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

Study at Emory: [http://eidd.emory.edu/curcumin-mimics](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
Camptothecan used as template for:

- **Irinotecan**
  - Marketed as Camptosar or Campto
  - Less toxic than camptothecan
  - 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
  – Caribbean: eye infections & diabetes
  – Reputation as a “magical plant”
    • Europeans thought it could ward off evil spirits. French called it “the violet of the sorcerers”

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*Catharanthus roseus* (Apocynaceae)
Madagascar Periwinkle

– Eli Lily 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

  - **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

Docetaxel was approved in 1995
  – marketed as **Taxotere**
  – more water soluble than taxol

• **Abraxane** – paclitaxel bound to albumin, approved in 2005
  – Breast cancer unresponsive to other chemotherapies

*Taxus baccata* (Taxaceae) – English Yew
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
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](image)
![Teniposide](image)
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