Herbal Supplements, Patient Safety and Drug Interactions - Oh My!

Ashley Glode, PharmD, BCOP
Assistant Professor,
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Faculty Disclosure

• Ashley Glode declares no existence of a financial interest in any amount related to the content of this activity.

• Advisory Board members and other individuals, not previously disclosed, who may review, propose recommendations, and/or edit the content of PharmCon CE activities declare no existence of a financial interest in any amount related to the content of this activity.
Learning Objectives

At the conclusion of this activity, participants should be better able to:

1. Recognize the epidemiology of herbal supplements in oncology
2. Identify the pros and cons of more commonly used herbal supplements
3. Recognize resources available for product evaluation with a focus on safety, efficacy, and potential interactions
4. Identify clinical pearls for discussing herbal supplement use with a patient

Patient Case

• MB is a 47 year old female with triple negative breast cancer who presents to clinic with her husband for chemotherapy education prior to C1D1
• As you are going through your education, she says “I take a bunch of vitamins and herbs. The doctor said I should talk to you about them.”
• How do you respond?
Epidemiology

Terminology

**Complementary**
Used with conventional medicine

**CAM** =
complementary + alternative

**Alternative**
Used in place of conventional medicine

**Integrative**
- Holistic, patient-focused approach
- Combines conventional and complementary approached in coordinated way

https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name

© 2020 PharmCon
Background

• Cancer survivors more likely to use CAM than general population
• Use following cancer diagnosis
  • 50-83% adults
  • 84% pediatrics
• ASCO National Cancer Opinion Survey
  • 75% believe alternative therapies are good supplement to conventional treatment
  • 39% believe alternative therapies can cure cancer without conventional treatment
  • 47% of those age 18-37 years
• 17% of adults who have/had cancer reported using vitamins/minerals/herbs for symptom management in past 12 months

Terminology

**Dietary Supplement**
- Taken orally
- Supplement the diet
- ≥ 1 dietary ingredient
  - Vitamins, minerals, herbs or other botanicals, amino acids, enzymes, tissues from organs or glands, or extracts of these
- Labeled as dietary supplement

**Herbal Supplement**
- Type of dietary supplement
  - Contains ≥ 1 herb
- AKA botanicals
- Made from plants, algae, fungi, or combination
- Teas, extracts, tablets, capsules, powders, or other forms


Patient Case

- You show no sign of concern and calmly ask, “So what are you taking? I’m happy to look them over and see what is safe to take with your cancer treatment and other medications.”
- She happily shows you pictures of about 10 different bottles of things she has been taking
- Some look familiar with just one ingredient while others have about 20 ingredients on the label
- What do you do next?
## Commonly Used Herbal Products

- Astragalus
- Black cohosh
- **Curcumin/Turmeric**
- Echinacea
- Essiac tea
- Garlic
- Ginger
- Grape seed extract
- **Green tea**
- Milk thistle
- **Mistletoe extract**
- Mushrooms: chaga, maitake, oyster, reishi, shiitake, **turkey tail**

---

**Pros/Cons**
### Benefits

- Potential anti-cancer activity
- Adverse effect mitigation/management
- Improve quality of life
- Possibly lower cost than prescription products
- Widely available
- Patient control

---

### Risks

- Lack of standardization
  - Not regulated by FDA
- Adverse events
  - Misdiagnosed as expected side effects
- Increased toxicity
  - Pharmacokinetic potentiation
  - Additive pharmacodynamic effects
- Decreased efficacy
  - Pharmacokinetic interaction
  - Interference at anticancer agent effector site
### Curcumin (Curcuma longa)

<table>
<thead>
<tr>
<th>Route</th>
<th>Oral, rectal, topical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spice, pills, tonic, extract, cream</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Induces apoptosis by upregulating p53 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiangiogenic</td>
</tr>
<tr>
<td></td>
<td>Antioxidant</td>
</tr>
</tbody>
</table>

| Evidence               | Limited evidence in cancer patients: improve cachexia and general health, decrease incidence of hand-foot syndrome with capecitabine |

| Adverse Effects        | GI discomfort: constipation, dyspepsia, diarrhea, distension, gastroesophageal reflux, N/V |

| Herb-Drug Interactions | Inhibits CYP3A4, CYP1A1/2, CYP2D6, P-gp |
|                       | Antioxidant activity: interfere with free radical generation by topoisomerase inhibitors, antitumor antibiotics, alkylating agents |

- [https://www.mskcc.org/cancer-care/integrative-medicine/herbs/turmeric#msk_professional](https://www.mskcc.org/cancer-care/integrative-medicine/herbs/turmeric#msk_professional)

### Green Tea (Camellia sinensis)

<table>
<thead>
<tr>
<th>Route</th>
<th>Oral, topical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Teas, extracts, pills, lotion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Polyphenols (EGCG, epigallocatechin-3-gallate):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antimutagenic: protect DNA by increasing DNA repair enzymes</td>
</tr>
<tr>
<td></td>
<td>Inhibits topoisomerase I</td>
</tr>
<tr>
<td></td>
<td>Antiangiogenic</td>
</tr>
<tr>
<td></td>
<td>Antioxidant</td>
</tr>
</tbody>
</table>

| Evidence               | Decrease risk of developing cancer (most evidence with endometrial and ovarian cancer) |

| Adverse Effects        | Caffeine: insomnia, HA |
|                       | High EGCG extracts: hepatotoxicity |

| Herb-Drug Interactions | Inhibits CYP3A4 (unlikely clinically significant in humans), modulates UGT enzymes (animal studies) |
|                       | EGCG inhibits transport of irinotecan and SN-38 into biliary elimination, increases oral bioavailability of tamoxifen, inhibits effect of bortezomib |
|                       | Antioxidant: interferes with free radical generation |

- [https://www.mskcc.org/cancer-care/integrative-medicine/herbs/green-tea#msk_professional](https://www.mskcc.org/cancer-care/integrative-medicine/herbs/green-tea#msk_professional)
**Mistletoe Extract**  
*(European, *Viscum album*)

<table>
<thead>
<tr>
<th><strong>Route</strong></th>
<th>• Oral, SQ, IV, intratumorally</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• SQ injections 2-3 times/week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mechanism</strong></th>
<th>• Enforce natural killer cell-mediated tumor lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Decrease migratory and invasive potential of tumor cells</td>
</tr>
<tr>
<td></td>
<td>• Stimulate immune system cells in <em>vivo</em> and <em>in vitro</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Evidence</strong></th>
<th>• Systematic review of 26 RCTs: 22 trials reported improvements in QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Improvements in fatigue, N/V, depression, emotional well-being, concentration</td>
</tr>
<tr>
<td></td>
<td>• Supported by Society of Integrative Oncology for breast cancer patients to improve QOL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Adverse Effects</strong></th>
<th>• Soreness and inflammation at injection sites, HA, fever, chills</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Herb-Drug Interactions</strong></th>
<th>• Inhibits CYP3A4 (minimal effect in clinically relevant concentrations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Antihypertensive drugs</td>
</tr>
<tr>
<td></td>
<td>• Hepatotoxic agents</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressants</td>
</tr>
</tbody>
</table>

---

**Turkey Tail Mushrooms**  
*(Trametes/Coriolus versicolor)*

<table>
<thead>
<tr>
<th><strong>Route</strong></th>
<th>• Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Extracts: Polysaccharide-K (PSK): Japan; Polysaccharide-peptide (PSP): China</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mechanism</strong></th>
<th>• Anti-inflammatory activity; inhibits nitric oxide, TNF alpha, IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Antineoplastic activity: <em>in vitro</em> cytotoxic activity, inhibits tumor cell motility and chemotactic activity of macrophages, antiangiogenic, stimulates/restores immune system, antioxidant effects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Evidence</strong></th>
<th>• Meta-analysis of 13 clinical trials with &gt;2500 patients with esophageal, gastric, rectal, breast, and nasopharyngeal cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• PSK + conventional chemotherapy reduced 5-year mortality by 9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Adverse Effects</strong></th>
<th>• Rare: dark colored stool, darkening fingernails, low-grade hematologic and GI toxicities</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Herb-Drug Interactions</strong></th>
<th>• Cyclophosphamide (PSP; increased AUC and $t_{1/2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Inhibits CYP2C9 (PSP; dose-dependent)</td>
</tr>
</tbody>
</table>

---

*References:*
• Fungus grows on dead logs

• Routes of Administration: oral
  • Extracts: Polysaccharide-K (PSK): Japan; Polysaccharide-peptide (PSP): China

• Mechanisms:
  • Anti-inflammatory activity: inhibits nitric oxide, TNF alpha, IL-6
  • Antineoplastic activity: *in vitro* cytotoxic activity, inhibits tumor cell motility and chemotactic activity of macrophages, antiangiogenic, stimulates/restores immune system, antioxidant effects

• Evidence:
  • Meta-analysis of 13 clinical trials with >2500 patients with esophageal, gastric, rectal, breast, and nasopharyngeal cancers
    • PSK + conventional chemotherapy reduced 5-year mortality by 9%

• Adverse Effects:
  • Rare: dark colored stool, darkening fingernails, low-grade hematologic and GI toxicities

• Herb-Drug Interactions:
  • Cyclophosphamide (PSP; increased AUC and t½)
  • Inhibits CYP2C9 (PSP; dose-dependent)

---

**Broad Categories of Potential Interactions**

• Herbs with antioxidant properties may interfere with radiation or chemotherapy efficacy (MOA: free radical generation)

• Herbs with anticoagulant or anti-platelet effects may be harmful in patients with thrombocytopenia, undergoing surgery, or used concurrently with anticoagulants or VEGF (vascular endothelial growth factor) inhibitors

• Phytoestrogenic herbs may interfere with hormonal therapies and have negative effects on hormone-sensitive cancers

• Immunostimulant herbs may impact efficacy of immunosuppressive therapy

• Direct organ toxicity

• Drug metabolism interactions
Managing Interactions

- Monitor high risk patients closely
- Consider altering dosing intervals
- Alternate routes of administration/dosage forms
- Change or discontinue supplement
- Encourage open dialogue
- Obtain relevant information

Resources
Resources

• Cancer.net
• Consumerlab.com
• Cancer.gov
• National Center for Complementary and Integrative Health (NCCIH)
• Memorial Sloan Kettering Cancer Center About Herbs
• Natural Medicines Database
• Society for Integrative Oncology

Cancer.net

• Patient focused
  • Definitions
  • How to evaluate safety of products
  • Encourages patients to talk with healthcare team
• 5 things you should know about herbs and supplements
  • No dietary or herbal product can cure cancer
  • FDA does not approve these products
  • Herbs may interact with chemotherapy and other treatments
  • Antioxidant supplements may make cancer treatment less effective
  • Some supplements may help reduce specific adverse effects

https://www.cancer.net/blog/2015-04/5-things-you-should-know-about-herbs-and-supplements
Consumer Lab

- Provider focused, with some patient friendly content
- Product Reviews
  - Basic information and evidence for use
  - Test specific brands and provide quality ratings
- Frequently Asked Questions
- Recalls and Warnings
- Encyclopedia
- Free Newsletter

https://www.consumerlab.com/

Cancer.gov

- Patient and provider information
  - Definitions
  - Addresses safety
  - Encourages patients talk to providers
  - Provides links to additional resources
    - National Center for Complementary and Integrative Health (NCCIH)
    - NCI Office of Cancer Complementary and Alternative Medicine
    - Office of Dietary Supplements
- PDQ Summaries on specific herbal products
  - Patient and provider versions
  - What it is, administration, potential mechanism, in vitro and in vivo studies, adverse effects

https://www.cancer.gov/about-cancer/treatment/cam
https://www.cancer.gov/about-cancer/treatment/cam/patient
National Center for Complementary and Integrative Health (NCCIH)

- Patient focused
  - Brief fact sheets of several products
    - Basic information, potential side effects and cautions, resources for more information
  - HerbList App
    - > 50 popular herbs with images
    - Research-based information on safety and effectiveness
    - Select favorite herbs to talk about with provider at a later time
  - Know the Science: How Medications and Supplements Can Interact
    - Questions to test knowledge
    - Basic concepts with examples

- https://www.nccih.nih.gov/health/herbsataglance
- https://www.nccih.nih.gov/health/herblist-app

Memorial Sloan Kettering Cancer Center
About Herbs

- Patient and provider information
  - Video recording of grand rounds presentation on herb-drug interactions in cancer care
  - Herbs, Botanicals & Other Products: FAQs
  - Monthly newsletter

- About Herbs Website and App (iOS)
  - > 200 monographs with artist images
    - Describes mechanism, use, warnings/interactions, side effects
    - Scientific references
  - Search by product name or medical condition
  - Share content by emailing link for monograph


© 2020 PharmCon
Natural Medicines Database

- Provider and patient information (Spanish, French)
  - Food, Herbs & Supplements Database
    - Background, use, safety, effectiveness, dosing & administration, adverse effects, toxicology, herb-herb and herb-drug interactions, MOA, pharmacokinetics
  - Natural Medicines Brand Evidence-based Rating (NMBER) System
    - Safety, effectiveness, and product quality
  - Interaction Checker
    - Includes prescription and OTC products and multi-ingredient supplements (brand)
  - Effectiveness Checker
    - Evidence for activity in specific medical conditions
  - Nutrient Depletion Checker
    - Which nutrients are depleted by prescription and OTC products
  - Pregnancy & Lactation Checker
    - Product safety in pregnant or breastfeeding women
  - Adverse Effects
    - Evaluate specific adverse effects to identify causative agents

Society for Integrative Oncology

- Patient and provider resource
  - Clinical Practice Guidelines
    - Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment
      - Endorsed by ASCO
    - Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer
    - Complementary Therapies and Integrative Medicine in Lung Cancer
    - Evidence-Based Clinical Practice Guidelines for Integrative Oncology: Complementary Therapies and Botanicals
  - Guide to Credible Internet Information for patients
    - Recommended approaches when reading medical information
    - Cautionary information for buying products online
  - Membership required to access full content
    - Natural Medicines Database
    - Webinars, podcasts, monthly newsletter
Patient Case

• So now you’ve had time to review her supplements and check for possible interactions
• You find that several items she’s taking have antioxidant activity and might interact with her chemotherapy.
• How do you tell the patient, making sure not to offend her?

Clinical Pearls
Discussion Steps

- Understand
  - Elicit the patient’s understanding of their situation
  - Determine concerns and goals
  - Clarify information preferences
- Respect
  - Cultural and linguistic diversity
  - Different belief systems
- Ask
  - Ask about use frequently and at key points in disease course
  - Utilize an inquisitive, open-minded approach
  - Avoid using terms “complementary” or “alternative”
  - Clarify reason for asking
- Explore
- Respond

Discuss
Advise
Summarize
Document
Monitor

Recommendations for Effective Discussions
Recommendations for Effective Discussions

- **Step 4: Explore**
  - Supplement and method of administration
  - Reasons for use and expected outcomes
  - Expected outcomes from conventional treatment
  - Identify if another provider is administering/providing therapy and their role
  - Financial considerations
  - Evidence for efficacy and safety

- **Step 5: Respond**
  - Encourage expression of feelings
  - Express empathy
  - Support desire for hope and control

- **Step 6: Discuss**
  - Discuss relevant concerns while respecting patient’s belief system
  - Consider a trial period
  - Explore alternative strategies to address underlying needs, hopes, fears

- **Step 7: Advise**
  - Encourage use that may be beneficial
  - Accept use where no evidence of physical harm or benefit
  - Discourage use if good evidence it is unsafe or harmful
  - Balance advice with patient’s right for self-determination and autonomy

Recommendations for Effective Discussions

• Step 8: Summarize
  • Main points of discussion
  • Verify understanding
  • Offer to talk to others
  • Provide resources

• Step 9: Document
  • Document in medical record
  • Inform other members of patient’s treatment team

• Step 10: Monitor
  • Follow-up at next encounter


Key Takeaways

• Many cancer patients use herbal supplements
• There are benefits and risks to supplement use
• Several resources are available to patients and providers
• It is very important to keep an open line of communication with patients and ask about their herbal supplement use frequently
Thank You