Published by the Purdue News in 1997:

Pawpaw shows promise in fighting drug-resistant tumors

WEST LAFAYETTE, Ind. -- The pawpaw tree, which bears the largest fruit native to North America, may bear new fruit for scientists seeking ways to fight cancer.

Purdue University researcher Jerry McLaughlin, working with doctoral student Nicholas Oberlies, has found compounds in the bark of the tree that have shown preliminary success in fighting some drug-resistant cancers.

The studies, published in two separate journal articles this summer, show that the pawpaw compounds not only are effective in killing tumors that have proven resistant to anti-cancer agents, but also seem to have a special affinity for such resistant cells. The findings were detailed in the journal Cancer Letters and the Journal of Medicinal Chemistry.

Though further studies are needed to pinpoint exactly how the pawpaw compounds work within the cancer cell, McLaughlin says their effect is to pull the plug on the energy-producing mechanisms in the cell.

McLaughlin notes, however, that the effect on drug-resistant cells has been studied only in laboratory cultures and will require additional study in animals before it can be tested in humans.

"Multidrug-resistant cancer is hard to treat because the cancer cell has developed a mechanism to get around the anti-cancer agent," says McLaughlin, professor of pharmacognosy in Purdue's School of Pharmacy and Pharmacal Science. "Tumor cells that survive chemotherapy treatments often recover with increased resistance to the agent used in the original treatment program as well as to other related drugs."

Such resistance can develop when surviving cancer cells develop one or more mechanisms to accelerate the removal of noxious substances, including anti-cancer drugs. One of the most common mechanisms used to circumvent the anti-cancer agents is to develop a "pump" that is capable of pushing anti-cancer agents out of the cell before they can kill it. These pumps are called P-glycoprotein mediated pumps and are named for the type of protein used to construct and operate them.

Though all cells have the ability to develop such a pump, normal cells seldom do. Even in cancer cells, which do not respond normally to the body's control

mechanisms, only a small percentage of cells develop this pumping mechanism.

"If having this pump was such a good deal, all cells would have it. But all cells don't," McLaughlin says. "In a given population of cancer cells in a person, maybe only 2 percent of the cancer cells possess this pump. But it's those 2 percent of cancer cells that eventually grow and expand to create drug-resistant tumors."

One of the tricks currently attempted in treating cancer patients is to flood the body with other compounds to keep the pump busy, and then administer high doses of an anti-cancer agent in hopes that some of it will be able to stay in long enough to kill the cancer cell.

"But the high doses of the drugs required for this treatment often produce side effects, such as loss of blood pressure, so the patient often succumbs to the side effects of the treatment," McLaughlin says.

Though this pump mechanism is efficient at eliminating most anti-cancer agents, McLaughlin, whose research group has identified more than 40 pawpaw compounds with anti-cancer properties, discovered a series of the compounds, called Annonaceous acetogenins, that were capable of killing cancer cells that employed this mechanism.

He then designed a laboratory study to analyze the cytotoxic or cell-killing effects of one of the compounds, called bullatacin, on human mammary cancer cells. The study compared bullatacin's effects on standard, nonresistant cancer cells and on multidrug-resistant cells.

In the June issue of Cancer Letters, the research team reported that bullatacin preferentially killed the multidrug-resistant cells by inhibiting the production of adenosine triphosphate, or ATP. ATP is a compound that works to release energy in a cell and is essential to all cell processes.

"A multidrug-resistant cell requires a tremendous amount of energy to run the pump and extrude things out of the cell," McLaughlin says. "By inhibiting ATP production, we're essentially pulling the plug on its energy source."

Though the pawpaw compounds also inhibited ATP production in noncancerous cells and nonresistant cancer cells, those cells were not affected as dramatically, McLaughlin says.

"Normal cells and standard cancer cells may be able to minimize the effects of this compound because they don't require the vast amounts of energy needed by the pump-running cells," McLaughlin says. "The resistant cell is using its extra energy for this pump as well as to grow, so it is really taxed for energy. When we mess with the energy supply, it kills the cell."

McLaughlin and his group then did a follow-up study to test a series of 14 structurally similar pawpaw compounds to determine the structural features that maximize this biological activity in multidrug-resistant cancer cells. The results were published in the June issue of the Journal of Medicinal Chemistry.

"This study tells us how to maximize this activity, so we have a pretty good idea what compounds we'd like to try in animals with multidrug-resistant tumors," McLaughlin says.

If proven effective in animals and humans, McLaughlin says, the compounds may be used to treat multidrug resistance in a variety of cancers, because many types of cancer cells develop resistance by employing a pump.

The studies were funded by National Institutes of Health/National Cancer Institute, the Indiana Elks Cancer Research Fund and Purdue Research Foundation. Purdue has filed a patent on the use of the pawpaw compounds.

ABSTRACT: ***Cancer Letters 115 (1997) 73-79***

The Annonaceous acetogenin bullatacin is cytotoxic against multidrug-resistant human mammary adenocarcinoma cells

Nicholas H. Oberlies, Vicki L. Croy, Marietta L. Harrison, Jerry L. McLaughlin

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University.

Cytotoxic effects of the Annonaceous acetogenin, bullatacin, were studied in multidrug-resistant (MDR) human mammary adenocarcinoma (MCF-7/Adr) cells vs. the parental non-resistant wild type (MCF-7/wt) cells. Bullatacin was effectively cytotoxic to the MCF-7/Adr cells while it was more cytostatic to the MCF-7/wt cells. ATP depletion is the mode of action of the Annonaceous acetogenins, and these agents offer a special advantage in the chemotherapeutic treatment of MDR tumors that have ATP-dependent mechanisms.

ABSTRACT: ***J. Med. Chem. 1997, 40, 2102-2106***

Structure-activity relationships of diverse Annonaceous acetogenins against multidrug-resistant human mammary adenocarcinoma (MCF-7/ Adr) cells

Nicholas H. Oberlies, Ching-jer Chang, Jerry L. McLaughlin

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University.

Fourteen structurally diverse Annonaceous acetogenins, representing the three main classes of bis-adjacent, bis-nonadjacent, and single-THF ring(s), were tested for their ability to inhibit the growth of adriamycin-resistant human mammary adenocarcinoma (MCF-7/Adr) cells. This cell line is resistant to treatment with adriamycin, vincristine, and vinblastine and is, thus, multidrug-resistant (MDR). Among a series of bis-adjacent THF ring acetogenins, those with the stereochemistry of threo-trans-threo-trans-erythro (from C-15 to C-24) were the most potent with as much as 250 times the potency of adriamycin. A spacing of 13 carbons between the flanking hydroxyl of the THF ring system and the gamma-unsaturated lactone seems to be optimum with a spacing of 11 and 9 carbons being significantly less active. Several single-THF ring compounds were also quite potent, with gigantetrocin A (11) being the most potent compound tested. The acetogenins may, thus, have chemotherapeutic potential, especially with regard to MDR tumors.

. *Med. Chem.*, **40** (13), 2102 -2106, 1997. jm9700169
S0022-2623(97)00016-2

Structure-Activity Relationships of Diverse Annonaceous Acetogenins against Multidrug Resistant Human Mammary Adenocarcinoma (MCF-7/Adr) Cells

Nicholas H. Oberlies, Ching-jer Chang, and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907-1333

Received January 9, 1997

Abstract:

Fourteen structurally diverse Annonaceous acetogenins, representing the three main classes of bis-adjacent, bis-nonadjacent, and single-THF ring(s), were tested for their ability to inhibit the growth of adriamycin resistant human mammary adenocarcinoma (MCF-7/Adr) cells. This cell line is resistant to treatment with adriamycin, vincristine, and vinblastine and is, thus, multidrug resistant (MDR). Among a series of bis-adjacent THF ring acetogenins, those with the stereochemistry of *threo-trans-threo-trans-erythro* (from C-15 to C-24) were the most potent with as much as 250 times the potency of adriamycin. A spacing of 13 carbons between the flanking hydroxyl of the THF ring system and the γ-unsaturated lactone seems to be optimum with a spacing of 11 and 9 carbons being significantly less active. Several single-THF ring compounds were also quite potent with gigantetrocin A (**11**) being the most potent compound tested. The acetogenins may, thus, have chemotherapeutic potential, especially

with regard to MDR tumors.

J. Nat. Prod., **62** (3), 504 -540, 1999. 10.1021/np980406d
S0163-3864(98)00406-6
Web Release Date: March 4, 1999

Annonaceous Acetogenins: Recent Progress

Feras Q. Alali, Xiao-Xi Liu, and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received September 18, 1998

Abstract:

The Annonaceous acetogenins are promising new antitumor and pesticidal agents that are found only in the plant family Annonaceae. Chemically, they are derivatives of long-chain fatty acids. Biologically, they exhibit their potent bioactivities through depletion of ATP levels via inhibiting complex I of mitochondria and inhibiting the NADH oxidase of plasma membranes of tumor cells. Thus, they thwart ATP-driven resistance mechanisms. This review presents the progress made in the chemistry, biology, and development of these compounds since December 1995.

Biochemistry, **37** (3), 854 -866, 1998. bi9723481
S0006-2960(97)02348-9
Web Release Date: January 6, 1998

Membrane Conformations and Their Relation to Cytotoxicity of Asimicin and Its Analogues‡

Hiroko Shimada, John B. Grutzner,§ John F. Kozlowski,‡ and Jerry L. McLaughlin*‡

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, and Department of Chemistry, School of Sciences, Purdue University, West Lafayette, Indiana 47907

Received September 22, 1997

Revised Manuscript Received November 10, 1997

Abstract:

Certain plant species belonging to the family Annonaceae produce Annonaceous acetogenins, which are a unique class of long-chain fatty acid derivatives with potent cytotoxicity. Putative protein targets of the acetogenins are membrane-associated proteins, including complex I. Asimicin and its analogues constitute a class of Annonaceous acetogenins containing two tetrahydrofuran (THF) rings with hydrocarbon chains tethered to each ring; an α,β-unsaturated γ-lactone ring is terminal to one of the alkyl chains. The compounds examined in this study differ in the length of the alkyl chain between the THF rings and the lactone ring. The positions of both the THF and the lactone rings within liposomal membranes were determined by proton (^{1}H) nuclear magnetic resonance spectroscopy. The depth of membrane penetration of acetogenins, coupled to membrane

diffusion, controls the conformation of acetogenins as they diffuse to an active site. Based on 1H intermolecular nuclear Overhauser effects (NOEs), the THF rings of all acetogenins studied reside near the polar interfacial head group region of the DMPC. This was corroborated by 1H two-dimensional NOE spectroscopy and differential scanning calorimetry studies. The 1H difference NOE spectra indicated that the lactone rings of asimicin and parviflorin, the latter of which has two fewer carbons in its alkyl chain, are located below the glycerol backbone in the membrane. In contrast with asimicin and parviflorin, the lactone ring of longimicin B, an asimicin analogue with an alkyl chain four carbons shorter, resides close to the midplane in the membrane. This was corroborated by manganese-induced broadening studies. Since the THF rings are located near the center of the acetogenin molecules and the lactone ring is terminal to a long alkyl chain, these observations indicate that an asimicin-type acetogenin can be in either sickle-shaped or U-shaped conformations, depending on the length of the alkyl chain between the THF rings and the lactone ring. Interestingly, longimicin B does not exhibit significant cytotoxicity, but parviflorin is as cytotoxic as asimicin. The cytotoxicity of the asimicin-type of acetogenins would seem to be strongly related to the membrane conformation. This is the first report elucidating the conformation of Annonaceous acetogenins in membranes.

1: Cancer Lett. **1997 May 1;115(1):73-9.** ELSEVIER FULL-TEXT ARTICLE **Links**

The Annonaceous acetogenin bullatacin is cytotoxic against multidrug-resistant human mammary adenocarcinoma cells.

Oberlies NH,
Croy VL,
Harrison ML,
McLaughlin JL.

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907-1333, USA.

Cytotoxic effects of the Annonaceous acetogenin, bullatacin, were studied in multidrug-resistant (MDR) human mammary adenocarcinoma (MCF-7/Adr) cells vs. the parental non-resistant

wild type (MCF-7/wt) cells. Bullatacin was effectively cytotoxic to the MCF-7/Adr cells while it was more cytostatic to the MCF-7/wt cells. ATP depletion is the mode of action of the Annonaceous acetogenins, and these agents offer a special advantage in the chemotherapeutic treatment of MDR tumors that have ATP-dependent mechanisms.

PMID: 9097981 [PubMed - indexed for MEDLINE]

oi:10.1016/S0304-3835(97)04716-2 Cite or Link Using DOI

The Annonaceous acetogenin bullatacin is cytotoxic against multidrug-resistant human mammary adenocarcinoma cells

Nicholas H. Oberlies, Vicki L. Croy, Marietta L. Harrison and Jerry L. McLaughlin,

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907-1333, USA

Received 19 December 1996; Revised 14 January 1997; accepted 14 January 1997. Available online 15 December 1997.

Abstract

Cytotoxic effects of the Annonaceous acetogenin, bullatacin, were studied in multidrug-resistant (MDR) human mammary adenocarcinoma (MCF-7/Adr) cells vs. the parental non-resistant wild type (MCF-7/wt) cells. Bullatacin was effectively cytotoxic to the MCF-7/Adr cells while it was more cytostatic to the MCF-7/wt cells.

ATP depletion is the mode of action of the Annonaceous acetogenins, and these agents offer a special advantage in the chemotherapeutic treatment of MDR tumors that have ATP-dependent mechanisms.

Author Keywords: Acetogenins; Bullatacin; Multidrug resistance; P-gp; Mammary adenocarcinoma

Corresponding author. Tel.: +1 317 4941455; fax: +1 317 4941414.

1: J Med Chem. **1997 Jun 20;40(13):2102-6.**

Structure-activity relationships of diverse Annonaceous acetogenins against multidrug resistant human mammary adenocarcinoma (MCF-7/Adr) cells.

Oberlies NH,
Chang CJ,
McLaughlin JL.

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907-1333, USA.

Fourteen structurally diverse Annonaceous acetogenins, representing the three main classes of bis-adjacent, bis-nonadjacent, and single-THF ring(s), were tested for their ability to inhibit the growth of adriamycin resistant human mammary adenocarcinoma (MCF-7/Adr) cells. This cell line is resistant to treatment with adriamycin, vincristine, and vinblastine and is, thus, multidrug resistant (MDR). Among a series of bis-adjacent THF ring acetogenins, those with the stereochemistry of threo-trans-threo-trans-erythro (from C-15 to C-24) were the most potent with as much as 250 times the potency of adriamycin. A spacing of 13 carbons between the flanking hydroxyl of the THF ring system and the gamma-unsaturated lactone seems to be optimum with a spacing of 11 and 9 carbons being significantly less active. Several single-THF ring compounds were also quite potent with gigantetrocin A (11) being the most potent compound tested. The acetogenins may, thus, have chemotherapeutic potential, especially with regard

to MDR tumors.

PMID: 9207950 [PubMed - indexed for MEDLINE]

Bioorg Med Chem. **1997 Mar;5(3):501-6.** ELSEVIER FULL-TEXT ARTICLE Links

Additional bioactive annonaceous acetogenins from Asimina triloba (Annonaceae).

He K,
Zhao GX,
Shi G,
Zeng L,
Chao JF,
McLaughlin JL.

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, USA.

Trilobalicin (1), a new nonadjacent bis-THF ring annonaceous acetogenin, 2,4-cis- (2) and 2,4-trans-trilobacinone (3), the ketolactones of trilobacin, an adjacent bis-THF ring acetogenin, were isolated from the stem bark of Asimina triloba (L.) Dunal (Annonaceae). Their structures were established based on chemical and spectral evidence. The relative stereochemistry of 1 was determined as trans/threo/threo/trans/erythro from C-10 to C-22 by comparisons of NMR data with those of model compounds. Compound 1 is the first example of a nonadjacent bis-THF acetogenin being isolated from the title species and represents a new type of these compounds. Bioactivities of these new structures against brine shrimp larvae and six human solid tumor cell lines were determined, and cytotoxic selectivities were shown for the lung (A-549) and breast (MCF-7) cell lines with up to a million times the potency of adriamycin.

PMID: 9113328 [PubMed - indexed for MEDLINE]

Bioorganic & Medicinal Chemistry
Volume 5, Issue 3 , March 1997, Pages 501-506

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Abstract
Abstract + References
PDF (474 K)
External Links

doi:10.1016/S0968-0896(96)00264-7

Additional bioactive annonaceous acetogenins from *Asimina triloba* (Annonaceae)

Kan He, Geng-Xian Zhao, Guoen Shi, Lu Zeng, Jin-Feng Chao and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, U.S.A.

Received 16 July 1996; accepted 9 October 1996. ; Available online 25 March 1998.

Abstract

Trilobalicin (**1**), a new nonadjacent bis-THF ring annonaceous acetogenin, 2,4-*cis*- (**2**) and 2,4-*trans*-trilobacinone (**3**), the ketolactones of trilobacin, an adjacent bis-THF ring acetogenin, were isolated from the stem bark of *Asimina triloba* (L.) Dunal (Annonaceae). Their structures were established based on chemical and spectral evidence. The relative stereochemistry of **1** was determined as *trans/threø threø trans/erythro* from C-10 to C-22 by comparisons of NMR data with those of model compounds. Compound **1** is the first example of a nonadjacent bis-THF acetogenin being isolated from the title species and represents a new type of these compounds. Bioactivities of these new structures against brine shrimp

larvae and six human solid tumor cell lines were determined, and cytotoxic selectivities were shown for the lung (A-549) and breast (MCF-7) cell lines with up to a million times the potency of adriamycin.

Graphical Abstract

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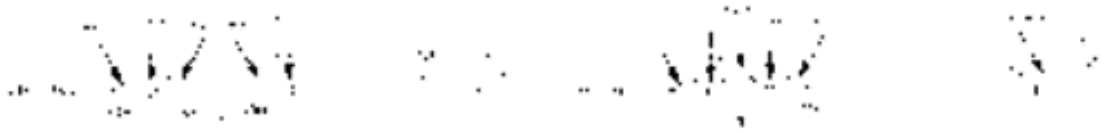

Bioorganic & Medicinal Chemistry
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Further reading:

http://www.pawpawresearch.com/articles-acs.htm

September 1997 -Pawpaw shows promise in fighting drug-resistant tumors

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Though further studies are needed to pinpoint exactly how the pawpaw compounds work within the cancer cell, McLaughlin says their effect is to pull the plug on the energy-producing mechanisms in the cell. McLaughlin notes, however, that the effect on drug-resistant cells has been studied only in laboratory cultures and will require additional study in animals before it can be tested in humans. "Multidrug-resistant cancer is hard to treat because the cancer cell has developed a mechanism to get around the anti-cancer agent," says McLaughlin, professor of pharmacognosy in Purdue's School of Pharmacy and Pharmacal Science. "Tumor cells that survive chemotherapy treatments often recover with increased resistance to the agent used in the original treatment program as well as to other related drugs."

Such resistance can develop when surviving cancer cells develop one or more mechanisms to accelerate the removal of noxious substances, including anti-cancer drugs. One of the most common mechanisms used to circumvent the anti-cancer agents is to develop a "pump" that is capable of pushing anti-cancer agents out of the cell before they can kill it. These pumps are called P-glycoprotein mediated pumps and are named for the type of protein used to construct and

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Though all cells have the ability to develop such a pump, normal cells seldom do. Even in cancer cells, which do not respond normally to the body's control mechanisms, only a small percentage of cells develop this pumping mechanism.

"If having this pump was such a good deal, all cells would have it. But all cells don't," McLaughlin says. "In a given population of cancer cells in a person, maybe only 2 percent of the cancer cells possess this pump. But it's those 2 percent of cancer cells that eventually grow and expand to create drug-resistant tumors."

One of the tricks currently attempted in treating cancer patients is to flood the body with other compounds to keep the pump busy, and then administer high doses of an anti-cancer agent in hopes that some of it will be able to stay in long enough to kill the cancer cell. "But the high doses of the drugs required for this treatment often produce side effects, such as loss of blood pressure, so the patient often succumbs to the side effects of the treatment," McLaughlin says.

Though this pump mechanism is efficient at eliminating most anti-cancer agents, McLaughlin, whose research group has identified more than 40 pawpaw compounds with anti-cancer properties, discovered a series of the compounds, called Annonaceous acetogenins, that were capable of killing cancer cells that employed this mechanism. He then designed a laboratory study to analyze the cytotoxic or cell-killing effects of one of the compounds, called bullatacin, on human mammary cancer cells. The study compared bullatacin's effects on standard, nonresistant cancer cells and on multidrug-resistant cells. In the June issue of Cancer Letters, the research team reported that bullatacin preferentially killed the multidrug-resistant cells by inhibiting the production of adenosine triphosphate, or ATP. ATP is a compound that works to release energy in a cell and is essential to all cell processes.

"A multidrug-resistant cell requires a tremendous amount of energy to run the pump and extrude things out of the cell," McLaughlin says. "By inhibiting ATP production, we're essentially pulling the plug on its energy source."

Though the pawpaw compounds also inhibited ATP production in noncancerous cells and nonresistant cancer cells, those cells were not affected as dramatically, McLaughlin says. "Normal cells and standard cancer cells may be able to minimize the effects of this compound because they don't require the vast amounts of energy needed by the pump-running cells," McLaughlin says. "The resistant cell is using its extra energy for this pump as well as to grow, so it is really taxed for energy. When we mess with the energy supply, it kills the cell." McLaughlin and his group then did a follow-up study to test a series of 14 structurally similar pawpaw compounds to determine the structural features that maximize this biological activity in multidrug-resistant cancer cells. The results were published in the June issue of the Journal of Medicinal Chemistry.

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The studies were funded by National Institutes of Health/ National Cancer Institute, the Indiana Elks Cancer Research Fund and Purdue Research Foundation. Purdue has filed a patent on the use of the pawpaw compounds.

Source: Jerry McLaughlin, (765) 494-1455; e-mail, jac@pharmacy.purdue.edu
Writer: Susan Gaidos, (765) 494-2081; e-mail, susan_gaidos@uns.purdue.edu

Purdue News Service: (765) 494-2096; e-mail, purduenews@uns.purdue.edu

ABSTRACT: Cancer Letters 115 (1997) 73-79

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NOTE TO JOURNALISTS: Copies of the journal articles mentioned in the story are available from Susan Gaidos, the Purdue News Service, (765) 494-2081.

The Pawpaw Asimina triloba Scientific Paper

Introduction

Cancer is a devastating disease for which there is yet no absolute cure. Genetic predisposition and mutations (abnormal changes in the nuclei of cells) caused by chemicals, radiation, hormones, and viruses account for 5-10% and 90-95% of all cancers, respectively. Cancer afflicts almost every part of the human body from the skin to the marrows and is indiscriminate of age. The annual U.S. death toll from cancer is over 555,000 and costs about $156 billion in direct medical, indirect morbidity and mortality expense and losses.

Different approaches are employed in the treatment of cancer, depending on type, site and stage. In situ cancers are surgically removed and followed up with other treatments if metastasized to the lymph nodes and other organs. Cancer cells grow and multiply rapidly and anticancer drugs (chemotherapy) normally destroy cancer cells by damaging their genetic material, thus stopping their proliferation. Some drugs work better together than alone, hence two or more drugs are often given at the same time. Unfortunately, most

anticancer drugs are not selective, thus healthy cells can also be harmed, especially those that divide quickly. Harm to healthy cells causes the side effects. Healthy cells, however, can replicate and re-establish a normal population and size after chemotherapy.

Radiation therapy, also called radiotherapy, is the treatment of cancer and other diseases with ionizing radiation, especially for localized solid tumors, such as cancers of the skin, tongue, brain, breast, or uterine cervix. Radiotherapy can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively). Ionizing radiation destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow. Both cancerous and normal cells are also damaged during treatment.

Newer forms of treatment involve angiogenesis inhibition, stimulating the immune system to fight cancer, bone marrow and peripheral stem cell transplantation, and gene and photodynamic therapy. Possible side effects of cancer treatment include loss of hair, skin irritation, infection, anemia (due to bone marrow depression), temporary change in skin color in the treated area, bleeding (platelet depletion), infections, chemo-induced cancer, and generalized weakness. Other side effects are largely dependent on the area of the body that is treated.

Pawpaw and Cancer

The pawpaw tree is native to the eastern U.S. It is a member of the family Annonacae, which also includes such tropical fruits as the Cherimoya and Guyabana. Pawpaws have been consumed by Native Americans for thousands of years. Eli Lilly and Company sold a liquid extract of its seeds at the end of the 1800’s as an emetic. Thus, it has a history of safe human use and consumption.

Annonaceous acetogenins are complex mixtures of long

chain fatty acids derivatives from the extracts of the twigs of the pawpaw tree. Many of the acetogenins have been isolated and characterized, and their numerous health benefits are being explored. Three, bullatacin, asimicin, and trilobacin, have been identified as the most potent, major, bioactive structural types of acetogenins in the paw paw concentrate.

Difficulties with most of the chemotherapeutic drugs emanate from their concurrent eradication of normal healthy cells, including those responsible for immunity.

Tumor cells grow and replicate more rapidly than normal cells. This is because they are better equipped to receive glucose, a good source of energy for fast replication. Also, cancer cells quickly develop a network of blood vessels (angiogenesis) to ensure an efficient supply of nutrients and oxygen. This is partly why cancer patients lose weight; the cancer cells rapidly take up nutrients meant for normal cells.

Furthermore, with chemotherapy cancer cells develop resistance to the drugs, rendering chemotherapy useless and futile after a period of remission. The same principle applies to other diseases that have become drug resistant, such as malaria. The organisms and cancer cells smartly find a way of protecting themselves from the damaging effects of drugs. They generate what is called the ABC transporter superfamily, which transports a variety of substrates including amino acids, sugars, inorganic ions, polysaccharides, peptides, and proteins into the cells. In cancer cells, a member of this superfamily, called the multidrug resistant (MDR) protein, is overexpressed and helps to pump drugs out of the cancer cells, making the cancer cells simultaneously resistant to a variety of drugs. Thus, the cancer cells are protected from the toxic effects of drug combinations.

Annonaceous acetogenins may be good chemotherapeutic agents for cancer. These compounds inhibit mitochondrial and cytoplasmic production of adenosine triphosphate (ATP),

which is the major source of energy for the cells and also a precursor of the nucleotides needed to produce DNA and RNA. Annonaceous acetogenins inhibit the enzymes of complex I in the electron transport system in mitochondria. They also inhibit the NADH oxidases found in the plasma membranes of tumor cells. Their net effect is depletion of ATP levels.

Tumor cells, being typically metabolically more active, are more susceptible than normal cells to the effects of the acetogenins. Angiogenesis requires ATP and angiostatin blocks angiogenesis by inhibiting ATP synthase. Thus, ATP depletion helps to block the growth of new vessels to nourish tumors. Tyrosine kinases, which play roles in tumor progression, are also inhibited by ATP depletion.

Annonaceous acetogenins also thwart MDR tumor cells. The protein pumps (glycoproteins), which extrude the drugs from the tumor cells are energized by ATP. Thus, by depleting ATP, the glycoproptein pumps become dysfunctional.

Ongoing studies confirm the benefits of pawpaw extracts in clinical cancer treatments. Pawpaw extracts can be used to inhibit the growth of cancer cells and as effective alternative or supplement to chemotherapeu- -tic agents. Research information suggests that the bioactive compounds in pawpaw will prevent the growth of cancer cells and shrink tumors. A standardized pawpaw extract, Pawpaw Cell-Reg, containing mixtures of annonaceous acetogenins is now available. Research studies also show that pawpaw extracts are antimicrobial, antifungal, and effective against intestinal worms and head lice.

Contraindication

It is not advisable to take Pawpaw with nutritional supplements like CoQ10 and thyroid stimulators, as these supplements enhance mitochondrial complex 1 activities and energy production, respectively. Likewise, antioxidants should not be taken since they block

programmed cell deaths (apoptosis) and can reverse the damaging effects of pawpaw on the cancer cells.

Safety/Toxicity

The acetogenins are not mutagenic. Unlike most antitumor drugs, acetogenins do not exert their effects by poisoning DNA; they selectively inhibit ATP production. These results have been confirmed in a recent publication in which two pawpaw acetogenins were found to be antimicrobial but not mutagenic. In other unpublished results (Asta Laboratories), bullatacin was emetic in pigs. This result demonstrated that the acetogenins very likely explain the former use of Eli Lilly's liquid extract of pawpaw seeds as an emetic preparation. Unpublished report shows that vomiting (emesis) prevented toxicity of pawpaw capsules in dogs. Emesis is a definite safety factor should someone ingest excessive amounts of this supplement either intentionally or unintentionally. Any potential systemic toxic effects are conveniently thwarted by emesis.

A recent study on the island of Guadeloupe suggested that a higher than usual incidence of atypical Parkinsonism there might be caused by the chronic consumption of herbal teas and fruits from the Annonaceae family (Annona muricata and A. squamosa); some of the benzyltetrahydroiso-quinoline alkaloids found therein are believed to be neurotoxic and, thus, may be responsible for the Parkinsonism. Such alkaloids are carefully excluded from the annonaceous extracts during manufacture of Pawpaw Cell-Reg.