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Inhibition of Protein Glycation by Extracts of Culinary Herbs and Spices

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ABSTRACT We tested whether polyphenolic substances in extracts of commercial culinary herbs and spices would inhibit fructose-mediated protein glycation. Extracts of 24 herbs and spices from a local supermarket were tested for the ability to inhibit glycation of albumin. Dry samples were ground and extracted with 10 volumes of 50% ethanol, and total phenolic content and ferric reducing antioxidant potential (FRAP) were measured. Aliquots were incubated in triplicate at pH 7.4 with 0.25 *M* fructose and 10 mg/mL fatty acid-free bovine albumin. Fluorescence at 370 nm/440 nm was used as an index of albumin glycation. In general, spice extracts inhibited glycation more than herb extracts, but inhibition was correlated with total phenolic content ($R^2 = 0.89$). The most potent inhibitors included extracts of cloves, ground Jamaican allspice, and cinnamon. Potent herbs tested included sage, marjoram, tarragon, and rosemary. Total phenolics were highly correlated with FRAP values ($R^2 = 0.93$). The concentration of phenolics that inhibited glycation by 50% was typically 4–12 μg/mL. Relative to total phenolic concentration, extracts of powdered ginger and bay leaf were less effective than expected, and black pepper was more effective. Prevention of protein glycation is an example of the antidiabetic potential for bioactive compounds in culinary herbs and spices.

KEY WORDS: • ***dietary*** • ***flavonoids*** • ***fructose*** • ***herbs*** • ***polyphenolics*** • ***protein glycation*** • ***spices***

INTRODUCTION

POLYPHENOLIC COMPOUNDS from edible plants are the main antioxidants in the human diet.[1–4] There is growing interest in the antioxidant and anti-inflammatory capacities of these compounds relative to prevention or treatment of chronic diseases that involve inflammation.[5] For example, dietary phenolics have been related to reduced risk of cancer,[6] cardiovascular disease,[7,8] neurodegenerative disease,[9] diabetes,[10,11] and osteoporosis.[12,13] In this regard, several herbs and spices are among the top 50 dietary sources of polyphenolics.[1,2] Not only do culinary herbs and spices provide high concentrations of bioactive compounds, they also tend to provide few calories. Low food energy content is an advantage in type 2 diabetes, which is often associated with abdominal obesity.

One of the best examples of the biological activities of spice constituents is that cinnamon and cinnamon extracts can lower blood glucose after meals in rodents[14,15] and humans.[16–19] Evidence suggests that compounds in cinnamon and probably other culinary spices and herbs may improve symptoms of diabetes in several ways. For example, they may delay gastic emptying,[20] improve insulin sensitivity,[21,22] or enhance antioxidant defenses.[23–25]

One of the consequences of elevated blood glucose is an increase in nonenzymatic glycation of proteins such as hemoglobin A1c and serum albumin.[26,27] Plant extracts have been shown to inhibit protein glycation.[7–10] Because many herbs and spices contain high concentrations of polyphenolics,[11,12] it is plausible that extracts of these substances may block the formation of advanced glycation end-products (AGE) compounds. Therefore, the present study tested whether extracts of culinary herbs and spices would inhibit fructose-mediated glycation of albumin. Because our intention was to examine herbs and spices that are widely available to the public, we limited our survey to products from one major manufacturer that were available at a major retail store.

MATERIALS AND METHODS

Chemicals and plant materials

Bovine serum albumin (Fraction V, essentially fatty acid free), D-(-)fructose, Chelex® 100 (sodium form) (Bio-Rad, Hercules, CA), Folin-Ciocalteu reagent, and 2,4,6-tri(2-pyridyl)-*s*-triazine were purchased from Sigma Chemical

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Co. (St. Louis, MO). Dried McCormick's brand (Hunt Valley, MD) herbs and spices were purchased at a major supermarket in Athens, GA. The following were "gourmet" varieties packaged in glass bottles: Jamaican allspice, apple pie spice, basil, cardamom, coriander, celery seed, curry powder, garam masala, mint, rosemary, tarragon, and turmeric. Product selection was based on convenience rather than being part of a screening strategy.

The botanical names of individual dried spices (less than 16% water as packaged) are listed in Table 1. Dried spice mixtures included apple pie spice (proprietary mixture of cinnamon bark, *C. burmannii*; nutmeg seed, *M. fragans*, and Jamaican allspice fruit, *P. dioica*), pumpkin pie spice (same ingredients as apple pie spice but including ginger root, *Z. officinale*), chili powder (chili pepper fruit, *Capsicum annuum*; cumin seed, *Cuminum cyminum*; and oregano leaf, *O. vulgare*), curry powder (coriander fruit, *Coriandum sativum*; fenugreek seeds, *Trigonella foenum-graecum*; turmeric root, *C. longa*; cumin, black pepper fruit, *P. nigrum*; bay leaves, *L. nobilis*; celery seed, *Apium graveolens*; nutmeg cloves, *S. aromaticum*; onion bulb, *Allium cepa*; red pepper fruit, *C. annuum*; and ginger), Italian seasoning (marjoram leaves, *O. hortensis*; thyme leaves, *T. vulgaris*; rosemary leaves, *R. officinalis*; savory leaves, *Satureja hortensis*; sage leaves, *S. officinalis*; oregano and basil leaves, *O. basilicum*), poultry seasoning (thyme, sage, marjoram, rosemary, black pepper, and nutmeg), and garam masala (coriander; black pepper; cumin; cardamom fruit, *Elettaria cardamomum*; and cinnamon). Parsley, an herb, is predominantly dried leaves.

Preparation of extracts

Dry culinary herbs and spices were ground into a fine powder and were extracted with 50% ethanol at a ratio of 10 mL/g with stirring at room temperature for 2 hours. The extracts were centrifuged at 430 *g* for 10 minutes at 10°C to remove precipitate. In this study, 24 commercially available herb and spice samples were tested for antioxidant activity and total phenolic content. The samples are listed in Table 1.

Total phenolic content

Total phenolic content was estimated using the Folin-Ciocalteu reagent as described by Singleton and Rossi.[28] Results were quantified using a Beckman (Palo Alto, CA) DU 600 series spectrophotometer at a wavelength of 760 nm with a gallic acid standard. Results were expressed as mg of gallic acid equivalents (GAE)/g of dry sample. All experiments were performed in triplicate.

Table 1. Antioxidant Activity and Total Phenolic Content of Commercial Herb and Spice Extracts Relative to Inhibition of Albumin Glycation *In Vitro*

Herb or spice	*Botanical name*	*Phenolic content (mg of GAE/g)*	*FRAP value (mmol/100 g)*	*Extract dilution that inhibits glycation 50%*[a]
Cloves, ground	*Syzygium aromaticum*	296 ± 3.7	271 ± 6.9	3,000
Cinnamon, ground	*Cinnamomum burmannii*	183 ± 11.5	137 ± 3.1	1,500
Ground Jamaican allspice	*Pimenta dioica*	122 ± 7.0	134 ± 0.6	1,500
Apple pie spice	Mixture[b]	116 ± 2.8	145 ± 2.1	1,500
Oregano, ground	*Origanum vulgare*	82.3 ± 0.9	84.0 ± 0.7	750
Pumpkin pie spice	Mixture[b]	69.7 ± 7.0	81.0 ± 0.3	750
Marjoram	*Origanium hortensis*	69.0 ± 2.1	66.0 ± 0.9	750
Sage	*Salvia officinalis*	59.8 ± 3.0	62.8 ± 3.1	600
Thyme	*Thymus vulgaris*	52.0 ± 2.0	59.1 ± 0.6	500
Gourmet Italian	Mixture[b]	51.9 ± 1.2	47.9 ± 0.3	500
Tarragon	*Artemisia dracunculus*	51.0 ± 2.7	46.1 ± 0.9	500
Mint	*Mentha spicata*	50.9 ± 2.3	60.9 ± 0.6	428
Rosemary	*Rosmarinus officinalis*	48.2 ± 1.0	47.9 ± 2.7	500
Italian	Mixture[b]	41.7 ± 1.4	51.9 ± 1.6	375
Poultry seasoning	Mixture[b]	37.6 ± 6.5	39.0 ± 0.3	300
Bay leaf	*Laurus nobilis*	36.3 ± 1.1	14.6 ± 0.58	120
Garam masala	Mixture[b]	34.8 ± 1.4	31.9 ± 1.1	750
Turmeric	*Curcuma longa*	25.9 ± 1.6	10.2 ± 0.06	500
Curry powder	Mixture[b]	21.6 ± 0.8	19.3 ± 0.8	265
Chili powder	Mixture[b]	19.5 ± 1.2	11.7 ± 0.2	300
Basil	*Ocimum basilicum*	18.0 ± 0.5	18.9 ± 0.9	213
Nutmet	*Myristica fragans*	17.6 ± 0.9	6.8 ± 0.2	229
Ginger	*Zingiber officinale*	17.7 ± 1.7	19.5 ± 0.3	37
Parsley	*Petroselinum crispum*	15.5 ± 0.7	4.31 ± 0.5	100
Black pepper	*Piper nigrum*	5.1 ± 0.3	4.7 ± 0.2	750

[a]Assays were conducted in 3-mL volumes. Dilution = 3,000/(μL of extract required to give 50% inhibition).
[b]The names and parts of plants used in herb and spice mixtures are described in Materials and Methods.

Ferric reducing antioxidant potential (FRAP)

FRAP values were determined using a method modified from that of Benzie and Strain.[29] Freshly prepared FRAP reagent [25 mL of acetate buffer, 2.5 mL of 2,4,6-tri(2-pyridyl)-*s*-triazine solution, and 2.5 mL of ferric chloride solution] was used to estimate the antioxidant potentials of the extracts. Ferrous sulfate was used as a reference standard. The assay was read using a Beckman DU series spectrophotometer at a wavelength of 593 nm with results expressed as mmol of ferrous sulfate/100 g of sample. All experiments were performed in triplicate.

Protein glycation

Albumin glycation was determined using the method of McPherson *et al*.[30] as follows: fatty acid-free bovine serum albumin (10 mg/mL) was incubated with 250 m*M* D-fructose in 200 m*M* potassium phosphate buffer (pH 7.4; 0.02% sodium azide) for 72 hours. During this time, samples were kept in a 37°C incubator gassed with air containing 5% CO_2. To reduce but not eliminate metal ions, the phosphate buffer was treated with a small amount of Chelex resin, and the resin was removed prior to adding the fructose. Results were read using a Perkin-Elmer (Norwalk, CT) model LS 55 luminescence spectrometer with an excitation/emission wavelength pair of 370/440 nm. The assay was routinely conducted using 5–30 μL of herb or spice extract in a 3-mL assay. Addition of ethanol in volumes equal to the samples had no effect. Complete inhibition of glycation was assumed to occur when fluorescence was reduced to that of albumin in the absence of fructose. All experiments were performed in triplicate, and all extracts were tested at least twice at a minimum of five dilutions.

Statistical analysis

Results are expressed as mean ± SD values. Inhibition of glycation by extracts of herbs and spices is expressed as a percentage of the difference between control samples containing albumin plus fructose versus those with albumin without fructose. Simple linear regression equations were used to determine a dose–response of standard solutions and correlation coefficients (R^2) for total phenolic and FRAP measures as well as to quantify a relationship between these measures and the inhibition of albumin glycation. Statistical tests were performed using Microsoft (Redmond, WA) Excel software.

RESULTS

Assay for fructose-mediated albumin glycation

When bovine serum albumin is incubated in the presence of 0.25 *M* fructose for 3 days in the presence of oxygen as described in Materials and Methods, the solution browns and becomes fluorescent. This reaction gives a maximum fluorescence that is an index of protein glycation plus autooxidation that does not depend on the presence of sugar. When incubated in the same mixture without fructose, albumin fluoresces at a lower level (line shown in Fig. 1). The difference between maximum fluorescence due to glycation and that due to autooxidation in the absence of fructose is an index of albumin glycation. Most herb and spice extracts inhibited fructose-mediated albumin glycation (Fig. 1 and Table 1). The concentrations of spice phenolics that inhibited glycation by 50% (50% inhibitory concentration [IC_{50}] values) were calculated using the difference between fructose-mediated glycation and albumin autooxidation as 100%. All extracts were prepared with 50% ethanol in water because this solution gave a higher value for total phenolics than equal volumes of water or methanol (data not shown).

Figure 1 shows a typical dose–response curve for effects of herb and spice polyphenolics on fructose-mediated glycation. Extracts included cloves, cinnamon, marjoram, and sage. Note that at high concentrations, polyphenolics inhibited the fluorescence contributed by albumin autooxidation.

Effects of herb and spice extracts on albumin glycation

Total extractable polyphenolics and FRAP measures for 24 commercial herbs and spices are shown in Table 1 as mean ± SD values. The dilution of extract giving 50% inhibition of albumin glycation is also shown in Table 1. The results are arranged in descending concentration of total phenolics (mg of GAE/g of sample) in the original extracts. Extracts of ground cloves, ground Jamaican allspice, and cinnamon inhibited glycation at the lowest dilutions. A dilution factor of 3,000 indicates that 50% inhibition of glycation oc-

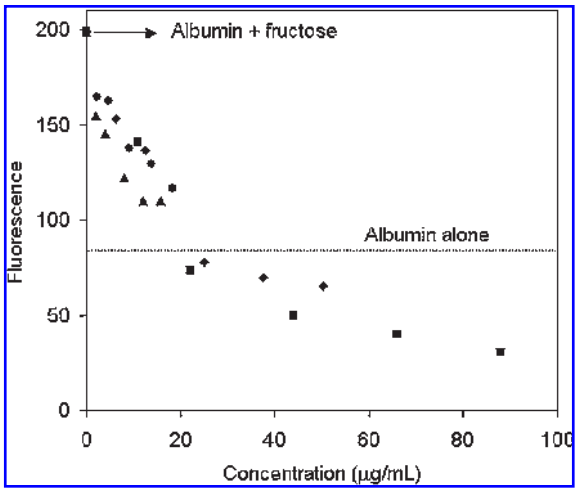

FIG. 1. Characteristics of the glycation assay. Albumin plus 0.25 *M* fructose gives maximum fluorescence (arrow); however, albumin without fructose fluoresces owing to autooxidation (dashed line). The difference between these two values was taken as 100% inhibition of glycation. Spice extracts inhibit fructose-mediated glycation and may also reduce autooxidation. Extracts include cloves (squares), cinnamon (rhombi), marjoram (circles), and sage (triangles).

curred at the equivalent of 1 μL of the original 10 mL extract in the 3-mL assay volume. The correlation between total phenolic content (mg of GAE/g of dry sample) and the dilution giving 50% inhibition was $R^2 = 0.89$. The same correlation coefficient (0.89) was found for FRAP values and half-maximal inhibition.

Concentrations of phenolics that inhibited albumin glycation by 50% (IC_{50} values) were calculated. For most samples, the IC_{50} was between 4 and 12 μg of phenolics/mL, as shown in the scatter plot in Figure 2. Inhibition by extracts of black pepper occurred at phenolic values lower than the typical range of inhibition. Bay leaf and powdered ginger extracts inhibited glycation only at higher concentrations. The most common Western seasoning, table salt, is neither an herb nor a spice. It contains no polyphenolics, and solutions containing 1 g/10 mL did not affect protein glycation (data not shown).

Figure 3 shows the relationship between total phenolic content in the extracts and 50% inhibition of albumin glycation ($R^2 = 0.89$). The correlation of FRAP values with inhibition of glycation was almost identical. The correlation coefficient between total phenolics and FRAP values was 0.93 ($P < .001$).

DISCUSSION

The present study shows that 50% ethanolic extracts of herbs and spices, which are among the major 50 sources of dietary polyphenolics,[2] inhibit fructose-mediated albumin glycation *in vitro*. In contrast, no effect was observed with table salt, the most widely used seasoning in the West. This is interesting because of the importance of protein glycation in the pathogenesis of diabetes[31] and the possibility that dietary antioxidants have a role in preventing or managing some disease complications.[21,32] Moreover, total phenolic content of herbs and spices and their antioxidant potential are both predictive of the samples' ability to inhibit protein

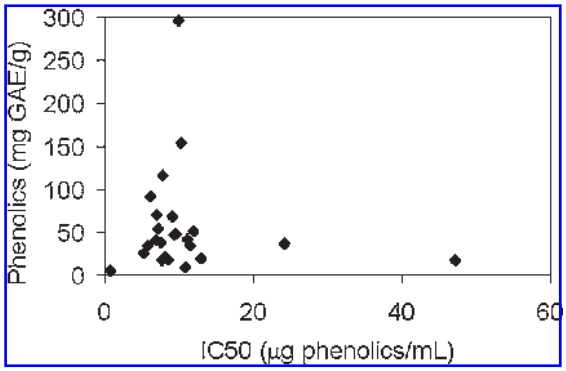

FIG. 2. Scatter plot of phenolic concentration in herb and spice extracts versus IC_{50} (μg of phenolics/mL at half-maximal inhibition). Half-maximal inhibition clustered in the range of 4–12 μg/mL for all but three samples. From the left, the outlying extracts are black pepper, bay leaf, and powdered ginger, respectively.

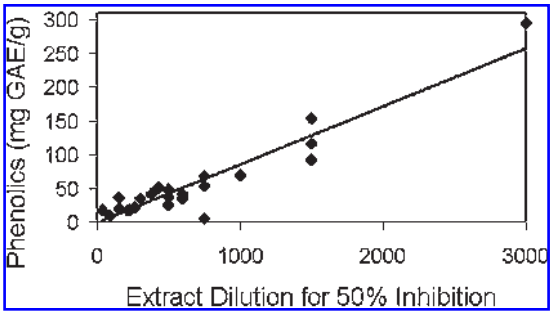

FIG. 3. Relationship of total phenolics to inhibition of albumin glycation ($R^2 = 0.89$). Samples are listed in Table 1.

glycation. It is known that flavonoids and other constituents in plants inhibit protein glycation.[33] However, the top dietary sources of these compounds have not been screened systematically for potential effects on this process. The results should be considered as representative, inasmuch as the quantities of phenolics observed depend upon the solvent used, as well as cultivars and conditions for plant growing, harvesting, drying, and storage.

In culinary usage, herbs are most commonly seasonings derived from leaves of plants (see Materials and Methods for a list with this information for the present samples). Spices, in contrast, are obtained from seeds, berries or fruit, bark, or roots. Some spices possess a higher total phenolic content than most herbs, but glycation is reduced to similar extents by both kinds of seasoning when the concentration of total phenolics is comparable. This is interesting because Maillard reaction products are formed during cooking and are absorbed after meals[34–36] as well as being formed in blood and tissues by glucose or fructose. Both glucose and fructose form glycation (AGE) products, but fructose is more reactive.[30,37] For example, postprandial fructose has been linked to retinopathy in diabetics,[38] and fructose has been implicated in symptoms of metabolic syndrome.[39] Fructose consumption has increased recently owing to greater consumption of high-fructose corn syrup and is one factor contributing to obesity and inflammation.[40,41] Therefore, herbs and spices have the potential to modify rates of protein glycation when incorporated into food during cooking and in the tissues after consumption of meals or beverages.

Protein glycation occurs when the carbonyl group of a sugar reacts with an amino group of a protein to form a Schiff base, which rearranges to form a more stable Amadori product. Post-Amadori reactions are catalyzed by transition metals and create reactive oxygen species. As shown in Figure 1, the development of maximum fluorescence in the model system involves both fructose-mediated glycation and protein oxidation. Glycation in the present system depends on generation of reactive oxygen species by trace amounts of redox-active metal ions, and the test is done after 3 days of incubation in an air atmosphere with 5% CO_2. Owing to the requirement for trace amounts of metal ions, chelating

agents totally block both processes (oxidation and glycation) if included at sufficiently high concentrations.[37] Likewise, antioxidants and scavengers of hydroxyl radicals block both processes.[37] Many dietary flavonoids such as quercetin and naringenin are antioxidants and chelating agents.[42–45] Non-flavonoid compounds that block glycation include pyridoxamine[46,47] and aminoguanidine.[48,49]

Extracts of cloves, ground Jamaican allspice, and cinnamon were the most effective inhibitors of glycation. Major phenolic constituents of cloves include eugenol, caryophyllin, vanillin, and eugenin. Allspice contains eugenol, cineole, phellandrene, and caryophyllene. Cinnamon contains cinnamaldehyde, furfural, cuminaldehyde, eugenol, and caryophyllene.[50,51] Due to the complexity of the phenolic composition of each extract, it would be a large undertaking to compare each chemical compound. Because foods are complex mixtures, it was not our intention to study isolated constituents, which is a drug-based approach. Other studies have shown that individual flavonoids inhibit glycation by 50% with IC_{50} values in the range of 10–100 m*M*. The values found here are comparable, assuming IC_{50} values of 4–12 mg/mL and typical flavonoid molecular weights.

The possibility of interactive effects is supported by the fact that many of the herb and spice blends such as apple pie spice, pumpkin pie spice, gourmet Italian seasoning, poultry seasoning, and Italian seasoning were effective inhibitors. In contrast, some powdered samples such as ginger (Table 1) and garlic (data not shown) had low activity. This could be due to loss of lipophilic or hydrophilic antioxidants[52] during commercial or laboratory processing. It is not known whether samples of fresh ginger or garlic would be more active. Higher activity than expected, such as with black pepper, could be explained if the active compound were not a polyphenolic substance. Black pepper[53] and bay leaf[54] contain pinene and terpenoids, which are not polyphenolic but may have other activities such as being free radical scavengers.

Constituents of culinary herbs and spices may act through various mechanisms to affect disease. The present report focuses only on direct inhibition by polyphenolic compounds of processes involved in nonenzymatic protein glycation. Although cinnamon was one of the most potent extracts in this respect, its constituents clearly act at multiple levels. Cinnamon significantly reduces serum glucose, triglycerides, low-density lipoprotein-cholesterol, and total cholesterol in type 2 diabetics at dietary intakes of 1, 3, and 6 g/day.[17] Aqueous cinnamon extract and cinnamon polyphenols were found to increase the anti-inflammatory protein tristetraprolin and glucose transporter-4, and cinnamon polyphenols increased the amount of insulin receptor-β in mouse 3T3-L1 adipocytes.[55] Anderson *et al*.[56] have identified a procyanidin oligomer from cinnamon as an active factor in regulation of postprandial blood glucose. These results show the numerous metabolic pathways that may be influenced by the chemical components of herbs and spices.

This survey of common culinary herbs and spices suggests that important chemoprotection may be added to the diet through products that have a long history of use and are generally recognized as safe. The bioactive constituents of herbs and spices almost certainly make foods more medicinal and anti-inflammatory. Future studies will show whether it is true that every kitchen may provide pharmacologically active agents that help maintain health.

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