Nutraceuticals: Challenges and Opportunities

Mark Hyman Rapaport MD
Emory University School of Medicine
Conflicts of interest relevant to this presentation

• Previous funding from NCCAM to investigate the mechanism of action of Swedish massage therapy in normal volunteers

• Previous funding from NCCAM and NIMH to investigate the efficacy of St. John’s Wort in minor depressive disorder

• Previous funding from NIMH investigating N-3 fatty acid therapy on immune function and the treatment of major depressive disorder

• Current funding from NCCIH to study the effects of massage on Cancer-related fatigue

• Current funding from NIMH for the GPC collection and RAPID trials

• Current funding from NCCIH investigating the impact of N-3 fatty acids on inflammation in obese, inflamed subjects with MDD
## Collaborators

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Mischoulon</td>
<td>Jeff Rakofsky</td>
</tr>
<tr>
<td>Andrew Nierenberg</td>
<td>Andy Miller</td>
</tr>
<tr>
<td>Russell Poland</td>
<td>Sherry Edwards</td>
</tr>
<tr>
<td>Lev Gertsik</td>
<td>Maurizio Fava</td>
</tr>
<tr>
<td>Catherine Bresee</td>
<td>Jennifer Felger</td>
</tr>
<tr>
<td>Pamela Schettler</td>
<td>Stefania Fava-Lemon</td>
</tr>
<tr>
<td>Becky Kinkead</td>
<td>Jisun So</td>
</tr>
<tr>
<td>Boadie Dunlop</td>
<td></td>
</tr>
</tbody>
</table>
YOU GOTTA KNOW THE TERRITORY!

Professor Henry Hill, “The Music Man”
It is important to remember

• Many of the medications commonly prescribed today were initially purified from plant extracts or fungi
What percent of pharmaceuticals manufactured in China are “traditional” natural products?

10%
27%
36%
56%
72%

The current answer is 36%; Thirty-six percent of all pharmaceuticals manufactured in China are derived from natural products identified by traditional medicine practitioners.
“Lost in Translation 1”

Many of the natural products on the US market are part of the other healing traditions:

TRADITIONAL:

Chinese Medicine
Tibetan Medicine
Hmong Medicine
Mongolian Medicine
Cunanderos/Yerberos
Ayurveda Medicine
Differences between ‘traditional medicine’ and allopathic medicine

<table>
<thead>
<tr>
<th>TRADITIONAL</th>
<th>ALLOPATHIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holistic Approach</td>
<td>Treatment focuses on a specific target</td>
</tr>
<tr>
<td>Individualized treatment based on “pattern differences”</td>
<td>Standardized Treatment</td>
</tr>
<tr>
<td>Practice based on traditions, clinical experience and individual observations</td>
<td>Practice and use of medications based on FDA guidelines, practice guidelines</td>
</tr>
<tr>
<td>Subjective Outcome Assessment of individuals</td>
<td>Standardized and validated target specific outcomes</td>
</tr>
</tbody>
</table>
Some of the challenges
“SQUARE PEG in a ROUND HOLE PHENOMENA”

Natural products are:

- Used for very different constellations of signs and symptoms in native cultures
- We in the US are employing them to treat our definition of disorders
What you see may be what you get

- Unsubstantiated Claims of Benefit
- Minimal GPC/GM Standards

2/3 of St. John’s wort compounds contained no St. John’s wort
Rate of deterioration of compounds are not known or standardized.
The dosage and formulation may vary between batches
“Natural may not be safe”

- Products may not be natural
- There may be many unforeseen interactions
  - Pharmacokinetic
  - Pharmacodynamic
Kava (Piper Methysticum)

- Anxiolytic, anticonvulsant, and muscle relaxant (kavapyrones)
- More than 12 studies, mostly RCTs
- Similar efficacy to venlafaxine, buspirone, opipramol (sigma antagonist)
- Effective for mild anxiety, not for panic attacks (Sarris et al, 2011)
- Antidepressant effect? (Sarris et al, 2009)
Kava: Adverse Effects

- 78 cases of severe kava-related liver toxicity
- 36 cases of hepatitis; cirrhosis
- 11 cases of liver failure requiring transplant
- 4 deaths
Effects of herbs on drug-metabolizing enzymes and transporters

<table>
<thead>
<tr>
<th>Herbs</th>
<th>In Vitro</th>
<th>Animal</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenseal (Hydrastis canadensis)</td>
<td>↓CYP2C9, 2C19, 3A4 and 2D6</td>
<td></td>
<td>↓CYPD26 and 3A4/5</td>
</tr>
<tr>
<td>Green Tea (Camellia sinensis)</td>
<td>↓CYP2C9, 2D6, and 3A4</td>
<td></td>
<td>↓CYP3A4</td>
</tr>
<tr>
<td>Milk Thistle (Sylimbus marianum)</td>
<td>↓CYP3A4, 2C9, 2E1, 2D6, 2C19, 1A2 and 2A6, P-gp, UGT1A1</td>
<td>↓CYP3A, 2C9 and P-gp</td>
<td>↑CYP3A4 and P-gp; ↓CYP2C9 and P-gp</td>
</tr>
<tr>
<td>St. John's Wort (Hypericum perforatum)</td>
<td>↑CYP3A4, 2C9 and P-gp</td>
<td></td>
<td>↑CYP3A4, OAT and P-gp</td>
</tr>
</tbody>
</table>

Effect of genetic polymorphisms on herb-drug interactions

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Drugs</th>
<th>Effect of genetic polymorphisms on herb-drug interaction</th>
<th>Effect of genetic polymorphisms on the activity/protein/mRNA levels of the drug-metabolizing enzymes and drug transporters</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s wort</td>
<td>Gliclazide</td>
<td>Treatment of St. John’s wort significantly increased the apparent clearance of gliclazide which was independent of CYP2C9 genotype</td>
<td>Reduced with the variant allele</td>
<td>[166]</td>
</tr>
<tr>
<td>Mephenytoin</td>
<td>St. John’s wort</td>
<td>St. John’s wort treatment significantly increased phenytoin clearance in CYP2C19 extensive metabolizers but not in PMs (*2,*3)</td>
<td>Reduced with the variant allele</td>
<td>[167]</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>St. John’s wort</td>
<td>After administration of St. John’s wort, the AUC $0-\infty$ of nifedipine and dehydronifedipine decreased by 42.4 and 20.2% in PXR H1/H2; 47.9 and 33.0% in H2/H2; whereas for the H1/H1 the AUC $0-\infty$ of nifedipine decreased 29.0%, but the AUC $0-\infty$ of dehydronifedipine increased by 106.7%.</td>
<td>Reduced basal transcriptional activity, but stronger induced transcriptional activity on CYP3A4 with H1/H1 compared with H1/H2 and H2/H2</td>
<td>[168]</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>St. John’s wort</td>
<td>St. John’s wort decreased the plasma concentrations of omeprazole in a CYP2C19 genotype-dependent manner</td>
<td>Reduced with the variant allele</td>
<td>[169]</td>
</tr>
</tbody>
</table>

AUC – Area under the curve; CYP- Cytochrome P450; INR – International normalized ratio; PK – Pharmacokinetic; PM – poor metabolizer; PXR – Pregnan X receptor

The Opportunities

The Example of Major Depressive Disorder
## CANMAT recommendations for natural products

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Evidence</th>
<th>Monotherapy or Adjunctive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s wort</td>
<td>Mild to moderate MDD</td>
<td>First Line</td>
<td>Level 1</td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second Line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Omega-3</td>
<td>Mild to moderate MDD</td>
<td>Second line</td>
<td>Level 1</td>
<td>Monotherapy or adjunctive</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>SAM-e</td>
<td>Mild to moderate MDD</td>
<td>Second line</td>
<td>Level 1</td>
<td>Adjunctive</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Crocus sativus</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Monotherapy or adjunctive</td>
</tr>
<tr>
<td>(saffron)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEA</td>
<td>Mild to moderate MDD</td>
<td>Third Line</td>
<td>Level 2</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Folate</td>
<td>Mild to moderate MDD</td>
<td>Third Line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Lavandula</td>
<td>Mild to moderate MDD</td>
<td>Third Line</td>
<td>Level 3</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>(Lavender)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inositol</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Level 2</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Rhodiala rosea</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Level 2</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>(rosersoot)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHEA – dehydroepiandrosterone; MDD – major depressive disorder; SAM-e – S-adenosyl-L-methionine

Inflammation: A Common Mechanism of Disease - Insight of the Decade (Science, 2010)
## Demographic Characteristics

Subjects with All 5 Biomarkers at Baseline

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (sd) [Range] (N)</th>
<th>EPA-Enriched (N = 52)</th>
<th>DHA-Enriched (N = 51)</th>
<th>Placebo (N = 52)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(21 - 73] (50)</td>
<td>(23 - 70] (49)</td>
<td>(22 - 69] (49)</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>46.7 (11.9)</td>
<td>45.9 (14.2)</td>
<td>45.6 (12.0)</td>
<td></td>
<td>0.11</td>
</tr>
</tbody>
</table>

| Study Site   | N (%)                 | N (%)                 | N (%)                 |                  | x²            | df  | P   |
|--------------|-----------------------|-----------------------|-----------------------|                  | 0.11         | 2   | 0.948 |
| Cedars-Sinai | 32 (61.5)             | 30 (58.8)             | 32 (61.5)             |                  |              |     |     |
| MGH          | 20 (38.5)             | 21 (41.2)             | 20 (38.5)             |                  |              |     |     |

| Gender       | N (%)                 | N (%)                 | N (%)                 |                  | x²            | df  | P   |
|--------------|-----------------------|-----------------------|-----------------------|                  | 0.81         | 2   | 0.666 |
| Female       | 33 (63.5)             | 28 (54.9)             | 30 (57.7)             |                  |              |     |     |
| Male         | 19 (36.5)             | 23 (45.9)             | 22 (42.3)             |                  |              |     |     |

| Race         | N (%)                 | N (%)                 | N (%)                 |                  | x²            | df  | P   |
|--------------|-----------------------|-----------------------|-----------------------|                  | 0.59 b       | 2   | 0.745 |
| Caucasian    | 37 (71.2)             | 33 (67.4)             | 34 (65.4)             |                  |              |     |     |
| African      | 10 (19.2)             | 8 (15.7)              | 11 (21.2)             |                  |              |     |     |
| American     | 3 (5.8)               | 5 (9.8)               | 5 (9.6)               |                  |              |     |     |
| Other        | 2 (3.8)               | 5 (9.8)               | 2 (3.8)               |                  |              |     |     |
| Prefer Not   | 2 (3.8)               | 5 (9.8)               | 2 (3.8)               |                  |              |     |     |
| to Say       |                       |                       |                       |                  |              |     |     |

| Ethnicity    | N (%)                 | N (%)                 | N (%)                 |                  | x²            | df  | P   |
|--------------|-----------------------|-----------------------|-----------------------|                  | 0.07         | 2   | 0.964 |
| Hispanic     | 8 (16.0)              | 8 (16.0)              | 7 (14.3)              |                  |              |     |     |
| Non-Hispanic | 42 (84.0)             | 42 (84.0)             | 42 (85.7)             |                  |              |     |     |

| Education    | N (%)                 | N (%)                 | N (%)                 |                  | x²            | df  | P   |
|--------------|-----------------------|-----------------------|-----------------------|                  | 1.29         | 2   | 0.525 |
| High School  | 16 (31.4)             | 13 (26.0)             | 10 (21.3)             |                  |              |     |     |
| or Less     | 35 (68.6)             | 37 (74.0)             | 37 (78.7)             |                  |              |     |     |
| Some College |                       |                       |                       |                  |              |     |     |
| or More     |                       |                       |                       |                  |              |     |     |

---

a. Information is missing for some subjects.
b. Categories were combined to avoid invalid x² due to cells with expected count < 5.
<table>
<thead>
<tr>
<th>Inflammatory Group Based on Number of High Inflammatory Markers</th>
<th>Least-Square Means (se) of Change at Treatment Week 8</th>
<th>Significance of Treatment-by-Time Interaction</th>
<th>Standardized Treatment Effect Size at Treatment Week 8 b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPA LS-Mean (se) [N]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DHA LS-Mean (se) [N]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo LS-Mean (se) [N]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F df (P-Value)</td>
<td>EPA vs. PLA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DHA vs. PLA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EPA vs. DHA</td>
</tr>
<tr>
<td>4 or 5 High (N=21)</td>
<td>-11.14 (1.79) [10]</td>
<td>0.94 2, 79.8 (P=0.396)</td>
<td>-1.11</td>
</tr>
<tr>
<td></td>
<td>-4.90 (2.17) [7]</td>
<td></td>
<td>+0.02</td>
</tr>
<tr>
<td></td>
<td>-5.02 (2.52) [4]</td>
<td></td>
<td>-1.10</td>
</tr>
<tr>
<td>2 or 3 High (N=38)</td>
<td>-12.38 (1.47) [13]</td>
<td>0.70 2, 135 (P=0.498)</td>
<td>-0.59</td>
</tr>
<tr>
<td></td>
<td>-11.52 (1.35) [13]</td>
<td></td>
<td>-0.44</td>
</tr>
<tr>
<td></td>
<td>-9.43 (1.35) [12]</td>
<td></td>
<td>-0.17</td>
</tr>
<tr>
<td>1 High  (N=50)</td>
<td>-11.76 (1.28) [13]</td>
<td>1.20 2, 177 (P=0.303)</td>
<td>-0.20</td>
</tr>
<tr>
<td></td>
<td>-7.31 (1.11) [17]</td>
<td></td>
<td>+0.73</td>
</tr>
<tr>
<td></td>
<td>-10.80 (1.10) [20]</td>
<td></td>
<td>-0.97</td>
</tr>
<tr>
<td>0 High (N=46)</td>
<td>-7.78 (0.85) [16]</td>
<td>4.09 2, 215 (P=0.018)</td>
<td>+0.91</td>
</tr>
<tr>
<td></td>
<td>-11.65 (0.96) [14]</td>
<td></td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>-10.85 (0.83) [16]</td>
<td></td>
<td>+1.11</td>
</tr>
</tbody>
</table>

a. MMRM analysis of N=155 evaluable subjects with all five biomarkers at baseline.
b. By Cohen’s d effect size = (difference between LS-Mean change) / pooled sd for each pair of treatments (sd estimated for one of LS-Mean from MMRM). A negative effect size indicates that the 1st group performed worse than the 2nd group.

Change in HAMD-17 Total Score from Baseline to Treatment Week 8 by Number of High Inflammatory Markers.
Omega-3 Fatty Acids for MDD with High Inflammation: A Personalized Approach: an UG3

Mark H. Rapaport, MD, Maurizio Fava, MD, David Mischoulon, MD, PhD, Boadie Dunlop, MD, Jennifer Felger, PhD, Becky Kinkead, PhD, Andrew Miller, MD, Jeffrey Rakofsky, MD, Pamela Schettler, PhD, Thomas Ziegler, MD, Andrew Nierenberg, MD, Jonathan Alpert, PhD, Christina Dording, MD, Stephania Fava, PhD

Funding: NCCIH UG3AT008857
## Flow of Randomized Subjects by Treatment Group

<table>
<thead>
<tr>
<th>Subject Status</th>
<th>1g/day</th>
<th>2g/day</th>
<th>4g/day</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized (n)</strong></td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>61</td>
</tr>
<tr>
<td><strong>Evaluable (n)</strong></td>
<td>15</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td>57</td>
</tr>
<tr>
<td>% of Those Randomized</td>
<td>100.0%</td>
<td>93.3%</td>
<td>100.0%</td>
<td>80.0%</td>
<td>93.4%</td>
</tr>
<tr>
<td><strong>Analyzable Data to Visit 9 (n)</strong></td>
<td>14</td>
<td>11</td>
<td>13</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>% of Those Randomized</td>
<td>93.3%</td>
<td>73.3%</td>
<td>81.2%</td>
<td>66.7%</td>
<td>78.7%</td>
</tr>
</tbody>
</table>
## IDS-C30 Response (>50% Reduction in Total Score)
(n=48 Completers)

<table>
<thead>
<tr>
<th>Tx Week</th>
<th>1g/day (%</th>
<th>2g/day (%</th>
<th>4g/day (%</th>
<th>Placebo (%</th>
<th>EPA Dose vs. Placebo</th>
<th>Risk Ratio: EPA Dose vs. Placebo</th>
<th>Odds Ratio: EPA Dose vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 8</td>
<td>3/13 (23.1)</td>
<td>4/11 (36.4)</td>
<td>8/13 (61.5)</td>
<td>5/10 (50.0)</td>
<td>1g vs. Pla 2g vs. Pla 4g vs. Pla</td>
<td>0.461 0.727 1.231</td>
<td>0.300 0.571 1.600</td>
</tr>
<tr>
<td>Week 12</td>
<td>5/14 (35.7)</td>
<td>4/11 (36.4)</td>
<td>9/13 (69.2)</td>
<td>4/10 (40.0)</td>
<td>1g vs. Pla 2g vs. Pla 4g vs. Pla</td>
<td>0.893 0.909 1.731</td>
<td>0.833 0.857 3.375</td>
</tr>
<tr>
<td>Both Tx Week 8 and 12</td>
<td>3/13 (23.1) includes all 3 responders at Wk 8</td>
<td>4/11 (36.4) includes all 4 responders at Wk 8</td>
<td>6/13 (46.2) includes 6 of 8 responders at Wk 8</td>
<td>2/10 (20.0) includes 2 of 5 responders at Wk 8</td>
<td>1g vs. Pla 2g vs. Pla 4g vs. Pla</td>
<td>1.154 1.818 2.308</td>
<td>1.200 2.286 3.429</td>
</tr>
</tbody>
</table>
Correlation of % Change in IDS-C30 with % Change Plasma hs-CRP
(n=48 Completers)

<table>
<thead>
<tr>
<th>Percent Change from Baseline</th>
<th>Spearman Rank-Order Correlation with Percent Change in IDS-C30 at Treatment Week 12 (Correlation, p=value, and n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1g/day</td>
</tr>
<tr>
<td>Plasma hs-CRP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.129</td>
</tr>
<tr>
<td></td>
<td>p=0.694</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>p=0.694</td>
</tr>
<tr>
<td></td>
<td>n=11</td>
</tr>
</tbody>
</table>
Lipid mediators in the acute inflammatory response, resolution and other outcomes

Cardinal signs of inflammation:
- Rubor, calor, tumor and dolor
- Vasoconstriction: TXA2 and CysLTs
- Vasodilation: PG12, PGD2, PGE1, PGE2
- Vascular permeability: CysLTs
- Chemotaxis, Adhesion: LTB4

Acute Inflammatory Response
- Pus (Purulent exudate)
- Neutrophil-monocyte sequence
- Lipid mediator class switching
- Lipoxins stimulate non-phlogistic monocyte recruitment
- Efferocytosis
- Neutrophil-apoptosis
- Resolving macrophage
- Resolved exudate
- T cells
- B cells
- Adaptive immunity

Homeostasis
- Restitution of normal structure
- SPM

Signs of resolution
- "Pro-resolving" stimulates:
  - Sequestration of proinflammatory cytokines
  - PMN clearance from epithelial surfaces
  - Phagocytosis of apoptotic PMNs
  - Removal of inflammatory debris

Time

SPM biosynthetic pathways

- **AA**
  - PG
  - LTs
  - LXs
  - **COX**
  - PGH2
  - 5-HETE
  - 15-HETE
  - 12-HETE
  - 5-LO
  - 15-LO
  - 12-LO
  - 2-PGs
  - 4-LTs
  - LXA4
  - LXB4

- **EPA**
  - PG
  - LTs
  - **COX**
  - PGH3
  - 5-LO
  - 5-HEPE
  - 15-HEPE
  - 12-HEPE
  - 5-LO
  - 15-LO
  - 2-PGs
  - 5-LTs
  - RvE1-2
  - RvE3
  - RvD1-6
  - PD1
  - MaR1

- **DHA/DP**
  - **COX**
  - 5-LO
  - 5-HEPE
  - 15-HEPE
  - 12-HEPE
  - 5-LO
  - 15-LO
  - 17-HDHA
  - 14-HDHA
  - 7-HDHA
  - **CYP450**
  - **RvEs**
  - **Maresilin**
  - **RvD1**
  - **6-LO**
  - **17-HDHA**
  - **14-HDHA**
  - **7-HDHA**

**Pro-inflammatory**

**Less-inflammatory**

**Anti-inflammatory**

**Pro-resolving**
EPA-derived HEPEs

EPA

Placebo (n=11)
1 g/d (n=12)
2 g/d (n=12)
4 g/d (n=11)

PG/T
CO
X

PGH

LTs
5-LOX

Rv
CYP4
50

5-HEPE

12-HEPE

15-HEPE

18-HEPE

Before
After
0
10
20
30
40
mol %

EPA

Before
After
0
500
1000
1500
pg/mL

Before
After
0
5000
10000
15000
20000
pg/mL

Before
After
0
500
1000
1500
pg/mL

Before
After
0
500
1000
1500
2000
2500
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL

Before
After
0
500
1000
1500
2000
2500
20000
pg/mL
EPA-derived RvEs

EPA → 0

18-HEPE

CYP45

EPA

5-LOX

LTA4H

RVE1

RVE2

RVE3

5-LOX

15-LOX

RvE2

Placebo
(n=11)
1 g/day
(n=12)
2 g/day
(n=12)
4 g/day
(n=11)

RvE3

Placebo
(n=11)
1 g/day
(n=12)
2 g/day
(n=12)
4 g/day
(n=11)

18-HEPE

Placebo
(n=11)
1 g/day
(n=12)
2 g/day
(n=12)
4 g/day
(n=11)

pg/mL

pg/mL

pg/mL
AA-derived SPM biosynthetic pathways

**AA**

- Placebo (n=11)
- 1 gid (n=12)
- 2 gid (n=12)
- 4 gid (n=11)

**PG/T**
- CO
- X

- **PGH**
- 2

**LTs**
- 5-
- LOX

- **5-HETE**

**12-HETE**

**LXs**
- 15-
- LOX

- **15-HETE**
AA-derived SPM biosynthetic pathways

AA

\[ \text{CO} \]

\[ \text{X} \]

\[ \text{PGH}_2 \]

\[ \text{PGE}_2 \]

\[ \text{TXB}_2 \]

\[ \text{PGH}_2 \]

\[ \text{TXB}_2 \]

\[ \text{5-LOX} \]

\[ \text{5-HETE} \]

\[ \text{15-LOX} \]

\[ \text{15-HETE} \]

\[ \text{5-HETE} \]

\[ \text{15-HETE} \]

\[ \text{LTA}_4 \]

\[ \text{12-LOX} \]

\[ \text{LBT}_4 \]

\[ \text{LXB}_4 \]

\[ \text{PGE}_2 \]

\[ \text{PGH}_2 \]

\[ \text{TXB}_2 \]

\[ \text{PGE}_2 \]

\[ \text{TXB}_2 \]
Our work with natural products suggest there needs to be rigorous investigation of:

a. The composition of the compound being tested
   a. What component of the plant?
   b. Purity of the formulation
   c. Stability of the formulation
b. The question being investigated
   a. Is it too broad to be informative?
   b. Are the correct measures being employed?
   c. Over-inclusive analysis plans
c. The toxicity of the compound
   a. Natural is not necessarily safe
   b. The unexpected happens!
d. The mechanism of action being evaluated
   a. You have to “place your bet” to design the appropriate experiment
e. The composition of the study population
   a. Heterogeneity may obscure an effect
f. Unexpected findings
Where research needs to go

**In silico studies**
Predicting the binding of properties of ligands to mammalian cells

**In vitro studies**
Employing drug metabolizing enzymes, tissues or organs, e.g. CVP-transfected cell lines, hepatic subcellular fractions, liver slices, intestinal tissues

**Animal studies**
Studies of metabolic and transporter pathways

**Human studies**
Case reports and clinical studies

**Theranostics, genomics and proteomics**
Genome-scale changes of genes, proteins and other biomarkers

Resources for reviewing integrative medicine therapies

- Summaries.cochrane.org – The Cochrane Collaboration is an international, independent, not-for-profit organization
- NCCIH.nih.gov – The National Center for Complementary and Integrative Health
- www.consumerlab.com – independent test results and information to help consumers and healthcare professionals identify the best quality health and nutrition products
- www.umm.edu/health/medical/altmed – University of Maryland – free
- http://naturaldatabase.therapeuticresearch.com – Evidence based science on integrated, complementary and alternative therapies
- https://www.healthwavehq.com – Fullscript – allows clinicians to “write a prescription” for preferred supplements