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Annonaceous acetogenins: A comparative analysis of insecticidal activity

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Abstract: The Annonaceae family besides its commercial value (*Annona cherimola*, *A. macroprophyllata*, *A. muricata*, A*. reticulata*, *A. purpurea*, *A. squamosa*, *Annona* x *atemoya*) also produces several active secondary metabolites. Among these metabolites, Annonaceous acetogenins which are exclusive in this family, are reported with insecticidal activity on various species of insects that are crop pests and disease vectors. This review systematizes what is reported in the scientific literature about them: aspects such as the plant species from which the acetogenins come, and the insecticidal potential using the comparative activity index; it also takes into account lethality, morphological, physiological, and behavioral changes, including deterrent and anti-feeding effects. Eighty-five annonaceous acetogenins are documented on thirty species of insects, as well as toxic activities at various stages of development, broad-spectrum, and differential. The studies on *Aedes aegypti* (Diptera) and *Spodoptera frugiperda* (Lepidoptera) and the activity of squamocin on fifteen species of insects stand out. Annonaceous acetogenins are toxic at low concentrations, considering evaluation standards and comparison with commercial insecticides, and are active at various stages of insect development. The low proportion of studied species of the Annonaceae means the opportunity to find molecules with this biological potential, and an argument for its conservation.

Keywords: Annonaceae, *Aedes aegypti*, *Spodoptera frugiperda*, squamocin, annonacin, asimicin.

Acetogeninas de Anonáceas: uma análise comparativa de sua atividade inseticida

Resumo: A família Annonaceae possui espécies frutícolas que, além do valor comercial (*Annona cherimola, A. macroprophyllata, A. muricata, A. reticulata, A. purpurea*, *A. squamosa* e *Annona x atemoya*), produzem diversos metabólitos especializados muito ativos. Dentre estes, relata-se o grupo das acetogeninas, que são moléculas específicas da família e que apresentam atividade inseticida em várias espécies de insetos, que são pragas de culturas e vetores de doenças. Esta revisão sistematiza o que é relatado na literatura científica sobre acetogeninas: tais como

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das espécies vegetais de onde provêm e seu potencial inseticida referido pelo índice comparativo de atividade; também leva em consideração a letalidade, as alterações morfológicas, fisiológicas e comportamentais, incluindo efeitos dissuasores e antialimentares. Oitenta e cinco acetogeninas anonáceas estão documentadas com atividades sobre trinta espécies de insetos, com atividades tóxicas em vários estágios de desenvolvimento, com amplo espectro de ação e de modo diferencial. Destacam-se os estudos sobre *Aedes aegypti* (Diptera) e *Spodoptera frugiperda* (Lepidoptera) e a atividade da acetogenina squamocina sobre quinze espécies de insetos. Acetogeninas anonáceas são tóxicas em baixas concentrações, considerando padrões de avaliação e comparação com inseticidas comerciais, e são ativas em vários estágios de desenvolvimento do inseto. A baixa proporção de espécies estudadas da família Annonaceae significa a oportunidade de encontrar muito mais moléculas com esse potencial biológico, e um argumento para sua conservação.

Termos para indexação: Annonaceae, *Aedes aegypti*, *Spodoptera frugiperda*, esquamocina, anonacina, asimicina.

Introduction

Over millions of years, herbivorous insects developed a series of behavioral and physiological mechanisms that allowed them to take advantage of plants as a food resource while evading their morphological and chemical protection (BRATTSTEN, 1988; WAR et al., 2012). With the emergence of crops, some insects proliferated, becoming pests that nowadays damage crops, totally or partially. In the search for new forms of control that are friendly to the environment, molecules with insecticidal activity have been detected from the secondary metabolism of plants that are not usually the target of pests. Among the most powerful are the so-called “annonaceous acetogenins”.

Annonaceous acetogenins (ACGs) are a group of secondary metabolites exclusive to the Annonaceae family. They are made of 35 to 37 carbon atoms, with a long alkyl chain that ends with a substituted methyl lactone ring, α, β unsaturated, saturated, or as a ketolactone. The alkyl chain can have double or triple bonds, oxygenated substituents such as ketones, hydroxyls, epoxides, tetrahydrofuran (THF), or tetrahydropyran (THP) rings (CAVÉ et al., 1997; LIAW et al., 2016).

Since its discovery, and because of the finding of the toxic and antiproliferative potential that accompanies these molecules (JOLAD et al., 1982), several investigations have focused on their search and the determination of their biological spectrum and pharmaceutical potential. Due to the vast information on the insecticidal activity of ACGs, in this paper is made a recount of the available data on the chemical structure and species from which these secondary metabolites have been isolated. Also, the insecticide potential on various insects, generally crop pests, and the activity of the ACGs in the stages of development are systematized and compared. Systematic and coordinated studies will allow for shortening the research times on the insecticidal capacity of these molecules.

Materials and Method

A retrospective bibliographic review was carried out, since January 2022, about the insecticidal activity reported in the literature about annonaceous acetogenins. The words used for the search were: secondary metabolites of annonaceous, annonaceous acetogenins, acetogenins, acetogenins toxicity, annonaceous toxicity, acetogenins activity, insecticidal activity of acetogenins, toxic metabolites, insecticidal activity of annonaceous, acetogenins insects, acetogenins against insects, acetogenins pests, ace-

togenins pesticides, pests of annonaceous, bioactive acetogenins, linear acetogenins, mono-tetrahydrofuran acetogenins, tetrahydrofuran acetogenins, lactone acetogenins, acetogenins action, acetogenins inhibitor, annonaceous extracts, acetogenins seeds, acetogenins leaves, acetogenins roots, acetogenins fruits, acetogenins plants, new acetogenins, novel acetogenins. Compound synonyms were also checked to avoid duplication in Cavé et al. (1997) and on the National Center for Biotechnology Information PubChem website (*https://pubchem.ncbi.nlm.nih.gov*). In addition, the names of the Annonaceae species in "Tropicos" of the Missouri Botanical Garden (*http://www.tropicos.org/*) were updated.

To compare and relativize the insecticidal activity between acetogenins, the amounts of ACGs used were converted to µmol, and the Comparative Activity Index (CAI) was calculated: CAI= % mortality/acetogenin concentration (µmol) (DE-LA-CRUZ-CHACÓN et al., 2020). The data was transformed to $\log_{10}$.

Results and discussion

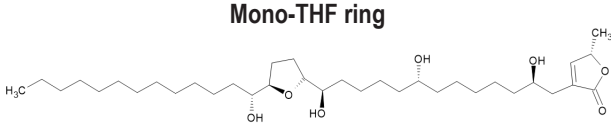
1. Chemical diversity of annonaceous acetogenins and their biological potential

The Annonaceae family comprises about 130 genera and more than 2,000 species. To date, many biological activity studies have been carried out with organic extracts obtained from 42 species of these plants, assessing their potential in controlling 60 species of insects (KRINSKI et al., 2014). There are reported 535 ACGs obtained from 16 genera and 59 species of plants (NESKE et al., 2020). Of these, 85 molecules with insecticidal activity are documented, 35 are of the mono-THF rings type structure, 30 are of the adjacent bis-THF rings type, six non-adjacent bis-THF rings, and one with non-adjacent THF-THP rings (Table 1).

There are also documented 13 acetogenins with chemical transformations (derivatives) (two mono-THF rings and 11 adjacent bis-THF rings), originally isolated from 11 species of the genus *Annona*, two from *Asimina*, one from *Disepalum*, and another from *Goniothalamus* (Table 2).

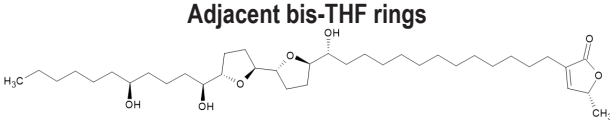
Table 1. Types of Annonaceae acetogenins with insecticidal activity.

Mono-THF ring



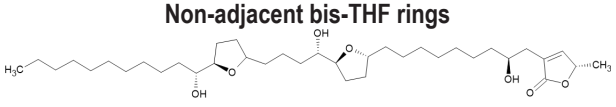
annomontacin	disepalin	montanacin D
annonacin	giganenin	montanacin E
annonacin-A	gigantetrocin A	montanacin K
annopentocin A	gigantetrocinone	montanacin L
annopentocin B	gigantetronenin	muricatetrocin B
annopentocin C	gigantetroneninone	muricatetrocin C
annoreticuin	gigantriocin	murihexocin A
annotemoyin-1	gigantrionenin	murihexocin B
cis-annonacin	goniothalamicin	rollinecin A
cis-annonacin-10-one	goniothalamicin B	rollinecin B
cis-gigantrionenin	longicoricin	tucupentol
densicomacin-1	longifolicin	

Adjacent bis-THF rings



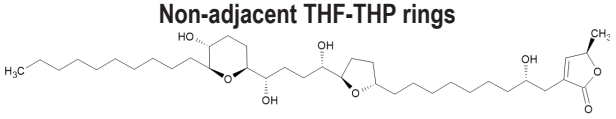
10-OH Asimicin	laherradurin	rollidecin B
12-OH Bullatacin A	longimicin B	rolliniastatin-1
12-OH Bullatacin B	longimicin C	rolliniastatin-2
annonin	longimicin D	rollinicin
asimicin	molvizarin	rollitacin
asiminacin	motrilin	squamocin
asiminecin	neoannonacin	trilobacin
bullatetrocin	neoannonin	trilobacinone
desacetyluvaricin	parviflorin	trilobin
itrabin	rollidecin A	tucumanin

Non-adjacent bis-THF rings



almunequin	cherimolin-2	
bullatalicin	cis-sylvaticin	
cherimolin-1	sylvaticin	

Non-adjacent THF-THP rings



mucocin

(to be continued)

Table 1. Types of Annonaceae acetogenins with insecticidal activity (Continuation).

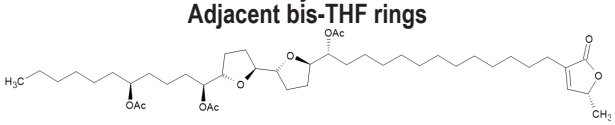
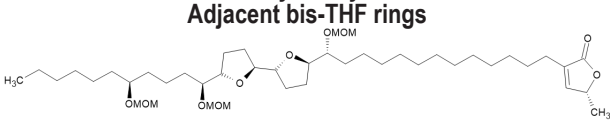
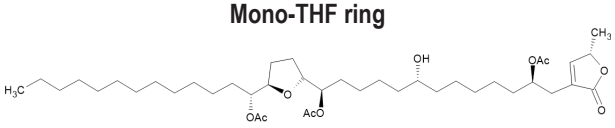
Derivatives		
Acetylated Adjacent bis-THF rings		**Methoxy methylated Adjacent bis-THF rings**
		
annonacin 4 OAc asimicin 3 OAc itrabin 3 OAc laherradurin 3 OAc	motrilin 3 OAc rolliniastatin-2 3 OAc squamocin 3 OAc xylomaticin 4 OAc	motrilin MOM rolliniastatin-2 MOM squamocin MOM
Mono-THF ring		
		
annonacin 3 OAc molvizarin 3 OAc		

Table 2. Acetogenins isolated from Annonaceae species.

Annona bullata	12-OH bullatacin B[21]; cherimolin-2[22]; rolliniastatin-2[21]
Annona cherimola	almunequin[3,4,5]; annonacin[13]; asimicin[3]; cherimolin-1[3,5]; cherimolin-2[3,5]; itrabin[3,4,5]; laherradurin[19]; molvizarin[4,5]; motrilin[3,21]; neoannonin[3]; rolliniastatin-2[19]; squamocin[3,4,5]; tucumanin[3,5]
Annona emarginata	desacetyluvaricin[39]; motrilin[39]; rolliniastatin-1[39]; rolliniastatin-2[29]; squamocin[40]; sylvaticin[40]
Annona glabra	annonacin[20]; asimicin[30]; desacetyluvaricin[30]; squamocin[30]
Annona macroprophyllata	laherradurin[26]
Annona montana	annonacin[4,11,12,13]; annonacin A[4]; cis-annonacin[35]; *cis*-annonacin-10-one[4,11]; densicomacin-1[4,11]; gigantetronenin[11]; itrabin[13]; montanacin D[36,37]; montanacin E[36,37]; montanacin K[36,37]; montanacin L[36,37]; murihexocin A[4]; murihexocin B[11]; rolliniastatin-1[12]; rolliniastatin-2[13]; tucupentol[11]
Annona mucosa	12-OH bullatacin-A[21]; annonacin[12]; cherimolin-1[1]; *cis*-sylvaticin[21]; mucocin[21]; muricatetrocin C[21]; rollidecin A[21]; rollidecin B[21]; rollinecin A[21]; rollinecin B[21]; rolliniastatin-1[6,12,14,22,38]; rolliniastatin-2[21]; rollinicin[33]; rollitacin[21]; squamocin[8,9,10,17]; sylvaticin[1]
Annona muricata	annonacin[15,21,18,32]; annonacin A[21]; annopentocin A[21]; annopentocin B[21]; annopentocin C[21]; *cis*-gigantrionenin[21]; muricatetrocin B[21]; murihexocin A[21]; murihexocin B[21]
Annona rensoniana	rolliniastatin-1[19]
Annona squamosa	almunequin[35]; annonacin[23,25]; annonin[29]; annotemoyin-1[31]; asiminacin[37]; asiminecin[37]; cherimolin-1[35]; cherimolin-2[35]; molvizarin[34]; motrilin[34]; neoannonacin[23]; parviflorin[1]; rolliniastatin-2[25]; squamocin[7,25,37]
Annona sylvatica	sylvaticin[21]
Asimina angustifolia	gigantetroneninone[21]; longicoricin[21]; longifolicin[21]; longimicin B[21]; longimicin C[21]; longimicin D[21]
Asimina triloba	10-OH asimicin[21,24,27,28]; asimicin[21]; asiminacin[21]; bullatetrocin[21]; gigantetrocinone[21]; trilobacin[21]; trilobacinone[21]; trilobin[21]
Disepalum anomalum	disepalin[16]
Goniothalamus giganteus	annomontacin[1]; annonacin[2]; giganenin[21]; gigantetrocin A[1]; gigantriocin[21]; gigantrionenin[21]; goniothalamicin[2]; goniothalamicin B[21]

[1]Alali et al.,1998; [2]Alkofahi et al., 1988; [3]Álvarez Colom et al., 2007; [4]Álvarez Colom et al., 2008; [5]Álvarez Colom et al., 2010; [6]Ansante et al., 2015; [7]Costa et al., 2014; [8]Costa et al., 2016a; [9]Costa et al., 2016b; [10]Costa et al., 2018; [11]Di Toto Blessing et al., 2010; [12]Di Toto Blessing et al., 2012; [13]Di Toto Blessing et al., 2015; [14]Ribeiro et al., 2020; [15]Domínguez-Martínez et al., 2003; [16]Ee et al., 1996; [17]Fiaz et al., 2018; [18]Goh et al., 1995; [19]González-Coloma et al., 2002; [20]Guadaño et al., 2000; [21]He et al., 1997; [22]Hui et al., 1989; [23]Kawazu et al., 1989; [24]Lewis et al., 1993; [25]Londershausen et al., 1991; [26]Luna-Cazáres et al., 2004; [27]Mikolajczak et al., 1988; [28]Mikolajczak et al., 1989; [29]Moeschler et al., 1987; [30]Ohsawa et al., 1991; [31]Parvin et al., 2003; [32]Rodrigues et al., 2019; [33]Rodrigues et al., 2021; [34]Ruiz Hidalgo et al., 2016; [35]Ruiz Hidalgo et al., 2018; [36]Ruiz Hidalgo et al., 2020; [37]Ruiz Hidalgo et al., 2021; [38]Souza et al., 2016; [39]Tolosa et al., 2012; [40]Tolosa et al., 2014.

The count indicates that 16 ACGs with some insecticidal activity have been isolated from *A. montana* and *A. mucosa* (formerly *Rollinia mucosa*), 14 from *A. squamosa*, 13 from *A. cherimola*, and nine from *A. muricata*; and from one to eight ACGs of the other species. Some ACGs are common, for example rolliniastatin-2 is in *A. bullata* (HUI et al., 1989), *A. cherimolia* (GONZÁLEZ-COLOMA et al., 2002), *A. emarginata* (TOLOSA et al., 2012), *A. montana* (DI TOTO BLESSING et al., 2015), *A. mucosa* (HE et al., 1997) and *A. squamosa* (LONDERSHAUSEN et al., 1991), or even in different genera such as the annonacin isolated from *Annona* species (ÁLVAREZ COLOM et al., 2008; DI TOTO BLESSING et al., 2010, 2012, 2015; DOMÍNGUEZ-MARTÍNEZ et al., 2003; GUADAÑO et al., 2000; HE et al. 1997; KAWAZU et al., 1989; LONDERSHAUSEN et al., 1991; RODRIGUES et al., 2019; RUIZ HIDALGO et al., 2018) and *Goniothalamus* (GOH et al., 1995). These rather circumstantial findings imply conserved biosynthetic pathways that suggest a genetic and or evolutionary closeness.

Secondary metabolites generally have an organ-specific distribution (GONZÁLEZ-ESQUINCA et al., 2014; RILEY-SALDAÑA et al., 2017). In the case of ACGs, its largest presence is in the oily endosperm of its seeds (LIAW et al., 2016). This fact indicates that is preferable the search for ACGs that does not imply the destruction of the plants, but rather obtaining them directly from seeds. Other acetogenins are also isolated from stems, leaves, and branches.

The insecticidal activity of ACGs has been evaluated in 30 species of insects, 24 of them are crop pests, five disease vectors, and one of them is considered an urban pest. These insects are distributed in seven orders, especially between Coleoptera and Lepidoptera (Table 3).

Table 3. Insect pests and disease vectors.

	Order	Specie	Stage
Crop pest	Coleoptera	*Acalymma vittatum*[27]	L
		Callosobruchus chinensis[30]	A
		Diabrotica undecimpunctata howardii[22]	A
		Epilachna varivestis[27,28]	L
		Henosepilachna vigintioctopunctata[30]	L
		Leptinotarsa decemlineata[19,20]	A
		Phaedon cochleariae[29]	A
		Sitophilus zeamais[14]	A
		Tribolium castaneum[31]	A/L
	Hemiptera	*Aphis gossypii*[22,27,28]	A
		Myzus persicae[20,29]	A
		Nephotettix cincticeps[30]	N
		Oncopeltus fasciatus[4]	N/A
	Lepidoptera	*Anticarsia gemmatalis*[17]	L
		Crocidolomia binotalis[30]	L
		Helicoverpa armigera[38]	L
		Mamestra brassicae[30]	L
		Ostrinia nubilalis[24]	M
		Plutella xylostella[29,30]	L
		Spodoptera frugiperda[3,7,11,12,13,34,35,36,37,39,40]	L/P/A
		Spodoptera littoralis[3,19]	L

(to be continued)

Table 3. Insect pests and disease vectors (Continuation).

	Order	Specie	Stage
Crop pest	Diptera	*Ceratitis capitata*[5]	L/A
		Drosophila melanogaster[23]	E/L/A
	Orthoptera	*Locusta migratoria*[25]	A
Disease vectors	Diptera	*Aedes aegypti*[2,7,8,9,10,15,16,18,21,22,25,27,28,32,33]	L/P
		Aedes albopictus[32,33]	L
		Calliphora vicina[2,27,28]	L
		Culex pipiens quinquefasciatus[26]	L
		Lucilia cuprina[25]	A
Urban pests	Blattodea	*Blatella germanica*[1]	N

Stage: E=eggs; L=larvae; P=pupae; A=adults; N=nymphs.
[1]Alali et al., 1998; [2]Alkofahi et al., 1988; [3]Álvarez Colom et al., 2007; [4]Álvarez Colom et al., 2008; [5]Álvarez Colom et al., 2010; [6]Ansante et al., 2015; [7]Costa et al., 2014; [8]Costa et al., 2016a; [9]Costa et al., 2016b; [10]Costa et al., 2018; [11]Di Toto Blessing et al., 2010; [12]Di Toto Blessing et al., 2012; [13]Di Toto Blessing et al., 2015; [14]Ribeiro et al., 2020; [15]Domínguez-Martínez et al., 2003; [16]Ee et al., 1996; [17]Fiaz et al., 2018; [18]Goh et al., 1995; [19]González-Coloma et al., 2002; [20]Guadaño et al., 2000; [21]He et al., 1997; [22]Hui et al., 1989; [23]Kawazu et al., 1989; [24]Lewis et al., 1993; [25]Londershausen et al., 1991; [26]Luna-Cazáres et al., 2004; [27]Mikolajczak et al., 1988; [28]Mikolajczak et al., 1989; [29]Moeschler et al., 1987; [30]Ohsawa et al., 1991; [31]Parvin et al., 2003; [32]Rodrigues et al., 2019; [33]Rodrigues et al., 2021; [34]Ruiz Hidalgo et al., 2016; [35]Ruiz Hidalgo et al., 2018; [36]Ruiz Hidalgo et al., 2020; [37]Ruiz Hidalgo et al., 2021; [38]Souza et al., 2016; [39]Tolosa et al., 2012; [40]Tolosa et al., 2014.

Most of the reports refer to the control of *Aedes aegypti* (48 ACGs) and *Spodoptera frugiperda* (42 ACGs), species that cause significant damage to sectors of the world population. For example, *S. frugiperda*, also known as the fall armyworm, threatens food security by being a pest of more than 80 species of crops, such as corn, wheat, rice, sugar cane, and cotton (FAO, 2022); and *A. aegypti* is a transmitter of diseases such as yellow fever, Zika, chikungunya, and dengue (KRAEMER et al., 2019; WHO, 2022).

Of the 85 acetogenins reported with insecticidal activity, those with the widest spectrum of activity are squamocin on 15 species of insects, followed by asimicin in nine, annonacin in eight, and rolliniastatin-1 and rolliniastatin-2 in seven species (Table 4). These data may be related to their abundance in some Annonaceae, their relative easy extraction, their high toxicity, or also the fact that they were among the first isolated acetogenins (1986-1989) (FUJITOMO et al., 1988; HUI et al., 1989; PETTIT et al., 1987, 1989; RUPPRECHT et al., 1986).

Table 4. Annonaceae acetogenins vs insects.

Acetogenins	Insects
10-OH Asimicin	
12-OH Bullatacin A	*Aedes aegypti*[21]
12-OH Bullatacin B	
almunequin	*Ceratitis capitata*[5]; *Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[3,35]
annomontacin	*Blatella germanica*[1]
annonacin	*Aedes aegypti*[2,15,18,25,32]; *Aedes albopictus*[32]; *Calliphora vicina*[2]; *Drosophila melanogaster*[23]; *Leptinotarsa decemlineata*[20]; *Locusta migratoria*[25]; *Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[11,12,13,35,37]
annonacin 3 OAc	*Spodoptera frugiperda*[13,35]
annonacin 4 OAc	*Aedes aegypti*[21] *Spodoptera frugiperda*[13,35]
annonacin A	*Aedes aegypti*[21]; *Oncopeltus fasciatus*[4]

(to be continued)

Table 4. Annonaceae acetogenins vs insects (Continuation).

Acetogenins	Insects
annonin	*Myzus persicae*[29]; *Phaedon cochleariae*[29]; *Plutella xylostella*[29]
annopentocin A	*Aedes aegypti*[21]
annopentocin B	
annopentocin C	
annoreticuin	*Spodoptera frugiperda*[37]
annotemoyin-1	*Tribolium castaneum*[31]
asimicin	*Acalymma vittatum*[27,28]; *Aedes aegypti* [21,27,28]; *Aphis gossypii* [27,28]; *Blatella germanica*[1]; *Calliphora vicina*[27,28] ; *Callosobruchus chinensis*[30]; *Epilachna varivestis*[27,28]; *Ostrinia nubilalis*[24]; *Spodoptera frugiperda*[3,35]
asimicin 3 OAc	*Spodoptera frugiperda*[35]
asiminacin	*Aedes aegypti*[21]; *Spodoptera frugiperda*[37]
asiminecin	*Spodoptera frugiperda*[37]
bullatetrocin	*Aedes aegypti*[21]
cherimolin-1	*Aedes aegypti*[21]; *Blatella germanica*[1]; *Ceratitis capitata*[5]; *Spodoptera frugiperda*[3,35]
cherimolin-2	*Ceratitis capitata*[5]; *Spodoptera frugiperda*[3,35]
cis-annonacin	*Spodoptera frugiperda*[35,37]
cis-annonacin-10-one	*Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[11,35]
cis-gigantrionenin	*Aedes aegypti*[21]
cis-sylvaticin	
densicomacin-1	*Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[11]
desacetyluvaricin	*Callosobruchus chinensis*[30]; *Spodoptera frugiperda*[39]
disepalin	*Aedes aegypti*[16]
giganenin	*Aedes aegypti*[21]
gigantetrocin A	*Aedes aegypti*[21]; *Blatella germanica*[1]
gigantetrocinone	*Aedes aegypti*[21]
gigantetronenin	*Spodoptera frugiperda*[11]
gigantetroneninone	*Aedes aegypti*[21]
gigantriocin	
gigantetronenin	
goniothalamicin	*Calliphora sp.* [2]
goniothalamicin B	*Aedes aegypti*[21]
itrabin	*Ceratitis capitata*[5]; *Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[3,13,35]
itrabin 3 OAc	*Spodoptera frugiperda*[13,35]
itrabin 3 MOM	*Spodoptera frugiperda*[13]
laherradurin	*Culex pipiens quinquefasciatus*[26]; *Leptinotarsa decemlineta*[19]; *Spodoptera frugiperda*[35]
laherradurin 3 OAc	*Spodoptera frugiperda*[35]
longicoricin	*Aedes aegypti*[21]
longifolicin	
longimicin B	
longimicin C	*Aedes aegypti*[21]
longimicin D	
molvizarin	*Ceratitis capitata*[5]; *Oncopeltus fasciatus*[4]; *Spodoptera frugiperda*[34]
molvizarin 3 OAc	*Spodoptera frugiperda*[34]
montanacin D	*Spodoptera frugiperda*[36]
montanacin E	
montanacin K	
montanacin L	
motrilin	*Aedes aegypti*[21]; *Spodoptera frugiperda*[3,34,39]
motrilin 3 OAc	*Spodoptera frugiperda*[34]
motrilin MOM	

(to be continued)

Table 4. Annonaceae acetogenins vs insects (Continuation).

Acetogenins	Insects
mucocin	
muricatetrocin B	*Aedes aegypti*[21]
muricatetrocin C	
murihexocin A	*Aedes aegypti*[21]; *Oncopeltus fasciatus*
murihexocin B	*Aedes aegypti*[21]; *Spodoptera frugiperda*[11]
neoannonacin	*Drosophila melanogaster*[23]
neoannonin	*Spodoptera frugiperda*[3]
parviflorin	*Blatella germanica*[1]
rollidecin A	
rollidecin B	*Aedes aegypti*[21]
rollinecin A	
rollinecin B	
rolliniastatin-1	*Aedes aegypti*[33]; *Aedes albopictus*[32]; *Helicoverpa armigera*[38]; *Leptinotarsa decemlineata*[19]; *Sitophilus zeamais*[14]; *Spodoptera frugiperda*[6,12,39]; *Spodoptera littoralis*[19]
rolliniastatin-2	*Aedes aegypti*[29]; *Aphis gossypii*[22]; *Diabrotica undecimpunctata howardi*[22]; *Leptinotarsa decemlineata*[19]; *Locusta migratoria*[25]; *Spodoptera frugiperda*[13,35,37,39]; *Spodoptera littoralis*[19]; *Lucilia cuprina*[25]
rolliniastatin-2 3OAc	*Spodoptera frugiperda*[13,35]
rolliniastatin-2 MOM	*Spodoptera frugiperda*[35]
rollinicin	*Aedes aegypti*[33]; *Aedes albopictus*[33]
rollitacin	*Aedes aegypti*[21]
squamocin	*Aedes aegypti*[7,8,9,10,25]; *Anticarsia gemmatalis*[17]; *Callosobruchus chinensis*[30]; *Ceratitis capitata*[5]; *Crocidolomia binotalis*[30]; *Henosepilachna vigintioctopunctata*[30]; *Leptinotarsa decemlineata*[20]; *Locusta migratoria*[25]; *Mamestra brassicae*[30]; *Myzus persicae*[20]; *Nephotettix cincticeps*[30]; *Oncopeltus fasciatus*[4]; *Plutella xylostella*[30]; *Spodoptera frugiperda*[3,34,37,40]; *Spodoptera littoralis*
squamocin 3 OAc	*Spodoptera frugiperda*[34,37]
squamocin MOM	
sylvaticin	*Aedes aegypti*[21]; *Blatella germanica*[1]; *Spodoptera frugiperda*[39]
trilobacin	
trilobacinone	*Aedes aegypti*[21]
trilobin	
tucumanin	*Ceratitis capitata*[5]; *Spodoptera frugiperda*[3]
tucupentol	*Spodoptera frugiperda*[11]
xylomaticin 4 OAc	*Aedes aegypti*[21]

[1]Alali et al., 1998; [2]Alkofahi et al., 1988; [3]Álvarez-Colom et al., 2007; [4]Álvarez-Colom et al., 2008; [5]Álvarez-Colom et al., 2010; [6]Ansante et al., 2015; [7]Costa et al., 2014; [8]Costa et al., 2016a; [9]Costa et al., 2016b; [10]Costa et al., 2018; [11]Di Toto Blessing et al., 2010; [12]Di Toto Blessing et al., 2012; [13]Di Toto Blessing et al., 2015; [14]Ribeiro et al., 2020; [15]Domínguez-Martínez et al., 2003; [16]Ee et al., 1996; [17]Fiaz et al., 2018; [18]Goh et al., 1995; [19]González-Coloma et al., 2002; [20]Guadaño et al., 2000; [21]He et al., 1997; [22]Hui et al., 1989; [23]Kawazu et al., 1989; [24]Lewis et al., 1993; [25]Londershausen et al., 1991; [26]Luna-Cazáres et al., 2004; [27]Mikolajczak et al., 1988; [28]Mikolajczak et al., 1989; [29]Moeschler et al., 1987; [30]Ohsawa et al., 1991; [31]Parvin et al., 2003; [32]Rodrigues et al., 2019; [33]Rodrigues et al., 2021; [34]Ruiz Hidalgo et al., 2016; [35]Ruiz Hidalgo et al., 2018; [36]Ruiz Hidalgo et al., 2020; [37]Ruiz Hidalgo et al., 2021; [38]Souza et al., 2016; [39]Tolosa et al., 2012; [40]Tolosa et al., 2014.

In the search for targets of insecticidal activity, the tests were carried out at various stages of the development of the insects, including eggs (1%), larvae (54%), pupae (10%), and or adults (23%) to holometabolous insects, and nymphs (7%) and or adults (5%) for hemimetabolous organisms. For example, squamocin activity is reported in larvae, adults, nymphs, and pupae (eight, five, two, one studies, respectively) (ÁLVAREZ COLOM et al., 2007, 2008, 2010; COSTA et al., 2014, 2016a, 2016b, 2018; FIAZ et al., 2018; GUADAÑO et al., 2000; LONDERSHAUSEN et al., 1991; OHSAWA et al., 1991; RUIZ HIDALGO et al., 2016, 2021; TOLOSA et al., 2014). Most of the experiments are oriented toward the larvae (Figure

1). The analyzes of the insecticidal activity of the ACGs are carried out using routes of administration topically, by ingestion or injection (ÁLVAREZ COLOM et al., 2008; ANSANTE et al., 2015; OHSAWA et al., 1991). Any variant of the chemo application is toxic.

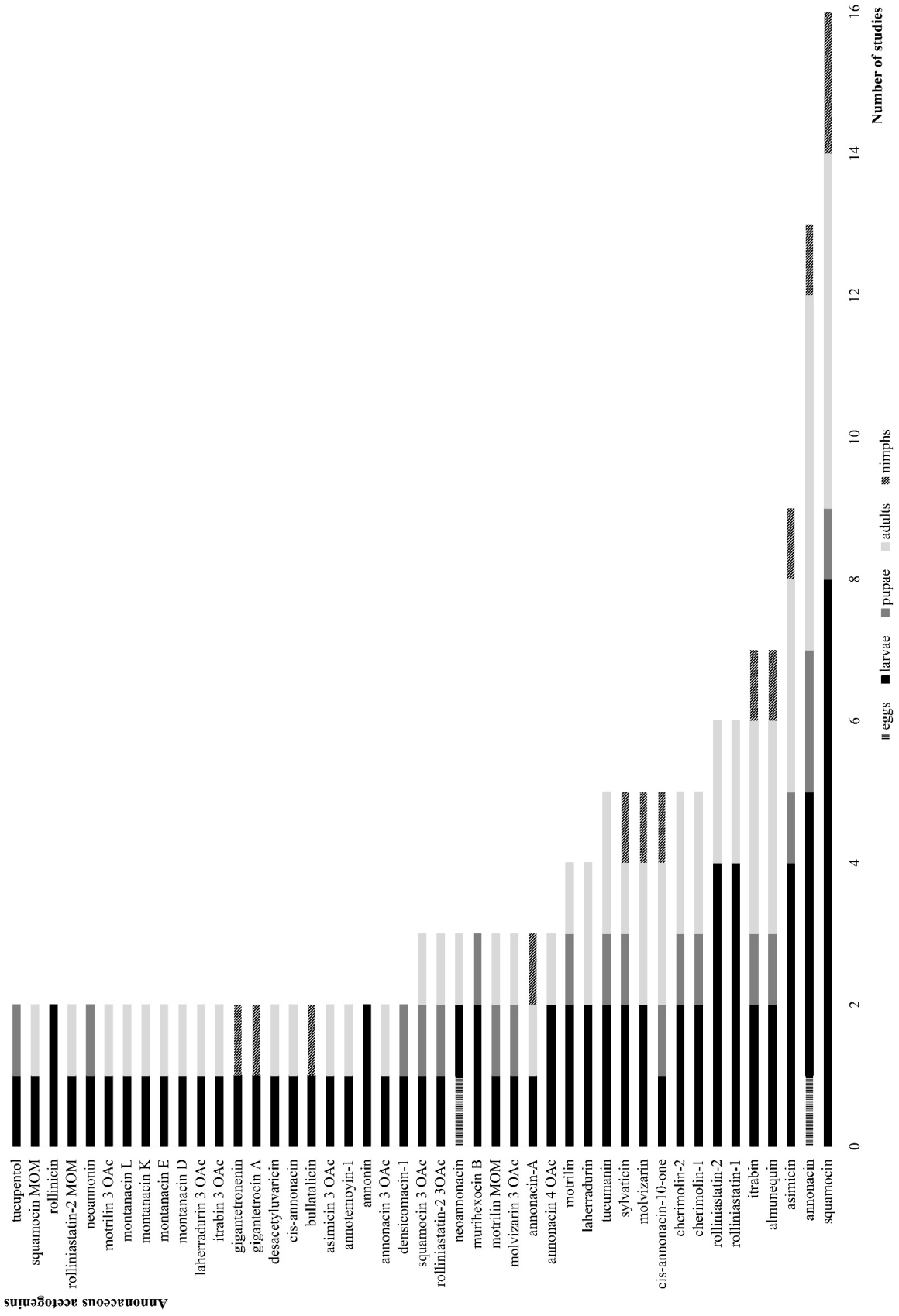


Figure 1 - Annonaceae acetogenins against insect development stages.

2. Comparative analysis of the potency and spectrum of ACGs

Consumption or exposure to ACGs causes behavioral, morphological, and or physiological changes in insects, although they can also be toxic and cause death, depending on the molecule, concentration, exposure time, insect, and stage of development (ÁLVAREZ COLOM et al., 2007; DI TOTO BLESSING et al., 2010. 2015; HE et al., 1997; KAWAZU et al., 1989; RUIZ HIDALGO et al., 2016, 2018, 2021). In this section, the ACGs are grouped and documented with an effect equal to or greater than 50% in [1.] Lethality and [2.] Morphological, physiological, and behavioral changes, including the deterrent and anti-feeding effects of the ACGs. For this, is used the Comparative Activity Index (CAI).

3. Lethality

According to the Comparative Activity Index (CAI), the most toxic acetogenin is squamocin (adjacent bis-THF rings), on the midgut model of *A. aegypti* larvae (COSTA et al., 2016a) with a CAI of 6.75. This molecule shows low CAI with various insect species and developmental stages (ÁLVAREZ COLOM et al., 2007, 2008, 2010; COSTA et al., 2014, 2016a, 2016b, 2018; FIAZ et al., 2018; GUADAÑO et al., 2000; LONDERSHAUSEN et al., 1991; OHSAWA et al., 1991; RUIZ HIDALGO et al., 2016; TOLOSA et al., 2014).

An example of the broad spectrum of acetogenins is documented in the asimicin acetogenin (adjacent bis-THF rings), which has larvicidal activity on several insects, such as *Acalymma vittatum*, *Epilachna varivestis* (MIKOLAJCZAK et al., 1988, 1989), *Callosobruchus chinensis* (Coleoptera) (OHSAWA et al., 1991), *A. aegypti*, *Calliphora vicina* (Diptera) (HE et al., 1997; MIKOLAJCZAK et al., 1988), *Aphis gossypii* (Hemiptera) (MIKOLAJCZAK et al., 1988), *Blatella germanica* (Blattodea) (ALALI et al., 1998), *Ostrinia nubilalis* (LEWIS et al., 1993) and *S. frugiperda* (Lepidoptera) (ÁLVAREZ COLOM et al., 2007; RUIZ HIDALGO et al., 2018). Likewise, the squamocin acetogenin has toxic activity on the dipterous *A. aegypti* (COSTA et al., 2014, 2016a; LONDERSHAUSEN et al., 1991), the Lepidoptera *Anticarsia gemmatalis* (FIAZ et al., 2018), *S. frugiperda* (ÁLVAREZ COLOM et al., 2007; RUIZ HIDALGO et al., 2016, 2021; TOLOSA et al., 2014), *Crocidolomia binotalis* and *Plutella xylostella* (OHSAWA et al., 1991), the beetles *C. chinensis*, *Henosepilachna vigintioctopunctata* (OHSAWA et al., 1991), *Leptinotarsa decemlineata* (GUADAÑO et al., 2000), the Hemiptera *Oncopeltus fasciatus* (ÁLVAREZ COLOM et al., 2008), and *Nephotettix cincticeps* (OHSAWA et al., 1991), and the orthopteran *Locusta migratoria* (LONDERSHAUSEN et al., 1991).

Surveys show that the toxicity of acetogenins is also different between organisms and stages of development, however, the comparison of potency reveals the absence of standardized tests that give certainty of the toxicity of the ACGs. For example, with the same concentration on *S. frugiperda* larvae, annonacin (ACG mono THF) is reported with mortality rates of 5% (CAI 1.47) (RUIZ HIDALGO et al., 2018), 50% (CAI 2.47) (DI TOTO BLESSING et al., 2010) and 70% (CAI 2.62) (DI TOTO BLESSING et al., 2012, 2015). Other ACGs, including semi-synthetic ones, with variations in their potency on this insect, are annonacin 3 OAc 5% (CAI 1.56) (RUIZ HIDALGO et al., 2018) or 75% (CAI 2.73) (DI TOTO BLESSING et al., 2015), annonacin 4 OAc 10% (CAI 1.88) (RUIZ HIDALGO et al., 2018) or 60% (CAI 2.66), itrabin 5% (CAI 1.47) (DI TOTO BLESSING et al., 2015) or 45% (CAI 2.43) (RUIZ HIDALGO et al., 2018), itrabin 3 OAc 10% (CAI 1.86) (DI TOTO BLESSING et al., 2015) or 65% (CAI 2.67) (RUIZ HIDALGO et al., 2018) rolliniastatin-2 5% (CAI 1.49) (DI TOTO BLESSING et al., 2015) or 100% (CAI 2.79) (RUIZ HIDALGO et al., 2018; TOLOSA et al., 2012).

It is also evident that the response of insects to ACGs is variable so that at the same con-

centration, a compound can be more or less active. For example, annonacin causes 70% mortality in *A. aegypti* (CAI 3.62) (ALKOFAHI et al., 1988) and only 23% in *O. fasciatus* (CAI 3.14) (ÁLVAREZ COLOM et al., 2008), while asimicin shows 85% activity (CAI 2.72) on *S. frugiperda* (RUIZ HIDALGO et al., 2018), 100% (CAI 2.79) on *Aedes aegypti* (Diptera) and *E. varivestis* (Coleoptera) and 20% for *A. gossypii* (CAI 2.09) (MIKOLAJCZAK et al., 1988, 1989); squamocin, shows 30% (CAI 2.27) activity on *M. persicae* (Hemiptera) (GUADAÑO et al., 2000), 100% for *A. egypti* (CAI 2.79) (COSTA et al., 2014) and for *S. frugiperda* (CAI 2.79) (RUIZ HIDALGO et al., 2016; TOLOSA et al., 2014).

ACGs can affect various stages of development of insects causing up to 100% mortality of eggs, larvae, pupae, nymphs, and adults. Most of the data refer to Diptera larvae (*A. aegypti*, *A. albopictus*, *C. vicina*, *Culex pipiens quinquefasciatus*, *Drosophila melanogaster*); Lepidoptera (*A. gemmatalis*, *C. binotalis*, *Helicoverpa armigera*, *S. frugiperda, P. xylostella*) and Coleoptera (*E. varivestis*, *Diabrotica undecimpunctata howardii*, *Phaedon cochleariae* and *Tribolium castaneum*). In the pupae, mortality seems to be caused as a result of malformations. In the adult phase, there are many reports of coleopteorous causing damage to stored seeds, for example, *L. decemlineata* is susceptible to the ACGs laherradurin, rolliniastatin-1, and rolliniastatin-2 (GONZÁLEZ-COLOMA et al., 2002); O*. fasciatus* to the ACGs almuñequin and itrabin (ÁLVAREZ COLOM et al., 2008) and *C. chinensis* to asimicin (OHSAWA et al., 1991) and, at this stage of development, also squamocin on the orthoptera *L. migratoria* (LONDERSHAUSEN et al., 1991). *B. germanica* nymphs are highly sensitive to the acetogenins annomontacin, cherimolin-1, gigantetrocin-A, asimicin, parviflorin, and sylvaticin (100% mortality at different times 6-34 days) (ALALI et al., 1998); and the nymphs of the Hemiptera *N. cincticeps* squamocin cause 100% mortality (OHSAWA et al., 1991). Eggs are also vulnerable to the toxic activity of ACGs, for example, neoannonacin and annonacin can cause 50% and 100% of *D. melanogaster* egg mortality (KAWAZU et al., 1989). In *S. frugiperda*, ACGs cause damage due to toxicity or malformations in larvae, pupae, and adults (ÁLVAREZ COLOM et al., 2007, 2008; DI TOTO BLESSING et al., 2010, 2015; RUIZ HIDALGO et al., 2016, 2018, 2020; TOLOSA et al., 2012).

4. Morphological, physiological, and behavioral changes

The ACGs also cause malformations in larvae, pupae, and adults of insects, which even when they survive its toxicity end up dying due to deformations in the head, thorax, and abdomen. In *A. aegypti* larvae, annonacin at 0.1007 $\mu mol \cdot g^{-1}$ (CAI 3.0), induced changes in the opening of the anal papilla, and head deformations, as well as changes in pigmentation. In pupae and adults, an excess of melanization and deformations were observed (DOMÍNGUEZ-MARTÍNEZ et al., 2003).

Morphological alterations in *S. frugiperda* caused by 16 natural and 6 semi-synthetic acetogenins that have toxic activity greater than or equal to 50% have been documented. The same ACGs can cause deformations at different stages of development, for example, those caused in larvae and pupae by gigantetronenin (CAI 2.64, 2.27), densicomacin-1 (CAI 2.38, 2.55), murihexocin-B (CAI 2.28, 2.64) and tucupentol (CAI 2.26, 2.63); in larvae and adult by annonacin (CAI 2.47, 2.75); in pupae and adults by almunequin (IAC 3.06, 2.71), itrabin (CAI 3.08, 2.52), asimicin (CAI 3.09, 1.97), cherimolin-1 (CAI 3.11, 2.73), motrilin (CAI 3.05, 2.09), cherimolin-2 (CAI 3.06, 2.78), tucumanin (CAI 3.00, 2.40), sylvaticin (CAI 2.95, 2.28), squamocin 3 OAc (CAI 2.35, 2.27), and molvizarin 3 OAc (CAI 2.33, 1.86) or in larval pupae and adults by cis-annonacin-10-one (CAI 2.55, 2.38, 2.75) (ÁLVAREZ COLOM et al., 2007; DI

TOTO BLESSING et al., 2010; RUIZ HIDALGO et al., 2016, 2018; TOLOSA et al., 2012).

The larval deformities included retention of residues in the head capsule and exuvia (DI TOTO BLESSING et al., 2010); in the pupae, low melanization and deformations in the wings, legs, and antenna cover were observed, while in adults malformations in the abdomen and wings were detected; these anomalies caused the death of the insects before having offspring (ÁLVAREZ COLOM et al., 2007; RUIZ HIDALGO et al., 2016, 2018; TOLOSA et al., 2012). Malformations also included damage at the cellular level, such as morphological and physiological disfigurement caused by squamocin in the digestive cells of the midgut of larvae of *A. aegypti* and *A. gemmatalis*, and in the case of the mosquito, impairment in the anal papillae of larvae and adults. Malformations also included loss of the original shape of epithelium cells, with cytoplasm highly vacuolated, and cell surface damage with loss or disorganization of microvilli (COSTA et al., 2014, 2016a, 2018; FIAZ et al., 2018). In the anal papillae wall of *A. aegypti*, vacuolization increased with cell disorganization and loss of mitochondria (COSTA et al., 2018).

ACGs in plants can have powerful deterrent effects to prevent insect herbivory, for example, *in vitro* squamocin, at 16.08 µmol·mL^{-1} causes a feeding deterrent on the butterfly *Mamestra brassicae* larvae (OHSAWA et al., 1991). This same effect is reported with asimicin at 8.04 µmol·mL^{-1} on the beetle *A. vittatum* (MIKOLAJCZAK et al., 1988, 1989). Moreover, Álvarez Colom et al. (2010) documented this effect on oviposition of *Ceratitis capitata* with itrabin at 0.05 µmol·cm^{-2} and squamocin at 0.05 µmol·cm^{-2}. The addition of itrabin, molvizarin, squamocin, almuñequin, tucumanin, cherimolin-1, and cherimolin-2 to the females' diet of this species affected the oviposition capacity without altering the viability of the eggs.

The antifeedant effects of ACGs are documented in *L. decemlineata* and *S. frugiperda*. In adults of the beetle *L. decemlineata*, annonacin at 0.17 µmol·cm^{-2} (CAI 2.74) (GUADAÑO et al., 2000) and rolliniastatin-2 at 0.03 µmol·insect^{-1} (CAI 3.19) have an antifeedant effect of 50% (GONZÁLEZ- COLOMA et al., 2002). In *S. frugiperda*, they are higher than 80%, caused by the ACG mono-THF: cis-annonacin-10-one at 0.17 µmol·g of diet^{-1} (CAI 2.75), densicomacin-1 at 0.17 µmol·g of diet^{-1} (CAI 2.68) and gigantetronenin at 0.16 µmol·g of diet^{-1} (CAI 2.75) (DI TOTO BLESSING et al., 2010), with annonacin-10-one being the most potent, causing 94% (DI TOTO BLESSING et al., 2010).

The low weight of the insects seems to be related to the alteration in the ability to transform food into biomass (ÁLVAREZ COLOM et al., 2007; DI TOTO BLESSING et al., 2015; TOLOSA et al., 2012). In *S. littoralis*, a significant decrease in weight gain was demonstrated by rolliniastatin-1 (0.0322 µmol·insect^{-1}) (GONZÁLEZ-COLOMA et al., 2002) and squamocin (0.0804 µmol·g of diet^{-1}) (ÁLVAREZ-COLOM et al., 2007); rolliniastatin-1 also limited the growth of *S. frugiperda* to 0.16 µmol·g of diet^{-1} (DI TOTO BLESSING et al., 2012) and 0.14 µmol·g^{-1} (ANSANTE et al., 2015).

Up to 13 ACGs have been reported to inhibit the larval growth of *S. frugiperda*. Asimicin 3 OAc (DI TOTO BLESSING et al., 2015), itrabin 3 OAc, laherradurin, and laherradurin 3 OAc (RUIZ HIDALGO et al., 2018) caused more than 90% reduction in larvae, at concentrations from 0.13 to 0.16 µmol·g of diet^{-1}. The acetogenin laherradurin 3 OAc is the most potent of them, a 97% decline in the growth of the larvae of this species has been recorded (CAI 2.86). Likewise, the ACGs squamocin (ÁLVAREZ COLOM et al., 2007), annonacin 3-OAc (DI TOTO BLESSING et al., 2015), rolliniastatin-1 (DI TOTO BLESSING et al., 2012), motrilin, squamocin 3 OAc, molvizarin 3 OAc, (RUIZ HIDALGO et al., 2016), rollini-

astatin-2 3 OAc, itrabin, asimicin and cis-annonacin (RUIZ HIDALGO et al., 2018) caused a decrease of more than 50%. Moreover, squamocin inhibits the growth of other larvae, such as the cabbage moth *M. brassicae* at 16.08 µmol·mL^{-1}, the cabbage moth *C. binotalis*, and the nymphs of the green rice leafhoppers *N. cincticeps*, at 0.16 µmol·mL^{-1} (OHSAWA et al., 1991).

The Efficiency in the Consumption Index is used to determine the ability of insects to convert food into biomass, and this efficiency is affected after ACGs treatments. The Efficiency in the Consumption Index is directly related to the growth rate of the insects, since the same ACGs (except for squamocin, molvizarin 3 OAc, and rolliniastatin-2 3 OAc, which cause a decrease in the growth of the larvae) have low rates of consumption efficiency (RUIZ HIDALGO et al., 2016, 2018). Asimicin 3 OAc (0.14 µmol·g of diet^{-1}) (CAI 2.83), laherradurin 3 OAc (0.13 µmol·g of diet^{-1}) (CAI 2.84), and laherradurin (0.16 µmol·g of diet^{-1}) (CAI 2.76) in *S. frugiperda* affected about 92% of consumption, allowing only assimilation of 7% and 8% of the food (RUIZ HIDALGO et al., 2018). Motrilin (CAI 2.72) (0.16 µmol·g of diet^{-1}) (RUIZ HIDALGO et al., 2016), annonacin 3 OAc (0.13 µmol·g of diet^{-1}) (CAI 2.77) (DI TOTO BLESSING et al., 2015) and itrabin 3 OAc (0.13 µmol·g of diet^{-1}) (CAI 2.76) (RUIZ HIDALGO et al., 2018), also reduced biomass gain, by 84, 82 and 80%, respectively. While squamocin 3 OAc (0.13 µmol·g of diet^{-1}) (CAI 2.69) (RUIZ HIDALGO et al., 2016), asimicin (CAI 2.53), cis-annonacin (0.16 µmol·g of diet^{-1}) (CAI 2.48), itrabin (0.16 µmol·g of diet^{-1}) (CAI 2.66) (RUIZ HIDALGO et al., 2018) and rolliniastatin-1 (0.16 µmol·g of diet^{-1}) (CAI 2.69) decreased more than 50% of biomass gain (GONZÁLEZ-COLOMA et al., 2002). For *S. littoralis* rolliniastatin-1 caused a 75% decrease in the consumption efficiency at a low concentration (0.03 µmol·insect^{-1}). The activity of other ACGs was almost nil, with rates lower than 50%.

Annonaceae acetogenins are molecules with great biotechnological potential due to their documented insecticidal activity against different species of insects and at all stages of their development. Insects cause significant damage to the health and agricultural sectors. Asimicin was patented 34 years ago as an insecticide due to its toxicity against insects such as the Mexican bean beetle *E. varivestis*, the melon aphid *A. gossypii*, *A. aegypti*, and the blowfly *C. vicina* (MIKOLAJCZAK et al., 1988).

Costa et al. (2016b) carried out a series of toxicological tests with squamocin on *A. aegypti* larvae for the use of acetogenins as insecticides, as well as to recognize the possible damage or secondary effects that the use of these molecules can cause in human cells and the natural predators of insects. This acetogenin in low concentrations (LC50= 1.60x10^{-5} µgmol·mL^{-1} and LC90= 0.0002 µmol·mL^{-1}) caused the mortality of these organisms, while with concentrations up to 1.60 µmol·mL^{-1} it did not affect their natural predators *Culex bigoti* and *Toxorhynchites theobaldi* (Diptera), neither to leukocytes from human cells. These results suggest a possible alternative of squamocin as an insecticide shortly.

It is thought that the use of ACGs as organic insecticides is possible since their toxic activity equals or exceeds that caused by commercial insecticides. For example, squamocin exceeded the toxicity of pyrethrum on *P. cochlearial* (Coleoptera) and *P. xylostella* (Lepidoptera) (LIEB et al., 1990), and rotenone toxicity in *L. migratoria* cells (LONDERSHAUSEN et al., 1991). Moreover, rolliniastatin-2 has a better effect than rotenone in midgut mitochondria of *Manduca sexta* (AHAMMADSAHIB et al., 1993) and *A. aegypti*, as well as trilobin in *A. aegypti* (HE et al., 1997) and rolliniastatin-1 in cells Sf-9 from *S. frugiperda* (GONZÁLEZ-COLOMA et

al., 2002). On the cockroach *B. germanica*, bullatalicin, sylvaticin, gigantetrocin-A, and annomontacin have equal or larger activity than hydramethylnon (amidinohydrazone), and even these four acetogenins showed low resistance, which places them as promising insecticides (ALALI et al., 1998).

Although the toxicity of acetogenins is undeniable, other less studied chemical relationships show that some insects have adapted to the intake of these molecules, possibly using them as a defense mechanism against their predators. Such is the case of the zebra swallowtail butterfly *Protographium marcellus* (syn. *Eurytides marcellus*), whose larvae retain and sequestrate the acetogenins asimicin, bullatalicin, trilobacin, and rolliniastatin-2, from their feeding on *Asimina triloba* leaves, which they preserve during their metamorphosis and store in their body and the wings tissues when they have already become butterflies (MARTIN et al., 1999). Likewise, it is thought that when the *Bephratelloides cubensis* wasp ingests the acetogenins laherradurin and rolliniastatin-2 from their consumption of the endosperm of the seeds of *Annona macroprophyllata*, they might be transformed in the metabolism of the wasp to be used as an energy reserve, or as a source for the production of other molecules, according to the hypothesis of Durán-Ruiz et al. (2019).

The studies on the mechanisms of action of ACGs were done with squamocin and rolliniastatin-2 on the mitochondria of the flight muscle of blowfly *Lucilia cuprina*, and on *P. xylostella* (LONDERHAUSEN et al., 1991); and with asimicin on the midgut of larvae of the corn borer *O. nubilalis* (LEWIS et al., 1993), as well as on Sf-9 cells from the ovary of pupae of the fall armyworm *S. frugiperda* (AHAMMADSAHIB et al., 1993; GONZÁLEZ-COLOMA et al., 2002; HOLLINGWORTH et al., 1994). From this, it was determined that acetogenins inhibit mitochondrial respiration due to their specific action on NADH-ubiquinone oxidoreductase (mitochondrial Complex I), a fact widely corroborated in eukaryotic cells (BARRACHINA et al., 2004; DEGLI-ESPOSTI et al., 1994; FEBRES-MOLINA et al., 2021; GONZÁLEZ et al., 1997; GONZÁLEZ-COLOMA et al., 2002; HERNÁNDEZ-FUENTES et al., 2019; LONDERHAUSEN et al., 1991; TORMO et al., 1999; ZAFRA-POLO et al., 1996). Toxic activity is also associated with the molecular arrangements of the polyketide structure and the formation of the chelating complex with Ca^{2+} and Mg^{2+} that interrupts the intracellular and mitochondrial calcium homeostasis (LIAW et al., 2011). Other studies mention that ACGs can induce cell death by autophagy (COSTA et al., 2018; FIAZ et al., 2018) or destabilize the mitochondrial membrane due to the dehydration they cause around the phosphate groups that constitute it (DI TOTO BLESSING et al., 2015).

Conclusions

There are eighty-five acetogenins with insecticidal activity on thirty different insects reported in this review. Acetogenins are toxic at low concentrations, considering evaluation standards and comparison with commercial insecticides, and are active at various stages of insect development. However, there is still no clarity about the insecticidal action sites of ACGs at a cellular level. The fact that acetogenins act on a specific target, mitochondrial complex I, suggests that Annonaceae have used these molecules for years as a defense mechanism against herbivorous insects, which explains the broad spectrum and potency of their insecticide activity. The low proportion of studied species of the Annonaceae family means the opportunity to find many more molecules with this biological potential, and an argument for its conservation. A biological approach that explains the interaction of these compounds with insects that are natural pests of Annonaceae is also required, and that contributes to the resolution

of ecological questions about the presence of acetogenins, as exclusive molecules, in the Annonaceae family.

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