In Vitro Absorption of Dietary *trans*-Resveratrol from Boiled and Roasted Peanuts in Caco-2 Cells

Yvonne Chukwumah,[†] Lloyd Walker,*,[†] Bernhard Vogler,[‡] and Martha Verghese[†]

[†]Department of Food and Animal Sciences, Alabama A&M University, P.O. Box 1628, Normal, Alabama 35762, United States
[‡]Department of Chemistry, University of Alabama in Huntsville, 301 Sparkman Drive, Huntsville, Alabama 35899, United States

ABSTRACT: Previous studies on the transport and absorption of resveratrol (3,5,4-*O*-trihydroxystilbene) were done using the pure compound. In this study, the absorption of resveratrol in digested peanut micellar from boiled and roasted peanuts was investigated using a human intestinal Caco-2 cell monolayer. The amount transported and rate of transport of both resveratrol glycosides and its hydrolytic product were quantified by a reverse-phase high-performance liquid chromatography method with mass spectrometric detection. Four peaks were identified in the digested peanut micellar of both boiled and roasted peanuts: two resveratrol glycosides, one resveratrol diglycoside, and possibly an acylated resveratrol glycoside. Resveratrol from roasted peanut micellar had a higher transport rate than those from the boiled peanut. This implies that resveratrol from roasted peanut is better absorbed than from boiled peanut. Also, the rate of transport and amount of resveratrol transported were higher for the hydrolytic product than the nonhydrolyzed glycosides. This has strong implications for in vivo absorption as the enzymatic activity of gut microflora could enhance the bioavailability of β-glycosides of dietary polyphenols.

KEYWORDS: In vitro absorption, *trans*-resveratrol, peanuts, Caco-2 cells

■ INTRODUCTION

Resveratrol (3,5,4-*O*-trihydroxystilbene) is a naturally occurring phytoalexin found in peanuts. It is produced in response to biotic stress factors such as fungal infection and oxidative stress generated by ultraviolet (UV) irradiation. In addition to its protective role in plants, resveratrol has been shown to have chemopreventive properties that are also beneficial to animals. They possess several biological activities such as antioxidative capacity, anti-inflammatory, antitumorigenic, and antiplatelet aggregation activities.[1] These bioactive compounds have to be present in amounts required to elicit a biological response. Thus, just as nutrients have to be absorbed in the gut and transported to the cells in adequate concentrations required by the cell, bioactive compounds also need to be absorbed in sufficient quantities necessary to elicit a favorable response. It is well-known that thermal processing of foods can result in either the release or the degradation of bioactive compounds. This can affect the bioaccessibility and bioavailability of such compounds. In addition to processing effects, when foods are consumed, they undergo enzymatic hydrolysis by gastrointestinal enzymes. Resulting compounds may be absorbed passively or undergo further modification by enzymes/transport molecules in the intestinal epithelial for active transport into plasma. Thus, chemical modification of compounds by digestive enzyme can affect their bioavailability by altering their absorption properties.[2] Plant polyphenols naturally exist as glycosides, and although subjected to enzymatic hydrolysis during digestion, polyphenols such as resveratrol-3-β-*O*-glycoside (piceid) has a β-*O*-glycosidic bond that cannot be readily hydrolyzed. This is because humans do not produce β-glycosidase enzymes. However, our intestinal microflora have the ability to produce these enzymes and can therefore hydrolyze such compounds.[2] This makes it possible for further absorption of phenolic aglycones, thereby increasing their bioavailability.

The phytochemical composition of peanut has been extensively studied,[3−6] and the effects of various processing methods on their stability have been reported.[7−10] Although peanuts are a dietary source of resveratrol, an anticarcinogenic and antioxidative polyphenol, it is important that we evaluate its absorption to critically assess its potential for biological activity. A previous study on resveratrol transport using human intestinal Caco-2 cells made use of pure compounds.[11] Although results from this study provide an insight to the absorption of resveratrol, this cannot be extrapolated to absorption from a dietary source. It is important that the effects of processing, food matrix, and gastric digestion on the chemical composition and/or modification of resveratrol from a dietary source be considered in evaluating its bioavailability. Thus, the objectives of this study are to evaluate the transport of resveratrol from a dietary source using human Caco-2 cell monolayer as an intestinal epithelial model and to determine the effect of processing and in vitro digestion on its absorption.

■ MATERIALS AND METHODS

Peanuts (in-shell raw and roasted) were purchased from Sunland Peanut Co. (New Mexico). The raw peanuts were boiled in shell and freeze-dried. *trans*-Resveratrol, porcine bile extract, pepsin (from porcine gastric mucosa), pancreatin (from porcine pancreas), Lucifer Yellow (LY) CH dipotassium salt, and fetal bovine serum were purchased from Sigma Chemical Co. (St. Louis, MO). Cellulase (38900 CMC units/g) from *Aspergillus niger* was purchased from Spectrum (New Brunswick, NJ). Dulbecco's modified Eagle's medium (DMEM) and Hank's balanced salt
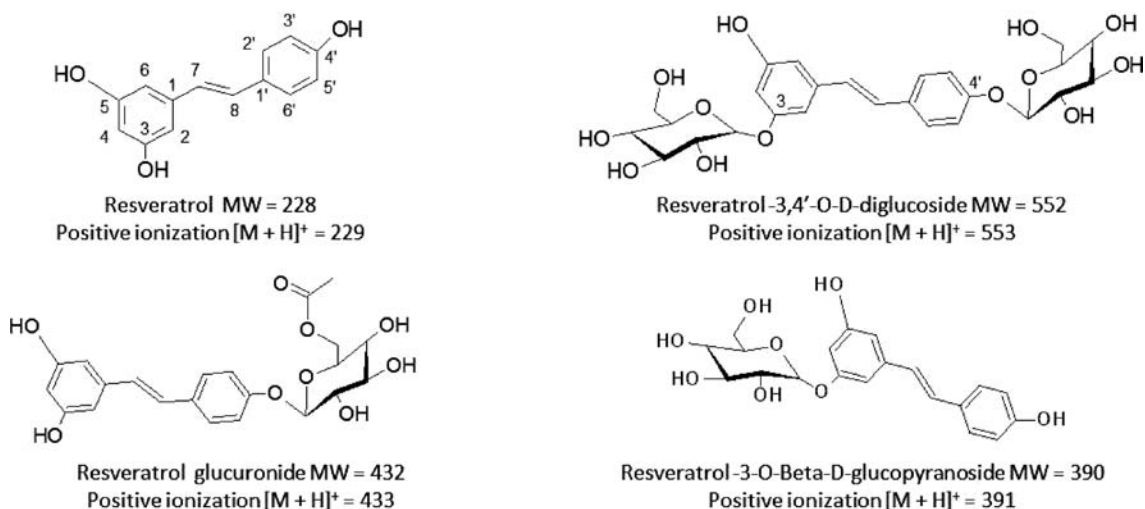
Figure 1. Chemical structure of resveratrol, resveratrol-O-glycosides, and acylation product resveratrol-O-glucuronide.
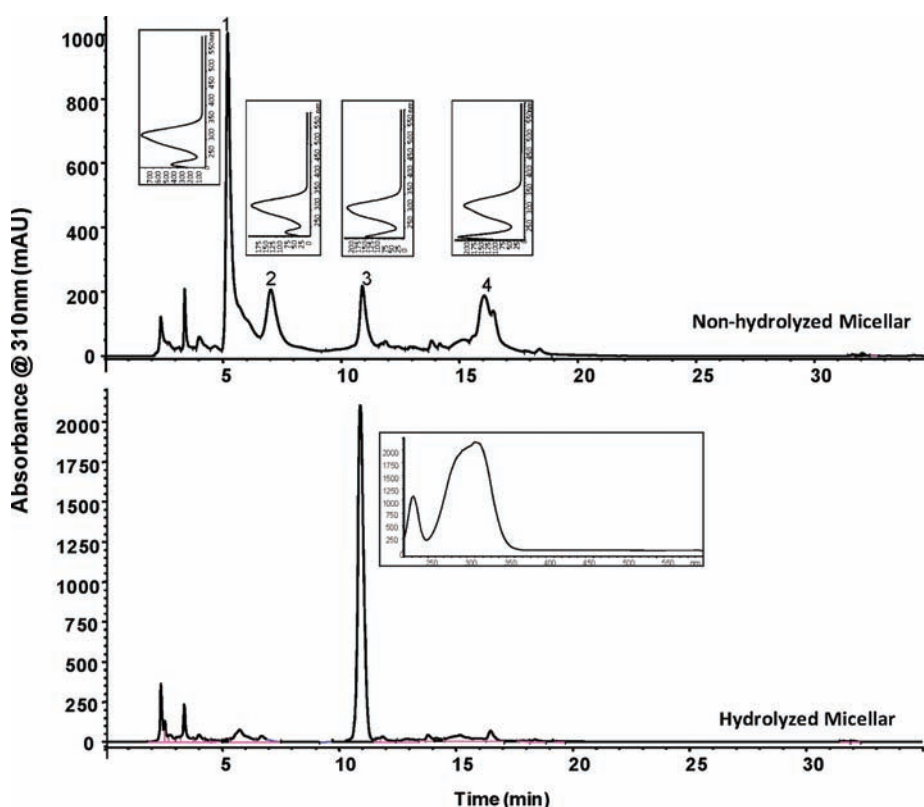

Figure 2. HPLC-DAD chromatogram of nonhydrolyzed and hydrolyzed micellar of boiled peanuts showing peaks with similar UV spectra having absorption maxima at 306 nm.

solution (HBSS) were purchased from Fisher Scientific, and human adenocarcinoma cells (Caco-2), purchased from American Type Culture Collection (ATCC, Rockville, MD), were obtained from Dr. J. Boateng (Alabama A&M University, Nutritional Biochemistry Lab).

In Vitro Digestion of Peanuts. Milled peanuts (42 g) were weighed into 250 mL flasks, and 70 mL of saline buffer (140 mM NaCl, 5 mM KCl, and 150 μM BHT), pH 2, was added and mixed. Pepsin-HCl was added at a rate of 0.5 g of pepsin per 100 g of peanut to the mixture and incubated in a shaking water bath at 37 °C for 2 h to achieve gastric digestion of the peanuts. The pH was adjusted to 6.9 with 1 M NaHCO$_3$

prior to the addition of 25 mL of pancreatin—bile solution containing 2 g/L pancreatin and 12 g/L porcine bile extract in 0.1 M NaHCO$_3$ to mimic in vivo pancreatic digestion. The digest was further incubated at 37 °C for 2 h in a shaking water bath. The resulting digest was centrifuged at 12000g for 5 min, and the supernatant, referred from here on as the micellar, was collected.

Enzymatic Hydrolysis of Micellar. The aqueous micellar from peanut digest was subjected to enzymatic hydrolysis using cellulase (a β-glucosidase) from A. niger. The cellulase enzyme solution (0.02 g/mL) was prepared using 0.1 M sodium acetate buffer (pH 4). Three milliliters
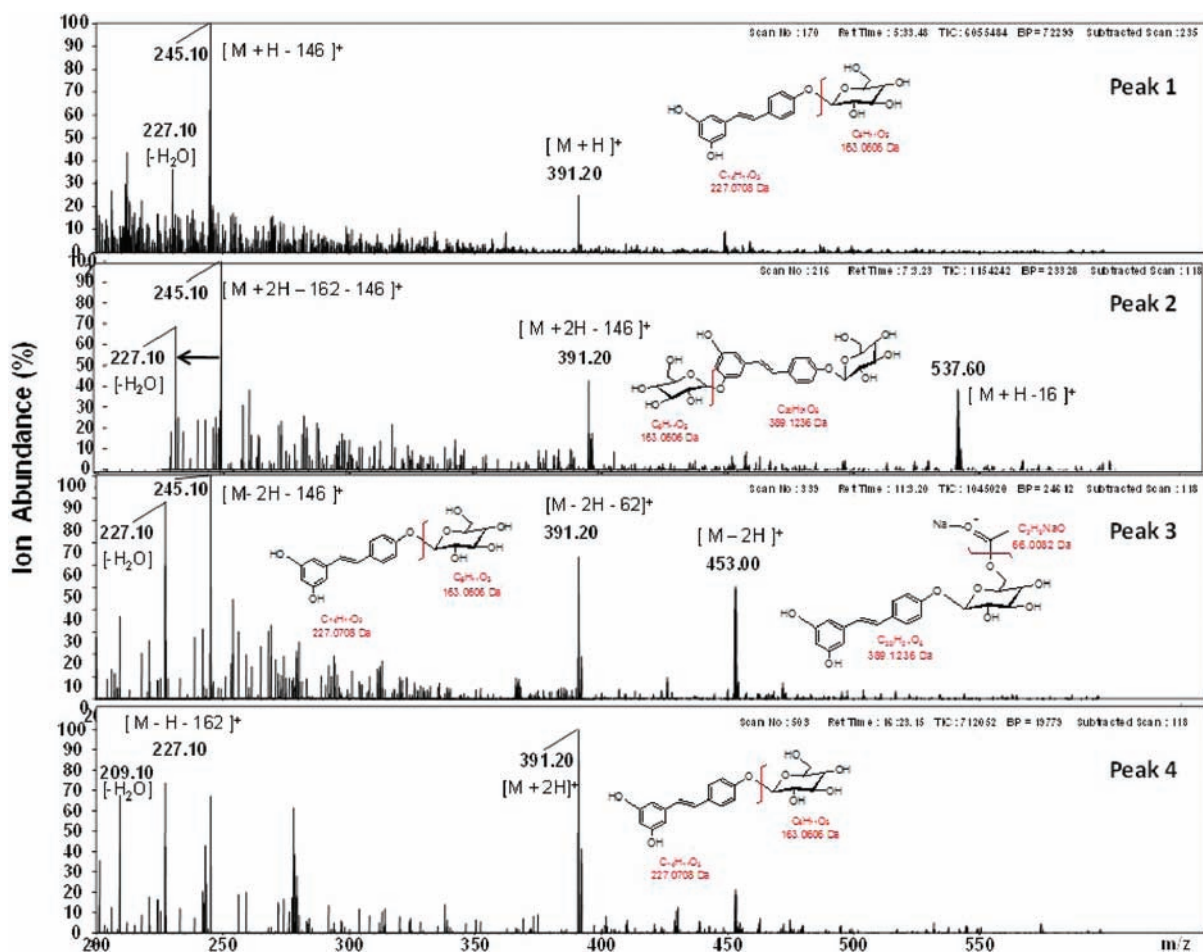
Figure 3. HPLC-APCI/MS spectra of major peaks in nonhydrolyzed and hydrolyzed micellar of boiled peanuts showing putative compounds based on m/z of molecular and product ions. Peaks 1 and 4, resveratrol-*O*-glucoside; peak 2, resveratrol-*O*-diglucoside; and peak 3, resveratrol-*O*-glucuronide.

(3 mL) of peanut micellar was incubated with 0.5 mL of enzyme solution for 3 h. The hydrolyzed micellar was used for transport assay.

Cell Culture. Caco-2 human adenocarcinoma cells at passage 20 were subcultured to passage 28 and seeded in 24-well inserts (0.33 cm² growth area, 0.4 μm pore size) at a seeding density of 5×10^5 cells/cm². The culture was maintained in DMEM with 10% fetal bovine serum at 37 °C and 5% CO for 2 weeks (14 days) and used for transport assay. Monolayer formation and integrity were determined by transepithelial electrical resistance (TEER) measurements using the EVOM2 m by World Precision Instrument (WPI, Sarasota, FL). The average TEER value for the 24-well plate was 806 ± 94 Ω cm². Insert wells with TEER values >500 Ω cm² were used for the assay.

In Vitro Transport of Resveratrol. Caco-2 cells at passage 28 were used 14 days postseeding in a 24-well collagen-coated transwell membrane. The inserts were washed with HBSS by incubating them at 37 °C for 30 min in a CO₂ incubator. Transport was initiated by replacing the HBSS in the apical chamber with 300 μL of micellar (hydrolyzed and nonhydrolyzed) diluted with HBSS, pH 6.8, while the basolateral chambers were replaced with 1 mL of fresh HBSS, pH 7.4. The plate was incubated at 37 °C in a CO₂ (5%) incubator for 4 h, as the previous assay with 2 h of incubation time showed no evidence of transport. After incubation, the basolateral solutions were collected and analyzed by high-performance liquid chromatography—diode array detection/mass spectrometry (HPLC-DAD/MS). The rate of transport was calculated as the total amount (nmol) transported to the basolateral chamber per min, while percent transport (% T) was calculated as the

ratio of the basolateral buffer concentration to the apical micellar concentration multiplied by 100.

Lucifer Yellow Diffusion and Permeability Assay. Naïve Caco-2 cells at passage 28 were used 14 days postseeding to test the permeability of the cell monolayers. Lucifer yellow solution (100 μM) was prepared in transport buffer (HBSS) and used for the permeability assay of the differentiated monolayer. For the apical to basal (A—B) transport, 300 μL of LY solution was added to the apical chamber, while for the basal to apical (B—A) diffusion, 1000 μL of LY solution was added to the basolateral chamber. The inserts were incubated at 37 °C in a CO₂ (5%) incubator for 4 h. For A—B transport, the basolateral solution was collected, and for B—A transport, the apical solution was collected for the fluorescence assay. The fluorescence was measured at an excitation wavelength of 485 nm and an emission wavelength of 528 nm using a Biotek microplate reader (Biotek Instruments Inc., Winooski, VT). Paracellular flux (%), apparent permeability (P_{app}), and efflux ratio were calculated to confirm the monolayer intergrity and membrane transport. A paracellular flux below 0.7% and an efflux ratio >3 (indicating transport) are acceptable.

HPLC-DAD/MS Analysis. Filtered extracts (50 μL) were analyzed on an Agilent 1100 Series Liquid Chromatography (LC) system (Agilent Technologies, Foster City, CA) equipped with a DAD with a UV range of 200—600 nm and an Agilent 1100 Series (LC/MSD) quadrupole mass spectrometer. Separation of the compounds was performed on a Zorbax SB C18 reverse-phase 250 mm × 4.6 mm column (Agilent Technologies Inc., Newcastle, DE) preceded by a

Table 1. Average TEER Values, LY Permeability, and Efflux Ratio of the Caco-2 Epithelial Monolayer[a]

TEER (Ω cm^2)	A–B direction		B–A direction		efflux ratio
	flux (%)	P_{app} ($\times 10^{-4}$ cm/s)	flux (%)	P_{app} ($\times 10^{-4}$ cm/s)	
806 ± 94	0.49 ± 0.05	0.31 ± 0.00	0.64 ± 0.08	1.35 ± 0.00	4.38 ± 0.78

[a] Values are means ± SDs.
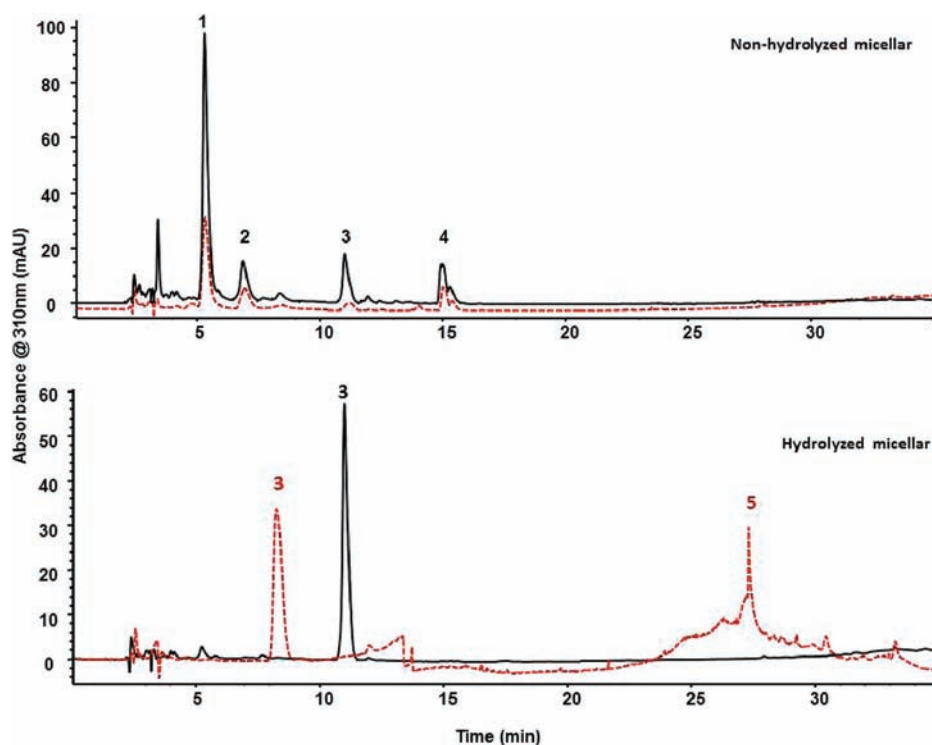
Figure 4. HPLC-DAD chromatograms of resveratrol composition of basolateral transport buffers for nonhydrolyzed and hydrolyzed micellar of boiled (- - -) and roasted (—) peanuts.

7.5 mm × 4.6 mm C18 guard column (Agilent Technologies Inc.). A gradient elution profile consisting of two solvents, 0.1% formic acid in water (A) and acetonitrile:water:acetic acid (80:19:1 v/v/v) (B), was used at a constant flow rate of 1 mL/min. The elution profile was as follows: 0–10 min, 78% A; 10–30 min, 0% A; and 30–35 min, 0%. The UV spectral trace of the analytes was acquired within the range of 200–600 nm in 2 nm, and spectral data for resveratrol were acquired at 310 nm.

The LC eluent was directly transferred to the MS interface without stream splitting. Mass spectra were acquired with an APCI source (positive ionization) under the following APCI conditions: nitrogen nebulizing pressure of 60 psi (4.2 bar), a vaporization temperature of 350 °C, a nitrogen drying gas temperature of 325 °C at 10 L/min, a capillary voltage of 4 kV, and a corona current of 5.0 μA for PI. The ion abundance was acquired in scan (50–600 amu) at 1.90 s per cycle.

Statistical Analysis. Data analyses (analysis of variance) were done using SAS version 9.1 (2005). Mean separation was done using Tukey's studentized test at $p \leq 0.05$.

■ RESULTS AND DISCUSSION

Enzymatic Hydrolysis of Peanut Micellar. The effect of enzymatic hydrolysis on the phenolic composition of boiled peanut micellar (similar to that of roast peanut micellar) is shown in Figure 2. Polyphenols naturally occur in plants in the glycosidic

form (Figure 1). Resveratrol β-3-O-glycoside is the most widely reported, and previous studies on the intestinal absorption of dietary polyphenols have shown that the glycosides are poorly absorbed and would require the removal of attached sugar units to facilitate their transport across the GI membrane. The sugar unit in resveratrol monoglycosides is attached via a β-3-O-glycosidic linkage and thus requires a β-glycosidase, found in intestinal microflora, for cleavage. Hydrolysis of micellar from boiled and roasted peanuts using cellulase, a β-glucosidase, resulted in the reduction of number of resveratrol peaks in the nonhydrolyzed micellar, which had four peaks to one main peak (Figure 2). The loss of peaks 1, 2, and 4 resulted in a corresponding increase in peak 3. Given the ambiguity of the UV spectra of resveratrol aglycone and glycosides (Figure 2), distinguishing the various forms of these compounds as observed in the micellar after GI digestion is an analytical challenge. MS spectral analysis of the peaks 1, 3, and 4 and comparison of their fragmentation patterns with mass spectra for piceid, a stilbenoid glucoside, from a mass databank[12] confirmed the compounds to be glycosides of resveratrol with the presence of molecular ion having a mass-to-charge ratio (m/z) of 391 amu and product ions having m/z of 245 and 227 amu (Figure 3). The product ions were due to mass losses of 146 or 162 and 18 amu, which are characteristic mass losses for sugar units and water, respectively. Peak 2, however, showed an
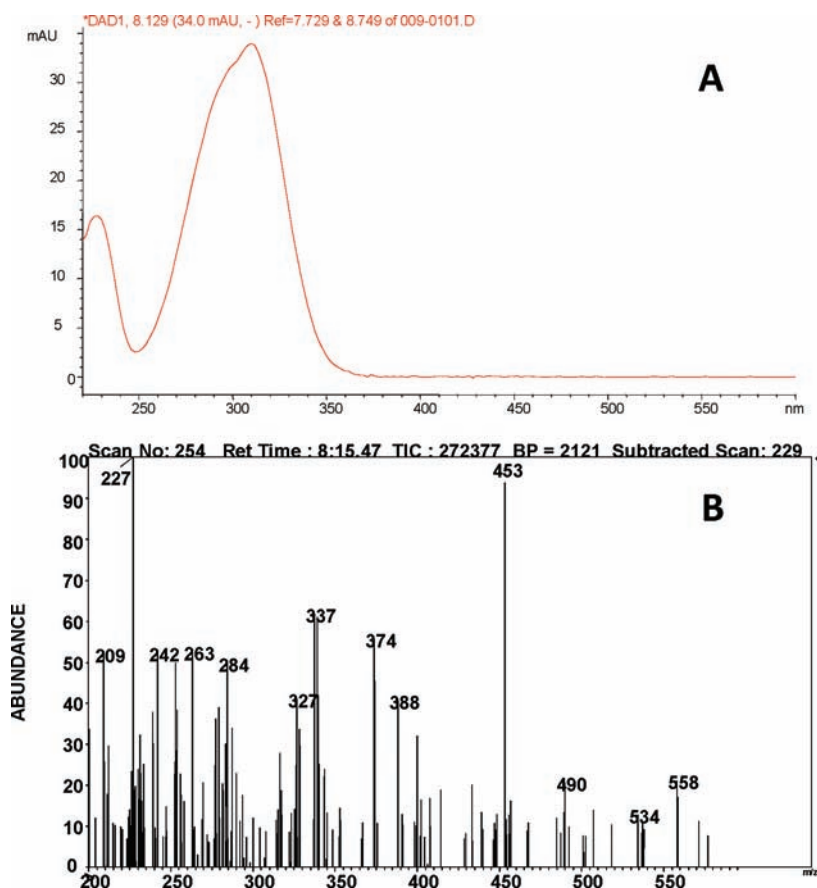
Figure 5. UV and mass spectra of peak 3 (RT = 8.13 min) in HPLC-DAD chromatograms of hydrolyzed micellar of boiled (- - -).

interesting fragmentation pattern in which the molecular ion has m/z of 537 amu with two product ions having m/z of 391 and 245 amu corresponding to the consecutive loss of two sugar units (Figure 3). This is indicative of the presence of a resveratrol-diglycoside. Resveratrol diglycosides have been reported in cell suspension cultures of *Vitis vinifera* as well as in transgenic *Arabidopsis* overexpressing a sorghum stilbene synthase gene.[2,13] This study is the first report indicating the presence of a resveratrol diglucoside in peanuts. According to Lo et al.,[14] there are two possible configurations for the diglucoside, either they are attached as a disaccharide to one hydroxyl group on the molecule or each such unit is attached to a separate hydroxyl group. A similarity in the fragmentation pattern between peak 3 in the nonhydrolyzed and the peak of the hydrolyzed micellar is the presence of a higher mass ion having a m/z of 443 amu. This corresponds to an additional mass of 62 amu usually indicative of acylation by an acid. The stability of this compound and known inability of β-glucosidases to hydrolyze such compounds support the nondisappearance of the peak 3 but does not explain its concomitant increase with the disappearance of peaks 1, 2, and 4. There is also the possibility that these could be adducts formed from the mobile phase. If this was the case, one would expect the 453 amu fragment to show up in all peaks, which was not the case. Thus, there is a strong possibility that the hydrolytic conditions (acetate buffer at pH 4.0) may have favored the formation and stabilization of acylated forms of resveratrol glycoside (Figure 3).

Lo et al.,[14] in their study to understand the glycosylation patterns of sorghum stilbenes using transgenic *Arapidopsis*, also observed a precursor ion with a m/z of 551 corresponding to a resveratrol diglycoside and a second precursor ion of m/z 431 with a product ion of 227 resulting from the loss of 204 amu. They concluded that this neutral loss was indicative of an acetyl hexose. On enzymatic hydrolysis of their plant extract with β-glucosidase, the resveratrol glycoside peaks disappeared, while the acylated glycoside peak remained unhydrolyzed. Resveratrol diglucoside has been previously reported in grape cell suspension cultures[13,15] and resveratrol acetylglucoside so far by Lo et al.[14]

Transepithelial Transport of Resveratrol. Differentiated human epithelial Caco-2 cell line has been shown to have enterocyte-like properties in vitro and therefore is suitable for transport studies so far as the intergrity of the epithelial mono-layer formed can be established. The integrity of the monolayer used for this study was determined by TEER measurements. TEER values $\geq 500 \; \Omega \; cm^2$ were considered acceptable for this study. To confirm the formation of tight junction and absence of leaks, a low permeability control assay using LY was conducted. A LY flux range of 0.3–2% indicates an intact cell monolayer, and an efflux ratio >2 or 3 shows evidence of transport. The monolayer used for this study falls within the above-mentioned values and confirms the integrity of the monolayer (Table 1).

HPLC-DAD chromatograms of resveratrol transport of both hydrolyzed and nonhydrolyzed peanut micellar from boiled and roasted peanuts were similar. There were similarities in the number of peaks present in the basolateral transport buffer (Figure 4); however, they differed in the relative amount transported with the roast peanut having higher amounts as compared to the boiled product. The hydrolyzed micellar from boiled peanut had a peak eluting at about 8.1 min as opposed to

Table 2. Resveratrol Concentrations in Apical Micellar, Rate of Transport, and Percent Transported to Basolateral Buffer during 4 h of Incubation[a]

peanut micellar	peak 1 resveratrol glycoside[b]	peak 2 resveratrol diglycoside[b]	peak 3 resveratrol glucuronide[b]	peak 4 resveratrol glycoside[b]
	resveratrol content of apical micellar (nmol)			
boiled	890.05 ± 10.95 b	264.46 ± 8.09 a	152.98 ± 29.88 b	359.71 ± 34.76 a
roast	977.42 ± 25.43 a	241.93 ± 17.80 a	222.64 ± 35.21 b	331.03 ± 46.57 a
boiled (hydrolyzed)	ND	ND	1410.81 ± 256.39 a	ND
roasted (hydrolyzed)	ND	ND	1370.39 ± 197.60 a	ND
	transport rate (nmol/min/cm^2)			
boiled	0.54 ± 0.09 b	0.25 ± 0.12 a	ND	0.33 ± 0.11 b
roast	2.60 ± 0.32 a	0.58 ± 0.17 a	0.64 ± 0.07 c	0.66 ± 0.09 a
boiled (hydrolyzed)	ND	ND	2.91 ± 0.15 b	ND
roasted (hydrolyzed)	ND	ND	4.70 ± 0.07 a	ND
	% transport			
boiled	5.23 ± 0.77 b	7.79 ± 3.51 b	ND	7.17 ± 2.48 b
roast	21.10 ± 2.59 a	18.94 ± 5.41 a	22.89 ± 2.62 b	15.86 ± 2.19 a
boiled (hydrolyzed)	ND	ND	17.24 ± 0.90 c	ND
roasted (hydrolyzed)	ND	ND	27.96 ± 0.40 a	ND

[a] Values are means ± SDs. Mean separation by Tukey's studentized test at $p \leq 0.05$. Means with the same letter in a column are not significantly ($p \leq 0.05$) different. ND, not detected. [b] Putative compound identity of peaks.

11.3 min for peak 3. UV and mass spectra of the peak were similar to peak 3 of the hydrolyzed micellar of roasted peanut and thus has a putative identity as an acylated resveratrol glycoside (Figure 5). The shift in retention time may be attributed to differences in the molecular constituents of the hydrolyzed boiled peanut micellar as opposed to the roasted peanut micellar. This is evident in the presence of peak 5, which on closer observation failed to yield UV and mass spectra that could provide useful information for peak identification (Figure 4).

While it has been reported that the chemical structure of polyphenols plays a role in the rate of intestinal absorption, their biovailability varies widely and seldom exceeds a plasma concentration of 1 μM.[16] Previous studies on the bioavailabilty of flavonoids and resveratrol have reported that aglycones are better absorbed than their glycosides.[16−20] Results obtained from this study are consistent with previous findings as the rate of transport of resveratrol glycosides in the nonhydrolyzed digests was 5−12 times lower than their hydrolytic product present in the hydrolyzed micellar (Table 2). Henry et al.,[21] in their study on the transport of resveratrol and piceid using Caco-2 monolayer, reported that *trans*-resveratrol was transported more than four times the rate of transport of its glycoside, *trans*-piceid. They attributed this to the lipophillicity of resveratrol as compared to the glycoside, thus, its ability to transverse the membrane lipid layer. This may explain the higher rate of transport of resveratrol from roasted peanut, which has a higher lipid content than boiled peanut. While previous authors have investigated the transport of resveratrol using the human intestinal Caco-2 cell monolayer, this is the first study using digested peanut samples for transport study; thus, marked differences in the rate of transport and the amount transported can be observed. Henry et al.[21] reported transport rates of 0.12−0.53 nmol/min/cm^2 for both resveratrol aglycone and glycosides. Transport rates observed in this study are much higher ranging from 0.25 to 4.7 nmol/min/cm^2, even though the amounts loaded in the apical chambers for each peak

(Table 2) were much lower than the amount of pure compounds used in their study (150 × 10^3 nmol). Li et al.[22] in their study of resveratrol transport using Caco-2 monolayer reported 53% transport after incubation for 4 h. The highest amount transported in our study was about 28%. Digests of roasted peanuts showed higher resveratrol transport as opposed to boiled peanuts. In our study on the bioaccessibility of peanuts from boiled and roasted peanuts, although boiled peanuts provided higher amounts of phenolic compounds, we find that resveratrol from boiled peanuts performed poorly in its transport across the intestinal epithelia (5−7%) even at similar concentrations. This supports the idea that a higher amount does not necessarily imply higher bioavailability. Henry et al.[21] have indicated that resveratrol uptake by intestinal epithelia is mediated by two mechanisms, namely, passive diffusion for the aglycones and the sodium-dependent transporter SGLT1 for the glycosides. Findings from our study indicate that there are other mechanisms or factors yet to be determined. These factors seem to regulate/faciltate the transepithelial transport of these compounds, especially with the presence of resveratrol glycosides in the transport buffer of nonhydrolyzed micellar in higher amounts (21%) as compared to hydrolyzed micellar from boiled peanuts (17%). This has implications for the absorption and bioavailability of dietary polyphenols. Another observation is the effect of processing on the absorption/transepithelial transport of resveratrol. Processing can alter the composition and/or properties of chemical constituents of a food. An example is the fermentation of tea resulting in the polymerization of monomeric flavanols to tannins. Therefore, while processing can affect bioavailability, they could form biologically active compounds that may be beneficial to health. There is therefore a need to evaluate processing techniques that not only favor the production of biologically active form but improve their bioavailability.

In conclusion, our results show that the hydrolytic product of resveratrol glycosides is transported at a higher rate across the

intestinal epithelia than its glycosides and that higher amounts are transported from roasted peanuts as compared to boiled samples. This implies that resveratrol from roasted peanuts is better absorbed. Also, enzymatic hydrolysis improves the absorption of resveratrol from peanuts.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 256-372-4166. Fax: 256-372-5432. E-mail: lloyd.walker@aamu.edu.

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