Venom from caterpillars of the Megalopygidae and Saturniidae families with therapeutic potential (Arthropoda: Insecta).

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Accidents caused by caterpillars, taturana, marandová, ruga, oruga, furry animals, or erucism is the clinical picture of poisoning resulting from contact with the stinging bristles where the poison is stored in the life cycle of moths and butterflies of the order Lepidoptera. Accidents caused by caterpillars, popularly called burns or irritations, have a benign evolution in most cases. Caterpillars of the genus *Lonomia* (Walker, 1855) are those of greatest relevance to public health, as they can cause serious accidents or deaths, due to the injection of poison into the body, which occurs through contact of the stinging bristles with the skin (Figure 1) [1-5].

Figure 1. genus *Lonomia* (Walker, 1855). Source: https://pt.wikipedia.org/wiki/Taturana_obl%C3%ADqua.

Accidents with caterpillars occur when the individual touches the animal, usually on tree trunks or when handling vegetation. Contact with the sharp bristles causes the poison contained in the spines to be injected into the person. The pain, in most cases, is violent, radiating from the burn site to other areas of the body. In the case of *Lonomia*, complications such as bleeding gums and blood in the urine sometimes appear and progress to acute kidney failure and death [1-5].

Local clinical manifestations are immediate pain and burning, radiating to the limb, with an area of erythema and edema in the contact region. Punctate erythematous lesions can be observed at the bristle inoculation points and painful regional adenomegaly. Blisters and superficial skin necrosis are rare. Symptoms usually disappear within 24 hours, without further complications (Figure 2) [1-5].

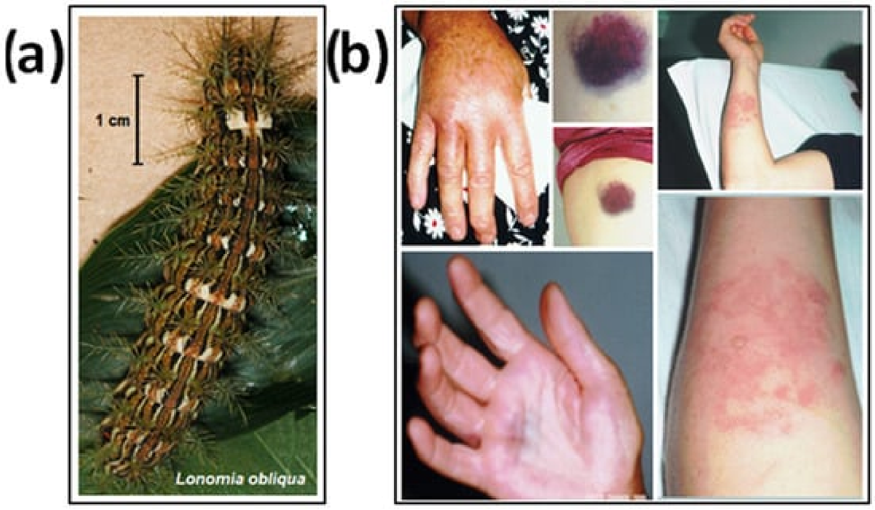

Figure 2. Clinical manifestations. (a) *Lonomia* (Walker, 1855), caterpillar. This photograph shows a caterpillar at the sixth stage or instar; and (b) Initial symptoms. This photograph shows some clinical manifestations that begin 12 to 24 hours after the accident involving contact with broken bristles. Edema (hands), erythema, heat, blisters (arm), and systemic symptoms have been reported. Ecchymosis, after 3 days of contact, of variable intensity, and hematuria (abdominal bruises, after 24 h), may occur. Sources: Photographs by Dra. Miryam P Alvarez-Flores, Dra. Marlene Zannin and Toxins. 2021; 13(12): 832; https://doi.org/10.3390/toxins13120832.

The presence of non-specific complaints of headache, malaise, nausea, and abdominal pain, which are often associated with or precede hemorrhagic manifestations of gingivorragia, spontaneous or traumatic ecchymoses, and epistaxis, hematuria, hematemesis, and hemoptysis may indicate greater severity. Acute kidney injury and intracranial hemorrhage have been linked to deaths (Figure 3) [1-5].

Figure 3. *Megalopyge opercularis* (Smith & Abott, 1797) (Insecta: Lepidoptera: Zygaenoidea: Megalopygidae). Source:

Photo#243713.

The main species of caterpillars that cause the most accidents in Brazil are**Family Megalopygidae**, hairy caterpillars are generally solitary and non-aggressive, 1 to 8 cm long, and have long, silky dorsal hairs of varying colors brown, white, black, and pink, which camouflage the real, sharp, stinging bristles. The short, pointed bristles contain poison glands, interspersed with long, colorful, and harmless ones [1-5].

The meglargats or asp caterpillar *Megalopyge opercularis* (Smith & Abott, 1797) (Insecta: Lepidoptera: Zygaenoidea: Megalopygidae), whose habitats are oaks and elms native to North America, have hair-like bristles that can cause "a sting as painful as placing a hot coal or a very sharp object, often sending victims to the hospital." According to researchers at the University of Queensland, the venom is unlike any substance ever seen in insects. (Figure 4) [1-5].

Figure 4. Puss caterpillar, *Megalopyge opercularis* (Smith & Abott, 1797) (Insecta: Lepidoptera: Zygaenoidea: Megalopygidae) (ventral view showing auxiliary prolegs without crochets). Sources: Photograph by Donald W. Hall, University of Florida and https://entnemdept.ufl.edu/creatures/misc/moths/puss.htm.

Its proteins are toxins produced by bacteria similar to *Escherichia coli* Nissle 1917 (Gammaproteobacteria: Enterobacteriaceae) and *Salmonella* Lignieres 1900 (Gammaproteobacteria: Enterobacteriaceae). These toxins could be used in the production of medicines due to their ability to penetrate cells **(Therapeutic Possibility)**   (Figure 5) [1-5].

Figure 5. Puss caterpillar, *Megalopyge opercularis* (Smith & Abott, 1797) (Insecta: Lepidoptera: Zygaenoidea: Megalopygidae) characteristic pattern of the sting. Source: Photograph courtesy of Armed Forces Pest Management Board.

Family Saturniidae spiny caterpillars live in groups and have stinging bristles in thorns, similar to small green pine trees distributed on the back of the caterpillar, without silky hairs. They have branched and pointed thorns with an arboreal appearance, with greenish tones often mimicking the plants they inhabit. This family includes the genus *Lonomia*, widely distributed throughout the country, causing hemorrhagic accidents (Figure 6) [1-5].

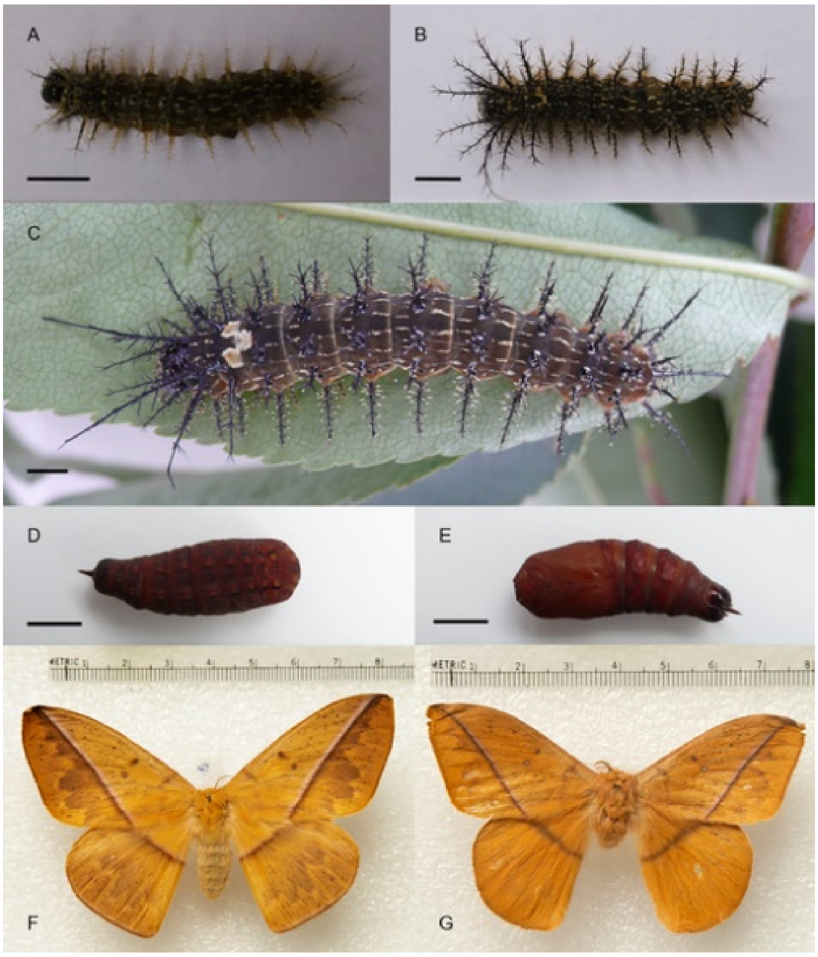

Figure 6. *Lonomia Columbiana* Lemaire, 1972, life cycle. (A) Eggs. (B) First instar larvae. (C) Third instar larva. (D) Fourth instar larva. (E) Fifth instar larva. (F) Sixth instar larva. (G) Pupae dorsal view. (H) Pupae ventral view. (I) Female. (J) Male. Bar = 0.5 cm. Source: https://doi.org/10.1371/journal.pone.0285010.g001.

Native to the forests of southern Brazil, they lived in communities on cedar and mastic trees. With deforestation, they began to live in domestic orchards and are found in other regions of Brazil. Some of its known natural enemies are two species of flies and one wasp. They lay eggs in the caterpillar's body and after the eggs hatch, their larvae devour the caterpillar. Since the antilonomic serum was developed and with the most immediate medical care, accidents with this taturana are no longer fatal [1-5].

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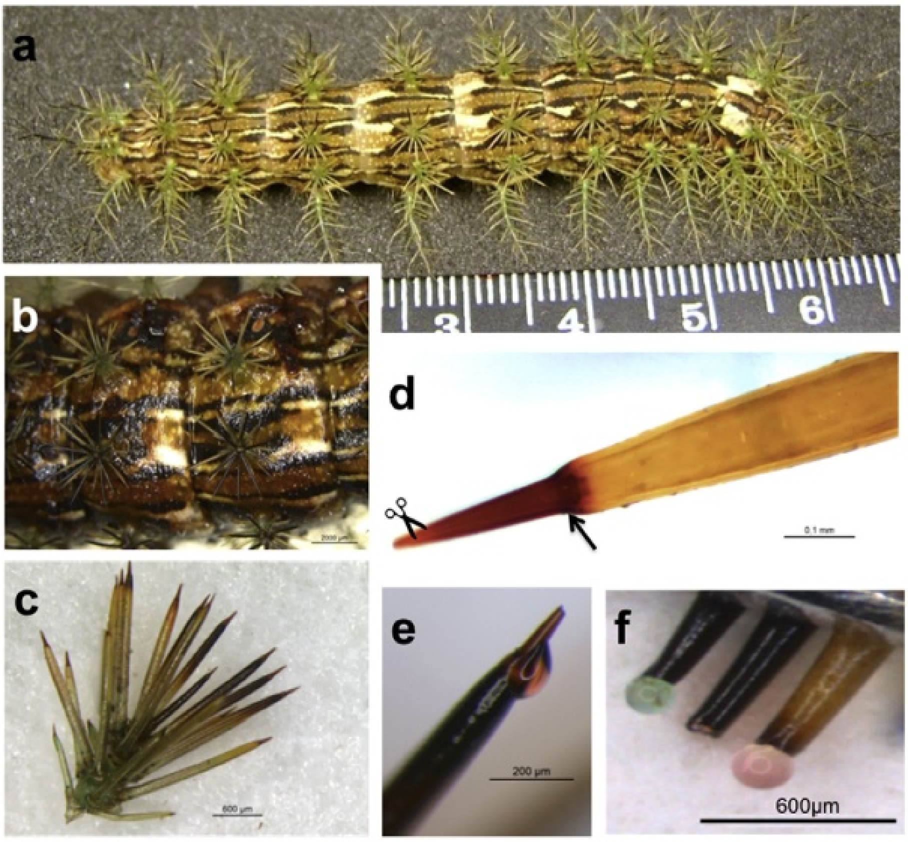

Figure 7. Photomicrographs of the *Lonomia obliqua* caterpillar (Saturnidae) at the sixth larval instar stage. a- General view. b- Details of scoli from the median dorsal region. c- Scolus isolated from the median dorsal region. Note that the scolus has a central axis from which originate lateral branches (spines) with different colors and sizes. d- Apical region of the spine where it was broken off (scissors) and subapical region where it was pressured (arrow) to collect secretions. e- Details of a spine broken at its tip showing a secretion derived from the interior of the spine. f- Observe a small drop with a green color on the left and orange on the right that exuded from the interior of different spines. Source: DOI:10.1016/j.toxicon.2016.06.008Corpus ID: 12698764.

At night, the caterpillars feed on the leaves of the host plant. During the day, they are grouped on the trunk, at rest. This phase lasts an average of 90 days. After growing, they descend to the lowest parts of the trunk, close to the ground, where they transform into pupae. During this period, the highest number of accidents occur [1-5].

As pupas permanecem no solo sob restos vegetais por um período que pode variar de 30 a 100 dias, dependendo das condições climáticas. Após esse período, as mariposas emergem das pupas, reiniciando o ciclo na natureza. Ovos, pupas e mariposas do gênero *Lonomia* não causam acidentes. As mariposas *Lonomia obliqua* Walker, 1855 (Lepidoptera: Saturniidae)são noturnas e vivem de 8 a 10 dias. Nesse período eles não se alimentam, apenas acasalam. Elas põem ovos nas folhas das plantas que servirão de alimento para futuras lagartas [1-5].

The oblique moth caterpillar is a species of moth caterpillar. This species is known for its stinging capacity during its larval period and for the serious accidents it can cause when its bristles come into contact with the skin of human beings which makes this an insect of great medical importance [1-5].

Scientists from the Butantan Institute have identified two proteins with great potential to combat degenerative diseases in the venom of the caterpillar *L. obliqua*, popularly known as a firecracker. The insect presents risks to humans when the venom comes into contact with the skin, resulting in burns, hemorrhages, and even kidney failure (Figure 8) [1-5].

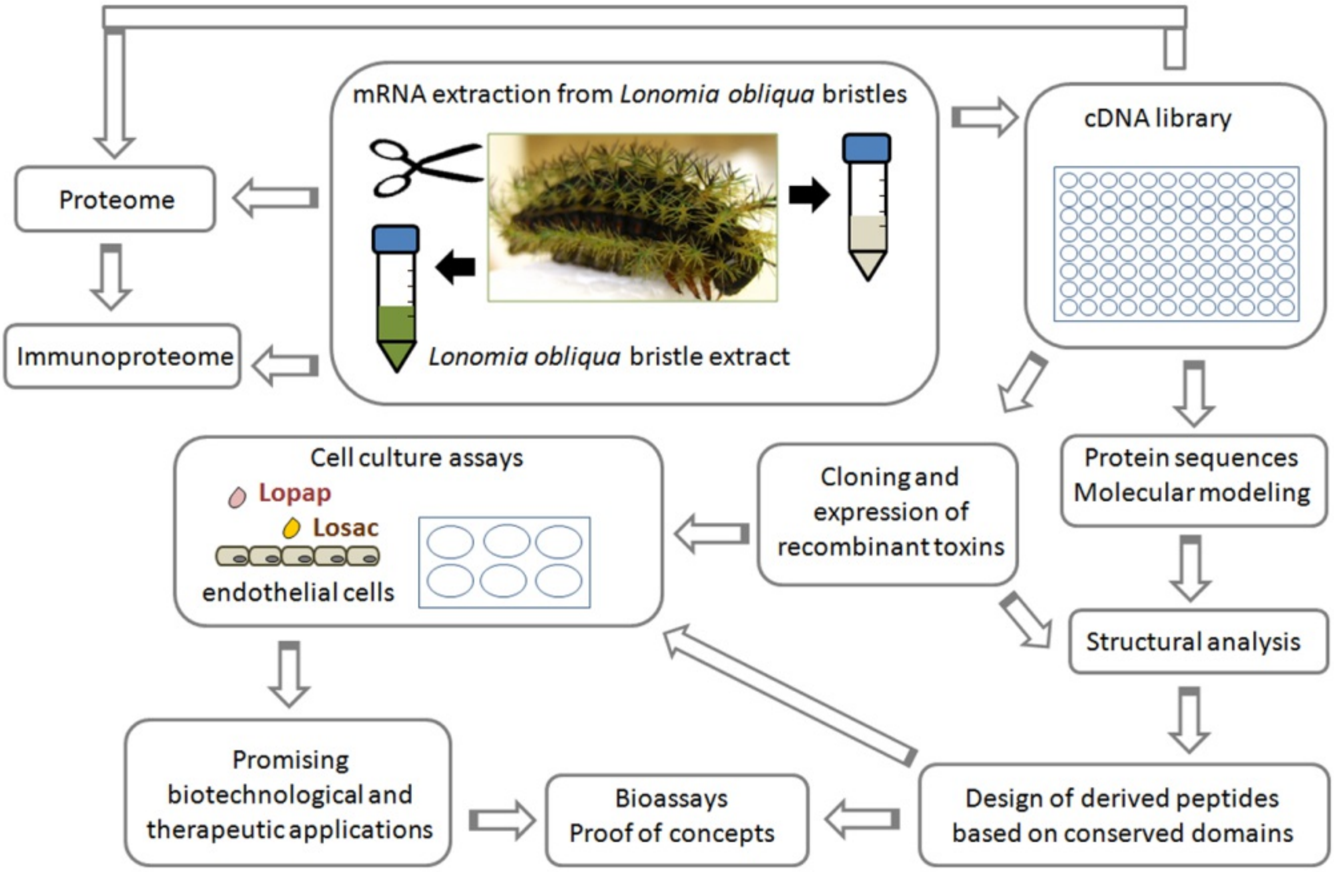

Figure 8. Schematic representation of the strategies to explore the*Lonomia obliqua* Walker, 1855 (Lepidoptera: Saturniidae) venom and toxins based on cellular and molecular approaches. Results obtained indicate promising applications for these proteins and derived peptides. Sources: DOI: 10.5772/53697 and https://www.intechopen.com/chapters/45118 and https://www.intechopen.com/chapters/45118.

According to the researchers who participated in the study, published in the journal Frontiers in Molecular Biosciences, these proteins, called rLosac and rLopap, can be explored to treat degenerative diseases and develop products aimed at healing and regeneration. They found that the peptides were present in all evolutionary stages of the caterpillar, and began to investigate whether they could also be involved in other processes related to the animal's metamorphosis [1-5].

Losac, in addition to activating blood coagulation factor X, has a neuroprotective function, while Lopap, which activates prothrombin, also induces the production of extracellular matrix molecules, such as collagen and fibronectin, related to regeneration. Proteins prevent cell death, in addition to activating the blood clotting factor, which can help in the development of new medicines for different areas, such as in the cosmetic industry, specifically targeting regenerative pharmacological activity, or even in the pharmaceutical sector that develops healing products **(Therapeutic Possibility)** (Figure 9) [1-10].

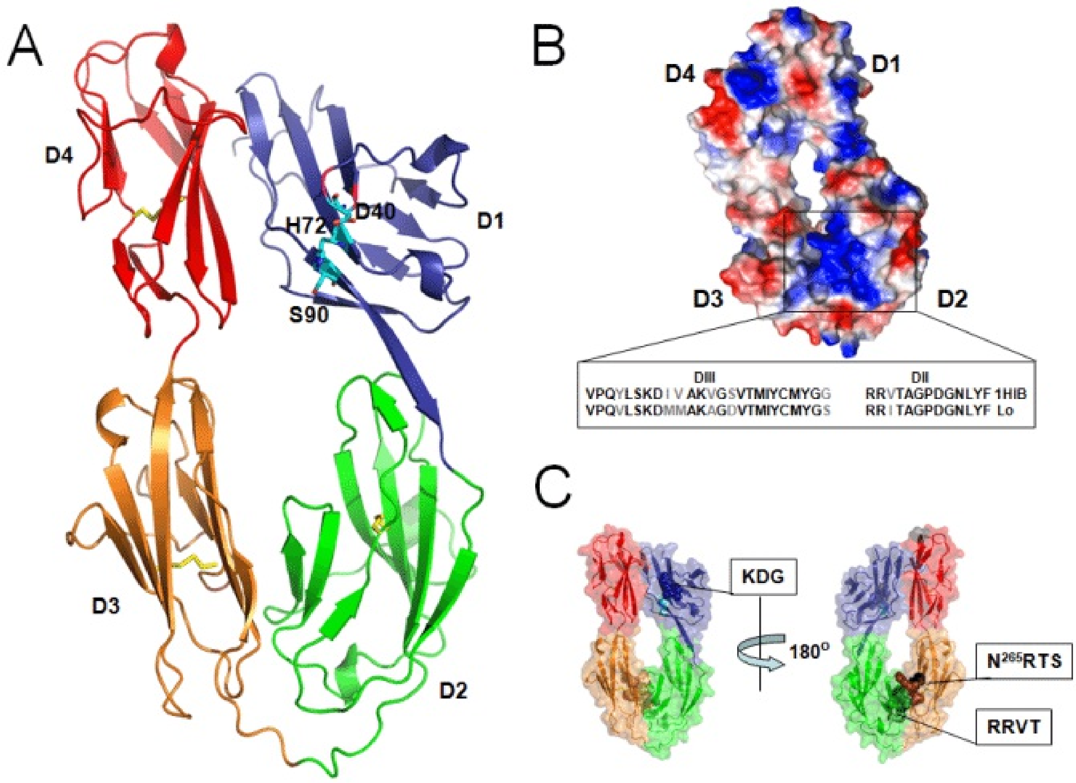

Figure 9. Three-dimensional structure model of Losac. (A) Cartoon view of the predicted model of Losac protein built from the structural coordinates of H. cecropia hemolin (PDB code 1BIH) using Modeller 9v1 [102]. Each domain (D1-D4) comprises α-helices and 7 strands arranged in 2 antiparallel β-sheets that are linked together by a disulfide bridge (shown in yellow stick). The residues of the putative catalytic triad predicted in D1 by the program catalytic program, are indicated as stick cyan color by the one letter code followed by the residue number, D 40, H 72, S 90. (B) The electrostatic potential surface of Losac shows inside the box the conserved phosphate-binding site at the D2-D3 interface domains. (C) Surface view of the Losac model evidencing the conserved adhesive motif KDG (deep blue) and the LPS-binding motif RRVT (green) and NRTS (chocolate), which contains the glycosylation site in N 265. All the figures were produced in Pymol v1.5. Sources: http://www.pymol.org/ and https://www.researchgate.net/figure/Three-dimensional-structure-model-of-Losac-A-Cartoon-view-of-the-predicted-model-of_fig10_256796470.

Once the protein was identified, their attention focused on its possible use as an active ingredient in an anticoagulant to treat thrombosis and degenerative diseases. Thrombosis is the interruption of blood flow due to the presence of clots. Isolation of caterpillar venom protein that causes hemorrhagic syndrome could lead to anticoagulant drugs (Sources: Ana Marisa Chudzinski-Tavass and Cleyson Reis) **(Therapeutic Possibility)** [1-10].

Antilonomia serum + heterologous immunoglobulin against *L. obliqua* venom is specifically indicated for the treatment of poisoning caused by contact with caterpillar bristles. The specific antibody immunoglobulins contained in the serum specifically bind to the venom not yet fixed in the cells of the elective tissues, neutralizing it. Doses of antivenom must be high enough, as recommended so that the antivenom is found in relative excess in the circulating bloodstream in a relatively short time. Under these conditions, the sooner the serum is administered, the greater its therapeutic potential will be. (Therapeutic) (Figure 10) [1-15].

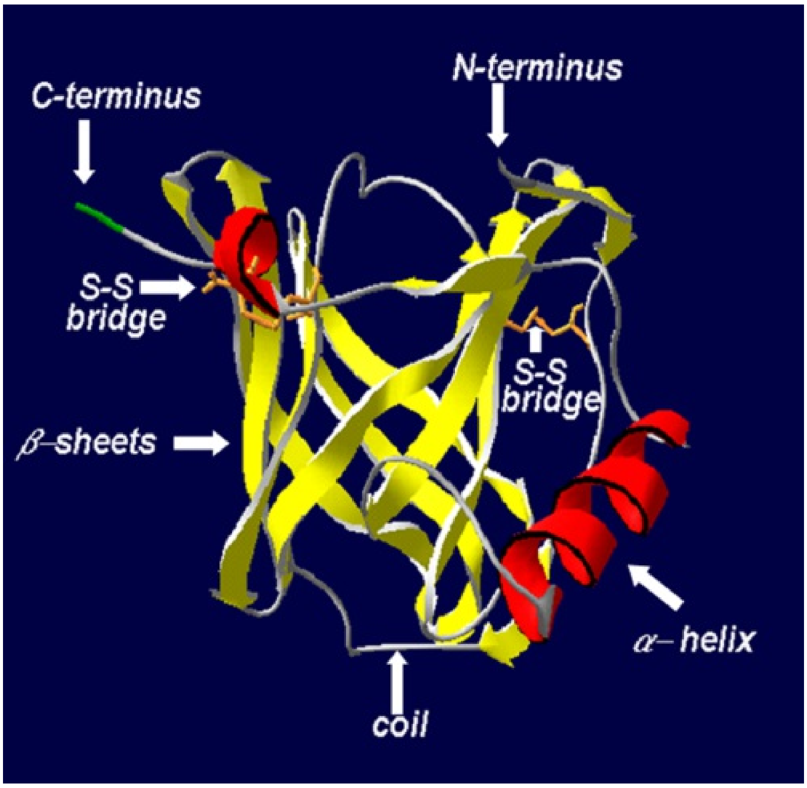

Figure 10. Model of the three-dimensional structure of Lopap*Lonomia obliqua* Walker, 1855, (Lepidoptera: Saturniidae).

The liquid that runs through the bodies of these animals can be important enough to make a difference in the search for antibacterial, fungal, and viral vaccines. Hemolymph, a colorless fluid whose function in invertebrates corresponds to that of blood, has proven to be of vital importance as it demonstrates the potential to reduce the action of microorganisms in the human body. Researchers at the Butantan Institute, in São Paulo, have taken advantage of this function by identifying promising substances in research with two families of caterpillars [1-20].

Studies focus on substances that have apoptotic and antiviral properties. Proteins are produced by recombinant DNA technology. While apoptotic action promotes apoptosis programmed or triggered cell death that eliminates damaged or excess cells an important process for controlling cancer, the antiviral currently used in Megalopygidae caterpillars combat specific viruses. Using DNA, the protein-coding gene is extracted from the hemolymph, cloned into a baculovirus a virus that attacks insects, and replicated in insect cells that produce defense proteins so-called recombinant proteins in large quantities (Figure 11) [15-20].

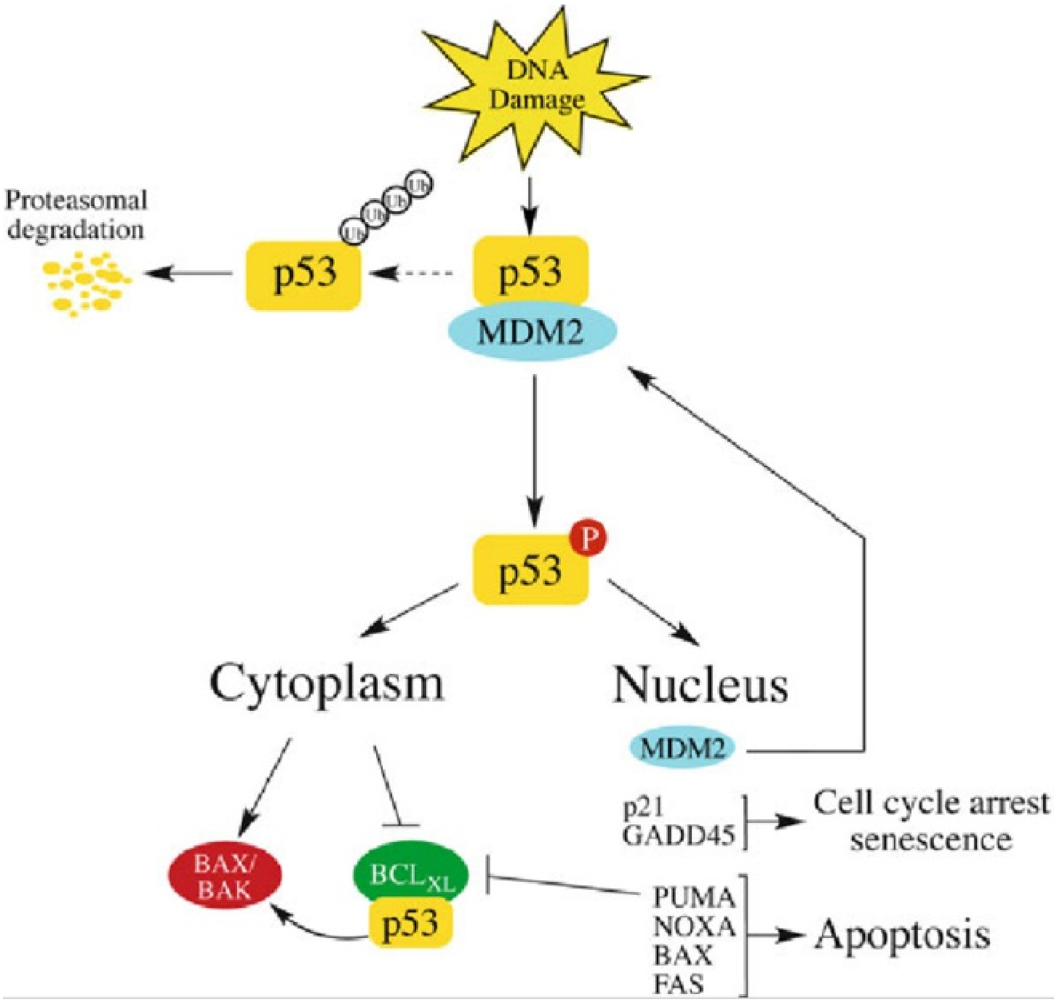

Figure 11. 3 DNA damage-induced p53 promotes apoptosis in a transcription-dependent and independent manner. In unstressed cells p53 levels are low due to its interaction with MDM2 where MDM2 polyubiquitylates p53, promoting its proteasomal degradation. Upon DNA damage residues within p53 and MDM2 are posttranslationally modifi ed generating a fully functional, stabilized p53 protein. P53 binds to the promoter regions and transactivates numerous genes that control the cell cycle, senescence, and apoptosis. P53 can have transcription-independent functions in the cytosol and act analogously to a pro-apoptotic BH3-only protein by promoting MOMP. Source: https://www.researchgate.net/figure/DNA-damage-induced-p53-promotes-apoptosis-in-a-transcription-dependent-and-independent_fig2_286007555.

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The invertebrate category was chosen due to the accumulation of carcasses, after the poison was removed, at the institute, for the production of anti-scald serum. The Megalopygidae family brings together more than 200 species, including *Megalopyge lanata* (Stoll, 1780) the popular fall armyworm, whose moth attacks corn crops in Brazil, in addition to *Megalopyge albicollis* (Walker, 1855), the fireworm. The studies open doors for other important research in Brazil, which has a mega biodiversity of insects (Figure12) [15-25].

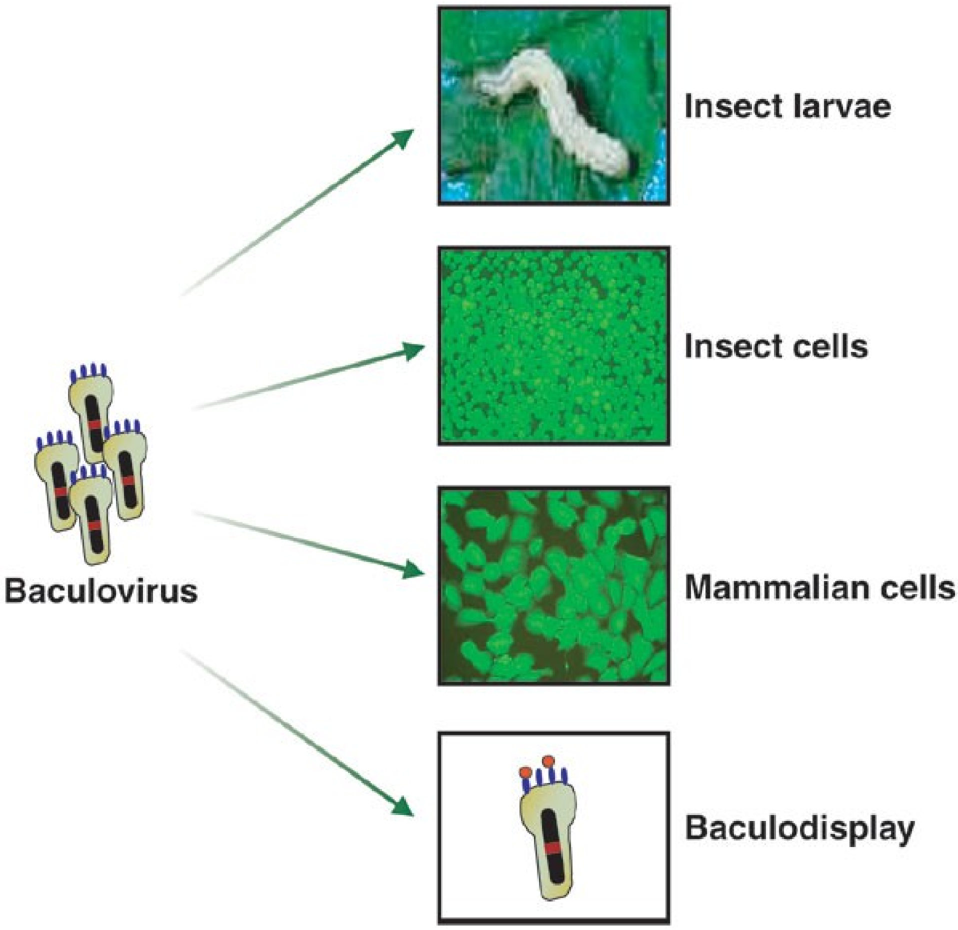

Figure 12. Baculovirus vectors can be used for a variety of applications. These include producing proteins in insect larvae, insect cells, and mammalian cells. The insect and mammalian cells in the photomicrographs were treated with baculoviruses expressing GFP. Viruses can also be produced that display peptides or proteins on the surface of viral particles. The red circles on the schematic virus particle represent displayed gp64 fusion proteins. Source: https://doi.org/10.1038/nbt1095.

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