engineering proceedings

MDPI

Proceeding Paper

Application of Molecular Imprinting Technique in Separation and Detection of Natural Products †

Wenwei Li [1], Axin Liang [1], Zijia Lu [2] and Yao Xie [2,*]

[1] Key Laboratory of Molecular Medicine and Biotherapy, School of Life Science, Beijing Institute of Technology, The Ministry of Industry and Information Technology, Beijing 100081, China; lax@bit.edu.cn (A.L.)
[2] Beijing Dawn Aerospace Bio-Tech Co., Ltd., Beijing 100043, China; luzijia@edongfanghong.com
* Correspondence: xieyao@edongfanghong.com
† Presented at the 8th International Symposium on Sensor Science—China, Nanjing, China, 29–31 March 2023.

Abstract: The content of effective components of natural products is small, generally requiring to be extracted and purified using complex technology, and the detection method is both time-consuming and costly. Molecular imprinting technology is an effective means to prepare highly selective media. Molecularly imprinted polymers have the advantages of strong selectivity, simple preparation, reusability and have shown a good prospect in the separation and detection of various natural products. Based on the types of active ingredients of natural products, this paper reviews the separation and detection of natural products via molecular imprinting technology in recent years, and discusses the advantages and disadvantages of molecular imprinting technology, in order to provide reference for the subsequent application of molecular imprinting technology.

Keywords: molecular imprinting; natural product; separation method; detection

Citation: Li, W.; Liang, A.; Lu, Z.; Xie, Y. Application of Molecular Imprinting Technique in Separation and Detection of Natural Products. *Eng. Proc.* **2023**, *49*, 1. https://doi.org/10.3390/engproc2023049001

Academic Editor: Huangxian Ju

Published: 20 October 2023

1. Introduction

Natural products refer to a class of compounds with unique functions and biological activities existing in plants, animals and microorganisms, including a variety of small molecular substances such as flavonoids, organic acids, alkaloids, terpenoids, phenols and large molecular substances such as proteins and polysaccharides. Many of the components have the effect of disease prevention and control, and have become an important source of raw materials for food and drugs [1]. The separation and analysis of natural products has always been an important form of technology, limiting the development of natural active products, because the drug effect of natural active products is closely related to its structure. At the same time, the extraction process of natural products will result in a lot of impurities, and the extraction and detection of active ingredients is difficult.

Common separation and purification methods include chromatography, membrane separation, macroporous resin method, etc. Although the traditional separation methods have the advantages of mature technology, good selectivity and a wide application range, these methods still have some problems, such as long processing time, high requirements for instrument operation technology, and large damage caused to the sample, resulting in a poor actual separation effect. In order to obtain high-purity compounds, it is often necessary to undergo multiple solvent extractions and repeated column chromatography, which not only consume large solvents and cause serious environmental pollution, but also take a long time and have low extraction efficiency [2]. At present, high-performance liquid chromatography (HPLC), mass spectrometry (MS) and nuclear magnetic resonance (NMR) are the main methods for the analysis of natural products, which also have the disadvantages of long processing time and great damage inflicted onto samples [3]. Different from synthetic drugs, natural products generally have relatively mild effects and less side effects on the human body, and many chemical synthetic drugs are also based on the structure of natural products. Because of the high research value of natural products, the research on

separation analysis surrounding it is also increasing year by year, and new methods are constantly proposed in order to solve the current problems.

2. Molecular Imprinting Technique

2.1. Principle of Molecular Imprinting Technique

Molecular imprinting technology is a new means of molecular recognition that has been developed in recent years. Molecular imprinting polymers (MIPs) are synthesized via molecular imprinting technology (MIT), which can specifically recognize and selectively adsorb specific target molecules (templates). MIPs originate from the imitation of the interaction between antigens and antibodies. In 1949, Dickey [4] first discovered the selective adsorption of dyes. Since then, MIPs have been applied in many fields. Compared with natural antibodies, MIPs have the advantages of high selectivity, simple preparation, and long-term stability [5].

The preparation of MIPs is an important part of molecular imprinting technology research. An MIP is prepared using functional monomers, crosslinked monomers and template molecules. The functional monomers and crosslinked monomers copolymerize in the presence of template molecules. According to the type of binding interactions that occur during polymerization, it can be divided into four main pathways: non-covalent binding, covalent binding, sacrificed spacer and metal chelation [6]. A pre-polymerization complex between an imprint molecule and functional monomers can be formed via noncovalent interactions (self-assembly), or be covalently coupled. The difference between covalent and noncovalent connections is that covalent bonds are more stable and can produce more uniform binding sites. However, noncovalent imprinting methods are more flexible in the selection of functional monomers, target molecules and imprinting materials. At the same time, most biological molecules in nature also interact through noncovalent bonds [7]. Therefore, in the actual experimental operation, the combination of noncovalent and covalent connection has more advantages.

In recent years, the demand for many new template molecules has led to the development of more preparation methods of MIPs. The properties of MIPs obtained by different preparation methods are also different, so it is very important to select the preparation method. Precipitation polymerization and electropolymerization are common preparation methods. Precipitation polymerization is usually used to add functional monomers, templates, crosslinkers and initiators on the surface of the carrier. The resulting MIPs are loose and uniform, which can avoid the damage to the binding site caused by grinding after bulk polymerization. In addition, deposition polymerization can effectively control the distribution of MIPs and the accumulation of nanoparticles on the surface. The process of electropolymerization involves the copolymerization of template molecules to the surface of the carrier to form an MIP membrane, which is polymerized by applying an appropriate potential to the surface of the carrier or through a potential scanning method within a specified range. Compared with other polymerization methods, electropolymerization can control the thickness of MIP membrane by controlling the number or time length of polymerization cycles. This highly plastic MIP membrane preparation method can achieve uniform deposition on carriers of various shapes and sizes, and is sensitive to template molecules [8].

After polymerization, the template molecules are eluted to form complementary cavities, forming binding sites that are complementary to the template molecules in size, shape and interaction. The target molecules can subsequently bind to functional monomers through non-covalent bonds, covalent bonds and metal complexes with ion–ligand coordination effects to achieve the purpose of specific molecular recognition [9]. The functional monomer has some substituents and participates in the crosslinking reaction with suitable crosslinking agents. Thus, the cavities formed in the MIP can specifically recognize template molecules and introduce molecular memory into the polymer.

2.2. Application of Molecular Imprinting Techniques

MIPs have enormous beneficial aspects like high selectivity and specificity toward the targeted molecules. They are easy to synthesize, are cost-effective and reliable under different conditions like pH, temperature and pressure [10]. Additionally, the changeable properties of MIPs could be achieved through the different combinations of the templates, functional monomers and crosslinkers. Based on these features, MIPs are used in multiple fields like environmental restoration, wastewater treatments, food analysis, chemical/biological sensing, targeted drug delivery, proteins recognition/purification and hormone detoxification [11,12]. The stated applications can be performed using MIPs as sorbents, stationary phases and catalysts [13].

As a sensor recognition element, MIPs have good commercial prospects and high practical application value in the field of sensor analysis. Compared with other types of sensors, electrochemical sensors have unique advantages such as high sensitivity, fast analysis speed, simple device operation and easy miniaturization. Therefore, MIPs as a molecularly imprinted electrochemical sensor for recognition elements has received extensive attention and has become an international research hotspot [14].

Food quality is a subject related to people's lives and safety. Although the government makes active efforts to control and monitor food quality, it is still very difficult to control food quality. At present, high-performance liquid chromatography (HPLC) combined with mass spectrometry (HPLC-MS), nuclear magnetic resonance (NMR), enzyme-linked immunosorbent assay (ELISA) and other analytical technologies are mainly used for food quality collection and monitoring [15]. These technologies have high accuracy, but they require qualified operators, expensive instruments and time-consuming and complex measurement methods. Therefore, a practical, economical and fast high-throughput detection method is needed, which can be used on an industrial scale and should also be suitable for the integration of portable handheld devices, so as to realize field sample analysis [16].

Biosensor is an instrument composed of biological sensitive elements and signal converters, which is sensitive to biological substances and can convert concentration into electrical signals for detection. Electrochemical biosensor is an important branch of biosensors. It is a device that converts the interaction between an analyte and the surface recognition element of an electrode into measurable signals. The signal is able to directly or indirectly indicate the relationship between the analyte and a quantifiable output signal, so as to qualitatively or quantitatively analyze the substance. Electrochemical technology has the advantages of high sensitivity, good selectivity, fast response time, low cost, simple instrument, portability and easy integration. It can also detect organic matter, inorganic matter, ions, neutral molecules or metal ions, with a wide range of applications [17].

According to the different biological materials used, electrochemical biosensors can be divided into enzyme electrode sensors, microbial electrode sensors, electrochemical immunosensors, tissue electrodes, organelle electrode sensors and electrochemical DNA sensors. On the other hand, when a different output signal is involved, the sensors can be divided into potential sensor, current sensor, conductance sensor, impedance sensor, amperometric sensor and voltammetry sensor. Among them, voltammetry and amperometry are the most widely used in electrochemical sensing [18].

The application of molecularly imprinted electrochemical sensors in food and drug detection has some limitations: due to the lack of effective sensor construction standards, it is difficult to achieve high sensitivity and accuracy; at the same time, a complex sample matrix has great influence on the stability and reproducibility of electrochemical signal output [19]. Therefore, it is urgent to improve electrochemical sensors to meet the requirements of food and drug safety detection. In order to enhance electrochemical sensors so that they have a higher performance, a lot of research has been carried out, including the development of new electrodes, electrode modification, the construction of new detection mode, etc. The combination of MIPs and electrochemical sensors has been recognized in many fields. This method has high selectivity and sensitivity, which is suitable for the detection of a variety of substances, and can also realize simultaneous detection [20].

3. Application of Molecular Imprinting in Separation and Detection of Natural Products

3.1. Flavonoids

Flavonoids, a typical natural product, occupy a large proportion in natural products and are also an important part of promoting plant growth and development. Its basic structural unit is 2-phenylbenzopyrone, and the nucleus is formed by connecting two benzene rings and a phenolic hydroxyl group through three carbon atoms in the center [21]. Flavonoids are widely found in various plants and have multiple effects such as anticancer, anti-inflammatory, antibacterial and cardiovascular protection [22].

Yang [23] successfully prepared a novel pseudo-molecularly imprinted polymer (MIP/CS/Fe_3O_4) for the selective enrichment of flavonoids in *Penthorum chinense* Pursh. The molecularly imprinted polymer was synthesized on the surface of chitosan-modified Fe_3O_4 nanoparticles using naringin as a dummy template and used as a solid adsorbent to enrich the analyte. Compared with the structural analogues, MIP/CS/Fe_3O_4 has fast binding kinetics, good selectivity and a higher adsorption capacity. The adsorption capacity and imprinting factor of MIP/CS/Fe_3O_4 were 8.56 $mg \cdot g^{-1}$ and 1.7, respectively. Finally, MIP/CS/Fe_3O_4 was used to enrich the flavonoids in the crude extract of *Penthorum chinense* Pursh, and 11 kinds of flavonoids were detected successfully, indicating that MIP/CS/Fe_3O_4 is a promising adsorbent for the separation and enrichment of flavonoids. Many excellent properties of the synthetic imprinted polymers also provide a new direction for the simultaneous enrichment of structural similarity.

Rutin (RT) is a kind of common flavonoid with significant antioxidant, antiviral and anti-inflammatory effects. Traditional enrichment methods of RT include solvent extraction, supercritical fluid extraction, microwave-assisted extraction and macroporous adsorption resin [24]. However, most of these methods are unsatisfactory. Song [25] reasonably constructed a novel magnetic molecularly imprinted polymer (HB-TI-MMIPs) with rich, high affinity and evenly distributed binding sites for the selective enrichment of Sophora RT by taking advantage of the structural characteristics of bayberry's dense packing and good honeycomb orientation. The polymerization conditions, physicochemical properties and adsorption properties of imprinted nanomaterials were systematically studied. The optimized HB-TI-MMIPs showed a large adsorption capacity, a fast adsorption rate and good selectivity for RT. At the same time, HB-TI-MMIPs as adsorbents were successfully used for the enrichment and detection of RT in *Sorbus tianschanica* leaves with high recovery rates (87.2~94.6%) and good RSDS (less than 4.3%). Therefore, the preparation of HB-TI-MMIPs has rapid magnetic response and good adsorption performance, which has important application prospects in the field of extraction of plant active ingredients.

Luteolin is one of the most common flavonoids. Its molecular formula is $C_{15}H_{10}O_6$, and its chemical structure is shown in Figure 1. Since the catechol group on its B ring is an electroactive compound, luteolin is an effective antioxidant and bioactive supplement in food, so it is of great significance to determine luteolin content quickly and selectively. You [26] prepared a magnetic molecularly imprinted polymer (Fe_3O_4@MIP) using luteolin as a template, and then modified it with reduced GO (Fe_3O_4@MIP/rGO/GCE) on the surface of a glass carbon electrode. Fe_3O_4@MIP has a spherical structure with a rough surface and good magnetic response in solution. The selectivity for luteolin is superior to that of molecularly imprinted polymers (SiO_2@MIP). By optimizing the preparation and electrochemical conditions, it has good anti-interference ability, linearity, detection limit, reproducibility and stability. The linear detection range of Fe_3O_4@MIP/rGO/GCE for luteolin was 2.5~0.1 μM, and the sensor remained stable for 6 days. The method can be used for the determination of luteolin in lotus leaf extract with high recovery.

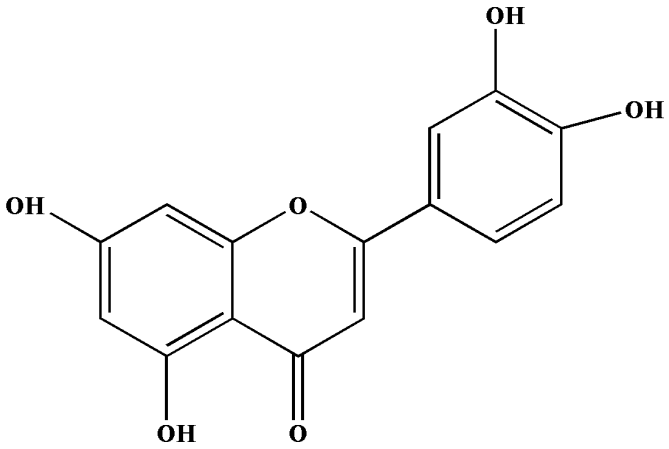

Figure 1. Schematic diagram of luteolin structure.

3.2. Alkaloids

Alkaloid compounds are widely distributed in nature and are generally extracted from Ranunculaceae, Papaveraceae, Fangke and other plants. Alkaloid molecules generally contain one or more nitrogen atoms [27]. Since alkaloid molecules are alkaline, acid is commonly used to extract alkaloids.

Camptothecin (CPT) is a quinoline alkaloid mainly present in medicinal plant Camptotheca acuminata, which has been widely used in the treatment of tumors, leukemia, psoriasis, cardiovascular diseases and cancer [28]. Traditional extraction methods have the disadvantages of low extraction rate, poor selectivity and high energy consumption. In addition, they rely heavily on the use of organic solvents. However, it is difficult to isolate and extract CPT from Camptotheca acuminata due to the diversity and similarity of other components in camptotheca acuminata. Ma et al. [29] prepared super-crosslinked molecularly imprinted resin (MIR) using chloromethylated polystyrene resin as the carrier through Friedel–Crafts reaction after crosslinking and surface imprinting. The prepared MIRs are grafted with a large amount of active group phenol and have good hydrophilicity, which is conducive to the application in water environment. The test results show that MIRs have good adsorption capacity and excellent hydrophilicity. In addition, MIRs have been successfully used as a solid-phase extraction (SPE) adsorbent for the separation and purification of CPT from Camptotheca acuminata fruits. The detection limit of CPT was 0.23 μg mL^{-1}. This method has a high recovery rate (91.2~103.4%), and the relative standard deviation is less than 4.5%. The reusability of MIR as an adsorbent was studied, and the adsorption efficiency remained above 95% after 5 times of recovery. It provides a feasible and efficient method for the selective separation and purification of CPT from complex systems.

As a traditional Chinese medicine, sophora flavescens has a variety of physiological functions, including antibacterial, anti-inflammatory, anti-tumor, anti-allergy, anti-asthma and anti-oxidation [30]. Matrine is the main medicinal active ingredient of matrine, which is mainly derived from the roots and seeds of Matrine. However, the content of this active ingredient in sophora flavescens is less than 0.3%, which makes the extraction and separation process relatively complicated. Guo et al. [31] prepared a temperature-sensitive molecularly imprinted polymer by using bifunctional monomers with critical-phase transition characteristics. The polymers were characterized via infrared spectroscopy, scanning electron microscopy and specific surface area. An SPE-HPLC method for the analysis of quinolazine alkaloids in *Sophora flavescens* extract was established and verified based on the prepared smart polymer. The concentration of quinolazine alkaloids was increased by 4.3~5.2 times by changing the temperature and solvent of solid-phase extraction conditions. The extraction process is mild, less time consuming and avoids the use of a large number of toxic reagents, indicating that the extraction process is more efficient and environmentally friendly.

3.3. Terpenes

Terpenes are a kind of natural compounds consisted of the isoprene unit (C5), as well as any of various olefin compounds whose molecular formula is an integral multiple of isoprene [32]. It is proven that terpenes are able to protect the cardiovascular system and resist oxidation [33].

Ganoderic acid is the main pharmacoactive substance in *Ganoderma lucidum*. In recent years, a number of domestic and foreign studies have proven that *Ganoderic* acid has drug effects in lowering blood sugar, anticancer, liver protection and detoxification, anti-inflammatory, antioxidant and other aspects [34,35]. *Ganoderic* acid A is one of the most abundant *Ganoderic* acids in Ganoderma lucidum. Huang et al. [36] used o-phenylenediamine as a functional monomer to prepare a layer of MIP film that can specifically identify *Ganoderic* acids A on the surface of glass carbon electrode for the rapid and sensitive detection of Ganoderma acid A (Figure 2). Under the best test conditions, the synthesized molecularly imprinted electrochemical sensor has good reproducibility, stability and selectivity. In the range of 1.0 pmol/L~1.0 μmol/L, the concentration (mol/L) of *Ganoderic* acid A had a good linear relationship with the peak current (μA). The fitting linear equation was Ip = 18.2−0.710lgC, the correlation coefficient R_2 = 0.9951, and the detection limit was 0.21 pmol/L. The recoveries of the samples were 98%~102%, which showed good detection performance.

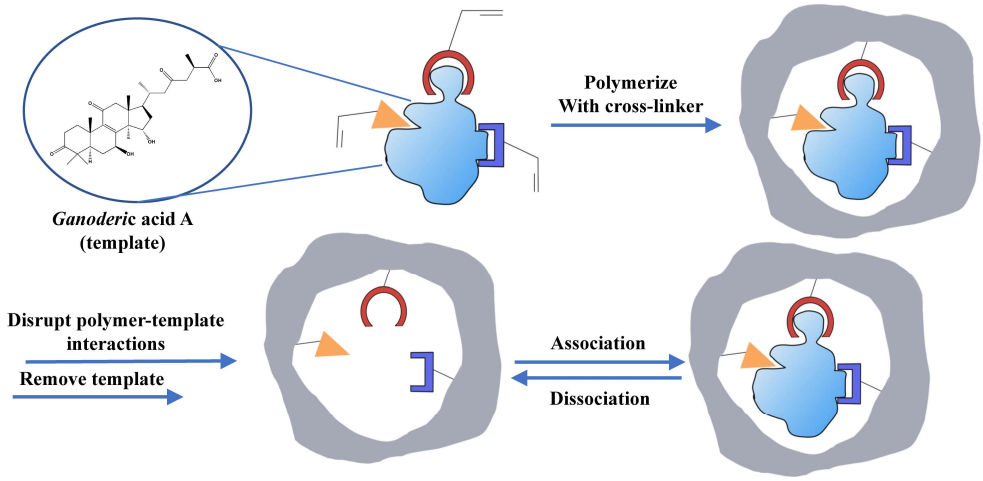

Figure 2. Schematic diagram of molecular imprinting principle of *Ganoderic* acid A as template.

Terpenes are hydrocarbons released into the environment from herbaceous vegetation. These biogenic volatile compounds include monoterpenes, sesquiterpenes and oxygenated terpenes [37]. The content of terpenes is very important for studying the freshness, shelf life and availability of plants. Iqbal [38] developed a QCM-arrays for sensing terpenes in fresh and dried herbs via biomimetic MIP layers for the selective quantification of terpenes emanated from fresh and dried Lamiaceae family species, i.e., rosemary (*Rosmarinus officinalis* L.), basil (*Ocimum basilicum*) and sage (*Salvia officinalis*). Linearity in reversible responses over a wide concentration range of <20–250 ppm has been achieved. The sensor array consisted of two quartz sheets; each containing three gold electrodes and an electrode structure was printed on the quartz surface via a screen printing procedure. MIPs were synthesized by mixing styrene as a functional monomer, DVB as a crosslinker, AIBN as a radical initiator and diphenylmethane as a porogen. The template was added to this mixture for imprinting as optimized from a number of observations, so six MIPs were prepared with different terpenes. Finally, each mixture was polymerized for 40 min at 70 °C. Layers of these polymers were coated on electrode via spin coating. Such an array in association with data analysis tools can be utilized for characterizing complex mixtures.

3.4. Organic Acid

Chlorogenic acid (CGA) is a degradation substance produced by caffeic acid and quinic acid, which has beneficial effects such as lowering blood pressure, anticancer, antioxidant and anti-inflammatory [39]. Due to its special pharmacological action, it has been widely used in the cosmetics industry for skin whitening, moisturizing and sunscreen, because it can avoid collagen damage caused by reactive oxygen species [40]. In addition, CGA is also a highly effective antioxidant and preservative for food processing and storage [41]. Liu [42] used molecularly imprinted polymers (MIPs) as fillers for solid-phase extraction to recover CGA from eutectic solvent (DES) extracts of eucommia ulmoides leaves (eula). Using CGA as the template molecule, MIPs were formed through bulk polymerization with three functional monomers (methacrylic acid (MAA), acrylamide (AM) and 2-vinylpyridine (2-VP)), respectively. Then, the interaction between CGA and these monomers was studied using computational simulation. The results showed that MAA-MIPs had high selectivity, high adsorption capacity (120.70 mg/g) and high adsorption rates (40 min to reach adsorption equilibrium). Their static and dynamic adsorption behaviors accord with Langmuir's model and the quasi-second-order kinetic model, respectively. The recovery of CGA was 75.15% and the purity was 65.20%. The specific adsorption and recycling of the template molecule CGA can be realized, which provides a new idea for the separation and purification of the target products in the DES-based extracts.

Vanillic acid (VA), a phenolic compound usually derived from secondary metabolites of fruits, plants and vegetables, has antioxidant activity and plays a crucial role in the prevention of a variety of degenerative diseases [43]. Buffon [44] developed and applied an electrochemical platform for the one-time detection of VA using a screen printing electrode modified with reduced GO, iron nanoparticles and molecularly imprinted polypyrrole film. The electrochemical platform was characterized via cyclic voltammetry, electrochemical impedance spectroscopy, scanning electron microscopy, X-ray energy spectrum and X-ray photoelectron spectroscopy. Under optimized conditions, the linear range of concentration was 1.0×10^{-9}~1.5×10^{-7} mol/L, and the limits of detection and quantitation were 3.1×10^{-10} and 1.0×10^{-9} mol/L, respectively. The electrochemical platform is selective for VA recognition and has good repeatability and stability in voltammetry response. The established method can be used for the determination of VA in banana and orange peels. The results show that the established electrochemical platform has good accuracy in the determination of VA.

4. Conclusions and Outlook

In conclusion, the application of molecular imprinting technology in the separation and detection of natural products can effectively improve the purity of extraction of natural products, and improve the sensitivity, efficiency and selectivity of detection. At present, the research on molecular imprinting technology of natural products is increasing year by year. For the rapid, sensitive and accurate detection of natural products, the establishment of molecular imprinting technology should be further designed and analyzed, and it is also necessary to design a technology that can detect multiple substances at the same time. The popularization of this technology can also promote the development of products of the same origin as medicine and/or food.

Author Contributions: Conceptualization, W.L., Z.L. and Y.X.; investigation, W.L.; writing—original draft preparation, W.L.; writing—review and editing, W.L. and A.L.; supervision, A.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors would like to express their gratitude to everyone who assisted them with their literature review.

Conflicts of Interest: The authors declare no conflict of interest.

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