Effect of Tannic Acid on Nutrition and Activities of Detoxification Enzymes and Acetylcholinesterase of the
Fall Webworm (Lepidoptera: Arctiidae)

Yufei Yuan,1 Lusha Li,1 Jingfen Zhao,2 and Min Chen1,3

1Beijing Key Laboratory for Forest Pest Control, College of Forestry, Beijing Forestry University, 35 Qinghua East Road, Beijing 100083, China, 2Forestry Station of Fengtai District Garden Greening Bureau, Beijing 100055, China, and 3Corresponding author, e-mail: minch@bjfu.edu.cn

Subject Editor: Yu-Cheng Zhu

Received 28 October 2019; Editorial decision 22 January 2020

Abstract

Plant tannins, polyphenolic plant secondary metabolites are involved in important chemical defense processes in plants. In this study, tannic acid was used as the standard of plant tannins to determine the effects on nutritional indices and activities of glutathione S-transferases (GSTs), cytochrome P450 monoxygenase (CYP450), carboxylesterase (CarE), and acetylcholinesterase (AChE) in fourth-instar larvae of Hyphantria cunea (Drury) by feeding on an artificial diet containing tannic acid under different treatments. We found that tannic acid significantly affected the digestive capacity and food utilization rate of H. cunea larvae. A tannic acid concentration of less than 2.0% promoted feeding and the utilization of undesirable food by H. cunea larvae, while inhibitory effects were observed at high concentrations (>2.5%). Tannic acid had a significant effect on the activity of detoxification enzymes and AChE in H. cunea larvae in concentration-dependent and time-dependent manners (P < 0.05). These results provide new insights into the potential mechanisms underlying detoxification in H. cunea larvae against tannic acid in host plants.

Key words: tannic acid, Hyphantria cunea, detoxification enzyme, nutritional effect

During long-term co-evolution with insects, plants developed a series of physical, chemical, and developmental defense mechanisms to prevent insect feeding, among which chemical defense systems involving secondary metabolites are the most important (Gong and Zhang 2014). To respond plant defense, insects developed multiple resistance mechanisms against plant secondary metabolites (Ivie et al. 1983, Zhu-Salzman and Zeng 2010). From the perspective of plants, strategies to prevent phytophagous insects from feeding on plants are beneficial, including antifeeding, repelling, and poisoning strategies as well as the inhibition of insect growth and development (Kelly and Curry 1991, Panzuto et al. 2002). From the perspective of phytophagous insects, ingested plant secondary metabolites can be tolerated or detoxified via detoxification enzymes (Schuler 1996, Simmonds 2003, Chen et al. 2015, Pan et al. 2016).

The fall webworm Hyphantria cunea (Drury) is a quarantined pest worldwide. This insect is native to North America and was introduced into Europe and Asia in 1940 and 1945, respectively, through human activities (Hidaka 1977, Wu et al. 2019). Based on the European and Mediterranean Plant Protection Organization (EPPO: https://gd.eppo.int/) Global database, H. cunea has since spread to three countries in the Americas, 23 countries in Europe, and seven countries in Asia. In China, H. cunea was first observed in Dandong City, Liaoning Province, in 1979 and has spread to 13 provinces (Ji et al. 2003). It has had devastating effects on forests, fruit trees, and field crops in invaded regions and has become one of the most important invasive forest pests in China (Li et al. 2018).

Hyphantria cunea is a polyphagous herbivorous worm with a wide range of host plants, including 636 species distributed worldwide (Firidin et al. 2008). A broad range of hosts confers a strong ability to survive in new environments, allowing H. cunea to adapt to various nutritional conditions and host plants with toxic secondary metabolites (Despres et al. 2007, Rane et al. 2019). Although polyphagous insects can generally adapt to a wide range of nutritional conditions, they require a certain balance of nutrients in their food sources for growth and development (Cao et al. 2014). Thus, the robust adaptability of H. cunea can probably be explained by the detoxification of plant secondary metabolites. A strong relationship between host adaptation and the ability of insects to metabolize plant secondary metabolites has been demonstrated at the biochemical and molecular levels (Dermauw et al. 2013, Chen et al. 2015).

During feeding and digestion, the detoxification system of phytophagous insects is induced to protect against plant secondary metabolites. The main detoxification enzymes of insects include glutathione S-transferases (GSTs), carboxylesterase (CarE), and acetylcholinesterase (AChE), and...
cytochrome P450 monooxygenase (CYP450) (Terriere 1984, Ziaee et al. 2009). In the metabolic processes of plant secondary metabolites in insects, GSTs conjugate their substrate with a glutathione molecule, which does make the substrate more water soluble; however, P450s oxidize their substrates to make them reactive for conjugation enzymes (Despres et al. 2007). CarE hydrolyze many compounds containing esters, both endogenous and exogenous (Wheelock et al. 2005). AcrE monooxygenase (AChE) is a key enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine to terminate nerve impulses (Senthil-Nathan 2013). The main detoxification enzymes and AChE generally have key functions in the interaction between insects and host plants or botanical insecticides (Zhou et al. 2016). However, it is still not clear which enzymes play a major role in detoxifying a certain kind of plant secondary metabolites.

Plant tannins are one group of the most abundant plant secondary metabolites, and exist in almost all vascular plants (Schoonhoven et al. 2005). They can protect leaves against insects by deterrence and/or toxicity (Li et al. 2017). They are polyphenolic compounds of around 500–3000 Da with two main types: hydrolyzable tannins (HTs) and condensed tannins (CTs) (Barbehenn and Constabel 2011). Plant tannins are protease inhibitors that combine with digestive enzymes to form a complex, precipitate proteins, and impede digestion and utilization by herbivorous insects (Blytt et al. 1988, Zhang and Liu 2003). Tannic acid is a commercial preparation of plant tannins composed of gallic and digallic acid with glucose (Pizzi et al. 2009). Previous research has shown that tannic acid enhances the activities of GSTs, CarE, CYP450, and AChE in the midgut and fat bodies (Chrzanski et al. 2012, Cheng et al. 2015, Chen et al. 2019). Other studies have suggested that tannic acid could reduce GSTs activity in Sitobion avenae (Fabricius) (Homoptera: Aphididae) and Helicoverpa armigera (Hubner) (Lepidoptera: Noctuidae) in a dose-dependent manner (Chen et al. 2003b, Tang et al. 2014). Plant tannins are widely found in the host plants of Helicoverpa armigera and the content in different plants was significantly different (Li et al. 2018). However, the effects of host plant tannins on the nutrition and detoxification enzymes of Helicoverpa armigera are unknown. By adding a secondary metabolite to an artificial diet, it is possible to investigate its role in defense against phytophagous insects. Due to the fact that the tannin compounds vary in different plants and are difficult to standardize, in the present study, we use tannic acid as standard plant tannins to explore its effects on nutrition, detoxification enzyme activity, and physiological and biochemical responses of Helicoverpa armigera larvae. The results could improve our understanding of the strong host plant adaptation in this pest and have practical implications for the design of novel pest control strategies using plant secondary metabolites.

**Materials and Methods**

**Insect Rearing**

Eggs of the fall webworm were sterilized with 10% formaldehyde solution for 15 min and larvae from same egg mass were reared on an artificial diet (Cao et al. 2014) at 25 ± 1°C and 70 ± 5% relative humidity under a photoperiod of 16:8 (L:D) h. The normal artificial diet was used for early larval stages to reduce mortality. Starting at fourth instar, larvae were moved to tannic acid-treated diet at different concentration (Frempong and Zalucki 1991). Larval molting times were recorded.

**Preparation of Tannic Acid Diets**

Tannic acid (CAS No. 1401-55-4) was purchased from Sigma–Aldrich, St Louis, MO (Cat#T0200). The impacts of various concentrations of tannic acid on nutrition and detoxification enzyme activity were determined by adding tannic acid to an artificial diet (Chen et al. 2003b, Wang 2016). The methods for making tannic acid supplemented diets were based on the artificial diet formula described by Cao et al. (2014). Briefly, tannic acid was weighed, dissolved in distilled water, and serially diluted to gradient concentrations of 1.0%, 1.5%, 2.0%, 2.5%, and 3.0% (W/V), based on the content of tannin (3.91–6.08 mg/g) in the leaves of several host plants of H. cunea, as determined in our previous experiments (Li et al. 2018). The solution was evenly mixed into the artificial diet and stirred constantly. Then, the diets were poured into a rearing cup (200 ml) and allowed to solidify. Afterward, 15 newly molted fourth-instar H. cunea larvae were put into each cup and placed in an incubator. The larvae of control group were provided normal diet with addition of the same volume of distilled water, instead of the tannic acid. The impacts of tannic acid on nutrition and detoxification enzyme activity were determined by adding tannic acid to an artificial diet (Chen et al. 2003b, Wang 2016). The methods for making tannic acid supplemented diets were based on the artificial diet formula described by Cao et al. (2014). Briefly, tannic acid was weighed, dissolved in distilled water, and serially diluted to gradient concentrations of 1.0%, 1.5%, 2.0%, 2.5%, and 3.0% (W/V), based on the content of tannin (3.91–6.08 mg/g) in the leaves of several host plants of H. cunea, as determined in our previous experiments (Li et al. 2018). The solution was evenly mixed into the artificial diet and stirred constantly. Then, the diets were poured into a rearing cup (200 ml) and allowed to solidify. Afterward, 15 newly molted fourth-instar H. cunea larvae were put into each cup and placed in an incubator. The larvae of control group were provided normal diet with addition of the same volume of distilled water, instead of the tannic acid.

**Nutritional Effect Assay**

Fourth-instar healthy larvae of H. cunea (molting in 4 h) were used in this study. Fifteen larvae were starved for 24 h, weighed, and fed on tannic acid diets for 48 h. The diets were removed from the larvae for 12 h and feces were collected. Each treatment (concentration) was repeated three times. Following feeding trials, the larvae, the discharged feces, and the remaining feed were weighed and dried at 80°C for 8 h until reaching a constant weight and weighed to determine mass loss from pre-feeding. Simultaneously, additional replicates were used to measure the fresh weight and dry weight. On the basis of the larval water content, the dry weights of the pre-feeding larvae and diet were calculated.

The approximate digestibility (AD), efficiency with which digested food is converted to body substance (ECD), efficiency of conversion of ingested food to body substance (ECI), relative growth rate (GR), and consumption index (CI) were selected as nutritional indices (Waldbauer 1968). The indices were calculated on the basis of dry weight.

The CI was calculated as follows:

\[ CI = \frac{F}{TA} \]

where:

\[ F = \text{fresh or dry weight of consumed food; } \]

\[ T = \text{duration of the feeding period; } \]

\[ A = \text{mean fresh or dry weight of the animal during the feeding period (as in the GR calculation below).} \]

The relative GR was calculated as follows:

\[ GR = \frac{G}{TA} \]

where:

\[ G = \text{fresh or dry weight gain of the animal during the feeding period.} \]

The ECI was calculated as follows:

\[ ECI = \frac{\text{wt gained}}{\text{wt food ingested}} \times 100 \]

where:

\[ \text{wt} = \text{weight (as in the AD and ECD calculation below)} \]

The AD was calculated as follows:

\[ AD = \frac{\text{wt of food ingested} - \text{wt of feces}}{\text{wt of food ingested}} \times 100 \]

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The ECD was calculated as follows:

\[
ECD = \frac{wt \text{ gained}}{wt \text{ of food ingested} - wt \text{ of feces}} \times 100
\]

Pretreatment of Larvae

The detoxification enzyme and AChE activities of fourth-instar larvae fed on diets for 24 h with different tannic acid concentrations (1.0%, 1.5%, 2.0%, 2.5%, and 3.0% [W/V]) were determined. Additionally, the detoxification enzyme and AChE activities of fourth-instar larvae fed on 1.0% tannic acid diets for different durations (12, 24, 36, 48, and 60 h) were measured. Each treatment had three replicates, and each replicate had 15 larvae.

The larvae from each treatment were cleaned in ice-cold physiological saline, dried with filter paper, weighed, and placed into a PE tube. Then, 0.86% cold physiological saline was added at the rate of nine times the weight of *H. cunea* larvae. The tissue sample was ground (Retsch MM400 Grinder, Haan, Germany) at 10,000–15,000 rpm to produce a 10% tissue homogenate and centrifuged at 3,000 rpm for 10 min at 4°C. The supernatant was collected for enzyme activity measurements.

Detoxification Enzyme Activity Assays

Procedures for activity assays of each enzyme were followed the manufacturer’s instructions for the relevant kits. The Total Protein Quantitative Assay Kit (Product ID: A045-3), AChE Assay Kit (Product ID: A024), GSTs Assay Kit (Product ID: A004), and CarE Test Kit (Product ID: A133) were purchased from Nanjing Jiancheng Bioengineering Institute, Nanjing, China. The insect CYP450 ELISA Kit (Product ID: JL22832-48T) was obtained from Shanghai Jianglai Bioengineering Institute, Nanjing, China. The insect CYP450 ELISA Kit (Product ID: A024), GSTs Assay Kit (Product ID: A004), and CarE Test Kit (Product ID: A133) were purchased from Nanjing Jiancheng Bioengineering Institute, Nanjing, China. The optical density was recorded using a microplate reader (Spectramax 190, Molecular Devices, San Jose, CA). Protein content was quantified using the Coomassie brilliant blue method following the procedures of total protein quantitative assay kit.

Data Analysis

All results were expressed as means ± SE. Data were analyzed using standard one-way ANOVA implemented in SPSS 24.0. Significant differences between means were calculated using Tukey’s post hoc test at P < 0.05.

**Results**

Effects of Tannic Acid on Nutrition in *H. cunea* Larvae

We measured nutritional indices of *H. cunea* larvae fed on artificial diets and found that tannic acid had significant effects on the nutritional indices decreased.

**Table 1. Nutritional indices of fourth-instar *Hyphantria cunea* larvae fed on tannic acid diets and control diet**

| Tannic acid content (%) | AD (%) | ECI (%) | ECD (%) | CI (g/g-d) | GR (g/g-d) |
|------------------------|--------|---------|---------|------------|------------|
| 1.0                    | 0.650 ± 0.01a | 0.107 ± 0.01a | 0.165 ± 0.02ab | 0.148 ± 0.01b | 0.329 ± 0.01b |
| 1.5                    | 0.610 ± 0.02a | 0.110 ± 0.01a | 0.182 ± 0.02ab | 0.189 ± 0.01a | 0.335 ± 0.02b |
| 2.0                    | 0.613 ± 0.02a | 0.123 ± 0.01a | 0.202 ± 0.03a | 0.178 ± 0.01a | 0.428 ± 0.01a |
| 2.5                    | 0.617 ± 0.03a | 0.078 ± 0.01b | 0.127 ± 0.02bc | 0.140 ± 0.01c | 0.209 ± 0.00c |
| 3.0                    | 0.372 ± 0.04a | 0.020 ± 0.00c | 0.035 ± 0.01d | 0.086 ± 0.01d | 0.042 ± 0.00e |
| CK                     | 0.666 ± 0.03a | 0.060 ± 0.01b | 0.092 ± 0.02cd | 0.144 ± 0.02bc | 0.138 ± 0.02d |

Data are presented as means ± SE and different lower letters in a column indicate significant differences (Tukey’s test, P < 0.05).
control group and showed a decreasing trend as the treatment time increased (Fig. 2b).

Discussion

Plant tannins are thought to play a critical role in plant chemical defense against phytophagous insects and are widely found in the host plants of *H. cunea* (Li et al. 2018). Previous studies on the mode of action of tannins in insects showed that tannins formed complexes with either leaf proteins or digestive enzymes in the gut, reduced digestion efficiency, and retarded insect growth (Feeny 1970, Chen et al. 2018a). Detoxifying enzymes in insects have important roles in metabolizing plant secondary metabolites and maintaining normal physiological functions (Wang et al. 2012, Fan et al. 2013). In this study, we investigated the effect of tannic acid on *H. cunea* nutritional indices, detoxification enzyme and AChE activities under different treatment conditions.

We found that high concentration of tannic acid (3.0%) in an artificial diet significantly reduces the CI and GR of *H. cunea* larvae compared with those of the control group. Senthil-Nathan (2013) obtained similar results for *Spodoptera litura* (Fabricius) (Lepidoptera: Noctuidae) fed on an artificial diet containing neem. In the present study, the fourth-instar larvae fed on a 3.0% tannic acid diet showed the lowest ECI and ECD, suggesting that most of the food intake provides energy for detoxifying secondary metabolites rather than growth in the *H. cunea* larvae. This result was consistent with those of Wang (1997), who discovered that 3.0% tannic acid significantly inhibits the growth of *H. armigera* larvae. Sintim (2009) showed that the ECI of sesame-fed *S. litura* larvae is reduced because more food is metabolized for energy and less food is converted to body weight. AlJabr (2017) also found that red palm weevil larvae provided a coumarin-containing diet allocated substantial energy to detoxification and exhibited slowed growth.

By contrast, *H. cunea* larvae showed good performance when feeding on the artificial diet mixed with 1.0–2.5% tannic acid. In these conditions, the relative consumption rate and food utilization efficiencies increased, and resistance to tannic acid was weakened. We speculated that the defense mechanism might be activated when the toxic substances accumulated in the body and exceed the normal tolerance range. Previous research revealed a similar nutritional effect with increases of the AD and the ECI in *Anacridium melanorhodon* (Walker) (Orthoptera: Acrididae) (Bernays 1981) and increase of ECD in *H. armigera* (Wang 1997). Hormesis was also observed in this study. Our data demonstrated stimulation at
low concentrations and inhibitory effect on growth at high concentrations of tannic acid, a typical biphasic response observed by other researchers (Hadacek et al. 2010, Celorio-Mancera et al. 2011). The maximum stimulatory concentrations of tannic acid on nutritional indices in *H. cunea* larvae may be located between 2.0% and 2.5%.

In the present study, the activities of detoxification enzymes and AChE in the fall webworm showed strong time- and concentration-dependent responses to tannic acid, consistent with previous observations in *Nilaparvata lugens* (Stål) (Hemiptera: Delphacidae) (Nathan et al. 2008). As similar as the response of *Aplysia lucorum* (Meyer-Dür) (Hemiptera: Miridae) to gossypol (Zhu et al. 2018), the dependence of detoxification enzyme induction on tannic acid concentrations was not unlimited in *H. cunea*. Once the maximal activity was reached, the concentration of tannic acid was no longer influential anymore. This phenomenon indicated that interactions among detoxification enzymes may exist. Therefore, *H. cunea* larvae may have developed different physiological adaptations to different degrees of exogenous secondary metabolites.

GSTs normally play an important role in protecting herbivorous insects from poisoning of plant secondary metabolites (Ramsey et al. 2010). In this study, we found that low-dose (1.0%) and short-term treatment (12 h) with tannic acid could induce the maximum activity of GSTs in *H. cunea* larvae. As the concentration increased, the toxicity of tannic acid to *H. cunea* larvae increased, followed by substantial increase of GSTs activity and fluctuations of CarE and CYP450 levels (Fig. 1); GSTs activity was always higher than that in the control group as treatment time increased (Fig. 2a), suggesting that GSTs play a central role of induced detoxification enzymes regulated by tannic acid in *H. cunea*. Tannic acid-induced increases of GST activity may have two underlying mechanisms, an over-expression of isozymes of the original GSTs in insects and an induction of the synthesis of new isozymes (Chen et al. 2003a, Cheng et al. 2015).

CYP450 is an important detoxification enzyme in insects (Schuler 1996). Snyder (1996) observed that the enzyme activities of CYP450 in *Manduca sexta* (Linnaeus) (Lepidoptera: Sphingidae) increased after feeding on plants containing nicotine. We found that tannic acid induces CYP450 activity over a long time period, indicating that the tannic acid-induced CYP450 enzyme was involved in the response to host toxins (Fig. 2d). CarE activity...
demonstrated that agricultural use of CarE by tannic acid may be a temporary response and could not be maintained for a long time. AChE is a major indicator of the neurophysiological activity of insects (Colovic 2013). Our results showed that AChE activity was not influenced by tannic acid in Hyphantria cunea. Wang (2016) reported no influence of tannic acid on AChE in Rhopalosiphum maidis (Fitch) (Homoptera: Aphididae) larvae. Thus, our findings suggested that tannic acid had little neurotoxic effect on Hyphantria cunea.

In general, the younger larvae have lower levels of detoxification enzymes than older larvae, but younger larvae used food more efficiently than older larvae (Berry et al. 1980, Ahmad 1986). It should be noted that we only examined the fourth-instar larvae of Hyphantria cunea and a certain concentration range of tannic acid. Further studies are needed to evaluate the effects of tannic acid in a wider concentration range on the whole developmental cycle of Hyphantria cunea larvae.

In addition, to understand the physiological adaptation of Hyphantria cunea to secondary metabolites, it is necessary to explore the regulatory mechanism of detoxification enzymes at the molecular level. The molecular mechanism underlying insect resistance to plant secondary metabolites mainly involves the over-expression of detoxification enzyme genes (Liu et al. 2016, AlJabr et al. 2017). Recent studies have investigated the expression of GSTs and the regulatory mechanism of CYP450 genes by RNA interference and assays of transcriptional responses (Chen et al. 2018b, Ma et al. 2019). Further studies will focus on the gene expression profile and regulatory mechanism of Hyphantria cunea in response to tannic acid using molecular methods.

In this study, we provide evidences of inducible activation of different physiological mechanisms to avoid the harmful effects of tannic acid in Hyphantria cunea. We found that tannic acid could significantly affect food utilization by Hyphantria cunea larvae. The larvae showed a stress response to tannic acid and exhibited an active defense strategy to maintain normal function by increasing the activities of detoxification enzymes. The consumption of toxic diet remained high while detoxification enzymes of Hyphantria cunea were significantly induced. These findings contribute to our understanding of mechanisms underlying the adaptation of Hyphantria cunea to host plant secondary metabolites and provide a basis for the development of new targets and technologies to control the polyphagous invasive pest.

Acknowledgements

We would like to thank Prof. Jing-Jiang Zhou, Department of Biological Chemistry, Rothamsted Research, Harpenden, United Kingdom, for reviewing the manuscript and providing valuable suggestions. Special thanks go to all the anonymous reviewers whose comments have improved this manuscript. This work was supported by the National Key Research & Development Program of China (2018YFC1200400) and the National Natural Science Foundation of China (30970462).

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