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Inhibition of Albumin Glycation at Different Stages by Four Anti-diabetic Plant Extracts Correlates with Polyphenols and Antioxidant Capacity *in vitro*

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Authors' contributions

This work was carried out in collaboration between all authors. Author APR contributed to the concepts, design, definition of intellectual content, literature search, experimental studies, data acquisition, manuscript preparation, manuscript editing and manuscript review. Author GS contributed to the experimental studies and data acquisition. Authors MME and AA contributed to the concepts, design, definition of intellectual content and literature search. Author GR contributed to the data analysis, statistical analysis and manuscript preparation. Author FG contributed to the manuscript preparation, manuscript editing and manuscript review. Author MRS contributed to the concepts, design, definition of intellectual content, literature search, manuscript preparation, manuscript editing and manuscript review. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Both glycation and oxidative stress play a critical role in the incidence of diabetic complications. Plants with antioxidative and antiglycative properties may attenuate such pathological conditions. The aim of this study is comparing the antiglycative and antioxidative effects of *Vaccinium arctostaphylos, Plantago ovata, Securigera securidaca* and *Rhus coriaria* on albumin glycation for the first time.

Methodology: Antiglycative property of methanolic extract (75%) of these plants was evaluated by co-incubation of extracts with bovine serum albumin and glucose. Various stages were assessed by measuring different markers of glycation (fructosamine, protein carbonyls and amyloid cross-β structure aggregation). Total phenolic and flavonoid contents as well as antioxidant capacity of extracts were determined. Finally, the correlations between antiglycation property, total phenol and flavonoid content and antioxidant capacity of extracts were evaluated.

Results: The results demonstrated that the extracts exert inhibitory effects on various stages of glycation and *V. arctostaphylos* showed maximum attenuating effect. A significant correlation was found between antiglycation and antioxidant properties of extracts with total phenolic and flavonoid content. In addition, the antioxidant capacity of extracts correlated with their antiglycation properties.

Conclusion: Our findings revealed that antioxidative and antiglycative activities of extracts may be related to their phenolic and flavonoid contents. These findings support the viewpoint that the medicinal plants with anti-diabetic properties may be beneficial resources for inhibition of glycation and oxidative stress in diabetic patients.

Keywords: Diabetes mellitus; glycation; antioxidants; flavonoids; herbal medicine.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that results in different clinical consequences [1]. Oxidation and non-enzymatic reaction of glucose with proteins (glycation) are very important in diabetic patients. Such reactions do not cause a serious problem under normal conditions; however, if enhanced and accumulated, they can be harmful. Albumin is a suitable target for glycation [2,3] which exerts detrimental modifications on its folding from globular form to amyloid β-sheet aggregates [4,5]. These alterations can adversely affect the binding abilities of drugs and other biological agents to albumin. The reactions are typically accelerated during diabetes due to chronically elevated blood glucose level [6,3]. Evidence suggests that glycation products are involved in the diabetes, aging and chronic diseases such as Alzheimer and cardiovascular disorders. Moreover, cardiovascular problems are the leading cause of morbidity and mortality among patients with type 2 diabetes [6-9]. Therefore, it can be deduced that antiglycative compounds are promising options to prevent Biomolecular damages in such conditions [4]. A number of glycation inhibitors have been studied such as amino guanidine, pyridoxamine and phenyl thiazolium bromide, and some of them have ameliorated diabetes complications in animal models; however, potential toxicity has limited their clinical application [10,11]. Although free radicals have an undeniable role in living organisms [12], several studies have shown that diabetes is associated with increased production of free radicals [13]. It has been generally suggested that antioxidative and antiglycative agents may prevent or alleviate the formation of glycation products [14]. Medicinal plants seem to be suitable candidates for finding efficient compounds with minimal side effects for inhibition of glycation and oxidative stress [4]. *Vaccinium arctostaphylos, Plantago ovata, Securigera securidaca* and *Rhus coriaria* have been traditionally employed for treatment of diabetes in Iran. Therefore, the present study was conducted to evaluate and compare the antiglycative and antioxidative properties of the mentioned plants.

2. MATERIALS AND METHODS

2.1 Chemicals

Bovine serum albumin (BSA), 2, 2-diphenyl-1-picrylhydrazyl (DPPH), 2, 4-dinitrophenylhydrazine (DNPH), Thiobarbituric acid (TBA), Congo red, Sodium phosphate dibasic (Na_2HPO_4), Sodium phosphate monobasic (NaH_2PO_4), Trichloroacetic acid (TCA), Ethyl acetate and Gentamicin sulfate

were purchased from Sigma Aldrich Chemical Company (Poole, UK). Glucose, Urea, and Ethyl alcohol were obtained from Carlo Erba (Milan, Italy). Methanol, *Ethylenediaminetetraacetic acid* (EDTA) and Hydrochloric acid (HCl) were purchased from Merck Millipore (Darmstadt, Germany). All the chemicals were of analytical grade.

2.2 Plant Materials and Extract Preparation

Vaccinium arctostaphylos, Plantago ovata, Securigera securidaca and *Rhus coriaria* were purchased from a local traditional medicine clinic in Hamadan, Iran, and were authenticated by the staff of the medicinal plants' section in department of horticulture, Bu-Ali Sina University of Hamadan. The plants were washed, dried at room temperature away from direct sunlight, pulverized (200 grams) and dissolved in methanol solution (2000 ml, 75%) at room temperature in darkness conditions. In the meantime, the solutions were stirred in regular intervals. After 24 hours, the suspensions were filtered through Whatman filter paper 1 and completely dried in an incubator (37℃) [15]. Eventually, three concentrations (0.5 ، 0.25 and 0.12 g/dl) were prepared from each extract in distilled water and were used for subsequent measurements [10].

2.3 Measurement of Antioxidant Capacity

Antioxidant capacity of extracts was evaluated using *DPPH* free radical scavenging activity method [14]. Briefly, different concentrations of extracts (50-250 µg/ml) were separately added (1 ml) to 4 ml DPPH solution (33 mg of DPPH in 1 L methanol) and incubated for 10 min in darkness. The absorbance was recorded by spectrophotometer (α-1860 Split beam UV/Visible spectrophotometer, China) at 517 nm. *DPPH scavenging percentage* was calculated by the following formula:

$$\text{Scavenging\% [DPPH]} = [(A_0-A_1)/A_0]\times 100$$

A_0: Absorbance of the extract-free solution, A1: Absorbance of the extract-containing solution.

2.4 Estimation of Total Phenolic and Flavonoid Contents

Total phenolic content of the extracts was measured using Folin–Ciocalteu colorimetric method. Gallic acid (GA) was used as the standard (0-200 mg/l). Finally, the amount of phenolic content was expressed as milligram gallic acid equivalent per 100 gram of extract (GAE/100 g EX). Aluminum chloride assay was used to determine total flavonoid content of extracts. Quercetin was chosen as the standard (0-50 mg/l). Finally, flavonoid content was calculated as milligram quercetin equivalent per 100 gram of extract (mg QE/100 g EX) [16].

2.5 Albumin Glycation Preparation *in vitro*

Albumin glycation was done according to McPherson et al. [14] method with some modifications. Briefly, 1 ml of *BSA (5*%) was incubated with 1ml of glucose (3%) in potassium phosphate buffer (200 mM, pH=7.4 containing 0.02% Gentamicin) at 37℃ for 72 hours in presence or absence of extracts in different concentrations. Before incubation, all the solutions were passed through 0.22 µm sterile membrane filters. After the incubation, it was ensured that all the solutions were free of microbiological contamination. Eventually, the solutions were dialyzed against the phosphate buffer, and the unbound glucose was removed from the solutions. The dialyzed mixtures were stored at 4℃ for further analysis.

2.6 Investigating Antiglycation Properties of Plant Extracts

2.6.1 Estimation of fructosamines

TBA assay was used to determine the level of fructosamine as early glycation product [17]. In brief, 1 *ml TCA (20*%) was *added* to 1ml of glycated samples as well as positive control and centrifuged for 10 min at 1200× g. This was done in duplicate, and the supernatants were discarded. The precipitate was dissolved in 1ml phosphate buffer and *0.5 ml TCA* (*40*%). After centrifugation at 1200× g for 10 min, the supernatant was mixed with 0.5 *ml of TBA* (0.05 M) and the absorbance was measured at 443 nm. The percentage *inhibition of fructosamine* was calculated according to the following formula:

$$\text{Inhibition\%} = [(A_0-A_1)/A_0]\times 100.$$

A_0: Absorbance of the extract-free solution, A_1: Absorption of the extract-containing solution.

2.6.2 Estimation of carbonyl groups

As intermediate stage markers of glycation, protein carbonyl compounds were estimated by DNPH method [14]. Briefly, 0.5 ml of glycated albumin samples were mixed with an equal volume of 2, 4- DNPH (10 mM solution in HCL 2.5 M) and incubated at room temperature for 1 hour. Then, the proteins were precipitated by adding 0.5 ml TCA (20%) and the precipitate was three times washed using ethanol-ethyl acetate (1:1 v/v) mixture. Finally, the precipitate was dissolved in *1 ml* of 8 M *Urea,* and the absorbance was measured at 365 nm. Protein carbonyl concentration was calculated by using the molar extinction coefficient (ε365 nm = 21 mM per cm).The percentage *inhibition* was calculated by the following equation:

$$Inhibition\% = [(A_0-A_1)/A_0] \times 100.$$

A_0: Absorbance of the extract-free solution, A_1: Absorption of the extract-containing solution.

2.6.3 Estimation of amyloid β-structures

The aggregation level in glycated samples was investigated using Congo red as a specific amyloid dye [4,14]. In brief, 0.5 ml of glycated sample was added to 100 µL Congo red (100 Mm solution in *phosphate-buffered* saline, 10% ethanol) and incubated for 20 min at room temperature. The absorbance was recorded at 530 nm. *Inhibition percentage of* amyloid formation was assessed according to the following formula:

$$Inhibition\% = [(A_0-A_1)/A_0] \times 100$$

A_0: Absorbance of the extract-free solution, A_1: Absorption of the extract- containing solution.

2.6.4 Total inhibition of glycation reaction

To determine the total antiglycation property of extracts, all the results obtained in the three methods (TBA, DNPH and Congo red dye) were summed up as IC_{50} and the average was calculated for each extract as Mean±SEM.

2.7 Statistical Analyses

All the experiments were done in triplicate, and the results were expressed as Mean±SEM. To analyze the data for comparing means in groups, ANOVA test followed by Tukey test were used for multiple comparisons. The correlation between variables was indicated using Pearson correlation coefficient. All the analyses were performed by SPSS 16 software. $p<0.05$ was considered as statistically significant.

3. RESULTS AND DISCUSSION

Antioxidant capacity as well as total *phenolic and* flavonoid *contents varied markedly in the extracts. V. arctostaphylos* and *S. securidaca* exhibited the highest (IC_{50}: 132.93±4.28) and lowest (333.31±17.37) antioxidant capacity, *respectively*. *V. arctostaphylos* contained 59.31±2.87 *mg GAE/100 g EX, the most phenolic content among the examined extracts but, S. securidaca* contained the least content among extracts (12.28±1.16 *mg GAE/100 g). V. arctostaphylos* and *S. securidaca* showed maximum and minimum total flavonoid content (15.13±0.96 vs. 7.54±1.13 mgQE/100 g EX), *respectively* (Table 1). The results demonstrated that all the extracts inhibited glycation at three different stages in a dose-dependent manner. Furthermore, in the same concentration, the inhibitory results for each extract were significantly different compared to other extracts (*P*<0.001). Interestingly, *V. arctostaphylos* showed maximum (IC_{50}: 1.09±0.03), (IC_{50}: 1.33±0.04), (IC_{50}: 0.007±0.002) and *S. securidaca* displayed minimum inhibitory effect (IC_{50}:1.91 0.11), (IC_{50}: 2.73±0.23), (IC_{50}: 1.89±0.12) in TBA, DNPH and Congo red methods respectively (Table 2). Total antiglycation property of extracts indicated the overall impact of plant extracts on albumin glycation. Accordingly, the most promising effect against glycation was displayed in presence of *V. arctostaphylos* (IC_{50}: 0.81±0.00) and *S. securidaca* (IC_{50}: 2.18±0.08) showed the weakest antiglycation activity (Table 3). It is obvious that there is a strong correlation between antiglycation property whether by TBA, DNPH and Congo red reactions or in total with antioxidant capacity in plants (Table 4). In other words, the higher the antioxidant capacity of an extract, the higher the inhibition of glycation reaction, and vice versa. On the other hand, the results indicated a direct correlation between antiglycation property whether by TBA, DNPH and Congo red reactions or in total and the antioxidant capacity with total content of phenol and flavonoid in extracts. Thus, higher total phenol and flavonoid content in the extracts caused further inhibition of glycation reaction as well as higher antioxidant capacity of the extracts (Table 5).

Table 1. Amount of total phenols, flavonoids and antioxidant capacity of plant extracts

Name	Total phenol (mg GAE / 100 g EX)	Total flavonoid (mg QE/100 g EX)	IC_{50} of DPPH-radical scavenging
Vaccinium arctostaphylos	59.31±2.87 [a]	15.13±0.96 [a]	132.93±4.28 [a]
Rhus coriaria	34.10±2.36 [b]	10.51±0.55 [b]	183.00±1.10 [b]
Plantago ovata	23.91±4.33 [c]	9.65±0.94 [c]	195.10±7.33 [c]
Securigera securidaca	12.28±1.16 [d]	7.54±1.13 [d]	333.31±17.37 [d]

The results were calculated as Mean±SEM.
Letters from "a" to "d" show from the highest up to the lowest values in a particular test, respectively

Table 2. Percent inhibition of glycation reactions in TBA, DNPH and Congo red by herbal extracts in different concentrations

Name	Inhibitory (%)			
	Concentration (g/dl)			
	0.5	0.25	0.12	IC_{50}
	TBA			
Vaccinium arctostaphylos	87.90±2.58$^{\alpha}$	70.77±1.29$^{\beta}$	60.70±3.05$^{\gamma}$	1.09±0.03 [a]
Rhus coriaria	66.67±1.41$^{\alpha}$	57.80±2.38$^{\beta}$	35.33 ±1.14$^{\gamma}$	1.37±0.01 [b]
Plantago ovata	52.89±2.91$^{\alpha}$	45.91±1.38$^{\beta}$	35.77± 3.94$^{\gamma}$	1.54±0.06 [c]
Securigera securidaca	37.81±4.16$^{\alpha}$	28.56±2.78$^{\beta}$	20.93±4.44$^{\gamma}$	1.91±0.11 [d]
	DNPH			
Vaccinium arctostaphylos	66.30±2.99$^{\alpha}$	56.09±3.14$^{\beta}$	42.84±1.66$^{\gamma}$	1.33±0.04 [a]
Rhus coriaria	38.56±1.81$^{\alpha}$	30.53±3.03$^{\beta}$	27.41±1.85$^{\gamma}$	2.05±0.18 [b]
Plantago ovata	30.99±2.44$^{\alpha}$	24.89±1.73$^{\beta}$	21.24±1.75$^{\gamma}$	2.50±0.50 [c]
Securigera securidaca	20.73±2.36$^{\alpha}$	15.34±1.74$^{\beta}$	10.24±1.41$^{\gamma}$	2.73±0.23 [d]
	Congo red			
Vaccinium arctostaphylos	80.80±4.26$^{\alpha}$	67.32±3.84$^{\beta}$	60.91±2.80$^{\gamma}$	0.007±0.002 [a]
Rhus coriaria	83.34±2.29$^{\alpha}$	75.58±2.60$^{\beta}$	66.19±2.50$^{\gamma}$	0.01±0.00 [b]
Plantago ovata	51.10±3.57$^{\alpha}$	38.49±2.70$^{\beta}$	35.56±2.00$^{\gamma}$	1.62±0.08 [c]
Securigera securidaca	38.37±3.59$^{\alpha}$	27.90±2.27$^{\beta}$	20.54±2.36$^{\gamma}$	1.89±0.12 [d]

The values were calculated as Mean±SEM of triplicate tests. α, β, γ: There is significant difference among extracts at the same concentration as compared with others (P<0.001). Letters "a" to "d": show from the most effective up to the least effective inhibitor

Table 3. Total Percent inhibition of glycation reactions by herbal extracts in different concentrations

Name	Inhibitory (IC_{50})			
	Tests			
	TBA	DNPH	RED	Total
Vaccinium arctostaphylos	1.09±0.03 [a]	1.33±0.04 [a]	0.007±0.002 [a]	0.81±0.00 [a]
Rhus coriaria	1.37±0.01 [b]	2.05±0.18 [b]	0.01±0.00 [b]	1.14±0.06 [b]
Plantago ovata	1.54±0.06 [c]	2.50±0.50 [c]	1.62±0.08 [c]	1.88±0.20 [c]
Securigera securidaca	1.91±0.11 [d]	2.73±0.23 [d]	1.89±0.12 [d]	2.18±0.08 [d]

The values were calculated as Mean±SEM.
Letters "a" to "d": show from the most effective up to the least effective inhibitor

Glycation reaction can be subdivided into three main stages. In the early stage, glucose reacts with free amino groups of albumin and generates unstable Schiff bases. After rearrangement, this base produces *keto-amine stable compound or fructosamine, known as* Amadori products [18]. In the intermediate stage and along with dehydration and oxidation reactions, Amadori products are degraded to different types of carbonyl compounds [19,2]. In the late stage, carbonyl compounds react with free amino groups of proteins, forming Advanced Glycation End Products (AGEs) together with oxidation and dehydration reactions. Glycation can cause alteration of protein folding from native globular form to amyloid structures containing beta plaques aggregation. Accumulation of these structures in different tissues can lead to serious problems [4,5]. Various medical plants are recruited in Iranian folk medicine for controlling

and treatment of diabetes. Several studies have reported the therapeutic properties of *V. arctostaphylos* [20], *P. ovata* [8], *S. securidaca* [21] and *R. coriaria* [22] for diabetes.

Table 4. Correlation coefficients of DPPH-radical scavenging with TBA, DNPH, RED and total antiglycation capacity

	DPPH scavenging (IC_{50})
	Coefficient (probability)
TBA (IC50)	0.944**
	0.000*
DNPH (IC50)	0.760**
	0.004*
RED (IC50)	0.782**
	0.003*
Total antiglycation (IC50)	0.846**
	0.001*

** There is a significant correlation between two variants (P<0.05), ** Whatever the correlation coefficient is closer to 1, more correlation is observed between properties*

Table 5. Correlation coefficients of total phenolic and flavonoids with DPPH-radical scavenging, TBA, DNPH, RED and total antiglycation capacity

	Total phenol	Total flavonoid
	Coefficient (probability)	
DPPH-scavenging (IC_{50})	-0.853**	-0.844**
	0.000*	0.001*
TBA (IC_{50})	-0.939**	-0.897**
	0.000*	0.001*
DNPH (IC_{50})	-0.896**	-0.898**
	0.000*	0.000*
RED (IC_{50})	-0.833**	-0.767**
	0.001*	0.004*
Total antiglycation (IC_{50})	-0.920**	-0.879**
	0.000*	0.000*

**P<0.05: there is a significant correlation between two variants, ** Whatever the correlation coefficient is closer to -1, higher correlation is observed between properties*

Total phenolic content represents the amount of polyphenols in plants, especially flavonoids, which are a class of secondary plant phenols [23-25]. Phenolic compounds have various physiological properties such as anti-inflammatory, anticoagulant, conservation [24] and antioxidant effects [23]. In the present study, the results indicated that the amount of phenolic and flavonoid contents and antioxidant capacity differ from highest to lowest ranging from *V. arctostaphylos*, *R. coriaria*, *P. ovata* and *S. securidaca*. Correlative analysis also indicated a significant association between the antioxidant capacity and the content of phenolic (r= -0.853, p = 0.000) and flavonoid compounds (r= -0.844, p = 0.001) in the extracts (Table 5). Several studies showed that antioxidant properties of plants are directly correlated with phenolic and flavonoid compounds [5,10].

Antiglycation analysis revealed that the extracts were capable of inhibiting glycation at three different stages in a dose-dependent manner. Interestingly, in all the experiments, the order of antiglycation property of extracts from highest to lowest was as follows: *V. arctostaphylos* > *R. coriaria* >*P. ovate* >*S. securidaca*. Average total antiglycation property as IC_{50} was quite consistent with the above pattern. In other words, *V. arctostaphylos* and *S. securidaca* revealed the maximum and minimum antiglycation activity, respectively, whether in total or distinct stages. In Sirichai Adisak wattana et al. [26] study on the *Mesona chinensis*, it was found that the extract reduces the level of fructosamine, carbonyl compounds and amyloid cross-β structure. In Rashmi S. Tupe et al. [5] study, *Terminalia bellirica* revealed the best total antiglycation effect and *Syzygium cumini* showed the poorest effect. *Azadirachta indica* was found as the most effective inhibitor of the first and second stages of glycation reaction. Besides, *S. cumini* showed the highest inhibitory effect on binding of Congo red dye to β-amyloid aggregates [5]. The results of this study demonstrated a significant relationship between total phenolic and flavonoid contents and antioxidant capacities with overall and distinct antiglycative properties of extracts at different stages. According to some findings, it can be concluded that higher amounts of total phenolic and flavonoid compounds lead to more effective antioxidant capacity, which in turn leads to increased antiglycation property of the extracts. Glycation products, specifically AGEs, mediate toxicity and tissue damages with different mechanisms [19]. At the cellular level, interaction of AGEs with cell surface RAGE (Receptor for advanced glycation end products) can lead to increased production of free radicals through stimulating the inflammatory pathways [4]. Moreover, auto-oxidation of glucose also contributes to generation of carbonyl compounds and AGEs [23,11]. Studies have found that auto-oxidation of glucose can generate ketoaldehydes

and hydrogen peroxide. The ketoaldehydes react with free amino groups of proteins and produce ketoimines, which finally produce AGEs. The hydrogen peroxides release highly reactive hydroxyl radicals during a process known as Fenton's reaction, which in turn induces oxidative degradation of proteins [23]. Therefore, it can be concluded that oxidative reactions not only induce the glycation process but also produce more free radicals and hence intensify oxidative stress [7,26]. Cory S. Harris et al. [7] demonstrated that the plant extracts rich in phenolic compounds can directly hinder the formation of AGEs in the blood. Su Chen Ho et al. [10] reported that antiglycation property of flavonoids is associated with free radical scavenging ability of these compounds. Sirichai Adisakwattana et al. [26] concluded that polyphenolic compounds may be major factors to prevent the formation of AGEs in *Mesona Chinensis* extract. Several important mechanisms have been reported to justify antiglycative activity of polyphenols, among which blocking carbonyl groups in reducing sugars and breaking the cross linking structures in AGEs can be mentioned; however, decreased production of free radicals due to antioxidant activity of these compounds is perhaps the major mechanism [26].

4. CONCLUSION

It is advisable to focus on the best options for prevention of glycation and oxidation reactions in order to reduce adverse effects in diabetes. Medicinal plants used in control of diabetes can be a valuable source for prevention of glycation and oxidative stress, and these features are associated with their chemical content, including the quantity and quality of phenolic compounds, especially flavonoids. Such results testify that besides hypoglycemic effects, anti-diabetic plants may have other valuable curative properties. More complementary studies on these plants *in vivo* may be the cornerstone for discovery of new therapeutic agents to deal with the lesions and complications caused by glycation, especially in diabetic patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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