



FLORIDA
**MASTER
GARDENER**
VOLUNTEER

Plant-Derived Cancer Therapy

James J. Stark, MD, FACP

Professor of Medicine, Eastern Virginia Medical School
Florida Master Gardener Volunteer Trainee



UF | IFAS Extension
UNIVERSITY of FLORIDA

mastergardener.ifas.ufl.edu

Background

- Internal Medicine Residency
- Medical Oncology Fellowship
- 34 years of caring for adults with cancer
- 44 years of teaching Oncology to medical students, interns, residents and practicing oncologists

This talk....

- Review the history of drug development in the treatment of advanced cancer
- Discuss the methodology of discovering new cancer drugs in the plant world
- Discuss the role of plants and plant extracts in the treatment of cancer
- Examine the structure of cancer-fighting chemicals discovered in plants
- Look at several well-established cancer drugs derived from plants
- Debunk the role of other plant derivatives that have attracted a cult following in the treatment of cancer

Plant-Derived Cancer Therapy

- 25% of all drugs in use today are derived from plants
- Another 25% are chemically altered natural products
- Fewer than 10% of all the plant species in the world have been investigated for possible medicinal uses
- Only recently have plants been found to possess anti-cancer properties
- As with many of the most important advances in science, most discoveries have been by serendipity.

A Very Brief History of Cancer Drugs

- The earliest modern cancer drug was a derivative of mustard gas, used in World War I when it was discovered that mustard gas damaged the bone marrow as well as the lungs. The drug that was harvested from mustard gas – nitrogen mustard – had usefulness against cancer. Mustard gas is not from mustard, however; only the color is the same.

Mustard Gas Poisoning in WW I



Unseen in picture is lethal damage to the bone marrow

From a German magazine article in 1948

Als Beispiel für die gute Rückbildung von Hautmetastasen, Halslymphknoten und Milztumoren seien an dieser Stelle einige Bilder eingefügt.



Abb. 3a.

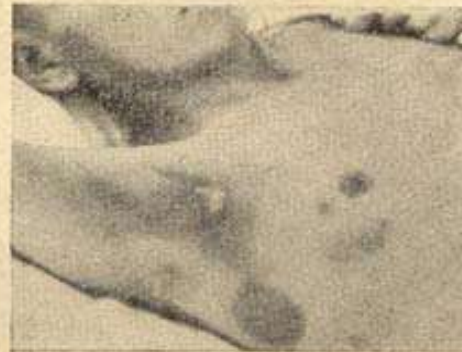


Abb. 3b.

Abb. 3. Hautmetastase eines Retothelsarkoms (Fall F). 3a) Vor der N-Lost-Behandlung. 3b) Nach der N-Lost-Behandlung.



Abb. 4a.



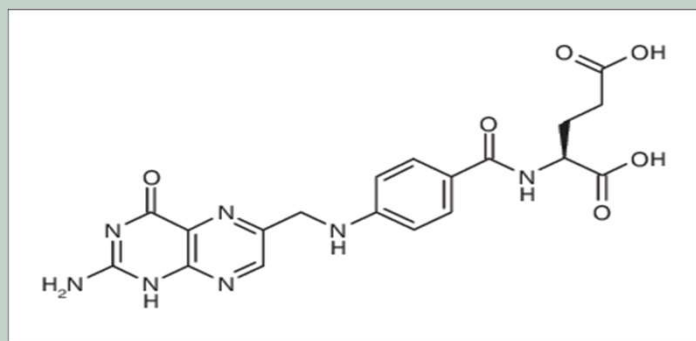
Abb. 4b.

Abb. 4. Halsdrüsen-entwelling bei Lymphogranulomatose a) vor, b) nach Behandlung mit N-Lost + Phenylurethan. (Fall Z.)

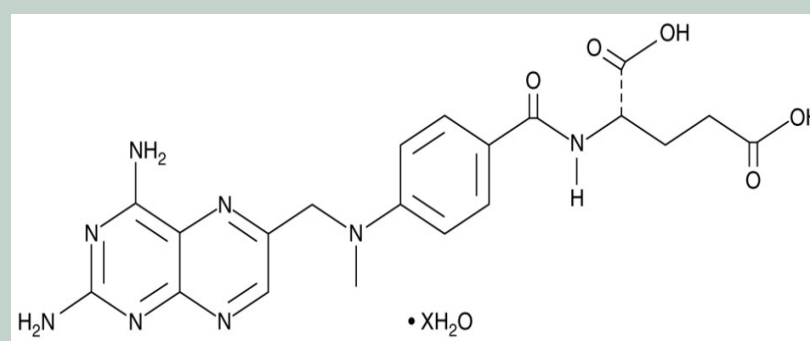
Serendipity

The Beginning of Designer Cancer Drugs

- In the 1940's new molecules were synthesized to mimic, and interfere with, the actions of key metabolites such as folic acid in the metabolism of the human cell...an exception to serendipity
- This approach is most useful in dividing cells – as are all cancer cells



Folic Acid



Methotrexate

Initial Efforts With Plants

- Scientists in the 1950's recognized from prior anecdotes, including stories of miracle cures in the Amazon jungle, the potential for plants to contain anti-cancer chemicals.
- In 1955 the National Cancer Institute created the *Cancer Chemotherapy National Service Center* to evaluate new compounds
- In 1960 the CCNSC partnered with the Department of Agriculture to screen potential new compounds derived from plants
- From 1960 to 1981 over 30,000 plant-derived compounds were tested as potential anti-cancer agents

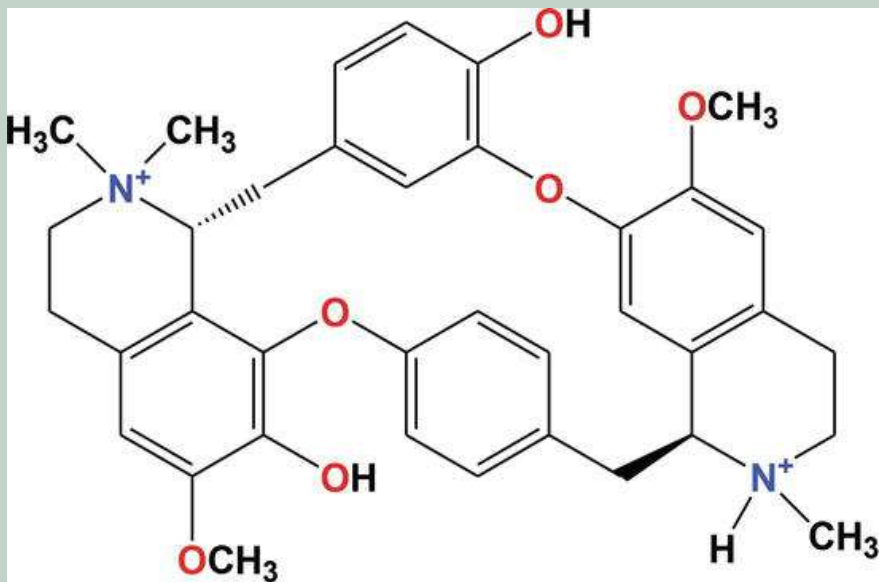
Cataranthus roseus, or
Madagascar Periwinkle



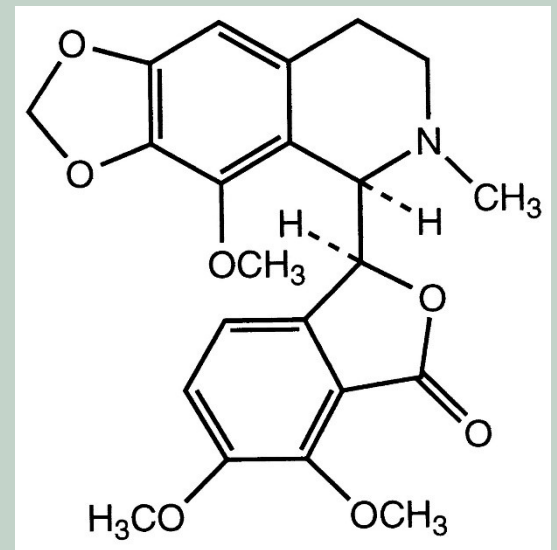
Catharanthus roseus, continued

- Used as a folk remedy for centuries
- Studies in 1950 revealed it contains over 120 alkaloids
 - (An alkaloid is a large multi-ringed molecule made by a plant containing nitrogen in at least one of its rings)
- One of the alkaloids – Vincristine – was initially thought to be a treatment for diabetes
- Didn't work but lowered blood counts as side effect – similar to nitrogen mustard
 - Then used against leukemia in mouse leukemia model; very effective
- Organic chemistry of extracting active alkaloids resulted in isolating several compounds
 - Three stood out as having anti-cancer activity
 - Vincristine
 - Vinblastine
 - Vinorelbine – not naturally occurring; made in the lab from precursors

Two Other Plant Alkaloids



Tubocurarine

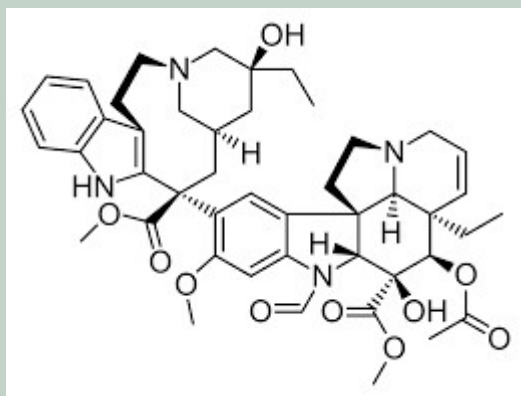


Opium

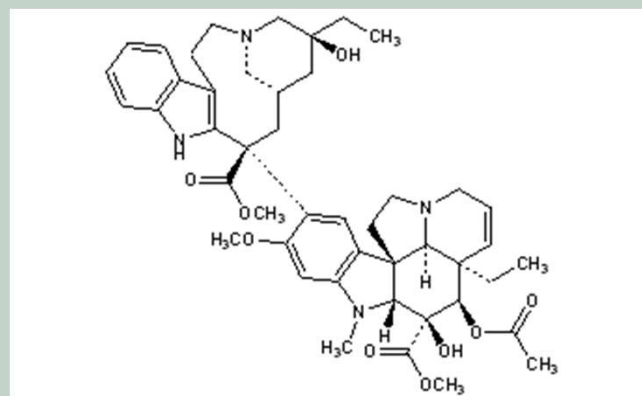
Catharanthus roseus, continued

- Takes one ton of dried periwinkle to produce one ounce of vincristine
 - Criticized by naturalists as bioprospecting – harvesting plants sufficiently to cause their exhaustion in nature – most of the drug was produced from periwinkle from Madagascar, a fragile biosphere
 - Some periwinkle from the Brazilian rain forests was used as well
 - The profit motive took precedence over conservation
 - Eventually, semi-synthetic, then fully synthetic organic chemistry evolved to allow the anti-cancer vinca alkaloids to be produced without decimating the biosphere

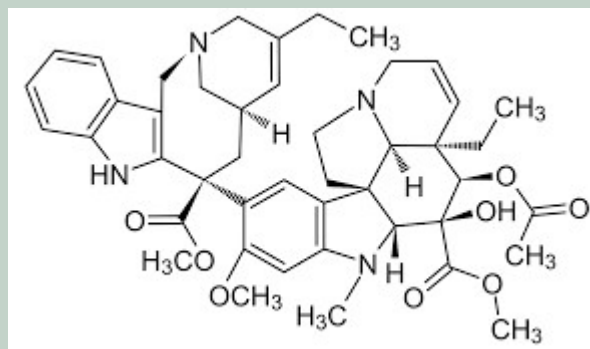
Structures of the Vinca Alkaloids Used in Cancer Therapy



Vincristine

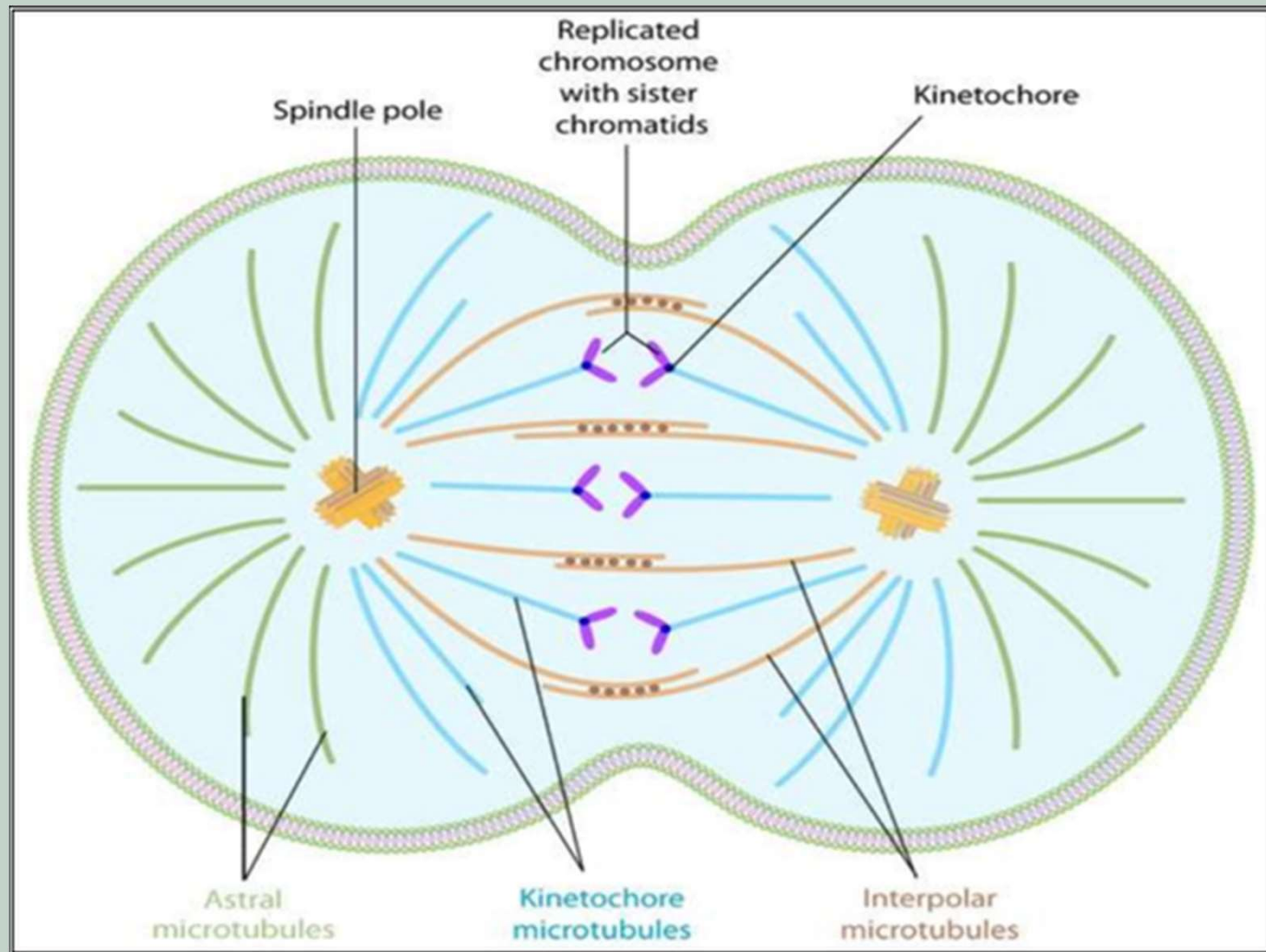


Vinblastine



Vinorelbine

Mechanism of Action of Vinca Alkaloids



Vinca Alkaloids today: Efficacy and Toxicity

- Vincristine a key component in the treatment of childhood leukemia and adult Hodgkin and non-Hodgkin lymphoma
- Vinblastine used in the treatment of testicular cancer and Hodgkin lymphoma
- Vinorelbine used in the treatment of advanced lung cancer
- All suppress the bone marrow and damage the nervous system; these toxicities are dose limiting

Arthur Barclay

- In the early 1960's worked as a botanist for the USDA
- Hiked all over the Pacific Northwest looking for promising plant specimens
- Spotted the Yew tree in the Pinchot National Forest
 - Named for Gifford Pinchot, Chief of US Forestry Service and then Governor of Pennsylvania
- Had intuition that the bark of the Yew tree might have medicinal properties
 - I have not been able to figure out how or why he knew this

The Yew Tree



Yew berries



The Yew Berry – close up



The Yew Berry

- Highly poisonous to animals and humans
- Contains a chemical similar to that produced in the bark

The Bark of the Yew Tree



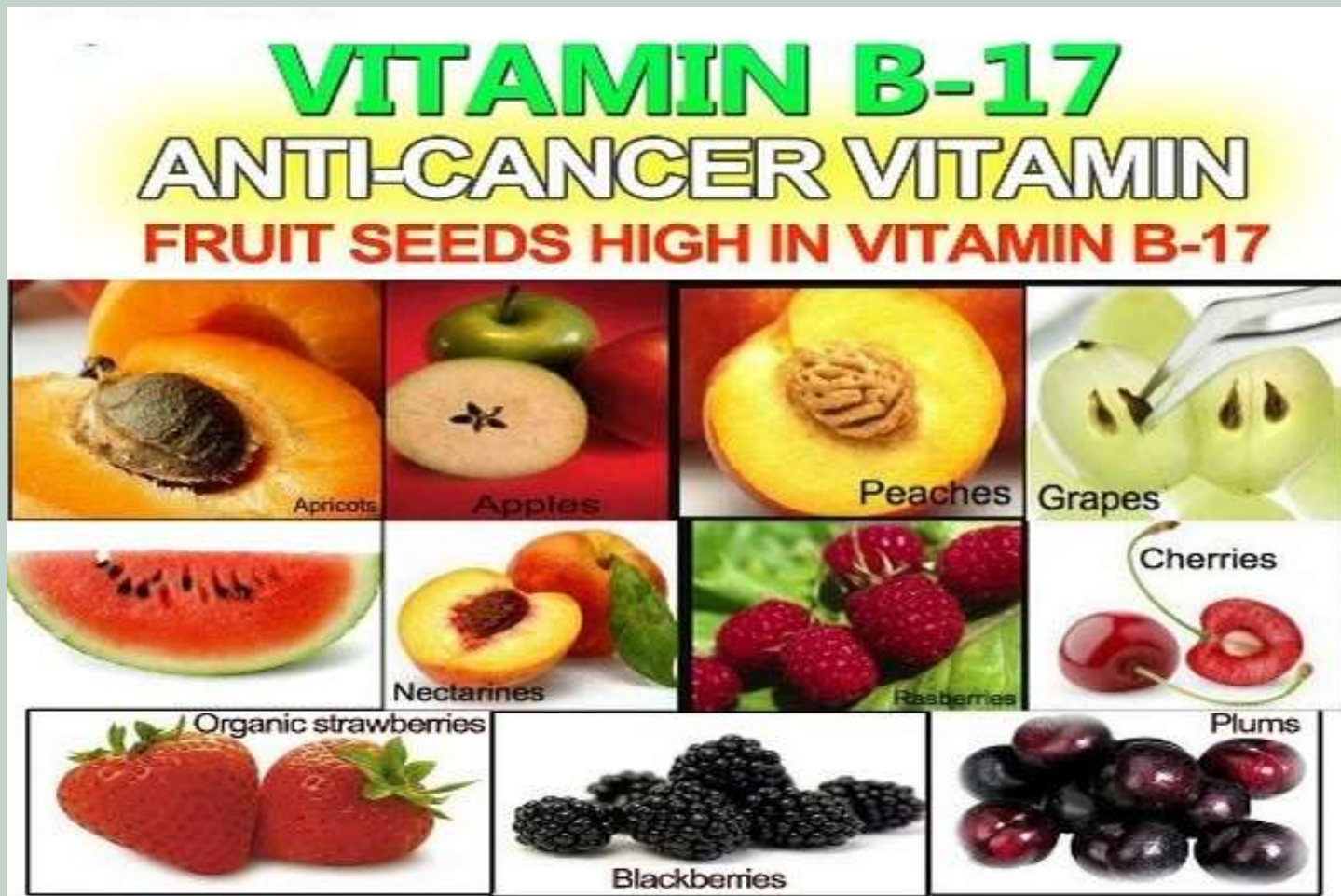
The Bark of the Yew tree

- After screening many compounds from the bark of the Yew tree, scientists identified the compound most toxic to cancer cells in the laboratory
- They called it taxol
- The drug worked by poisoning the cells as they were undergoing mitosis by interfering with the mitotic spindle – similar to the vinca alkaloids
- After considerable work in mouse models they determined that it merited trials in humans
 - Turned out to be very effective in the treatment of breast and ovarian cancers

The Fate of the Yew Tree

- Because taxol became such an important drug in the treatment of cancer, the Yew tree was threatened with over harvesting and eventual extinction
- Scientists in the laboratory have devised a way to produce totally synthetic taxol, sparing the Yew tree from further harvesting
- Today all taxol is made synthetically and the Yew tree has been saved

Bogus Anti-Cancer Botanicals

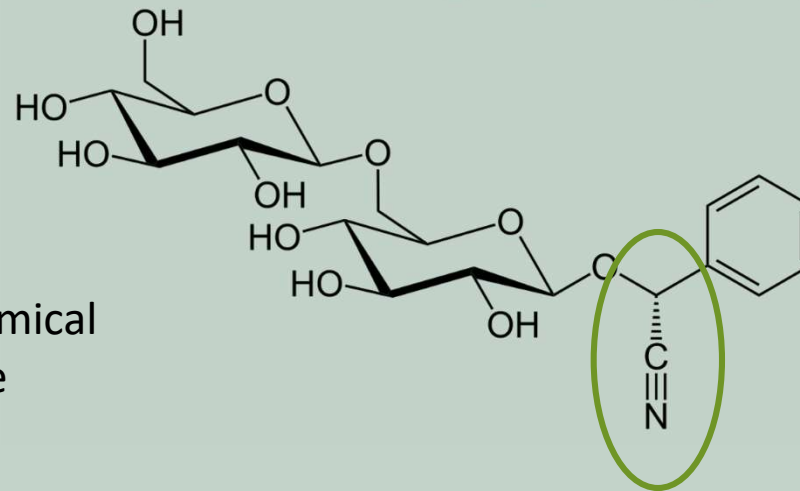


What does it mean when something is a vitamin?

Side effects of laetrile

- Semi-synthetic derivative of amygdalin
- Contains cyanide radical, which is converted to cyanide in the body
 - Prevents cells from taking up oxygen, suffocating them

Amygdalin, the chemical precursor to laetrile

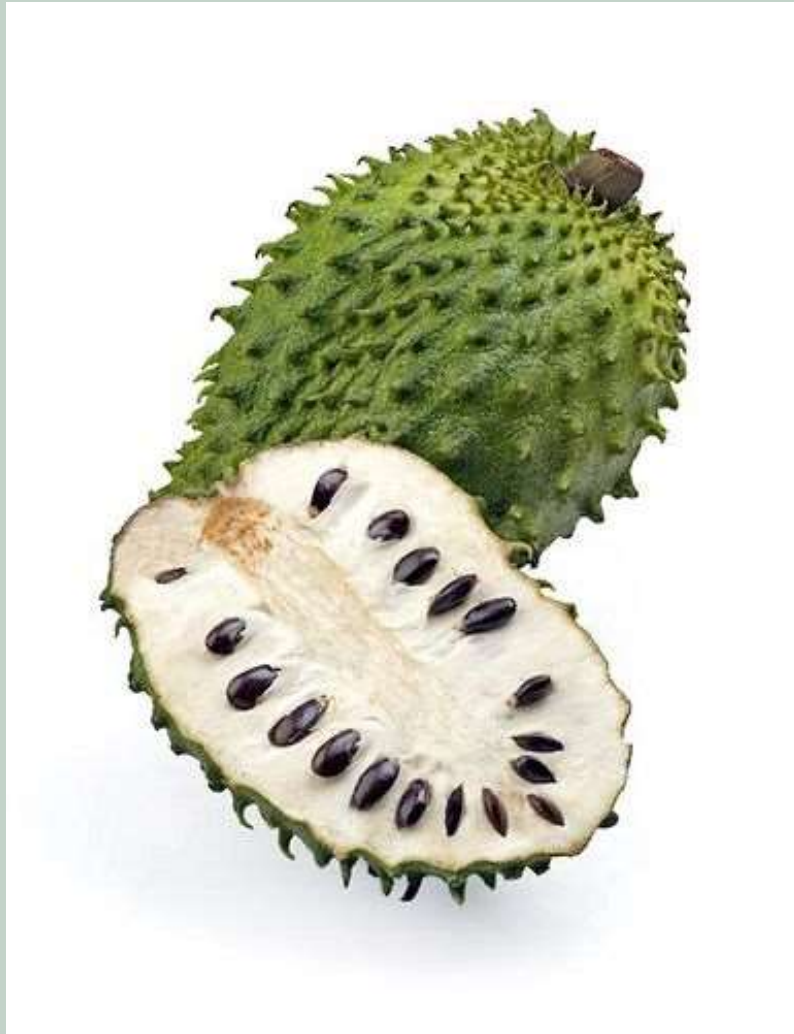


Laetrile

- Huge following in the 80's and 90's
- Some laboratory evidence that it might have anti-cancer properties using *in vitro* models with human cancer cells
- No reproducible anti-cancer effect was seen in humans; concern about cyanide poisoning
limited doses used
 - Currently manufactured in Mexico; no batch-to-batch uniformity

Soursop – touted in one of our lectures as having anti-cancer properties

A fruit with many synonyms: paw paw, guanabana, sirsak and graviola



Soursop, continued

- One fruit contains 215% of the MDR for vitamin C, a powerful anti-oxidant and possible inhibitor of cancer
- Contains small amounts of other antioxidants as well: phytosterols and flavonoids
- Contains 83% of the MDR for fiber
- Limited experimental evidence that it inhibits cancer cells *in vitro*
- NO EVIDENCE one way or the other that it helps combat cancer in humans once a tumor is large enough to be discovered and diagnosed

Screening our 250,000 plant species for potential human drugs

- High throughput analysis allows scientists today to screen thousands of new compounds for biologic (anti-cancer) activity
- One would imagine a new world of drugs
- Not so fast....this methodology has not borne fruit yet
- The next great drug discovery could result in depletion of additional plant species

Finally....

Seed storage – the next frontier

- The biosphere is under attack from climate change, capitalism and potential catastrophic global war
- How can we protect our biodiversity?
- One approach....

What is this?



The Svalbard Global Seed Vault



The vault contains over a million varieties of seeds deep inside a mountain maintained at -18°C .

Inside the Vault



The Global Seed Vault, continued

- Offers permanent protection of our plant diversity against natural and man-made intrusions.
- Keeps our sources of food and medicines stable indefinitely
- An international treaty governs how it is managed

Conclusions

- Plants as a source of life-saving cancer drugs are a new phenomenon that is still evolving
- The ability to synthesize the compounds – mostly alkaloids – found in plants in the laboratory will help protect the biosphere from depletion
- Our ability to analyze the structure of thousands of new plant-derived molecules for anti-cancer activity is in its infancy
- Our challenge – to protect the world of plants from ourselves and our greed – continues, with some new and radical approaches