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Application of a Molecularly Imprinted Polymer for the Extraction of Kukoamine A from Potato Peels

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ABSTRACT: A molecularly imprinted polymer (MIP) for the purification of N^1,N^{12}-bis(dihydrocaffeoyl)spermine (kukoamine A) was computationally designed and tested. The properties of the polymer were characterized. The protocol of the solid phase extraction (SPE) of kukoamine A from potato peels was optimized. A HPLC-MS method for the quantification of kukoamine A was developed and used for all optimization studies. The capacity of the MIP in relation to kukoamine A from the potato peels extract was estimated at 54 mg/g of the polymer. The kukoamine A purified from potato extract using MIP was exceptionally pure (≈90%). Although the corresponding blank polymer was less selective than the MIP for the extraction of kukoamine A from the potato extract, it was shown that the blank polymer could be effectively used for the purification of the crude synthetic kukoamine (polymer capacity = 80 mg of kukoamine A/g of the adsorbent, kukoamine A purity ≈ 86%). Therefore, selective adsorbents could be computationally designed for other plant products, allowing their purification in quantities that would be sufficient for more detailed studies and potential practical applications.

KEYWORDS: *kukoamine A, potato, SPE, HPLC-MS, molecular modeling, molecular imprinting, spermine*

INTRODUCTION

There is a growing interest in the replacement of synthetic bioactive chemicals with naturally sourced compounds from sustainable, natural/biological feedstocks. In particular, the food-processing industry generates substantial quantities of phenol-rich byproducts that could be valuable natural sources of such compounds. These components are often high value and have potential applications in the pharmaceutical, cosmetic, and neutraceutical sectors. These compounds often represent only a small percentage of the source biomass and require the development of special protocols and adsorbent, which would ensure their effective extraction and recovery. The traditional metabolomic techniques that are used for the characterization and identification of these compounds are mainly based on NMR, HPLC-MS, and GC-MS, which are considered to be powerful instruments for the characterization of the chemical nature of the studied metabolites but require a high degree of purity of the analytes. Custom-made specific adsorbents based on the molecular imprinting technique are widely publicized as effective resins in the purification of natural and pharmaceutical products.[1−3] It was shown that such adsorbents could be prepared in a relatively short time and demonstrate good efficacy and sufficient specificity under any required specific conditions. The benefits of the custom-designed resins include their high capacity, regeneration capability, and cheap price. In the present paper we describe the design and development of an adsorbent for the extraction and purification of kukoamine A from potato waste. Kukoamine A is a bioactive phenolic polyamine found in potato (*Solanum tuberosum*) tubers as well as in other solanaceous species, such as tomato, eggplant, and tobacco. Kukoamine A attracted attention because of its reported hypertensive effects and an antitrypanosomal action mediated by the inhibition of tripanothione reductase.[4,5] Becausee kukoamine A is found in substantial quantities in potato peels, potato waste could be considered to be an inexpensive source of this biologically active compound. Potentially, kukoamine A could be used as a food supplement or pharmaceutical product.

MATERIALS AND METHODS

Chemicals. Itaconic acid (IA), ethylene glycol dimethacrylate (EGDMA), 1,1′-azobis(cyclohexanecarbonitrile), *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), trifluoroacetic acid (TFA), 3,4-dihydroxyhydrocinnamic acid, *N*-hydroxysuccinimide, *N*,*N*′- dicyclohexylcarbodiimide, and spermine were purchased from Aldrich (Sigma-Aldrich, Gillingham, U.K.). α-Solanine and α-chaconine were purchased from Sigma-Aldrich (Gillingham, U.K.). Deuterated chloroform was bought from Goss Scientific Instruments Ltd. (Worleston, U.K.). Methanol and formic acid were obtained from Acros Organics (Fisher, Loughborough, U.K.). Potato samples (cv. Maris Piper) were kindly supplied by Sutton Bridge Crop Storage Research (The Potato Council Ltd.). One milliliter empty SPE cartridges were purchased from Supelco (Sigma-Aldrich, Gillingham, U.K.).

Computational Modeling. Molecular modeling was performed using a workstation from Research Machines running the CentOS 5 GNU/Linux operating system. This system was used to execute the software package SYBYL 7.3 (Tripos Inc., St. Louis, MO). The LEAPFROG algorithm was used to screen the library of functional monomers for their possible interactions with the template, resulting in a table, ranking the monomers with the highest binding score (kcal mol^{-1}) as the best candidates for polymer preparation. The library contained 20 functional monomers commonly used in molecular imprinting, which possess polymerizable residues and residues able to interact with a template through ionic and hydrogen bonds, van der Waals', and dipole−dipole interactions.[6] The charges for each atom were calculated, and the structures of the monomers were refined using molecular mechanical methods. Energy minimization was performed on each of the monomers in the database to a value of

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0.01 kcal mol^{-1}. A refining step for optimization of the monomer composition was performed.[7] It involved a molecular dynamics simulation of the prearrangement of the itaconic acid functional monomer around the template prior to polymerization. This was carried out by saturating the space around the template with monomers in a defined box that is heated to 600 K and cooled slowly to 300 K and minimizing the box using molecular mechanics at every 100 K interval. Energy minimization was carried out to 0.05 kcal mol^{-1}. At the end of the program, the number and the position of the functional monomers were examined. The type and quantity of the monomers participating in the molecular complex with template indicated the type and ratio of the template and monomers for the optimized MIP composition.

Kukoamine A Synthesis. 3,4-Dihydroxyhydrocinnamic acid (0.012 mol) was added to 0.013 mol of *N*-hydroxysuccinimide in 20 mL of THF and allowed to dissolve upon constant stirring a nitrogen atmosphere. Then 0.013 mol of *N*,*N*′-dicyclohexylcarbodiimide was added, and the mixture was left to stir overnight at room temperature. After 12 h of stirring, a white precipitate (dicyclohexylurea) was filtered off and washed with 50 mL of THF. An aliquot of 0.006 mol of spermine was then added to the combined filtrate and washing fractions. All manipulations were carried under nitrogen atmosphere. The mixture was stirred again at room temperature for another 4 h. During this time a yellow amorphous solid had precipitated. Further precipitation of a white crystalline solid also occurred at this stage. The white precipitate and THF were decanted, leaving the yellow amorphous solid, which was recrystallized by mixing it with methanol. THF was then added until the product precipitated.

The synthesized kukoamine was dissolved in deuterated chloroform and analyzed using a JEOL ECX-400 NMR spectrometer (JEOL, U.K.) operating at 400 MHz. The resulting spectra were compared to model spectra, produced by the ChemStation software package (www.Cambridgesoft.com).

Polymer Preparation. The molar ratio 1:10 between kukoamine A and IA monomer was used for the calculation of the polymer composition on the basis of the results of the molecular dynamics (Figure 1). Synthetic kukoamine A was used as a template for the preparation of the MIP. The polymer composition was as follows: kukoamine A (0.53 g), functional monomer IA (1.3 g), cross-linker EGDMA (7.2 g), DMF (9 g), initiator 1,1′-azobis-(cyclohexanecarbonitrile) (90 mg). The corresponding blank polymer was made using the same composition but in the absence of the template (kukoamine A). The polymers were prepared by thermopolymerization at 80 °C for 12 h. After synthesis, the polymer was ground, washed with methanol, and sieved to obtain fractions with the size 63−125 μm. The polymers were washed with methanol for 12 h in the Soxhlet extractor, dried, and used for SPE. The MIP was also extensively washed with methanol containing 0.2% of TFA until any trace of the template (kukoamine A) was eliminated. The removal of the template during washing was evaluated using HPLC-MS. The surface area of the polymers was characterized using a Nova 1000e series high-speed gas sorption analyzer (Quantachrome, U.K.).

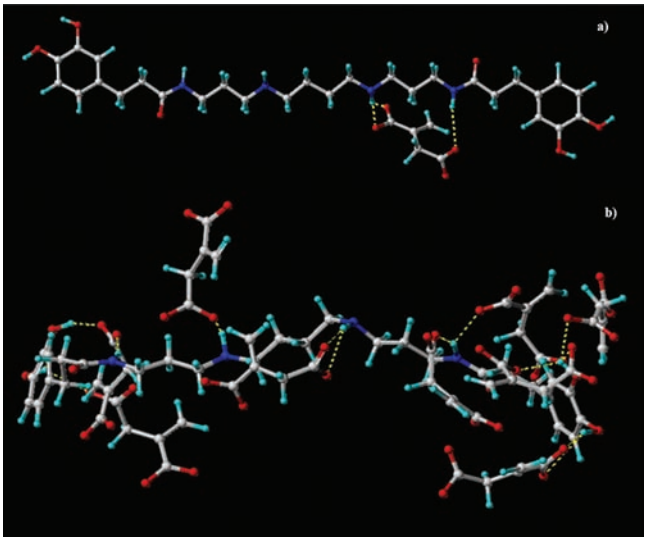

Figure 1. Molecular complex between kukoamine A and a molecule of IA (a); result of molecular dynamics study which shows that 1 molecule of kukoamine A could bind 8 molecules of IA (b). The yellow dotted lines show the hydrogen bonds between the molecules.

Quantification of Kukoamine A Using HPLC-MS. To measure and quantify kukoamine A, the HPLC-MS method was optimized. A Waters 2795 separation module in tandem with a benchtop triple-quadrupole mass spectrometer model Micromass Quatro Micro (Waters, U.K.) equipped with an electrospray probe was used, and the molecular ion of kukoamine A (m/z 531) was detected by selected ion recording mode (SIR) using positive ionization (Figure 2). The values of the voltages applied to the sampling cone (28 V), capillary (3.5 V), and extractor (1 V) were optimized by continuous infusion. A 150 × 3 mm Luna C18 column, 3 μm particle size (Phenomenex, U.K.), at 55 °C was used. For the quantification of kukoamine A an isocratic HPLC method was optimized (solvent, 40% methanol containing 0.5% formic acid; flow, 0.2 mL/min; run time, 5 min; injection volume,10 μL). Standard solutions containing a range of concentrations of kukoamine A from 312 ng mL^{-1} to 10 μg mL^{-1} in methanol/0.2% TFA (injection volume, 10 μL) were used for optimization of the kukoamine A quantification method. To reduce the impact of the matrix on MS performance when potato extracts were used, a solvent delay was introduced such that the sample was injected into the MS detector only from 2 min after injection until 4 min. The solvent before 2 min and after 4 min was diverted to waste.

Preparation of Potato Peels. The potato peel was removed using a potato peeler to produce a peel of just over 1 mm thickness. All samples were immediately frozen in liquid nitrogen. The samples were then dried in a freeze-dryer (Scanvac, Lynge, Denmark) in the dark for 7 days at −50 °C. After lyophilization, the samples were ground using a Retsch mill (Glen Creston Ltd., Stanmore, U.K.) and stored at −40 °C.

Preparation of Potato Peel Extract. Two hundred milligrams of lyophilized potato peels was resuspended in 15 mL of methanol and ultrasonicated for 10 min using the ultrasonic bath at HF frequency of 40 kHz (Hilsonic, U.K.). The suspension was then filtered through a paper filter (no. 3, Whatman, U.K.) to remove solids. Aliquots of peel extract (3 mL) were loaded into disposable 15 mL centrifuge tubes and dried for 30 min at 60 °C under a nitrogen flow using a TurboVap LV evaporator (Zymark, U.K.). Each pellet was reconstituted with 1 mL of 0.1% acetic acid aqueous solution and loaded into the SPE tubes.

SPE Optimization. The optimization of the SPE method was conducted using blank polymer. Blank polymer (25 or 50 mg) was packed into 1 mL SPE tubes (Phenomenex, U.K.) between two polyethylene frits. The SPE protocol included the following steps: conditioning (1 mL of water); loading (1 mL of 0.1% acetic acid spiked with 10 μg of synthetic kukoamine A); washing (2 × 1 mL of reverse osmosis (RO) water, 2 × 1 mL of 50% methanol), and elution (3 × 1 mL of methanol containing 0.2% of TFA). The concentration of kukoamine A in each fraction was measured using HPLC-MS as previously described.

The optimized SPE method was also tested for the extraction of kukoamine A from the potato extract. For this experiment MIP- and blank-polymer-packed cartridges were used. The concentration of eluted kukoamine A was analyzed using HPLC-MS.

The regeneration of the polymers was also optimized. The regeneration included washing of the polymers packed in SPE cartridges with 1 mL of ethyl acetate, 2 mL of methanol, and 5 mL of RO water using a vacuum manifold.

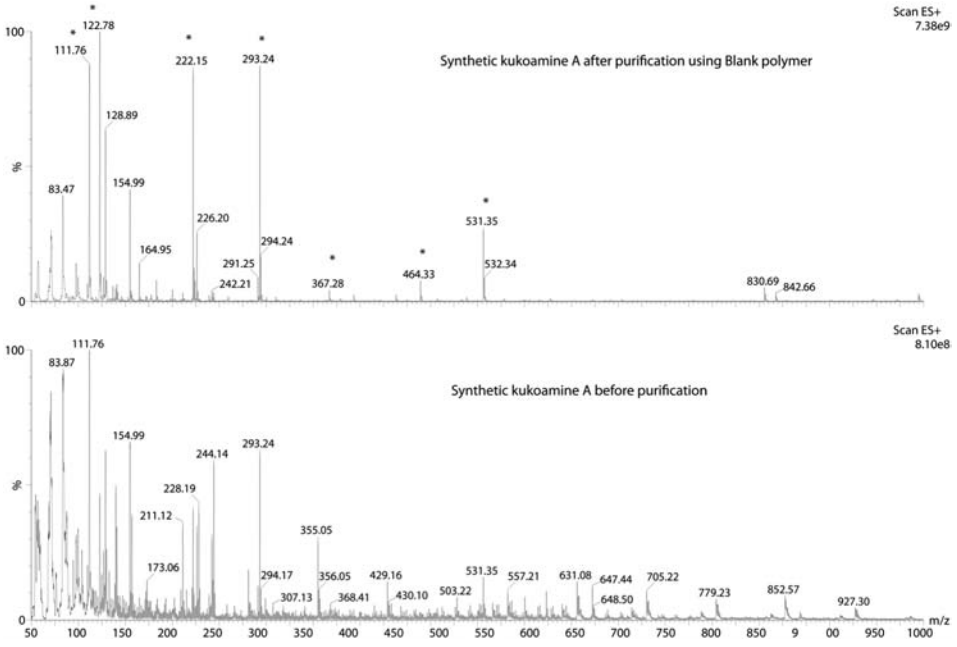

Figure 2. Mass spectra of synthetic kukoamine A after (top) and before purification using blank polymer (bottom). The kukoamine A molecular ion ($[M + H]^+$ m/z 531) and its fragments are labeled with an asterisk (∗).

Table 1. Recovery of Synthetic Kukoamine A from IA-Based Blank Polymer after SPE

	recovery of kukoamine A, μg	
elution step	25 mg of polymer	50 mg of polymer
E1	9.9	6.4
E2	1.1	1.24
E3	0	0.9
total recovery	11	8.6
recovery,[a] %	96	75

[a]Percentage of recovery was calculated according to the amount of kukoamine A (11.5 μg mL^{-1}) in solution before the SPE, which was quantified using HPLC-MS. The measurements were done in triplicate; the deviations from the average values were under 5%.

Table 2. Extraction of Kukoamine A from Potato Peels Using the MIP and Blank Polymer

	kukoamine, mg	
SPE step	MIP	blank polymer
washing	0.11	0.04
elution	1.36	1.13
total dry weight of the eluent	1.5	6.75
purity, %	90	15

RESULTS AND DISCUSSION

Computational Modeling. A molecular model of kukoamine A was designed and minimized to a value 0.001 kcal mol^{-1}. Then in silico screening of a library of functional monomers against kukoamine A was performed as described earlier. Among the monomers that demonstrated the highest binding scores by forming the strongest complexes with kukoamine A were ethylene glycol methacrylate phosphate (EGMP), 2-acrylamido-2-methylpropanesulfonic acid (AMPSA), and itaconic acid (IA).

It is interesting to note that the distance between two carboxyl groups of IA matched the distance between the complementary secondary amino groups of kukoamine A (Figure 1). It is expected that such two-point interactions between template and functional monomers could provide a strong and specific binding.

Preparation and Characterization of the Polymers. The MIP based on a molar ratio of 1:10 between the template (kukoamine A) and functional monomer (IA) was prepared. The corresponding blank polymer was made in the absence of the template.

The surface area of the synthesized MIP was 276 m^2 g^{-1} (total pore volume, 0.611 cm^3 g^{-1}; and average pore radius, 44.30 Å), and the surface area of blank polymer was 279 m^2 g^{-1} (total pore volume, 0.5677 cm^3 g^{-1}; and average pore radius, 40.68 Å).

To assess the effectiveness of the imprinting process, the capacity of the MIP and blank polymers for the adsorption of kukoamine A in acetonitrile was measured. Although acetonitrile is less commonly used for the preparation of the plant extract than methanol, it is apolar and provides better conditions for the demonstration of the imprinting phenomenon, which is mainly based on electrostatic interactions. Acetonitrile was spiked with synthetic kukoamine A and loaded into the cartridges packed with 100 mg of MIP, blank polymer, and C18 resin. The test showed that the MIP had twice higher capacity toward kukoamine A than the blank polymer (0.4 mg g^{-1} of the polymer and 0.22 mg g^{-1} of the polymer, correspondingly) and >4-fold higher capacity than the C18 resin, which is traditionally used for extraction of phenolic compounds (0.09 mg g^{-1} of the resin).

SPE Protocol. To optimize the SPE protocol, 1 mL of 0.1% acetic acid aqueous solution was spiked with 10 μg of synthetic kukoamine A and loaded into cartridges packed with 25 and 50 mg of IA-based blank polymer. After loading, the polymer was washed with 2 × 1 mL of water and 2 × 1 mL of 50% methanol. Elution was performed using 3 × 1 mL of methanol containing 0.2% TFA. The acidified methanol was selected as the eluent because acid was used for the neutralization of the carboxylic

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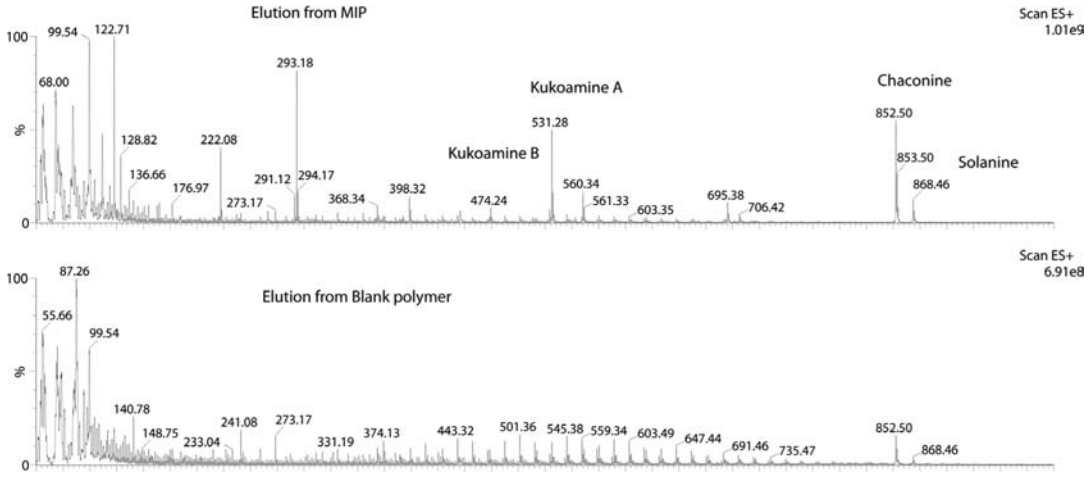

Figure 3. Mass spectra of the potato extract purified using MIP (top) and blank (bottom) polymers.

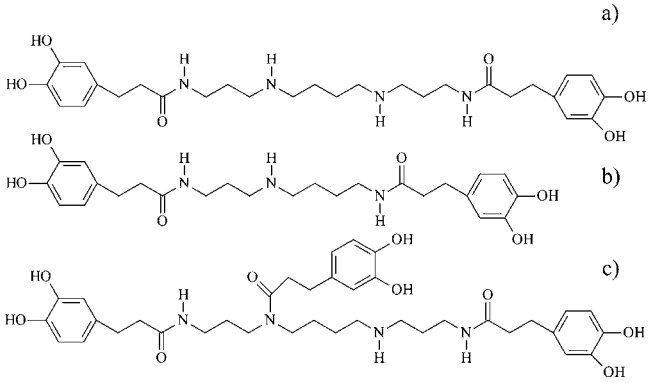

Figure 4. Molecular structures of the compounds extracted from potato using designed polymers: (a) N^1,N^{12}-bis(dihydrocaffeoyl)-spermine (kukoamine A, template); (b) N^1,N^6-bis(dihydrocaffeoyl)-spermidine (kukoamine B); (c) tris(dihydrocaffeloyl)spermine.

groups of IA and allowed the effective elution of kukoamine A from the resin. It is also necessary to mention that such conditions are favorable for maintaining the stability of the eluted phenolic polyamine compounds.[8]

The analysis of the elution profile by HPLC-MS demonstrated that 90% of kukoamine A was eluted from 25 mg of IA-based polymer in the first milliliter of the eluent (Table 1). Because the quantitative recovery of kukoamine A was demonstrated, it is possible to conclude that the tested polymer had sufficient affinity toward kukoamine A under the tested conditions. The recovery of kukoamine A from 50 mg of the polymer was insufficient (74%), which suggested that a larger volume of the eluent might be required for complete elution (Table 1).

The possibility of purifying synthetic kukoamine A using blank polymer was assessed following optimization of the SPE protocol. The obtained mass spectra demonstrated that the purity of the synthetic kukoamine A was significantly improved when compared with that of the nonpurified sample (Figure 2). Assessment of synthetic kukoamine A purity was made by comparing the dry weight of the purified sample (2.5 mg) and the amount of kukoamine A in the eluted sample (2.16 mg), which was quantified using HPLC-MS. The kukoamine A purity after SPE using the blank polymer was estimated as 86.4%. The optimized regeneration protocol allowed reuse of the cartridges for >10 times without loss of polymer efficacy.

Optimization of Potato Extract Preparation. To optimize the protocol for extraction of kukoamine A from potato samples, several different extraction conditions were used. First, the aqueous solution containing 10% methanol and 0.1% acetic acid was tested. Although it was found that this solvent extracted ≈0.38 mg of kukoamine A from 1 g of dry potato peels, it also extracted a significant quantity of other water-soluble compounds, particularly starch, which was not desirable as this can reduce the purity of extracted kukoamine A and impede the filtration. Much better results were demonstrated when neat methanol was used as the extraction solvent. Methanol extracted much higher quantities of kukoamine A (≈1.12 mg g^{-1} of dry potato peels). Moreover, the methanol extract was also much easier to filter to remove the solid impurities and easier to evaporate to preconcentrate and reconstitute in 0.1% acetic acid solution, which in turn was preferable for loading onto the polymer.

A similar experiment was made using dry potato pulp. It was found that potato pulp contained an approximately 7 times smaller quantity of kukoamine A (0.18 mg g^{-1} of dry potato pulp when extracted using neat methanol). All subsequent experiments were made using lyophilized potato peels because they were considered to be a richer source of kukoamine A.

The assessment of the MIP and blank polymers for the extraction of kukoamine A from potato peels was made using the optimized SPE protocol. The concentration of kukoamine A in the SPE fractions was quantified and the total amount of eluted kukoamine A calculated (Table 2).

The MIP capacity toward kukoamine A was estimated at 54 mg g^{-1} of the polymer. Corresponding data for the blank polymer was as follows: 1.13 mg of kukoamine A was eluted from 25 mg of the polymer; polymer capacity, 45 mg of kukoamine A g^{-1} of the polymer.

The MS spectra of kukoamine purified using MIP and blank polymers from potato extract were compared. It was found that kukoamine A extracted from potato using the MIP had a much higher purity than kukoamine A extracted using the blank polymer (Figure 3).

Among the compounds that were eluted from the MIP, it was possible to identify kukoamine A and some traces of its close structural and functional analogues kukoamine B ($[M + H]^+$ m/z 474) and tris(dihydrocaffeloyl)spermine ($[M + H]^+$ m/z 695)[9] (Figure 3). The structures of all these compounds have identical features such as an *o*-dihydroxyphenol moiety

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and a regular pattern of nitrogens that are separated by two hydrocarbons. Such close structural homology could explain why all of these kukoamine A-related compounds were extracted by the kukoamine A-imprinted polymer (Figure 4). Among other extracted potato metabolites some trace quantities of α-solanine ($[M + H]^+$ m/z 868) and α-chaconine ($[M + H]^+$ m/z 852)[10,11] were also detected; both compounds are known to be present in high quantities in potato peels. One gram of potato peels (as per dry weight) could contain as high as 48 mg of the glycoalkaloids,[11] so the amount of extracted glycoalkaloids using MIP and blank polymers (about 1.5 mg g^{-1} of the freeze-dried dry peels) was <3% of the original amount, which demonstrates the high degree of kukoamine A purification.

It is known that chlorogenic and caffeic acids and tyrosine constitute a significant proportion of the methanol extract from potatoes.[12,13] Chlorogenic acid alone represents >90% of the total phenolics in potato.[14] The mass spectra analysis of the purified fraction showed that the solution of eluted kukoamine A did not contain even trace quantities of chlorogenic, caffeic, *p*-coumaric, and ferulic acids, which could suggest that the designed material is mainly specific for phenolic polyamines such as kukoamines A and B. The purity of kukoamine A obtained from potato extract using MIP was 90%. The blank polymer was also able to extract kukoamine A from the potato extract, but it did not demonstrate a sufficient degree of purification in comparison with the MIP. The purity of kukoamine A extracted from the potato using the blank polymer was around 15%. Nevertheless, blank polymer was shown to be a valuable material for the purification of the crude synthetic kukoamine A. The binding capacity of the blank polymer toward the solution of the crude synthetic kukoamine A, when loaded in 0.1% acetic acid, was 80 mg g^{-1} of the polymer and the purity of kukoamine A after SPE, 86%.

It is possible to conclude that the polymers reported herein could be used for the effective extraction of generic phenolic polyamines from plant material or for the purification of crude synthetic kukoamine. The extraction of pharmaceutically important compounds from potato peels is a very interesting development considering the easy availability and low price of this material.

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