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journal homepage: <https://www.sciopen.com/journal/2097-0765>Residue behaviors and dietary risk assessment of dinotefuran and its metabolites in *Lycium barbarum* from farm to forkOuli Xiao^{a,1}, Minmin Li^{b,1}, Jieyin Chen^{a,c}, Ran Wang^{d,*}, Xiaofeng Dai^{a,c,*}, Zhiqiang Kong^{a,c,*}^a State Key Laboratory for Biology of Plant Diseases and Insect Pests, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China^b Key Laboratory of Agro-products Quality and Safety Control in Storage and Transport Process, Ministry of Agriculture and Rural Affairs; Institute of Food Science and Technology, Chinese Academy of Agricultural Sciences, Beijing 100193, China^c Western Agricultural Research Center, Chinese Academy of Agricultural Sciences, Changji 831100, China^d Institute of Plant Protection, Beijing Academy of Agriculture and Forestry Sciences, Beijing 100097, China

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ABSTRACT

Lycium barbarum, known as wolfberry or goji berry, is consumed by humans as a medicine and a food homology product. Conventionally grown wolfberry is often treated extensively with pesticides, which could pose a hazard to humans. Here, the degradation dynamics of dinotefuran and its 2 metabolites (1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF) and 1-methyl-3-(tetrahydro-3-furylmethyl) guanidine (DN)), during wolfberry cultivation and processing was investigated. The half-life ($T_{1/2}$) of dinotefuran was 11.36 and 9.76 days, respectively, under the recommended dosage and double the recommended dosage. During the oven and sun drying processes, processing factors (PFs) of dinotefuran were 1.07–1.34, implying the enrichment of pesticide residues. Decoction process made the removal rate of dinotefuran reach 87.48%, which is higher than that of the brewing process (14.7%), while dinotefuran remained in the wine with high ethanol content in the alcohol soaking process. The hazard quotient (HQ) of dinotefuran, as determined via dietary risk assessment combined with PFs, was < 1, indicating an acceptable risk for human consumption. Bioaccessibility of dinotefuran in the three digestive stages were intestinal (18.20%–88.08%) > gastric (5.45%–86.72%) > oral (23.18%) via *in vitro* simulated digestive system. These findings provide scientific evidence for reasonable application and risk assessment of dinotefuran residues in wolfberry.

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1. Introduction

Lycium barbarum, known as Chinese wolfberry, or goji berry, is the dry mature fruit of wolfberry as well as a deciduous perennial and thorny shrub of Solanaceae that is native to Asia^[1]. As a dual-functional traditional Chinese medicine (TCM)/food, wolfberry is widely used as medicine and food. It exhibits antioxidant, immune boosting, and vision improvement properties; therefore, it is referred

to as a “superfood”^[2]. Due to its medicinal and edible effects, wolfberry is used in daily life for brewing tea, stews, and brewing wine. In addition, it has been offered as a trustworthy healthy food and nutritional supplement in several other nations, such as those in North America, Europe, Oceania, and Southeast Asia^[3–4]. With the increase of the planting years of wolfberry and its nutrient-rich characteristics, diseases and insect pests during its growth period are a serious concern. Rust mite, psylla, aphids, anthrax, and powdery mildew are often encountered, concurrently or alternately^[5]. As chemical agents for improving crop yields while controlling for diseases and insect pests, pesticides play a major role in cultivation and standardized management of wolfberry. However, the frequent, overuse and irregular pesticide application has led to occurrence of excess pesticide residues in wolfberry. After their applications to control powdery mildew and anthracnose, substantial amounts

¹ These authors contributed equally to this paper.

* Corresponding authors at: Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China.

E-mail address: wangran@ipepbaafs.cn (R. Wang); daixiaofeng_caas@126.com (X.F. Dai); kongzhiqiang@caas.cn (Z.Q. Kong)

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of pesticides, including triadimefon, flusilazole, tebuconazole, and difenoconazole have been found in wolfberry^[6]. Moreover, dichlorvos residues were detected in wolfberry samples from supermarkets^[7]. Thus, the extensive application of pesticides during cultivation impairs with the quality and safety of wolfberry products for human consumption.

Neonicotinoids are broad-spectrum systemic insecticides that are commonly applied for crop protection. As a third-generation neonicotinoid insecticide, dinotefuran (MTI-446: *N*-methyl-*N'*-nitro-*N''*-[(tetrahydro-3-furanyl) methyl] guanidine) is a widely used neonicotinoid pesticide and has been registered for insects controlling in China since 2013^[8-9]. As a result of its permeability and effectiveness against sucking insects, it is used to enhance the production of various plant species, including vegetables^[10], some pesticide enterprises started using dinotefuran in the cultivation of wolfberry^[9]. According to the dinotefuran report of the Joint Food and Agriculture Organization of the United Nations and World Health Organization Meeting (JMPR) in 2011, dinotefuran residues in plants were defined as the sum of parent and 2 main metabolites, 1-methyl-3-(tetrahydro-3-furlylmethyl) urea (UF), and 1-methyl-3-(tetrahydro-3-furlylmethyl) guanidine (DN)^[11]. As the major metabolites of dinotefuran in rice plants, UF and DN are included in the list of residues to be tested during pesticide registration residue tests and during tests of residues for dietary risk assessment of plant-derived foods. The toxic effects of UF and DN have been shown to be comparable to those of dinotefuran, however, their mobility and persistence effects are stronger than those of the parent compound^[12-13]. In China, the maximum residue limits (MRLs) of 16 pesticides, including 12 insecticides and 4 fungicides in wolfberry have been documented^[14]. Neonicotinoids dinotefuran has been registered for use in wolfberry cultivation, however, the MRLs of dinotefuran in wolfberry has not been established^[15]. Dinotefuran has a good control effect on wolfberry disease. At present, there have been studies on the residues of such agents in cucumber, rice, and tobacco. In fact, the dissipation study and dietary risk assessment of dinotefuran and its metabolites in wolfberry have been reported^[9], but there is no such study on the effect of dinotefuran residue degradation in the cultivation and processing of wolfberry. Therefore, to ensure food safety, there is a need to elucidate on the effects of dinotefuran in wolfberry.

Wolfberry is usually processed into Chinese herbal medicine compounds and decoctions after washing, concocting, and cooking, which affects the abundance of pesticide residues to varying degrees^[16-17]. In a prior study, it was found that oven drying, sun drying and shade drying have a concentration effect of 3.52–11.20 times on 11 typical pesticides, while decoction improves the removal rate of pesticides from 92.8% to 99.8%^[18]. Currently, during processing, various pesticide residue processing factors (PFs) are internationally used to characterize changes in pesticide residues in agricultural products. PFs refer to the ratio of pesticide residue levels in the product after processing to pesticide residue levels in the product before processing.

The current health risks of contaminants in foods are mainly associated with total amounts of residual contaminants, ignoring the dissolution of pesticide residues in human diets from food to digestive fluids^[19]. Bioaccessibility refers to the maximum value of pesticide residues and other pollutants in food that can be digested

and absorbed by the human gastrointestinal tract. Currently, various static experiments are used to assess the bioaccessibility of pesticides in papaya, blueberry, and cherry tomatoes^[20-22]. The presence of food matrix during the digestion of blueberries was shown to reduce the concentration of pesticide residues (total bioaccessibility was about 7%)^[22]. Moreover, it was reported that there were correlations between levels, primary sources, risks of clofenotane dietary exposures and bioaccessibility in the general population^[23]. The dynamic simulated digestive system is an important method for bioaccessibility studies as it truly simulates the biomimetic state of gastrointestinal secretion and peristalsis. Liu et al.^[24] found that there were higher gastric lipase hydrolysis efficiency and smoother changes in digestive behavior in the dynamic digestion model compared with the static digestion model. Dynamic model could also more closely estimate the effect of cinnamon on starch hydrolysis during digestion^[25]. Accurate assessment of actual exposures to pesticide residues is vital for health risk assessment. Health risk assessment realistically reflects the digestion of pesticide residues *in vitro*^[26].

In this study, residue behaviors and dietary risks of dinotefuran and its metabolites (UF and DN) in *L. barbarum* were systematically evaluated from farm to fork. Field experiments were conducted to assess the residual dynamics of various pesticides (with different applied dosages) during the growth of wolfberry. Furthermore, PFs and bioaccessibility were further investigated in the processing and decoction of wolfberry to carry out quantitative assessment of the dietary exposure of pesticide residues in wolfberry. Our findings form the basis for establishment of dinotefuran MRLs in wolfberry and provides a reference and research model for the follow-up study of pesticide residue behavior during the cultivation and processing of TCM plants.

2. Experimental section

2.1 Material and reagents

Analytical standards of dinotefuran and its metabolites UF, DN (purity $\geq 99.0\%$) were provided by Tianjin Alta Technology (Tianjin, China). Commercial dinotefuran 20% soluble granules were acquired from Mitsui chemical agro Co., Ltd. (Japan). Acetonitrile (HPLC grade) and formic acid (LC-MS grade) were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Acetic acid was obtained from Shanghai Aladdin Biochemical Technology (Shanghai, China), primary and secondary amine (PSA, 40–60 μm) was purchased from Agela Technologies Co., Ltd. (Tianjin, China). Analytical grade reagents (NaCl and anhydrous MgSO_4) were provided by Sinopharm Chemical Reagent (Shanghai, China). Saliva (SSF), gastric fluid (SGF), intestinal fluid (SIF) simulated fluid electrolyte stock liquid powder, alpha amylase, pepsin, pancreatin, bile salts, $\text{CaCl}_2(\text{H}_2\text{O})$, $\text{MgCl}_2(\text{H}_2\text{O})_6$ were purchased from Xiaodong Yijian Instrument Equipment Co., Ltd. (Suzhou, China). Pure water was obtained from a Milli-Q purification system (MilliporeSigma, Burlington, MA, USA).

2.2 Field trials

Field trials were performed in Yinchuan City of Ningxia province, China, at 38°48' N and 106°18' E. The Ningxia provinces are the prominent wolfberry cultivation areas in China^[27]. The

experimental plots were examined and confirmed that there was no previous exposure to dinotefuran. Through the Organization for Economic Cooperation and Development (OECD), 20% soluble granules of dinotefuran were sprayed one time at 150 g a.i./ha (recommended dosage) and 300 g a.i./ha (double dosage) in each separate experimental plot, respectively. A windless environment was established to ensure that adequate sediments would be available for subsequent processes and degradation studies^[28]. In accordance with Guidelines on Pesticide Residue Trials in China^[29], all treatments and blank experiments were performed in 30 m² trial plots in triplicate, leaving two rows of bushes between the control plot and the different treatments to act as guard rows. Approximately 5 kg wolfberry fruits were collected at 2 h after pesticide spraying for subsequent drying and decocting, while 1 kg wolfberry fruits were harvested 1, 3, 5, 7, 14, 21, and 28 days after pesticide spraying for residue dynamic analysis. Then, all samples were labelled and transported to the laboratory, stored at −20 °C for further analyses.

2.3 Wolfberry processing and decocting

To ensure that the PFs of dried wolfberry and wolfberry decoction can be obtained, the wolfberry used for the processing test must contain quantifiable residues. According to OECD Test No. 508^[28], the pesticide residues obtained and their effects on health including dietary risk assessment were determined after applying double dosages of those recommended and the PFs.

2.3.1 Drying

Wolfberries are usually processed *via* drying (sun-drying or oven-drying). Double dose-treated wolfberry was harvested after 2 h to assess the PFs. For sun-drying, 100 g wolfberry samples were placed under direct sunlight and dried for 40 h (the temperature range was 22–31 °C). For oven-drying, samples (100 g) were evenly spread in an oven at 40, 50, and 60 °C and dried for 18, 20, and 22 h, respectively. Then, the corresponding dried wolfberry samples were collected for pesticide residue analysis, as shown in Fig. 1. Assays were performed in triplicates.

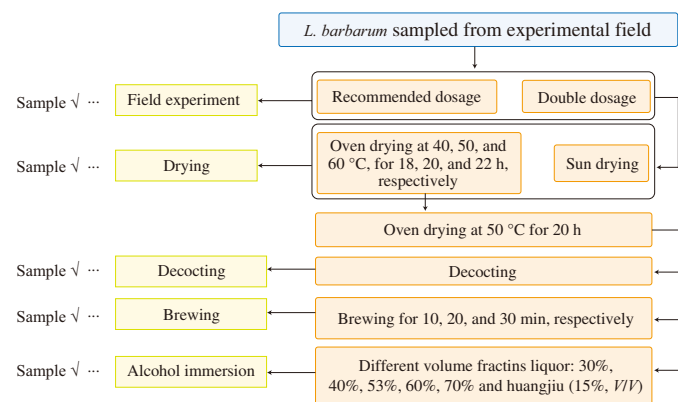


Fig. 1 Steps of wolfberry processing.

2.3.2 Decocting

In accordance with the technical requirements of quality control (QC) and standard formulations of Chinese medicine granules^[30].

The decoction was processed by firstly boiled the soaked wolfberry samples over high fire and then simmering them over low heat. In this study, 30 g of oven-dried (processed at 50 °C for 20 h) wolfberry samples were soaked in 250 mL water for 30 min at room temperature (25 °C) and thereafter boiled over high heat (100 °C) for 20 min. For the second decoction, appropriate amounts of hot water (150 mL) were added into the residue of the first decoction (the herb was immersed in 3 cm). The decocting time was 10 min. The two decoctions were combined and concentrated under pressure (concentration temperature did not exceed 65 °C) until the volume was 5 times the mass of wolfberry. Both decoction samples and the spent wolfberry samples after decocting were separately collected for pesticide residue analysis. Assays were performed in triplicates.

2.3.3 Brewing

Wolfberry brewing refers to preparation of hot water infusions of wolfberry. In this experiment, tap water boiled in a stainless steel electric kettle was used to prepare the infusion, and 10 g of wolfberry samples that oven dried at 50 °C for 20 h were immersed in 500 mL of boiling water and allowed to stand at room temperature for 10, 20, and 30 min, respectively. After filtration and cooling, both infusion and spent wolfberry samples after brewing were separately collected for pesticide residue analysis. Assays were performed in triplicates.

2.3.4 Alcohol immersion

During this processing step, 5 g of oven dried (50 °C for 20 h treatments) wolfberry samples were soaked in 50 mL liquor with various volume fractions of wines (30%, 40%, 53%, 60%, and 70%) and huangjiu (15%, *V/V*) at room temperature for 30 days, respectively. After soaking, wine samples were filtered and separated. Both liquor and spent wolfberry samples after soaking were separately collected for pesticide residue analysis. Assays were performed in triplicates.

2.4 Bioaccessibility measurements using *in vitro* human digestion models

The Dynamic Human Stomach-Intestine IV (DHS-IV), which includes 5 parts that correspond to the esophagus, stomach, duodenum, small intestines, and large intestines was used in this study (Fig. 2). The experimental operation parameters, including digestive juice secretion rate, gastric peristalsis frequency, pyloric opening size, and small intestinal peristalsis frequency were set in accordance with the standard biological conditions of the human organism (simulation of semi-solid digestion parameters). For specific parameters, digestion parameters of simulated semi-solid food provided by Xiaodong Yijian (Suzhou) Instrument Equipment Co., Ltd. were adhered to (Table S1). In this assay, 310 mL of gastric simulant and 528 mL of intestinal simulant were injected into the human digestive model prior to instrument initiation. During the digestion stage, online pH meter was used monitor pH changes of gastrointestinal juices in real time. Gastric digestion was designed for 3 h while intestinal digestion was performed for 4 h. Experimental samples were purchased from the Ningxia wolfberry market which was free of target pesticides. Wolfberry samples were lyophilized, mechanically pulverized into

a homogeneous powder, and sifted through a No. 40 mesh sieve ($(425 \pm 13) \mu\text{m}$ aperture). After adding 1.0 mg/kg of target pesticide level, spiked samples were vortexed for 2 min and left to stand for 30 min.

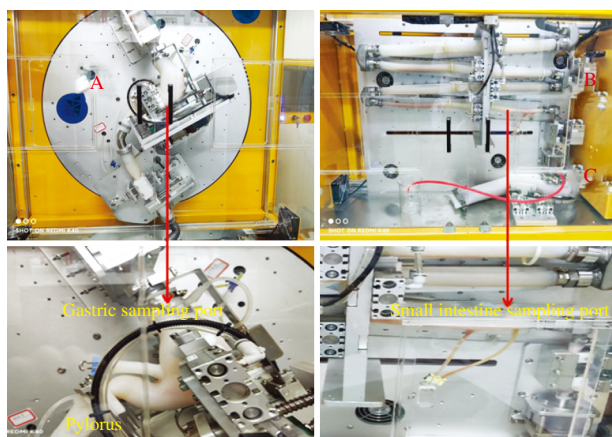


Fig. 2 Schematic presentation of the fourth-generation dynamic *in vitro* bionic human gastrointestinal digestive system (DHS-IV) device (A: gastric model; B: small intestine model; C: large intestinal filtration model).

2.4.1 Oral phase

In this assay, 500 μL $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ solution was added to 99 mL of saliva electrolyte stock solution after which the pH was adjusted to 7 using 1 mol/L HCl. Then, α -amylase was dissolved in the above solution to a final concentration of 150 U/mL. Subsequently, 80 g wolfberry powder sample, 120 g water and 80 mL of saliva simulant were mixed in a water bath at 37°C for 5 min at $27 \times g$. A total of 5 mL of the saliva digestion solution was transferred to a centrifuge tube for spare. Assays were performed in triplicates.

2.4.2 Gastric phase

Firstly, 50 μL of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ solution was added to 98.5 mL of gastric electrolyte stock solution after which the pH was adjusted to 1.58 using 6 mol/L HCl. Then, pepsin was dissolved in the above solution to a final concentration of 800 U/mL, and 5 mL of gastric chime, which had been digested for 60, 120, and 180 min were transferred to a centrifuge tube for spare. Assays were performed in triplicates. The pH of gastric digestion samples was quickly adjusted to 7.0 ± 0.1 using the NaOH solution (1 mol/L) to terminate the enzymatic hydrolysis reaction. Finally, pH was adjusted to 7.5 ± 0.1 after which samples were stored at -80°C for subsequent assays.

2.4.3 Intestinal phase

The amount of 200 μL of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ solution was added to 98.3 mL of intestinal electrolyte stock solution and the pH was adjusted to 6.8 using 6 mol/L HCL. Pancreatin and bile salts were added to final concentrations of 200 U/mL and 20 mmol/L, respectively. Then, 5 mL of intestinal chime that had been digested for 90, 150, and 240 min were transferred to a centrifuge tube in triplicates. The intestinal digestion samples were water bath heated for 5 min to terminate the enzymatic hydrolysis reaction.

2.5 QC/quality assurance (QA)

Ultra-performance LC system (Xevo TQ-S micro-Triple Quadrupole, Waters, Milford, MA, USA) was used to separate the analyzers. The column utilized was an ACQUITY UPLC BEH C_{18} column ($2.1 \text{ mm} \times 50 \text{ mm}$, $1.7 \mu\text{m}$). Sample preparation and instrument parameters were as shown in the Supplementary Information. The QA/QC for pesticide analysis includes linearity, precision, recovery, and accuracy. A linear relationship with dinotefuran correlation coefficient of $R^2 > 0.99$ was obtained over concentration range of 5–1 000 $\mu\text{g/kg}$. The limits of detection (LODs) for target compounds, calculated using the lowest concentration levels were detected in the system with signal-to-noise ratios of 3/1 at a concentration range of 0.04–2.61 $\mu\text{g/kg}$, while limits of quantification (LOQs) were determined at an signal-to-noise ratios of 10 range from 0.14 $\mu\text{g/kg}$ to 8.73 $\mu\text{g/kg}$ for target compounds (NY/T 788-2018) (Table S3). At three fortification levels, the average recovery rates of dinotefuran in different matrices (fresh wolfberry, decoction pieces, wolfberry decoction, alcohol immersion solution, and digestive fluid) were 70.20%–115.20% with relative standard deviations (RSDs) below 16.57% (Tables S4 and S5).

2.6 Calculation of half-life, PFs, dietary risk assessment and bioaccessibility

2.6.1 Half-life ($T_{1/2}$) calculations

$T_{1/2}$ of dinotefuran were determined using Eqs. (1) and (2)^[31]:

$$C = C_0 e^{-kt} \quad (1)$$

$$T_{1/2} = \frac{\ln 2}{k} \quad (2)$$

whereby C denotes the residue concentration (mg/kg) at time t (day), C_0 is the initial residue concentration (mg/kg), and k is the dissipation rate constant (day^{-1}).

2.6.2 PF calculation

The PFs values were calculated from JMPR data on the effect of food processing methods on pesticide residue levels^[32], as follows:

$$\text{PF} = \frac{\text{Residues in processed fraction (mg/kg)}}{\text{Residues in raw agriculture materials (mg/kg)}} \quad (3)$$

$\text{PF} < 1$ (= reduction factor) indicates a depletion of the residual pesticide levels after processing. $\text{PF} > 1$ (= concentration factor) indicates increased residual pesticides after processing^[33].

The ratio of transfer of dinotefuran from dry wolfberry to decoction solution or wolfberry infusion was determined as shown in Eq. (4)^[18]:

$$\text{Transfer (\%)} = \frac{C_i \times V_i}{C_0 \times m_0} \times 100 \quad (4)$$

whereby C_i denotes the concentration of dinotefuran in the wolfberry decoction liquor ($\mu\text{g/mL}$), V_i is the volume (mL) of wolfberry decoction liquor, C_0 is the content of dinotefuran in dried wolfberry ($\mu\text{g/g}$), and m_0 is the mass (g) of dried wolfberry for making infusion.

2.6.3 Dietary exposure risk assessment calculations

To ensure safe use of dinotefuran on wolfberries, the hazard quotient (HQ) model was used to assess the risk of dietary exposure^[34]. The risk is unacceptable when the HQ value is greater than 1. HQ values < 1 is acceptable without long-term negative health implications^[35]. The safety of dinotefuran as food was evaluated using Eqs. (5) and (6):

$$\text{NEDI} = \frac{\sum \text{STMRi} \times \text{PF} \times \text{Fi}}{\text{bw}} \quad (5)$$

$$\text{HQ} = \frac{\text{NEDI}}{\text{ADI}} \quad (6)$$

whereby NEDI denotes the national estimated long-term daily intake (mg/kg bw), STMRi is the median residue (mg/kg) of supervised trials, PF is the PF of dinotefuran after the decocting, brewing, and alcohol soaking process. Fi is 0.009 kg/day (average consumption of wolfberry for an adult in China (kg/day), with bw in kg)^[36]. bw is the global average body weight (60 kg for adults and 15 kg for children)^[37]. ADI is the acceptable daily intake derived from WHO and JMPR (0.2 mg/kg bw)^[38].

2.6.4 Determination of bioaccessibility

Bioaccessibility was determined using Eq. (7):

$$\text{BA} (\%) = \frac{C_1 V_1}{Cm} \times 100 \quad (7)$$

whereby BA denotes the bioaccessibility of the target compound; C_1 is the concentration of the tested pesticide in the gastrointestinal fluid (mg/L); V_1 is the added amount of gastrointestinal fluid (mL); C is the concentration of test pesticide (mg/L) in wolfberry and m is the mass (kg) of sample matrix added to the reaction system.

2.7 Data statistics

All of the experiments were repeated in triplicate, and the calculated values were presented as mean $\pm$ SD. SPSS Statistics 26.0.0 (IBM, Armonk, NY, USA) was used for the one-way analysis of variance followed by Duncan's post hoc test to analyze statistical significance. Significant difference was defined at the level of $P < 0.05$.

3. Results and discussion

3.1 Dissipation kinetics of dinotefuran in wolfberry

The dinotefuran residue in the sample was calculated as the sum of dinotefuran, UF, and DN^[13]. The degradation trends of dinotefuran residues in wolfberry are shown in Fig. 3A. At the recommended and double doses, initial deposits of dinotefuran in wolfberry were 0.245 and 0.480 mg/kg, respectively, with a dissipation rate of 73.18%–84.28% over 14 days. Moreover, dinotefuran degradation was well described by first-order kinetics, with $C = 225.25e^{-0.061t}$ ($R^2 = 0.9266$) and $C = 370.03e^{-0.071t}$ ($R^2 = 0.9042$), respectively. The corresponding $T_{1/2}$ values were 11.36 and 9.76 days. Chen et al.^[39] reported that $T_{1/2}$ values for dinotefuran in eggplants and soil were 8.35–11.40 days. In previous studies, $T_{1/2}$ values of dinotefuran in wolfberry and *Oryza sativa* varied from 1.4 days to 3.1 days

and 1.0 days to 2.6 days, respectively^[9,13]. This difference may be affected by various factors such as application concentration, soil type, pH, microorganisms and environmental climate on pesticide degradation^[40]. The primary dinotefuran metabolites, DN and UF, were detected, as shown in Figs. 3B and C. With increasing sampling intervals, the dissipation of DN and UF in wolfberry exhibited an 'increasing-decreasing' trend, and they began to decrease after reaching the maximum amount of residue in samples after 7 and 1 days, respectively. This may have been due to extension of time, a faster rate of degradation than conversion was observed for metabolites^[41]. Among them, the residual amount of DN was greater than that of UF, and there was a certain residual amount after 28 days, up to 19.76 $\mu\text{g/kg}$. UF concentration started to decrease at day 1, while DN concentrations were maximum at day 7. Then, the total concentrations for both metabolites began to decrease after day 7. DN in particular may formed from the degradation and transformation of dinotefuran and UF^[42] (Fig. 3D).

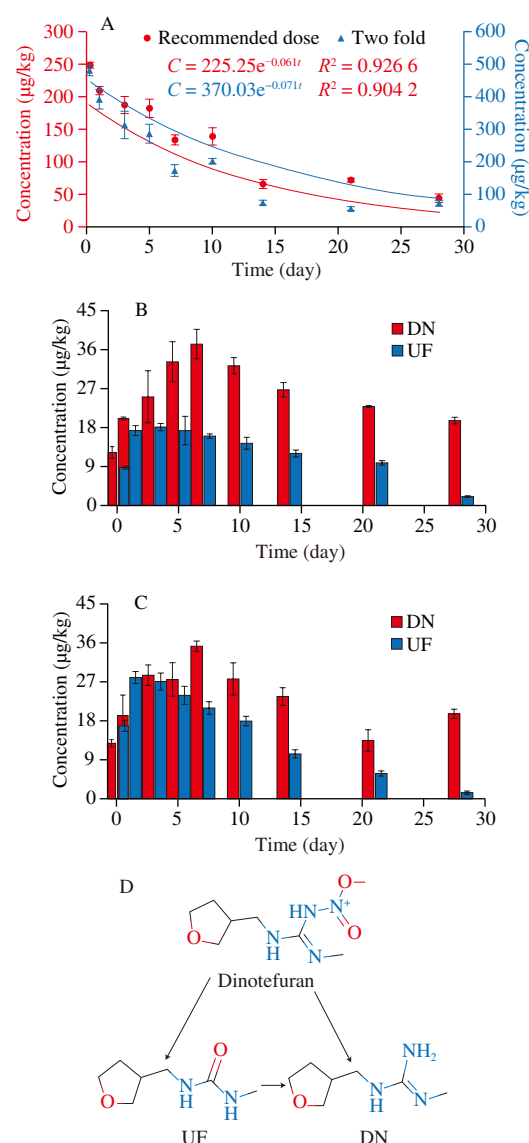


Fig. 3 Degradation trends of dinotefuran residues in wolfberry. (A) Residual digestion dynamics of dinotefuran in wolfberry; (B) Degradation trends of UF and DN residues in wolfberry at the recommended dose; (C) Degradation trends of UF and DN residues in wolfberry at double dose; (D) Proposed metabolic pathway of dinotefuran and its metabolites UF and DN.

3.2 Dinotefuran behaviors in wolfberry during processing

3.2.1 Effects of drying on dinotefuran in wolfberry

By reducing moisture levels, the drying process is an effective preservation method and also affects pesticide residue levels^[43]. The increase in pesticide concentrations exhibited variations at different drying temperatures, processing methods and time. The drying process resulted in enrichments of dinotefuran residues (106.55%–133.79%) in wolfberry (Fig. 4A). At the recommended and double doses, pesticide residues of dinotefuran during drying exhibited the same trend. During drying in the oven at 40 and 50 °C, residual amounts of dinotefuran slowly increased with prolonged drying time and increasing drying temperature. However, as the drying temperature increased to 60 °C, dinotefuran concentrations slightly decreased when the drying time increased to 20 h, which may be because the dissipation rate of the pesticide was greater than the water loss rate of wolfberry, which resulted in concentration effects^[44]. Amvrazi et al.^[45] reported that sunlight photodegrades

pesticide residues to a certain extent. Fig. 4B shows that sun drying had the least enrichment effects on dinotefuran (106.55%) compared to oven drying (108.12%–133.79%). Sood et al.^[46] showed that during green tea drying using hot air at 95–100 °C to a final moisture content of 5%–6%, residue dissipation rate of dimethoate reached 76.6%. Disappearance of pesticides during processing may be via chemical (i.e. hydrolysis, oxidation, reduction) or physical (i.e. photolysis and volatilization) degradation to their metabolites^[47]. In Fig. 4C, it is shown that oven drying of wolfberry decreased UF and DN residue concentrations by 90.29%–100%. Undetectable UF levels indicate that this compound is not stable under roasting. The major reason caused the loss of pesticides under heat processing conditions was the physicochemical properties of pesticides that lead to evaporation or thermal degradation^[42]. Initial residues of UF and DN in wolfberry were 16.83 and 12.80 µg/kg, respectively. After sun drying, residual concentrations of UF and DN decreased by 88.02% (3.5 µg/kg) and 79.20% (1.53 µg/kg), respectively. UF could have been significantly reduced by volatilization and photolysis after heat treatment and converted to DN via carbonyl reduction during

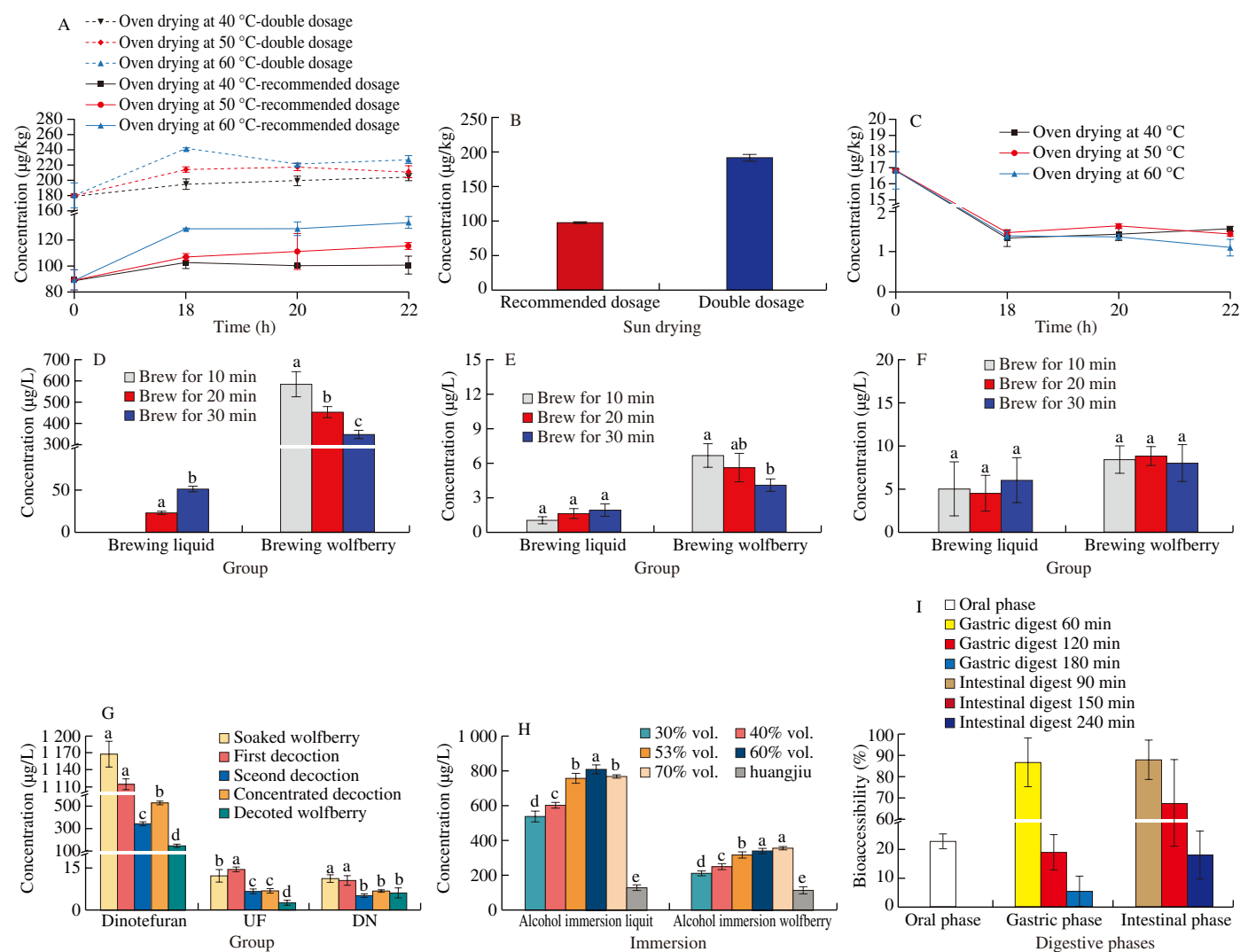


Fig. 4 (A) Effects of different drying temperatures and time in an oven on dinotefuran in wolfberry; (B) Effects of sun drying on dinotefuran in wolfberry; (C) Effects of different drying temperatures and time of oven drying on DN in wolfberry at double dose; (D) Effects of brewing on dinotefuran residues in wolfberry; (E) Effects of brewing on UF residues in wolfberry; (F) Effects of brewing on DN residues in wolfberry; (G) Effects of decoction on dinotefuran and its metabolites UF and DN residues in wolfberry; (H) Effects of alcohol immersion on dinotefuran residues in wolfberry; (I) Average estimated bioaccessibility of dinotefuran in different digestive phases. Different lowercase letters in same group indicate significant difference ($P < 0.05$).

hydrolysis^[48]. Plant metabolism studies revealed that when sprayed onto apples, dinotefuran remained on the fruit surface, with only a small percentage of it that slowly penetrated into the fruit being extensively metabolized to polar products^[48]. However, enantiomers concentrations of dinotefuran and UF in tomato juice were higher than those of the tomato pulp, revealing that they were easily transported into interior of the tomato fruit^[49]. This could have been attributed to their favorable solubility in water^[50].

3.2.2 Effects of decocting on dinotefuran in wolfberry

In this study, the decocting process resulted in reduction of dinotefuran (87.48%) residues in wolfberry (Fig. 4G). For the initial decoction, the transfer rate of dinotefuran from soaked wolfberry to decoction was 45.23%. Heating accelerates the processes of volatilization, hydrolysis, and other chemical degradation, thereby reducing residual levels^[51]. In this study, 69.08% of dinotefuran was lost after second decocting, suggesting that the degradation of pesticides or water evaporation caused by heating was the main reason. Moreover, the dissipation of dinotefuran residue in wolfberry residue was significantly increased to 87.48% after the decocting process. Decocting reduces the intake of harmful pollutants, including heavy metals and pesticides by humans^[44,52]. The pesticide residues increased by 1.03–1.55 times after reduction of the decoction extract under pressure (Fig. 4G). A comparable increase in relative concentrations of pesticides has been observed in *Paeoniae radix lactiflora*^[44]. These results demonstrate that the decrease under pressure leads to the concentration of pesticide residues, which may be ascribed to water evaporation^[53]. Regarding the initial decoction, concentrations of UF residues were higher than those of wolfberry after soaking, suggesting that the first decoction promotes the migration of UF in the decoction. After the second decoction, the degradation rate of UF was 53.23% (Fig. 4F). After the first and second decoction, DN residues were degraded by 7.06% and 53.53%, respectively. Reduction of the pesticide residue during boiling may be attributed to physicochemical properties of the pesticide^[44]. Dinotefuran has a very high solubility in water^[41] (water solubility (SW) = 39 800 mg/L, Table S6), thus, it maintains a large residual amount in the decoction liquid, and the transfer rate in the concentrated decoction is as high as 91.61%. Compared to dinotefuran, UF and DN have higher melting points (107.5, 347.2, and 228.2 °C, respectively), therefore, the stable structure may have made them less affected by temperature and lower transfer rate during decoction.

3.2.3 Effects of brewing on dinotefuran in wolfberry

Brewing is convenient way of preparing wolfberry for daily life consumption. Usually, about 10 g of it can be eaten with hot water. Fig. 4D shows the behaviors of dinotefuran during wolfberry brewing. After wolfberry was brewed in hot water, dinotefuran residues in wolfberry residues were relatively high, and only 0–14.7% of dinotefuran was transferred to the brewing solution. These findings imply that for wolfberry brewing, pesticides are mostly left in the residue. Various factors influence the transfer of pesticides^[54]. They include interior elements (physico-chemical characteristics of pesticides and natural components of wolfberry) as well as external

factors (water temperature and brewing duration). Generally, the leaching rate of pesticides from dry material to infusion is typically determined by their water solubility and octanol-water partition coefficient^[55]. In Bai's^[41] study, the transfer rate of dinotefuran (high SW value = 39 830 mg/L and low K_{ow} = -0.549) in dry tea to infusion through boiling was as high as 98.1%. While for tolfeprad (low SW value = 0.087 mg/L and high K_{ow} = 5.61), the transfer rate from green tea to infusion was only 2.3%. Jaggi et al.^[56] reported that the solubility of pesticides may be affected by temperature and therefore water solubility does not necessarily indicate a shift in the direction of preferential accumulation of residues in infusions. In our previous study, the transfer rate of 11 pesticides, including imidacloprid, acetamiprid, and tebuconazole in a honeysuckle decoction ranged from 1.95% to 55.63%, meanwhile, the transfer rates of neonicotinoid insecticides were highest, ranging from 14.53% to 55.6%^[18]. Generally, extraction efficiencies of pesticides in decoctions are directly proportional to their solubility in water. Oh et al.^[57] reported that insecticides with low water solubility (0.1 mg/L or less), such as chlorfenapyr, fenvalerate, p,p'-DDE and bifenthrin had relatively high transfer rates (42.2%, 64.3%, 48.9% and 22.0%, respectively) during the brewing process of wolfberry. With prolonged brewing time, UF residue concentrations in the brewing solution increased, exhibiting comparable residue behaviors as dinotefuran (Fig. 4E). However, UF concentrations in the brewing wolfberry residue were decreased. Differences in DN concentrations in residual amounts of wolfberry brewing solutions were insignificant ($P < 0.05$) (Fig. 4F). Since UF and DN have low lg K_{ow} (0.34 and -0.27, respectively) and high melting points (347.2 and 228.2 °C, respectively) compared to dinotefuran (the melting point is 107.5 °C), differences in concentrations of UF and DN in brewed liquid and brewed wolfberry under brewing times of 10, 20, and 30 min were insignificant.

3.2.4 Effects of alcohol immersion on dinotefuran in wolfberry

Distilled spirits have a long production history and are favored by consumers in China. Many businesses and individuals use wolfberry as the raw material and soak it in wine. In this process, nutrients migrate into the wine while pesticide residues used for the control of pests and diseases also partially migrate into the liquor^[58]. As shown in Fig. 4H, during alcohol immersion processing, dinotefuran residues reflect different residue behaviors in liquor with different volume fractions. As alcohol levels of the liquor increase, dinotefuran residues exhibited an increasing trend. As the alcohol volume fraction increased to 53%, there was a significant increase in dinotefuran pesticide residues in liquor ($P < 0.05$). Consistent with our findings, Xing et al.^[59] found that residues of 8 pesticides in wolfberry immersion liquor with high alcohol volume fractions were higher than those of the low-level alcohol volume fraction. This may be because dinotefuran has a certain solubility in water while more easily soluble in organic reagents^[59]. Compared to huangjiu, dinotefuran concentrations in the wolfberry alcohol immersion liquid and the residue were significantly decreased, which may be due to its low alcohol volume fraction (15%, *V/V*). Dinotefuran residues in alcohol immersion of wolfberry exhibited the same trend as in alcohol immersion liquors with different volume fractions. Dinotefuran residues in the alcohol immersion wolfberry residue (120.1–359.0 µg/kg) were not as high as those in alcohol immersion

liquors (136.0–813.5 µg/kg), which may be because dinotefuran majorly remains on wolfberry surface, thus, most of it was dissolved in the alcohol liquid^[42]. However, UF and DN metabolites were not detected during the alcohol soaking process, which may be because residual amounts of UF and DN had been degraded during the 30-day soaking time.

3.3 PFs of dinotefuran in wolfberry

Agro-processing procedures usually lead to different behaviors of pesticide residues. In this study, PFs of the drying process were 1.07–1.34, indicating that oven drying and sun drying enriched the concentrations of dinotefuran in wolfberry (Fig. S1A). Zhao et al.^[43] reported that the PFs of nine pesticides, including malathion, triazolone, and hexazolone in *Ziziphus jujuba* Mill were all > 1 during drying, which confirms the significant effects of water evaporation during drying. In addition, the behaviors of pesticide residues during processing are affected by the physicochemical properties of pesticides (SW, lg K_{ow} , and chemical structure). In our previous study, we found that pesticides with low lg K_{ow} values and high melting point as well as vapor pressure values could be enriched in honeysuckle via drying^[18]. In Martin's study, it was found that pesticides with low lg K_{ow} values has the highest PFs during apple juice processing^[60]. Enrichment of dinotefuran may have been due to its low lg K_{ow} (−0.549).

All PFs during decocting and brewing were < 1 (0.000–0.461; Fig. S1B). The significant reduction in dinotefuran residue concentrations after decocting may be due to high SW values (3.98×10^4 mg/L). In our previous study, the removal rate of pesticides after boiling reached 65%, while for non-systemic pesticides such as chlorothalonil, the amounts of residues were completely removed by boiling from juice to puree^[61–62]. During brewing, the PF gradually increased with prolonged brewing time. Compared to the brewing process, PFs in the decoction were higher, indicating that heat treatment in the decoction process increased the transfer rate of pesticides in water. After soaking in alcohol, PFs ranged from 0.145 to 0.870, implying that pesticide residues in wolfberry decreased after alcohol immersion (Fig. S1C). With increasing volume fractions of alcohol immersion, PFs of dinotefuran were increased while PFs of Huangjiu were lower than those of the liquor, as its low alcohol volume fraction (15%, *V/V*).

3.4 Pesticide bioaccessibility in different digestive phases

The dinotefuran bioaccessibility in the oral digestion stage was 23.18% (Fig. 4I). Xiao et al.^[21] reported that the bioaccessibility of 6 pesticides in papaya (chlorpyrifos, water tick, imidacloprid, thiamethoxam, fenothrin, and abamectin benzoate) at the oral stage were 8.15%–21.77%. In a previous study, increasing alpha amylase concentrations in saliva during oral digestion had progressive increasing effects on pesticide bioavailability, possibly due to increased amounts of chyme in saliva and the functions of α -amylase in saliva to convert starch to glucose through hydrolysis^[21,63]. As shown in Fig. 4I, dinotefuran bioaccessibility during gastric digestion was 5.45%–86.72%. With gastric digestion time being prolonged from 60 min to 150 min, its bioaccessibility decreased from

88.72% to 19.32% and decreased to 5.45% when gastric digestion was performed for 180 min. Generally, the pH of human gastric environment is acidic (1.0–5.0)^[64]. In this study, pH values of gastric fluid with digestion time of 60, 150, and 180 min were 4.78, 4.34, and 2.06, respectively, indicating a gradual decrease in pH after dietary intake. Yu et al.^[65] found that pH changes the physical and chemical properties of test substances, affecting bioaccessibility. In addition, dinotefuran bioaccessibility varied with intestinal digestion stage (Fig. 4I). The bile salts and pancreatin enzymes in the intestinal fluid produce surfactant effects that dissolve the pesticide residues in food and improve bioaccessibility^[66]. Dinotefuran bioaccessibility in the three digestive stages were intestinal (18.20%–88.08%) > gastric (5.45%–86.72%) > oral (23.18%), and bioaccessibility decreased with increasing digestion time. The pH of the human intestinal environment is usually around neutral (pH 5.5–7.5)^[64]. Intestinal fluid pH with digestion time of 60, 150, and 180 min in this study were 5.79, 6.58, and 7.55, respectively. The bioaccessibility decreased with increasing digestion time, it may be that dinotefuran is unstable under alkaline conditions^[67]. Previous studies have shown that the intake of dietary fiber can significantly reduce the absorption of some pesticides^[68]. It is suggested to improve people's daily balanced diet and moderately strengthen the intake of dietary nutrients.

3.5 Dietary risk assessment

The HQ for dinotefuran is considered with PFs of the wolfberry decoction, brewing liquid, and alcohol soaking liquid analyzed in the present study. Table 1 shows that the range of total NEDI of dinotefuran in the wolfberry decoction, brewing liquid, and alcohol soaking liquid was 1.14×10^{-6} – 4.79×10^{-5} mg/kg bw. The corresponding HQ values ranged from 5.71×10^{-6} to 2.39×10^{-4} . For adults and children, the greatest risk of dietary intake is associated with wolfberry alcohol-soaked processing, followed by decocting. The exposure value of dinotefuran was significantly lower than ADI. In addition, the HQ of dinotefuran after decocting, brewing, and alcohol immersion processing were < 1, indicating an acceptable dietary intake risk of dinotefuran to humans after these processes.

Table 1
Dietary risk assessments of dinotefuran.

Processing	STMRI (mg/kg)	ADI (mg/kg bw)	IEDI (mg/kg bw)		HQ	
			Adults	Children	Adults	Children
Decocting			1.20×10^{-5}	4.79×10^{-5}	5.98×10^{-5}	2.39×10^{-4}
Brewing	0.173	0.2	1.14×10^{-6}	4.57×10^{-6}	5.71×10^{-6}	2.28×10^{-5}
Alcohol soaking			2.15×10^{-5}	/	1.07×10^{-4}	/

Note: “/” means alcohol not appropriate for children's dietary exposure risk assessments.

The lack of good agricultural practices (GAP) for the use of pesticides in Chinese medicine crops has led to a limit on the number of pesticide registrations. In addition, dietary intake risks that are as a result of possible enrichments of pesticides in wolfberry processing cannot be ignored. The main factors affecting dietary risk include PFs, pesticide metabolite residues and initial deposition on wolfberry crops. For pesticides with a high-water solubility, high toxicity and high initial residues, agricultural product processing converts pesticide residues into metabolites with a higher toxicity, thereby increasing the health risk posed by pesticide residues^[43].

4. Conclusions

Dissipation of dinotefuran residues in wolfberry at recommended and double doses fits a first-order kinetics pattern with degradation $T_{1/2}$ of 11.36 and 9.76 days, respectively. DN residues were greater than those of UF and peaked on days 5 and 7, respectively. The oven drying process enriched dinotefuran residues, which was attributed to temperature degradation and dehydration enrichment. The decoction process was more effective at removing dinotefuran residues than brewing. In the alcohol soaking process, dinotefuran remained in the wine with high ethanol content. The detected HQ for all processes was < 1 , indicating an acceptable dietary intake risk of dinotefuran to humans. However, dietary risks of pesticides in food for children should be evaluated further. Pesticide bioaccessibility in wolfberry was studied using an *in vitro* simulated digestive system, and the bioaccessibility of dinotefuran varied with pesticide types and digestion stages. By systematically studying the residue behaviors of dinotefuran and its metabolites (UF and DN) in wolfberry cultivation and processing. Through this study, the results of $T_{1/2}$ of dinotefuran from the field trials will guide the rational use of pesticides during *L. barbarum* planting, and processing studies provide enterprises with reasonable processing methods to reduce pesticide residues. Meanwhile, our findings form the basis for quantitative assessment of dietary exposures to pesticide residues in wolfberry and inform the revision of pesticide MRLs.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://doi.org/10.26599/FSHW.2024.9250106>.

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