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Article

Metabolization of Insecticidal Amides from Leaves of *Piper tuberculatum* by *Heraclydes hectorides* and *Naupactus bipes*

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Amides have been recognized as potent insecticidal natural products but, despite their variety of targets and mechanisms of action, their metabolic fate in insects is virtually unknown. The currently accepted hypothesis is that specialist herbivores are capable of biotransforming xenobiotics rendering them more polar and excretable while generalist insects do not have comparable capacity. The leaves from *Piper tuberculatum*, rich in insecticide amides, were offered to two insect species found on *Piper* leaves under natural conditions and also to four generalist grasshoppers in order to compare their capacity of biotransforming xenobiotics. The amides **1**-**7** were identified in the *P. tuberculatum* leaves and their corresponding carboxylic acids **8**-**13** were detected in frass samples of two host insects suggesting that these species promote the amides hydrolysis. The four generalist grasshoppers when offered *P. tuberculatum* leaves, starved to death after 72 h, indicating a strong antifeedant activity of *P. tuberculatum* leaves.

Keywords: *Piper tuberculatum*, Piperaceae, amides, metabolization, insects

Introduction

Natural amides found in members of the Piperaceae family have received considerable attention due to their potent insecticidal activity against several agricultural pests.[1-9] The isobutyl amides pellitorine and 4,5-dihydropiperlonguminine isolated from *Piper tuberculatum* seeds have shown 100% mortality at doses of 200 and 700 μg, respectively, to the velvetbean caterpillar *Anticarsia gemmatalis* (Lepidoptera: Noctuidae), a typical pest of beans, peanuts, soybeans, cotton, kudzu, alfalfa, cowpeas, horse beans, snap beans, lima beans, and coffee weeds.[1] The 4-methylpentyl amides pipnoohine and pipyahyine isolated from *P. nigrum* fruits exhibited toxicity at 35 and 30 ppm, respectively, against fourth-instar larvae of *Aedes aegypti*.[10]

The most abundant amides from *P. nigrum* fruits piperine and piperiline and some of their analogues had their topical toxicity evaluated against several natural pests including *Ascia monuste orseis* (Lepidoptera: Pieridae), *Acanthoscelides obtectus* (Say) (Coleoptera: Bruchidae), *Brevicoryne brassicae* (L.) (Hemiptera: Aphididae), *Protopolybia exigua* (Hymenoptera, Vespidae) and *Cornitermes cumulans* (Isoptera, Nasutitermitinae).[11] The *N*,*N*-diisopropyl analogue of piperine was the most active against *A. monuste orseis*. Guineensine, an isobutyl amide isolated from seeds of *P. guineense*, showed insecticidal activity (0.84 μg *per* male; 48 h, lethal dose 50% (LD_{50})) when tested topically on the cowpea weevil *Callosobruchus maculatus*. Amides such as piperettine, piperine, thichonine and piplartine were toxic to fruit flies and to several other insect species.[12] Pipericide from *P. nigrum* showed insecticidal activity against the adzuki bean weevil *Callosobruchus chinensis*.[13] *Piper cenocladum* is protected against herbivores by a mutualistic interaction with ants and also contains the amides piplartine, 4'-demethylpiplartine and cenocladamide.[14] *P. cenocladum*

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tissues from which ants were removed had significantly higher concentrations of total amides, indicating that amides are part of the plant defense system.[15] Recent studies[16-18] have revealed that new synthetic amides have promising insecticidal activity. Novel chiral amides as (2*Z*)-*N*,*N*-diethyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enamide and (2*Z*)-*N*,*N*-diisopropyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enamide were effective against the beetle *Rhyzopertha dominica* (Coleoptera: Bostrichidae), one of the main wheat pest, with mortality comparable to the commercial insecticide Bifenthrin®.[16] The trifluoromethylphenyl amides showed potential mosquitocides and repellents properties against *Aedes aegypti* mosquitoes,[17] while phenolic acid amides showed moderate to good insecticidal activity with the lowest LC_{50} value of 63 ppm against brown planthopper (*Nilaparvata lugens*).[18]

In summary, amides are generally associated to the chemical defense strategy in plants because of their potent insecticidal or repellent action against a broad range of insect species but, despite the variety of activities, their metabolic fate in insects is virtually unknown. Thus, as part of the study of metabolism of plant secondary compounds by insects,[19-24] herein we describe the metabolism of the major amides from leaves of *P. tuberculatum* by the insects *Heraclides hectorides* (Lepidoptera: Papilionidae) and *Naupactus bipes* (Coleoptera: Curculionidae), which are observed as herbivores of *P. tuberculatum* leaves in the field. For comparison purposes, four generalist herbivores *Elaeochora trilineata* (Orthoptera: Romaleidae), *Chromacris speciosa* (Orthoptera: Romaleidae), *Tropidacris collaris* (Orthoptera: Romaleidae) and *Xyleus discoideus* (Orthoptera: Romaleidae) were also offered leaves of *P. tuberculatum* to test the hypothesis that specialization on *Piper* hosts correlates with biotransformation of their toxic amides as a mechanism to circumvent toxicity.

Experimental

Plants

Piper tuberculatum Jacq. var. *tuberculatum* leaves Jacq. were collected from specimens growing in the garden of the Institute of Chemistry (University of São Paulo) in São Paulo state, Brazil. The specimen was identified by Dr Elsie F. Guimarães (Instituto de Pesquisas Jardim Botânico do Rio de Janeiro). A voucher specimen (Kato-0240) was deposited at Herbarium of the Instituto de Botânica (Secretaria de Estado do Meio Ambiente).

Insects

Naupactus bipes (Germ., 1824) (Curculionidae, Coleoptera) and *Heraclides hectorides* (Esper, 1794) (Papilionidae, Lepidoptera) were collected in the Campus of the University of São Paulo (USP) and were identified by Dr Sérgio A. Vanin (Instituto de Biociências e Museu de Zoologia-USP). Voucher specimens of *N. bipes* (CSR-001) and *H. hectorides* (CSR-006) were deposited at the Museu de Zoologia da Universidade de São Paulo. The specimens of *N. bipes* adults and *H. hectorides* were reared in the laboratory and maintained in cages under artificial light (15 h light-9 h dark) at room temperature (24 ± 2 ºC) and relative humidity of 72 ± 10% for a month with diet consisting of leaves of *P. tuberculatum*. The grasshoppers (Orthoptera: Romaleidae) *Elaeochora trilineata* (Serville, 1831), *Chromacris speciosa* (Thunberg, 1824), *Tropidacris collaris* (Stoll, 1813) and *Xyleus discoideus angulatus* (Stal, 1873) were collected at Dois Irmãos State Park (Recife, PE, Brazil) and identified by Dr Argus Vasconcelos de Almeida (Department of Biology, UFPRE). The grasshopper species were reared separately in cages in the University's entomology laboratory, and fed on leaves of *Mangifera indica* (*T. collaris*), *Solanum paniculatum* leaves (*C. speciosa* and *X. discoideus*) and *Ipomoea alba* (*E. trilineata*) for several generations under artificial light (15 h light-9 h darkness) at a temperature of 30 ± 2 ºC and relative humidity of 72 ± 10%. Voucher specimens of *E. trilineata*, *C. speciosa*, *T. collaris* and *X. discoideus* were deposited in the same laboratory. The insects were then left starving for 24 h and offered exclusively *P. tuberculatum* leaves. Only *X. discoideus* was capable to feed the leaves and the initial frass collected in the subsequent 2 h were discarded and then collected for 48 h. The frass from *X. discoideus* were freeze-dried and maintained under –20 ºC until chemical analyses were carried out.

Instruments

Gas chromatography mass spectrometry (GC-MS) analyses were carried out using a Shimadzu system (CG-MS-QP2010, Ultra) operating in the electron ionization (EI) mode at 70 eV with a Rxi®-5ms (Crossbond 5% diphenyl/95% dimethyl polysiloxane; 30 m × 0.25 mm × 0.25 μm) column. The oven temperature increased from 100 to 280 °C at 6 °C min^{-1} and a carrier gas (helium) was used at flow rate of 1 mL min^{-1}. Injector and detector temperatures were 260 °C. ^1H nuclear magnetic resonance (NMR) was recorded at 300 MHz (Bruker 300, Bruker BioSpin GmbH, Rheinstetten Germany). Samples were dissolved in $CDCl_3$, with tetramethylsilane (TMS) as

internal standard. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Spots were visualized under UV light (254 and 365 nm) and by spraying with ceric sulfate followed by heating.

Extraction, isolation and analysis of amides **1-7**

The extraction and isolation of the amides **1-7** from *P. tuberculatum* were carried out as previously reported.[25,26]

Isolation of the compounds **8-13**

Freeze dried frass of *N. bipes* (150 mg) and *H. hectorides* (400 mg) fed on leaves of *P. tuberculatum* were milled and extracted with EtOAc (10 mL) three times. The concentration of the EtOAc solutions under vacuum yielded 55 and 118 mg of crude extracts, respectively. These extracts were dissolved in EtOAc (50 mL) and extracted with a solution of NaOH (1 mol L^{-1}, 20 mL) three times. The aqueous solution was acidified with HCl (conc.) to pH 5.0 and extracted three times with EtOAc. The organic phase was extracted with water until neutralization and dried over anhydrous Na_2SO_4, then concentrated under vacuum yielding 15 and 49 mg of acidic fraction, respectively. These fractions were further purified over a silica C_{18} cartridge (Waters, 500 mg) using H_2O:MeOH (2:3) as eluent and further submitted to silica gel prep-TLC eluted with hexanes-EtOAc (3:2) yielding **8** (2.0 mg), **9** (1.5 mg), **10** (2 mg), **12** (1 mg) and **13** (4 mg) from frass of *H. hectorides* and **11** (8 mg) from frass of *N. bipes*.

Preparation of piperic acid

Piperine (0.35 mmol) was refluxed with ethanolic KOH (2 mol L^{-1}) for 2 h. Ethanol was evaporated under reduced pressure and cooled in ice salt bath. The solid potassium salt of piperic acid was suspended in hot water and acidified with hydrochloric acid, yellow precipitate was collected, washed with cold water and recrystallized from ethanol yielding 68.8 mg of piperic acid (90% yield).[27]

Saponification of the crude extract from leaves of *P. tuberculatum*

An amount of 30 mg of leaf extract (EtOAc) was dissolved in dimethyl sulfoxide (DMSO) (10 mL) and treated with a solution of KOH 2 mol L^{-1} (5 mL) and heated at 40 °C for 10 h. The solution was then acidified with HCl (conc.) to pH 5 and extracted with EtOAc (15 mL, three times). The organic phase was extracted twice with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum yielding 3 mg of a fraction, which was analyzed by GC-MS.[27]

3,4,5-Trimethoxycinnamic acid (**8**)

$C_{12}H_{14}O_5$; EI-MS, *m/z* (rel. int.): 238 $[M]^{+\bullet}$ (100), 223 (48), 163 (23) and 181 (13). Identified by comparison with authentic standard and with that reported.[28]

3,4,5-Trimethoxyphenyl-propanoic acid (**9**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (s, 2H, H-2 and H-6), 3.84 (s, 6H, 3-OCH_3 and 5-OCH_3), 3.82 (s, 3H, 4-OCH_3), 2.91 (t, *J* 5.6 Hz, 2H, H-8), 2.68 (t, *J* 5.6 Hz, 2H, H-7); EI-MS, *m/z* (rel. int.): 240 $[M]^{+\bullet}$ (100), 225 (60), 195 (13) and 181 (90), compared with authentic standard and similar to that reported.[29]

3,4,5-Trimethoxybenzoic acid (**10**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 2H, H-2 and H-6), 3.94 (s, 3H, 4-OCH_3), 3.93 (s, 6H, 3-OCH_3 and 5-OCH_3); EI-MS, *m/z* (rel. int.): 212 $[M]^{+\bullet}$ (100), 197 (66), 169 (20) and 141 (41), compared with authentic standard and similar to that reported.[29]

Piperic acid (**11**)

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33-7.26 (m, 1H), 7.25 (s, 1H), 7.03-6.92 (m, 4H), 6.06 (s, 2H), 5.90 (d, *J* 15.2 Hz, 1H); EI-MS, *m/z* (rel. int.): 218 $[M]^{+\bullet}$ (37), 173 (64), 143 (31) and 115 (100), compared with authentic standard and similar to that reported.[30]

7,8-Dihydropiperic acid (**12**)

EI-MS, *m/z* (rel. int.): 220 $[M]^{+\bullet}$ (1.2), 174 (12), 135 (100) and 77 (15), compared with authentic standards and similar to that reported.[31]

Piperonylic acid (**13**)

^{1}H NMR (200 MHz, DMSO-d_6) δ 7.75 (dd, *J* 8.5, 2.5 Hz, 1H, H-6), 7.52 (d, *J* 2.5 Hz, 1H, H-2), 6.89 (d, *J* 8.5 Hz, 1H, H-5), 6.07 (s, 2H); EI-MS, *m/z* (rel. int.): 166 $[M]^{+\bullet}$ (97), 165 (100), 149 (38), 119 (26) and 63 (46), compared with authentic standard purchased from Sigma Aldrich (St. Louis, USA).

Results and Discussion

The insects *N. bipes* (adults), *H. hectorides* (caterpillars), *E. trilineata* (adults and nymphs), *C. speciosa* (adults and nymphs), *T. collaris* (adults and nymphs) and *X. discoideus* (adults and nymphs) were offered exclusively fresh *P. tuberculatum* leaves for 72 h. While the weevil *N. bipes* (adults), the caterpillar *H. hectorides* and grasshoppers

X. discoideus consumed the leaves, the grasshoppers (adults and nymphs) of *C. speciosa*, *E. trilineata* and *T. collaris*, did not feed, possibly because of the leaves deterrence, starving to death. The insects *X. discoideus*, *H. hectorides* and *N. bipes* on contact with leaves of *P. tuberculatum* responded by reducing food intake as compared with leaves of *P. solmsianum*.[23] The analysis of the crude extract from *P. tuberculatum* leaves by GC-MS indicated the presence of amides **1**-**7** (Figure 1).

The possibility of biotransformation of amides (**1**-**7**) found in leaves of *P. tuberculatum* during the digestive process of *X. discoideus*, *H. hectorides* and *N. bipes* was investigated under laboratory conditions. Frass samples of the three species fed on leaves of *P. tuberculatum* were collected and freeze-dried. The dried frass were extracted with EtOAc and analyzed by GC-MS. The chemical profile of *X. discoideus* frass was similar to that from *P. tuberculatum* leaf extracts (data not shown), suggesting that the amides **1**-**7** did not undergo detectable biotransformation during the grasshopper's digestive process leading to the formation of compounds of similar polarity. On the other hand, the chromatograms of the frass extracts of *H. hectorides* and *N. bipes* displayed six additional peaks (**8**-**13**) not detectable in the chromatograms of the leaf extracts (Figure 2). Thus, the frass extracts were submitted to purification steps, yielding the isolated compounds **8**-**13**.

The structures of the compounds **8**-**13** were determined based on the analysis of MS and ^{1}H NMR data and identified as 3,4,5-trimethoxycinnamic acid (**8**), 3-(3',4',5'-trimethoxyphenyl)-propanoic acid (**9**), 3,4,5-trimethoxybenzoic acid (**10**), piperic acid (**11**), 7,8-dihydropiperic acid (**12**) and piperonylic acid (**13**), as previously reported from other *Piper* species.[28,29]

The analysis of the set of GC-MS chromatograms allowed to draw a hypothesis on the biotransformation of the amides by the herbivores. The amide piplartine (**1**) was partially hydrolyzed into the corresponding carboxylic acid **8** during the digestive process of *P. tuberculatum* leaves by *N. bipes* and *H. hectorides*. The amide **2** was fully hydrolyzed by both insects, producing the carboxylic acid **9**. The benzoic acid **10** could be either a product from the oxidative cleavage of **1** as well as from the cinnamic acid **8**. Metabolite **11** could originate from the partial hydrolysis of amides **3** and/or **6**. The 7,8-dihydropiperic acid (**12**) could be produced similarly from the amides **4**, **5** and/or **7**, while the piperonylic acid (**13**) could be a product of oxidative cleavage of amides **3-6** and/or from the carboxylic acids **11**-**12** (Figure 3).

The amides from *Piper* species have been described as insecticidal or deterrent against generalist herbivores,[6] but their metabolic fate has remained unknown. The only reported case of detoxification of amides refers to the capsaicin, but rather than hydrolysis, the glycosylation of the phenolic moiety was observed in three *Helicoverpa* species.[32]

The identity of the carboxylic acids produced by the hydrolysis of the amides **1**-**7** were further confirmed by hydrolysis of the crude extracts that yielded the corresponding carboxylic acids. In general, amides are very

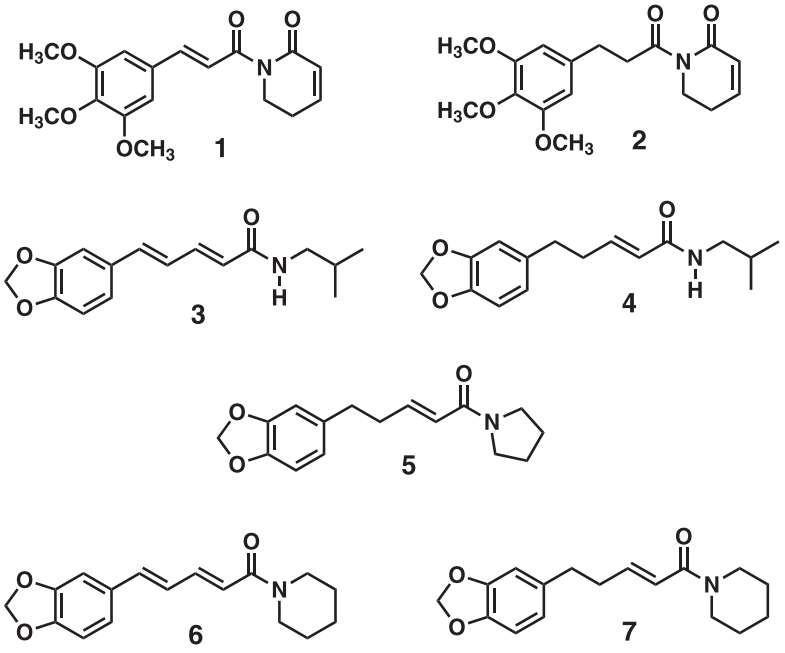

Figure 1. Chemical structures of the amides from leaves of *P. tuberculatum*.

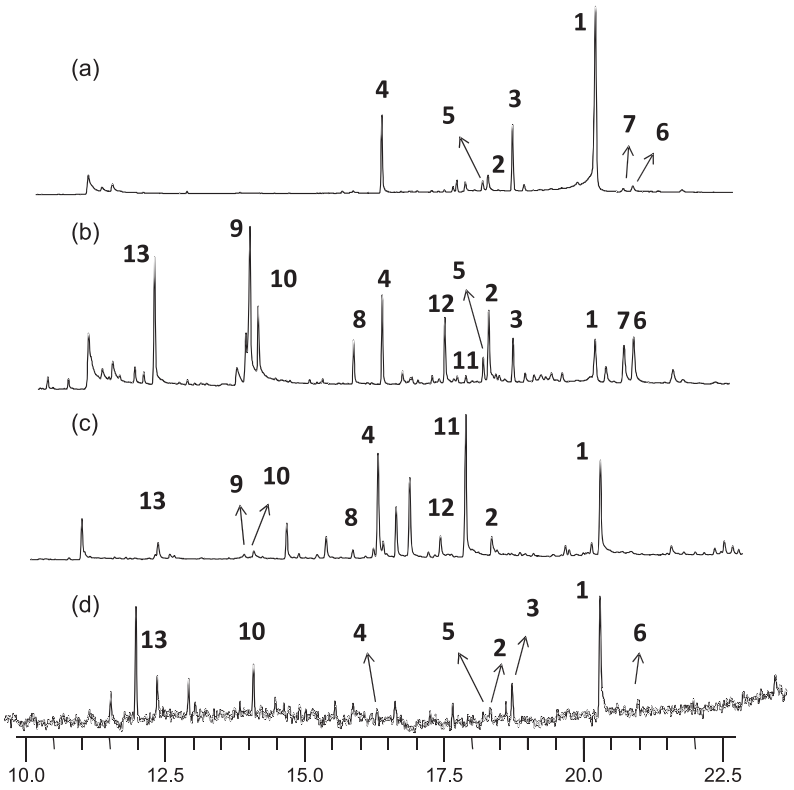

Figure 2. Chromatographic profile (GC-MS) of the extracts of the leaves of *P. tuberculatum* (a); fecal extracts of *H. hectorides* (b) and *N. bipes* (c) and leaves extracts from *P. tuberculatum* after saponification with KOH (d).

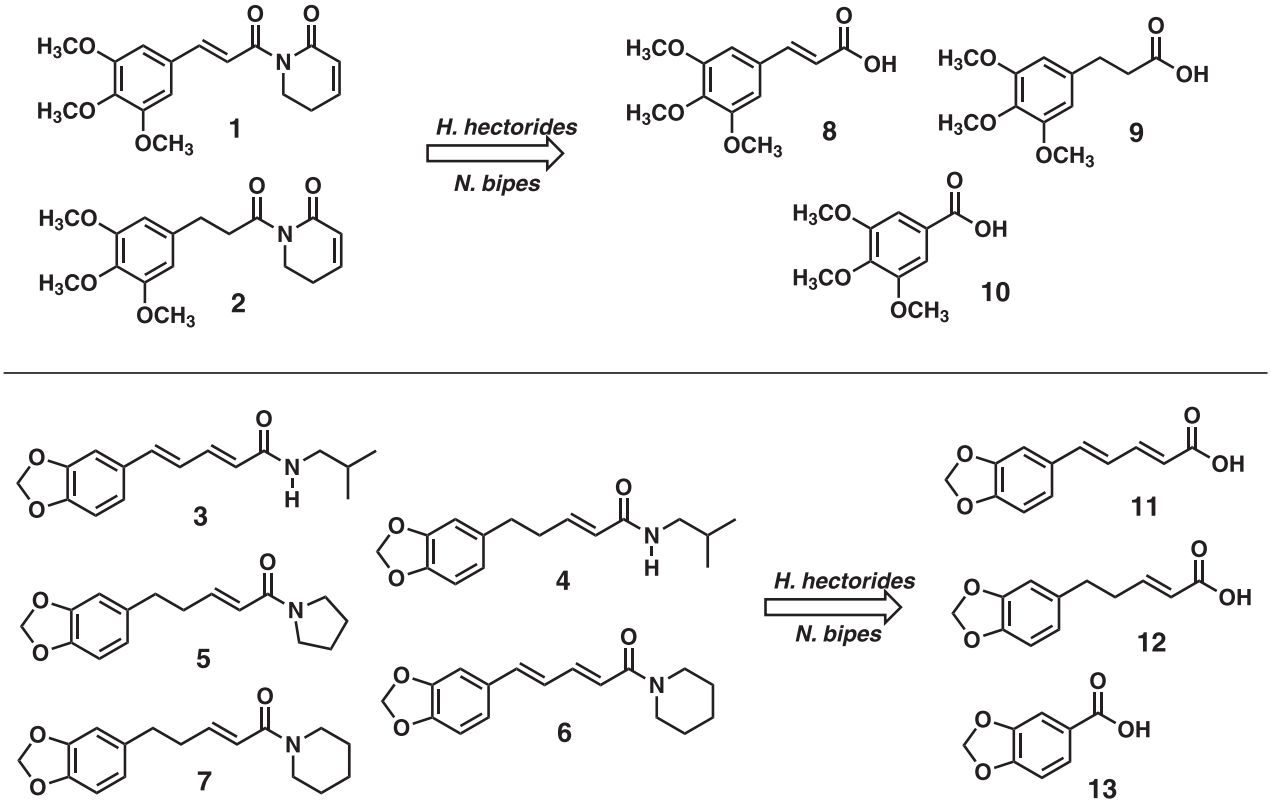

Figure 3. Hydrolysis of amides from *P. tuberculatum* after digestion by *N. bipes* and *H. hectorides*.

stable to hydrolysis under physiological conditions due to the resonance stabilization.[33-35] Thus, their hydrolysis in the insect's gut should be a highly specialized mechanism to circumvent insecticidal or repellent properties. In this case, the detoxification of amides was observed only for *H. hectorides* and *N. bipes*, while the three generalist Orthoptera species were not even able to consume the leaves. The weevil *N. bipes*, a beetle with polyphagous diet, is considered a pest in Southern Brazil, where it damages crops of flax, soybeans, corn and citrus fruits as well as forage grasses.[36] The adult insect feeds on leaves but the larvae with below-ground habits feeding on roots of several host plants impose difficulties in controlling populations of *Naupactus* species. The Lepidoptera *H. hectorides* is formerly considered to be specific to Rutaceae,[34] but more recently, it has frequently been observed damaging leaves of several *Piper* species.[23,37] The damaging of *Piper* leaves by generalist insects such as grasshoppers has also been observed under field conditions. The chemical composition in frass of grasshoppers as compared with consumed leaves has been investigated in few cases. The feces of *C. speciosa* fed on leaves of *Solanum paniculatum* or *Mangifera indica* had several elicited volatile compounds by herbivory as compared to the normal leaves.[21] The migratory grasshopper *Melanoplus sanguinipes* was capable of biotransforming acetylchromenes by ketone reduction and hydroxylation of methyl group when applied topically.[38]

In our study, the biotransformation of amides from leaves of *P. tuberculatum* during the digestion by insects could be associated not only to the digestive enzymes of the insect gut, but also to the action of plant enzymes released during insects chewing. Besides, some of the compounds detected in the frass such as the free carboxylic acids could be released from cell walls of the leaves by hydrolysis and not necessarily from hydrolysis of amides.

Conclusions

The metabolic profile of frass samples from insects feeding on *P. tuberculatum* leaves suggests that all seven amides (**1**-**7**) are hydrolyzed by the weevil *N. bipes* and by the caterpillar of *H. hectorides*. However, the amides were deterrent to generalist herbivores such as the grasshoppers (adults and nymphs) of *C. speciosa*, *E. trilineata* and *T. collaris*, which were apparently not able to cope with the antifeedant properties of amides. The grasshoppers *X. discoideus* is an intermediate case in which it still can feed on *P. tuberculatum* leaves but is not capable to carry out hydrolysis of the amides.

Supplementary Information

Supplementary information (NMR, GC-MS) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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