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Computational Assisted-Molecular Imprinted Polymer Design for Magnetic Solid Phase Extraction of Pinostrobin from Krachai

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Abstract

The Covid-19 pandemic is driving the use of herbal extracts to treat early stages of Covid-19 symptoms, particularly in light of the increased demand for Krachai (Boesenbergia rotunda (L.) Mansf.) with significant pharmacological properties. However, the relevance of establishing extract methods is still necessary for Krachai standardization at an industrial level for continued industrial development of food and health products. The purpose of this work was to develop a unique solid phase extraction with particular recognition produced by imprinting technology on the suface of Fe3O4 nanoparticles that may enable selective absorption of pinostrobin, an active ingredient in Krachai. Pre-polymerization procedure of molecularly imprinted polymer (MIP) nanoparticles specific to pinostrobin was critical to computational aided-design MIP nanoparticles in this preliminary study. The molecular modeling interactions between two mixed functional monomers, methacrylic acid and vinylpyridine, in the presence of pinostrobin, a printed molecule were used by Hyperchem 7.5 software package. The complex was built and simulated in various ratios of template and functional monomer conformations in order to geometrically optimize it to the lowest energy state in the gas phase. The estimated free binding energies of each conformation were calculated using the semi-empirical PM3 simulation method. The results showed that interactions with the ratio of 1:2:2 (pinostrobin: methacrylic acid: vinylpyridine) had the maximized free binding energy when compared to interactions with other ratios. Additionally, the FT-IR approach was used to characterize the supporting nanoparticles for the surface coating of the optimized MIPs.

Keywords: *Molecularly imprinted polymers, Krachai, Pinostrobin, Computational chemistry*

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INTRODUCTION

The usage of simulations based on mathematical approaches involving the use of thermodynamic models has become more prevalent in recent years due to the creation of new and improved software and advances in processing capacity. Instead of studying reactions and compounds experimentally, computational chemistry enables scientists to analyze chemical processes through computer calculations. This can greatly aid in understanding some experimental results and enhance new experimental recipes. There are two basic approches of all calculations; the first is molecular mechanics simulations, which employ the rules of classical physics to predict the structures and characteristics of molecules. Electronic structure approaches, on the other hand, base their computations on the rules of quantum mechanics rather than conventional physics. The renowned Schrödinger equation may be used to calculate energy and other characteristics of molecules of interest (Atta et al., 2011).

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Molecular modeling is now utilized successfully to investigate features of the molecular imprinting process as well as the performance and characteristics of polymers, and it is crucial for understanding and designing research in polymer science. In some cases, these efforts were effective in establishing optimal configurations or providing structural and thermodynamic data on the target complex. It has been reported that computational screening based on molecular mechanics calculations was used to test functional monomers and polymerization solvents in the rational design of MIPs. (Buszewski et al., 2010, Riahi et al., 2009, Suedee et al., 2008). The approach was based on comparing the binding energies of the most stable complexes created between the template and several functional monomers. Such initiatives have shown promise for expediting the assessment of molecular imprinting parameters and for assisting in the logical design of MIP synthesis (Suryana et al., 2021). In this preliminary study, Computational calculation was used as assisting the molecular design of molecular imprinted polymer for magnetic solid phase extraction of pinostrobin from Krachai, abundant herb in Thailand.

LITERATURE REVIEW

Molecular imprinting is a highly effective approach for integrating particular substrate recognition biding sites into polymers. By using this method, materials with a specific recognition site for the target compound can be produced. This method comprises copolymerizing a functional monomer and a cross-linking monomer during the presene of template of interest in an optimal porogen solvent. The functional monomers interact with the template through cleavable covalent bonds or non-covalent bonds (hydrogen bonding, ionic, hydrophobic contact, etc.). The template is then extracted, leaving behind corresponding binding sites that are specific to templates with its size, shape, properties, and chemical functionality in the polymeric cavities. MIPs offer excellent stability, pre-designed selectivity, and are easy to produce and store. In light of this, they have a variety of uses, including enantiomeric separations, sensors, catalytic synthesis, and drug delivery (Han et al., 2022). In analytical chemistry, solid phase extraction (SPE) based on imprinted materials offer potential for chemical separation applications for sample pre-concentration and clean-up (Tamayo et al., 2007, Marć et al., 2018). MIPs are more cost-effective, stable in a variety of conditions, more selective than conventional sample treatment techniques when employed as SPE materials. Additionally, MIP-SPE can be used immediately following a solvent pre-extraction phase. SPE appears to be one of the most promising MIP application areas today and is also the application that is most near to commercialisation.

Krachai (Boesenbergia rotunda (L.) Mansf.) is the Zingiberaceae family commonly known as Fingerroot, or Chinese's ginger distributes throughout Southeastern Asian countries. Rhizomes are underground stems that break into a big group with light brown skin. Many Asian cuisines make use of it. Krachai also aids in the expulsion of gas and lessens inflammation, colic, oral and urinary

illnesses, dysentery, and other medical conditions (Abdelwahab et al., 2011). Pinostrobin, another active ingredient in Krachai, has significant pharmacological effects in nourishing the body because of its qualities as an antioxidant, anti-inflammatory, stomach ulcer-prevention agent, anti-diarrheal, stimulator of bone cells, inhibitor of the formation of fat cells, anti-toxicity, inhibitor of the growth of cancer cells, as well as antiviral and antibacterial (Isa et al., 2012).

As far as we known, literature on MIP-SPE selective to active ingredients in the standardized extracts for Boesenbergia rotunda are limited or less discussed. As a result, creating an analytical separation technique for the standardized extracts from Boesenbergia rotunda is a critical first step in their development as industrial raw materials for food and health products.

RESEARCH METHOD

3.1 Preparation of supporting nanoparticles

The Fe_3O_4 nanoparticles are prepared following a previous work with minor modification (Bunkoed et al., 2020). Briefly, 1.6 g of $FeCl_2.4H_2O$ and 4.3 g of $FeCl_3.6H_2O$ in 70 in 75 mL of deionized water and heating to 80 °C. Under vigorous stirring at 80 °C, 10 ml of NH_4OH (30% v/v) are added to the mixed solution. Then, the solid phase was separated by a magnet and rinsed with 20 ml of deionized water when the resulting suspension has cooled to room temperature. The prepared Fe_3O_4 nanoparticles are dried at 60 °C for 5 hours.
To synthesize Fe_3O_4@MIP nanoparticles, a polymerizable group is subsequently introduced to the surfaces of the dried Fe_3O_4 nanoparticles. Breifly, 2.6 ml of NH_4OH (30% v/v), 110 ml of deionized water, and 150 ml of ethanol were added to a solution containing 2.0 g of Fe_3O_4. After 20 minutes of ultrasonication, 0.5 ml of 3-(trimethoxysilyl) propyl methacrylate (MPS) was added to suspension solution for 12 hours of stirring at a constant temperature of 45 °C. After rinsing with 65 ml of deionized water and dried at 65 °C for 8 hours, the resulting black powder of Fe_3O_4@PMS nanoparticles is collected using a magnet.

3.2 Selection of functional monomer toward pinostrobin

All computations were carried out using a PC with an Intel(R) Core(TM) i5-2400 core 3.10 GHz CPU, 8.00 GB of memory, and a 1 TB hard drive. The GaussianView 5.0 programs were used to perform all theoretical computations for this investigation. Using GaussianView 5.0 software, which itself underwent an initial optimization using the AM1 approach, the 3D chemical structures of the methacrylaic acid (MAA), polyvinylpyridine (PVD), and pinostrobin template were created in the first stage. The ability of MAA and PVD functional monomers molecule to build complex structures utilizing template molecules in the gas phase was theoretically compared using a Restricted Hartree-Fock (RHF) semi-empirical method. The PM3 method was used to structural optimize the complexation of the template and functional monomers at the ground state by lowering the molecular binding energies (Cojocaru et al., 2013). All equations used to determine the best

functional monomers treated it as an isolated gas phase molecules. The geometry optimization procedure (Polak-Ribier) used conjugate gradients, with the convergence set to 0.01 Kcal/(mol). The simulation, which attempts to minimize energy, looks for a molecular structure where the most stable configuration was produced by even the slightest changes in geometry. The entire root-mean-square gradient (RMS-gradient) was almost zero. The most stable template-monomer complexes for each functional monomer chosen were sought for, and their interaction energy, ΔE, was determined using the following equation:

$$\Delta E = E_{(template/monomer\ complex)} - (E_{template} + \Sigma E_{monomer(s)})$$

FINDINGS AND DISCUSSION

4.1 Fourier-transform infrared spectroscopy (FTIR)

The surface chemistry of the synthesized Fe_3O_4 and Fe_3O_4/MPS nanoparticles was characterized by FT-IR technique as shown in Fig. 1. The functional peak at roughly 3,440 cm^{-1} was caused by the stretching vibrations of hydroxyl groups, which were attributed to -OH absorbed by Fe_3O_4/MPS nanoparticles. While the strong absorptions at around 552 cm^{-1} were attributed to the vibration of the Fe-O group, the two absorption peaks at around 1,079 and 812 cm^{-1} were ascribed to the asymmetric and symmetric stretching of Si-O-Si. Two different bands at 2,946 and 2,841 cm^{-1} were ascribed to symmetric and asymmetric CH_2 stretching vibrations, respectively. The distinctive absorptions at 1,717 and 1,635 cm^{-1} were assigned to the C=O and C=C groups, respectively, suggesting that MPS modified Fe_3O_4/MPS nanoparticles were created by polymerizible groups of MPS and then coating it with Fe_3O_4/MPS nanoparticles (Zhang et al., 2017).

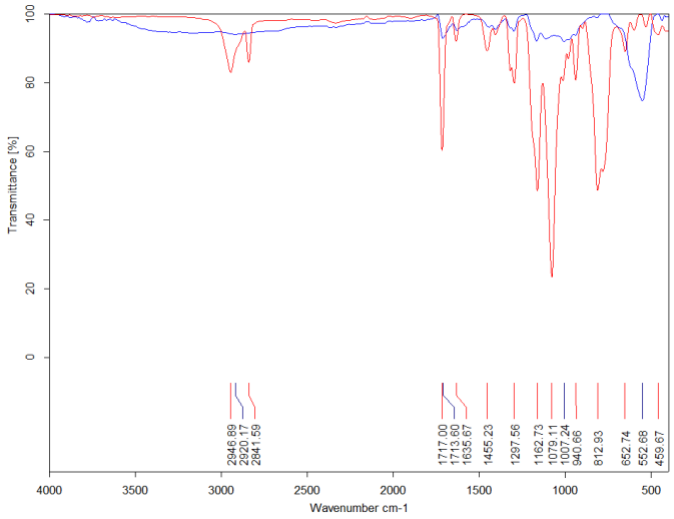

Figure 1: FT-IR spectra of Fe_3O_4/MPS (blue line) and MPS nanoparticles (red line)

4.2 Molecular modeling in imprinted polymer

Molecular imprinting is a potent designable approche for producing binding sites in cross-linked polymers in the presense of template. Understanding the intermolecular interactions that result in molecular complexation and generating of specific binding sites during polymerization is one major issue in the study of molecular imprinting. A better understanding of the function of the various elements during the imprinting process is provided by the computer models that were created in this work for all imprinting species at the appropriate ratios. To investigate the interactions in the imprinting species, the hydrogen bonding analysis was combined. Understanding how the aromatic moiety of functional monomers interacts with the template required the identification of π-π stacking interactions. The creation of specific binding cavities, which results in the effective imprinting of the pinostrobin, depends on the functional monomer forming a stable combination with the template molecule. The initial stage in the creation of MIPs included the template molecule and the functional monomers forming a complex. The complex with the highest level of stability will be produced by the monomer that has the strongest interactions with the template. The most stable complexes of predicted binding energies and the number of activity sites produced by pinostrobin template's interactions with the monomers under investigation (MAA and PVD) are compiled in Fig. 2 and Table 1. Pre-polymerization of the template, two functional monomers, and mixtures of them in the ratios of 1:4, 1:4, and 1:2:2 are shown in Fig. 2. The pibostrobin template and the two functional monomers have distinct mole ratios. When comparing the estimated binding energy values for the 1:4 template/MAA and template/PVD complexes, it should be observed that the template/PVD complex has achieved the higher binding energy. Through hydrogen, the tiny MAA molecules demonstrated an easy access to the pinostrobin template molecule. By using hydrogen bonds interactions to construct a more complex PVD monomer with the template, the configurational rotation between the two pinostrobin rings was reduced. Pre-polymerization of the template, two functional monomers, and mixtures of them in the ratios of 1:4, 1:4, and 1:2:2 are shown in Fig. 2. It should be noticed that the template/PVD complex has the higher binding energy when comparing the computed binding energy values for 1:4 template/MAA and 1:4 template/PVD complexes. The tiny MAA molecules demonstrated straightforward access to the pinostrobin template molecule through hydrogen. Even the PVD monomer became more complicated with the template through hydrogen bonds and interactions to lessen the configurational rotation between the pinostrobin's two rings. In case of 1:2:2 template/MAA/PVD complex, results provided the greatest binding affinity with high binding sites from possible strong hydrogen bonding and π-π interactions (Mamo, et al., 2020). Therefore, the results of calculations suggest that the molecular interaction of pinostrobin template molecule and combination of MAA and PVD functional co-monomers show the most stable complex and maximize the number of binding sites.

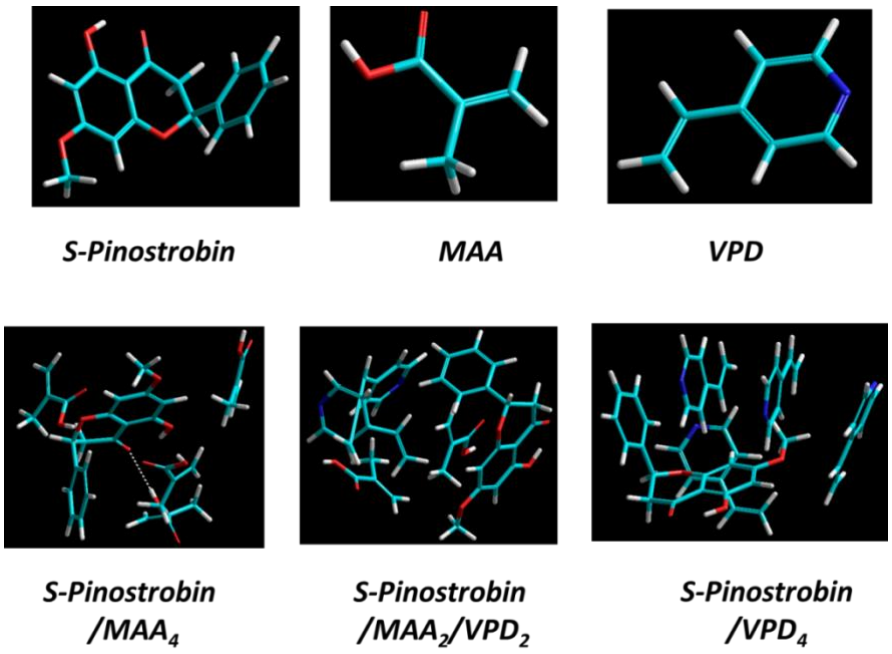

Figure 2: Pre-polymerization of pibostrobin template and two functional monomers with mole ratio of (a) 1:4 (template/MAA), (b) 1:4 (template/VPD) and (c) 1:2:2 (template/MAA/VPD) in gas phase.

Table 1: Interaction energies of pre-polymerization complexes of pinostrobin template and MAA and PVD functional monomers after calculation.

Molecular system	**Energy (Hartree)**	**ΔE (interaction energy) (Hartree)**
S-Pinostrobin	-3809.7659	-
MAA	-1197.7541	-
4-vinylpyridine	-1628.023	-
S-Pinostrobin/MAA_4	-8611.2898	-10.5075
S-Pinostrobin/VPD_4	-10322.9119	-1.0540
S-Pinostrobin/MAA_2/VPD_2	-9443.7930	-17.5271

** 1 Hartree = 1.5936x10^{-3} kcal/mol*

CONCLUSION AND FURTHER RESEARCH

Molecular modeling was selected to study for better understanding in imprinted supramolecular nanoparticles system. Using of co-functional monomers, both MAA and VPD,

suitably provided for preparing pinostrobin selective MIP nanoparticles, which provided the most energetically complex stability (-2.79 x 10-2 kcal/mol) with the maximized contact binding site. The possible multiple interations of template and functional monomers were hydrogen bonding and π-π interactions, providing high affinity in various solvent conditions. Additionally, the FT-IR approach was proved that the supporting nanoparticles had vinyl groups on the surface of supporting nanoparticles for futher MIPs polymerization. The optimized MIP nanosorbents further are applied to analyze pinostrobin of Krachai in the available market. Thus, developing analytical separation technique from imprinting technology for the standardized extracts from Boesenbergia rotunda is important step towards the development as industrial raw materials for production of Industrial food and health products.

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