Review Article

Annonaceous Acetogenins: The Unrevealed Area for Cytotoxic and Pesticidal Activities

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ABSTRACT

The World Health Organization (WHO) redefined traditional medicine recently as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern scientific medicine and are still in use today (WHO, 1991).[1] Traditional healers have used the drugs of herbal, herbomineral, and animal origin since the dawn of civilization to maintain health and treat disease. According to WHO, about 80% of the world's population use herbal drugs for their primary health care. These drugs are cheap with no or less side effects. The Annonaceous acetogenins are C-32 or C-34 long-chain fatty acids that have been combined with a 2- propanol unit at C-2 to form a terminal α,β-unsaturated γ-lactone. They often cyclize to form one, two, or three tetrahydrofuran or tetrahydopyran rings near the middle of the alphabetic chain. To date, nearly 400 of these compounds have been isolated from several genera of the plant family, *Annonaceae*. The potential application of acetogenin molecules is linked to their marked properties: cytotoxic and antitumor (gigantecin, bullatacin, and rolliniastatin) and pesticidal (asimicine and annonin). Biochemically, acetogenins block mitochondrial respiration by inhibiting NADH-cytochrome-c oxidoreductase; this would explain their pesticidal activity among others.

Introduction

The Annonaceous acetogenin are an important new group of long-chain fatty acid derivatives found exclusively in the plant family, *Annonaceae*. Nearly 400 compounds from this class have been published in the literature since the discovery of uvaricin in 1982. Chemically, they are waxy substances that usually contain one to two tetrahydrofuran (THF) or tetrahydropyran (THP) rings (adjacent or nonadjacent) and have a long aliphatic chain on one side and aliphatic chain ending in an α,β-unsaturated γ-lactone (or ketolactone) on the other side. Various hydroxyls, double bonds, carbonyls, and acetyls can be located throughout the molecule.

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The structure of bullatacin (1), asimicin (2), and trilobacin (3) [Figure 1] are illustrated; these are the major bioactive acetogenins (among over 40) that are found in the North American papaw tree, *Asimina triloba* (L) Dunal.[1-3]

The Annonaceae (custard-apple) family is a large plant family composed of approximately 130 genera and 2300 species; it is the largest family of the Order Magnoliales.[4] The family is well developed in the Old and New Worlds, and members are mostly confined to tropical regions. An exception is the *Asimina* genus, which is located in the eastern portion of the United States.[5] *A. triloba* occurs as far north as the Great Lakes region, west to eastern borders of Texas, Oklahoma, Kansas, and Nebraska, and in the east it extends from New York to northern Florida.[5] Figure 2 shows the classification of *A. triloba*.

The Annonaceae consist of trees, shrubs, or lianas with simple, alternate, entire, pinnately veined, typically distichous leaves.[4] Often, the leaves possess secretory cells. The flowers are solitary or in various sorts of mostly basically cymose inflorescences, mostly entomophilous. The flowers are perfect or rarely unisexual. The petals are commonly trimerous perianths; sepals (2) 3 (4); petals commonly come in six or two series of three.[4] The seeds are often arillate, $X = 7, 8, 9$.[4]

KINGDOM: Planta
DIVISON: Magnoliophyta (Angiospermae)
CLASS: Magnoliopsida (Dicotyledons)

SUBCLASS: Magnolidae
ORDER: Magnoliales
FAMILY: Annonaceae (Custard-Apple Family)
SUBFAMILY: Annonoideae
TRIBE: Unoneae
GENUS: Asimina
SPECIES: A. triloba

The fruits of this family are commonly separate, stipulate, fleshy, indehiscent, berry-like carpels, varying to sometimes dry and dehiscent, or the carpels are sometimes coalescent to form an aggregate fruit; seeds come with small basal to axile, dicotyledins, embryo, and abundant firm, ruminate, oily (sometimes starchy) endosperm.[4] *A. triloba* (paw paw, Indiana banana, or poor man's banana) is the largest fruit native to the United States.[5] Many people are trying to improve cultivars as a replacement crop for tobacco farmers, especially in Kentucky. Selected cultivars would produce superior fruit and/or high levels of the acetogenins.

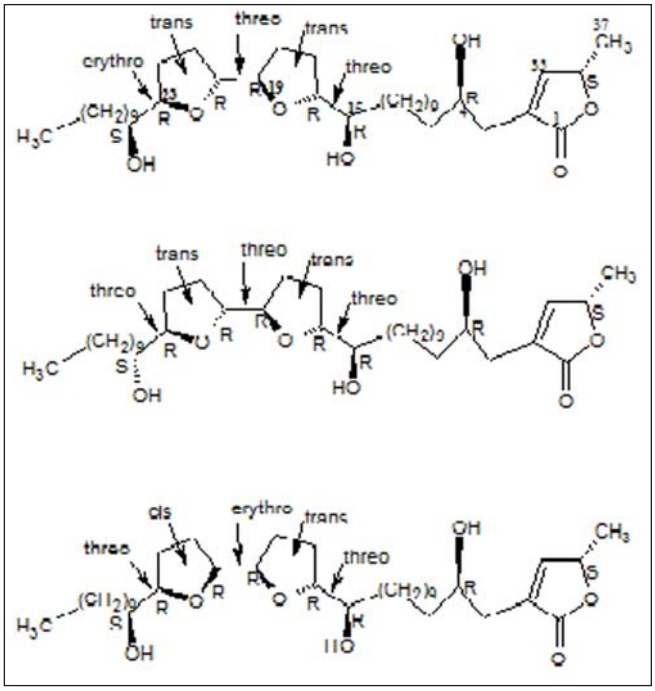

Figure 1: Structures of bullatacin (1), asimicin (2) and trilogacin (3)

The genera that have been reported to contain acetogenins, thus far, are Uvaria, Asimina, Annona, Goniothalamus, rollinia, and xylopia.[6] Many of the genera have similar compounds, a few have shown unique substructures. The new substructures often yield selective cytotoxicities among human tumor cell lines.

Biosynthesis

It has been hypothesized that the acetogenins arise from a polyketide biosynthetic pathway. A series of diene, triene, or triene ketone groups can undergo a series of epoxidations and cyclizations. Among the acetogenins found, some contain double bonds, where placement along the aliphatic chain strongly suggests this biogenetic pathway. The biogenetic pathways of acetogenins isolated from *Goniothalamus giganteus*, *Annona bullata*, *Asimina triloba*, etc. have been hypothesized.[7,8]

The configurations of the starting double bonds determine the final configurations between the hydroxylated carbinol centers and the THF rings; i.e., trans double bonds become erythro, and *cis* become threo, while the *cis* and *trans* types of THF rings are dependent on the epoxidation direction from which the C-19/20 double bond is formed.[7] Figure 2 shows schemes for the production of mono and adjacent and nonadjacent bis THF ring acetogenins, respectively.

The radiolabeling of potential precursor units would be the best way to study acetogenin biosynthesis; however, the Annonaceous plants have proved very difficult to grow with any degree of speed in tissue culture. It seems that when the acetogenins are produced and released in to the aqueous media, they often inhibit the growth of the callus and eventually lead to the death of the callus. If leaves do successfully differentiate in to plantlets, it is sometimes very difficult to grow roots. Growing of Asimina callus has been attempted many times in the laboratories, and the technique has not been developed as of yet due to the presence of persistent fungus. The cost of radiolabeling experiments combined with the difficulty of

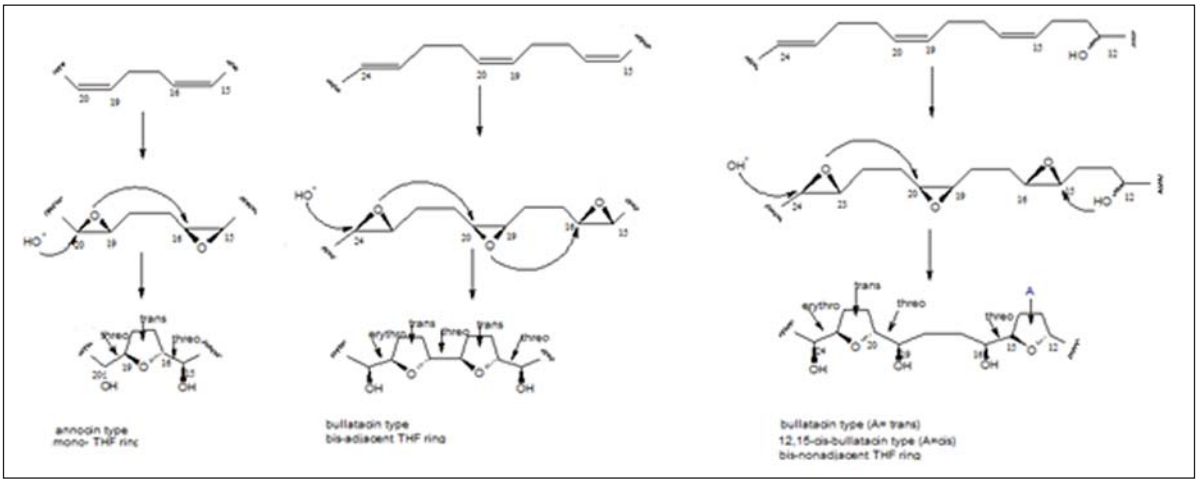

Figure 2: Proposed biosynthetic pathways for selected representatives of the three main classes of acetogenins.[6]

establishing plant tissue cultures has discouraged the publication of experimental data in the area of biogenesis.

Extraction, Isolation and Purification From Paw

The acetogenins have been found in the bark, twigs, green fruit, and seeds of the paw paw tree, *A. triloba*.[9] The compounds are usually extracted from the plant material with 95% ethanol. The residue (F001) is partitioned between H_2O and CH_2Cl_2, and the CH_2Cl_2 residue (F003) is partitioned between hexane (F006) and 10% aqueous methanol (F005). Most acetogenins are somewhat polar, so they migrate to the F005 fraction. After the extraction/partition steps, the F005 residue is passed over several open silica gel columns to purify the compounds. All the pools from chromatography are monitored by the brine shrimp lethality assay (BST).[10-12] In this way, only bioactive fractions will be pursued further. The brine shrimp respond very well to the acetogenins; hence it is a convenient, rapid, and inexpensive bioassay. Phosphomolybdic acid (5%) in ethanol followed by heating is used as a general TLC spray reagent, while a pink coloration with Kedde's reagent can be used to identify specifically the α,β-unsaturated γ-lactone moiety of these compounds.[13] Normal-phase HPLC (NP-HPLC) and reverse-phase HPLC (RP-HPLC) are used to purify the final products of these chemical derivatives. Usually, acetogenins are placed on RP-HPLC because they are more easily detected in the low-ultraviolet range. The weak UV absorbance at 210 nm for the α,β-unsaturated γ-lactone is one reason to use an RP-HPLC system. This weak absorbance is often overshadowed by impurities that have larger absorbances. Another reason for choosing RP-HPLC is because the solvent cutoff for the RP solvent is lower than NP solvents. In their pure form, acetogenins are white, waxy substances.

Our original work with the bark of paw dealt with biomass that had been collected in the month of July,[13] and we subsequently were disappointed when a large collection made in November was subpotent. This prompted a study of monthly variation of biological activity (BST) of twigs obtained from a single tree.[14] The activity and concentrations of bullatacin (1), asimicin (2), and trilobacin (3), as determined by HPLC/MS/MS,[15] all peak in the months of May to July, demonstrating significant seasonal fluctuation of over 15 times in potency. This study was followed by a careful analysis of the BST activity of 135 individual trees; with the genetics of the tree as the only variable, differences of 900 times in potency were found in the highest vs. the lowest producers.[16]

Structure Elucidation Strategies

Using synthetic models with known relative stereochemistry, the relative stereochemistry of bis-adjacent, bis-nonadjacent, and mono-THF ring acetogenins of an unknown acetogenin can be solved quickly by comparing ^{1}H-NMR (nuclear magnetic resonance) chemical shift and J-coupling values.[7] No model compounds of bis-adjacent THF ring acetogenins bearing one flanking hydroxyl, tris-adjacent THF rings bearing one flanking hydroxyl, or THP rings have been synthesized, making structural elucidation of these types more of a challenge. The relative stereochemistry of diols derivatized by acetonides or formaldehyde acetals can be solved by ^{1}H-NMR analysis of these derivatives.[8,17,18]

Advanced Mosher ester methodology[19] has been used extensively in acetogenin structure elucidation to determine the absolute stereochemistry of the carbinol centers. The absolute stereochemistry of bis-nonadjacent THF ring acetogenins can be determined using Mosher methodology coupled with formaldehyde acetal formation about the 1,4-diol between the two THF rings (except for the aromicin type).[17] Isolated hydroxyls on the terminal alkyl chain or near the γ-lactone can be determined if the distance is not too far from distinctive protons.[8] Mass spectrometry is very useful in the identification of the location of the THF ring system. EI-MS (electron impact mass spectrometry) generally works well for the THF ring placement because the molecules tend to split adjacent to the THF rings in the mass spectrometer. Other additional functional groups (i.e., single hydroxyls, vicinal diols, double bonds) can be placed fairly easily using EI-MS. For molecular-weight determination of multihydroxylated acetogenins, it is advantageous to make TMS (tetramethylsilane) derivatives of the hydroxyl groups. FAB-MS and MS/MS are becoming more and more useful in quantitation and screening.[18,20] Sometimes a combination of ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry is needed for the correct placement of the THF and/or THP ring groups.

Biological Activity

Folkloric medicine has led many scientists to discover important plant-derived medicines. It has been known for some time that the seeds of several Annonaceous species have an emetic property.[21] Eli Lilly, Inc. in 1898 sold a fluid extract made from paw paw seeds (*A. triloba*) for inducing emesis.[48] Folkloric uses of Annonaceous species also suggest pesticidal properties. The Thai people use extracts of *Annona squamosa*, *A. muricata, A. cherimolia*, and *A. reticulata* for the treatment of head lice.[22] For this, 10 to 15 fresh leaves of *A. squamosa* L. are finely crushed and mixed with coconut oil, and the mixture is applied uniformly onto the head and washed off after 30 min.

This class of compounds has interesting and potent biological activities, including cytotoxic, *in vivo* antitumor, antimalarial, parasiticidal, and pesticidal effects.[7,8,23] The major site of action of the acetogenins is complex I of the electron transport system in mitochondria.[24-28] The acetogenins have been described as among the most potent of the complex I inhibitors of electron transport systems.[29] Their pesticidal and cytotoxic (antitumor) effects seem to have the most practical economic applications.

Pesticidal Properties

In addition to their potential as antitumor agents, acetogenins have great potential as natural "organic" pesticides.[30-32] Bullatacin (1) and trilobacin (3) [Figure 1] were more potent than rotenone, a classic complex I mitochondrial inhibitor, in a structure–activity relationship (SAR) study using yellow fever mosquito (YFM) larvae.[33]

Table 1 shows the results of insecticide trials with pure asimicin (2) [Figure 1] and crude paw paw extracts. Standard insecticides, pyrethrins, and rotenone are compared with the paw paw extract. The methanol fraction (F005) of the paw paw bark was 30% more effective than rotenone in a mosquito larvae assay.[30] In a nematode assay (*Caenorhabditis elegans*), this extract showed 100% lethality at 10 ppm after 72 h, whereas pyrethrins showed no nematocidal activity at the same dose and time period. Thus, it is unnecessary to purify the acetogenins from crude extracts for practical applications, and it could be economically and environmentally advantageous to use suitably constituted crude extracts for pesticidal uses.[32] A diverse mixture of acetogenins (over 40 are present in the paw paw extracts) could target a variety of different insect species, and

Table 1: Comparison of pesticidal activity of asimicin (2) (figure 1) and Paw extract (F2005) vs Standard Insecticide

Compound	Test Organism	Time of Exposure (h)	Mortality Rate						
			0.1 ppm	1 ppm	10 ppm	50 ppm	100 ppm	500 ppm	5000 ppm
Asimicin (2), purified	MBB	72			70	100			
F2005 extract	MBB	72					60		
Pyrethrins (75%)	MBB	72			0	100			
Asimicin (2)	MA	24					20	100	
F2005 Extract	MA	24							80
Pyrethrins	MA	24			20	100			
Asimicin(2)	ML	24		100					
F2005 extract	ML	24		10	80				
Pyrethrins	ML	24			100				
Rotenone, (97% Pure)	ML	24			50		100		
Asimicin (2)	NE	72	100						
F2005 extract	NE	72		0	100				
Pyrethrins	NE	72			0				

MBB = Mexican Bean Beatle; MA = melon aphid; ML = Mosquito larvae; NE = nematode (Caenorhabditis elegans)[20]

their structural diversities may minimize the probability of pesticide resistance.[34,35] To thwart the problems of pesticide resistance and minimize economic constraints, crude extracts of the twig biomass, containing a "cocktail" of acetogenins may soon provide a marketable product.[32]

Six acetogenins were compared with five commercially available pesticide used in cockroach baits. All compounds were tested at 1000 ppm and the lethal time to kill 50% (LT_{50} values) were recorded with second and fifth instar roaches of insecticide-resistant and -susceptible strains. The acetogenins were equipotent or superior in potency to the commercial bailts, and the resistance ratios were near 1, suggesting equipotency against the resistant strains. Thus, the acetogenins thwart resistant insects.[46]

Cytotoxic Properties

The primary site of action of the acetogenins is complex I of the electron transport chain in mitochondria.[24-29,36] The acetogenins are also inhibitors of the NADH oxidase which is prevalent in the plasma membranes of cancer cells.[37] Both modes of action deplete ATP (adenosine triphosphate) and induce programmed cell death (apoptosis).[38] Cancer cells are better targets for the acetogenins than normal cells because they have elevated levels of NADH oxidase accompanied by higher ATP demand.[37]

Bullatacin (1) [Figure 1] has been extensively evaluated in *in vivo* human tumor cell culture studies.[13] More recently parental nonresistant wild-type (MCF-7/wt) human mammary adenocarcinoma cells and multidrug-resistant (MDR) (MCF-7/ADR) cells exposed to **1** yielded surprising results, wherein **1** inhibited the MDR cells at a lower dose than was required to inhibit the wild-type cells.[39] After completing cell refeeding assays, it was determined that **1** is cytotoxic to MCF-7/ADR cells and is cytostatic to the wild-type cells (MCF-7/wt).[39] With most other anticancer drugs, this is reversed, and usually a higher dose is required to inhibit resistant cells than normal (wild-type) cells. It is postulated that MDR cancer cells have a 170-kDa glycoprotein (P-gp).[40] The P-gp forms a channel or pore in the plasma membrane and pumps out the intracellular drugs. This mechanism is very efficient at keeping the resistant cells functioning. Being ATP dependent (i.e., the pump requires energy), the P-gp would make the resistant cells more susceptible to compounds which inhibit ATP formation. Hence, when the acetogenins, as potent complex **1** and NADH oxidase inhibitors, decrease intracellular ATP levels, they, therefore, decrease the effectiveness of the P-gp efflux pump.

Oberlies *et al*.[41] evaluated 14 acetogenins (7 bis-adjacent, 2 bis-nonadjacent, and 5 mono-THF ring compounds) against the same MCF-7 adriamycin-resistant cell line, to establish their SARs. All compounds were tested with adriamycin, vincristine, and vinblastine, as standard chemotherapeutic agents. Of the 14 acetogenins, 13 were generally more potent than all three of the standard drugs. Bullatacin (**1**) [Figure 1] is 258 times more cytotoxic against MCF-7/ADR than adriamycin. Acetogenins with the stereochemistry *threo-trans-threo-trans-erythro* from C-15 to C-24 were the most potent of those having bis-adjacent THF rings. The most potent compound, gigantetrocin A (a mono-THF ring acetogenin), was two times as potent as Bullatacin (**1**). The optimal length of the alkyl chain between the THF ring and the γ-lactone is 15 carbons, as recently corroborated by Miyoshi *et al*.,[36] with the purified mitochondrial enzyme. Shortening the length of the alkyl chain decreases the potency significantly.

In Vivo Experiments

Several *in vivo* antitumor tests of the Annonaceous acetogenins have been performed and more are needed in the future. These compounds suffer from a common misconception that they are only cytotoxic and must be too toxic for *in vivo* effectiveness. This is not the case. Uvaricin showed *in vivo* activity against 3PS (murine lymphocytic leukemia) [157% test over control (T/C) value at 1.4 mg/kg], rollinone showed 147% T/C at 1.4 mg/kg, and asimicin (**2**) [Figure 1] showed 124% T/C at 25.0 g/kg.[13] This demonstrates that asimicin (**2**) is about 50 times more potent, but has less efficacy, than the other two. Ahammadsahib *et al*.,[25] reported the activity of bullatacin (**1**) [Figure 1] and (2,4-*cis* and *trans*)-bullatacinones against L1210 (murine leukemia) in normal mice, and bullatacin and bullatacin (a bis-nonadjacent THF ring isomer) quite effectively inhibited tumors of A2780 (human ovarian carcinoma) in athymic mice.[25] Bullatacin (**1**), effective at only 50 μg/kg, was over 300 times more potent than Taxol against 1210, and bullatalicin, effective at 1 mg/kg, was nearly as effective as cisplatin against A2780 [75% TGI (tumor growth inhibition) vs. 78% TGI]. In these studies, the acetogenins caused much less weight loss than the standard compounds, Taxol and cisplatin, indicating better tolerance and less toxicity.

Plasma Membrane Conformation

The positions of the THF and lactone moieties of asimicin (**2**), parviflorin, longimicin B, and bullatacin (**1**) within liposomal membranes (artificial membranes which mimic plasma and mitochondrial membranes) were recently determined using ^{1}H-NMR.[42] Both **1** and **2** [Figure 1] have 13 carbon units in the space group between the hydroxylated THF ring system and the γ–lactone, parviflorin and longimicin B have 11 carbons and 9 carbons, respectively. ^{1}H intermolecular nuclear Overhauser effects (NOE) showed that the THF rings of all the acetogenins studied reside near the polar interfacial head group region of DPMC (dimyristoylphosphatidyl choline) of the liposome. The length of the carbon chain between the THF and the γ-lactone determines the conformation within the membrane. Those with longer hydrocarbon spacer groups (**1**,**2**, and parviflorin) extend the γ-lactone below the glycerol backbone and form either a sickle shape or a U-shape. Longimicin B, with its alkyl chain two carbon units shorter than parviflorin, extends its γ-lactone closer to the midplane in the membrane. This study suggested that the alkyl chain length, contributing to the membrane conformation, may be one of the reasons for observed variable and selective cytotoxicities.[43]

Summary

The Annonaceous acetogenins offer a unique mode of action (ATP depletion) against MDR tumors and against insecticide-resistant pests and are predicted to become important future means of thwarting ATP-depleting resistance mechanisms. Their SARs in several systems have been determined,[33,36,39,41,44,45] and optimum structural features generally point to the bis-adjacent THF compounds such as bullatacin (**1**) and asimicin (**2**)

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