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Venomous caterpillars: From inoculation apparatus to venom composition and envenomation

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ABSTRACT

Envenomation by the larval or pupal stages of moths occurs when the victim presses their hairs. They penetrate the subcutaneous tissue, releasing toxins such as proteolytic enzymes, histamine and other pro-inflammatory substances. Cutaneous reactions, including severe pain, oedema and erythema are frequent local manifestations of caterpillar envenomation, but, in some cases, the reactions can evolve into vesicles, bullae, erosions, petechiae, superficial skin necrosis and ulcerations. Alternatively, some individual can develop allergic reactions, renal failure, osteochondritis, deformity and immobilization of the affected joints and intracerebral bleeding. Caterpillars produce venom to protect themselves from predators; contact with humans is accidental and deserves close attention. Their venoms have not been well studied, except for toxins from some few species. The present review brings together data on venomous caterpillars of moths, primarily addressing the available literature on diversity among the different families that cause accident in humans, the structures used in their defense, venom composition and clinical aspects of the envenomations. Understanding the molecular mechanisms of action of caterpillars' toxins may lead to the development of more adequate treatments.

1. Introduction

The order Lepidoptera is a monophyletic group originated from a Jurassic ancestor around 200 million years ago (Grimaldi and Engel, 2005). It is the second largest order of insects: there are approximately 160,000 species described. In addition, the total number of extant species is estimated to be around half a million (Gullan and Cranston, 2007; Kristensen et al., 2007; van Nieukerken et al., 2011). The classification of Lepidoptera has been undergoing constant modifications, and 133 Lepidoptera families were reorganized in 43 superfamilies (van Nieukerken et al., 2011). Approximately 12 families, mostly caterpillars of moths, are venomous and can cause severe injuries to humans, such as urticarial dermatitis, allergic reactions, renal failure, osteochondritis and intracerebral bleeding (Diaz, 2005). Various of these venomous species are mainly found in temperate and tropical climate zones (French and Brillhart, 2015).

Envenomation occurring at the larval or pupal stages in moths or butterflies is known as “erucism” or “caterpillar dermatitis”, since, at this stage, the larvae is also called caterpillar, a word derived from the Latin, *catta pilosa*, meaning “hairy cat”. Some caterpillars present urticating hairs and, generally, injuries occur when the victim presses the hairs. They penetrate the subcutaneous tissue, releasing toxins such as proteolytic enzymes, histamine and other pro-inflammatory substances (Haddad and Lastória, 2014; Stipetic et al., 1999). Cutaneous reactions, such as severe pain, oedema and erythema are frequent local manifestations of caterpillar envenomation. In later stages, the reaction can evolve into vesicles, bullae, erosions, petechiae, superficial skin necrosis and ulcerations (Haddad et al., 2012).

In addition to erucism, contact with adults from these families can result in urticant clinical manifestations, including a dermatitis known as “lepidopterism”. Lepidopterism cases are reported throughout the world (Battisti et al., 2011; Hossler, 2010; Lamy and Werno, 1989). However, the most severe manifestations are caused by adult animals from the genus *Hylesia* (Saturniidae family), found in South and Central Americas (Fornés and Hernández, 2000; Iserhard et al., 2007; Lemaire, 2002; Willat et al., 2003). The accidents with this moth can produce epidermic and dermic manifestations, ophthalmological lesions, such as conjunctivitis, irritation of the respiratory system and focal hemorrhages (Lemaire, 2002).

This review presents data on venomous caterpillars of moths, addressing the available literature on diversity among the different families, venom composition, and clinical aspects of the envenomations. In addition, the review contributes to understanding the different anatomical structures used in their defense, which can accidentally come in contact with humans. Lack of information on toxins from these animals and their molecular mechanisms of action can lead to

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inadequate treatment. Thus, this reinforces the necessity of studies on these animals that can cause serious human health problems.

2. The venom apparatus: production, secretion and injection

In contrast to other insects that can also cause injury to humans, such as bees and wasps, which have egg-laying organs or stingers attached to venom glands, caterpillars contain hollow hairs and spines connected to venom glands to resist predator attacks (Diaz, 2005; Henwood and MacDonald, 1983; Lamdin et al., 2000). Caterpillar venom components, produced by glandular cells, can enter in contact with the haemolymph and accumulate in the tegument, in special structures such as the tubercles or scoli, urticating hairs or setae and spines, depending on the caterpillar family (Diaz, 2005).

Caterpillars are polyphagous animals, *i.e.*, they feed on plant leaves from taxonomically diverse families. Some caterpillars are able to sequester toxic compounds or produce them from precursors obtained in their food plants. In this sense, caterpillars from the tiger moth, *Arctia caja*, are able to sequester or produce biogenic amines (*e.g.,* histamine), pyrrolizidine alkaloids, cardiac glycosides and other noxious substances. Another example, is the smoky moth caterpillar (family Zygaenidae), which is avoided by birds and other predators because both adult and larva are able to release hydrogen cyanide (HCN). As a rule, brightly coloured caterpillars are either protected by toxic substances or are mimicking unpalatable species (Wagner, 2005).

As mentioned before, caterpillars use specialized structures for their defense against predators, as spines or hairs/setae. Spines are relatively fixed and cause adverse reactions only when the caterpillar directly contacts human skin. However, the setae or hairs may be removed to become airborne. In some cases, they can also be incorporated into the cocoon structure for pupal protection (Mullen, 2002; Southcott, 1987).

Venomous spine and setae/hairs were classified by Gilmer in the 1920s and, subsequently, reclassified by Eaton and Veiga (Eaton, 1988; Veiga et al., 2001) as follows: (*i*) Gilmer's urticating hair (Gilmer, 1925), characterized by a simple setae with a single glandular cell at its base; (*ii*) a branched setae or scolus, that contains a single glandular cell in its base; (*iii*) Gilmer's urticating spine, which the setae is formed by a cuticular evagination with venom-secreting cells in the lumen, at the spine base; and (*iv*) a setae is formed by a cuticular evagination, without basal venom-secreting cells.

Recently, Battisti et al. (2011) have proposed a more general classification for the caterpillars' urticating hairs, establishing three main categories, *i.e.*, (*i*) true setae, (*ii*) modified setae, and (*iii*) spines. A schematic representation of the three categories of urticating hairs is presented in Fig. 1.

Several studies have been conducted on the lepidopteran urticating apparatus and most of them concluded that the venom is typically produced by glandular cells, which are in contact with the haemocoel or present inside the spines (Barth, 1956, 1954a; 1954b; Barth and Junqueira, 1954; Deml and Dettner, 2002; Foot, 1922; Gilmer, 1925; Lamdin et al., 2000; Veiga et al., 2001; Spadacci-Morena et al., 2016).

3. Caterpillars of medical importance: morphology and distribution

In this review, we first present the main superfamilies/families containing venomous caterpillars of moths, their morphology and distribution, followed by a summary of their venoms and the clinical envenomation aspects they cause. Table 1 shows the taxonomic classification of venomous caterpillars of moths that have been described in the present review.

3.1. Superfamily Bombycoidea

3.1.1. Family Saturniidae

The caterpillar *Automeris io*, known as io moth caterpillar, (subfamily Hemileucinae), is widely distributed throughout North America, from Southern Canada, throughout the United States and Mexico. Pale yellow to green in colour, this caterpillar has a length of 5–6 cm, with red true legs and prolegs. It presents a wide white stripe on both sides, with a similar red stripe and a thinner red-purple line below it. On each dorsal segment, raised tubercles or scoli, are composed of green spines with black tips (Diaz, 2005). When the spines (Fig. 1) penetrate the skin, the tips break off and release venom, which can remain in the skin and increase irritation (Hossler et al., 2008). In *Automeris incisa*, a caterpillar of the same subfamily, as *Lonomia obliqua* caterpillar, the glandular cell is present inside the spines (Barth, 1954a). Fig. 2 (panel A) shows a representative caterpillar of the genus Automeris.

The caterpillar *Hemileuca maia* (subfamily Hemileucinae), known as buck moth caterpillar (Fig. 2B), is found in the southeastern and southwestern United States and northern Mexico. It is a large caterpillar, 5.25–6.0 cm in length, containing rows of urticating spines on its back and sides. The head is dark red-brown, and the body colour ranges from grey to black with many white to yellow dots. Double rows of orange spines and longer spines line the back coloured red to black on both sides (Diaz, 2005).

The South American *Lonomia* caterpillars (subfamily Hemileucinae), *L. achelous* and *L. obliqua* (Fig. 2C) are found from Venezuela to northern Argentina. Mature caterpillars are large, with a length of 4.5–5.5 cm, and range from green to brown in colour. *Lonomia* caterpillars in the 5th or 6th instar stage present rows of scoli full of spines (Diaz, 2005; Lorini, 2008). The scolus (Fig. 1), formed by epithelial cell evaginations in the tegument, is characterized by a main central axis and lateral branches, the spines, which are rigid, with colours ranging from light to dark brown (Gilmer, 1925; Spadacci-Morena et al., 2016). The mechanism for ejecting venom from the spine remains unclear. One possibility is that the haemolymph induces local pressure, and another is that the intersegmental muscles contract to promote the release (Maschwitz and Kloft, 1971).

Veiga et al. (2001) analysed the structures responsible for producing, secreting and injecting venom found in Brazilian L. *obliqua* caterpillars. Microscopic and histochemical investigations demonstrated (*i*) several cuticular specializations in a complex tegument; (*ii*) no pores in the tegument or spines; (*iii*) hollow internal canals in all the spines, where the venom is deposited; (*iv*) venom produced by secretory epithelial cells that are in contact with the haemocoel, which pumps into the hollow spines; and (*v*) venom storage in the subcuticular space and spine tips (Veiga et al., 2001). Contrasting with Veiga et al. findings (2001), Spadacci-Morena et al. (2016) verified, after histological analysis of spine sections, the presence of a large glandular cell, occupying almost the entire region of the spine, and absence of secretory cells related to venom production. Moreover, they described the presence of spines with circular grooves, similar to rings, while some spines lacked grooves, even those located in the same scolus. It was also found that some spines produce orange secretions, while others produce green secretions, which were more similar to the haemolymph. Thus, Spadacci Morena et al. (2016) suggested that the grooved spines, which produce the orange secretions, contain the venom glands. The spines without grooves, which produce the green secretions, lack toxin-producing cells. This is possibly due to *L. obliqua* caterpillars feeding on leaves containing green pigment (Lorini, 1999), which can supply this colour to the haemolymph. To nourish the cells, the haemolymph circulates inside the scolus and spines. When a spine breaks off, the green secretion is released.

Recently, Quintana et al. (2017) found these two types of spines in *L. obliqua* caterpillars from Argentina; however, the authors observed only ungrooved spines in *Leucanella memusae* (subfamily Hemileucinae), a caterpillar from the same family (Fig. 2D). Since injuries caused by *L. memusae* are less severe than those provoked by *L. obliqua*, the authors reinforced Spadacci-Morena and colleagues' (2016) hypothesis that the grooved spines are associated with the toxin-

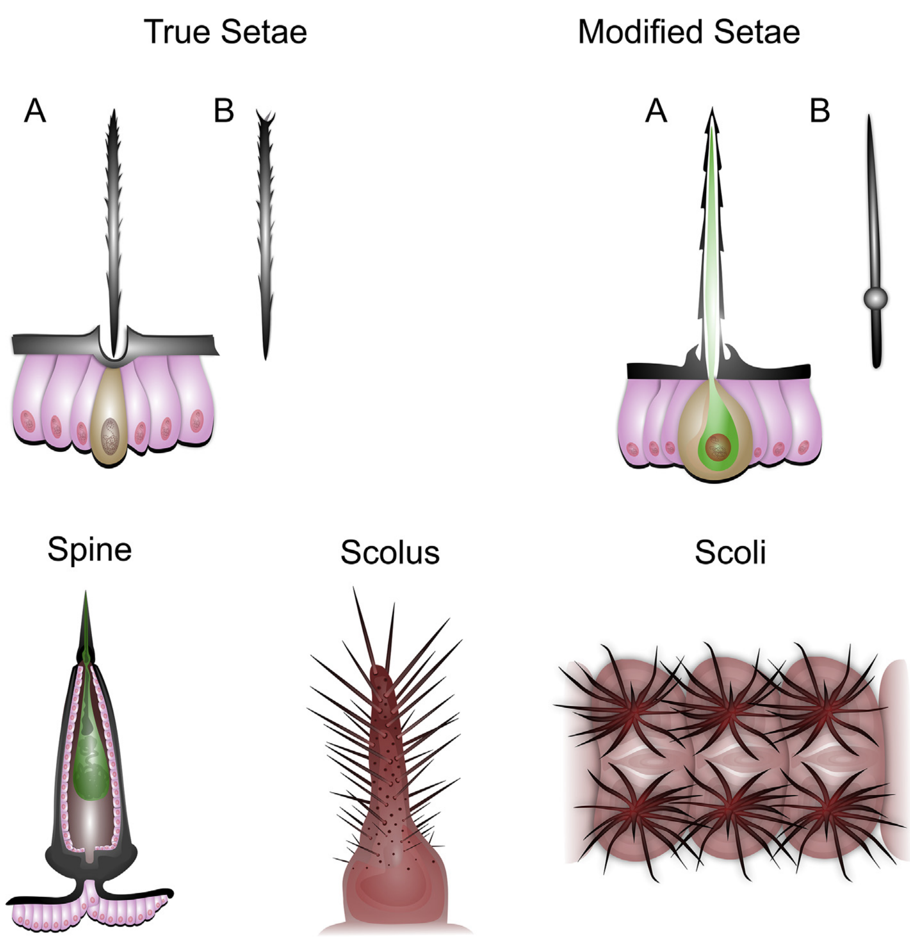


Fig. 1. Schematic representation of the caterpillars' urticating hairs. *True setae:* panels A and B show possible setae shapes. *Modified setae:* panels A and B show possible modified setae shapes. *Spines; Scolus:* a structure characterized by a main central axis and lateral branches containing various spines; *Scoli:* a group of several scolus. These basic structures and variations of them are found in some caterpillars described in this review. This illustration was adapted from Battisti et al. (2011).

producing venom glands (Quintana et al., 2017; Spadacci-Morena et al., 2016).

3.2. Superfamily Lasiocampoidea

3.2.1. Family Lasiocampidae

An example from the Lasiocampidae family is the caterpillar *Dendrolimus pini* (subfamily Lasiocampinae), also known as pine-tree lappet moth caterpillar. This caterpillar is widely distributed across Eastern Europe, Central and Northern Asia and Northern Africa. It is a hairy, brown to grey-brown, tree-dwelling, communally feeding caterpillar, 2.5–3.5 cm in length, with bands of white scale-like hairs hiding hollow spines along its back or dorsal surface (Fig. 2E). The caterpillar feeds preferentially on pine needles in the temperate, mountainous pine forests of Central and Southern China. The caterpillars also feed communally within other coniferous forests in China, including spruce and fir forests (Diaz, 2005).

3.3. Superfamily Noctuoidea

3.3.1. Family Erebidae

Erebidae is a large family of moths in the Noctuoidea superfamily. Molecular phylogenetic studies led to the proposition of a new phylogeny for this family, establishing the existence of 18 subfamilies in this group. Traditional families, such as Arctiidae and Lymantriidae, have been transferred to the family Erebidae, as subfamilies (Arctiinae and Lymantriinae), and the former subfamilies, such as Lithosiinae, are now treated as tribes (Lafontaine and Schmidt, 2010; Zahiri et al., 2012, 2011).

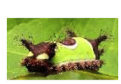
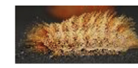
Examples in this family include the garden tiger moth caterpillar, *Arctia caja* (subfamily Arctiinae). It is distributed throughout North America, from Labrador and Nova Scotia to New York, west to Minnesota, and across southern Canada to British Columbia, as well as south and west to Colorado, Utah, Nevada, northern California and throughout Eurasia. The larva is black on top and brownish-orange below, with four white lateral spots on each segment (Fig. 3A). Its body is completely covered by setae/hairs (Fig. 1), with a mix of long black hairs and some dorsal white hairs (Roth, 2005).

Lophocampa caryae (subfamily Arctiinae), more commonly known as the hickory tussock moth caterpillar, is found from the southeast Canada through Maine and Minnesota, South and North Carolina, and Southwest Texas in the United States. It feeds on hickory, birch, elm, and black locust tree leaves that are prolific in the hardwood forests of southwest Pennsylvania. The caterpillar has a length of 2.5–3.8 cm and is covered with white or greyish hairs when mature (Fig. 3B). Rows of black tufts line several of its body segments. The caterpillar's toxicity after contact with humans is attributed to these tufts (Lyons, 1995; Wagner, 2010).

The caterpillar, *Premolis semirufa* (subfamily Arctiinae), traditionally known as pararama, is found in South America, particularly in the rubber tree (*Hevea brasiliensis*) plantations of the Amazonian region, where it feeds (Costa et al., 1995). In the larvae's mature state (Fig. 3C), the *P. semirufa* body is approximately 4.5 cm in length, with black, yellow, red and white colours merging with brown and silver hairs of three different sizes (large, medium, and small) distributed along its body (Rodrigues, 1976). Various types of setae are also woven into the pararama's dun-coloured cocoon (Fig. 3D), which is shaped like a spindle, except that one side is flattened where the cocoon attaches to a surface. The small setae are erect and disposed perpendicularly about the outer surface, giving the cocoon a velvety appearance (Dias and de Azevedo, 1973; Rodrigues, 1976).

Euproctis chrysorrhoea (subfamily Lymantriinae), known as the

Table 1
Taxonomy of venomous caterpillars of moth described in this review.

Kingdom Animalia	
Phylum Arthropoda	
Class Insecta	
Order Lepidoptera	
Suborder Glossata	
Infraorder Heteroneura	
► Superfamily Bombycoidea	
Family Saturniidae	
Subfamily Hemileucinae	
Genus *Automeris*	
Automeris sp	
Genus *Hemileuca*	
Hemileuca maia	
Genus *Leucanella*	
Leucanella memusae	
Genus *Lonomia*	
Lonomia achelous	
Lonomia obliqua	
► Superfamily Lasiocampoidea	
Family Lasiocampidae	
Subfamily Lasiocampinae	
Genus *Dendrolimus*	
Dendrolimus pini	
► Superfamily Noctuoidea	
Family Erebidae	
Subfamily Arctiinae	
Genus *Arctia*	
Arctia caja	
Genus *Lophocampa*	
Lophocampa caryae	
Genus *Premolis*	
Premolis semirufa	
Subfamily Lymantriinae	
Genus *Euproctis*	
Euproctis chrysorrhoea	
Genus *Lymantria*	
Lymantria dispar	
Family Notodontidae	
Subfamily Thaumetopoeinae	
Genus *Thaumetopoea*	
Thaumetopoea pityocampa	
► Superfamily Zygaenoidea	
Family Limacodidae	
Subfamily Limacodinae	
Genus *Acharia*	
Acharia stimulea	
Subfamily uncertainly assigned	
Genus *Doratifera*	
Doratifera oxleyi	
Genus *Latoia*	
Latoia consocia	
Family Megalopygidae	
Subfamily Megalopyginae	
Genus *Lagoa*	
Lagoa crispata	
Genus *Megalopyge*	
Megalopyge opercularis	
Subfamily uncertainly assigned	
Genus *Podalia*	
Podalia sp	

► indicates the superfamilies of some venomous caterpillars of moths described in this review.

brown-tail moth caterpillar, is distributed throughout Europe, with a small population also existing in the United States (de Jong et al., 1975). This caterpillar presents orange or red subdorsal tufts or papilae (where the urticating hairs are inserted) and a characteristic white lateral stripe (Blair, 1979) (Fig. 3E). The urticating setae/hairs (Fig.1: panel setae, B) of the brown-tail caterpillar are of a very different type. They are pointed at the base, gradually enlarge toward the tip and have three rows of barbs extending their entire length (Kephart, 1914). *Lymantria dispar* (subfamily Lymantriinae), the gypsy moth caterpillars, are found in the northeast United States, and present a series of paired warts on the head, with blue and red pairs along the dorsal surface of the caterpillar (Fig. 3F) (Wagner, 2005). *L. dispar* caterpillars present a venom gland at the base of their balloon-shaped hairs (Fig. 1: panel modified setae, B) (Deml and Dettner, 1995).

3.3.2. Family Notodontidae

The family Notodontidae, represented by caterpillars known as processionary tree caterpillars, contains 20 genera and 101 species distributed across five geographical regions: mainland Africa, Madagascar, Europe, India and Australia (Kiriakoff, 1970; Miller, 1991; Schintlmeister, 2013; Zahiri et al., 2013, 2011). Processionary caterpillars include the European *Thaumetopoea* caterpillars (Fig. 3G) and the Australian *Ochrogaster lunifer*, both from subfamily Thaumetopoeinae. The European pine processionary caterpillar, *T. pityocampa*, is present in all Mediterranean countries, while the European oak processionary caterpillar, *T. processionea*, is present in Northern Europe and North Africa. The American pine processionary caterpillar, *T. wilkinsonii*, is found from Southern Canada to Mexico, and the Australian processionary caterpillar is present throughout coastal and inland Australia (Diaz, 2005).

These caterpillars are grey-black, with dark red to brown tubercles and fine hairs varying from white to black. At the fourth and fifth instar stages, their tegument presents both non-removable hairs and removable urticarial hairs, dorsally and medially disposed on the first eight abdominal larval segments (Vega et al., 2011). When disturbed, the latter setae/hairs (Fig. 1) which are short and thin with barbs along the shaft, are easily removed by any mechanical stimulation and can be carried by wind for several kilometres, persisting in the environment for a long time (Battisti et al., 2017, 2011; Petrucco Toffolo et al., 2014).

3.4. Superfamily Zygaenoidea

3.4.1. Family Limacodidae

In the family Limacodidae, the most well-known caterpillar is *Acharia stimulea* (the saddleback, subfamily Limacodinae), formerly known as *Sibine stimulea*, which is common in the United States, from Texas to Florida (Wagner, 2010). The saddleback caterpillar has a truncated, slug-like body form that differs from other Lepidopteran

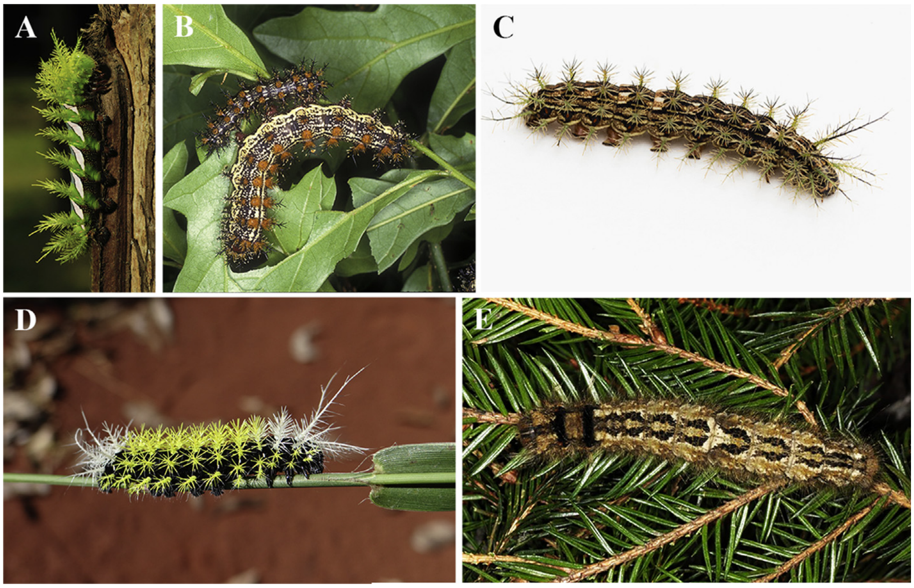


Fig. 2. Representatives of venomous caterpillars from the superfamilies Bombycoidea and Lasiocampoidea. [A] *Automeris* sp. (Bombycoidea): mature caterpillar stage showing the green spines with black tips. **[B]** *Hemileuca maia* (Bombycoidea): mature caterpillar' stage showing the rows of spines on its back and sides. Its head is dark red-brown, and the body colour ranges from grey to black with many white to yellow dots. **[C]** *Lonomia obliqua* (Bombycoidea): general view of the caterpillar, showing the scoli with colours ranging from light to dark brown. **[D]** *Leucanella memusae* (Bombycoidea): Mature caterpillar stage showing the scoli and the spines. **[E]** *Dendrolimus pini* (Lasiocampoidea): mature caterpillar stage showing bands of white hairs, which hide hollow spines along its back or dorsal surface. The images were kindly provided and reproduced by permission of Dr. Rafael Marques Porto, Molecular Biology Laboratory, Butantan Institute, Brazil (panels A and C); James Castner, Department of Entomology and Nematology, "Featured Creatures", Institute of Food and Agricultural Sciences, University of Florida, USA (panel B); Marcos Cesar Campis, Brazil (panel D) and Dr. Wolfgang Wagner, Stuttgart, Germany, www.pyrgus.de (panel E). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

families, measuring 2–3 cm in length. These caterpillars are brown with green back and flanks and have a central oval area resembling a saddle (Fig. 4A). A variable marking occurs at the posterior end where a cream-coloured set of spots imitates a large face. The saddleback caterpillar has tufts of urticating spines (Fig. 1: panels spines, scolus) lined with hypodermal cells that secrete toxins, whose chemical nature remain obscure. The larvae feed on a variety of plants. In Florida and Alabama, USA, they feed on ornamental palms such as the Manila palm (*Adonidia merrillii*) (Hossler, 2010, 2009).

Doratifera oxleyi, known as painted cup moth caterpillar, occurs widely in the southern half of Australia. The caterpillars are stout bodied (ranging from 20 to 35 mm in length) and slug-like. Brightly coloured, they have stinging hairs and their body is surrounded by a skirt of fleshy spines (Fig. 4B). The upper surface of the caterpillar is saddle-shaped and at each end, the raised sections are topped with four spiny, fleshy tubercles, each bearing bunches of sharp spines, which are normally hidden but displayed when the caterpillar is disturbed (Kent and State Forests of New South Wales. Research Division, 1996).

Latoia consocia, also known as *Parasa consocia* (subfamily Limacodinae), is found in the Russian far east, China and Taiwan. The caterpillar has a bright blue dorsal stripe with a broken outline of green. They present longitudinal rows of tubercles bearing clusters of stinging spines disposed laterally and dorsolaterally. Thickened spines tipped in black are present in the third and largest dorsolateral pair of tubercles. In the first two instars, the larvae are gregarious, grazing only the surface of leaves (James et al., 2017).

3.4.2. *Family Megalopygidae*

Caterpillars of the Megalopygidae family (flannel moth caterpillars) are distributed throughout North America and the New World tropics. In temperate regions, they often cause injury during late summer or early fall, and, in tropical regions, cases occur during both spring and fall. *Megalopyge crispata* or *Lagoa crispata* (subfamily Megalopyginae), commonly called black-waved flannel caterpillar, is found in fields with woody growth, woodlands, and forests, from Missouri to New Hampshire (especially along the coast in New England), south to Florida and Louisiana. These caterpillars are orange to grey, densely hairy with variously developed middorsal crest of darker hairs (Fig. 4C). Body tapering rearward to wispy tail that scarcely extends beyond body and a length less than 3 cm (Wagner, 2005).

Megalopyge opercularis (subfamily Megalopyginae), commonly called as puss caterpillar, "el perrito" or little dog, wooly asp, Italian asp, opossum bug or wooly slug, is the most widely distributed and studied species in the United States and Latin America (Fig. 4D). Their hairs are long and silky; their colour varies from dirty white to reddish-brown or a mix of colours. Each ecdysis produces a caterpillar with an increased spine number and size and a length of 2.5–3.5 cm at maturity. The toxins are thought to be contained within the spines and are produced by specialized basal cells. Upon contact, the hollow spines release the venom, which remains uncharacterized (Bishopp, 1923; Diaz, 2005; El-Mallakh et al., 1986; Foot, 1922; McMillan and Purcell, 1964; Pinson and Morgan, 1991). Caterpillars can sting throughout their lifecycle; however, the severity increases with the caterpillar's size (Bishopp, 1923). The caterpillars use their hairs, as well as the silk they produce, to make the cocoon, giving it a similar appearance to the caterpillar. The emerging adult moths are yellowish-brown with wings that have long, wavy, white-streaked hairs (Stipetic et al., 1999). A recent study demonstrated that the caterpillar *Podalia* sp. (subfamily Megalopyginae) (Fig. 4E) exhibited structures similar to those described for *Megalopyge opercularis*, presenting long hairs with transverse striations and spicules, in addition to short and hollow spines that penetrate the skin and release their contents after contact. Each hollow spine is connected to a specialized basal cell (Quintana et al., 2017).

4. Envenomation by caterpillars of moths: venom composition and clinical aspects

A variety of caterpillar species has shown to produce toxic components that can be involved in human pathology. Most studies on caterpillars' toxins and envenomations (Table 2) are single studies and no follow-up studies or detailed mechanisms have been reported. Few venoms, mostly from the Erebidae and Saturniidae families, have been more extensively investigated, mainly because of the severity of the accident they can produce. Here, we would like to summarize some of these studies.

4.1. *Automeris incisa and Hemileuca maia (Saturniidae)*

Despite the painful and pruritic sting of the *A. incisa* caterpillar, the contact urticarial dermatitis resolves quickly, approximately six hours of duration, with rare systemic sequels or anaphylaxis. Thus, it causes no great risk to human health, and the venom production mechanisms

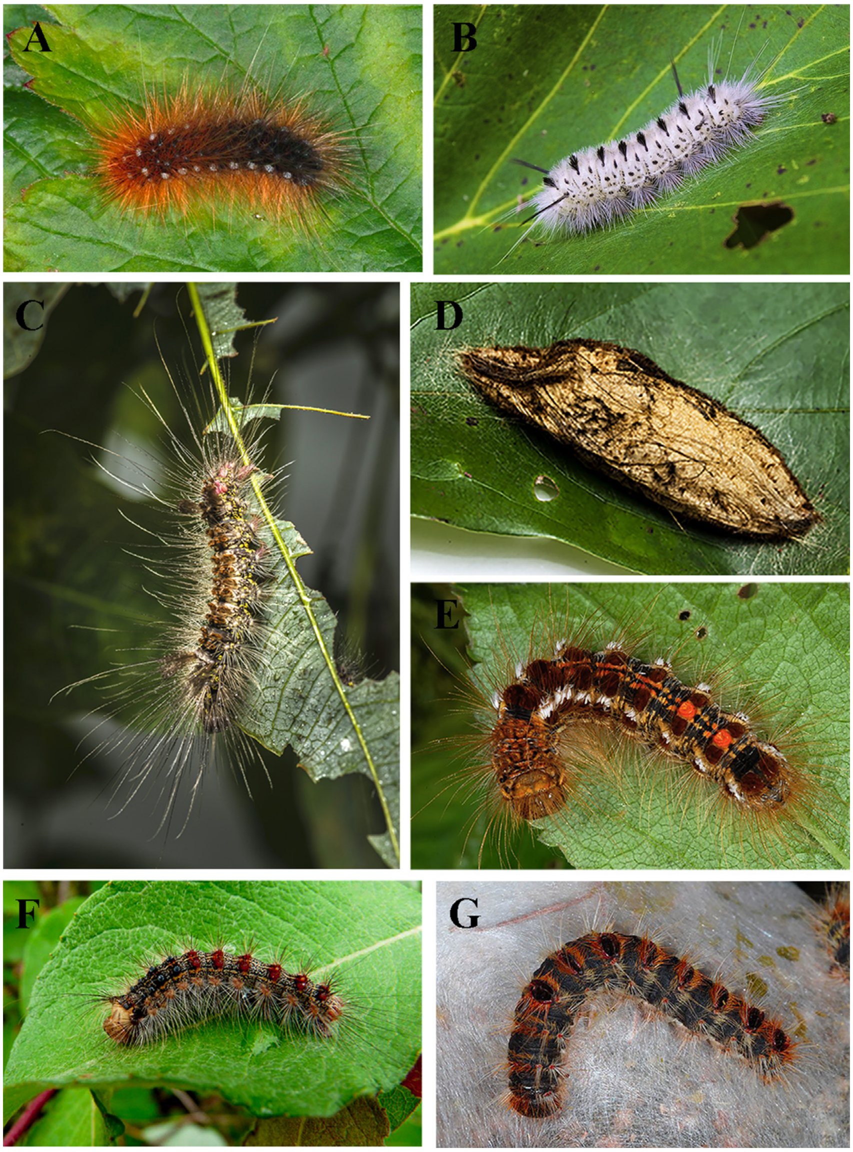


Fig. 3. Representatives of venomous caterpillars from the superfamily Noctuoidea. **[A]** *Arctia caja*: mature caterpillar stage showing the body completely covered by hairs, which are black on top and brownish-orange below. **[B]** *Lophocampa caryae*: mature caterpillar stage covered with white or greyish hairs, presenting rows of black tufts lining up several of its body segments. **[C]** *Premolis semirufa*: mature caterpillar stage, with body characterized by black, yellow, red and white colours merging with brown and silver hairs of three different sizes. **[D]** Pararama's cocoon: note the velvety appearance. **[E]** *Euproctis chrysorrhoea*: mature caterpillar stage showing the tufts and the characteristic white lateral stripe. **[F]** *Lymantria dispar*: mature caterpillar stage, which presents a series of paired warts on the head, with blue and red pairs along the dorsal surface. **[G]** *Thaumetopoea pityocampa:* mature caterpillar stage, colour grey-black, with dark red to brown tubercles and fine hairs varying from white to black. The images were kindly provided and reproduced by permission of Dr. Wolfgang Wagner, Stuttgart, Germany, www.pyrgus.de (panels A, E, F and G); Michael Nerrie, Walpole, New Hampshire, USA (panel B); and Dr. Rafael Marques Porto, Molecular Biology Laboratory, Butantan Institute, Brazil (panels C and D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and toxin characterization have not been extensively studied (Diaz, 2005; Jones, 1959). However, the venom appears to lack histamine or its action does not involve histamine-mediated reactions, since intradermally injecting anti-histamine at sting sites in human volunteers failed to block the reactions (Hughes and Rosen, 1980).

Contact with the buck moth caterpillar, *Hemileuca maia,* causes immediate pain radiating to the regional lymph nodes, with localized erythema and oedema. The contact dermatitis lasts 2–8 h and others symptoms, such as swelling, systemic reactions and anaphylaxis are rare (Diaz, 2005). Despite these symptoms, data on the composition of the content in the *H. maia* spines has not been described in the literature.

4.2. *Leucanella memusae (Saturniidae)*

L. memusae caterpillar venom contains proteins related to the coagulation disturbance, such as serpins, serine proteases, serine protease inhibitors (Quintana et al., 2017). Nonetheless, there are no reports of haemostatic disturbances after accident with these caterpillars, in which the incidents are mostly caused by contact with only one specimen (Espindula et al., 2009; Specht et al., 2009). Haemorrhagic symptoms seem to occur only when the contact involves a large number of caterpillars, thus exposing the victims to a large amount of venom (Gamborgi et al., 2006).

4.3. *Lonomia sp. (Saturniidae)*

Envenomation by the South American *Lonomia* caterpillars occurs mainly by the contact with its dorsal scoli (Fig. 1). Their venoms cause clinical manifestations, similar to contact dermatitis, characterized by pain and burning sensation at the site of contact. During the envenomation progression, within a period up to 72 h after contact, severe symptoms appear, such as bleeding from skin and mucous membranes and generalized hemorrhaging, characteristic of haemorrhagic syndrome known as lonomism (Fig. 5A). High fatality rates occur due to intracerebral hemorrhaging, consumptive coagulopathy, and acute renal failure. However, renal insufficiency is more frequent after contact with *L. obliqua* than with *L. achelous*. These reactions are possibly due to nephrotoxicity of the venom associated with the microcirculatory fibrin deposition it induces (Arocha-Piñango and Guerrero, 2003, 2001; 1999; Burdmann et al., 1996; Carrijo-Carvalho and Chudzinski-Tavassi, 2007; Duarte et al., 1996, 1990; Gamborgi et al., 2006; Kelen et al., 1995).

L. obliqua and *L. achelous* venoms cause similar clinical effects but differ in their mechanisms for inducing adverse effects. *L. obliqua* venom has procoagulant activity (Donato et al., 1998; Reis et al., 1999),

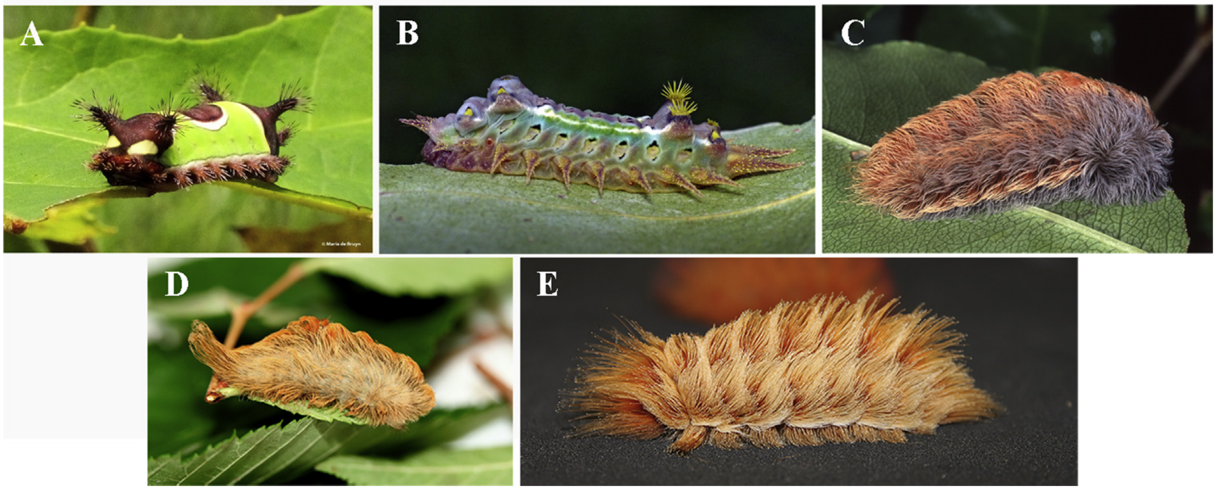


Fig. 4. Representatives of venomous caterpillars from the superfamily Zygaenoidea. **[A]** *Acharia stimulea*: mature caterpillar stage showing the back and flanks brown with green and a central oval area resembling a saddle. It is characterized by a variable marking occurs at the posterior end, where a cream-coloured set of spots imitates a large face. **[B]** *Doratifera oxleyi*: mature caterpillar stage showing the stout body, brightly coloured and surrounded by a skirt of fleshy spines. **[C]** *Lagoa crispata*: mature caterpillar stage showing the body with colour orange to grey, densely hairy with variously developed middorsal crest of darker hairs. **[D]** *Megalopyge opercularis*: Mature caterpillar stage showing their long and silky hairs. **[E]** *Podalia* sp.: Mature caterpillar stage showing long hairs. The images were kindly provided and reproduced by permission of Maria de Bruyn, Chapel Hill, USA (panel A); Simon Grove, Tasmanian Museum & Art Gallery (panel B); Dr. David L. Wagner, Department of Ecology & Evolutionary Biology, University of Connecticut (panel C); Dr. Donald W. Hall, Department of Entomology and Nematology, Institute of Food and Agricultural Sciences, University of Florida, USA (panel D); and Dr. Roberto Henrique Pinto Moraes, Special Laboratory of Zoological Collections, Butantan Institute, Brazil (panel E). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

which leads to a consumption coagulopathy associated with intravascular thrombin generation and secondary fibrinolysis (Zannin et al., 2003). *L. achelous* venom has both procoagulant and anticoagulant activities (Arocha-Piñango and Guerrero, 2001), being the envenomation characterized by an initial mild disseminated intravascular coagulation, which is masked by overwhelming fibrinolytic activity due to their fibrinolytic enzymes (Arocha-Piñango et al., 2000, 1992).

In Brazil, skin contact with *Lonomia* caterpillars is successfully managed using antilonomic serum therapy, produced in Butantan Institute (São Paulo, Brazil), which reduced the number of fatalities. However, as an alternative, antifibrinolytic drugs and transfusion of concentrated red blood cells, fresh frozen plasma and cryoprecipitate have been described in the replacement of coagulation factors and reposition of blood (Caovilla et al., 2004; Dias da Silva et al., 1996; Duarte et al., 1996, 1990; Kelen et al., 1995; Rocha-Campos et al., 2001).

The fibrinolytic molecules found in the haemolymph of *L. achelous* are Achelase I and Achelase II, also known as Lonomin II, which have plasmin-like activity (Amarant et al., 1991; Arocha-Piñango and Guerrero, 2003), and Lonomin V, which degrades fibrin, fibrinogen and human factor XIII, impairing fibrin cross-linking (Guerrero et al., 1997a, 1997b). The latter also has urokinase-like activity that activates plasminogen (Arocha-Piñango et al., 2000; Arocha-Piñango and Pepper, 1981). Two prothrombin activators, calcium-independent Lonomin III and a factor Xa-like activity, Lonomin IV (Guerrero and Arocha-Piñango, 1992), have been described, in addition to Lonomin VI:a, a factor V activator, and Lonomin VI:i, a factor V inhibitor (López et al., 2000). The venom also contains Lonomin VII, a toxin with kallikrein-like activity (Arocha-Piñango and Guerrero, 2001). *L. achelous* haemolymph is able to induce endothelial and macrophage activation, which could generate pro-inflammatory mediators, such as TNF-α, fibrinolytic enzymes and tissue factor. Together, these molecules may increase the haemostatic effect and amplify hemorrhagic manifestations observed in humans (Taylor et al., 2016).

L. obliqua venom has been extensively studied and some active compounds were found in the *L. obliqua* haemolymph, as a 35-kDa fibrinogenolytic protein, named as Lonofibrase, which preferentially cleaves fibrinogen α-chain (Pinto et al., 2004). Several biological activities have also been described in spine extracts from this caterpillar, among them, a phospholipase A_2 (PLA_2)-like toxin, a 15-kDa calcium-dependent thermolabile enzyme (Seibert et al., 2003), and two hyaluronidases, known as Lonoglyases, with apparent molecular masses of 49 and 53 kDa, that degrade hyaluronic acid and chondroitin sulphate, contributing to the venom's local effects (Gouveia et al., 2005). It was also demonstrated that *L. obliqua* venom is able to activate endothelial cells, with the increase of permeability and expression of adhesion molecules, such as E-selectin and vascular cell adhesion molecule-1 (VCAM-1), and of matrix metalloproteinases (MMPs) −2 and −9 (Nascimento-Silva et al., 2012). In addition, it was demonstrated that the venom can act directly on vascular smooth muscle cells, inducing oxidative stress and modification of the functionality of vascular cells (Moraes et al., 2017).

A direct calcium-independent factor X activator, Losac, and a prothrombin activator, Lopap, were isolated from spines extract (Alvarez Flores et al., 2006; Donato et al., 1998; Reis et al., 2001b). Intriguingly, these molecules differ from known procoagulant molecules in humans or any other species. Losac (*L. obliqua* Stuart-factor activator), is a serine protease purified as a single polypeptide chain of approximately of 45 kDa (Alvarez Flores et al., 2006). It was demonstrated, in studies using the native or recombinant form of Losac, the rLosac, specificity towards factor X having no effect on fibrin or fibrinogen, indicating its specificity for inducing blood coagulation and, consequently, participating in consumption coagulopathy in patients. Losac also induced proliferation and inhibited endothelial cell death while stimulating nitric oxide and tissue plasminogen activator release (Alvarez-Flores et al., 2011; Alvarez Flores et al., 2006; Chudzinski-Tavassi and Alvarez Flores, 2005). In addition, it was also observed that the treatment of rats with rLosac, in skin full-thickness wound model, promoted wound healing by the activation of fibroblasts, proliferation of epithelial cells, increase of type I collagen and decrease of inflammatory infiltrate (Sato et al., 2016). In human fibroblast cultures submitted to serum deprivation, rLosac demonstrated cytoprotection effects by reducing mitochondrial dysfunctions, such as loss of mitochondrial membrane

Table 2
Venom composition/activity from caterpillars of moths described in this review.

Superfamily	Family	Specie	Venom composition/activity	References
Bombycoidea	Saturniidae	*Automeris* sp.	Not defined.	–
		Hemileuca maia	Not defined.	–
		Leucanella memusae	Serpins, serine proteases, serine protease inhibitors and coagulation disturbance.	Quintana et al., 2017.
		Lonomia achelous[a,b]	Haemolymph: Lonomin II to V, Lonomin VI:a, Lonomin VI:i and Lonomin VII; endothelial and macrophage activation *in vitro*.	Amarant et al., 1991; Arocha-Piñango and Guerrero, 2003; Guerrero et al., 1997a,1997b; Guerrero and Arocha-Piñango, 1992; López et al., 2000; Arocha-Piñango and Guerrero, 2001; Taylor et al., 2016.
		Lonomia obliqua[a,b]	Spine extracts: phospholipase A2, 15-kDa calcium-dependent thermolabile enzyme, hyaluronidases, Lonoglyases, serine proteases Losac and Lopap; endothelial cells activation. Haemolymph: Lonofibrase, haemolymph antiviral activity.	Pinto et al., 2004; Seibert et al., 2003; Gouveia et al., 2005; Alvarez Flores et al., 2006; Donato et al., 1998; Reis et al., 2001b; Carmo et al., 2012; Greco et al., 2009; Nascimento-Silva et al., 2012.
Lasiocampoidea	Lasiocampidae	*Dendrolimus pini*	Formaldehyde, histamine analogues.	Huang, 1991.
Noctuoidea	Erebidae	*Arctia caja*	Acetylcholine.	Frazer, 1965.
		Lophocampa caryae	Not defined.	–
		Premolis semirufa	Hyaluronidase, metalloproteases, serine proteases, serine protease Ps82, complement activation in *in vitro* model and inflammation in mice model.	Villas-Boas et al., 2012, 2013, 2015.
		Euproctis chrysorrhoea	Kallikrein-like serine proteases, phospholipase A, trypsin-like, histamine, nicotine, chymotrypsin-like esterase, fibrinolytic, haemolytic and anticomplement activities.	Bleumink et al., 1982; de Jong et al., 1982; Deml and Dettner, 1995.
		Lymantria dispar	Histamine, nicotine.	Deml and Dettner, 1995; Shama et al., 1982; Deml, 2003.
	Notodontidae	*Thaumetopoea pityocampa*	Thaumetopoein, Tha p 1, Tha p 2 and serine proteases.	Lamy et al., 1985; Berardi et al., 2017; Moneo et al., 2003; Rodriguez-Mahillo et al., 2012.
Zygaenoidea	Limacodidae	*Acharia stimulea*	Haemolytic and vesicating venom.	Edwards et al., 1986; Murphy et al., 2010.
		Doratifera oxleyi	Histamine.	Southcott, 1988.
		Latoia consocia	Histamine, polypeptides.	Itokawa et al., 1985; Kawamoto and Kumada, 1984.
	Megalopygidae	*Lagoa crispata*	Tannins.	Lamdin et al., 2000.
		Megalopyge opercularis	Not defined.	–
		Podalia sp.[a]	Hairs extracts: serpins, serine proteases and serine protease inhibitors; fibrinogen and fibrin human cleavage, caseinolytic and phospholipase A2 activities. Haemolymph: antiviral activity.	Quintana et al., 2017; Carvalho et al., 2017.

[a] In these species haemolymph may be involved in the accidents.
[b] Envenomation by these caterpillars may be lethal.

Fig. 5. Representatives of some clinical manifestations induced in humans by the venomous caterpillars. [A] Patient with cutaneous hemorrhage after contact with *Lonomia obliqua* (Saturniidae). **[B]** Rash from contact with *Euproctis chrysorrhoea* (Erebidae). **[C]** Pruritic eruption from contact with *Lymantria dispar* (Erebidae). **[D]** Patient hand presenting deformity (including loss of one finger) and immobilization of the affected joint, after contact with *Premolis semirufa* caterpillar (Erebidae). **[E]** Patient with typical cutaneous reaction after contact with *Thaumetopoea pityocampa* (Notodontidae). **[F]** Hemorrhagic "grid-like" appearance after contact with *Megalopyge opercularis* (Megalopygidae). The images were kindly provided and reproduced by permission of Dr. Roberto Henrique Pinto Moraes, Special Laboratory of Zoological Collections, Butantan Institute, Brazil (panel A); Jan Samanek, Phytosanitary Administration, Bugwood.org. Reprinted from Publication Caterpillars and moths Part II. Dermatologic manifestations of encounters with Lepidoptera, 62(1):13–28, Hossler EW, Copyright (2010), with permission from Elsevier (panel B); Reprinted from the publication: Caterpillars and Moths, Part II. Dermatologic manifestations of encounters with Lepidoptera, 62(1):13–28, Hossler EW, Copyright (2010), with permission from Elsevier (panel C); Dr. Giselle Pidde, Immunochemistry Laboratory, Butantan Institute, Brazil (panel D); Dr. Andrea Battisti, Department of Agronomy, Food, Natural Resources, Animals and the Environment, University of Padova, Italy (panel E); Dr. Dirk M. Elston, Geisinger Medical Center-reprinted from the publication: Caterpillars and Moths, Part II. Dermatologic manifestations of encounters with Lepidoptera, 62(1):13–28, Hossler EW, Copyright (2010), with permission from Elsevier (panel F).

potential and reactive oxygen species (ROS) generation (Bosch et al., 2016).

Lopap (*L. obliqua* Prothrombin Activator Protease) (Reis et al., 2001b), another serine protease, was purified as a 69-kDa protein. The recombinant protein, rLopap, was obtained as a 21-kDa enzymatically active monomer (Chudzinski-Tavassi and Alvarez Flores, 2005). Since Lopap's deduced amino acid sequence was similar to the lipocalin family, it was the first lipocalin described with proteolytic activity (Reis et al., 2006). In addition, Lopap induced blood clotting in microvessels, resulting in fibrinogen consumption and blood incoagulability, in *in vivo* experiments (Reis et al., 2001a), similar to the consumption coagulopathy triggered by whole venom, demonstrating its importance in envenomation (Reis et al., 1999). A recent study (Quintana et al., 2017) demonstrated that the most striking feature of *L. obliqua* venoms from Brazil and Argentina is the presence of a 20-kDa protein, likely related to Lopap (Chudzinski-Tavassi et al., 2013).

4.4. Dendrolimus pini (Lasiocampidae)

Direct contact with urticating hairs and spines of living or dead pine-tree lappet caterpillars, *Dendrolimus pini*, or their cocoons, may result in dendrolimiasis, characterized by urticating maculopapular dermatitis, migratory inflammatory polyarthritis, migratory inflammatory polychondritis, chronic osteoarthritis, and, rarely, acute scleritis. Common symptoms consist of pyrexia, anorexia, malaise, rigors, headache or dizziness (Diaz, 2005; Lawson and Liu, 1986). In *D. pini*, venom glands, or more likely, toxin-producing epithelial cell clusters, occur at the base of the spines and can release toxic substances or haemolymph from both live and dead caterpillars and their cocoons, which are lightly armed with spines to frustrate predators (Huang, 1991). The tegument-produced venom contains formaldehyde and several uncharacterized histamine analogues with tropism for receptors in bone, joints, and cartilage. Multiple factors are believed to be involved in the pathogenesis; however, the reaction mechanisms and the nature of the toxic substances are poorly understood (Huang, 1991).

4.5. Arctia caja (Erebidae)

Contact with this caterpillar can cause dermatitis and ophthalmia nodosa (Corkey Belfast, 1955; Hellier and Warin, 1967; Henwood and MacDonald, 1983; Watson and Sevel, 1966). Despite these symptoms, data on the composition of the content in the *A. caja* setae has poorly been described in the literature. *A. caja* sequesters pyrrolizidine alkaloids, cardiac glycosides and cannabinols from its food (Rothschild, 1972; Rothschild et al., 1977). Some components have been isolated, such as acetylcholine, in caterpillar hairs and silk glands (Frazer, 1965; Morley and Schachter, 1963).

4.6. Euproctis sp. and Lymantria dispar (Erebidae)

After contact with *Euproctis* sp. caterpillars, most reactions in humans are mild, but some are more severe. Reactions (Fig. 5B) are characterized by eczematous dermatitis, papular urticaria, urticarial wheals, vesicopustular eruptions, bruising, conjunctivitis, rhinitis, and possibly fatal allergic reactions, as reported in one case attributed to an overwhelming allergic reaction to this insect (Blair, 1979; Kephart, 1914). The recommended treatment is the removal of the fine hairs using a sticky tape and, after that, the treatment of the dermatitis is essentially symptomatic and supportive (Balit et al., 2001).

E. chrysorrhoea and *E. subflava* caterpillars' venoms have been partially characterized. Interestingly, *E. chrysorrhoea* caterpillar hair extracts exert fibrinolytic, haemolytic and anticomplement activities. Moreover, the presence of phospholipase A and esterase in hair extracts from both species was associated to patients' cutaneous reactions (de Jong et al., 1982). It was also demonstrated that *Euproctis* venom contains ester hydrolases, trypsin-like, chymotrypsin-like esterase, serine proteases, being the kallikrein-like serine esterases described as major factors causing clinical symptoms after the caterpillar contact (Bleumink et al., 1982; Deml and Dettner, 1995; Rosen, 1990). In addition, histamine and nicotine have been isolated from *E. chrysorrhoea* caterpillars and from the gypsy moth caterpillar, *Lymantria dispar* (subfamily Lymantriinae) (de Jong and Bleumink, 1977; Deml, 2003; Shama et al., 1982). Although L. *dispar* caterpillars cause dermatitis outbreaks characterized by a self-limited pruritic eruption (Fig. 5 C), lasting 4–7 days, few clinical and epidemiological studies have been performed on these animals (Anderson and Furniss, 1983; Kikuchi et al., 2012).

4.7. Lophocampa caryae (Erebidae)

Contact with this caterpillar produces an irritant or histamine reaction in humans, causing itchy rashes (contact dermatitis) in many, particularly those prone to allergies, and may resemble exposure to urushiol, a plant oily organic compound with allergenic properties (Wagner, 2010). However, the exact mechanism and chemical composition of the venom found in *L. caryae* larvae hairs is undetermined. The symptoms generally occur after dermal and oral exposure to the caterpillar and removal of the hairs or spines is the primary treatment. After removal, the actions recommended are the administration of supportive care, focusing on pain control, and alleviating the resultant rash, using oral antihistamines and/or corticosteroid (Kuspis et al., 2001).

4.8. Premolis semirufa (Erebidae)

Rubber extractors may deal with an occupational disease called "pararamose" that results from accidental contact with the hairs present on *Premolis semirufa* larvae or cocoons during latex harvesting, since these caterpillars feed on rubber tree plantations present in the Amazonian region. Immediate symptoms usually involve intense itching, oedema and pain in the fingers. Symptoms persist for only a few days, but, in some cases, the inflammatory process becomes chronic, leading to deformity (Fig. 5D) and immobilizing the affected joint (Dias and de Azevedo, 1973; Gilmer, 1925).

In 1973, Dias and Azevedo conducted an experiment that placed *P. semirufa* caterpillars or isolated hairs in contact with mice. In this experiment, the authors observed an inflammatory reaction similar to those observed in humans with "pararamose" and suggested that substances associated with the hairs facilitate tissue penetration after skin injury (Dias and de Azevedo, 1973). Recently, it was demonstrated that the crude extract from *P. semirufa* hairs presents strong proteolytic activity and induce intense inflammatory process in the paw tissues of injected mice (Villas-Boas et al., 2012). In the murine model, it was also observed strong cellular and humoral immune responses, induced by the hairs' toxic components. They consisted of intense neutrophil and macrophage infiltration to the envenomation site, proliferation/migration, activation of T and B lymphocytes to the draining lymph nodes, elevated plasma levels of IL-6, 10, 12, 17, and 23 and a high production of specific antibodies (Villas-Boas et al., 2013). It was shown that the hairs extract was able to activate the human complement system, generating biologically active fragments, such as C3a, C4a and C5a anaphylatoxins and that it contains a serine protease, named as Ps82, with similar activities in the complement system to those of the whole extract. These data led the authors to consider that the complement system may play a role in the inflammatory process seen in humans after envenomation (Villas-Boas et al., 2015).

4.9. Thaumetopoea pityocampa (Notodontidae)

Accidental contact with urticating hairs from the *T. pityocampa* caterpillar induces cutaneous lesions (Fig. 5E), respiratory responses and anaphylactic shock in humans, and tongue lesions and ptyalism in dogs and cats (Maier et al., 2003; Pouzot-Nevoret et al., 2017a, 2017b). There are reports about the prevalence of pine processionary cutaneous reactions (Vega et al., 2011, 2003), but the largest available case series involve patients diagnosed with occupational immunologic urticaria (Vega et al., 2004). Additionally, osteomyelitis and ophthalmia have been recorded (Battisti et al., 2011; van Bockxmeer and Green, 2013). The treatment is supportive and shows low efficacy. Examples of treatment are systemic antihistamines, topical anti-itching products containing menthol or phenol and topical steroids. Systemic steroids are used in severe cases (Cuevas et al., 2011).

A study showed that *T. pityocampa* hairs contain a complex mixture of at least 70 proteins, including 7 allergens (Rodriguez-Mahillo et al., 2012). Three proteins with allergenic activity, that causes degranulation of mast cells and starts the release of histamine and inflammatory reaction, were found in this caterpillar (Lamy et al., 1986, 1985; Moneo et al., 2003; Rodriguez-Mahillo et al., 2012). The first protein, thaumetopoein, is a potent skin irritant and systemic histamine and kinin releaser, and comprises two subunits with estimated molecular weights of 13 and 15 kDa (Kalender et al., 2004; Lamy et al., 1986, 1985; 1983; Werno et al., 1993). Thereafter, a second IgE-binding protein, Tha p 1, with an estimated molecular weight of 15 kDa, was isolated from larvae extracts of *T. pityocampa* (Moneo et al., 2003). The last protein identified, Tha p 2, is an allergen unrelated to Tha p 1 (Rodriguez-Mahillo et al., 2012). A recent study showed that Tha p 2 is the major component of the hair proteome in *T. pityocampa*, as determined by the liquid chromatography tandem-mass spectrometry (LCMS/MS) analyses. In addition, serine proteases are present in the proteome of this species and show some similarity with proteins occurring in *Bombyx*, *Helicoverpa*, and *Mamestra* (Berardi et al., 2017).

4.10. Acharia stimulea (Limacodidae)

The venom of this caterpillar can cause a systemic condition with severe symptoms that include migraines, gastrointestinal problems, asthma complications, anaphylactic shock, erythrocyte rupture and hemorrhaging (Hossler, 2009). Contact dermatitis caused by *A. stimulea* includes immediate intense burning sensations around the contact zone, tightened erector pili muscles causing hair to stand on end, increased perspiration in the affected area, red blanching of the skin and blistering. Symptoms can last for five hours and leave red blotches at the envenomation site (Edwards et al., 1986; Hossler, 2010, 2009). The treatment is entirely supportive and includes washing of the site, removal of the hairs or spines using adhesive duct tape, application of ice packs and administration of antihistamines and corticosteroids (Diaz, 2005). *A. stimulea* spines contain haemolytic and vesicating venom secreted from nearby glands that directly damage tissue (Edwards et al., 1986; Murphy et al., 2010).

4.11. Doratifera oxleyi and Latoia consocia (Limacodidae)

Venoms from hairs and spines of *Doratifera oxleyi*, formerly known as *Bombyx oxleyi*, and *Latoia consocia* caterpillars contain histamine (Itokawa et al., 1985; Southcott, 1988). Contact with spines of *D. oxleyi* can cause a sharp painful sting and swelling (Kent and State Forests of New South Wales. Research Division, 1996), but the pain and dermatitis producing activity of *L. consocia* has been studied more extensively. Crude venom was separated into low molecular weight (LM) and high molecular weight (HM) fractions. Two LM-fractions, histamine and a polypeptide produced slight pain in humans, while two HM-fractions caused wheal formation with erythema (HM-I) and pharmacological effects consistent with endogenous mediator release (HM-II) (Kawamoto and Kumada, 1984).

4.12. Megalopyge opercularis, Lagoa crispata and Podalia sp. (Megalopygidae)

Megalopygidae caterpillars are considered the most dangerous Lepidopteran insects known to envenomate humans in North America (Daly and Derrick, 1975; Eagleman, 2008; Neustater et al., 1996). The contact with *Megalopyge opercularis* caterpillar causes intense and burning pain and erythema or rash (Fig. 5F). Hemorrhagic vesicles or pustules appear in few hours and can last for several days. The person may experience numbness in the affected site, headache, fever, nausea, vomiting and abdominal pain. The treatment includes applying tape to the site to remove the spines, ice packs, antihistamines, sodium bicarbonate and analgesic drugs (Avilán et al., 2010; Bishopp, 1923; Eagleman, 2008; Foot, 1922; Forrester, 2018; Stipetic et al., 1999). Despite being so dangerous, very little is known about the activities/composition of the venom.

The sting of a closely related species of the puss caterpillar *Megalopyge opercularis*, *Lagoa crispata*, more widespread throughout the United States, is much less severe. However, there is a report of a physician who found it more painful than the bite of a rattlesnake (reviewed by Pinson and Morgan, 1991). The venom presents high amount of tannins, which may be a reflection of the tannin content in its diet (Lamdin et al., 2000).

Recently, proteins related to the coagulation disturbance, such as serpins, serine proteases and serine protease inhibitors were identified, by mass spectrometry, in hairs extracts of *Podalia* sp. In addition, components of the venom were able to cleave human fibrinogen and fibrin and also presented caseinolytic and phospholipase A2 activities (Quintana et al., 2017). Interestingly, antiviral activity was described in *Podalia*'s haemolymph. Results suggested that haemolymph inhibited Rubella virus entry into SIRC cells (Statens Serum Institute Rabbit Cornea), by interfering with virion binding and adsorbing to the cellular receptor. Besides, cells treated with haemolymph, after viral infection, showed reduced viral titres and decreased cytopathic effects and viral protein synthesis (Carvalho et al., 2017).

5. Conclusion

Envenomation by different venomous caterpillar species can produce a variety of pathologic effects, ranging from mild events, such as cutaneous reactions, to severe reactions as renal failure, osteochondritis, deformity and immobilization of the affected joints and intracerebral bleeding. Venom apparatus organization varies from family to family, but the most urticating caterpillars possess hollow hairs or spines containing venom, with a heavily chitinized cone at the tip that is readily detached. Biochemical studies on the nature of the caterpillars' venom have been hindered by the minimal amount of it in each hair. Advanced technology and molecular approaches have recently facilitated the analysis of the biochemical nature of some caterpillars' venoms. However, there is still much to study in this universe of caterpillars' toxins that cause human health damage. Understanding the molecular mechanisms responsible for the triggering of envenomation may lead to an effective treatment of injury or even to the development of new targets or new drugs for the cure of diseases, using caterpillars' toxins as tools.

Ethical statement

This contribution is a review and does not warrant an ethical statement.

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