

A Vitamin A Day Keeps The Pharmacist Away...Or Does It?

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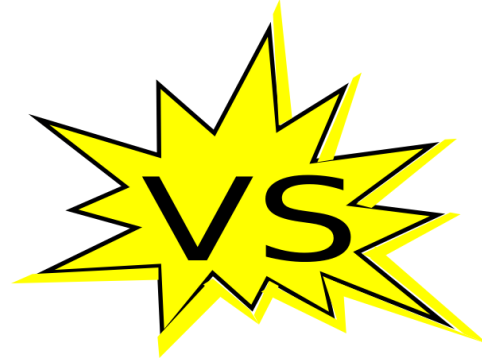
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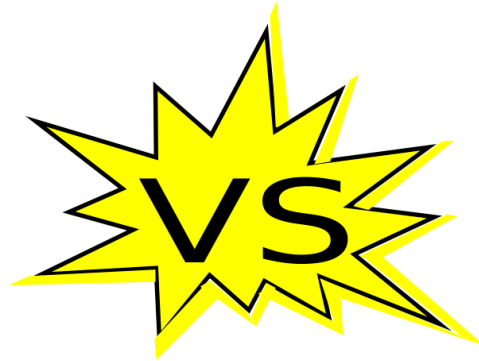
Objectives

- Identify the more common supplements, minerals and integrative therapies patients seek
- Evaluate the literature (or lack thereof) and information available for integrative therapies
- Analyze the appropriateness of integrative therapies in combination with patient's medication regimens
- Identify reliable sources for information and products
 - What “seals” can you look for to ensure safety, good compounding procedures?

Alternative



Complementary

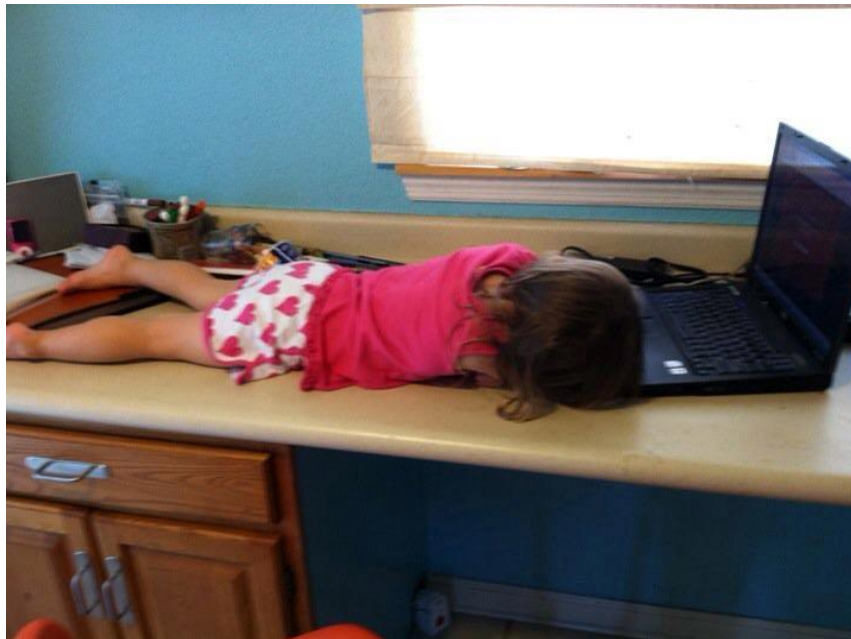


Integrative

We LOVE Our Supplements

- 33% of adult Americans used complementary health approaches
 - >11% of children 4-17 years old
 - \$30.2 billion per year out-of-pocket
- Nonvitamin, nonmineral dietary supplements are the most commonly used complementary health approach
- >30% of adult Americans take a multivitamin-mineral product
 - \$5.5 billion spent each year
- <5% used complementary medicine **INSTEAD OF** traditional medicine

Most Common Natural Products?



Clinical Questions:

- Frankincense (boswellia extract) orally
- Continuing diffused and topical oils
- Turmeric (curcumin)
- Garlic extract

Essential Oils

- Extracted from aromatic plant materials
 - Steam distillation
 - Mechanical expression
- Oils that are extracted using chemical solvents are NOT true essential oils
- Inhalation (aromatherapy) and topical



Essential Oils

- Animal and human data exist!
 - Address role as supportive therapy on stress and anxiety levels
- Both aromatherapy and topical

References

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8. Kite SM, Maher EJ, Anderson K, et al.: Development of an aromatherapy service at a Cancer Centre. *Palliat Med* 12 (3): 171-80, 1998. [PubMed: 9743836]
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- What is the risk?

Essential Oils

- Adverse effects
 - Contact dermatitis/local irritation
 - Phototoxicity (use just prior to sun exposure)
- Oxidized with aging
 - Chemical composition changes
- Lavender and tea tree oils
 - Possible estrogenic and antiandrogenic activity
 - Case reports and in vitro tests

Clinical Questions:

- **Continuing diffused and topical oils** 😊
- Frankincense (boswellia extract) orally
- Turmeric (curcumin)
- Garlic extract

Boswellia serrata

Frankincense



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1. [Reversal of the multidrug resistance of human ileocecal adenocarcinoma cells by acetyl-11-keto- \$\beta\$ -boswellic acid via downregulation of P-glycoprotein signals.](#)

Xue X, Chen F, Liu A, Sun D, Wu J, Kong F, Luan Y, Qu X, Wang R. Biosci Trends. 2016 Aug 19. PMID: 27545217 [Free Article](#) [Similar articles](#)

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Activation of p53/p21/PUMA alliance and disruption of PI-3/Akt in mul [Mol Carcinog. 2009]

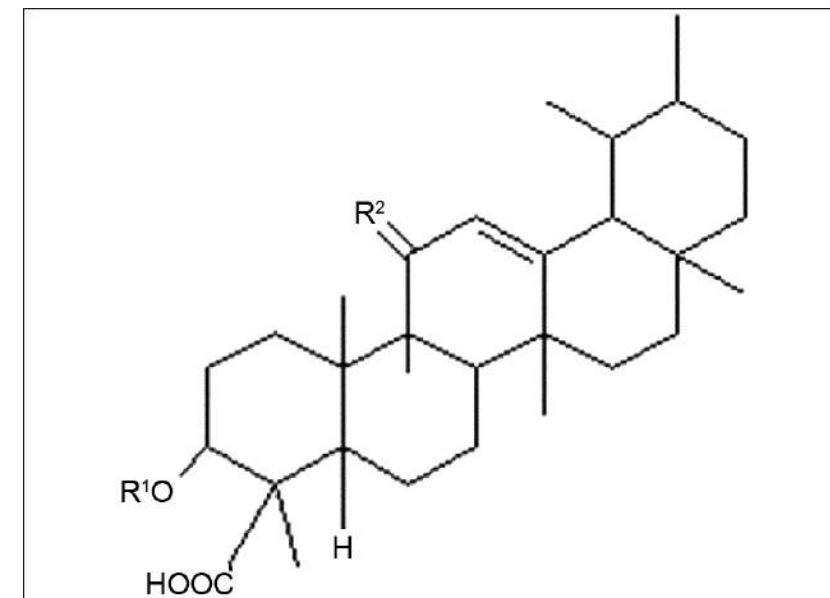
Temporary anti-cancer & anti-pain effects of mechanical stir [Acupunct Electrother Res. 2009]

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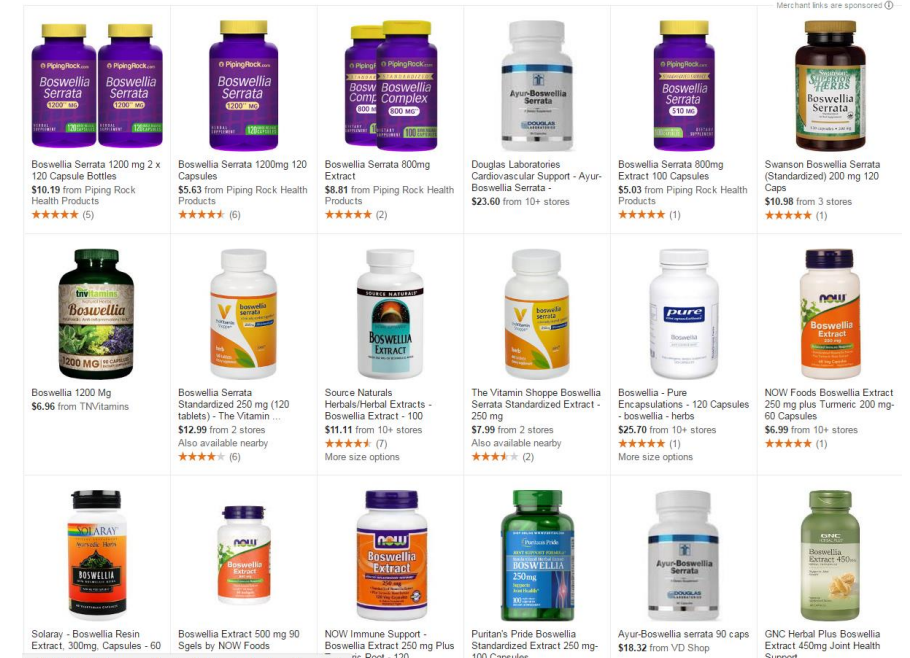
Database:

- Resin contains 4 major pentacyclic triterpenic acids (boswellic acids)
 - Responsible for inhibition of pro-inflammatory enzymes
- Shown in in vitro and animal models to inhibit synthesis of 5-lipoxygenase and leukotriene B₄



Boswellia serrata

- Dose, formulation, frequency?
 - Inconsistent product use in trials
 - Many formulations available – capsules, tablets
 - Be wary of amount of boswellic acids per dosage form
 - Goal: 65% boswellic acid
 - 300-400 mg per dose, 2-3 times per day
 - Start lower for kids, increase gradually in 3-4 weeks
- Adverse effects
 - GI upset
- Interactions
 - Minimal



Clinical Questions:

- Continuing diffused and topical oils
- **Frankincense (boswellia extract) orally** 😊
- Turmeric (curcumin)
- Garlic extract

Turmeric (curcumin)

- Shown to inhibit various apoptotic/necrotic pathways
 - Antiangiogenic properties
 - Anti-inflammatory effects
- Interaction with chemo
- Inhibition of metabolizing enzymes
- Possible kidney stones

Herb-Drug Interactions

Anticoagulants / Antiplatelets: Turmeric may increase risk of bleeding, as it also has antiplatelet properties ⁽⁵⁴⁾ ⁽⁵⁵⁾ ⁽⁶⁶⁾.

Camptothecin: Turmeric inhibits camptothecin-induced apoptosis of breast cancer cell lines in vitro ⁽²⁸⁾.

Mechlorethamine: Turmeric inhibits mechlorethamine-induced apoptosis of breast cancer cell lines in vitro ⁽²⁸⁾.

Doxorubicin: Turmeric inhibits doxorubicin-induced apoptosis of breast cancer cell lines in vitro ⁽²⁸⁾.

Cyclophosphamide: Dietary turmeric inhibits cyclophosphamide-induced tumor regression in animal studies ⁽²⁸⁾.

Norfloxacin: Pretreatment with curcumin resulted in increased plasma elimination half-life, thereby reducing the dosage of norfloxacin ⁽⁵⁶⁾.

Amphotericin B: Curcumin may enhance the effect and decrease the toxicity of amphotericin B ⁽⁵⁷⁾.

Drugs metabolized by CYP3A4 enzyme: Curcumin inhibits cytochrome 3A4 enzyme, altering the metabolism of some prescription drugs ⁽²⁶⁾. But according to conflicting data, short-term use of curcumin may not result in a clinically relevant interaction ⁽⁶⁷⁾.

Drugs metabolized by CYP1A2 enzyme: Curcumin inhibits cytochrome 1A2 enzyme, affecting the metabolism of certain prescription medicines ⁽²⁷⁾.

Drugs metabolized by CYP2A6 enzyme: Curcumin enhances cytochrome 2A6 enzyme, and can affect the metabolism of certain prescription drugs ⁽²⁷⁾.

Celiprolol and Midazolam: Curcumin was shown to downregulate intestinal P-gp levels, thereby increasing the concentrations of celiprolol and midazolam ⁽⁴⁸⁾.

Verapamil: Curcumin inhibited intestinal P-gp expression and function, thereby increasing concentrations of verapamil ⁽⁴⁷⁾.

Tacrolimus: Pretreatment with turmeric increases the plasma levels of tacrolimus ⁽⁵⁹⁾.

Acetaminophen: The cytotoxic effects of curcumin increased significantly in the presence of Acetaminophen ⁽⁶⁰⁾.

Ibuprofen: The cytotoxic effects of curcumin increased significantly in the presence of ibuprofen ⁽⁶⁰⁾.

Aspirin: The cytotoxic effects of curcumin increased significantly in the presence of aspirin ⁽⁶⁰⁾.

Garlic


- Actual placebo-controlled trials for cholesterol-lowering - variable
- Human studies in cardiovascular disease, blood pressure – known to decrease platelet aggregation
- Most case reports of adverse effects = bleeding!
 - Also stomach upset, headache, fatigue, offensive odor
- Drug interactions
 - Warfarin; watch out for other medications with bleeding effects
 - Inhibits AND Increases medication metabolic processes



Clinical Questions:

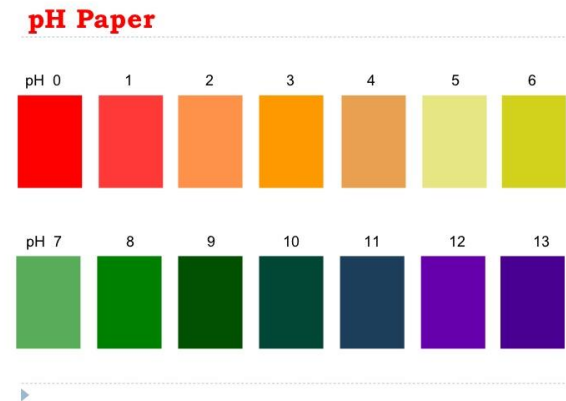
- Continuing diffused and topical oils
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- **Garlic extract** ✕

Clinical Questions:

- Probiotics: when patient completes chemotherapy
- Garlic and curcumin extracts: when patient completes chemotherapy
- Vitamin D and multivitamin 
- Liquid oxygen

Liquid Oxygen

- "Stabilized oxygen" in liquid form
 - Usually a combination of hydrogen peroxide
- Some products must be diluted before using
 - pH: 12-13
- "Safe" products are made up of 4 molecules of oxygen

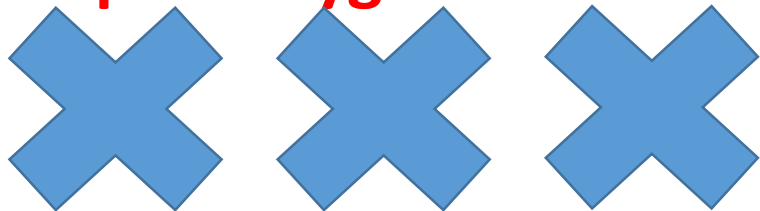


"The Liquid Stabilized Oxygen is processed by a secret, proprietary method...."

Clinical Questions:

- Probiotics: when patient completes chemotherapy
- Garlic and curcumin extracts: when patient completes chemotherapy
- Vitamin D and multivitamin

- **Liquid Oxygen**



Probiotics

- "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" (WHO definition)
- Common strains:
 - Lactobacillus
 - Bifidobacterium
 - Saccharomyces cerevisiae (yeast)
- Prevent/limit infectious diarrhea, antibiotic-associated diarrhea, diarrhea from recurrent C.diff
 - Possible utility in other gastrointestinal diseases, allergic disorders

Probiotics In Cancer

- Questionable role in alleviating chemotherapy-induced diarrhea
- Primary concern: NEUTROPENIA
- Case reports of microorganism in probiotic being isolated from blood cultures of patients
- Current recommendation: Avoid probiotics when expected to be neutropenic

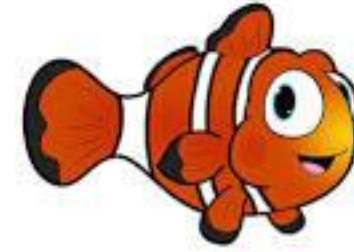
Clinical Questions:

- **Probiotics: when patient completes chemotherapy** 😊
- Garlic and curcumin extracts: when patient completes chemotherapy
- Vitamin D and multivitamin
- Liquid Oxygen

Back to our other favorites...



Fish Oil



- Well established: primary and secondary prevention studies show reduction in all-cause mortality and cardiovascular disease outcomes such as sudden death, cardiac death, myocardial infarction
 - Best evidence: fish and fish oil supplements
- Lower triglyceride levels
- Small beneficial effect on blood pressure

Fish Oil – Impact on Other Diseases

Inconclusive

- Asthma
- Inflammatory bowel disease
- Renal disease
- Lupus
- Bone density
- Diabetes
- Cognitive function

Greater Potential

- Rheumatoid arthritis

Fish Oil Products

- Prescription product (Lovaza)
 - Higher amounts of EPA/DHA
- Multiple dietary supplements
 - Check label for content of EPA and DHA as well as source
- Alternatives to fish oil products
 - Algal oils provide a vegetarian source of DHA
 - Krill oil becoming more popular

Table 1

The original sources, prices and contents of EPA and DHA in ten batches of fish oil capsule samples bought in Hong Kong ($n = 3$)

Sample no.	Labelled origin	Price (HK\$/g)	Labelled contents (mg/g)		Determined contents (mg/g)	
			EPA	DHA	EPA	DHA
1 ^a	USA	1.98			200.45	201.45
2	Australia	1.68			148.05	137.15
3	USA	1.53			509.16	501.18
4	USA	1.49			418.54	645.70
5	Australia	1.02	180	120	132.44	123.26
6	USA	0.98			361.36	419.73
7	New Zealand	0.65			208.42	204.72
8	USA	0.64			166.42	125.33
9	USA	0.34			39.52	35.14
10	USA	0.23			112.19	153.11

^aSamples are listed in order of decreasing price; that is, the most expensive are listed first.

Fish Oil and Chemotherapy

- Question of whether a specific fatty acid found in fish oil (supplemental and natural) can cause resistance to chemotherapy
 - Seen in mouse models with cisplatin
 - Ingestion of recommended daily amount of fish oil by health volunteers raised levels of this fatty acid
- Not concrete, but given potential harm, we recommend to hold fish oil (and not to eat fatty fish) the day before, during and day after chemotherapy

Melatonin

- Use has more than doubled from 2007 to 2012
 - 0.6% up to 1.3%
- Significant evidence (in children too!) to show improvement in sleep duration and quality
 - This is generally the only sleep aid we recommend in pediatric patients
 - Often used in patients with underlying neurological disorders and cancer

Melatonin

- Evidence to support possible anti-tumor effects
 - Free radical scavenger
 - Stimulates IL-4 production in T-lymphocytes
 - Antimitotic effect – interrupts tumor growth
 - Interferes with estrogen receptor expression
- Adverse effects: drowsiness
- Interactions: minor medication metabolic inhibition

What To Look For

- The guys on TV are good, but do not always present the most robust information
- Guidelines?
- While studies may find a “statistically significant” difference within the numbers and confines of their design (in vitro versus in vivo), the CLINICAL SIGNIFICANCE is very important to note
 - So while in vitro testing may show the desired effect at the cellular level, translation to in vivo effect is often unknown

Guidelines Exist!

- American Association of Clinical Endocrinologists:
<https://www.aace.com/files/nutraceuticals-2003.pdf>
- U.S Preventive Services Task Force:
<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/vitamin-supplementation-to-prevent-cancer-and-cvd-counseling>
- American Academy of Neurology:
<http://www.neurology.org/content/78/17/1346.full.pdf+html>
- Journal of Pediatric Gastroenterology and Nutrition:
<http://www.naspghan.org/files/documents/pdfs/position-papers/probiotics.pdf>
- National Cancer Institute:
<http://jncimono.oxfordjournals.org/content/2014/50/346.full.pdf+html>
- American College of Obstetricians and Gynecologists: Clinical Management Guidelines for Management of Menopausal Symptoms



What To Look For

- If it claims to “cure” a disease or has a “money-back guarantee”

BEWARE!

- Check the label for all ingredients listed (THEY HAVE TO DO THIS!)
 - Look for wheat, soy, dairy, nuts, other allergens
- Check the company online
 - Do they have a 3rd party source/lab that provides product checking?
 - Do they provide this information on their website?
- These are ideal to see on a label:
 - **NSF International (nsf.org)**
 - **US Pharmacopeia**
 - (www.usp.org/usp-consumers/dietary-supplements-consumers)
 - **Consumer Lab seal**
 - Need a subscription for full information online



Conclusions

- Use of complementary therapies is increasing
 - Not just your typical fish oils, calciums and black cohosh anymore!
- Data, literature, resources exist to help guide use and decision making
 - ESPECIALLY in combination with conventional therapies
- When possible, we try to help patients pick a product and give them information to support safe use

Zinc



- Cold preparations
 - Multiple studies show a decrease in duration and severity of cold symptoms
 - Multiple studies show no difference
 - Most recent large review of literature done supports benefit
- Lozenges >>>> Nasal products
 - Multiple case reports of anosmia (loss of smell)
 - 3 products recalled in 2009
- If needed, use the lozenges and use sparingly
 - No specific data to support recommendations on doses, length of treatment

Black Cohosh



- Potential use in postmenopausal women for hot flashes
 - Binds estrogen receptors
- Most well studied product – Remifemin
- While majority of studies (small and short duration) showed benefit, there is difficulty in evaluating the effect
 - Short duration (6 months or less) of study
 - Varying amounts used from different sources
- New study being conducted by NIH: 12 months long
 - Will also try to better determine mechanism of action

CBD Oil – Over the Counter



- Extracted from hemp plant
- Must come from hemp plant that contains <0.3% THC
- Oils, gummies, lollipops, capsules, topical preparations
- Potential benefits:
 - Anxiety
 - Sleep
 - Pain

