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Research Progress of Detection Methods in Tenuazonic Acid

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Abstract: Since the 20th century, food safety has been widely valued by the people. Mycotoxins are an important source of biological contamination in food. Alternaria is one of the most common fungi that contaminate food. Its metabolite Streptococcal ketoic acid is one of the most important streptotoxin, which can widely contaminate vegetables, fruits and grains. In this paper, the pollution status, toxicological properties and detection methods of TeA were reviewed, and the future research direction was prospected, hoping to attract attention at home and abroad and promote the establishment of the national limit standard of Streptomyces toxin in advance.

1. Introduction

Food contamination is mainly divided into three categories, namely biological pollution, chemical pollution and radioactive pollution. Among them, biological contamination of food is mainly caused by mycotoxins, secondary metabolites secreted by fungi [1]. The most common mycotoxins found in agricultural products are aflatoxin, vomitoxin, ochratoxin, fumonitoxin, zearalenone, tricillin and T-2 toxin. Streptospora is a kind of pathogen and saprophytic bacteria in the environment. It is commonly found in filamentous fungi in vegetables, fruits and grains [2] and can produce more than 70 kinds of streptospora mycotoxins [3], which have carcinogenic and teratogenic toxic effects on humans and animals. At present, the most widely studied is the ketoacid of Leptospora, which mainly comes from the genus Leptospora, which is a genus in the order of Cladospora and includes many plant pathogens, such as the pathogenic bacteria of potato early blight and carrot black disease. It has been reported that many streptospora.It can produce fine alternaria keto acid, such as interseptum alternaria, citrus alternaria, radish Alternaria, oryzobiasis alternaria, Kikuchi alternaria, allium alternaria, rhizogenic alternaria, Eggplant alternaria, fine alternaria can produce TeA. Other molds, such as pyridospora oryzae, rhizophorus, penicillium flavescens and penicillium flavescens, can also produce TeA. The only nitrogenous metabolite in alternaria toxin is alternaria tenuis ketoacid, which is recognized as the most important alternaria toxin in the world [4]. The European Food Safety Authority (EFSA) has conducted extensive research and published scientific opinions on the health risks of streptosporin in food and feed. Efsa has analyzed the risk of chronic dietary exposure to four streptosporin toxins, streptosporin monotetraethers, streptosporin ketoacids, and tentotoxin, using 15,563 analysis results. 4249

samples (3648 for alternarol (AOH), 3654 for alternarol monomethyl ether (AME), 4168 for alternaria tenuis ketoacid (TeA) and 4093 for tenutoxin(TEN). The analysis found that toddlers had the highest dietary exposure to the four Streptomyces.

Up to now, the limit standards of mycotoxins in food at home and abroad often do not include mycotoxins from alternithine [5]. In this paper, the sources, pollution status, physicochemical properties, toxicological properties and detection methods of the ketoic acid of Streptospora leptospora were reviewed in detail, in order to promote the establishment of food safety regulations on streptospora mycotoxin in China as soon as possible

2. Introduction to TeA

2.1. Discovery of TeA and pollution status at home and abroad

The ketoacid of Streptospora leptospora is one of the metabolites produced by Streptospora, blastomyces oryzae, and Spodemia sorghum [6]. The ketoacid of Streptospora leptospora was originally isolated from the culture filtrate of Streptospora as an anti-tumor substance [7]. Stickings[8] then analyzed their structures using traditional methods and determined that they were derivatives of four amino acids. However, its structure is unstable and its functional group is a tautomer. TeA pollution is widespread throughout the world. Such as North America and South America, the United States, Canada, Brazil, Argentina, etc.; In Europe, Britain, Switzerland, Italy, Germany, Spain; It has been found in Australia and other Asian countries. It can widely contaminate grains, vegetables, fruits and fermented foods, such as wheat, sorghum, oats, tobacco, rice, spinach, olives, oranges, peppers, melons, tomatoes, apples, oranges, lemons, blueberries, sunflower seed meal, rapeseed meal, wine, beer, cooking oil and dozens of other foods [9-10]. Compared with grains, green plants or fruits and vegetables with higher relative humidity are more susceptible to TeA infection, such as tomatoes and citrus [11].

The detection rate of TeA in tomatoes in the United States was 51.4%-63.2%, and the detection limit was 100μg/kg. In Germany, the positive rate of tomatoes was as high as 100%. In China, Li Fengqin has reported that the detection rate of TeA in wheat has also reached 100%, the detection limit is 100μg/kg, the detection minimum value is 260μg/kg, the maximum value is 6432μg/kg, and the pollution level is extremely high. Patriaca et al. [12] isolated 123 Streptospora strains from Argentine wheat, and found that 72% of the strains produced TeA, with an average toxic production of 1757 mg/kg. Marina et al. [13] found in the survey of 1064 wheat strains harvested in northeast Germany that 332 (30.3%) of them contained TeA, and the maximum toxin content was 422.2 mg/kg, respectively. Logrieco et al. found that Altispora could infest both immature and ripe tomato fruits. TeA is often isolated from infected tomatoes. The results showed that 73 out of 142 samples (51.4%) contained TeA, and the TeA content was up to 70 mg/kg. Noser et al. studied tomato products in the Swiss and German markets and found that almost 100% of the products were contaminated with TeA. Logrieco et al. tested the TeA content in oranges naturally contaminated by alteralterium alternatum, and found that the TeA content in black rotten oranges ranged from 21 to 87.2 mg/kg.

2.2. Physical and chemical properties of TeA

Ketoic acid is an oily, brown substance, easily soluble in methanol, ethanol, dimethyl sulfoxide and other organic solvents, but not easily soluble in chloroform, benzene, acetone, TeA can also chelate with many substances [14]. This substance has biological properties that include anti-tumor, anti-tumor viral, antibacterial, and insecticidal effects.[15].

3. Toxicological properties of TeA

3.1. Cultures of TeA Producers

TeA is mainly produced by Cyclospora genus, and there are about 300 virus-producing strains, and some specific plant pathogens and saprophytic species in soil can also be produced [16]. The genus can grow rapidly on potato glucose AGAR medium and can form colonies of 3 to 9 cm in diameter under 25℃ for 7 days. The colony is flat, showing grayish white in the early stage, and the colony edge gradually changes to black green to black brown in the later stage due to the production of black and brown pigments by Alternativespora [17]. Battilani et al. [17] found that the black and brown mycelia and conidia of crossspore could be seen under the microscope. The spores are ovate and septate, rounded at the end and tapering toward the other end. Some spores have serrated edges. These spores can grow alone to form strains. The virulence of TeA strains is mainly affected by physical factors (temperature, humidity, pH, atmospheric pressure, etc.) and chemical factors (insecticides, insecticides, atmospheric pressure, etc.)

The effects of fungicides, etc. [18]. The optimum growth temperature of Streptospora is generally between 20℃-25℃, the lowest growth temperature is -2℃-5℃, and the highest is 31℃-32℃. In the natural state, the spore production temperature is 25℃-27℃. Mycelium can only grow normally at a pH of 4.0-4.5. When pH value is 2.7-8.0, the minimum water activity (aw) of mycelium growth is 0.85, and the optimal aw is 0.98. When Oviedo et al. [19] studied the influence of environment on TeA toxin production in soybean medium, they found that the growth temperature of TeA ranged from 5℃ to 30℃, aw was 0.920-0.995, and the optimal aw temperature was 0.98 (with slight differences depending on strain). The optimum growth temperature is 25℃ to -30℃. Hasan et al. [20] believed that the most suitable temperature for TeA production was 21℃. Combina et al. [17] found that heating and pressure could effectively reduce the formation of TeA in sunflower pollen. Dalcero et al. [21] found that chemical reagents such as insecticides and fungicides also had significant effects on the synthesis of TeA.

3.2. Toxicological effects of TeA

Of the more than 70 streptosporin toxins we know, TeA is the most toxic, and is the only streptotoxin listed by the U.S. Food and Drug Administration (FDA) Toxic chemicals Registry, which is characterized by a low detection rate, but its strains are very potent in producing poison. TeA toxicity includes acute toxicity, subacute toxicity, potential carcinogenicity, cytotoxicity and synergistic effect. TeA is one of the most acute toxic mycotoxins of alternaria genus, which often causes dizziness, salivation, vomiting followed by tachycardia, massive bleeding of esophagus and gastrointestinal tract, circulatory failure, motor dysfunction, and death in mammals, accompanied by blood concentration, prolonged retention time of bromosulfonphthalide in the blood, and ammonia aspartate in the blood.

The activity of base transferase was increased [22,23]. The toxic mechanism of TeA on mammals is mainly to inhibit the release of newly synthesized proteins from the proteome into the serum, during which the proteins may be selectively complexed with some trace metal ions in the body and affect the active sites of peptide bonds in key steps [24]. Toxicology showed that the transoral LD50 of male mice was 182mg/kg, and that of female mice was 81mg/kg. Long-term intake of food contaminated with TeA may cause serious harm to human health [25-27]. It has been reported that in the toxicity test of dogs, the daily intake of 10mg/kg TeA (measured by body mass) can cause bleeding in some organs of dogs; Long-term gastrointestinal exposure to 10mg/kg of TeA can produce subacute toxicity to chickens, which can lead to the reduction of body mass. Long-term daily feeding experiment of 25mg/kg can cause precancerous changes of esophageal mucosa in

mice [28]. In addition, it has been reported that TeA has a synergistic effect on a variety of other mycotoxins, such as ochratoxin, streptosporol, streptosporol methyl ether, etc., which can enhance acute toxicity even at low doses and greatly threaten and increase food safety risks [29].

4. TeA detection method

At present, the commonly used mycotoxin detection methods are mainly divided into sample pretreatment detection methods, physicochemical detection methods and biosensing detection methods. First of all, the samples in the test need to go through extraction, extraction, purification and other pre-treatment steps before testing. Physical and chemical detection methods mainly include thin-layer chromatography, gas chromatography, GC-MS, liquid chromatography, LC-MS and high performance liquid chromatography. Biosensing detection method is a technique by which biomolecules interact with target molecules and convert this interaction into a measurable signal. These methods are often used to monitor molecules, cells, proteins, nucleic acids and other biomolecules in biological systems. Biosensing technology is widely used in medical diagnosis, environmental monitoring, food safety and other fields. However, at present, the detection of TeA is mainly carried out by high performance liquid phase tandem mass spectrometry. The following is a review of the main detection methods of TeA.

4.1. Sample pretreatment method

In the process of TeA sample analysis, the choice of pretreatment method is very important, which can affect the accuracy and sensitivity of the analysis. The following are some common TeA sample pretreatment methods. The first is sample collection and pretreatment: sample collection should ensure that the samples collected are representative and prevent contamination and degradation. Samples should usually be pre-treated immediately after collection, including refrigeration or cryostorage, to maintain the stability of TeA. The second step is sample extraction, such as acid extraction, solvent extraction, solid phase extraction, etc. In order to improve the sensitivity of the analysis, the extracted sample solution was concentrated to the required volume by a rotary evaporator. The final sample was purified, and the TeA and interfering substances were separated by chromatography. Sample derivatization is performed by introducing appropriate.

Chemical derivatives that convert TeA into compounds that are easier to analyze in order to improve the sensitivity of the analysis.

4.2. Physical and chemical detection method

4.2.1. Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) is a classical method for the detection of toxins, and it is a qualitative analysis method widely used by laboratories around the world in food, medicine, environment and other fields. It was also the most commonly used method originally used to detect ketoacids of Alternaria tenuis [30]. Sauer et al. used the ratio of toluene - ethyl acetate - formic acid (5:4:1, V/V) as the mobile phase, and finally measured the Rf value of TeA as 0.65. Muller et al. used benz-methanol-glacial acetic acid (90:5:5, V/V) as the mobile phase and silica gel plate as the stationary phase. After spraying with 1% ethanol FeCl3, color was developed at 254nm ultraviolet wavelength, and the Rf value was finally measured as 0.47-0.52[31]. Hasan et al. [20] used the ratio of chloroform-acetone (97:3, V:V) as the mobile phase to detect the TeA content in tomatoes by thin-layer chromatography. The lowest detection limit of TeA was 0.7μg/kg. The advantages of TLC are that the entire experimental process is low cost, requires only simple sample pretreatment, and can

separate multiple samples at the same time. The disadvantage is that the detection sensitivity is low, the random error is large, and the experimental operation is cumbersome, time-consuming, the amount of organic reagents is large, most of the reagents are also toxic, poor safety. There have been fewer and fewer applications in recent years.

4.2.2. Gas Chromatography (GC), Gas Chromatography-Mass spectrometry (GC-MS)

Gas chromatography has the characteristics of fast analysis speed, high efficiency and sensitivity, especially gas chromatography-mass spectrometry technology, not only has higher detection sensitivity, low detection limit, but also can detect a specific substance in the mixture. Therefore, this method based on gas chromatography and GC is also widely used in the quantitative detection of mycotoxins. But gas chromatography is suitable for detecting substances that are volatile or that evaporate at the operating temperature of the chromatograph. Therefore, TeA can be detected only after a certain derivatization treatment, and the derivatization reagent is mainly trimethylsilane. The base Due to the limitation of expensive equipment and derivatives, gas chromatography is rarely used for TeA detection.

4.2.3. High Performance Liquid Chromatography (HPLC) Ultra-high performance liquid chromatography Tandem Mass Spectrometer (UPLC-MS)

In recent years, liquid chromatography has almost completely replaced thin layer chromatography and gas chromatography in the detection of mycotoxins in Europe [32]. Used to detect streptosporin in food. The advantage of liquid chromatography is that it is fast, accurate, stable, sensitive and highly automated, but the disadvantage is that the pretreatment process is complex and the equipment used is more expensive. High performance liquid chromatography (HPLC) is often used in laboratory arbitration detection of mycotoxins. It is sensitive, accurate and reliable. High performance liquid chromatography is also the most commonly used method for TeA detection at present, and its detection limit is decreasing with the optimization of extraction and purification conditions.

4.3. Biosensor detection methods

Biosensing detection method is a technique by which biomolecules interact with target molecules and convert this interaction into a measurable signal. There are many detection methods for biosensing, such as ELISA kits, colloidal gold strips, microfluidic chips, immunobiosensor technology, molecular imprinting technology, etc. These methods are often used to monitor molecules, cells, proteins, nucleic acids and other biomolecules in biological systems. Biosensing technologies have a wide range of applications in medical diagnosis, environmental monitoring, food safety and other fields because they can provide highly sensitive, specific and real-time analysis.

4.3.1. Optical biosensing

Optical biosensing is a sensitive technique commonly used in biological analysis, based on the principle of detecting the presence and concentration of molecules by monitoring changes in optical signals. In TeA detection, researchers have successfully realized the highly sensitive detection of TeA by using surface plasmon resonance and optical fiber spectroscopy. In addition, fluorescence spectroscopy and Raman spectroscopy have also been applied to the detection of TeA with high sensitivity and selectivity, providing powerful tools for the study of TeA. It is mainly used in bacteriological research, food safety and medical diagnosis.

4.3.2. Lateral flow tomography sensing

Lateral flow tomography is a microfluid-based detection method that utilizes separation and recognition properties in tiny fluid channels to detect molecules. In recent years, researchers have developed TeA detection methods based on lateral flow chromatography, using technologies such as microfluidic chips and adsorbent materials, which can achieve highly sensitive detection of TeA, and have the advantages of high throughput and automation. It is mainly used in environmental monitoring or medical diagnosis.

4.3.3. Electrochemical biosensing

Electrochemical biosensing is a method of detecting biomolecules by measuring electrochemical signals and is often used in the construction of biosensors. In TeA detection, the researchers successfully achieved highly sensitive detection of TeA using modified electrodes and biometric elements, such as antibodies or nucleic acid probes. Electrochemical biosensing has the advantages of fast response, low cost and portability, and has gradually become one of the important methods for TeA detection. It is mainly used in biosensors, medical applications, and food safety detection.

4.3.4. Immunochromatography

Immunochromatography is a kind of detection method commonly used in biological analysis. The principle of immunochromatography is to realize the detection of molecules by the specific binding of antibodies to target molecules. In recent years, researchers have developed immunochromatograph-based TeA detection methods, which can achieve rapid detection of TeA by fixing anti-TEA antibodies on the test strip. This method has the advantages of simple operation, no need for complex equipment and low cost, and is suitable for TeA detection in the field and resource limited environment. However, the limitations are low sensitivity and the need for specific antibodies. Therefore, in recent years, many scholars have devoted themselves to the preparation of highly sensitive and highly specific TeA antibodies.

In 2011, Gross et al. [33] derived TeA by succinic anhydride method, conjugated TeA with bovine serum albumin and keyhole hemoglobin to form artificial antigen by active ester method, immunized the conjugate to obtain its polyclonal antibody, and constructed a direct competitive ELISA method using this polyclonal antibody. IC50=320±130μg/kg. This ELISA method has certain sensitivity to TeA, but it will have strong cross-reaction with TeA acetate. The average standard curve detection limit of TeA acetate was (5.4±2.0)ng/mL, and the detection limit of TeA in apples and tomatoes was 25-50ng/g.

In 2012, Yang Xingxing et al. [34] used hydrazine hydrate and glyoxylic acid to derivate TeA, immunized the conjugate, and screened the polyclonal antibodies of TeA derivatives. Using this polyclonal antibody, an indirect competitive enzyme-related immunosorbent assay was constructed with IC50=1.61μg/L. The detection limit was 0.08μg/L. The rapid detection of TeA toxin was also realized.

In 2014, Jiang Tao et al. [35] modified TeA hapten with succinic anhydride method and found that the solubility of carrier protein and hapten is the key link that affects the coupling effect by controlling reaction environment, protein and other conditions. It is concluded that the coupling effect of BSA with TeA is better than that with OVA and KLH under EDC reaction conditions. Under DCC conditions, the coupling effect of BSA and KLH is comparable to that of TeA, and better than that of OVA. Finally, the TeA artificial antigen was successfully synthesized, which has a very important influence on the preparation of high specificity and high affinity antibodies and the development of immune products, and lays a foundation for the rapid detection of TeA pollution in fruits and vegetables, oil crops and related products.

In 2016, Ma Liang et al. [36] introduced the connecting arm after TeA derivation, and then coupled the carrier protein. Finally, TeA polyclonal antibody was screened and a direct competitive enzyme-linked immunosorbent assay was established. IC50=355.55ng/mL, the minimum detection limit is 19.00 ng/mL, the linear detection range is 200.00-1563.00ng/mL.

In 2017, Zhou Xiaowen [37] combined with the characteristics of TeA, introduced spacer arms into the five-membered ring to synthesize hapten, coupled it with carrier protein KLH by active ester method, and then immunized mice and screened monoclonal antibodies. An indirect competitive enzyme-linked immunosorbent assay for TeA was established. After optimization, the detection limits of the method were IC10=1.00ng/mL and IC50=18.50ng/mL. The linear detection range was 3.56-96.24ng/mL, and there was no cross-reaction with other structural analogues of alternarin, and the specificity was high.

In 2017, Zhong Hong[38] et al., based on the analysis of TeA structural characteristics, prepared hap10 by derivatization of TeA structure, coupled with carrier protein by active ester method, immunized artificial antigen after ultrafiltration purification, and prepared polyclonal antibody with high titer and good specificity. The indirect competitive enzyme-linked immunosorbent (ELISA) method for TeA was established and studied, and the kit was prepared. The detection limit was 0.02ng/mL, and the detection range was 0.06-35.95ng/mL.

From the above experimental conclusions, it is obvious that immunoassay has many advantages. Not only the detection sensitivity is almost the same as the instrument detection, but also has the advantage that the instrument detection does not have, which is fast and easy. However, up to now, the immunodetection of TeA is mainly based on polyclonal antibodies, and polyclonal antibodies have no obvious advantages over monoclonal antibodies. Polyclonal antibodies are not sensitive and unstable, and are prone to produce a large number of non-specific antibodies, which may produce background signals in some applications. Due to the presence of multiple epitopes, it is very important to detect the cross-reactivity of immunogen sequences, which can easily affect the accuracy of experimental results.

5. Conclusion and prospect

After the above review, we can find that at present, China has not established relevant national food safety standards on streptosporin, and streptosporin is toxic and potentially harmful to human body. We should pay attention to this toxin, so it is urgent to establish a limit standard for streptosporin in China. Secondly, the study of strong immunogenic macromolecular artificial antigens, the preparation of highly specific TeA monoclonal and polyclonal antibodies, and the development of a series of rapid immunoassay products for streptomycin will become a research hotspot. Therefore, it is urgent to establish relevant rapid detection methods, such as microfluidic chip, immunobiosensor technology, molecular imprinting technology, etc. Another option would be to create fast and effective detection tools like ELISA kits and test strips. These rapid detection methods have not been widely used in the detection of streptosporin so far. The main reason is that the establishment of most methods requires the use of antibodies to streptosporin. However, compared with aflatoxin, ochratoxin and other fusarium toxins, TeA has a smaller molecular weight of only 197D and is less toxic. Therefore, it is more difficult to stimulate the body to produce an immune response and produce antibodies with high specificity than other toxins, and the antibody titer is not high. Therefore, scientists need to invest more time and effort to develop relevant rapid detection reagents and establish relevant rapid detection methods for the detection of streptomycin. It can be predicted that the traditional detection technology of alternarin will be gradually replaced by a variety of new, portable, real-time and rapid detection technologies. Streptosporin has been widely distributed in the world, and its potential harm to human and animal health can not be

ignored, which has aroused great concern of countries all over the world. In view of its toxicity, pollution scope and potential harm to human body, China and other countries in the world should speed up the establishment of the limit standard of streptotoxin in the future, so as to better protect food safety [39]

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