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Research progress of plant-derived aconitine as insecticide

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ABSTRACT: In recent years, increasing attention is being given to the effective protection of the environment. The use of pesticides is a common practice in agriculture. At present, finding effective and safe pesticides is important for research in agricultural application. Botanical insecticides are environmentally friendly because of their environmental viability and easy degradation. However, there are still some problems in the development and utilization of botanical insecticides leading to a bottleneck in the process. In order to facilitate the development of botanical insecticides, this review uses aconitine as an example to summarize the research progress, the detection and analysis, and the carrier materials to optimize its usage and storage.

KEYWORDS: botanical insecticide, aconitine, safe pesticides, aconitum, green agriculture, environmental protection

INTRODUCTION

The changes of human lifestyle in the present world with high-technology and new things emerging around are recognized. In such an environment, people have paid more attention to the development concept of environmental protection, green practices, and food security. For high agricultural productivity, though the use of chemical insecticides is effective in prevention of insect pests [1], but a large number of agricultural products, soils, and even water sources for drinking or irrigation production, especially the increasingly abundant food markets, have been damaged by residues from the use of chemical pesticides. Therefore, research on effective and safe pesticides and insecticides is important. In particular, botanical insecticides have several advantages such as environmental survivability, easy degradation, and environmental friendliness [2–4]. However, the applications of these natural products in agricultural insecticides still have some limitations.

Therefore, studying the structural characteristics of botanical insecticides, the mechanism of structural changes in the environment, the safety evaluation of beneficial organisms and the introduction of inorganic materials as a carrier to solve the easy hydrolysis or difficult degradation of plant-derived insecticides or in drug application will play a crucial role in the development and application of botanical insecticides. This review describes research progress on aconitine as an attractive example of plant-based insecticides for a sustainable green environment.

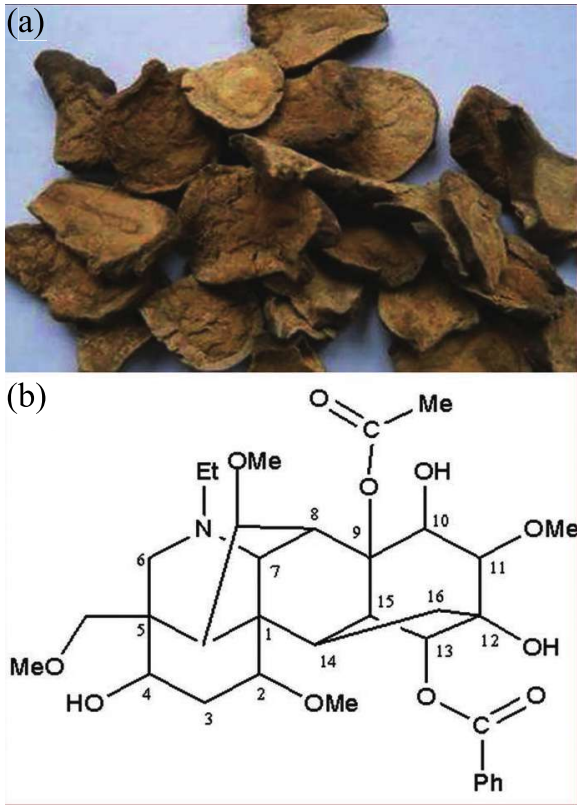

Fig. 1 (a) Medicinal herbs from *Aconitum carmichaeli* Debx and (b) the molecular structure of aconitine.

ACONITINE FROM A BOTANICAL EXTRACT

It is urgent for researchers in related fields to find ideal pesticides that are not only in line with the development of modern safe, green, and environmental protection agriculture, but are also widely accepted and used [5–7]. There are many extraction methods for aconitine such as acid extraction, alcohol extraction, semi-bionic extraction, and supercritical CO_2 extraction. The main method is extraction of aconitine with anhydrous ethanol. The common separation methods of

aconitine are silica gel column chromatography, Al_2O_3 column chromatography, high speed countercurrent chromatography, macroporous resin separation, and ion exchange resin separation. Through continuous improvement of extraction and separation technology, several kinds of typical double ester alkaloids have been separated from high top Ranunculaceae plant, including aconitine, neoconitine, mesaconitine, and hypaconitine [8–10]. Among them, aconitine has the strongest insecticidal activity [11–14]. According to the literature, different aconitum (aconite or monkshood) sources contain varied alkaloids. For example, mesaconitine is the main compound of *Aconitum kusnezofi*, aconitine is the main alkaloid in *Aconitum napellus*, and the main constituents of *Aconitum carmichaeli* are hypaconitine and mesaconitine [15]. Aconitine is the main ingredient in the roots (Radix Aconiti Kusnezoffii and Radix Aconiti Carmichaeli), stems, and leaves of these plants (Fig. 1). Three hydroxyl and two ester groups are present in this alkaloid; the latter is reported to be a toxic part [16]. Due to its high toxicity, aconitine has been used as a pesticide for a long time, and a good insecticidal effect on *Plutella xylostella*, *Pieris rapae*, and *Armyworm* was found. In recent years, Wang et al [17] introduced sulfonyl groups into aconitine ($S(=O)_2C_{34}H_{47}NO_{11}$). Moreover, Xu et al [18] prepared new alkyl and acyl aconitines ($(COC_2H_5)C_{34}H_{47}NO_{11}$ and $(COC_6H_5)C_{34}H_{47}NO_{11}$, respectively). Wang [19] synthesized 3,13-ester based aconitines, $(COC_2H_5)(COC_6H_5)C_{34}H_{47}NO_{11}$ and tested their insecticidal activity. These molecular structures of aconitine were modified to improve its properties, which provided great achievements. It was concluded that the modification of aconitine required the retention of the hydroxyl group of C3, which was crucial to the insecticidal activity.

THE CRYSTAL STRUCTURE OF ACONITINE

Natural botanical insecticides have attracted wide attention because of their high efficiency, less residues, and compliance with environmental factors. Since the 1960s, many scholars have conducted in-depth studies on the separation [20, 21], determination [22], and application of aconitine [23–25]. Pu et al [26] reported an unexpected crystal structure of aconitine and revealed the main reason for the spontaneous transformation of aconitine solid powders into crystals in air. The crystal was characterized by X-ray single crystal diffraction analysis and elemental analysis. Its main structure consists of four six-membered rings and two five-membered rings (Fig. 2). Intramolecular and intermolecular O—H···O and C—H···O hydrogen bonds extend neighboring molecules into one-dimensional chains and two-dimensional skeletons, which may be the primary factor for this change.

THERMAL STABILITY AND HYDROLYSIS CHARACTERISTICS OF ACONITINE

Though botanical pesticides are highly favored [27], the insecticidal aconitum alkaloids are easily hydrolyzed. As a result, their potency is not long lasting [28–32]. In order to solve such disadvantages, it is necessary to study the structural characteristics of aconitine itself such as its thermal stability and hydrolysis characteristics, which provides theoretical basis for its storage and pharmacodynamic conditions in the process of use. Our research group discussed the thermal degradation mechanism of aconitine and the thermal effect of hydrolysis mechanism by using microcalorimetry and thermogravimetric method as shown in Fig. 3 [33]. The thermal degradation of aconitine in air exhibited one further additional step at 484–579 °C compared to the degradation under nitrogen atmosphere (Fig. 3a). This was because small molecules containing C compounds were further oxidized to CO_2 by oxygen in the air. Under nitrogen atmosphere, aconitine was not completely oxidized and decomposed. Fig. 3b showed that the pyrolysis process at different heating rates was basically consistent. Aconitine underwent an exothermic reaction in both pure water and soil filtrate environments (Fig. 3c). In general, aconitine readily hydrolyzes to subaconitine and other molecules, which will greatly reduce the drug activity. Aconitine was thus unstable in air and should be stored under low temperature and dry conditions.

Many natural plant-derived insecticides which are unstable in structure and easily hydrolyzed can improve the degradation rate of insecticides and reduce the amount of the pesticide residue. Problems caused by degradation can be avoided by drug loading before and during pesticide use, such as the introduction of mesoporous materials as carriers.

THE DETECTION METHOD OF ACONITINE

Aconitine has some value in the treatment of arthritis and rheumatic diseases due to its analgesic effect [34, 35], but it is also known for its toxicity. Ingestion of 0.2 mg aconitine will cause vomiting, diarrhea, sensory paralysis, and other toxic symptoms. More than 3 mg can cause heart and lung failure and even death [36, 37]. It is necessary to develop a rapid detection method for aconitine in order to avoid the accidents caused by overdose and sudden food poisoning.

At present, high performance liquid chromatography [38, 39] and chromatography tandem mass spectrometry [40] have been used for the determination of aconitine, hypaconitine, and neoconitine in blood and other biological samples. Zhang et al [41] qualitatively and quantitatively determined a variety of aconite alkaloids and related metabolites in the blood and urine of aconite poisoning patients and compared the metabolite contents in blood and urine using ul-

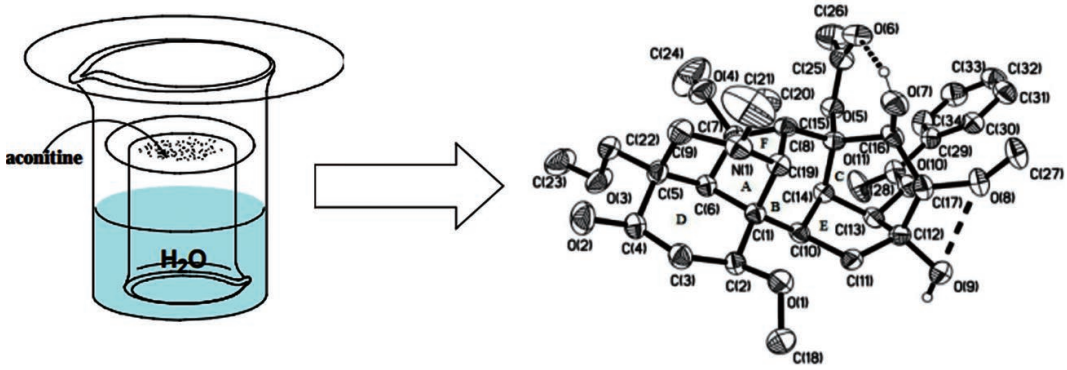

Fig. 2 Diagram of the experimental setup. Two-dimensional structure of aconitine viewed from the b-axis. The dashed lines represent the C—H···O hydrogen bonds. The black spheres represent carbon atoms, the red ones show oxygen atoms, and the blue ones are the nitrogen atoms [26]. Figure reprinted with permission from *Chinese J Struct Chem*.

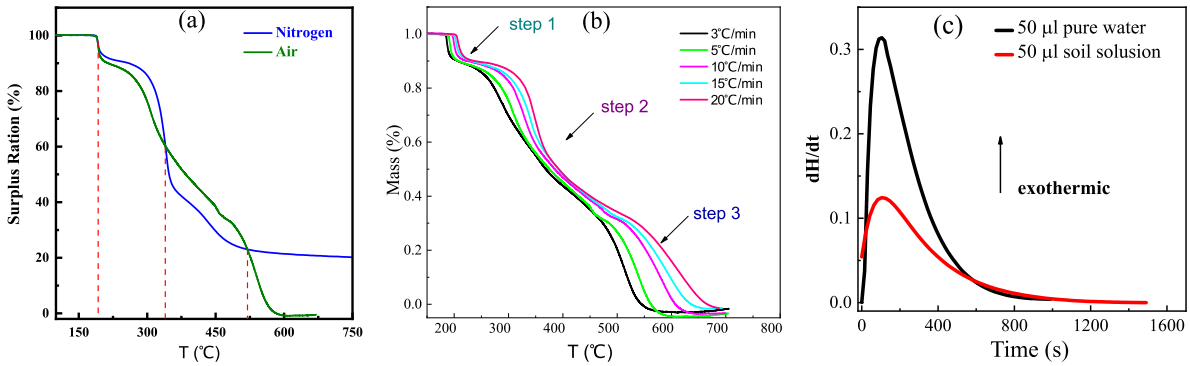

Fig. 3 (a) TG curve of aconitine ($\beta = 5$ °C/min), (b) TG curve of aconitine in air ($\beta = 3$, 5, 10, 15, 20 °C/min) and (c) heat release rate (dH/dt) in the entire reaction process of aconitine [33]. Figure reprinted with permission from *CIESC J*.

tra performance liquid chromatography coupled with quadrupole-time of flight mass spectrometry (UPLC/Q-TOF-MS). This method is simple and accurate and can quickly detect aconite alkaloids in samples.

Pang et al [42] established an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for the simultaneous determination of three kinds of aconitoid alkaloids. The determination was performed on ACQUITY UPLC BEH C18 column (50 mm, 2.1 mm, 1.7 μm) at 35 °C with mobile phase consisting of 0.1% formic acid – acetonitrile solution at the flow rate of 0.25 ml/min. Multiple reaction monitoring (MRM) was performed using electrospray ion source (ESI) and positive ion mode. The mass concentrations of aconitine, hypaconitine, and neoconitine were 0.9198–91.9800 ng/ml ($r = 0.9978$, $n = 7$), 1.048–104.800 ng/ml ($r = 0.9974$, $n = 7$), and 1.268–126.800 ng/ml ($r = 9998$, $n = 7$), respectively. The method was found to be simple, precise, reproducible, highly specific, and accurate. It can be used for simultaneous determination of three kinds of aconitoid alkaloids in the *Zouchuan Guci Tincture*, a Chinese traditional medicine.

Zhang et al [43] modified the surface of C18 column with positive charge to significantly improve the peak shape and sample load of alkaline compounds. This type of column uses an electrostatically controlled bonding on unique surface to introduce a partial charge onto the surface of the reversed bonded silica gel, achieving a perfect balance of hydrophobicity/hydrophilicity and electrostatic characteristics on the packing surface, which significantly improves the performance of all columns. In this study, alkaline compounds with high separation selectivity were selected as analytes for separation on this improved chromatographic column with 0.05% water phosphate and acetonitrile as mobile phase. This method avoided the use of tetrahydrofuran, chloroform, and other highly toxic organic solvents.

However, the use of these methods is limited because they require sophisticated instruments and professional operators. Several other detection methods are being developed. Enzyme-linked immunosorbent assay (ELISA) combines highly sensitive enzyme biocatalysis with highly selective antigen and antibody recognition. The enzyme-catalyzed oxidation of 3,3′,5,5′-tetramethyl benzidine (3,3′,5,5′-tetramethyl benzidine, TMB) produces different shades of yel-

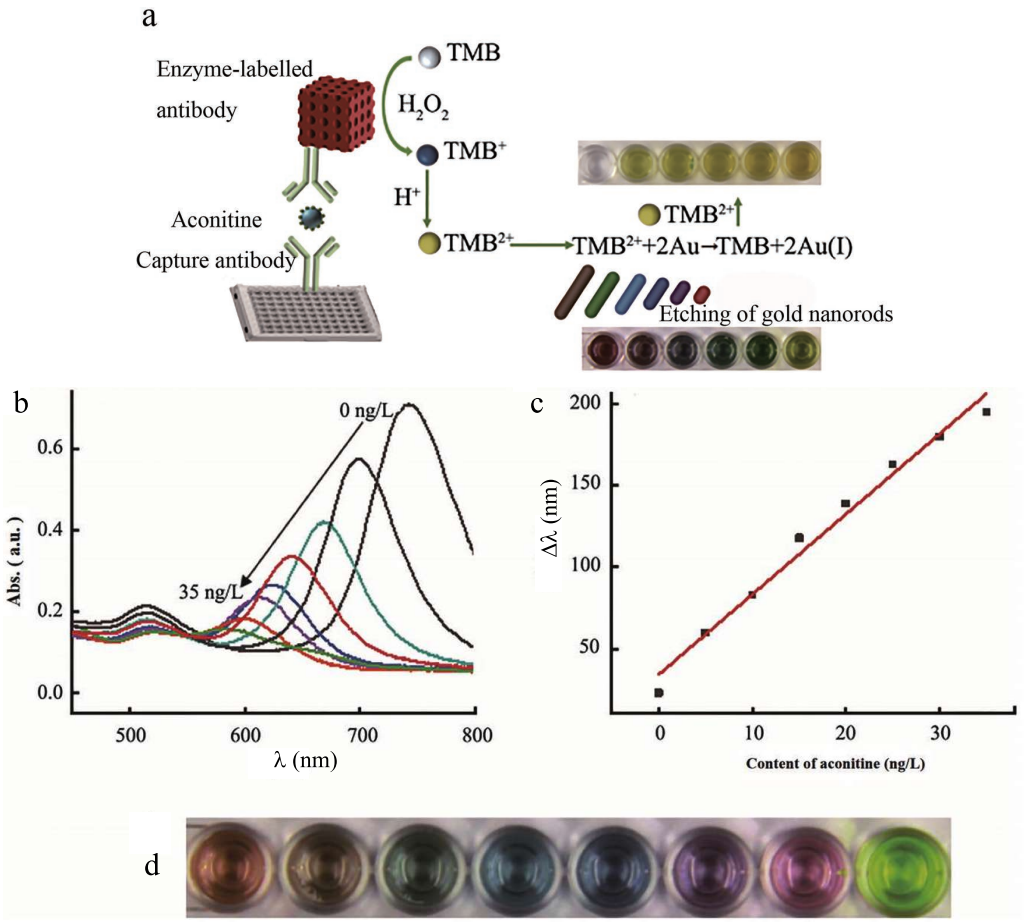

Fig. 4 (a) Scheme of the proposed ELISA biosensor for aconitine detection with naked eyes; (b) UV-Vis spectra of etched gold nanorods caused by different concentrations of aconitine; (c) standard curve of LSPR shift (λ) and concentration of aconitine for gold nanorods; (d) the sensor color changes with different doses of aconitine. The concentrations of aconitine are as follows: 0, 5, 10, 15, 20, 25, 30, and 35 ng/l [48]. Figure reprinted with permission from *J Food Safety Quality*.

low solution after adding termination solution. This method has been widely used in the analysis and detection of supernatant of aconitine in plant tissues/cells and related liquid samples [44].

Lin et al constructed a series of multicolor ELISA sensing platforms to regulate the aspect ratio of gold nanorods based on target objects [45–47]. As a result of the compaction effect of Localized Surface Plasmon Resonance (LSPR), the metal rod solutions with different aspect ratios exhibit colorful colors [44]. The transition from the traditional single-color change to the multi-color change greatly improves the sensitivity and accuracy of the detection. In this study [48], a multicolor colorimetric enzyme linked immunosensor was constructed for the visual detection of aconitine by naked eyes (Fig. 4). In the presence of aconitine, the horseradish peroxidase (HRP)-conjugated antibody forms a complex with aconitine. HRP fixed on the micropore oxidizes TMB to TMB^+, which is converted to TMB^{2+} in an acidic environment. TMB^{2+} can rapidly etch gold nanorods, forming gold nanorods with different aspect ratios and presenting rich color changes so as to realize the naked-eye visual semi-quantitative detection of aconitine [46]. According to the relationship between the shift of the LSPR absorption peak and the concentration of aconitine, it was used for the quantitative detection of aconitine in order to improve its on-site real-time detection ability.

In addition, near infrared spectroscopy (NIRS) is widely used in various fields of traditional Chinese medicine (TCM) due to its advantages of fast and non-destructive and no need for sample pretreatment. Some examples include quality analysis of TCM raw materials and TCM preparations [49–51], an online monitoring and control of TCM pharmaceutical process [52–54], and real-time release strategy of TCM products [55, 56]. A fast non-destructive method for the detection of multi-index components in aconite

was developed by using NIRS combined with partial least squares (PLS) and least squares support vector machine (LS-SVM) [57]. PLS and LS-SVM were used to establish the quantitative correction model between the determination value of each component by HPLC and the NIRS map of aconite samples. The relative prediction deviations (RPD) of the LS-SVM models for total amount of benzoylneocaconitine, benzoylaconitine, benzoylhypaconitine, mesaconitine, hypaconitine, aconitine, monoester alkaloids, and diester alkaloids were 3.3, 3.2, 4.1, 7.7, 8.8, 7.6, 4.0, and 8.6, respectively. Their verification set correlation coefficients were 0.9486, 0.9475, 0.9668, 0.9909, 0.9946, 0.9969, 0.9669, and 0.9927, respectively. These results showed that the NIRS model verification set has a good nonlinear relationship with the measured values by HPLC. NIRS technology combined with LS-SVM model can be used to quickly detect the contents of the above six alkaloids as well as the total amount of single ester alkaloids and double ester alkaloids in Radix Aconite.

ACONITINE AS A PESTICIDE

P. xylostella and *P. rapae* are the main pests for cruciferous vegetables at present, which cause the decline in vegetable yield and quality or even failure of harvest in severe cases, posing a serious threat to vegetable production [58]. Due to the continuous, frequent, and high dosage of insecticides, the resistance and mutual resistance of these two pests to various insecticides are continuously strengthened. Drug prevention and control effects are not ideal. Pesticide dosage is getting higher, and the interval between applications is getting progressively shorter. These problems lead to excessive pesticide residues in vegetable products, drastically affecting the food safety of consumers. Therefore, exploring the use of new pesticides with high efficiency, low toxicity, and low residue is of great importance for the production of pollution-free vegetables. As a kind of biological pesticides, botanical pesticides usually have the characteristics of high efficiency, easy degradation, no pollution, and non-toxic side effects, making them green pesticides. The first consideration of this pesticide is its environmental compatibility, and the second is its biological activity. Phytogenic pesticides refer to plants and their secondary metabolites used in the prevention and control of diseases and insect pests, mainly including plant toxins that cause effects such as insect food resistance, growth inhibition, avoidance, repellent, oviposition rejection, etc. Pesticides extracted from plants have medicinal and fertilizing functions. They have no residual poison and pesticide harm and play an important role in the control of crop diseases and insect pests. Yang et al [59] measured the inhibitory effects of several plant-derived active substances on the proliferation activity of *in vitro* cultured cells of *Spodoptera exigua*. The results demonstrated that camptothecin, hydroxycamptothecin, and rotenone had better inhibitory effects on the cells of *S. exigua*. Jiang et al [60] investigated the field control effects of two new insecticides, aconitine and sodium aminobenzate, on rapeseed moth. The results showed that 0.15% aconitine emulsion and 10% sodium aminobenzate aqueous solution had a good control effect on the cabbage insect. Hence, they are two kinds of high efficiency, low toxicity, and safety control agents for the cabbage insect. Aconitine, hypaconitine, pseudogarnetine, strychnine, and evoidine had a certain time effect on cytotoxicity, but there was no obvious dose relationship. Chen and his colleagues [61] isolated several diterpene alkaloids from *Song Guolin* (Aconitum plant of North China) including total alkaloids, mesaconitine, and aconitine. The results showed that these alkaloids had obvious inhibitory effects on rice plant hoppers and alfalfa aphids. Toxicity analysis in mice reported that the LD_{50} is 0.12 mg/kg after intravenous injection of aconitine. For humans, the lethal dose of aconitine is estimated to be 1–2 mg for a healthy man with a body weight of 70 kg (15–30 μg/kg) [15]. In insects, detoxification enzymes mainly include mixed function oxidases, carboxylesterases, glutathione-s-transferases, etc. Insects could reduce toxicity by enhancing the transformation and degradation of pesticides or protect their target sites. Studies have shown that exogenous toxic substances can increase the activity of carboxylesterase in the larvae of *S. schopenhaeria* to fight against external toxic substances, which is an instinctive reaction of biological detoxification [62]. Activating glutathione-s-transferase can enhance the metabolism and play a detoxification role, which is the stress protection response of the test insects to non-feeding substances [63]. However, at high aconitase insecticide concentration, the carboxylesterase activity was significantly inhibited, and its detoxification ability was lost [63].

ACONITINE ACTS AT DNA LEVEL

DNA carries the important information of reproduction and heredity of an organism, which is closely related to the survival and evolution of plants and animals. Aconitine was found to act at DNA level. Our group investigated the interaction to determine the binding sites and the types of forces between aconitine and DNA of calf thymus, salmon sperm, and armyworm [64]. Two kinds of binding forms were found. One form is groove binding with the binding constant K_{a1} of 10^5. The number of binding sites is 0.40–0.60, and the reaction is a spontaneous process driven by enthalpy. The other form is the binding of aconitine molecules to the surface of DNA with binding constant K_{a2} of 10^3. In addition, molecular simulations of the binding sites showed that armyworm DNA, salmon sperm DNA, and calf thymus DNA base chains

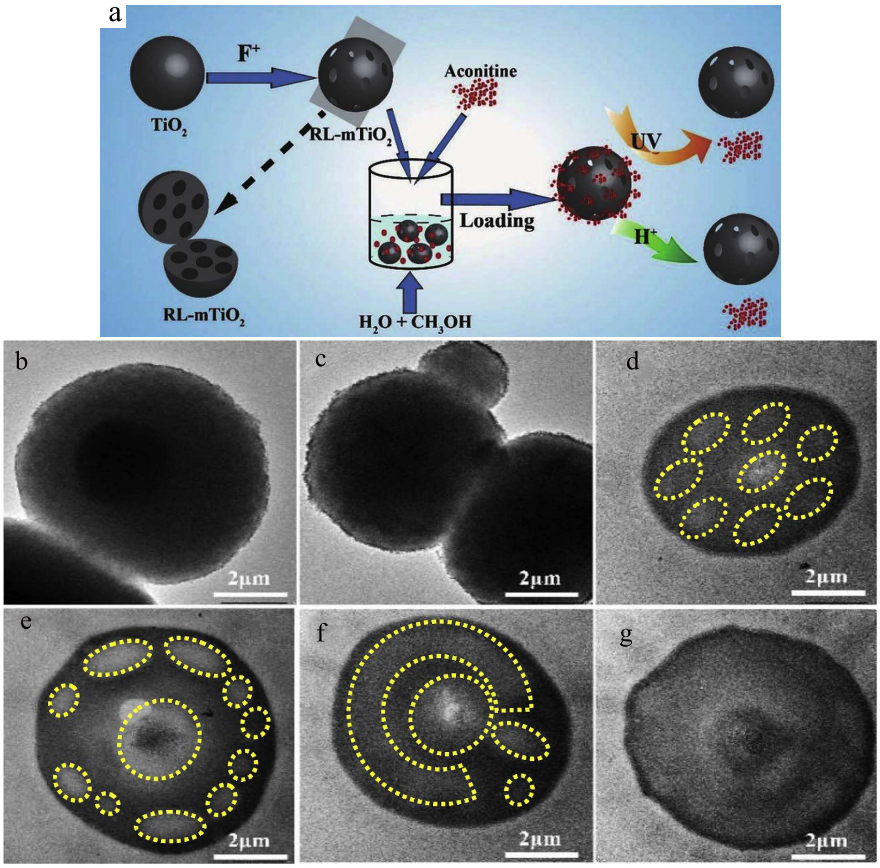

Fig. 5 (a) Scheme of preparation process of lotus mesoporous TiO_2 and ultraviolet stimulation for release of aconitine. (b–g) The TEM patterns of TiO_2 treated with NH_4F at different concentrations [65]. Figure reprinted with permission from *Elsevier, J Alloy Compd*.

and aconitine molecules acted at C8, T33/T34, and G16/C9/C8, respectively. It is of great significance to screen or modify drug samples effectively at the biomolecular level to prevent the harmful effects of gene damage on living environment.

TiO_2 NANOPARTICLES AS A DRUG CARRIER MATERIAL

Due to the easy hydrolysis of aconitine under natural conditions, its efficacy cannot be guaranteed during drug storage and use. If aconitine can be loaded onto some inorganic material, then it can be stored for a long time, and the drug can be released during use by external natural conditions such as sunlight exposure. This will solve some problems existing in the use of aconitine as an agricultural insecticide. Therefore, it is necessary to find an inorganic material with both loading properties and photosensitive properties. The inorganic compound titanium dioxide (TiO_2) is extremely sensitive to ultraviolet light. Different TiO_2 crystals with different structures are sensitive to ultraviolet light to varied degrees. Such a photosensitive material with excellent properties plays a very important role in scientific research, production, and application. If this carrier material can be effectively introduced into the field of pesticide production and application, it can improve the utilization rate of natural products. The interaction mechanism between the drug molecule and the carrier material is a key factor. In our research group, porous titanium dioxide with "lotus root" structure was synthesized for the first time by an improved template-free method (Fig. 5) [65]. Aconitine could be supported in porous TiO_2 by simple immersion with the maximum loading rate of 17.6%. According to the ultraviolet spectrum of drug release behavior, the aconitine loaded-porous titanium dioxide particles could be successfully released by UV irradiation with release rate of 46.24% (Fig. 6). The "lotus root" porous titanium dioxide material thus has potential application value in the storage and use of aconitine. Similarly, inorganic nanomaterials such as photosensitive mesoporous zinc oxide, tungsten trioxide, and molybdenum trioxide can also be used as drug carriers for research and application. The specific materials can be selected according to cost control and other aspects such as loading ability.

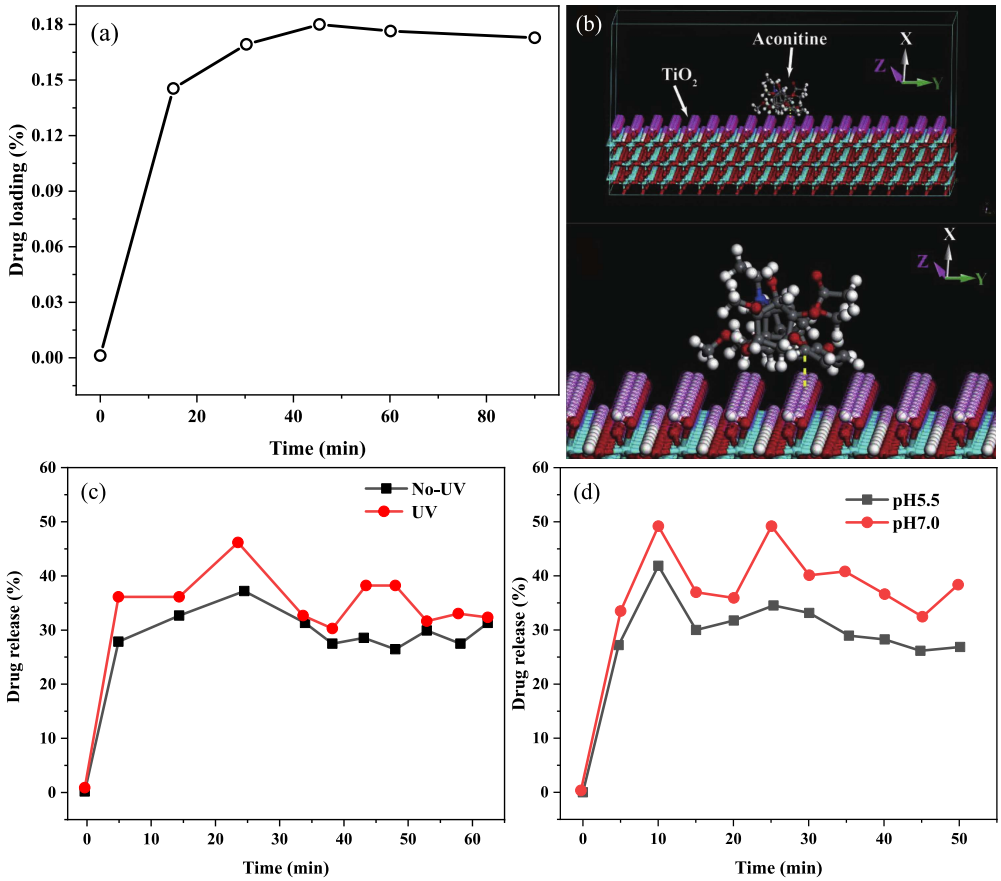

Fig. 6 (a) mTiO$_2$-aconitine cycles release as a function of time. (b) Molecular simulation diagram of aconitine molecule and titanium dioxide (white, gray, red, light blue, and dark blue spheres representing elements H, C, O, Ti, and N, respectively). Drug loading analysis with different time intervals: (c) drug loading as a function of time and (d) UV-vis absorption spectra) [65]. Figure reprinted with permission from *Elsevier, J Alloy Compd*.

CONCLUSION

The plant source, extraction, and detection analysis of a botanical insecticide aconitine were reviewed. The unstable structure and easily hydrolyzed properties made the molecule attractive as an agricultural insecticide for green environment. The interaction between aconitine and biomolecular DNA studied reflected possible damages at the gene level. Besides insecticidal activity, aconitine can be used as an analgesic drug able to treat arthritis and rheumatic diseases. Potential applications of aconitine might be enhanced by loading it in a low toxic, cheap, and light-sensitive porous inorganic material like TiO$_2$ nanoparticles to protect the active group of aconitine drug and optimize its storage and usage conditions. This study can provide new ideas for the production and processing of botanical insecticides.

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