Dietary Supplement Modulation of Autoimmune Disease

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Inflammation

Infection Immunity

Pro-Inflammation
Innate (Macrophage, Dendritic cells)
Adaptive (B, Th2, Th1, Th17)

Anti-Inflammation
Innate (Macrophages)
Adaptive (Th2, Tregulatory cells)
Impact of Imbalance

- Effector
  - Pro-Inflammation
    - Hypersensitivity
    - Autoimmune Diseases
    - Chronic Inflammation
  - Regulatory
    - Anti-Inflammation
Chronic Inflammation is the underlying cause of all major clinical disorders.

Clinical disorders with inflammatory component:
1. Autoimmune diseases
2. Cancer
3. Cardiovascular disease
4. Neurodegenerative diseases
5. Obesity
6. Diabetes
Impact of autoimmune diseases on healthcare costs

- There are over 80 autoimmune diseases.
- NIH estimates that ~22 million Americans suffer from autoimmune diseases.
- Cost: >$120 billion annually

Image Source: Wikimedia Commons
Dietary Supplements

- Include vitamins, minerals, probiotics, herbs or other botanicals, amino acids, and substances such as enzymes, tissues and metabolites.
- Available as extracts, concentrates, tablets, capsules, softgels, gelcaps, liquids or powders.
Effect of Dietary Supplements (Botanicals) on Epigenome and Immunity

- Inflammation
- Hypersensitivity
- Autoimmune Diseases
- Chronic Inflammation
- Obesity
- Cancer
- Neurodegenerative Diseases
- Cardiovascular Diseases

Image Source: Wikimedia Commons
~38% of U.S. (83 million) adults and ~12% of children use some form of Complementary and Alternative Medicine (CAM).

U.S. adults spend ~$33.9 billion out-of-pocket on visits to CAM practitioners and purchases of CAM products.

Thus, it is critical to determine the **risks and benefits** of CAM approaches.
Regulation of Dietary Supplements

- Consumers spend over 20 billion/year on dietary supplements.
- In the US, dietary supplements are regulated as foods and not as drugs.
- Thus, while drugs must be approved by the FDA as safe, FDA is not directly involved in the evaluation of the safety and efficacy of dietary supplements.
- However, FDA can ban the sale of supplements if found unsafe (ex: ephedra).
<table>
<thead>
<tr>
<th>Name</th>
<th>Immunomodulatory effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat’s Claw</td>
<td>Immune booster</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immune booster</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Thunder God vine</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Anti-inflammatory</td>
</tr>
</tbody>
</table>
## Toxicity of some herbal products

<table>
<thead>
<tr>
<th>Name</th>
<th>Use</th>
<th>Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aristolochia</td>
<td>Weight reducing</td>
<td>Genitourinary cancer</td>
</tr>
<tr>
<td>Kava</td>
<td>Anti-anxiety agent</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Weight loss, athletic performance</td>
<td>Strokes</td>
</tr>
<tr>
<td>St John’s wart</td>
<td>Depression</td>
<td>Increases cytochrome oxidases—interferes with other drugs</td>
</tr>
</tbody>
</table>
Importance of disclosing use of dietary supplements

- Patients often do not disclose their use of dietary supplements to physicians.
- Physicians fail to ask their patients.
- Example: St John’s wort upregulates cytochrome oxidases and affects metabolism of half of all conventional drugs.
Botanicals and drug discovery

- World’s 25 best selling pharmaceuticals in 1991 were either natural products/derivatives.
- There are over 250,000 higher plant species on earth. Only about 6% have been screened for biological activity, and only 15% have been pharmacologically screened.
- Thus, botanicals offer potential resource for drug discovery.
Almost half of all pharmaceuticals are derived from natural products:

- morphine (opium)
- digitalis (foxgloves)
- quinine (Cinchona tree)
- vincristine (periwinkle)
- taxol (Pacific yew tree)
- aspirin (willow tree)

Why botanicals are important?
Aryl hydrocarbon (AhR) signaling pathway: Do some dietary supplements act through AhR?

Role for dietary ligands of AhR in immune regulation?

Image Source: Wikimedia Commons
AhR dietary ligands

- **Resveratrol**: Plant polyphenol in red grapes
- **Extends the lifespan in yeast, worms, flies, mice**
- **Plant-derived indoles**: I3C (Indole-3-carbinol) and DIM (3,3'-diindolylmethane).

Image Source: Wikimedia Commons
Prevention and treatment of Autoimmune and Inflammatory diseases

- There are more than 80 serious chronic illnesses.
- There is no cure.
- Current drugs used to suppress inflammation are toxic.
- New anti-inflammatory drugs are critical.

Grave’s disease  Arthritis  Lupus

Image Source: Wikimedia Commons
Multiple Sclerosis (MS)

- Inflammatory autoimmune disease of the CNS
- Leading cause of disability in young adults
- Characterized by myelin protein-specific Th1 and Th17 cells migrating into the CNS
  - Results in inflammation due to cytokines such as IFN$\gamma$, TNF$\alpha$ and IL-17
  - Demyelination of neurons leads to impaired motor function $\rightarrow$ PARALYSIS

Image Source: Wikimedia Commons
Experimental Autoimmune Encephalomyelitis (EAE): A model for MS

MOG35-55 peptide (s.c.): Day 0

PTX (i.p.): Day 0 and 2

Treatment: Day 2 Vehicle or Resveratrol (100-250 mg/kg) by Oral gavage
Resveratrol treatment significantly suppresses development and progression of EAE

5 = complete paralysis
4 = Two limb paralyzed
3 = One limb paralyzed
2 = Tail down
1 = Limp tail
0 = no symptoms

Clinical Score

Control
Res 100 mg/Kg
Res 250 mg/Kg

Normal
EAE+V
EAE+RES

Mol Pharmacol. 72(6):1508-21, 2007
Resveratrol reduces IL-17 and increases Fox-P3 during EAE
Resveratrol induces expression of Fas and FasL

Resveratrol

Vehicle

10

25

50

µM

Hrs

12

24

12

24

12

24

12

24

FasL

T cells

T cells + ConA

Fas

18S

T cells

T cells + ConA

AhR

RES

FasL

T cell

Fas

Apoptosis

(cell-death)

Mol Pharmacol. 72(6):1508-21, 2007
Resveratrol induces apoptosis through AhR

Mol Pharmacol. 72(6):1508-21, 2007
Inflammatory Bowel Disease

- Inflammatory Bowel Disease (IBD) is caused by chronic inflammation of the GI tract.
- The two most common forms: Ulcerative colitis and Crohn’s disease.
- It is estimated that ~1.4 million people in the US suffer from IBD.
- There are various animal models of colitis.
Resveratrol attenuates dextran sodium sulfate (DSS)-induced colitis

J Pharmacol Exp Ther. 2010 Mar;332(3):829-39
Effect of Resveratrol on Inflammation in the Colon in $Apc^{\text{Min/+}}$ mice

![Graph showing total number of polyps and number of polyps in colon only.](image)

- **A**: Total Number of Polyps
  - Control
  - DSS+V
  - DSS+R

- **B**: Number of Polyps in Colon Only
  - Control
  - DSS+V
  - DSS+R

- **C**: Comparison of colon tissue samples
  - DSS + V
  - DSS + R

- **D**: Histological images of colon tissue
  - DSS + V
  - DSS + R

- **E**: Close-up of colon tissue
  - Histological images

- **F**: Histological images of colon tissue
  - DSS + V
  - DSS + R

- **G**: Histological images of colon tissue
  - DSS + V
  - DSS + R

*J Pharmacol Exp Ther. 2014 Jul;350(1):99-109*
Resveratrol inhibits cytokines and chemokines
Indole 3 Carbinol (I3C) is found in cruciferous vegetables.

3,3′-Diindolylmethane or DIM is a digestion product of I3C.

A ligand for Aryl hydrocarbon receptor (AhR).

DIM has been shown to have anti-tumor property.

Anti-inflammatory?
Treatment with I3C and DIM attenuates inflammation in the CNS of EAE mice

Average Clinical Scores

Days After MOG Immunization

* p < 0.003

Mechanisms anti-inflammatory effects of Resveratrol and Indoles

MOG Ag

RES/I3C/DIM

AhR

FasL

T cell

Apoptosis

Dendritic Cell

Decreased cytokines and Inflammation

T17 cell

Treg cell
MicroRNA

- MicroRNA are small non-coding RNA molecules (~22 nucleotides)
- Cause RNA silencing by transcriptional and post-transcriptional regulation of gene expression.
- Mediate through miRNA binding to 3’ UTR of one or more mRNAs
Resveratrol-mediated regulation of miRs
miRNA Profiles induced by various AhR ligands
AhR ligands sharing miRs

- FoxP3
  - miR-190
  - miR-217
  - miR-490

- IL-17
  - miR-203
  - miR-320
  - miR-494
Some Botanicals act as AhR ligands and reciprocally regulate Tregs & Th17 cells through epigenetic mechanisms.
Summary

- Dietary supplements have risks and benefits
- Some can act as AhR ligands and can suppress inflammation
- Dietary supplements can modulate microRNA and the epigenome, which regulate inflammatory pathways.
- They may play a crucial role in the prevention and treatment of inflammatory and autoimmune diseases
- Understanding the mechanisms of action of dietary AhR ligands could lead to novel anti-inflammatory drug discovery.
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