein had a more negative effect on the inhibition percentage of glycation, and although casein was used at a lower concentration due to its lower solubility than whey protein, it ultimately led to the formation of a large amount of advanced glycation end products. The results of this study showed that the type of protein and sugar is effective on the formation of advanced glycation end products and the use of phenolic compounds of pomegranate peel can prevent the formation of these compounds. It seems that by conducting more and complete investigations, this extract can be proposed to control the formation of advanced glycation end products (AGEs) in foodstuffs.

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بررسی اثر بازدارندگی عصاره پوست انار بر تشکیل محصولات نهایی گلیکاسیون پیشرفته در سامانه‌های مدل

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چکیده

محصولات نهایی گلیکاسیون پیشرفته (AGEs)، گروهی از ترکیبات مضر هستند که در حین واکنش میلارد توسط یک سری واکنش‌های پیچیده تولید می‌شوند. در مطالعه حاضر از روش آماری سطح پاسخ برای بررسی اثر دو نوع پروتئین ((پروتئین آب پنیر (۲/۰، ۳/۵ و ۵/۰ درصد وزنی/حجمی) و کازئین (۱/۰، ۲/۰ و ۳/۰ درصد وزنی/حجمی))، سه نوع قند گلوکز و فروکتوز (۰/۲، ۰/٦ و ۱/۰ مولار) و لاکتوز (۰/۱، ۰/۳ و ۰/۵ مولار) و عصاره آبی پوست انار (۰/۲۵۰، ۰/۵۰۰ و ۰/۷۵۰ قسمت در میلیون) و بر بازداری از تشکیل محصولات نهایی گلیکاسیون پیشرفته با خاصیت فلوئورسانس استفاده شد. بر اساس نتایج این مطالعه نوع پروتئین، نوع قند و غلظت عصاره فنولی پوست انار بر ممانعت از تشکیل AGEs موثر بود و عصاره پوست انار (به ویژه در غلظت ۷۵۰ قسمت در میلیون) توانست به خوبی از واکنش گلیکاسیون جلوگیری نماید. نتایج نشان داد که نوع پروتئین و غلظت آن بر تشکیل این محصولات موثر است. قدرت بازداری عصاره در سامانه مدل حاوی کازئین کمتر از سامانه حاوی پروتئین آب پنیر بود و در کل با افزایش غلظت پروتئین قدرت بازدارندگی کاهش یافت. با تغییر نوع قند موجود در سامانه مدل، رفتار بازداری عصاره پوست انار پیچیده بود و در برخی موارد اثر افزایشی، کاهشی یا بی اثر نشان داد. با بررسی‌های کامل تر می‌توان پیشنهاد داد تا از این عصاره در فرمولاسیون مواد غذایی به ویژه در فرمولاسیون غذاهای کودک استفاده کرد.

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