Why do patients take herbs and nutritional supplements?

- **Dissatisfaction with conventional medicine**
  - Relieve cancer-related symptoms
  - Treat adverse effects of anticancer drugs
  - Treat cancer
  - Promote general well being
- **More active in own health care**
- **Philosophical orientations**
Use in cancer survivors

- 54-81%: any vitamins or supplements
- 26-77%: multivitamins
- Within first months of diagnosis
- Women
- Higher economic status

20-30% adverse effects < drug interactions
Concomitant use: growing concern
Communication disconnect

38-85%: no consultation with physician

- Physicians do not ask
- Physicians do not record
- Patients fear disapproval
Drug interactions

- **Drug-drug**
  - Food, nutritional supplements, formulation excipients, environmental factors

- **Interactions**
  - Pharmacokinetics
    - Absorption, distribution, metabolism, elimination
  - Pharmacodynamics
    - Similar molecular targets
    - Opposite effects
    - Similar effects
Drug interactions: clinical relevance

**Depends on**

- **Co-administered drug**
  > Dose, dosage regimen, therapeutic range
  > Administration route, pharmacokinetics

- **Herb**
  > Dose, dosage regimen
  > Administration route

- **Patient**
  > Genetic polymorphism
  > Age, gender
  > Co-morbid conditions
Pharmacokinetics: absorption

Oral drugs and pro-drugs

• **Food**
  > Delays gastric emptying
  > Raises intestinal pH
  > Raises hepatic blood flow
  > Slows gastrointestinal transit

• **Known drug interactions**
  > Increases absorption erlotinib
  > Decreases absorption capecitabine
  > Delays absorption topotecan, fluorouracil
Pharmacokinetics: absorption, metabolism, elimination

- **Cytochrome 450 family CYP450**
- **Drug transporters**
  - Efflux: P-glycoprotein P-gP
  - Influx: organic anion transporting polypeptide OATP
Pharmacokinetics: absorption, metabolism, elimination
Pharmacokinetics: absorption, metabolism, elimination

The CYP family

- **Metabolizes 60% of drugs**
  - Biotransformation lipophilic substrates into hydrophilic metabolites
- **CYP3A4**
  - Most abundant
  - Liver, gastrointestinal tract
  - Chemical carcinogenesis
- **Expression regulation**
  - Hormones and nuclear receptors
    - Pregnane X receptor, constitutive androstane receptor, farnesol X receptor
Pharmacokinetics: absorption, metabolism, elimination

Anticancer drugs: substrates of CYP3A4

- **Hormones**
  - Anastrazole, letrozole, exemestane, tamoxifen
- **Tyrosine kinase inhibitors**
  - Erlotinib, gefinitib, imatinib
- **Taxanes**
  - Docetaxel, paclitaxel
- **Vinca alkaloids**
  - Vinblastin, vincristin, vinorelbine
- **Topo-isomerase inhibitors**
  - Doxorubicine, irinotecan, etoposide, teniposide
- **Alkylating agents**
  - Cyclophosphamide, iprophosphamide
Pharmacokinetics: absorption, metabolism, elimination

- **P-glycoprotein P-gp**
  - Encoded by multidrug resistance genes ABCB1
  - Liver, kidney, intestines, brain, testis, uterus, adrenal gland, tumor cells
  - Up-regulation by stress responses
    - Cytotoxic agents, heat shock, irradiation, inflammatory mediators, cytokines, growth factors
  - Hepatic P-gp: 2.4 fold lower in women
Pharmacokinetics: absorption, metabolism, elimination

- **Anticancer substrates of P-gP**
  - Tyrosine kinase inhibitors
    - **Imatinib**
  - Taxanes
    - **Docetaxel, paclitaxel**
  - Vinca alkaloids
    - **Vinblastin, vincristin**
  - Topo-isomerase inhibitors
    - **Doxorubicine, irinotecan, etoposide, teniposide, topotecan**
Pharmacokinetics: absorption, metabolism, elimination

- **Organic anion transporting polypeptide OATP**
  - Protein family
  - Influx into plasma
  - Regulated by small intestinal pH
Pharmacokinetics: absorption, metabolism, elimination

**Herbal supplements: brand specific effects**

- **Garlic**
  - Inhibition of CYP3A4, inducer in very high doses
- **Gingko**
  - Inhibition of CYP3A4, inducer of CYP2C19
  - CYP2C19 substrates: letrozole, gefinitib
- **Valerian**
  - Inhibition of CYP2C19, CYP2D6
  - CYP2D6 substrate: tamoxifen
Pharmacokinetics: absorption, metabolism, elimination

- **Echinacea**
  - Inhibitor intestinal CYP3A4
  - Inducer CYP3A4

- **Ginseng**
  - Moderate inhibitor hepatic CYP3A4

- **Grape seed**
  - In high doses: inducer of hepatic CYP3A4

- **Kava**
  - Pregnane X receptor activator

- **St John’s Worth**
  - Potent inducer of CYP3A4 and P-gp
  - Activator pregnane X receptor
Pharmacokinetics: absorption, metabolism, elimination

- **Grape fruit**
  > Potent inhibitor intestinal CYP3A4
  > inhibitor P-gp and OATP

- **Black pepper**
  > Inhibitor of CYP3A4, P-gp

- **Seville orange**
  > Inhibition of CYP3A4, P-gp, OATP

- **Goldenseal**
  > Inhibition of CYP3A4, CYP2D6

- **No interaction with**
  > Saw palmetto, black cohosh, cranberry, bilberry, milk thistle
Pharmacokinetics: distribution

- **Binding properties**
  > Albumin, alpha-1-acid glycoproteins, lipoproteins, immunoglobulines, erythrocytes

- **Highly bound anticancer drugs**
  > Paclitaxel, etoposide

- **Competitive binding with albumin**
  > Evening primrose
Pharmacodynamics

- **Synergistic interactions**
  > Leucovorin and 5-fluorouracil

- **Antagonistic interactions**
  > Corticosteroids and IL-2

- **Additive interactions**
  > Vinorelbine with previous or concurrent paclitaxel on neurotoxicity

- **Sequence-dependent interactions**
  > Paclitaxel preceding doxorubicine on cardiotoxicity
Drug interactions: clinical relevance?

- Drugs: narrow therapeutic range
- Drugs: steep dose-response curve
- Potent inhibitor of inducer
- Metabolism and elimination: single pathway
- Interactions results in diversion into alternative pathway
Antioxidants and anticancer drugs

• **Lower antioxidant status**
  > Cancer
  > Anticancer treatment

• **Supplements**
  > Selenium
  > Vitamin C
  > Sufficient fruit and vegetables
Antioxidants and anticancer drugs

- **Antioxidants**
  - Detoxifying free radicals
    - Inhibition of free radical intermediates
    - Mitomycin C, bleomycin
  - Strong nucleophiles
    - Reducing adverse effects
    - Glutathion
    - Coenzyme Q10
- **High level antioxidant stress**
  - Anthracyclines, alkylating agents, platinum, camptothecins, epipodophylotoxines
Antioxidants and anticancer drugs

- **Vitamin E**
  - Prevents peroxidation poly-unsaturated fat
  - Evidence not strong
    - Radiation fibrosis
    - Mucositis chemotherapy
    - Cell growth inhibition by 5-FU
    - Pro-oxidant: cigarette smokers + fatty acid diet
  - Avoid depletion

- **ß-Carotene**
  - Few and fragmentary studies
  - Beneficial during chemo- and radiotherapy?
Antioxidants and anticancer drugs

- **Selenium**
  - Selenoproteins: glutathion peroxidase
  - Insufficient data
    - Adverse effect chemo- and radiotherapy
    - Cisplatin resistance in ovarian cancer
  - Narrow dose range

- **Vitamin C**
  - Excessive quantities: pro-oxidants
  - High dose methotrexate + high dose vitamin C: renal insufficiency

**No data on survival**
Conclusions

Be aware

- **Avoid**
  - Grape fruit and St John’s Worth

- **Caution with**
  - Gingko, ginseng, echinacea, kava, grape seed: CYP3A4 substrates
  - Gingko: letrozole, gefinitib
  - Valerian (paroxetine, fluoxetine): tamoxifen
  - Evening primrose: paclitaxel, bleomycin

- **No antioxidants**
  - Mitomycin C, bleomycin

- **Avoid antioxidant depletion**
  - Vitamin E
Conclusions

• **Studies should specify**
  > Dosage
  > Duration
  > Time interval
  > Life style
  > Exposure to carcinogens

• **In a well-defined population**