Safety & Efficacy of Supplement Drug Interactions

Russell Jaffe, MD, Ph.D., CCN, NACB FASCP, FACN, FACAAI, FAMLÍ, FOCIS, FRCM
Fellow, Health Studies Collegium
Director, ELISA/ACT Biotechnologies, LLC.
Director, PERQUE, LLC.
Meaning of words used

• **Safety**: Freedom from danger, risk, or injury.
• **Efficacy**: Evidence based effective results.
• **Supplement**: *Food for special dietary use.*
• **Drugs**: Therapeutic substances approved by the drugs & devices sections of FDA
DSHEA 1994 supplement

- product that contains substances like vitamins, minerals, foods, botanicals, amino acids & is intended to supplement the usual intake of these substances. Dietary supplements are found in pill, tablet, capsule, powder or liquid form and are meant to be taken by mouth.
Natural Products: Cradle to Cradle

- Inherently or intrinsically no waste
- End product used as feedstock
- Inherently high efficiency
- Wholism ‘obvious’
- Interdependence
- Physiology
- Quality and sustainability high values
- Was hard to standardize natural products
Extra-natural: Cradle-to-Grave

- Waste disposed, assumed inherent, NIMBY
- End product discarded or abandoned
- Inherently low efficiency
- Reductionism a given
- Autonomy, independence
- Chemical engineering
- Quantity and ROI are high values
- Standardized doses & delivery of drugs
Adverse Events (AE)

What data says comparing AE events from dietary supplements compared to all AE reports (2006)
Dietary supplements AE 2006

• 275 of 450,000 total AE reported. 2/3 rated as probably or possibly related to supplement use (N=183); coincidental, unrelated (N=92).

41% cases symptomatic self-limited (N=113): caffeine (47%; N=53) & yohimbe (18%; N=20) & 70 TBD. Suspected drug-herb interactions occurred in 6 cases, including *yohimbe* co-ingested with bupropion (1), methamphetamine (3), additive anticoagulant/anti-platelet effects of NSAIDs taken with fish oils (1) & ginkgo (1). 8 AE required hospital admission [2,200,000/100,000]. Lab tests confirmed adulteration with pharmacologically active substances in 4 cases & negative in 5 cases.

ASA or NSAID + Omega 3 EFA

- Fish oil did not affect bleeding time or plasma levels of beta-thromboglobulin; an increase in platelet count after operation was slightly less pronounced in fish-oil group. Apart from a small increase in PAI-1 antigen borderline sig., no long-term effects by fish oil on parameters of coagulation & fibrinolysis were seen.

ASA or NSAID + Omega 3 EFA

• Bleeding time & mesenteric vascular reactivity to noradrenaline were ↑2-4 weeks after receiving a moderate intake of EPA & effects persisted 5-21 d after switching to control diet...

in male Wistar rats under stress... not found for people in either PubMed or Google Scholar [myths linger on... Linus Pauling]

Adverse Event (AE) US


http://www.fda.gov/cber
# Natural v Extra-Natural Products

<table>
<thead>
<tr>
<th>Category Condition</th>
<th>Natural Product</th>
<th>Extra-Natural Product</th>
<th>Safety ratio</th>
<th>Efficacy ratio</th>
<th>Lives/ year (Est.)</th>
<th>$/year $100K/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria Prophylaxis</td>
<td>Chincona Bark</td>
<td>Quinine</td>
<td>100</td>
<td>1</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Malaria Treatment</td>
<td>Artemesia Annua</td>
<td>Artemisinin</td>
<td>75</td>
<td>0.2</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Food Preserve Anti-oxidant</td>
<td>Vitamins E Tocopherols/Tocotrienols</td>
<td>BHA/BHA</td>
<td>&gt;500</td>
<td>0.5</td>
<td>1,500</td>
<td>$0.3 Bn</td>
</tr>
<tr>
<td>Balance Calcium</td>
<td>Magnesium</td>
<td>Calcium channel blockers</td>
<td>&gt;500</td>
<td>0.5</td>
<td>5,000</td>
<td>$0.5 Bn</td>
</tr>
<tr>
<td>Digestion</td>
<td>Probiotics/ Prebiotics</td>
<td>Antibiotics/ Biocides</td>
<td>&gt;500</td>
<td>0.4</td>
<td>20,000</td>
<td>$2 Bn</td>
</tr>
<tr>
<td>Comfort</td>
<td>Polyphenolics</td>
<td>Cox-2 modulators</td>
<td>&gt;500</td>
<td>0.5</td>
<td>50,000</td>
<td>$5 Bn</td>
</tr>
<tr>
<td>Pain</td>
<td>Poppies</td>
<td>Morphine/Heroin</td>
<td>50</td>
<td>0.25</td>
<td>15,000</td>
<td>$1.5 Bn</td>
</tr>
<tr>
<td>Cancer risk</td>
<td>Sulforophane/ ECGC</td>
<td>Preventive chemo</td>
<td>&gt;500</td>
<td>??</td>
<td>??</td>
<td></td>
</tr>
<tr>
<td>Gut repair Energy</td>
<td>Glutamine/ PAK</td>
<td>Cross-link enhancers</td>
<td>&gt;500</td>
<td>0.4</td>
<td>5,000</td>
<td>$0.5 Bn</td>
</tr>
</tbody>
</table>
Malaria Prophylaxis

• Traditional tree bark or isolated ingredient: Safety, efficacy, risk
Chincona Bark Medicinals

- Chincona, Jesuit’s or Peruvian bark: Active alkaloids including anti-malarial quinine interferes w/ reproduction of malaria-causing protozoa, & quinidine antiarrhythmic. Bark stripped from tree, dried, & powdered as medicinal herb. Plants from South America, & transported for cultivation in other tropical regions notably India Sri Lanka by British & Java by Dutch (19th century)

- Quinine causes liver scars; chincona has protective antioxidants; both effective.

Chincona Bark Tree
Malaria Treatment

• Artemesia Annua v Artemesinin: Safety, efficacy, risk, outcomes
Malaria treatment

• Artemesia Annua & synthetic Artimesinin work
• Artemesia Vulgaris or Sweet Annie; mugwort do not work
  [workalikes often don’t work]
Artemisia Annua or Artemisinin

- Artemisia annua L., Asteraceae; quinghao Asian annual herb is Artemisinin source. Grows in Argentina, Bulgaria, France, Hungary, Romania, Italy, Spain, U.S. & Yugoslavia. Leaf secretory cells 89% total artemisinin in plant w/uppermost foliar portion of plant (top 1/3 of growth at maturity) containing almost 2X that of lower leaves. Natural product not provoke resistance; synthetic artemisinin has resistance & >AE.

Antioxidant Food Protectors

Natural Vitamins E

Synthetic BHA / BHT
Compare antioxidant activity

Synthetic Antioxidants

- **BHA** is mixture of isomers 3-tert-butyl-4-hydroxyanisole and 2-tert-butyl-4-hydroxyanisole. A/K/A BOA, tert-butyl-4-hydroxyanisole, (1,1-dimethylethyl)-4-methoxyphenol, tert-butyl-4-methoxyphenol, antioxyne B; Molecular formula C\(_{11}\)H\(_{16}\)O\(_2\)
- **BHT** (3,5-di-tert-butyl-4-hydroxytoluene; methyl-di-tert-butylphenol; 2,6-di-tert-butyl-para-cresol) Molecular formula C\(_{15}\)H\(_{24}\)O

## Tocopherol & Tocotrienol AO

![Chemical structures of Tocotrienol and Tocopherol](image)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Tocopherol</th>
<th>Tocotrienol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>α - Tocopherol</td>
<td>α - Tocotrienol</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>β - Tocopherol</td>
<td>β - Tocotrienol</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>γ - Tocopherol</td>
<td>γ - Tocotrienol</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>δ - Tocopherol</td>
<td>δ - Tocotrienol</td>
</tr>
</tbody>
</table>

Induce Repair 1st Responders or Suppress Inflammation for comfort, safety, risk

- Polyphenolic vs ASA, NSAIDs, Acetaminophen
Polyphenolics v NSAIDs, ASA

- Polyphenolic flavanoids & flavanols activate 1\textsuperscript{st} responder repair cells.
- NSAIDs, ASA, & acetominophen inhibit COX-1&2 enzymes; 50±25,000 deaths/yr; toxicities multiply in concurrent use.
Quercetin Dihydrate & OPC: Safer Repair Stimulation

Repair Guard delivers highest, safer antioxidant protection
Pain: Opium, Morphine, Heroin

• Compare options for serious pain management: Safety, Efficacy, Risk
Natural Pain Killers from Poppy

- Latex alkaloids from immature seed capsules 1 - 3 weeks > flowering. Incisions made in walls of green seedpods, & milky exudation is collected & dried. Opium & isoquinoline alkaloids morphine, codeine, noscapine, papaverine, & thebaine isolated from dried material.

Poppy seeds & pressed oil are not narcotic; they develop after capsule has lost opium-yielding potential. Total yield of alkaloids depends on light, temperature, plant species, & time of harvest.

Angelo HR, Kaa E. *Ugeskr Laeger* 1993 Dec 6; 155(49): 4011-4013
Poppy Juice v. Morphine, etc

Biosis: Microbial Interdependence

• Prebiotics & Probiotics

Antibiotics & Biocides
Probiotic v Antibiotic

- Probiotic viable microbial dietary supplement beneficially affects host through its effects on intestinal tract… Several health-related effects associated with intake of probiotics include alleviation of lactose intolerance & immune enhancement. Some evidence probiotics reduce risk of rotavirus-induced diarrhea & colon cancer.

Prebiotic fibers

- Prebiotics are nondigestible food ingredients that benefit host by selectively stimulating growth or activity of...beneficial bacteria in colon. Inulin-type fructan prebiotics generate sufficient data for thorough evaluation regarding their possible use as functional food ingredients.

Prebiotics & Probiotics

• **Benefits**: Constipation relief, suppression of diarrhea, & reduction of osteoporosis, atherosclerotic cardiovascular disease associated with dyslipidemia & insulin resistance, obesity, & type 2 diabetes risk. Synergy of probiotics & prebiotics deserves study. This combo might improve survival of bacteria crossing upper part of GI tract, enhancing their effects in large bowel. Effects might be additive or even synergistic.

Natural Cancer Risk Reduction

• Vitamin D3 hormone vitamin
• EGCG
• Sulforaphane

As possible enhancers of innate anti-cancer mechanisms
D3 hormone vitamin & v Chemo

Recent NCI Consensus Conference & Dr Michael Holick ‘Dr Sunshine’

People with D3 blood levels of 50-80 have < half cancer compared to people with < 25 ng/dl.
EGCG: Green tea benefit

- Green tea is EGCG rich & drunk by low cancer people
- EGCG ‘sits’ at cell multiplication site.
- Weinberg @ Whitehead

en.wikipedia.org/wiki/Health_effects_of_tea
Sulforaphane: Brassica sprouts

www.brassica.com/press/pr0012.htm
Calcium Channel

• Magnesium: Uptake enhanced through choline citrate; natures balance to calcium

or

• Calcium Channel Blockers
Magnesium & Choline Citrate: Nature’s Calcium Channel Blocker
1st Do No Harm; 2nd Think Mg++

- Enhanced uptake forms available, use Mg++ as cell function balancer

MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF DISEASE
Repair: Connective Tissue

- Glutamine recycled by PAK

- Better basement membrane, collagen & elastin cross-linking
Glutamine Recycled 10x by PAK

Glutamine $\xleftrightarrow{\text{Energy+}}$ Glutamate + NH$_3$ + PAK

www.perque.com/pdfs/PERQUE-Endura-Guard.pdf
Recycled Glutamine or Cross-Links

- Photo-induced increased cross-links allow sculpting of surfaces
- Does this accelerate aging? TBD
## Natural v. Extra-Natural Products

<table>
<thead>
<tr>
<th>Category Condition</th>
<th>Natural Product</th>
<th>Extra-Natural Product</th>
<th>Safety ratio</th>
<th>Efficacy ratio</th>
<th>Lives/year (Est.)</th>
<th>$/year $100K/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria Prophylaxis</td>
<td>Chincona Bark</td>
<td>Quinine</td>
<td>100</td>
<td>1</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Malaria Treatment</td>
<td>Artemesia Annuan</td>
<td>Artemisinin</td>
<td>75</td>
<td>0.2</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Food Preserve Anti-oxidant</td>
<td>Vitamins E Tocopherols/Tocotrienols</td>
<td>BHA/BHA</td>
<td>&gt;500</td>
<td>0.5</td>
<td>1,500</td>
<td>$0.3 Bn</td>
</tr>
<tr>
<td>Balance Calcium</td>
<td>Magnesium</td>
<td>Calcium channel blockers</td>
<td>&gt;500</td>
<td>0.5</td>
<td>5,000</td>
<td>$0.5 Bn</td>
</tr>
<tr>
<td>Digestion</td>
<td>Probiotics/Prebiotics</td>
<td>Antibiotics/Biocides</td>
<td>&gt;500</td>
<td>0.4</td>
<td>20,000</td>
<td>$2 Bn</td>
</tr>
<tr>
<td>Comfort</td>
<td>Polyphenolics</td>
<td>Cox-2 modulators</td>
<td>&gt;500</td>
<td>0.5</td>
<td>50,000</td>
<td>$5 Bn</td>
</tr>
<tr>
<td>Pain</td>
<td>Poppies</td>
<td>Morphine/Heroin</td>
<td>50</td>
<td>0.25</td>
<td>15,000</td>
<td>$1.5 Bn</td>
</tr>
<tr>
<td>Cancer risk</td>
<td>Sulforaphane/D3, EGCG</td>
<td>Preventive chemo</td>
<td>&gt;500</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Gut repair Energy</td>
<td>Glutamine/PAK</td>
<td>Cross-link enhancers</td>
<td>&gt;500</td>
<td>0.4</td>
<td>5,000</td>
<td>$0.5 Bn</td>
</tr>
</tbody>
</table>
Natural v. Extra-Natural Products

Result of using Natural rather than Extra-Natural Products on lives and costs:

* Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies * by Mitchell Bebel Stargrove, Jonathan Treasure, Dwight L. McKee

- Save **100,000 lives** per year
- Reduce direct healthcare costs by **$9.8 Bn/year**
- Reduce *suffering* for affected people
- Use **best of both**: Respect for nature & science
- ReThink choices in light of what we now know
Natural Compared to Extra-Natural

- Inherently or intrinsically no waste
- End product used as feedstock next cycle
- Inherently high efficiency
- Wholism ‘obvious’
- Interdependence
- Physiology
- Quality & sustainability high values

- Waste disposed, assumed inherent, NIMBY
- End product discarded or abandoned
- Inherently low efficiency
- Reductionism a given
- Autonomy, independence
- Chemical engineering
- Quantity & ROI are high values
Safety & Efficacy of Supplement Drug Interactions

Russell Jaffe, MD, Ph.D., CCN, NACB FASCP, FACN, FACAAI, FAMLÍ, FOCIS, FRCM
Fellow, Health Studies Collegium
Director, ELISA/ACT Biotechnologies, LLC.
Director, PERQUE, LLC.