

Emory University

HLTH 385: Botanical Medicine & Health

Remedial Plants: Cancer

Cassandra L. Quave, Ph.D.
Center for the Study of Human Health



EMORY

Learning Objectives

- What is the link between diet and cancer and why do some edible plants have protective effects against cancer?
- What are the main anti-cancer drugs (therapeutic agents) derived from plants; their historical use in traditional medicine; the types of cancer they are used to treat; and the basic concepts behind their mechanism of action?

The Botanical Stars



Catharanthus roseus



Taxus brevifolia



Camptotheca acuminata

NCI and Discovery of Anti-cancer drugs

- National Cancer Institute (NCI) established in 1937 & Developmental Therapeutics Program (DTP) established in 1950s
 - Screened natural products from fermentation of microbes (little interest in plants until 1960s – only 1500 looked at until this point)
 - Early success with plants like Madagascar periwinkle and mayapple drove further focus on plants
 - Between 1960-1982, 114,000 extracts from 35,000 plants were screened (collected from 60 countries)
 - Major discoveries included taxol & camptothecin

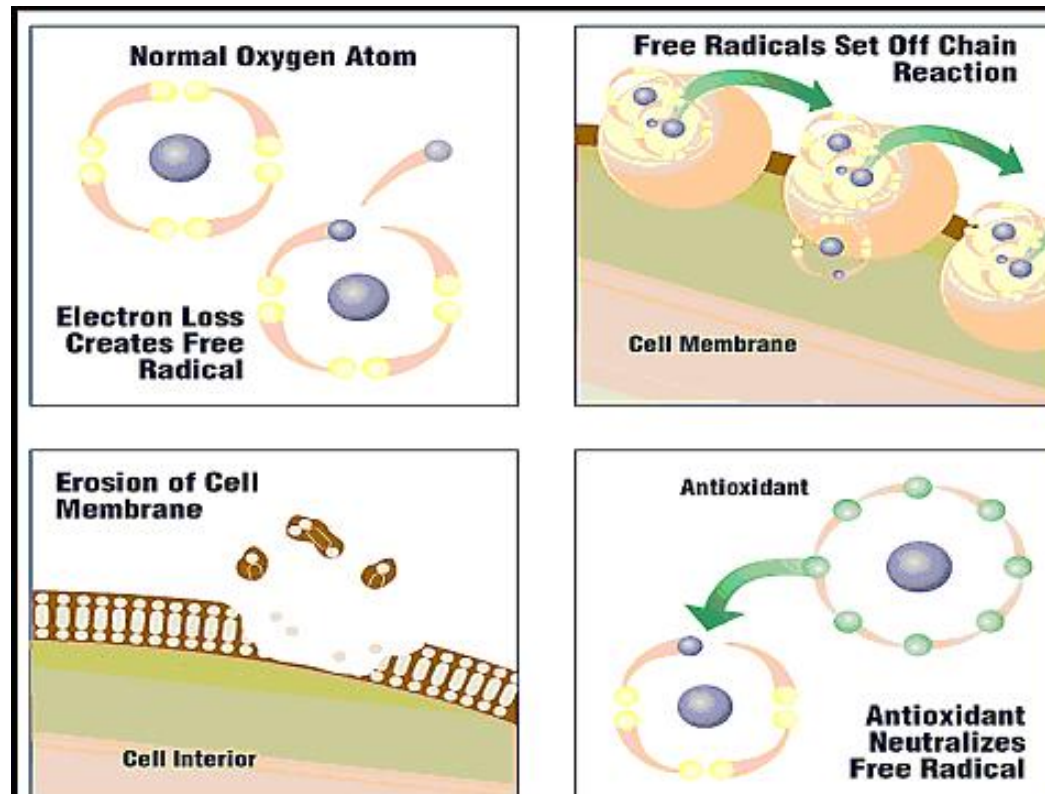
Overview

- **Cancer** is a class of diseases in which a group of cells display
 - uncontrolled growth (division beyond the normal limits)
 - invasion (intrusion on and destruction of adjacent tissues)
 - and sometimes metastasis (spread to other locations in the body via lymph or blood).
- Remedial Plants:
 - Prevention
 - *Camellia sinensis*
 - *Curcuma longa*
 - Therapy
 - *Camptotheca acuminata*
 - *Catharanthus roseus*
 - *Taxus brevifolia*
 - *Podophyllum peltatum*

What is an antioxidant???

- Molecule that inhibits oxidation of other molecules
- Oxidation reactions produce free radicals
- Free radicals start chain reactions that lead to cell damage or death
- Examples of antioxidant compounds:
 - Polyphenols
 - Ascorbic acid (vitamin C)
 - Carotenes
 - α -Tocopherol (vitamin E)

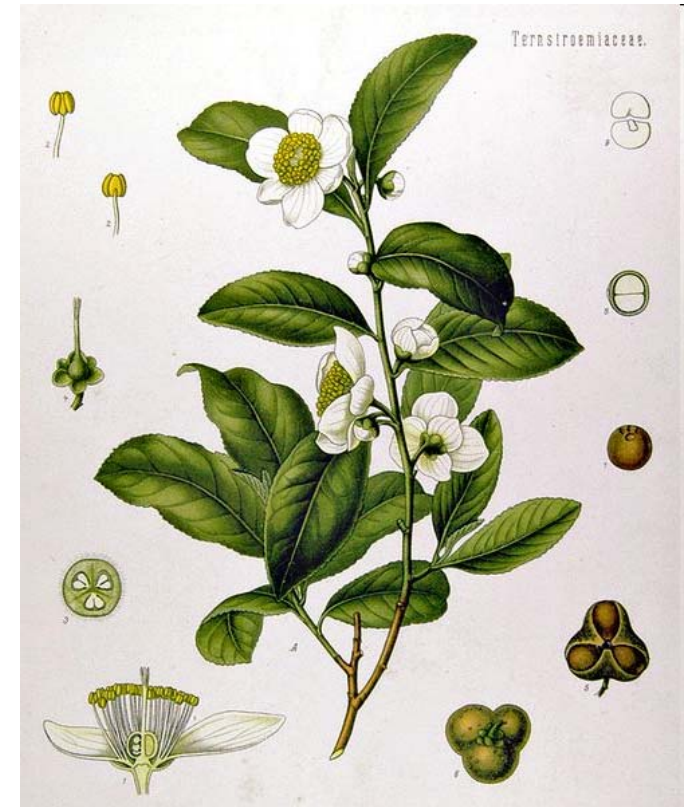
What is an antioxidant???



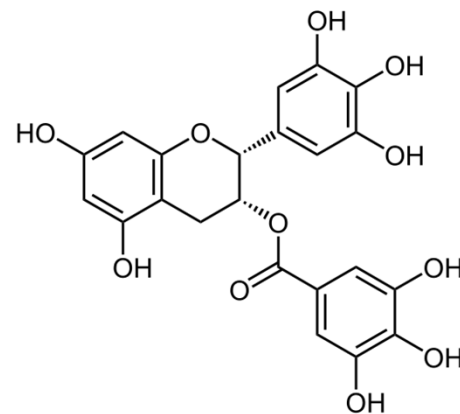
- Antioxidants are molecules that can inhibit the oxidation of other molecules.
- Recall that oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. This oxidation process produces **free radicals**, leading to oxidative stress if not neutralized.

Green & black tea

- Epicatechin derivatives (polyphenols like aflavins & thearubigins) in green & black tea show strong anticarcinogenic effects
 - Antioxidant & free-radical scavenging activity
 - Inhibit proteinkinase C & cellular proliferation
 - Anti-inflammatory
- Leaves used in TCM for asthma & cardiovascular diseases



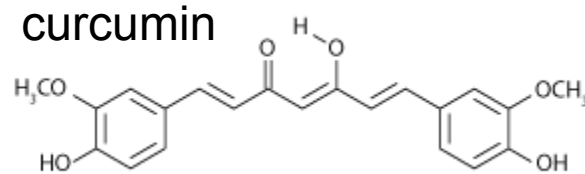
***Camellia sinensis* (Theaceae)**



(-)-epigallocatechin-3-gallate



Turmeric



- CAM for anti-inflammatory activity; important in Ayurvedic medicine
- Native to S. Asia & rhizome powder used as a spice, for dyeing, and giving food color
- **Curcumin** found in *Curcuma* spp. & *Acorus calamus*
 - Antimutagenic & anticarcinogenic
 - inhibits preneoplastic lesions in breast, colon & neoplastic lesions in skin, stomach, duodenum, & colon
 - Suppresses phosphokinase C



Curcuma longa
(Zingiberaceae)



Turmeric powder

Study at Emory: <http://eidd.emory.edu/curcumin-mimics>

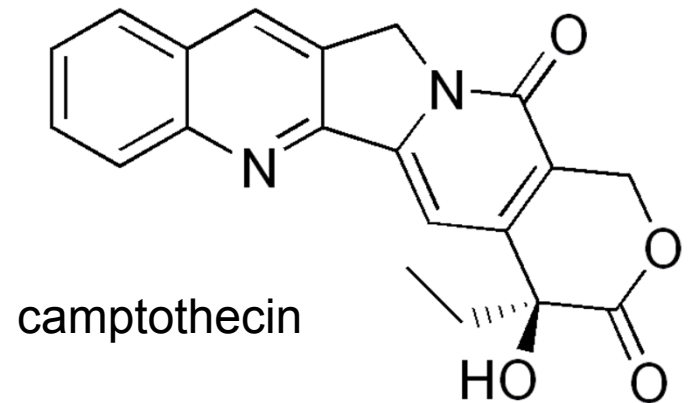
Camptothecin

- Alkaloid discovered in 1957 NCI screen of wood and bark
- Works by inhibition of Topoisomerase I, which prevents DNA unwinding
- Activity against leukemia, but toxic side effects
- 2 products evolved from this research:
 - Irinotecan
 - Topotecan



Camptotheca acuminata
(Nyssaceae)

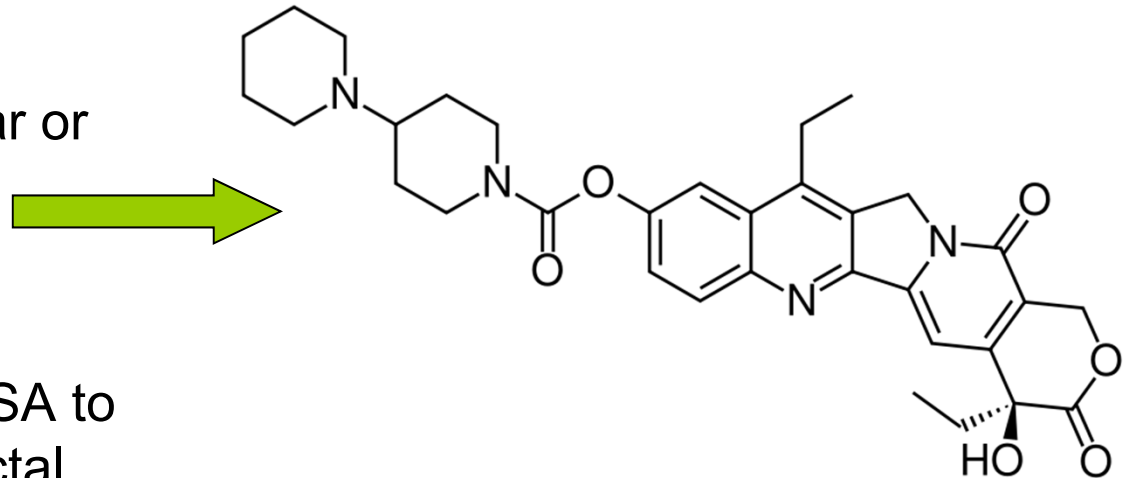
Chinese Happytree



Camptothecin used as template for:

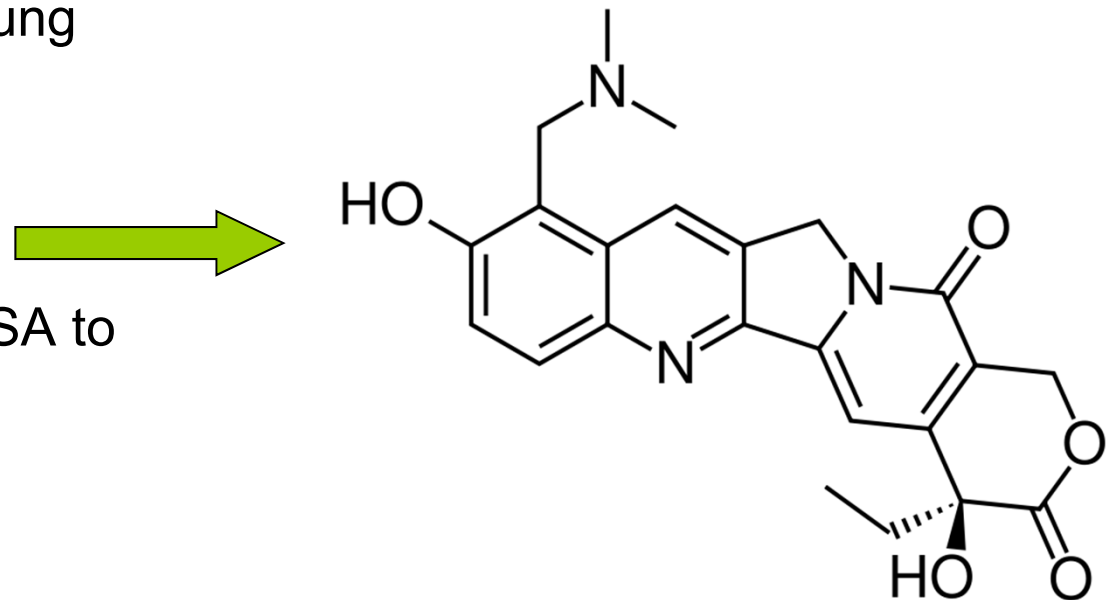
- **Irinotecan**

- Marketed as Camptosar or Campto
- Less toxic than camptothecin
- Approved in 1994 in USA to treat metastatic colorectal cancer
- Also effective against lung cancer and leukemias



- **Topotecan**

- Marketed as Hycamtin
- Approved in 1996 in USA to treat ovarian cancer



Vincristine & Vinblastine

- Vinca alkaloids
- *C. roseus* has a long history in TM:
 - Europe: diabetes remedy
 - China: astringent & diuretic properties; cough remedy
 - Carribean: eye infections & diabetes
 - Reputation as a “magical plant”
 - Europeans thought it could ward off evil spirits. French called it “the violet of the sorcerers”

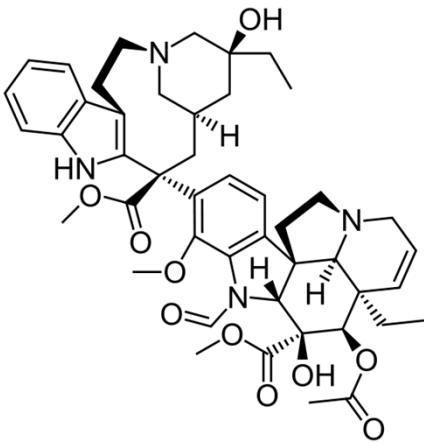


***Catharanthus roseus* (Apocynaceae)**
Madagascar Periwinkle

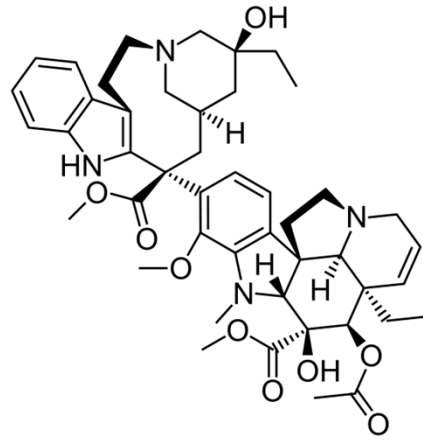
- Eli Lilly screening program
1st identified activity against
certain cancer cells

Vincristine & Vinblastine

- MOA: inhibit mitosis by binding to tubulin, preventing cells from making spindles needed to move chromosomes during cell division



vincristine



vinblastine

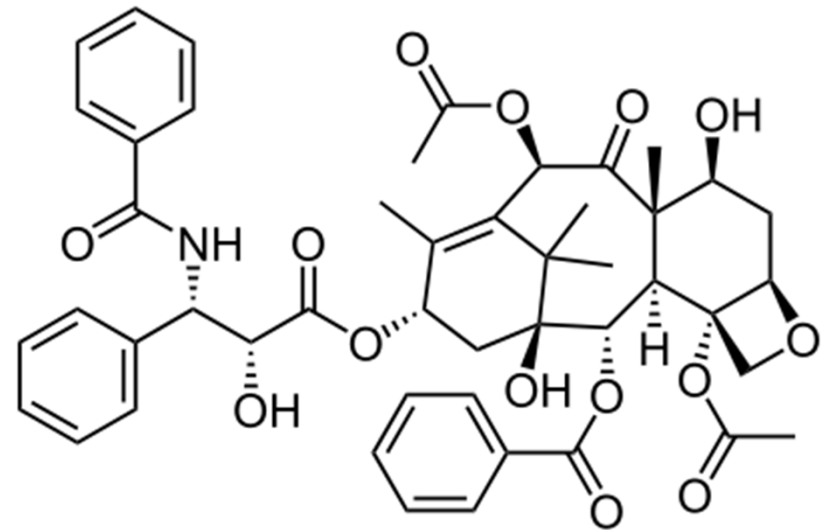
- **Vinblastine** marketed as Velbe by Eli Lilly
 - Hodgkin's disease, lymphoma, advanced testicular cancer, advanced breast cancer, Kaposi's sarcoma
 - **Vincristine** marketed as Oncovin by Eli Lilly
 - acute leukemia, Hidgkin's disease & other lymphomas
- **Semi-synthetic derivatives**:
 - **Vindesine** marketed as Eldisine
 - treats leukemia & lung cancers
 - **Vinorelbine** marketed as Navelbine
 - Treats ovarian cancer

Paclitaxel



- Taxane diterpene discovered in 1960s NCI screen
 - Showed strong activity against solid tumors, melanoma, and leukemia models
 - New MOA: taxol inhibits mitosis, but also stabilized microtubules and inhibited depolymerization back to tubulin

Taxus brevifolia (Taxaceae) – Pacific Yew



Paclitaxel

Paclitaxel

- One **BIG** problem – very low yield in plant (0.004%)
 - Solution: semi-synthesis of taxol by conversion of metabolites available in larger quantities in needles of English Yew (*Taxus baccata*)
 - Needles were a renewable source.
 - no need to kill the tree by removing bark
- **Taxol** (Bristol Meyers Squibb) approved in USA in 1993
 - Treatment for ovarian cancer and secondary treatment for breast and non-small cell lung cancers



***Taxus baccata* (Taxaceae) – English Yew**

- **Docetaxel** was approved in 1995
 - marketed as **Taxotere**
 - more water soluble than taxol
Breast and ovarian cancer
- **Abraxane** – paclitaxel bound to albumin, approved in 2005
 - Breast cancer unresponsive to other chemotherapies

Podophyllin

- Long history of traditional use of rhizomes as medicine by Native Americans (Penobscot Indians of Maine)
 - Dried & made into powder, then
 - eaten or drunk as laxative or antihelmintic
 - poultice applied to warts & skin growths
- Currently plant extracts used as topical treatment for warts & skin growths



Podophyllum peltatum (Berberidaceae)

Mayapple

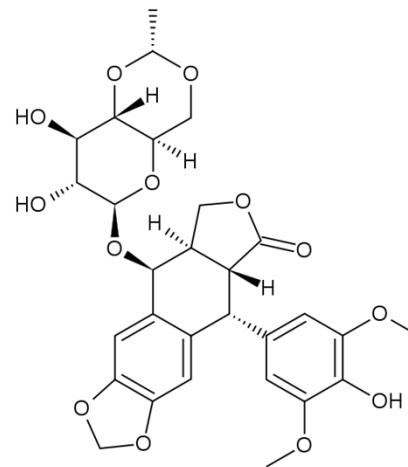


Podophyllin

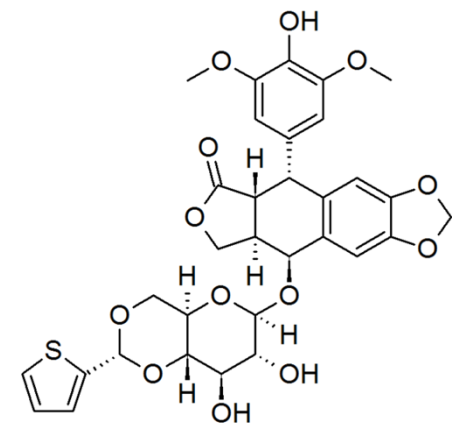
- Podophyllotoxin lignans
 - Binds to tubulin and is member of “spindle poison” group of agents
 - Functions by preventing microtubule formation
- **Podofilox** is purified form of podophyllin that acts a poison against cells undergoing mitosis
 - Not for systemic use
 - Used topically in genital wart creams

- **Synthetic derivatives:**

- **Etoposide** marketed as Vepesid
 - Small cell lung cancer, testicular cancer & lymphomas
- **Teniposide** marketed as Vumon
 - brain tumors, childhood acute leukemia



Etoposide



Teniposide

Summary Points

- NCI & other pharma have tested > 35,000 plant species for anticancer activity in past century
- A few important drugs have emerged (taxol, vincristine, vinblastine) & are used today
- Traditional medicine has given clues
- There is much more work to be done