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Enrichment of (*E*)-Resveratrol from Peanut Byproduct with Molecularly Imprinted Polymers

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ABSTRACT: Molecularly imprinted solid phase extraction (MISPE) has been employed to isolate and concentrate bioactive polyphenols from peanut press waste. To this end, a molecularly imprinted polymer (MIP) templated with the phytoalexin (*E*)-resveratrol has been prepared via self-assembly with the functional monomer 4-vinylpyridine (4VP) in a 1:3 molar ratio. Subsequent molecular interrogation of the MIP binding sites demonstrated preferential structural selectivity for (*E*)-resveratrol with respect to other structurally related naturally occurring compounds. This selectivity was subsequently exploited to achieve substantial sample cleanup of peanut press waste under aqueous conditions with significant enrichment of (*E*)-resveratrol (>60 fold) requiring minimal sample preparation.

KEYWORDS: molecularly imprinted polymers, solid phase extraction, resveratrol, polyphenolics, peanut meal, procyanidins

INTRODUCTION

Molecularly imprinted polymers (MIPs) are synthetic materials with the capability of selective molecular recognition of targeted compounds. These polymeric materials are generating increasing interest within the scientific community due to their versatility of design, molecular selectivity, durability and reusability. MIPs are particularly suited to fields of scientific study that employ highly selective molecular recognition processes as a key attribute, including but not limited to sensors, catalysis, separations and solid phase extraction applications all of which have been extensively reviewed elsewhere.[1−6] Two principal techniques have been employed to impart the molecular memory to these polymers, namely, the noncovalent and covalent templating approaches. Both approaches involve the preparation of a stable complex between the molecular template and a functional monomer by either self-assembly or labile covalent linkages, respectively. Upon polymerization in the presence of a cross-linker and subsequent removal of the template, highly selective cavities, which act as molecular receptors and which are both chemically and spatially complementary to the template molecule, are produced within the porous polymer network.[7]

As part of our current investigations to improve sustainability and productivity within the food and agricultural industry, we have focused on the isolation and purification of bioactive compounds from food processing waste streams, many of which are either disposed of as landfill or used as low value stock feed. An exemplar of a bioactive compound present in such wastes is the polyphenol (*E*)-resveratrol, a phytoalexin that has been associated with several beneficial health effects such as anti-carcinogenic, anti-inflammatory, cardiovascular protective effects[8] and increased longevity.[9] Similar pharmacological effects have also been reported for oligomeric polyphenolic compounds.[10,11] (*E*)-resveratrol is a known constituent of over 72 plant species, with the main dietary sources for humans found in grape and peanut products, both of which generate high volume waste. There is thus considerable scope for the application of MIP-based separation technologies for the extraction of (*E*)-resveratrol and other bioactive polyphenols from food processing and associated agricultural waste materials, thereby providing an efficient and sustainable path to resource utilization.

Prior examples of MIP-based analyses of plant-derived bioactives include the extraction of (*E*)-resveratrol from *Polygonum cuspidatum*,[12] the separation and identification of quercetin from red wine,[13,14] the fluorescence detection of flavonol in fortified olive oil using a flow-through optosensing system[15] and the extraction of polyphenols from olive mill waste waters.[16] In the latter of these examples, the caffeic acid- and *p*-hydroxybenzoic acid-templated MIPs were used sequentially to isolate multiple polyphenol species, including the two template compounds and several structurally related components such as gallic acid, protocatechuic acid and vanillic acid.[16]

In this paper, we report a rapid technique for the isolation and enrichment of (*E*)-resveratrol and the determination of related polyphenols from peanut press waste using molecular imprinting solid phase extraction (MISPE) technology.

MATERIALS AND METHODS

Compounds. 4-Vinylpyridine (4VP), ethyleneglycol dimethacrylate (EGDMA) and 2,2′-azobis(2-methylpropionitrile) (AIBN), formic acid (FA), (±)-catechin hydrate (lyophilized prior to use), caffeic acid and (*E*)-piceid were obtained from Sigma-Aldrich (Sydney, NSW, Australia). 4VP and EGDMA were purified prior to use via vacuum distillation and alumina column chromatography, respectively. All solvents used were HPLC grade. (*E*)-Resveratrol **1** was synthesized using a procedure modified from the method reported previously by Andrus et al.,[17] with 2 mol % of Pd(II) acetate used in the absence of the ligand for the coupling procedure. Column chromatography returned a product in 51% yield that was pure by NMR (^{1}H and ^{13}C) and mass spectroscopy.

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MIP Preparation. An (*E*)-resveratrol imprinted polymer (MIP_{RES}) was prepared by dissolving (*E*)-resveratrol and 4VP (in ratio 1:3 molar equiv) in acetonitrile/EtOH (5:1 v/v). The resulting mixture was purged with N_2(g) for 2 min and sonicated for 10 min prior to addition of EGDMA (15 molar equiv) and the free radical initiator, AIBN (0.31 molar equiv). The mixture was sealed, purged with N(g) for 5 min and then placed in a 50 °C water bath (18 h) followed by a thermal annealing treatment at 60 °C (24 h). A non-imprinted polymer (NIP) was prepared as a control material in the same manner without the inclusion of the (*E*)-resveratrol template. The resulting hard bulk monoliths were ground using a Retsch 200 ball mill to produce particulate materials with size distribution of 60−100 μm, which were isolated by sieving. The template molecule was extracted by repeated washings with MeOH/AcOH (9:1 v/v) until the template was no longer visible in the extraction media by absorbance at 321 nm. The MIP particles were washed with MeOH to remove traces of AcOH and fines removed by repeated sedimentation in acetone. The remaining MIP particles were subsequently dried *in vacuo* at 40 °C overnight.

Static Binding Selectivity Studies. Selectivity studies, carried out under static binding conditions,[18,19] were conducted for both MIP and NIP using a constant polymer amount (30 mg). The NIP was used to determine the extent of random, nonspecific binding resulting from interactions with the cross-linked, dispersed functional monomer. The polymer was incubated in 1.5 mL of analyte solution (0.5 mM) in acetonitrile. The resulting mixture was mixed at 40 rpm for 18 h and then centrifuged at 13,000 rpm (16060*g*) for 15 min in a Heraeus Biofuge Pico. An aliquot (200 μL) of the supernatant was then analyzed by RP-HPLC with UV spectroscopy at 280 and 321 nm, and the concentration of free analyte determined from a linear 5 point calibration curve. The amount of bound analyte (*B*), expressed as μmol/g polymer, was calculated by subtracting the free analyte concentration from the initial total analyte solution concentration.

MISPE Validation Studies. Small scale MISPE studies were conducted on SPE columns containing 100 mg of either the MIP or NIP stationary phases. Polymeric stationary phase (100 mg) was slurry packed in MeOH into 3 mL polypropylene syringe barrels fitted with polypropylene frits (20 μm pore size). The resulting SPE columns were subsequently conditioned with 1.5 mL (3 column volumes) of either acetonitrile or EtOH/H_2O (1:1, v/v) for the organic solvent or aqueous studies respectively, after which 1 mL of an (*E*)-resveratrol (0.5 mM) solution in acetonitrile or EtOH/H_2O (1:1, v/v) was loaded on-column. Multiple loadings of the crude peanut waste extract and selective cleanup steps (1 mL each) were then applied to each column using either acetonitrile or 1% AcOH in EtOH/H_2O (1:1, v/v) after which each column was eluted using 10% AcOH in MeOH (2 mL). The fractions collected from the clean up and elution steps were evaporated to dryness, reconstituted to 1 mL in EtOH/H_2O (1:1, v/v) and analyzed by RP-HPLC. The (*E*)-resveratrol concentration was determined using a 5 point calibration curve ($R^2 = 0.999$) prepared by the serial dilution of a 5.0×10^{-1} mM standard to concentrations of 1.0×10^{-1}, 1.0×10^{-2}, 5.0×10^{-3} and 2.5×10^{-3} mM.

Reversed-Phase Chromatography (RP-HPLC). The RP-HPLC separation was performed on an Agilent Technologies 1100 LC system (Waldbronn, Germany) consisting of a binary pump with a vacuum degasser, autosampler with a 900 μL sample loop, thermostated column compartment and a diode-array detector. Samples were analyzed on a Zorbax Eclipse XDB-C_{18} column (4.6 × 150 mm, 5 μm particle size) at 40 °C. The mobile phase consisted of 0.1% AcOH in H_2O (solvent A) and 0.1% AcOH in EtOH/H_2O (8:2 v/v) (solvent B) with the following gradient: 0−2 min, 25% B isocratic; 2−6 min, 25−37.5% B; 6−9 min, 37.5% B isocratic; 9−12 min, 37.5−62.5% B; 12−15 min, 62.5% B isocratic; 15−18 min, 62.5−100% B; 18−22 min, 100% B isocratic; 22−25 min, 100−25% B, 25−29 min; 25% B isocratic. The flow rate was 0.5 mL min^{-1}. Injection volume was 5 μL with the UV−vis diode array detector (80 Hz) set to the absorbance wavelengths of λ = 280, 321, and 370 nm.

LC−ESI-MS/MS Analysis. All LC−ESI-MS/MS separations were performed using an Agilent 1100 capillary LC system (Agilent Technologies, Palo Alto, CA, USA) coupled to an ion-trap MS system (Agilent 1100 series LC/MSD-SL). Separation of the MIP eluates was performed using a Zorbax 300SB-C_{18} (0.3 mm × 150 mm i.d.) capillary column packed with 3.5 μm particles. The outlet of the column was directly connected to the electrospray source of the ion-trap mass spectrometer, with the UV detector bypassed. A 0.3 mg/mL MIP eluate sample in acetonitrile/H_2O (60:40, v/v) containing 0.1% FA was separated using a mobile phase consisting of 0.1% FA in H_2O (solvent A) and 0.1% FA in acetonitrile (solvent B) applying the following gradient: 0−15 min, 10% B; 15−65 min, 10−65% B; 65−70 min, 65−95% B. The flow rate was 4 μL min^{-1}. Injection volume was 0.2 μL. ESI-MS/MS analysis was carried out in the positive ion mode. The mass spectrometer was operated in a data-dependent mode, whereby the two most intense ions in the precursor ion scan were subjected to subsequent automated MS/MS. All system control and data acquisition were conducted with Agilent ChemStation and MSD Trap Control software.

Preparation of Peanut Press Waste Extract. Peanut press waste (200 g) in EtOH:H_2O (1000 mL, 4:1 v/v) was sonicated for 60 min, after which the mixture was filtered and the solvent evaporated to obtain the soluble extract (17.9 g). An aliquot (10.0 g) of this peanut press waste extract was reconstituted to 500 mL in EtOH/H_2O (1:1 v/v) in a volumetric flask and stored at 4 °C until required. Prior to use, the peanut press waste extract was warmed to room temperature and sonicated to clarify the solution.

MISPE of Peanut Press Waste Extract. MISPE studies were conducted to examine the ability of the MIP_{RES} to selectively retain and enrich (*E*)-resveratrol from the peanut press waste extract using either MIP_{RES} (1.0 g) or the corresponding NIP (1.0 g) as functional and control stationary phases respectively. The stationary phases were slurry packed in MeOH into 30 mL polypropylene columns, after which they were conditioned using 3 column volumes each of MeOH, then EtOH and finally EtOH/H_2O (1:1, v/v) containing 0.1% AcOH. Peanut press waste extract (2 × 50 mL) was applied to each column. The breakthrough fractions were collected under suction and recycled back through the columns to maximize the interaction between the stationary phase and the polyphenolic components within the peanut press waste extract. Each column was then washed with EtOH/H_2O (1:1 v/v) (20 mL), followed by successive elution steps comprising EtOH/H_2O (1:1 v/v) containing 1% AcOH (20 mL) and then acetone/H_2O (1:1 v/v) (30 mL) to desorb weakly binding species. An acidic elution step with 10% AcOH in MeOH (25 mL) was then applied to desorb the compounds of interest from each column. Elution fractions evaporated to dryness under vacuum and the residue made up to 1.0 mL in EtOH/H_2O (1:1 v/v) and analyzed by RP-HPLC.

RESULTS AND DISCUSSION

Preparation of Molecularly Imprinted Polymers. Studies on the design and nature of the imprinting mechanism of MIP_{RES} has been described in detail elsewhere.[18] Briefly, (*E*)-resveratrol-imprinted polymer cavities were generated by taking advantage of the self-association between the acidic phenolic hydroxyl groups of (*E*)-resveratrol with the electron rich pyridinyl nitrogen of the 4VP functional monomer. The resultant prepolymerization complex, formed primarily from self-assembling hydrogen bonding interactions, presumably also involved the stabilizing participation of aromatic $\pi-\pi$ interactions due to the close proximity of phenolic and pyridinyl aromatic groups. The self-assembled complex was then polymerized via the styryl functionalities in

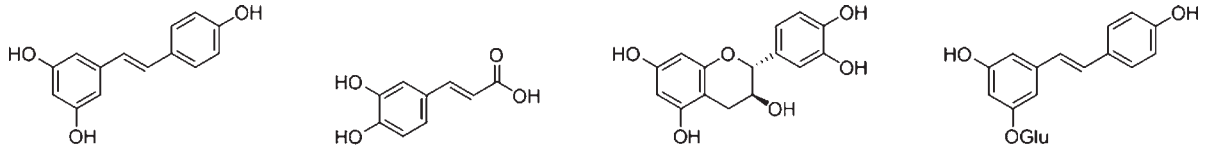

Figure 1. Structures of polyphenols used in this study: (*E*)-resveratrol **1**, caffeic acid **2**, (−)-catechin **3** and (*E*)-piceid **4**.

Table 1. Cross-Reactivity Studies with the MIP_{RES} and the Respective NIP Control Polymer with (*E*)-Resveratrol 1, Caffeic Acid 2, (±)-Catechin 3 and (*E*)-Piceid 4

	binding μmol/g			
			recognition	selectivity
analyte	B_{MIP}	B_{NIP}	$B_{MIP} - B_{NIP}$	$(B_{MIP} - B_{NIP})/B_{NIP}$
1	10.28	4.19	6.09	1.45
2	9.27	6.07	3.20	0.53
3	9.63	7.44	2.19	0.29
4	2.23	1.42	1.66	0.57

the presence of the cross-linker EGDMA. Removal of the template molecule resulted in the generation of MIP cavities that are complementary in physicochemical terms to (*E*)-resveratrol. The ability of these cavities to recognize (*E*)-resveratrol has been confirmed using static binding isotherm measurements.[18,19]

The extent of cross-reactivity of MIP_{RES} was evaluated using several structurally related, naturally occurring polyphenols (Figure 1). For MIP_{RES}, the order of recognition (MIP−NIP) was (*E*)-resveratrol **1** > caffeic acid **2** > catechin **3** > (*E*)-piceid **4** (Table 1). Although the binding capacity of MIP_{RES} for both caffeic acid **2** and (±)-catechin **3** was comparable to that observed for the template molecule (*E*)-resveratrol **1**, the magnitude of this binding was offset by increased nonspecific binding of these compounds by the NIP. It can be concluded that the greater number of groups on caffeic acid and (±)-catechin, compared to (*E*)-resveratrol, that can form hydrogen bonds is responsible for higher level of nonselective binding to the NIP control polymer, thereby leading to reduced specific recognition. Negligible recognition of the glucosylated resveratrol molecule, (*E*)-piceid **4**, was observed, which is presumably due to the presence of the bulky glucose substituent preventing access of this analogue to the MIP_{RES} binding cavities. Further, the reduced binding capacity of the NIP for (±)-catechin compared to (*E*)-resveratrol provides additional support for the involvement of H-bond interactions in the binding of this compound to both the MIP_{RES} and NIP. Based upon the selectivity displayed by MIP_{RES} toward (*E*)-resveratrol over other structurally related molecules, such as those present in polyphenol-rich extracts from plant sources, it was anticipated that MIP_{RES} based SPE extraction procedures could be deployed to selectively isolate the target (*E*)-resveratrol from complex food processing/agricultural by-product matrix.

To establish the utility of the MIP_{RES} as a MISPE adsorbent for the recovery of (*E*)-resveratrol, preliminary small scale experiments were conducted with MIP_{RES} stationary phase in both organic and aqueous environments. The binding capacity of MIP_{RES} for (*E*)-resveratrol was determined in this format to establish the composition of the elution conditions, as an aqueous cleanup step to remove weakly bound or nonspecific bound compounds compared to an organic cleanup step to recover the target molecule (Figure 2).

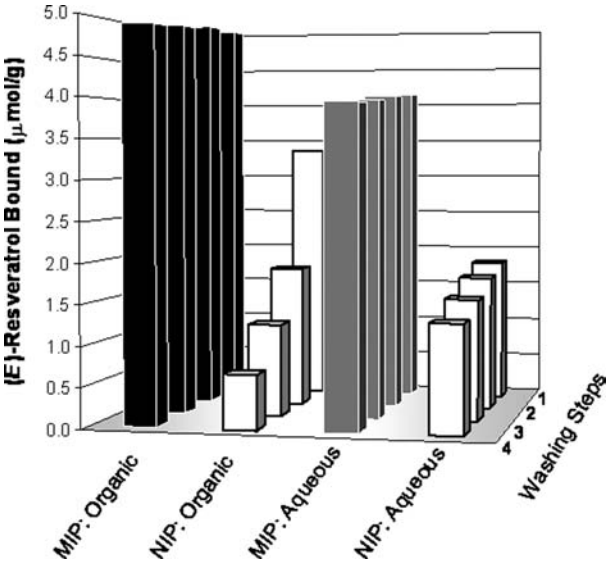

Figure 2. Relative binding capacity of MIP_{RES} for (*E*)-resveratrol. (*E*)-Resveratrol standard (0.5 μmol) was loaded onto MIP_{RES} (100 mg) in either acetonitrile (black) or EtOH/H_2O (1:1, v/v) (gray) respectively. Each column was subsequently washed using the loading solvent and the amount of (*E*)-resveratrol remaining on-column determined from a 5 point calibration curve.

Typically, organic solvents such as acetonitrile or dichloromethane are employed for the cleanup step with MIPs to overcome nonspecific hydrophobic interactions and to disrupt other weak binding interactions. As apparent from the results, MIP_{RES} displayed superior binding capacity for (*E*)-resveratrol under organic solvent conditions. More importantly, the results confirmed the ability of MIP_{RES} to extract (*E*)-resveratrol from an aqueous solution, albeit with slightly reduced efficacy, clearly demonstrating the applicability of using this MIP for the extraction and elution of this compound under conditions typically encountered in a processing or manufacturing environment (Figure 2). Accordingly, larger scale studies in the MISPE format with either the MIP_{RES} or the corresponding NIP control were employed for the extraction of (*E*)-resveratrol from an aqueous peanut press waste extract containing a complex mixture of bioactive polyphenols including (*E*)-resveratrol and catechin based oligomers.

MISPE of Peanut Press Extract. Peanut press waste is a byproduct of peanut oil preparation, constituting the remains of the peanut and husk after pressing, and contains a range of

bioactive constituents including phytosterols, flavanols and other polyphenols. As this byproduct is regularly disposed of as landfill or stock feed, the value-added benefits of these bioactives often remain underutilized. As peanuts and peanut derivatives are consumed in large quantities globally, the resulting peanut meal represents a significant reservoir of bioactive components such as the polyphenol (*E*)-resveratrol, notwithstanding the fact that this compound is present in relatively low amounts ranging from 0.02 to 1.79 μg/g in various process fractions of the peanut market.[20] Therefore, we have employed MIP_{RES} in a MISPE format to examine the potential of this approach for the selective enrichment and isolation of (*E*)-resveratrol from a peanut meal liquid extract.

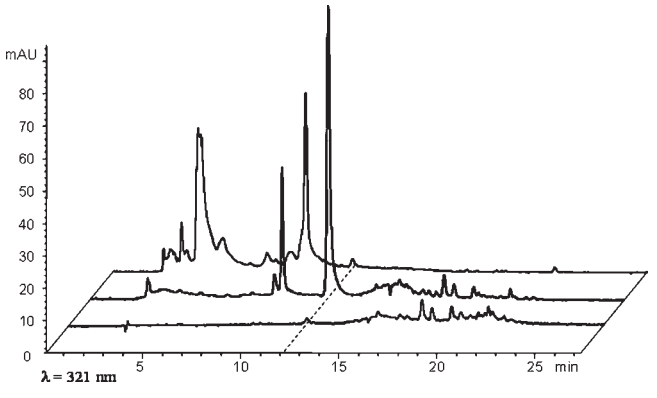

Figure 3. RP-HPLC chromatograms of peanut meal extract and MISPE eluates: untreated peanut meal extract (back), eluate from MIP_{RES} MISPE column (center) and eluate from NISPE column (front). Chromatograms were obtained at 321 nm. (*E*)-resveratrol elutes at t_R = 12.2 min.

RP-HPLC chromatograms of the peanut meal extract and subsequently recovered fractions from the MIP separation are shown in Figure 3. For these studies, compound detection was carried out at three wavelengths (280, 321 and 370 nm) since a broad range of polyphenols (particularly catechin-based), resveratrol (including stilbene analogues and hydroxycinnamic acids) and quercetin-based compounds display significant λ_{max} and extinction ε_{max} values at these wavelengths respectively. The MIP_{RES} clearly resulted in significant sample clean up of the peanut meal extract and enrichment of (*E*)-resveratrol (t_R = 12.2 min) and several unknown compounds. The presence of these unknown compounds appear to affect the overall recovery of (*E*)-resveratrol (60.8%) due to competitive binding. The amount of (*E*)-resveratrol recovered in the eluate from MIP_{RES} fractionation represented an approximate 60-fold enrichment of this important bioactive from the crude feedstock, i.e. an increase in concentration to 39.5 μg/mL from 0.65 μg/mL (on a mass and volume normalized basis). This enrichment can be solely attributed to the (*E*)-resveratrol imprinting effect as the chromatogram of the NIP eluate shows no significant enrichment of (*E*)-resveratrol, which is present in similar quantity to that measured in the untreated peanut meal extract.

The MIP_{RES} eluate was analyzed by liquid chromatography−ESI-tandem mass spectrometry (LC−ESI-MS/MS) in positive ion mode, which confirmed the presence of (*E*)-resveratrol (t_R = 12.2 min, 229 m/z $[M + H]^+$) by comparison to an authentic, chemically synthesized (*E*)-resveratrol standard. In addition to (*E*)-resveratrol, the MIP_{RES} cavities also exhibited affinity for a secondary molecule as evidenced by the RP-HPLC peak at t_R = 9.9 min. This peak is associated with a more polar compound, which was not retained by the NIP control polymer. LC−ESI-MS of this peak fraction revealed the presence of mass peaks

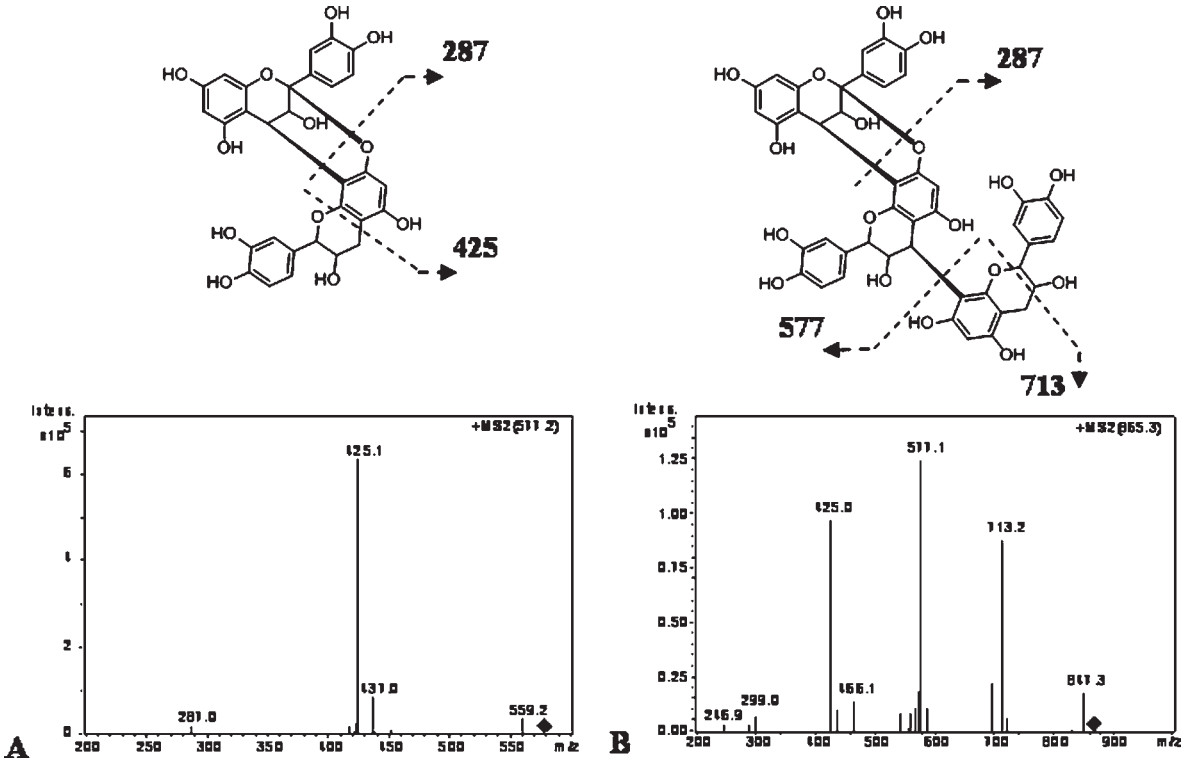

Figure 4. Product ion spectra and fragmentation positions for (A) A-type procyanidin dimers (m/z 577 $[M + H]^+$) and (B) A-type procyanidin trimers (m/z 865 $[M + H]^+$) isolated from peanut meal extract in the MIP_{RES} eluate (Figure 3, t_R = 9.9 min).

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corresponding to $[M + H]^+$ ions at 577 m/z and 865 m/z, both of which correlate with the expected mass of the bioactive A-type procyanidin dimers and trimers, respectively (Figure 4). The 577 m/z ion was selected for MS/MS, which produced a fragmentation pattern that is characteristic for interflavanoid bonds, whereby the parent ion (577 m/z) underwent a retro-Diels−Alder fragmentation to produce the doubly charged catechin monomer product ion at 287 m/z via the intermediate at 425 m/z[21,22] (Figure 4A).

A similar fragmentation pattern was observed in positive ion mode for the A-type procyanidin trimer with characteristic mass ion of 865 m/z (Figure 4B) with the fragmentation pattern producing product ions, consistent with previous observations for the A-type procyanidin trimer obtained in the negative ion mode product ion (MS/MS) spectrum reported by He et al.[23] and Gu et al.[24] taking into account the 2 Da difference in the mass peaks that arises due to measurement in the positive and negative ion spectral modes.

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