Fire Ant Venom Alkaloids

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Venoms produced by arthropods act as chemical weapons to paralyze prey or deter competitors. The utilization of venom is an essential feature in the biology and ecology of venomous arthropods. *Solenopsis* fire ants (Hymenoptera: Formicidae) are medically important venomous ants. They have acquired different patterns of venom use to maximize their competitive advantages rendered by the venom when facing different challenges. The major components of fire ant venom are piperidine alkaloids, which have strong insecticidal and antibiotic activities. The alkaloids protect fire ants from pathogens over the course of their lives and can be used to defend them from predators and competitors.

Solenopsis invicta | venom gland | piperidine | piperideine | venom toxicity

1. Introduction

Venom is a toxic secretion produced in animals by specialized glands that are often connected to teeth, stingers, or other sharp organs and delivered to target organisms to disrupt their normal physiological or biochemical processes [1][2]. The animals that utilize highly toxic venom for predation, defense, and competitor deterrence are believed to possess evolutionary advantages [2][3][4]. Among the venomous taxa (including cnidarians, echinoderms, mollusks, vertebrates and arthropods encompassing ants, bees, wasps, spiders, and scorpions), ants are the most abundant social insects and one of the most successful animals in number and geographical range in the world [5], having complex social organization and being found in a variety of ecosystems around the planet. In the ant community, venoms are chemically diverse and used by venomous ants as a chemical weapon to protect their own nests or to seize food resources from competitors [6].

Fire ants in the genus *Solenopsis* (Hymenoptera: Formicidae) are venomous and aggressive, and their common name “fire ants” derives from the burning sensation and pain felt by humans after being stung. Through their stingers, these ants secrete a venom in which major components are piperidine alkaloids (over 95%) and minor components are water-soluble proteins (less than 1%) [7][8][9][10][11]. The composition of alkaloids in the venom of different *Solenopsis* species are qualitatively and quantitatively different [12][13], which is an important feature in *Solenopsis* taxonomy, especially within the *Solenopsis saevissima* species complex that exhibits the greatest diversity of piperidine components [14][15][16][17]. The more basal *Solenopsis* species (e.g., *Solenopsis geminata* and *Solenopsis xyloni*) produce simpler piperidines compared to more derived lineages (e.g., *Solenopsis richteri* and *Solenopsis invicta*), which produce more complex analogs [18].

As an invasive ant, *S. invicta* has invaded multiple areas in the world [19]. The invaded populations are ecologically dominant, often reduce native ant diversity, and have negative impacts on other organisms in both agricultural and natural ecosystems [20][21][22]. Possessing chemical weaponry is one of the important factors that contribute to the success of *S. invicta*. The alkaloids in the venom of fire ants are used to hunt, to defeat their opponents, or as a defensive measure against pathogens [23][24][25][26][27]. The effective utilization of venom by several fire ants, such as *S. geminata*, *S. richteri*, and *S. invicta*, may have facilitated their successful invasions and rapid spread to multiple areas, where they establish new populations, or even replace the dominant native ant species [28][29][30][31]. In the text below, “fire ant” refers to *S. invicta*, unless otherwise specified.

2. Alkaloids in Fire Ant Venom

Alkaloids in fire ant venom are derivatives of 2-methyl-6-alkylpiperidines and 2-methyl-6-alkenylpiperidines [32][33]. The length of their side carbon chain at the 6-position of the piperidine ring ranges from 7 to 17 carbons [16]. The two carbon atoms at the 2- and 6-positions of the piperidine ring are chiral. Thus, the absolute configuration of an alkaloid component can be (2*R*,6*R*), (2*R*,6*S*), (2*S*,6*R*), and (2*S*,6*S*) [34][35][36]. Most studied *Solenopsis* species produce a single enantiomer of both the *cis* (2*R*,6*S*) and *trans* (2*R*,6*R*) forms of each piperidine alkaloid. The other two enantiomers, *cis* (2*S*,6*R*) and *trans* (2*S*,6*S*), are only found in the Brazilian fire ant *S. saevissima* [34][36]. Absolute configuration of these piperidines is a useful tool to differentiate sympatric *Solenopsis* species from *S. saevissima* [36].

Since the first identification of the piperideine alkaloid $\Delta^{1,2}$-C11 from *Solenopsis xyloni* [37], a series of $\Delta^{1,2}$- and $\Delta^{1,6}$-piperideine alkaloids have been reported from *Solenopsis* fire ant venom [13][15][16][38][39][40]. The two $\Delta^{1,2}$- and $\Delta^{1,6}$-C11 piperideines can be thermochemically reduced to *cis*-C11 and *trans*-C11 at a ratio of 4:1 [41][42]. This ratio of the equilibrium mixture of *cis*- and *trans*-C11 formed during their chemical synthesis matches that of these two major components (*cis*- and *trans*-C11) in the venom of *S. aurea* [43]. This match-up supports the hypothesis that $\Delta^{1,2}$- and $\Delta^{1,6}$-piperideines function as precursors for the biosynthesis of piperidine alkaloids in the fire ant venom [13][38][44][45]. The two *Solenopsis* fire ants in the *saevissima* species complex, *S. richteri* and *S. invicta*, and their hybrid, *S. richteri* × *S. invicta*, produce predominant *trans* alkaloids. Enantioselective enzymes present in these species have been proposed to reduce $\Delta^{1,2}$-piperideines exclusively into (2*R*,6*R*)-dialkylpiperidines, and $\Delta^{1,6}$-piperideines mainly into (2*R*,6*R*)-dialkylpiperidines and partially into (2*R*,6*S*)-dialkylpiperidines [38]. Because $\Delta^{1,2}$-piperideines and corresponding $\Delta^{1,6}$-piperideines are quantitatively indistinguishable, the two reduction routes may be equally important in the biosynthesis of *trans* alkaloids in the imported fire ants [38]. However, the fact that the ratio of *cis*-C11 to *trans*-C11 is about 1:2 in *S. geminata*, [46] suggests that the $\Delta^{1,2}$-C11 pathway (enantioselectively reduced to (2*R*,6*R*)-*trans*-C11) could be more important than the $\Delta^{1,6}$-C11 pathway (enantioselectively reduced to (2*R*,6*S*)-*cis*-C11) in more ancient *Solenopsis* species. Since all four stereoisomers are present in *S. saevissima* [34][36], the enzymes used to catalyze the reduction of $\Delta^{1,2}$-piperideines and $\Delta^{1,6}$-piperideines may lack enantioselectivity. It seems likely that *Solenopsis* fire ants utilize similar enzymes with very different enantioselectivity to synthesize both *cis* and *trans* alkaloids. The New World *Solenopsis* fire ants may have evolved specific enzymes to synthesize piperidines with favorable stereochemical composition and longer and unsaturated side carbon chains associated with biological advantages [17][38][45].

In addition to piperidine and piperideine alkaloids, ten pyridine alkaloids have recently been found to be present in trace amounts in *S. invicta* venom [47]. Structures of the three pyridines with a saturated side carbon chain, including 2-methyl-6-undecylpyridine (2M6UP11), 2-methyl-6-tridecylpyridine (2M6TP13), and 2-methyl-6-pentadecylpyridine (2M6PP15), have been confirmed through comparisons with synthetic compounds. The three pyridines with an unsaturated side carbon chain, including two isomers of 2-methyl-6-tridecenylpyridine (2M6TP13:1) and 2-methyl-6-pentadecenylpyridine (2M6PP15:1), were tentatively identified with mass spectra [47]. Saturated/unsaturated pyridine alkaloids are also present in *Solenopsis geminata* venom, including 6-undecylpyridine, 2-methyl-6undecyl-pyridine, and 2-methyl-6-(1)-undecenylpyridine [48]. Unfortunately, the biological function and ecological significance of these trace components, except for 2M6UP11 (see below), remain unknown.

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