



Acetogenin Update

Kirk W. Pomper, Ph.D.

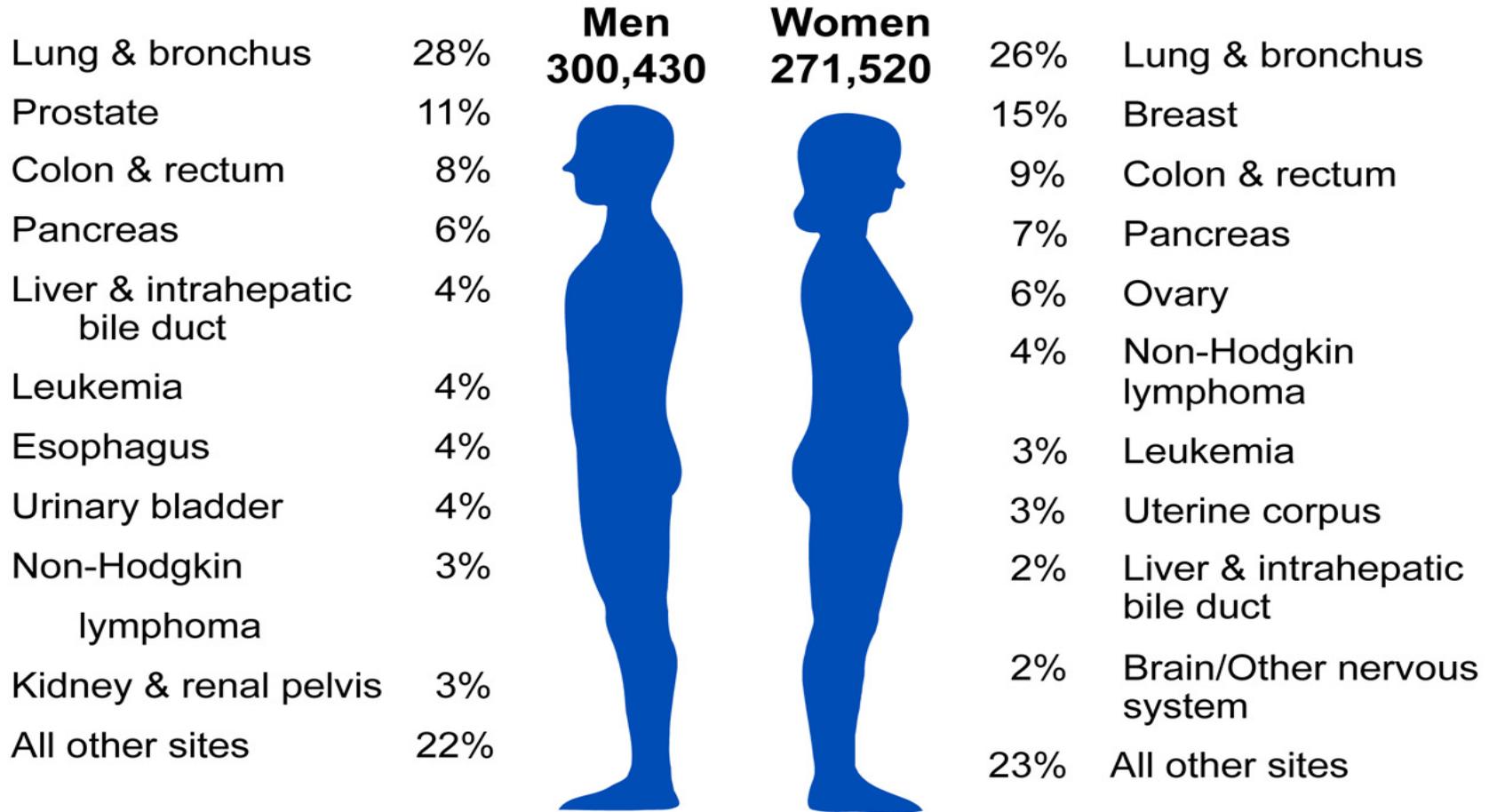
Principal Investigator of Horticulture/ Kentucky State University
Adjunct Assistant Professor of Horticulture/ Univ. of Kentucky



Disclaimer

- The following information is for educational purposes only and is not intended for the mitigation, cure or treatment of medical conditions.
- KSU does not endorse any products by any companies

2011 Estimated US Cancer Deaths



The Lifetime Probability of Developing Cancer for Men, 2005-2007*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 13
Colon and rectum	1 in 19
Urinary bladder‡	1 in 26
Melanoma§	1 in 37
Non-Hodgkin lymphoma	1 in 43
Kidney	1 in 53
Leukemia	1 in 66
Oral Cavity	1 in 71
Stomach	1 in 91

* For those free of cancer at beginning of age interval.

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and in situ cancer cases

§ Statistic for white men.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.5.0 Statistical Research and Applications Branch, NCI, 2010. <http://srab.cancer.gov/devcan>

The Lifetime Probability of Developing Cancer for Women, 2005-2007*

Site	Risk
All sites [†]	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 20
Uterine corpus	1 in 39
Non-Hodgkin lymphoma	1 in 52
Urinary bladder [‡]	1 in 87
Melanoma [§]	1 in 55
Ovary	1 in 72
Pancreas	1 in 71
Uterine cervix	1 in 147

* For those free of cancer at beginning of age interval.

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and in situ cancer cases

§ Statistic for white women.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.5.0 Statistical Research and Applications Branch, NCI, 2010. <http://srab.cancer.gov/devcan>

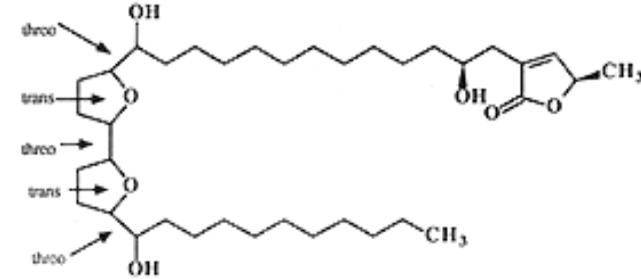
Acetogenin Compounds and Cancer: Research at Purdue University



- Dr. Jerry McLaughlin
 - Professor of pharmacognosy
- Extracts of pawpaw were among the most potent of the 3500 species of higher plants screened for bioactive compounds in his laboratories

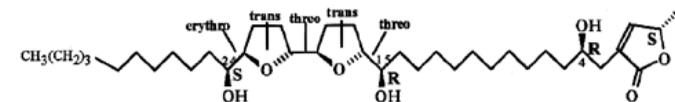
Pawpaw Acetogenin Compounds

- Annonaceous acetogenins
 - Long unbranched fatty acid chain
 - over 50 unique annonaceous acetogenins



Asimicin

- Inhibitor of complex I of the mitochondrial respiratory chain.
- Present in young pawpaw twig and other tissues



Bullaticin

Anti-tumor Activity

Table 1. The bioactivities of bullatacin in the brine shrimp test and human solid tumor cell lines.

Compound	BST LC ₅₀ (µg/ml)	ED ₅₀ (µg/ml)	MCF-7 ED ₅₀ (µg/ml)	HT-29 ED ₅₀ (µg/ml)
Bullatacin	1.59×10^{-3}	1.25×10^{-13}	>10	1.0×10^{-12}
Adriamycin	2.57×10^{-1}	1.04×10^{-4}	1.76×10^{-2}	1.53×10^{-4}

BST = brine shrimp lethality test

A-549 = human lung carcinoma

Adriamycin® = standard anticarcinoma drug

MCF-7 = human breast carcinoma

ED₅₀ = effective dose resulting in 50% cell death

HT-29 = human colon carcinoma

LC₅₀ = lethal concentration resulting in 50% deaths

Bullatacin inhibits mammalian solid tumor cells at concentrations often a billion times lower than Adriamycin., as shown in Table 1 (Zhao, et al. 1994b).

Pawpaw Acetogenin Compounds

- The powerful cytotoxicity, in vivo antitumor, pesticidal, antimalarial, antiviral, and antimicrobial effects indicated a myriad of potentially useful applications.
- Commercial development of these compounds
 - shampoo, highly effective in treating infestations of head lice, fleas, and ticks.
 - pesticidal sprays, which protects host plants against a diversity of pests.
 - an ointment for treatment of oral herpes (HSV-1) and other skin afflictions.
 - The extract (in capsule form) has been used by certain cancer patients as a botanical supplement product.



NATURE'S SUNSHINE[®]

United States

Country: [United States](#) Language: [English](#)

[Need help with sign in?](#)

[Shop](#) | [Opportunity](#) | [About Us](#) | [Members](#) | [Healthy Living](#) | [Blog](#)

You have in your shopping cart:
0 products: \$0.00

Customer Service
1-800-223-8225

Ordering Tools



Customer Favorites

- Top Sellers
- Weekly Specials
- JumpStart Packs
- New Products
- A-Z Product Listing
- Health Assessment

Core Health - Nutrition

- Super Trio
- Probiotics
- Antioxidants

Paw Paw Cell-Reg™ (180 caps)



Stock Number: 515-6

Retail Cost: \$59.95
Member Cost: \$39.95

Qty:

[View Product Guide](#)

[View Product Label](#)

- Selectively affects specific cells.
- Modulates the production of ATP in mitochondria of specific cells.
- May help modulate the growth of blood vessels near specific cells.

Paw Paw Cell-Reg™ [Immune]. Because health begins in the body's cells, it is important to support the health of all cells. Paw Paw Cell-Reg is a **unique product that selectively targets specific cells to enhance the overall health of the body**.

Over 50 active compounds exist in Paw Paw Cell-Reg and these complex chemicals are called acetogenins. Acetogenins affect the production of ATP in the mitochondria (the powerhouse) of the cell. ATP is the major source of cellular energy. By selectively modulating the production of ATP in specific cells, the acetogenins affect the viability of specific cells and the growth of blood vessels that nourish them.

A clinical study with **over 100 participants showed that the paw paw extract, containing a**

[Read more...](#)

Botany and Genetic Resources



■ *Asimina triloba* is a member of the tropical Custard Apple or Annonaceae family.

- custard apple (*Annona reticulata* L.)
- cherimoya (*A. cherimola* Mill.)
- sweetsop or sugar apple (*A. squamosa* L.)
- atemoya (*A. squamosa* x *A. cherimola*)
- soursop (*A. muricata* L.)



Consumption of Annona fruit and tea- A Link to Parkinsonism?

- Caparros-Lefebvre and Elbaz (1999) reported in Guadeloupe, atypical parkinsonism was abnormally frequent, and represented 75% of progressive parkinsonism while Parkinson's disease accounted for only 25% of the cases.
 - inversed percentage in comparison with patients living in Europe and North America.
- A higher proportion of patients with atypical parkinsonism (consumed soursop fruit 97%; consumed herbal tea 83%) than patients with Parkinson's disease (fruit 59%; herbal tea 18%) or control with no Parkinson symptoms (fruit 60%; herbal tea 43%).

Consumption of an Acetogen Compound-Annonacin

- Champy et al. (2005) determined the concentrations of annonacin, the major acetogenin in soursop.
 - An average fruit contains about 15 mg of annonacin.
- When directly injecting rats for one month with the estimated amounts of annonacin ingested in a year by eating one fruit daily, this induced neurodegeneration in the basal ganglia and mesencephalon (Champy et al., 2004).
- Purified extract and bioavailability upon digestion not examined.

Consumption of *Annona* fruit and tea-A Link to Parkinsonism?

- The prevalence of Parkinson's disease is roughly 150 per 100,000 inhabitants in the United States or Europe (Schrag et al., 1999).
- Caparros-Lefebvre et al. (2005) calculated that the number of PD cases in Guadeloupe would be approximately 640 (out of 420,000 people)
 - 152 per 100,000
 - Younger people who had symptoms and stopped consuming *Annona* products reversed their symptoms

Atypical Parkinsonism in Guadeloupe

- Sensitivity to acetogenin compounds may be limited to those with a specific genetic predisposition in Guadeloupe
- The H2 allele has been reported to carry variants that are protective PSP and is rare (5% vs. 20%) in the Guadeloupian population
 - may contribute, in association with unidentified genetic or environmental risk factors, to disease susceptibility (Camuzat et al., 2008).

Table 1. Brine shrimp lethality and percentage yields of F005 (90% aqueous methanol fraction) from various plant parts of *Asimina triloba*.

Plant part extracted	LC ₅₀ (ppm) ^z	Yield of F005 (%)
Twigs ^y	0.042 (0.02-0.09)	1.78
Unripe fruit ^x	0.060 (0.03-0.08)	5.11
Root wood ^w	0.060 (0.03-0.08)	1.27
Seed ^v	0.065 (0.03-0.10)	4.03
Stem bark ^{x,u}	0.077 (0.04-0.12)	2.71
Stem bark ^{y,u}	0.102 (0.06-0.15)	1.96
Stem bark ^y	0.104 (0.03-0.20)	2.52
Root bark ^w	0.135 (0.09-0.21)	2.72
Whole stem: wood, bark and leaves ^y	0.202 (0.14-0.31)	1.60
Stem wood ^y	4.86 (0.37-11.93)	0.90
Leaves ^y	53.6 (33-82)	4.36

Objective

To determine if extracts of ripe pawpaw fruit pulp display acetogenin activity.

Brine Shrimp Lethality Assay (BST)

- *Artemia saline* or Sea Monkeys
- Rapid, in house, and low cost substitute for cytotoxic assays developed by Dr. McLaughlin
- Responsible for the isolation of numerous, chemical and pharmacologically diverse antitumor and pesticidal compounds.
- Records the lethal concentration to kill 50% of the shrimp (LC50 value with upper and lower 95% confidence levels)

Brine Shrimp Test-Acetogenin Activity

- About nine grams of pawpaw pulp was extracted with ethanol and concentrated through a series of methanol and chloroform extractions as described by Ratnayake et al., (1993).
- Twenty brine shrimp larvae, taken 48 h after initiation of hatching in artificial sea water were added to each vial (5mL) containing 0, 10, 100 and 1000 ppm concentrations of extract.
- After 24 h, survivors were counted. SD from three extracts.

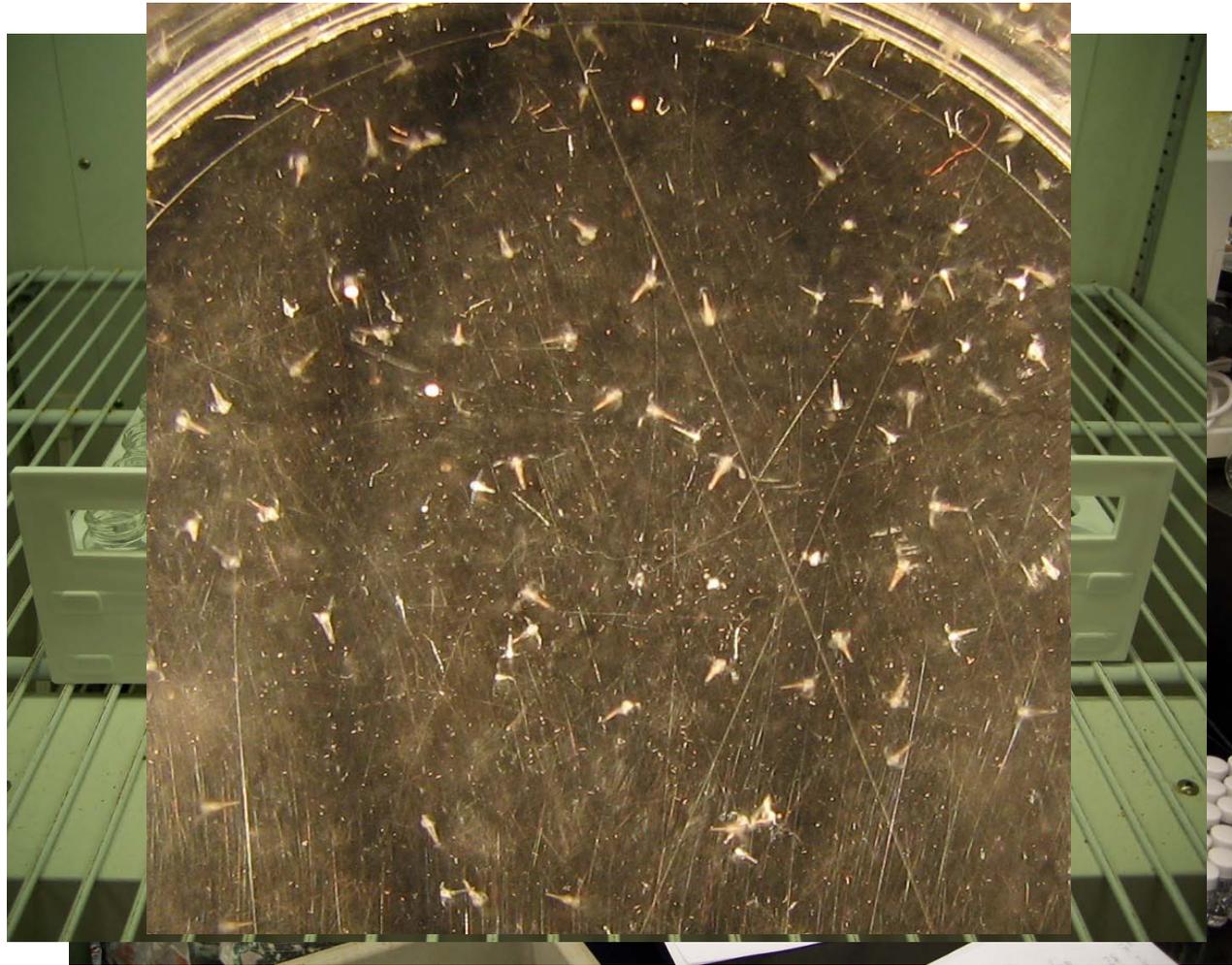
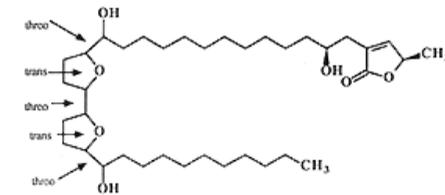
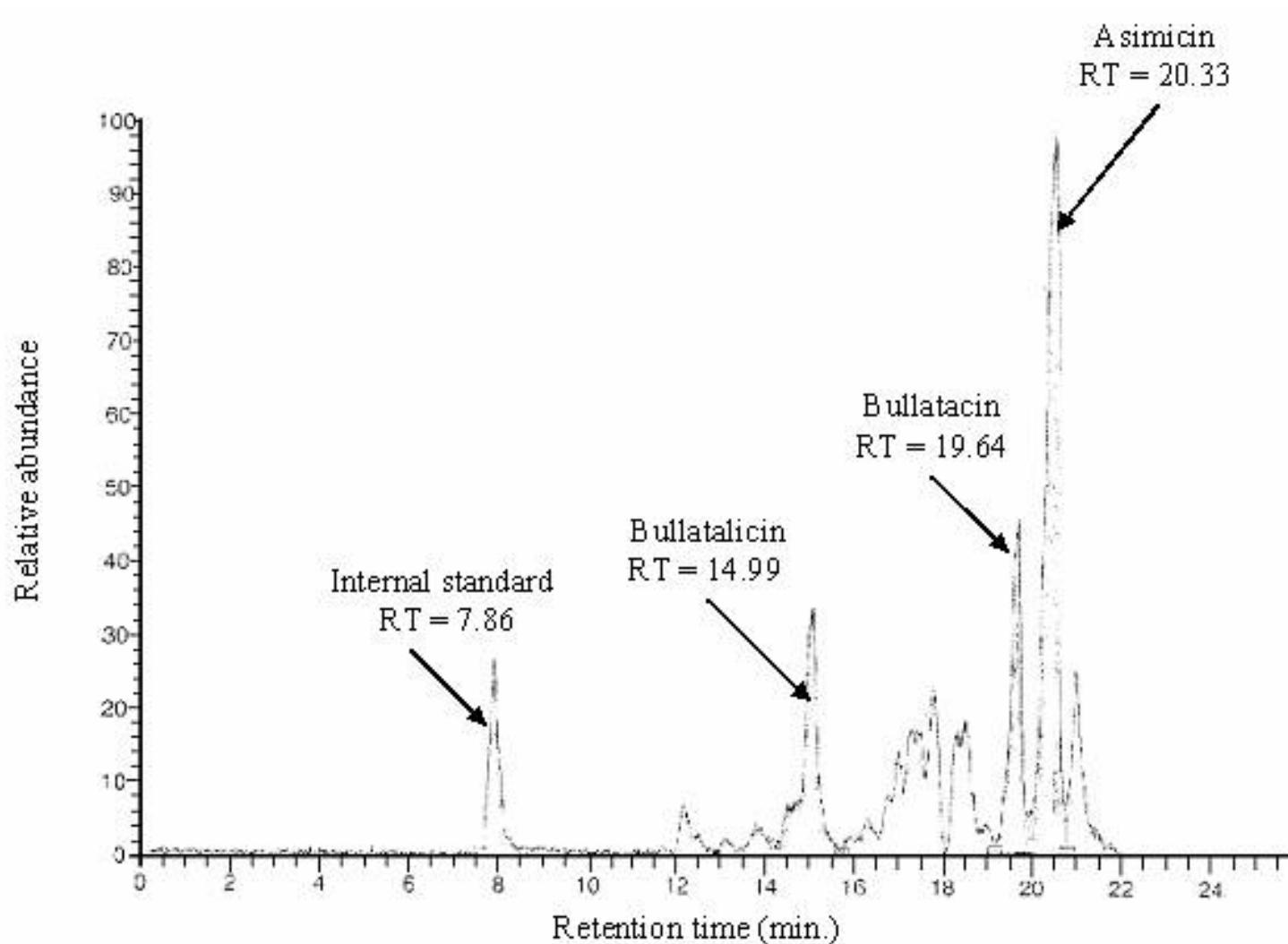


Table 3. Brine Shrimp Mortality (LC₅₀) Values for the Pawpaw Cultivars ‘Mitchell’, ‘NC-1’, ‘Overleese’, ‘Zimmerman’, ‘Wells’, and ‘Sunflower’ from Frozen Pulp of Ripe Fruit^a

pawpaw cultivar	LC ₅₀ (ppm)	pawpaw cultivar	LC ₅₀ (ppm)
‘Mitchell’	0.31 (±1.02)	‘Zimmerman’	4.09 (±0.49)
‘Overleese’	0.38 (±1.48)	‘Wells’	7.33 (±1.27)
‘NC-1’	0.89 (±1.41)	‘Sunflower’	8.60 (±0.42)

^a Parentheses enclose standard error.

Confirmation of Acetogenins in 'NC-1' Pulp Subjected to HPLS-Mass Spec Analysis



What the FDA Says:

- Kentucky State University asked the U.S. Food and Drug Administration (FDA) for an opinion on this topic, and their conclusion was that pawpaw has a long history of food use and the FDA does not currently have any evidence that pawpaw is unsafe to eat.

Table 1. Highest and Lowest Brine Shrimp Test LC₅₀ Values of Extracts from 135 Individual Paw Paw Trees Growing at the WMREC Plantation^{a,b}

high producers		low producers	
tree sample	BST-LC ₅₀ (ppm)	tree sample	BST-LC ₅₀ (ppm)
4-11	0.033 ± 0.0010	2-32	32 ± 12
5-82	0.053 ± 0.015	1-19	12 ± 4.7
4-70	0.056 ± 0.0354	4-46	10 ± 0.55
2-88	0.063 ± 0.020	5-14	8.4 ± 2.5

^a Grand mean LC₅₀ value of 1.2 ppm ± 0.30 ppm. ^b Twig samples were collected, September 26, 1995, from trees planted in the spring of 1984.

Summary

- We are screening current pawpaw cultivars for acetogenin activity:
 - High: NC-1, Overleese, Mitchell, Middletown, Susquehanna,...
 - Low: Sunflower, Wabash, Potomac, Zimmerman, Wells,...
- In the KSU pawpaw breeding program, we are selecting both high and low acetogenin genotypes.

Questions?