

## MEXICAN ANNONACEAE WITH INSECTICIDAL METABOLITES

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### Abstract

Plants of the Annonaceae family are characterized by diverse biological properties, among which insecticidal activity, a function derived from the presence of secondary metabolites. This review aims to present the state-of-the-art research demonstrating the insecticidal activity of Annonaceae plants found in Mexico, the secondary metabolites involved, and the target insects. A retrospective search was conducted for works on the insecticidal activity of Annonaceae plants, from 1982 to June 2025. Compounds that caused at least 50 % mortality in individuals, and the deterrent effects, or sublethal effects, were selected. This work reports insecticidal compounds obtained from seven species. *Annona mucosa*, *A. squamosa*, and *A. cherimolia* are the most studied species, and acetogenins from Annonaceae are the most notable molecules. The compounds are toxic to 21 insect species, the *Aedes aegypti* mosquito and the *Spodoptera frugiperda* corn fall armyworm being the most evaluated. Plants of the Annonaceae family constitute a natural resource for the study on secondary metabolites with insecticidal potential.

**Keywords:** *Aedes aegypti*, annonaceous acetogenins, phenols, *Spodoptera frugiperda*, terpenes.

### Resumen

Las plantas de la familia Annonaceae se caracterizan por tener diversas propiedades biológicas entre las que destaca la insecticida, actividad dada por la presencia de metabolitos secundarios. El objetivo de esta revisión es dar a conocer el estado de arte de las investigaciones que demuestran la actividad insecticida de las anonáceas que habitan México, los metabolitos secundarios que participan y los insectos sobre los que actúan. Se realizó la búsqueda retrospectiva de trabajos sobre la actividad insecticida de las Anonáceas, abarcando el periodo de 1982 a 2025 (junio). Se eligieron compuestos que provocaron al menos el 50 % de la mortalidad de los individuos, efectos disuasorios o efectos subletales. En este trabajo se reportan compuestos insecticidas obtenidos de siete especies. *Annona mucosa*, *A. squamosa* y *A. cherimolia* son las especies más estudiadas y las acetogeninas de anonáceas las moléculas más notorias. Los compuestos son tóxicos contra 21 especies de insectos, el mosquito *Aedes aegypti* y el cogollero del maíz *Spodoptera frugiperda* son los más evaluados. Las plantas de la familia Annonaceae constituyen un recurso natural para el estudio de metabolitos secundarios con potencial insecticida.

**Palabras clave:** acetogeninas de anonáceas, *Aedes aegypti*, fenoles, *Spodoptera frugiperda*, terpenos.

Insecticides are chemicals used to control crop pests or stored products, including vectors of diseases that affect humans, domestic animals, and/or farm animals. However, it is well known that these compounds can generate resistance in some insects and cause environmental and health damage. Prolonged exposure to insecticides, for example, pyrethroids and organophosphates, is directly linked to the risk of cancer, including prostate cancer, Hodgkin's lymphoma, leukemia, multiple myeloma, and breast cancer (Alavanja *et al.* 2013). For these reasons, the search for organic molecules of plant origin with insecticidal potential has increased. Hundreds of plant species are being evaluated for this purpose, including those from the Annonaceae family, due to the presence of secondary metabolites that confer diverse biological properties, such as cytotoxicity, antibacterial, antifungal, antitumor, leishmanicidal, antimalarial, and insecticide properties (Cavé *et al.* 1997, Cortés *et al.* 2014, González-Esquinca *et al.* 2014, De la Cruz-Chacón *et al.* 2019). Among these compounds, acetogenins from Annonaceae (ACGs) stand out as the most important insecticidal molecules (Cavé *et al.* 1997, Liaw *et al.* 2016).

The insecticidal activity of Annonaceae is one of their most researched properties; however, few studies have compiled or systematized the available information. The most recent reviews were conducted in 2014 and 2024. In 2014, Krinski *et al.* conducted a search for studies involving extracts and essential oils, and the authors documented 42 species with toxic activity on 60 insect species. The most recent research was conducted by Durán-Ruiz *et al.* (2024), who documented 85 ACGs from 15 Annonaceae species with insecticidal potential on 30 insect species. Given the above, it is relevant to scrutinize studies on the insecticidal potential of Annonaceae species found in Mexico.

## Materials and methods

To identify the insecticidal activity of Annonaceae species distributed in Mexico, a targeted literature search was conducted for each species reported in Mexico according to De-la-Cruz-Chacón *et al.* (2016) and Villaseñor (2016) and for newly discovered species (Moreno-Méndez & Ortiz-Rodríguez 2020, Ortiz-Rodríguez 2022, Martínez-Velarde *et al.* 2023). Some data were obtained from our previous review (Durán-Ruiz *et al.* 2024, De-la-Cruz-Chacón *et al.* 2026), compiling information from PubMed, Science Direct, Scielo and Google Scholar scientific databases. Additional and update information was compiled using a combination of search terms including the species name was used (and its synonyms) along with words “insecticidal”, “insecticides”, “pest”, “pesticidal”, “toxic”, “lethal”, and “insects”.

Data were recorded exclusively for activity against organisms of the class Insecta. Only studies reporting compounds with at least 50 % insecticidal activity were included. The following were excluded: duplicate articles, theses, reviews, inaccessible articles, conference proceedings, studies on extracts, Annonaceae species not distributed in Mexico, articles not involving Annonaceae species, and studies reporting non-insecticidal activity. Out of a total of 440 documents, only of 26 articles met the selection criteria and were analyzed.

To avoid duplication, compound synonyms were verified using the Cavé *et al.* (1997), Liaw *et al.* (2016) sources and the National Center for Biotechnology Information PubChem database ([pubchem.ncbi.nlm.nih.gov](https://pubchem.ncbi.nlm.nih.gov)). Additionally, the scientific names of Annonaceae species were updated based on the “Tropicos” database of the Missouri Botanical Garden ([www.tropicos.org](https://www.tropicos.org)).

## Results

The Annonaceae family is composed of at least 2,400 species, of which 70 are distributed in Mexico (Chatrou *et al.* 2012, González-Esquinca & De la Cruz-Chacón 2020). Of the 13 genera reported in Mexico, only seven species have metabolites with insecticidal activity: *Annona cherimolia* Mill, *Annona glabra* L., *Annona macrophyllata* Donn. Sm., *Annona mucosa* (Jacq.) Baill., *Annona muricata* L., *Annona purpurea* Moc. & Sessé ex Dunal, and *Annona squamosa* L. (Table 1). These species represent 0.3 % of the total species in the family and 10 % of those distributed in Mexico.

This review reported 58 compounds, of which 46 are ACGs, eight are terpenes, and four are phenols (Table 1, Figure 1). More than half of compounds come from seeds (61 %), followed by leaves (38 %), to a lesser extent stems (1 %), and none from flowers or roots. *Annona mucosa* is the most studied species, followed by *A. cherimolia* and *A. squamosa*.

**Table 1.** Annonaceae species from Mexico with insecticidal secondary metabolites.

|                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Annona cherimolia</i>                                                                                                                                                                                                                                                                                                                                                            |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Seeds:</b> almunequin <sup>1,2</sup> , cherimolin-1 <sup>1</sup> , itrabin <sup>1,2</sup> , laherradurin <sup>3</sup> , molvizarin <sup>2</sup> , motri-<br>lin <sup>4</sup> , neoannonin <sup>1</sup> , rolliniastatin-2 <sup>3</sup> , squamocin <sup>1,2,3,5</sup> , tucumanin <sup>1</sup>                                                                                   |
| <i>Annona glabra</i>                                                                                                                                                                                                                                                                                                                                                                |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Seeds:</b> annonacin <sup>3,5</sup> , asimicin <sup>6</sup> , desacetylurvaricin <sup>6</sup> , squamocin <sup>6</sup>                                                                                                                                                                                                                                                           |
| <i>Annona macrophyllata</i>                                                                                                                                                                                                                                                                                                                                                         |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Seeds:</b> laherradurin <sup>7</sup>                                                                                                                                                                                                                                                                                                                                             |
| <i>Annona mucosa</i>                                                                                                                                                                                                                                                                                                                                                                |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Leaves:</b> 12-OH bullatacin A <sup>4</sup> , bullatalicin <sup>8</sup> , <i>cis</i> -sylvaticin <sup>4</sup> , mucocin <sup>4</sup> , murica-<br>tetrocin C <sup>4</sup> , rollidecin A <sup>4</sup> , rollidecin B <sup>4</sup> , rollinecin A <sup>4</sup> , rollinecin B <sup>4</sup> , rollitacin <sup>4</sup> ,<br>sylvaticin <sup>8</sup>                                 |
| <b>Seeds:</b> rolliniastatin-1 <sup>9-12</sup> , rolliniastatin-2 <sup>4</sup> , squamocin <sup>13-15</sup>                                                                                                                                                                                                                                                                         |
| <b>Phenols</b>                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Leaves:</b> quercetin <sup>16</sup> , quercetin 3-O- $\alpha$ -D-arabinoside <sup>17</sup> , quercetin 3-O- $\beta$ -D-<br>glucoside <sup>17</sup> , kaempferol 3-O- $\beta$ -D-galactoside <sup>17</sup>                                                                                                                                                                        |
| <b>Terpenes</b>                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Leaves:</b> (3 R, 20S)-3-acetoxy-20-hydroxydammar-24-ene <sup>16</sup> , 3-oxo-11 $\alpha$ -<br>hydroxyurs-12-ene <sup>16</sup> , 3 $\alpha$ , 24-diacetoxy-12-oleanane <sup>16</sup> , 3 $\beta$ -acetoxy-12-oleanene <sup>16</sup> ,<br>3 $\beta$ -acetoxyursolic acid <sup>16</sup> , $\beta$ -sitosterol <sup>16</sup> , lupeol <sup>16</sup> , oleanolic acid <sup>16</sup> |
| <i>Annona muricata</i>                                                                                                                                                                                                                                                                                                                                                              |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Leaves:</b> annonacin A <sup>4</sup> , annopentocin A <sup>4</sup> , annopentocin B <sup>4</sup> , annopentocin C <sup>4</sup> , <i>cis</i> -<br>gigantrionenin <sup>4</sup> , muricatetrocin B <sup>4</sup> , murihexocin A <sup>4</sup> , murihexocin B <sup>4</sup> .                                                                                                         |
| <b>Seeds:</b> annonacin <sup>4,18-20</sup>                                                                                                                                                                                                                                                                                                                                          |
| <i>Annona purpurea</i>                                                                                                                                                                                                                                                                                                                                                              |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Leaves:</b> rolliniastatin-1 <sup>21</sup> , bullatacin <sup>21</sup> , sylvaticin <sup>21</sup> , cherimolin 2 <sup>21</sup> , purpureacin 2 <sup>21</sup>                                                                                                                                                                                                                      |
| <i>Annona squamosa</i>                                                                                                                                                                                                                                                                                                                                                              |
| <b>ACGs</b>                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Seeds:</b> annonacin <sup>22,23</sup> , annonin <sup>24</sup> , annotemoyin-1 <sup>25</sup> , neoannonacin <sup>22</sup> , rolliniastatin<br>2 <sup>23</sup> , squamocin <sup>23,26</sup>                                                                                                                                                                                        |
| <b>Bark:</b> parviflorin <sup>8</sup>                                                                                                                                                                                                                                                                                                                                               |

<sup>1</sup>Álvarez Colom *et al.* 2007, <sup>2</sup>Álvarez Colom *et al.* 2008, <sup>3</sup>González-Coloma *et al.* 2002, <sup>4</sup>He *et al.* 1997, <sup>5</sup>Guadaño *et al.* 2000, <sup>6</sup>Ohsawa *et al.* 1991, <sup>7</sup>Luna-Cazáres *et al.* 2004, <sup>8</sup>Alali *et al.* 1998, <sup>9</sup>Souza *et al.* 2016, <sup>10</sup>Ribeiro *et al.* 2020, <sup>11</sup>Di Toto Blessing *et al.* 2012, <sup>12</sup>Ansante *et al.* 2015, <sup>13</sup>Costa *et al.* 2016a, <sup>14</sup>Costa *et al.* 2016b, <sup>15</sup>Costa *et al.* 2018, <sup>16</sup>Makenzi *et al.* 2020, <sup>17</sup>Makenzi *et al.* 2019, <sup>18</sup>Rodrigues *et al.* 2019, <sup>19</sup>Goh *et al.* 1995, <sup>20</sup>Domínguez-Martínez *et al.* 2003, <sup>21</sup>Cepleanu *et al.* 1993, <sup>22</sup>Kawazu *et al.* 1989, <sup>23</sup>Londershausen *et al.* 1991, <sup>24</sup>Moeschler *et al.* 1987, <sup>25</sup>Parvin *et al.* 2003, <sup>26</sup>Costa *et al.* 2014.

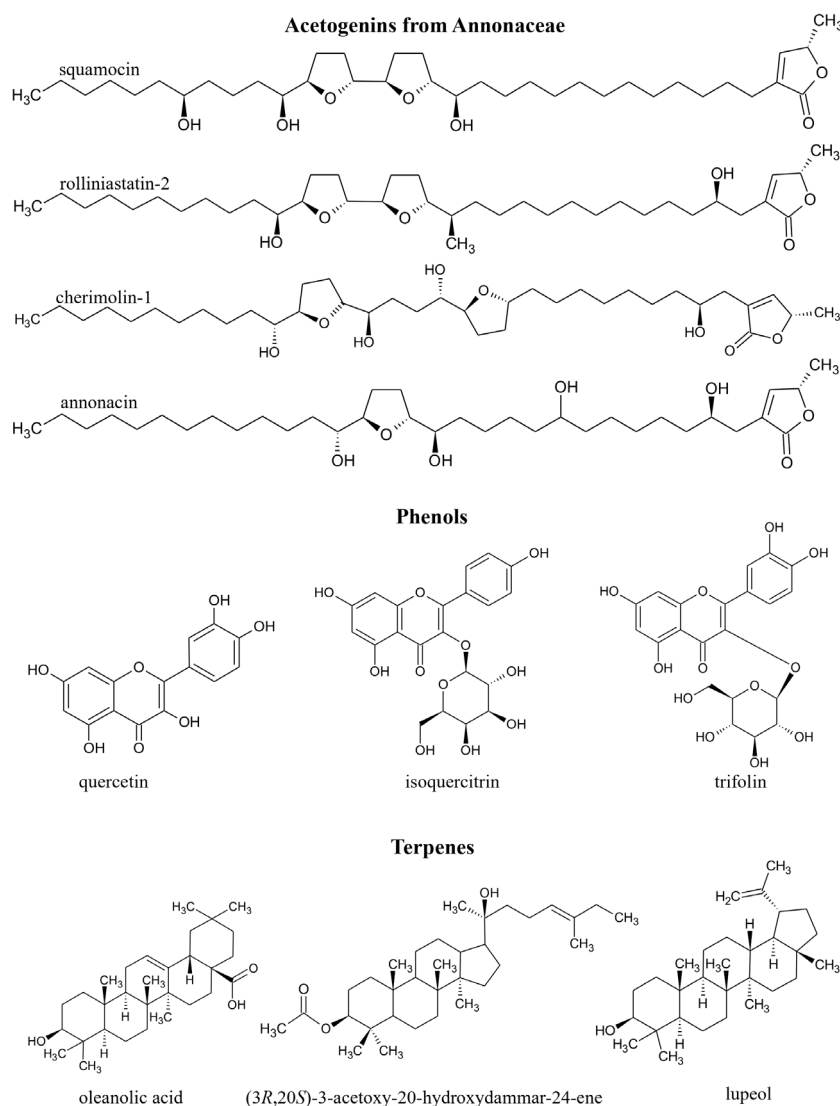


**Figure 1.** Examples of secondary metabolites of Mexican Annonaceae with insecticidal activity.

Insecticidal activity was found on 21 insect species belonging to six orders: Blattodea, Coleoptera, Diptera, Hemiptera, Lepidoptera, and Orthoptera (Table 2). The reported insects are pests of crops or stored products, and are also urban pests or disease vectors. *Aedes aegypti* L., the yellow fever mosquito, is the most frequently evaluated species, with 27 ACGs isolated from five species (*Annona cherimolia*, *A. mucosa*, *A. muricata*, *A. purpurea*, and *A. squamosa*). Similarly, the fall armyworm, *Spodoptera frugiperda* J.E.Smith, with 20 ACGs isolated from *A. cherimolia*, *A. muricata*, and *A. squamosa* (Table 3).

The insecticidal activity of the following *Annona* species has been documented, including the ability to cause death, act as a repellent, have anti-feeding effects, inhibit growth, and cause morphological, histological, and behavioral changes that lead to the death of individuals.

***Annona cherimolia*.** Of this species, 10 ACGs obtained from seeds have been evaluated on five insect species (Tables 1-3).

In almost all cases, ACGs caused up to 100 % of species mortality (Table 3). For example, asimicin, itabin, neoannonin, squamocin, and cherimolin-1 at concentration of 50  $\mu\text{g g}^{-1}$  of diet, caused 100 % of mortality in the fall

**Table 2.** Insect species susceptible to the insecticidal activity of mexican Annonaceae.

|                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><i>Annona cherimolia</i></b>                                                                                                                                                                                                                                                                                                                                                                              |
| <i>Aedes aegypti</i> <sup>*1</sup> , <i>Leptinotarsa decemlineata</i> <sup>*2</sup> , <i>Oncopeltus fasciatus</i> <sup>*3</sup> , <i>Spodoptera frugiperda</i> <sup>*4</sup> , <i>Spodoptera littoralis</i> <sup>*2</sup>                                                                                                                                                                                    |
| <b><i>Annona glabra</i></b>                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Callosobruchus chinensis</i> <sup>*5</sup> , <i>Crocitolomia binotalis</i> <sup>*5</sup> , <i>Henosepilachna vigintioctopunctata</i> <sup>*5</sup> , <i>Leptinotarsa decemlineata</i> <sup>*6</sup> , <i>Spodoptera littoralis</i> <sup>*7</sup>                                                                                                                                                          |
| <b><i>Annona macrophyllata</i></b>                                                                                                                                                                                                                                                                                                                                                                           |
| <i>Culex quinquefasciatus</i> <sup>*8</sup>                                                                                                                                                                                                                                                                                                                                                                  |
| <b><i>Annona mucosa</i></b>                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Aedes aegypti</i> <sup>*1,9-11</sup> , <i>Anticarsia gemmatilis</i> <sup>*9</sup> , <i>Blatella germanica</i> <sup>+12</sup> , <i>Helicoverpa armigera</i> Hübner <sup>♦13</sup> , <i>Prostephanus truncatus</i> <sup>*14,15</sup> , <i>Sitophilus zeamais</i> <sup>*14-16</sup> , <i>Spodoptera frugiperda</i> <sup>♦17-18</sup>                                                                         |
| <b><i>Annona muricata</i></b>                                                                                                                                                                                                                                                                                                                                                                                |
| <i>Aedes aegypti</i> <sup>*1,19-21</sup> , <i>Aedes albopictus</i> <sup>*19</sup>                                                                                                                                                                                                                                                                                                                            |
| <b><i>Annona purpurea</i></b>                                                                                                                                                                                                                                                                                                                                                                                |
| <i>Aedes egypti</i> <sup>*22</sup>                                                                                                                                                                                                                                                                                                                                                                           |
| <b><i>Annona squamosa</i></b>                                                                                                                                                                                                                                                                                                                                                                                |
| <i>Aedes aegypti</i> <sup>*23,24</sup> , <i>Blatella germanica</i> <sup>+12</sup> , <i>Drosophila melanogaster</i> <sup>*25</sup> , <i>Locusta migratoria</i> <sup>Φ23</sup> , <i>Myzus persicae</i> <sup>*26</sup> , <i>Phaedon cochleariae</i> <sup>*26</sup> , <i>Spodoptera frugiperda</i> <sup>*27</sup> , <i>Plutella xylostella</i> <sup>*26</sup> , <i>Tribolium castaneum</i> Herbst <sup>*28</sup> |

Orden: + Blattodea, • Coleoptera, \* Diptera, ♣ Hemiptera, Φ Orthoptera, ♦ Lepidoptera

<sup>1</sup>He *et al.* 1997, <sup>2</sup>González-Coloma *et al.* 2002, <sup>3</sup>Álvarez Colom *et al.* 2008, <sup>4</sup>Álvarez Colom *et al.* 2007, <sup>5</sup>Ohsawa *et al.* 1991, <sup>6</sup>Guadaño *et al.* 2000, <sup>7</sup>Álvarez Colom *et al.* 2010, <sup>8</sup>Luna-Cazáres *et al.* 2004, <sup>9</sup>Costa *et al.* 2016a, <sup>10</sup>Costa *et al.* 2018, <sup>11</sup>Costa *et al.* 2016b, <sup>12</sup>Alali *et al.* 1998, <sup>13</sup>Souza *et al.* 2016, <sup>14</sup>Makenzi *et al.* 2019, <sup>15</sup>Makenzi *et al.* 2020, <sup>16</sup>Ribeiro *et al.* 2020, <sup>17</sup>Di Toto Blessing *et al.* 2012, <sup>18</sup>Ansante *et al.* 2015, <sup>19</sup>Rodrigues *et al.* 2019, <sup>20</sup>Goh *et al.* 1995, <sup>21</sup>Domínguez-Martínez *et al.* 2003, <sup>22</sup>Cepleanu *et al.* 1993, <sup>23</sup>Londershausen *et al.* 1991, <sup>24</sup>Costa *et al.* 2014, <sup>25</sup>Kawazu *et al.* 1989, <sup>26</sup>Moeschler *et al.* 1987, <sup>27</sup>Ruiz Hidalgo *et al.* 2018, <sup>28</sup>Parvin *et al.* 2003.

armyworm, *S. frugiperda* (Álvarez Colom *et al.* 2007); as did laherradurin and rolliniastatin-2 (10 µg insect<sup>-1</sup>) in the Colorado potato beetle, *Leptinotarsa decemlineata* Say (González-Coloma *et al.* 2002); almuñequin, itrabin, and molvizarin (10 µg nymph<sup>-1</sup>) in the large milkweed bug, *Oncopeltus fasciatus* Dallas (Álvarez Colom *et al.* 2008). Likewise, motrilin showed toxicity against the yellow fever mosquito *Aedes aegypti*, with LC<sub>50</sub> of 4.7 mg L<sup>-1</sup>.

Although ACGs laherradurin, rolliniastatin-2, and squamocin did not cause death in cotton leafworm, *Spodoptera littoralis* Boisduval individuals at dose of 20 µg insect<sup>-1</sup>, they caused post-digestive effects that resulted in decrease in their biomass (González-Coloma *et al.* 2002).

***Annona glabra.*** Four ACGs isolated from the seeds of this species were evaluated on five insect species (Tables 1-3).

One of the most important contributions was that made by Ohsawa *et al.* (1991), who demonstrated that squamocin at concentration of 10 mg mL<sup>-1</sup> caused 100 % mortality in the Large cabbage-heart caterpillar, *Crocitolomia binotalis* Zeller and the 28-spotted potato ladybird, *Henosepilachna vigintioctopunctata* Fabricius; and at 5 µg insect<sup>-1</sup>, it caused 90 % mortality in the Azuki bean weevil, *Callosobruchus chinensis* L. At the same concentration, the population of this insect was also reduced by desacetylurvaricin and asimicin, causing 90 and 100 % mortality, respectively (Ohsawa *et al.* 1991).

Although squamocin is lethal in some insects, it can have deterrent and growth-inhibiting effects in others, such as those of the cabbage moth *Mamestra brassicae* L., the diamondback moth *Plutella xylostella* L., and *Crocidolomia binotalis* (Ohsawa *et al.* 1991).

***Annona macrophyllata*** (syn. *Annona diversifolia* Saff.). The only report evaluating an isolated ACG from this species is that conducted by Luna-Cazáres *et al.* (2004) ([Tables 1-3](#)), who evaluated the toxic activity of laherradurin,

**Table 3.** Secondary metabolites isolated from Mexican Annonaceae species with insecticidal activity.

| Compound                 | Insect                           | Doses                         | Potency          | Type of activity       | References                         |
|--------------------------|----------------------------------|-------------------------------|------------------|------------------------|------------------------------------|
| <i>Annona cherimolia</i> |                                  |                               |                  |                        |                                    |
| Almunequin               | <i>Oncopeltus fasciatus</i>      | 11.23 µg nymph <sup>-1</sup>  | LD <sub>50</sub> | Lethality              | Álvarez Colom <i>et al.</i> 2008   |
| Almunequin               | <i>Spodoptera frugiperda</i>     | 50 µg g <sup>-1</sup> of diet | 100 %            | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| Cherimolin-1             | <i>Spodoptera frugiperda</i>     | 50 µg g <sup>-1</sup> of diet | 100 %            | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| Itrabin                  | <i>Oncopeltus fasciatus</i>      | 14.91 µg nymph <sup>-1</sup>  | LD <sub>50</sub> | Lethality              | Álvarez Colom <i>et al.</i> 2008   |
| Itrabin                  | <i>Spodoptera frugiperda</i>     | 50 µg g <sup>-1</sup> of diet | 100 %            | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| Laherradurin             | <i>Leptinotarsa decemlineata</i> | 10 µg insect <sup>-1</sup>    | 97-100 %         | Lethality              | González-Coloma <i>et al.</i> 2002 |
| Laherradurin             | <i>Spodoptera littoralis</i>     | 20 µg insect <sup>-1</sup>    | 86 %             | Feeding reduction      | González-Coloma <i>et al.</i> 2002 |
| Laherradurin             | <i>Spodoptera littoralis</i>     | 20 µg insect <sup>-1</sup>    | 78 %             | Biomass gain reduction | González-Coloma <i>et al.</i> 2002 |
| Molvizarin               | <i>Oncopeltus fasciatus</i>      | 0.34 µg nymph <sup>-1</sup>   | LD <sub>50</sub> | Lethality              | Álvarez Colom <i>et al.</i> 2008   |
| Motrilin                 | <i>Aedes aegypti</i>             | 4.7 mg L <sup>-1</sup>        | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |
| Neoannonin               | <i>Spodoptera frugiperda</i>     | 50 µg g <sup>-1</sup> of diet | 100 %            | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| Rolliniastatin-2         | <i>Leptinotarsa decemlineata</i> | 2.3 µg cm <sup>2</sup>        | EC <sub>50</sub> | Antifeedant activity   | González-Coloma <i>et al.</i> 2002 |
| Rolliniastatin-2         | <i>Leptinotarsa decemlineata</i> | 10 µg insect <sup>-1</sup>    | 97-100 %         | Lethality              | González-Coloma <i>et al.</i> 2002 |
| Rolliniastatin-2         | <i>Spodoptera littoralis</i>     | 20 µg insect <sup>-1</sup>    | 56.2 %           | Biomass gain reduction | González-Coloma <i>et al.</i> 2002 |
| Squamocin                | <i>Leptinotarsa decemlineata</i> | 5 µg insect <sup>-1</sup>     | 92.18 %          | Lethality              | Guadaño <i>et al.</i> 2000         |
| Squamocin                | <i>Oncopeltus fasciatus</i>      | 0.16 µg nymph <sup>-1</sup>   | LD <sub>50</sub> | Lethality              | Álvarez Colom <i>et al.</i> 2008   |

Mexican Annonaceae with insecticidal metabolites

| Compound                    | Insect                                    | Doses                           | Potency          | Type of activity       | References                         |
|-----------------------------|-------------------------------------------|---------------------------------|------------------|------------------------|------------------------------------|
| Squamocin                   | <i>Spodoptera frugiperda</i>              | 50 µg g <sup>-1</sup> of diet   | 100 %            | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| Squamocin                   | <i>Spodoptera littoralis</i>              | 20 µg insect <sup>-1</sup>      | 64 %             | Feeding reduction      | González-Coloma <i>et al.</i> 2002 |
| Squamocin                   | <i>Spodoptera littoralis</i>              | 20 µg insect <sup>-1</sup>      | 53 %             | Biomass gain reduction | González-Coloma <i>et al.</i> 2002 |
| Tucumanin                   | <i>Spodoptera frugiperda</i>              | 50 µg g <sup>-1</sup> of diet   | 80 %             | Lethality              | Álvarez Colom <i>et al.</i> 2007   |
| <i>Annona glabra</i>        |                                           |                                 |                  |                        |                                    |
| Annonacin                   | <i>Leptinotarsa decemlineata</i>          | 100 µg cm <sup>2</sup>          | 93 %             | Feeding reduction      | Guadaño <i>et al.</i> 2000         |
| Annonacin                   | <i>Spodoptera littoralis</i>              | 20 µg insect <sup>-1</sup>      | 97 %             | Biomass gain reduction | González-Coloma <i>et al.</i> 2002 |
| Annonacin                   | <i>Spodoptera littoralis</i>              | 20 µg insect <sup>-1</sup>      | 86 %             | Feeding reduction      | González-Coloma <i>et al.</i> 2002 |
| Asimicin                    | <i>Callosobruchus chinensis</i>           | 0.5-1.0 µg insect <sup>-1</sup> | 60-85 %          | Lethality              | Ohsawa <i>et al.</i> 1991          |
| Asimicin                    | <i>Callosobruchus chinensis</i>           | 5.0 µg insect <sup>-1</sup>     | 100 %            | Lethality              | Ohsawa <i>et al.</i> 1991          |
| Desacetylurvaricin          | <i>Callosobruchus chinensis</i>           | 5.0 µg insect <sup>-1</sup>     | 90 %             | Lethality              | Ohsawa <i>et al.</i> 1991          |
| Squamocin                   | <i>Callosobruchus chinensis</i>           | 5.0 µg insect <sup>-1</sup>     | 90 %             | Lethality              | Ohsawa <i>et al.</i> 1991          |
| Squamocin                   | <i>Crocidolomia binotalis</i>             | 10 mg mL <sup>-1</sup>          | 100 %            | Lethality              | Ohsawa <i>et al.</i> 1991          |
| Squamocin                   | <i>Henosepilachna vigintioctopunctata</i> | 10 mg mL <sup>-1</sup>          | 100 %            | Lethality              | Ohsawa <i>et al.</i> 1991          |
| <i>Annona macrophyllata</i> |                                           |                                 |                  |                        |                                    |
| Laherradurin                | <i>Culex quinquefasciatus</i>             | 100-1000 mg mL <sup>-1</sup>    | 56.7 % 76.7 %    | Lethality              | Luna-Cazáres <i>et al.</i> 2004    |
| <i>Annona mucosa</i>        |                                           |                                 |                  |                        |                                    |
| 12-OH bullatacin A          | <i>Aedes aegypti</i>                      | 8.0 mg L <sup>-1</sup>          | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |
| cis-sylvaticin              | <i>Aedes aegypti</i>                      | 6.0 mg L <sup>-1</sup>          | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |
| Mucocin                     | <i>Aedes aegypti</i>                      | 2.1 mg L <sup>-1</sup>          | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |
| Muricatetrocin C            | <i>Aedes aegypti</i>                      | > 50 mg L <sup>-1</sup>         | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |
| Rollidecin A                | <i>Aedes aegypti</i>                      | 11.2 mg L <sup>-1</sup>         | LC <sub>50</sub> | Lethality              | He <i>et al.</i> 1997              |

| Compound                      | Insect                        | Doses                     | Potency          | Type of activity | References                          |
|-------------------------------|-------------------------------|---------------------------|------------------|------------------|-------------------------------------|
| Rollidecin B                  | <i>Aedes aegypti</i>          | > 50 mg L <sup>-1</sup>   | LC <sub>50</sub> | Lethality        | He <i>et al.</i> 1997               |
| Rollinecin A                  | <i>Aedes aegypti</i>          | > 50 mg L <sup>-1</sup>   | LC <sub>50</sub> | Lethality        | He <i>et al.</i> 1997               |
| Rollinecin B                  | <i>Aedes aegypti</i>          | > 50 mg L <sup>-1</sup>   | LC <sub>50</sub> | Lethality        | He <i>et al.</i> 1997               |
| Rolliniastatin-1              | <i>Helicoverpa armigera</i>   | 41.55 ppm                 | 100 %            | Lethality        | Souza <i>et al.</i> 2016            |
| Rolliniastatin-1              | <i>Helicoverpa armigera</i>   | 41.55 ppm                 | 92.50 %          | Lethality        | Souza <i>et al.</i> 2016            |
| Rolliniastatin-1              | <i>Helicoverpa armigera</i>   | 41.55 ppm                 | 61.25 %          | Lethality        | Souza <i>et al.</i> 2016            |
| Rolliniastatin-1              | <i>Sitophilus zeamais</i>     | 57.66 mg kg <sup>-1</sup> | 51 %             | Lethality        | Ribeiro <i>et al.</i> 2020          |
| Rolliniastatin-1              | <i>Spodoptera frugiperda</i>  | 100 ppm                   | 100 %            | Lethality        | Di Toto Blessing <i>et al.</i> 2012 |
| Rolliniastatin-1              | <i>Spodoptera frugiperda</i>  | 84.3 mg kg <sup>-1</sup>  | 88 %             | Lethality        | Ansante <i>et al.</i> 2015          |
| Rolliniastatin-2              | <i>Aedes aegypti</i>          | 0.10 mg L <sup>-1</sup>   | LC <sub>50</sub> | Lethality        | He <i>et al.</i> 1997               |
| Rollitacin                    | <i>Aedes aegypti</i>          | 4.7 mg L <sup>-1</sup>    | LC <sub>50</sub> | Lethality        | He <i>et al.</i> 1997               |
| Squamocin                     | <i>Aedes aegypti</i>          | 0.01 µg mL <sup>-1</sup>  | LC <sub>90</sub> | Cytotoxic action | Costa <i>et al.</i> 2016a           |
| Squamocin                     | <i>Aedes aegypti</i>          | 0.01 µg mL <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Costa <i>et al.</i> 2016b, 2018     |
| Squamocin                     | <i>Aedes aegypti</i>          | 0.11 µg mL <sup>-1</sup>  | LC <sub>90</sub> | Lethality        | Costa <i>et al.</i> 2016b           |
| Squamocin                     | <i>Anticarsia gemmatilis</i>  | 37.14 mg L <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Fiaz <i>et al.</i> 2018             |
| Squamocin                     | <i>Anticarsia gemmatilis</i>  | 155.57 mg L <sup>-1</sup> | LC <sub>75</sub> | Lethality        | Fiaz <i>et al.</i> 2018             |
| Squamocin                     | <i>Anticarsia gemmatilis</i>  | 83.14 mg L <sup>-1</sup>  | LC <sub>90</sub> | Lethality        | Fiaz <i>et al.</i> 2018             |
| Squamocin                     | <i>Anticarsia gemmatilis</i>  | 200.30 mg L <sup>-1</sup> | LC <sub>99</sub> | Lethality        | Fiaz <i>et al.</i> 2018             |
| Sylvaticin                    | <i>Blattella germanica</i>    | 1,000 ppm                 | 50 %             | Lethality        | Alali <i>et al.</i> 1998            |
| Quercetin 3-O-β-D-glucoside   | <i>Sitophilus zeamais</i>     | 20.9 µg mL <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Makenzi <i>et al.</i> 2019          |
| Quercetin 3-O-β-D-glucoside   | <i>Prostephanus truncatus</i> | 22.2 µg mL <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Makenzi <i>et al.</i> 2019          |
| Quercetin 3-O-α-D-arabinoside | <i>Sitophilus zeamais</i>     | 21.7 µg mL <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Makenzi <i>et al.</i> 2019          |
| Quercetin 3-O-α-D-arabinoside | <i>Prostephanus truncatus</i> | 24.9 µg mL <sup>-1</sup>  | LC <sub>50</sub> | Lethality        | Makenzi <i>et al.</i> 2019          |

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| Compound                                     | Insect                        | Doses                     | Potency           | Type of activity     | References                 |
|----------------------------------------------|-------------------------------|---------------------------|-------------------|----------------------|----------------------------|
| Kaempferol 3-O-β-D-galactoside               | <i>Sitophilus zeamais</i>     | 29.3 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2019 |
| Kaempferol 3-O-β-D-galactoside               | <i>Prostephanus truncatus</i> | 24.2 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2019 |
| Quercetin 3-O-β-D-glucoside                  | <i>Sitophilus zeamais</i>     | 14.9 µg mL <sup>-1</sup>  | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Quercetin 3-O-β-D-glucoside                  | <i>Prostephanus truncatus</i> | 16.8 µg mL <sup>-1</sup>  | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Quercetin 3-O-α-D-arabinoside                | <i>Sitophilus zeamais</i>     | 17.3 µg mL <sup>-1</sup>  | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Quercetin 3-O-α-D-arabinoside                | <i>Prostephanus truncatus</i> | 20 µg mL <sup>-1</sup>    | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Kaempferol 3-O-β-D-galactoside               | <i>Sitophilus zeamais</i>     | 21.6 µg mL <sup>-1</sup>  | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Kaempferol 3-O-β-D-galactoside               | <i>Prostephanus truncatus</i> | 20.2 µg mL <sup>-1</sup>  | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2019 |
| Quercetin                                    | <i>Sitophilus zeamais</i>     | 29.26 µg mL <sup>-1</sup> | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020 |
| Quercetin                                    | <i>Sitophilus zeamais</i>     | 22.20 µg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020 |
| Quercetin                                    | <i>Prostephanus truncatus</i> | 20.15 µg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020 |
| Quercetin                                    | <i>Prostephanus truncatus</i> | 24.51 µg mL <sup>-1</sup> | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020 |
| (3 R, 20S)-3-acetoxy-20-hydroxydammar-24-ene | <i>Sitophilus zeamais</i>     | »59 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020 |
| (3 R, 20S)-3-acetoxy-20-hydroxydammar-24-ene | <i>Prostephanus truncatus</i> | »65 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020 |
| 3-Oxo-11a-hydroxyurs-12-ene                  | <i>Sitophilus zeamais</i>     | »62 mg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020 |
| 3-Oxo-11a-hydroxyurs-12-ene                  | <i>Sitophilus zeamais</i>     | 57.76 mg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020 |

| Compound                     | Insect                        | Doses                     | Potency           | Type of activity     | References                   |
|------------------------------|-------------------------------|---------------------------|-------------------|----------------------|------------------------------|
| 3-Oxo-11a-hydroxyurs-12-ene  | <i>Prostephanus truncatus</i> | »68 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3-Oxo-11a-hydroxyurs-12-ene  | <i>Prostephanus truncatus</i> | 53.31 mg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020   |
| 3a, 24-diacetoxy-12-oleanane | <i>Sitophilus zeamais</i>     | »40 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3a, 24-diacetoxy-12-oleanane | <i>Sitophilus zeamais</i>     | 53.43 µg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020   |
| 3a, 24-diacetoxy-12-oleanane | <i>Prostephanus truncatus</i> | 42.07 µg mL <sup>-1</sup> | AFI <sub>50</sub> | Antifeedant activity | Makenzi <i>et al.</i> 2020   |
| 3a, 24-diacetoxy-12-oleanane | <i>Prostephanus truncatus</i> | »38 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3b-acetoxy-12-oleanene       | <i>Sitophilus zeamais</i>     | »98 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3b-acetoxy-12-oleanene       | <i>Prostephanus truncatus</i> | »100 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3b-acetoxyursolic acid       | <i>Sitophilus zeamais</i>     | »38 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| 3b-acetoxyursolic acid       | <i>Prostephanus truncatus</i> | »34 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| b-sitosterol                 | <i>Sitophilus zeamais</i>     | »105 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| b-sitosterol                 | <i>Prostephanus truncatus</i> | »110 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| Lupeol                       | <i>Sitophilus zeamais</i>     | »59 mg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| Lupeol                       | <i>Prostephanus truncatus</i> | »63 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| Oleanolic acid               | <i>Sitophilus zeamais</i>     | »38 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| Oleanolic acid               | <i>Prostephanus truncatus</i> | »42 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Makenzi <i>et al.</i> 2020   |
| <i>Annona muricata</i>       |                               |                           |                   |                      |                              |
| Annonacin                    | <i>Aedes aegypti</i>          | 2.65 µg mL <sup>-1</sup>  | LC <sub>50</sub>  | Lethality            | Rodrigues <i>et al.</i> 2019 |
| Annonacin                    | <i>Aedes aegypti</i>          | 4.83 µg mL <sup>-1</sup>  | LC <sub>90</sub>  | Lethality            | Rodrigues <i>et al.</i> 2019 |
| Annonacin                    | <i>Aedes aegypti</i>          | 9.5 µg mL <sup>-1</sup>   | LC <sub>50</sub>  | Lethality            | Goh <i>et al.</i> 1995       |

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| Compound                      | Insect                         | Doses                               | Potency           | Type of activity | References                            |
|-------------------------------|--------------------------------|-------------------------------------|-------------------|------------------|---------------------------------------|
| Annonacin                     | <i>Aedes aegypti</i>           | 60 µg g <sup>-1</sup>               | 100 %             | Lethality        | Domínguez-Martínez <i>et al.</i> 2003 |
| Annonacin                     | <i>Aedes aegypti</i>           | 3.0 mg L <sup>-1</sup>              | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Annonacin                     | <i>Aedes albopictus</i>        | 13.56 µg mL <sup>-1</sup>           | LC <sub>90</sub>  | Lethality        | Rodrigues <i>et al.</i> 2019          |
| Annonacin                     | <i>Aedes albopictus</i>        | 8.34 µg mL <sup>-1</sup>            | LC <sub>50</sub>  | Lethality        | Rodrigues <i>et al.</i> 2019          |
| Annonacin A                   | <i>Aedes aegypti</i>           | 10.8 mg L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Annopentocin A                | <i>Aedes aegypti</i>           | > 50 mg L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Annopentocin B                | <i>Aedes aegypti</i>           | > 50 mg×L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Annopentocin C                | <i>Aedes aegypti</i>           | > 50 mg L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| cis-gigantri-onenin           | <i>Aedes aegypti</i>           | 8.6 mg L <sup>-1</sup>              | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Muricatetrocin B              | <i>Aedes aegypti</i>           | 2.2 mg L <sup>-1</sup>              | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Murihexocin A                 | <i>Aedes aegypti</i>           | > 50 mg L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| Murihexocin B                 | <i>Aedes aegypti</i>           | > 50 mg L <sup>-1</sup>             | LC <sub>50</sub>  | Lethality        | He <i>et al.</i> 1997                 |
| <b><i>Annona purpurea</i></b> |                                |                                     |                   |                  |                                       |
| Rolliniastatin-1              | <i>Aedes egypti</i>            | 0.2 µg mL <sup>-1</sup>             | LC <sub>100</sub> | Lethality        | Cepleanu <i>et al.</i> 1993           |
| Bullatacin                    | <i>Aedes egypti</i>            | 0.3 µg mL <sup>-1</sup>             | LC <sub>100</sub> | Lethality        | Cepleanu <i>et al.</i> 1993           |
| Sylvaticin                    | <i>Aedes egypti</i>            | 1 µg mL <sup>-1</sup>               | LC <sub>100</sub> | Lethality        | Cepleanu <i>et al.</i> 1993           |
| Purpureacin-1 (cherimolin-2)  | <i>Aedes egypti</i>            | 2 µg mL <sup>-1</sup>               | LC <sub>100</sub> | Lethality        | Cepleanu <i>et al.</i> 1993           |
| Purpureacin-2                 | <i>Aedes egypti</i>            | 1 µg mL <sup>-1</sup>               | LC <sub>100</sub> | Lethality        | Cepleanu <i>et al.</i> 1993           |
| <b><i>Annona squamosa</i></b> |                                |                                     |                   |                  |                                       |
| Annonacin                     | <i>Aedes aegypti</i>           | 20 µg mL <sup>-1</sup>              | 65 %              | Lethality        | Londershausen <i>et al.</i> 1991      |
| Annonacin                     | <i>Drosophila melanogaster</i> | 62.5 µg·2g <sup>-1</sup> of diet    | LD <sub>50</sub>  | Lethality        | Kawazu <i>et al.</i> 1989             |
| Annonacin                     | <i>Drosophila melanogaster</i> | 125-250 µg·2g <sup>-1</sup> of diet | 50-60 %           | Lethality        | Kawazu <i>et al.</i> 1989             |
| Annonacin                     | <i>Locusta migratoria</i>      | 50 µg·g <sup>-1</sup> fresh weight  | 75 %              | Lethality        | Londershausen <i>et al.</i> 1991      |

| Compound         | Insect                                                          | Doses                                  | Potency          | Type of activity | References                          |
|------------------|-----------------------------------------------------------------|----------------------------------------|------------------|------------------|-------------------------------------|
| Annonin          | <i>Myzus persicae</i>                                           | 0.004 %                                | 100 %            | Lethality        | Moeschler <i>et al.</i> 1987        |
| Annonin          | <i>Phaedon cochleariae</i>                                      | 0.004 %                                | 100 %            | Lethality        | Moeschler <i>et al.</i> 1987        |
| Annonin          | <i>Plutella xylostella</i><br>(= <i>Plutella maculipennis</i> ) | 0.004 %                                | 100 %            | Lethality        | Moeschler <i>et al.</i> 1987        |
| Annotemoyin-1    | <i>Tribolium castaneum</i>                                      | 101.68-920.54 µg<br>cm <sup>-2</sup>   | LD <sub>50</sub> | Lethality        | Parvin <i>et al.</i> 2003           |
| Neoannonacin     | <i>Drosophila melanogaster</i>                                  | 62.5 µg 2g <sup>-1</sup> of diet       | LD <sub>50</sub> | Lethality        | Kawazu <i>et al.</i> 1989           |
| Neoannonacin     | <i>Drosophila melanogaster</i>                                  | 140-280 µg 2g <sup>-1</sup> of<br>diet | 50 %             | Lethality        | Kawazu <i>et al.</i> 1989           |
| Parviflorin      | <i>Blattella germanica</i>                                      | 1,000 ppm                              | 50 %             | Lethality        | Alali <i>et al.</i> 1998            |
| Rolliniastatin-2 | <i>Aedes aegypti</i>                                            | 20 µg mL <sup>-1</sup>                 | 65 %             | Lethality        | Londershausen<br><i>et al.</i> 1991 |
| Rolliniastatin-2 | <i>Locusta migratoria</i>                                       | 50 µg·g <sup>-1</sup> fresh<br>weigh   | 90 %             | Lethality        | Londershausen<br><i>et al.</i> 1991 |
| Squamocin        | <i>Aedes aegypti</i>                                            | 10 ppm                                 | 100 %            | Lethality        | Costa <i>et al.</i> 2014            |
| Squamocin        | <i>Aedes aegypti</i>                                            | 6.4 ppm                                | LC <sub>50</sub> | Lethality        | Costa <i>et al.</i> 2014            |
| Squamocin        | <i>Aedes aegypti</i>                                            | 20 µg mL <sup>-1</sup>                 | 100 %            | Lethality        | Londershausen<br><i>et al.</i> 1991 |
| Squamocin        | <i>Aedes aegypti</i>                                            | 20 ppm                                 | 100 %            | Lethality        | Costa <i>et al.</i> 2014            |
| Squamocin        | <i>Aedes aegypti</i>                                            | 20 µg mL <sup>-1</sup>                 | 50 %             | Lethality        | Londershausen<br><i>et al.</i> 1991 |
| Squamocin        | <i>Aedes aegypti</i>                                            | 50 ppm                                 | 100 %            | Lethality        | Costa <i>et al.</i> 2014            |
| Squamocin        | <i>Aedes aegypti</i>                                            | 80-100 ppm                             | 100 %            | Lethality        | Costa <i>et al.</i> 2014            |
| Squamocin        | <i>Locusta migratoria</i>                                       | 50 µg g <sup>-1</sup> fresh<br>weigh   | 100 %            | Lethality        | Londershausen<br><i>et al.</i> 1991 |

\*AFI<sub>50</sub>: Antifeedant activity 50\*LC<sub>100</sub>: Lethal Concentration 100\*LC<sub>50</sub>: Lethal Concentration 50\*LD<sub>50</sub>: Lethal Dose 50\*LC<sub>90</sub>: Lethal Concentration 90

the most abundant ACG in *A. macropophyllata* seeds (Durán-Ruiz *et al.* 2019), which caused mortality of 56.7 to 76.7 % of Southern house mosquito, *Culex quinquefasciatus* Say individuals at concentration of 100  $\mu\text{g mL}^{-1}$  and 1,000  $\mu\text{g mL}^{-1}$ . This species biosynthesizes one of the most toxic reported ACG, rolliniastatin-2.

***Annona mucosa.*** The toxic activity of 14 ACGs, eight terpenes, and four flavonoids from this species was evaluated on seven insect species (Tables 1-3).

Specifically, the insecticidal activity of ACGs was analyzed on six insects. Costa *et al.* (2016a, b, 2018) and Fiaz *et al.* (2018) observed the lethal effects of squamocin on the larvae of the *A. aegypti* and the velvetbean caterpillar, *Anticarsia gemmatilis* Hübner, among which they observed behavioral, morphological, and physiological changes. Treatments with squamocin caused mortality in mosquito larvae, which initially caused violent movements that gradually decreased until they remained rigid. Histological analyses showed damage to the digestive cells of both insects, which primarily included the loss of the original epithelial cell shape, elevated cytoplasmic vacuolization, evident damage to the cell surface with loss or disorganization of microvilli, autophagy, and cell death. Furthermore, vacuolization was also increased in the anal papilla of *A. aegypti*, causing cell disorganization and mitochondria loss (Costa *et al.* 2018).

The German cockroach, *Blattella germanica* L. is also susceptible to the action of bullatalicin, sylvaticin, gigantetrocin-A, and annomontacin, which, at concentration of 1,000 ppm, caused mortality in 50 % of individuals. An important fact to highlight is that these molecules present low risk of generating resistance, as demonstrated by analyses of susceptible and resistant cockroach strains (Alali *et al.* 1998).

There are few studies evaluating the insecticidal activity of secondary metabolites other than ACG, which shows the relevance of the work carried out by Makenzi *et al.* (2019, 2020). These authors reported the lethality and anti-feeding effects of terpenes and flavonoids isolated from *A. mucosa* leaves on two beetles that infect stored grains: the maize weevil, *Sitophilus zeamais* Motschulsky and the larger grain borer, *Prostephanus truncatus* Horn. Flavonoids quercetin, isoquercitrin (quercetin 3-O- $\beta$ -D-glucoside), quercetin 3-O- $\alpha$ -D-arabinoside, and kaempferol 3-O- $\beta$ -D-galactoside (trifolin) were toxic to both beetle species, with median lethal concentrations ( $\text{LC}_{50}$ ) ranging from 20.9  $\mu\text{g mL}^{-1}$  to 29.3  $\mu\text{g mL}^{-1}$ .

Terpenes, although not lethal, exerted anti-feeding activity on *S. zeamais* and *P. truncatus* at concentration of 500  $\text{mg mL}^{-1}$ . The most effective were oleanolic acid, (3R,20S)-3-acetoxy-20-hydroxydammar-24-ene and lupeol. However, flavonoid quercetin surpassed the toxicity of terpenes with mean anti-feeding activity (AFI50) of 22.20  $\mu\text{g mL}^{-1}$  for *S. zeamais* and 20.15  $\mu\text{g mL}^{-1}$  for *P. truncatus* (Makenzi *et al.* 2020).

***Annona muricata.*** This is one of the best-known and most economically and biotechnologically important species. Nine ACGs from *A. muricata* seeds have been evaluated on *A. aegypti* (Goh *et al.* 1995, He *et al.* 1997, Domínguez-Martínez *et al.* 2003, Rodrigues *et al.* 2019) (Tables 1-3). All ACGs caused mosquito larval mortality, with lethal concentrations ranging from 2.65  $\text{mg L}^{-1}$  to values above 50  $\text{mg L}^{-1}$ . Annonacin was toxic at lower concentrations with  $\text{LC}_{50}$  of 2.65  $\mu\text{g mL}^{-1}$ ; and this ACG also caused mortality of the Asian tiger mosquito, *Aedes albopictus* Skuse at  $\text{LC}_{50}$  of 8.34  $\mu\text{g mL}^{-1}$  (Rodrigues *et al.* 2019). Morphological damage caused by annonacin was documented by Domínguez-Martínez *et al.* (2003), who pointed out that larvae, pupae and adults, exposed to concentration of 60  $\mu\text{g mL}^{-1}$ , showed malformations and changes in organ function, for example, head deformations, changes in tissue pigmentation and serious damage to thorax, legs and sexual organs.

***Annona purpurea.*** The only contribution is that of Cepleanu *et al.* (1993), who isolated six ACGs from the leaves of this species (Table 1). They demonstrated that these compounds are toxic to *A. aegypti* larvae at very low concentrations, reaching up to 2  $\mu\text{g mL}^{-1}$ ; and rolliniastatin-1 and bullatalicin are the most toxic, with  $\text{LC}_{100}$  of 0.2  $\mu\text{g mL}^{-1}$  and 0.3  $\mu\text{g mL}^{-1}$ , respectively (Tables 2, 3).

***Annona squamosa.*** The insecticidal activity of seven ACGs was estimated on nine insect species (Tables 1-3). Annonin is one of the first ACGs patented as an insecticidal agent by Moeschler *et al.* (1987), which, at concentration

of 0.004 %, caused 100 % lethality of the green peach aphid, *Myzus persicae* Sulzer, the mustard beetle, *Phaedon cochleariae* Fabricius, and the diamondback moth, *Plutella xylostella*. Shortly thereafter, Kawazu *et al.* (1989) demonstrated the toxicity of annonacin and neoannonacin on different developmental stages of the fruit fly, *Drosophila melanogaster* Meigen, with LD<sub>50</sub> of 62.5 µg 2 g<sup>-1</sup> of diet.

One of the notable investigations was conducted by Costa *et al.* (2014), who recorded the cellular damage caused by squamocin in *A. aegypti* larvae, specifically in the midgut epithelial cells, in which concentration of 100 ppm caused high vacuolization, damage to the apical surface of tissues, and cell protrusion into the intestinal lumen. The same ACG also caused 100 % mortality in the migratory locust, *Locusta migratoria* L. at concentration of 50 µg g<sup>-1</sup> fresh weight (Londershausen *et al.* 1991).

Another study was conducted by Ruiz Hidalgo *et al.* (2018), who evaluated the effect of natural, acetylated (OAc), and methoxymethylated (MOM) ACGs from *A. squamosa* and *A. muricata* on *S. frugiperda*. Of these molecules, rolliniastatin-2 at concentration of 100 µg g<sup>-1</sup> of diet was the most toxic, causing 100 % larval mortality; rolliniastatin-2 (3 OAc) impaired larval growth, while rolliniastatin-2 (MOM) had strong anti-feeding effect. Furthermore, laherradurin (3 OAc) and itrabin (3 OAc) caused abdominal and wing deformities in adults, which led to the death of insects before they had the chance to produce offspring.

## Discussion

The study of the insecticidal activity of *Annona* species distributed in Mexico is incipient. Of the 70 species, belonging to 12 genera found in the country, the toxic activity of compounds isolated from only seven *Annona* species has been evaluated, which represents less than 0.3 % of the total *Annona* species worldwide and 10 % of species distributed in Mexico.

The most studied *Annona* species, such as *A. cherimolia* (cherimoya), *A. mucosa*, *A. muricata* (soursop), and *A. squamosa* (saramuyo), are plants whose nutritional, economic, medicinal, and/or biotechnological importance is well-established. However, there is little information about wild species widely distributed in Mexico, such as *A. macrophyllata* (papaya), *A. purpurea* (chincuya), and *A. reticulata* (red custard apple). Furthermore, no data have been reported on native Mexican species belonging to genera such as *Cymbopetalum*, *Desmopsis*, *Mosannonna*, *Oxandra*, *Sapranthus*, *Tridimeris*, *Stenanona*, *Unonopsis*, and *Xylopia* (De-la-Cruz-Chacón *et al.* 2016, Villaseñor 2016). Similarly, little is known about threatened species, such as *Desmopsis guerrensis* Gonz.-Martínez & J. Jiménez Ram., *Stenanona flagelliflora* T. Wendt & G.E. Schatz, and *Tridimeris huatuscoana* Marinero-Sobal & Ortiz-Rodr., which are listed as “Critically Endangered” on the International Union for Conservation of Nature Red List of Threatened Species (IUCN 2024). Conducting studies with other species, especially native and wild ones, could contribute to the understanding of the diversity of secondary metabolites in the Annonaceae family. This would not only enable the isolation of new organic compounds with biotechnological potential but would also help us better understand the role these compounds play in plants, thus strengthening arguments for the conservation of these species and where they occur.

Compounds have been primarily isolated from seeds and leaves, perhaps because they are easier to obtain. However, the use of seedlings, as demonstrated in the studies by González-Esquinca *et al.* (2014) and Riley-Saldaña *et al.* (2017), represents an alternative that would allow the study of all plant tissues.

This paper reports 46 ACGs with insecticidal activity, out of the more than 500 ACGs isolated to date. The insecticidal activity of ACGs is well documented, and their exclusivity within this family and distribution in all tissues, especially seeds, suggests that they have played an important role in plant defense mechanisms (Durán-Ruiz *et al.* 2024). Although some insects have adapted to the toxicity of these compounds, for example, the *Annona* seed wasp, *Bephratelloides cubensis* Ashmead completes almost its entire life cycle inside *A. macrophyllata* seeds, whose larvae feed on the acetogenic endosperm without causing toxic effects (Durán-Ruiz *et al.* 2019). Furthermore, the zebra swallowtail, *Protographium marcellus* Cramer (syn. *Eurytides marcellus* Cramer) stores ACGs asimicin, rolliniastatin-2, bullatalicin, and trilobacin, ingested from leaves, for protection against predators (Martin *et al.* 1999).

The toxic activity of Annonaceae has been evaluated in 21 insect species, including mosquitoes of the genus *Aedes*, especially *Aedes aegypti*. The effort to evaluate the insecticidal activity of plant compounds against mosquitoes responds to the need to find organic compounds that can control these organisms, which are responsible for thousands of deaths worldwide. For example, *A. aegypti* and *A. albopictus*, according to reports from early 2023, infected 6.5 million people with the dengue virus and caused more than 7,300 deaths (OMS 2024a, b); while *C. quinquefasciatus*, the transmitter of lymphatic filariasis (elephantiasis), infects millions of people. Although mortality rates from this disease are low, it causes enlargement in some areas of the body, pain, and disability (OMS 2023).

The best-known insect among crop pests belongs to the genus *Spodoptera*, among them, the corn armyworm, *S. frugiperda*, a crop pest that affects more than 80 cultivated species and can cause losses of up to 100 % in corn, rice, wheat, bean, sugarcane, and cotton crops, among others (SADER/SENASICA 2021, FAO 2022). Four Annonaceae species have been tested against this insect: *A. cherimolia*, *A. mucosa*, *A. muricata*, and *A. squamosa* (Table 3).

Studies on the insecticidal activity of Annonaceae have excluded forest pests, but their inclusion could contribute to combating these insects, thus promoting forest conservation or regeneration. Among the most important forest pests are the western conifer seed bug, *Leptoglossus occidentalis* Heidemann (Hemiptera), the bow-legged fir aphid, *Cinara curvipes* Patch (Homoptera), and bark beetles, *Dendroctonus adjunctus* Blandford, *Dendroctonus mexicanus* Hopkins, and *Dendroctonus frontalis* Zimmermann (Coleoptera) (SEMARNAT/CONAFOR s.f.).

The toxic activity of Annonaceae has been studied on a variety of insects, but to date, only one study has been reported on non-target organisms. Costa *et al.* (2016b) demonstrated that squamocin is toxic to *Aedes aegypti*; however, it did not show toxicity against its natural predators *Culex bigoti* Bellardi (sin. *Lutzia bigoti* Bellardi) and *Toxorhynchites theobaldi* Dyar & Knab (Diptera), even at concentrations up to 1,000 mg mL<sup>-1</sup>. Given the limited research on this topic, it is critical to expand the number of studies on compound toxicity on other organisms, such as pollinators, parasitoids, human cells, and/or *in vivo* studies, to determine or rule outside effects, determine safe doses, and ensure safety for the environment and organisms.

This review showed studies demonstrating the insecticidal activity of seven Annonaceae species found in Mexico, all belonging to the genus *Annona*. The isolated compounds provide an overview of the chemical diversity of Annonaceae species. Terpenes, flavonoids, and primarily ACGs are responsible for conferring insecticidal activity to plants (Figure 1). Annonaceae plants inhabiting Mexico are toxic to 21 insects, included in seven genera, which correspond to agricultural pests, stored food pests, urban pests, and disease vectors. This demonstrates that species of the Annonaceae family are a source of organic compounds with insecticidal potential against various insects and also demonstrates the scarcity of studies evaluating the insecticidal activity of the rest of the Annonaceae plants distributed in Mexico.

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