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## Herb-Drug Interactions In Cancer Care

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UConn Schwarting Symposium



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### Disclosure

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- Dr. Shamilov has no financial relationships with ineligible companies

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### Objectives

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By the end of this lecture, learners should be able to

- Describe various formulations of herbal products
- Compare complimentary versus alternative medicine
- Describe different mechanisms of pharmacokinetic and pharmacodynamic based herb drug interactions
- Identify common herb / chemotherapy interactions
- Name helpful resources for a pharmacist to investigate these interactions

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### What Are Herbal Supplements?

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- Products made from plants that are used to treat diseases or to maintain health
- Various forms: dried, chopped, powdered etc
- Can be used in many ways:
  - Pills, powders, or tinctures
  - Brewed as tea
  - Applied to the skin as cream or gel

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### Use Of Supplements In Oncology

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- A study reviewed 32 studies conducted between 1999- 2006
- Noted 64-81% of cancer survivors overall reported using vitamins or minerals (excluding multivitamins) compared to 50% in the general population
- Rationale varied:
  - “strengthen their immune system”
  - “gain a sense of control”

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Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol. 2008.

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- Herbal supplements are usually consumed through:
  - A. Various forms of plants that are dried, chopped, powdered etc
  - B. Eating the raw plants whole
  - C. Administered inhalationally

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### Why Are Cancer Patients More Susceptible To Drug/Drug and Drug/Herb Interactions?

- Cancer patients may take **many** medications
- Herbs can interfere with the metabolism of the anti cancer therapy (less effective) or may potentiate the side effects of the anti cancer therapy (more toxic)
- Most herbal supplements have not been formally studied with anti cancer therapy

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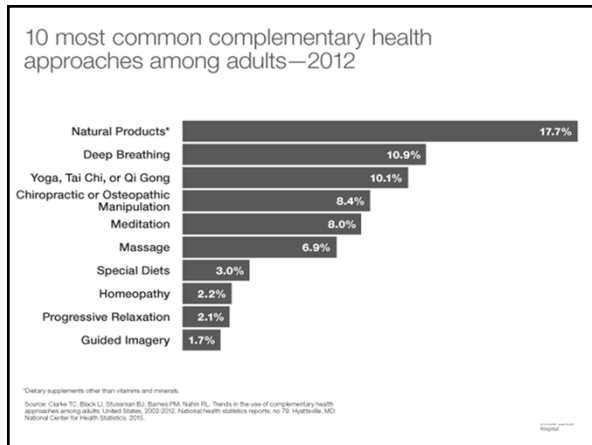
### Complementary Versus Alternative Medicine

Complementary medicine is used along with standard medical treatment but is not considered by itself to be standard treatment

Alternative medicine is used instead of standard medical treatment

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National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: what's in a name? 2018. <https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-what-s-in-a-name> (revised March 9, 2021)

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### Complementary medicine is usually defined as:

- Medicine used along with standard medical treatment but is not considered by itself to be standard treatment
- Medicine used instead of standard medical treatment
- Medicine at no cost –it's complementary!

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### Mechanisms Of Herb Drug Interactions

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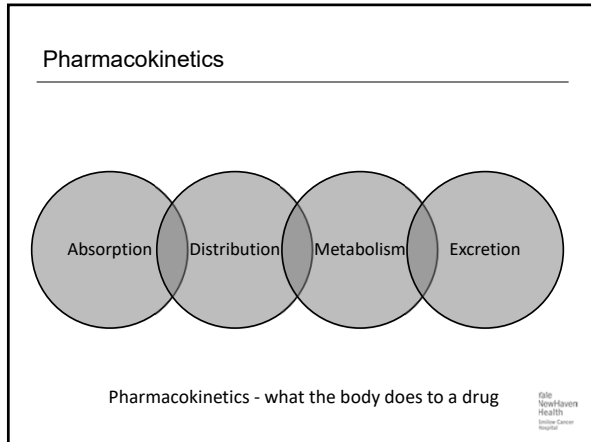
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### Review of Drug Interactions

- Change in action/side effects of a drug caused by concomitant administration with a food, beverage, **supplement**, or another drug
- Can affect a drug's pharmacokinetic (PK) or pharmacodynamic (PD) properties
- Can lead to increase adverse effects or a loss of efficacy
- Chemotherapy has a narrow therapeutic index

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V. Schmith, Drug-Drug Interaction (DDI) Studies in Clinical Pharmacology  
Available: <https://www.nuventra.com/services/pharmacokinetics-pharmacodynamics/drug-drug-interaction-studies/>

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Pharmacokinetic Interactions: **Absorption**

- The environmental conditions of gastrointestinal tract affect the absorption of drugs

Mechanisms of herb-drug interactions:

- Affect GI motility
- Affect gastric pH can change gastrointestinal absorption
- Inhibit the P-glycoprotein drug transporter in the intestine

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Fasinu P.S., Rapp G.K. Herbal Interaction With Chemotherapeutic Drugs-A Focus on Clinically Significant Findings. *Front Oncol.* 2019

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Pharmacokinetic Interactions: **Distribution**

Mechanisms of herb-drug interactions

- Drug distribution affected by other drugs that compete for binding sites on proteins
- Drugs in the bound form are usually inactive, free drug exert pharmacological activities
- Herbs can displace drugs from their typical binding sites → increase of the level of free drug
- Δ in physical compartment in which another drug distributes

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Pharmacokinetic Interactions: **Metabolism**

- Phase I metabolism:
  - Introduces polar functional groups to drug
  - Mainly mediated by **cytochrome P450**
- Phase II metabolism:
  - Drugs and/or metabolites are conjugated with a polar compound
  - Enzymes such as UDP-glucuronosyltransferase, and glutathione-S-transferase
- Δ in enzyme activity affects metabolism

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Genuska FJ, Coughlin M, Tuley BH. Drug Metabolism. In: Brunton LL, Hliel-Dandan R, Knollmann SC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed. McGraw Hill; 2017

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Pharmacokinetic Interactions: **Metabolism**

- Well documented
- Clinical significance
- Herbs can potentially induce or inhibit drug metabolizing enzymes
- Herbs can alter hepatic blood flow

Fasinu, P.S., & Rapp, G.K. Herbal Interaction With Chemotherapeutic Drugs-A Focus on Clinically Significant Findings. *Frontiers in Oncology* 2019

Y.Y. Cheng, C.H. Hsieh, T.H. Tsai. Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics. *J. Food Drug Anal.* 2018

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CYP P450 Drug Interactions

CYP P450 Inhibition causes increased drug concentrations due to lower drug-metabolizing activity → **excess toxicity**

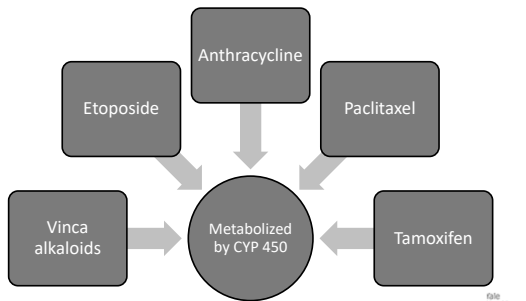
CYP P450 enzyme induction causes an increased rate of enzyme synthesis → lower drug concentrations → **decreased efficacy**

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Genuska FJ, Coughlin M, Tuley BH. Drug Metabolism. In: Brunton LL, Hliel-Dandan R, Knollmann SC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed. McGraw Hill; 2017. Accessed March 24, 2022. <https://accessmedicine.mhprofessional.com/content.aspx?bookid=1218&sectionid=41888441>

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### Anti Cancer Agents Metabolized By CYP P450



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### St John's Wort (*Hypericum perforatum*)

- Perennial herb with bright yellow flowers
- Marketed to support emotional well-being
- One of the most well documented herb/drug interactions
- Hyperforin: agonist of Pregnane X Receptor → activates the transcription of CYP3A4 and P-glycoprotein

Loughren, Michael J et al. "Influence of St. John's Wort on Intravenous Fentanyl Pharmacokinetics, Pharmacodynamics, and Clinical Effects: A Randomized Clinical Trial." *Anesthesiology*. 2021

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### St. John's Wort & Irinotecan

- Five cancer patients were treated with irinotecan (350 mg/m<sup>2</sup> IV + SJW (900 mg daily, orally for 18 days)
- The plasma levels of the active metabolite SN-38 decreased by 42% following SJW cotreatment
- Effects still observable **three weeks** after the last dose of SJW
- Could affect treatment outcome

Mathijssen RH et al. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst*. 2002.

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### St. John's Wort & Imatinib

- Open-label study
- N= 12 patients
- Patients received imatinib orally on day 1, St John's wort (300 mg 3 times daily) on days 4 to 17, and 400 mg imatinib again on day 15
- Results: St John's wort administration increased imatinib clearance by 43% and decreased the half life

Frye RF, Fitzgerald SM, Lagattuta TF, et al. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther*. Oct 2004.

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### Black Cohosh (*Cimicifuga racemosa*) & Tamoxifen

- Perennial herb that grows in woodland areas with activity against pre menstrual symptoms
- Tamoxifen is a nonsteroidal selective estrogen receptor modulator (SERM)
- Conversion into active metabolites is dependent on CYP 2D6 and CYP 3A4
- Available evidence contradictory if black cohosh affects CYP 2D6

Li, Jingyu et al. "In vitro metabolic interactions between black cohosh (*Cimicifuga racemosa*) and tamoxifen via inhibition of cytochromes P450 2D6 and 3A4." *Xenobiotics: the Journal of Drug Metabolism and Clinical Pharmacology*. 2013.

Gurley B, Hubbard MA, Williams DC, et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to placebo and clarithromycin. *Clin Pharmacol Ther*. 2012.

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### Echinacea (*Echinacea purpurea*)

- Perennial herb native to North America
- Used as an immune system stimulant
- Known to inhibit CYP P450
- Should not be used by persons with allergy to members of the Asteraceae family (eg, ragweed, daisy, marigold)

Zadayan G, Fuhr U. Phenotyping studies to assess the effects of phytopharmaceuticals on in vivo activity of main human cytochrome p450 enzymes. *Phyto Med*. Sep 2012.

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- St. John's Wort is known to alter which aspect of pharmacokinetics?

- Absorption- by affecting gastric pH
- Metabolism- by increasing drug clearance
- Metabolism- by decreasing drug clearance
- Distribution- by competing with albumin binding sites

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### Echinacea (*Echinacea purpurea*) & Etoposide

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- Case report of a man with lung cancer began chemoradiation with cisplatin and etoposide
- Admitted to the hospital on day 8
- Found to be thrombocytopenic + required platelet transfusion support
- Echinacea discontinued during admission
- Improvement during his subsequent cycle of chemotherapy

Yale New Haven Health  
Bossaer JB, Odle BL. Probable etoposide interaction with Echinacea. *J Diet Suppl.* 2012.

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### Astragalus (*Astragalus membranaceus*)

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- Flowering plant used in traditional Chinese medicine
- Root is used for health care purposes
- Marketed to improve immune function and to decrease fatigue

Yale New Haven Health  
Astragalus. "About Herbs" Website. Memorial Sloan-Kettering Cancer Center. Available: <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/astragalus>. Accessed March 24, 2022

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### Astragalus & Anti Cancer therapy

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- Rats pretreated with Astragalus extract showed a change in pharmacokinetics, leading to **increased clearance of gemcitabine**
- Another model showed astragalus **reversed the immunosuppressive effects of cyclophosphamide**

Yale New Haven Health  
Chu Z, Wang Z, Liu T, Xiong S, Liu B. Evaluation of the Effects of Astragalus membranaceus on the Pharmacokinetics of Paclitaxel and Gemcitabine in Rats by a Single Herb. *Journal of Chromatography B: Biomedical Applications*. 2019  
Chu DT, Wong WL, Mavligt GM. Immunotherapy with Chinese medicinal herbs. 6. Reversal of cyclophosphamide-induced immune suppression by administration of fractionated Astragalus membranaceus in vivo. *Journal of Clinical & Laboratory Immunology*. 1988

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### Pharmacokinetic Interactions: **Elimination**

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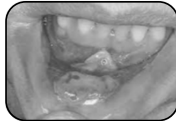
- The kidney is the primary organ responsible for the elimination of drugs and their metabolites
- Mechanisms of herb-drug Interactions:
  - Herbs can inhibit specific renal transport mechanisms
  - Herbs can alter urinary pH

Yale New Haven Health  
Fasinu, P. S., & Rapp, G. K. Herbal Interaction With Chemotherapeutic Drugs: A Review on Clinically Significant Findings. *Frontiers in oncology*. 2019.


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### Cancer Itself May Affect PK Parameters


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Impaired absorption from mucositis



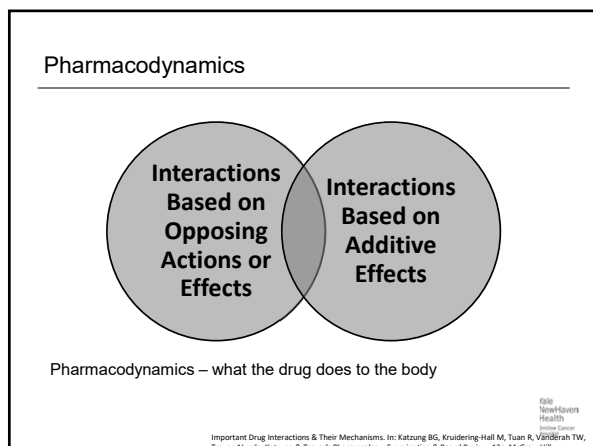
Increased volume of distribution resulting from edema



Altered excretion secondary due organ dysfunction

Yale New Haven Health  
Riechelmann, R. P., & Del Giglio, A. Drug interactions in oncology: how common are they?. *Annals of oncology* 2009

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Free Radicals and Anti oxidants: **The Basics**

- Free radicals are highly reactive chemicals created when a molecule either gains/loses an electron
- Play an important role in normal cellular processes
- Antioxidants are chemicals that **interact with and neutralize free radicals** (preventing them from causing damage)

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Interim Cancer Hospital

Antioxidants and Cancer Prevention was originally published by the National Cancer Institute. Available: [Antioxidants and Cancer Prevention - National Cancer Institute](#)

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Interactions Between Antioxidants and Chemotherapy

- Chemotherapies such as anthracyclines, platinum compounds and alkylating agents **generate free radicals for their cytotoxic effects**
- **Theoretically, antioxidants may render these drugs less effective**
- Hard to draw conclusions - variations in study design, type of antioxidant, cancer and treatment

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Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *Journal of the National Cancer Institute*. 2008

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Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial

- Led by researchers at the SWOG Cancer Research Network
- N= 1,134 patients receiving cyclophosphamide, doxorubicin, and paclitaxel answered questions about supplement use
- Those who reported taking any antioxidants – such as vitamins A, C, E, carotenoids, and Coenzyme Q10 – **both** before and during treatment were 41% more likely to have a cancer recurrence (P = .06) and 40% more likely to die, death (P = .14)

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Strength/Limitations

Strengths	Limitations
- Conducted in the context of a therapeutic clinical trial	- Overall low number of patients taking antioxidants and other supplements
- Surveys <b>before beginning chemotherapy and at completion of treatment</b>	- Overall low use precluded evaluation of anti oxidant dose on effect
	- Recall bias

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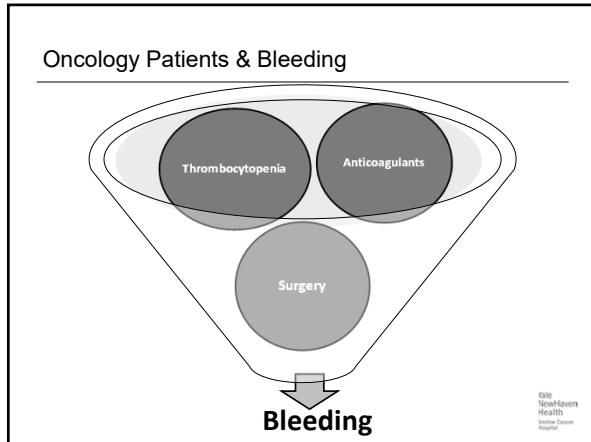
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Herbal supplements and bleeding that have anticoagulant effects

- Many herbal products are reported to possess antiplatelet and/or anticoagulant properties
  - ginko, garlic, ginseng, feverfew
- Can impair hemostasis and cause/promote bleeding

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### Surgery and Cancer Care

- Many reasons for surgery in cancer care
- Some herbs possess anticoagulant and anti platelet effect
- Kava (*Piper methysticum*) is used as an anxiolytic and known to **potentiate the activity of anesthesia**
- Gingseng may cause hypoglycemia

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Ang-Lee MK, Moss J, Yuan C. Herbal Medicines and Perioperative Care. JAMA. 2001

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### Phytoestrogens & Breast Cancer Risk

- Plant-based compounds mimic estrogen in the body
- Activity depends structure, metabolism, concentration etc
- Concerns for herbal products containing phytoestrogens in patients with breast cancer (estrogen sensitive cancer)
- Consider patient's cancer when recommending herbal supplements

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Ginkgo, garlic, ginseng, feverfew may increase the risk of which complication?

- QTc prolongation
- Neutropenia
- Hypertension
- Bleeding risk

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## Drug Information Resources For Pharmacists

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### Natural Medicines Comprehensive Database

- Useful information for the clinical decision making process
- Monographs:
  - Vitamins, herbs, minerals, non-herbal supplements
  - Safety, effectiveness, commercial products, pharmacokinetics, mechanism of action, condition interaction etc
  - Professional / Patient version
- Charts for herbs with anti coagulant and anti platelet properties

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- Patient LI is on numerous herbal products and has been complaining of nausea since starting them. Which of the following resources has a adverse effects checker for herbal supplements?

- A. Natural Medicines Comprehensive Database
- B. Up to Date
- C. National Institute of Health Office Of Dietary Supplements



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So Much Information, What Should We Do With It?

- **As pharmacists we need to differentiate between potential herb–drug interactions reported in preclinical research from actual interactions observed in the clinical setting**
- Limitations:
  - Fewer clinical trials on herbal products
  - Herbal medicine is sometimes part of the exclusion criteria for pharma funded trials



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Patient Counseling

- Being on anti cancer therapy and a herbal supplement together **may** increase the cancer drug's effects (extra side effects)
- Being on anti cancer therapy and a herbal supplement together **may** decrease the cancer drug's effects (you may not be getting the full benefit)
- Most chemotherapy regimens have **not** been formally tested with herbal products



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Patient Counseling

- If you use supplements, provide team with:
  - All the drugs and supplements you take
  - Doses/Frequency
- Watch out for outrageous claims
- Use brands with third-party certifications (determine if the marketed product meets standards for safety and quality)



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**Plant Based Chemotherapy**

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Plants & Cancer

- Plants have been used for medical purposes since the beginning of human history
- Many chemotherapeutic drugs used in cancer treatment are derived from plants
- Developed after rigorous clinical trials for safety and efficacy



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### Plant Based Chemotherapies

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1. **Vinca alkaloids** (vinblastine, vincristine)
  - Periwinkle plant *Catharanthus roseus*
2. **Epipodophyllotoxins** (etoposide)
  - Wild mandrake *Podophyllum peltatum*
3. **Taxanes** (paclitaxel and docetaxel)
  - Pacific yew tree *Taxus brevifolia*
  - European yew tree *Taxus baccata*
4. **Camptothecin derivatives** (irinotecan)
  - Chinese ornamental tree *Camptotheca acuminata*

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### Take Home Points

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- Herb-drug interactions exist within cancer care and have PK or PD mechanisms
- Concerns about herb-drug interactions are often not based on large clinical trials
- Caution is warranted due to the narrow therapeutic index of anti cancer agents
- More well-designed clinical studies evaluating herbal supplement–drug interactions are needed

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