Prepare for Ebola or any new Virus

US troops prepare to go to war with Ebola: 101st Airborne receives safety training before being deployed to Liberia

- Soldiers from 101st Airborne Division took part in a course at Fort Campbell
- Families are desperate to know how military can keep their loved ones safe
- Ebola is a different threat to what troops are used to in Afghanistan and Iraq
- There are already more than 350 US troops on the ground in West Africa
- Number is set to grow and could even top current projection of nearly 4,000

4000 + Soldiers most without a High School Education, Do you Think they won't bring it Back??

Ebola outbreak expected to accelerate in October + 2015
Projected cases assuming current level of control effort

- Real Cases
- Projected Cases
- 2015

DEC. 6
SEPT. 22
OCT. 26
2015
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There will be a new virus sooner or later. This is an unavoidable fact. There are enemies planning to make and distribute virulent viruses on their enemies. This is also a fact. It is better to make a good immune system and learn how to defend yourself and your family than to wait for the armies to
protect you. This book teaches you how to scientifically protect yourself.

The new EDUCTOR/SCIO Software 8-8-2014

This new procedure will help protect your family, friends and patients. There are many new functions and
improvements of functions in this new 8-8 2014 version.

It is not mandatory but for those of you who care, - Please UPGRADE

Go to www.qxsubspace.com, login, and download the newest version from Downloads/Software Manager
Spanish Ebola Nurse Cleared Of Deadly Virus

A blood test reveals Teresa Romero is no longer infected as the UN health agency takes Nigeria off the list of affected countries.

A Spanish nurse who became the first person to contract ebola outside West Africa in the current outbreak is clear of the deadly virus.

A blood test has revealed Teresa Romero, who treated two patients who died of ebola at a hospital in Madrid, is no longer infected.

The 44-year-old has been in quarantine after testing positive for the virus on October 6.

A statement by the Spanish authorities said Ms Romero's immune system had eliminated the virus from her body, although a second test would shortly be done to be sure.

Her husband was also placed in isolation, while the couple's dog, Excalibur, was put down as a precaution, triggering outrage among animal rights activists.

A Strong Immune system can defend you.
Here is published evidence on how to stop the virus at the start.

**THE LANCET**

Human asymptomatic Ebola infection and strong inflammatory response

*Background*

Ebola virus is one of the most virulent pathogens, killing a very high proportion of patients within 5–7 days. Two outbreaks of fulminating hemorrhagic fever occurred in northern Gabon in 1996, with a 70% case-fatality rate. During both outbreaks we identified some individuals in direct contact with sick patients who never developed symptoms. We aimed to determine whether these individuals were indeed infected with Ebola virus, and how they maintained asymptomatic status.

Asymptomatic individuals had a strong inflammatory response characterized by high circulating concentrations of cytokines and chemokines.

This study showed that asymptomatic, replicative Ebola infection can and does occur in human beings. The lack of genetic differences between symptomatic and asymptomatic individuals suggests that asymptomatic Ebola infection did not result from viral mutations. Elucidation of the factors related to the genesis of the strong inflammatory response occurring early during the infectious process in these asymptomatic individuals could increase our understanding of the disease.

More about this later, but first Prevention with immunity.
The problem is a weak immune system from Antibiotics, Sugar, Tobacco, Stress

UCSF Scientists Declare WAR on Sugar in Food

Ron Allgen, Chronicle Staff Writer

Like alcohol and tobacco, sugar is a toxic, addictive substance that should be highly regulated with taxes, laws on where and to whom it can be advertised, and even age-restricted sales, says a team of UCSF scientists. (University of California San Francisco)

In a paper published in Nature on Wednesday, they argue that increased global consumption of sugar is primarily responsible for a whole range of chronic diseases that are reaching epidemic levels around the world. The health care expense of sugar caused diseases is massive.

Sugar is so heavily entrenched in the food culture in the United States and other countries that getting people to kick the habit will require much more than simple education and awareness.
Prof Nelson - Desiré  
Towards a new Safe and Effective truly Modern Medicine

Dr. János (Hans) Selye

This is a new common sense method of modern medicine, that is Health motivated not just symptom control. We respect the complexity and the whole body, and respect the Natural process of health.

HEALTH IS EASE OF FLOW

Stressors block Flow, Stress is more than Just personal stress.
Stress Reduction is the key to Medicine.

When the stressor or stressors weaken the defenses of the body, the weakest link of the body (from nature or nurture) is most prone to distress and thus disease.

We Often Only Remember the "LAST STRAW" NOT the Accumulated Stressors that Really Caused the Diseases we have

Dr. Selye saw the Effect of Accumulated Stress as the Main Cause of Disease

STRESS
LACK OF AWARENESS OR LACK OF EDUCATION
HEREDITY
MENTAL FACTORS
(Greed, anger, delusions, arrogance, etc.)
ALLERGY
BAD POSTURE
TOXICITY
TRAUMA INJURY
PATHOGENS (microorganisms, bacteria, fungi, virus, prions, worms, etc.)
PERVERSE ENERGY (heat, cold, wind, dryness, radiation, magnetic, etc.)
DEFICIENCY OR EXCESS OF NUTRIENTS
“Education and Treatment Starts with Teaching Patients what NOT to Eat, Say and Do”

Desire’ Dubouret

4 Horsemen of the Apocalypse

The Bible Predicts

Avoid Sugar, Tobacco, Boiled Oil + Synthetic Drugs

4 Industries of Death
SUPER IMMUNE Diet Tips

STARTS With

What NOT To EAT

1. AVOID Synthetic Foods
2. AVOID Hi Glycemic Foods
3. AVOID Processed Foods
4. AVOID White Sugars
5. AVOID Foods Boiled in Oil
6. AVOID Nitrite/Nitrate meat

'Everytime You Eat or Drink You are Feeding Disease or Fighting it'

Hippokrates of Kos
"Then Teach What to Eat. How to Exercise, Reduce Stress, Interact. Teach How To Show Love, and Respect"

Desire' Dubouret

'Let food be Thy Medicine'

Hippocrates of Kos
1. Eat Natural Foods with little preservatives
2. Eat more fruits, seed products, leafy greens, salads
3. Let Fruit be your Sweetener,
4. Drink ONLY 100% Fruit juice diluted with water
5. Boil foods in WATER, NOT OIL
6. Use fresh, cold processed UNHEATED olive oil, sunflower oil, safflower oil etc.
7. Less Cooking, Use stir fry well washed veggies
8. Foods made with Love and Nature is Blessed Nutrition, Foods made and eaten with Hate and Anger are poisons.
9. Celebrate each meal with friends, family or at least your joyous self. Celebrate
10. Listen to your inner self what to eat, and when to stop, do not eat with your eyes


http://indavideo.hu/video/Bad_Gut_Bacteria_make_for_Obese_Patients

http://www.downloads.imune.net/medicalbooks/RULES%20FOR%20THE%20STOMACH%20Disease%20starts%20in%20the%20gut.pdf
Immune Boosting Foods

**Grapefruit**
- Packed with vitamin C, which makes this an immune-boosting essential. They are packed with bioflavonoids, which are phytonutrients.

**Cruciferous Vegetables**
- Rich in antioxidant vitamins which give an immune system boost, and also contain Choline which keeps your cells functioning properly and helps maintain healthy gastrointestinal tract.

**Carrots**
- A great source of beta carotene which support the body’s mucus membrane, which lines the respiratory and intestinal tracts, making it harder for bacteria to enter the bloodstream.

**Cinnamon**
- Cinnamon is an antiviral, antifungal, and antibacterial and an immune system booster. It actually fights the pathogens that cause illness.

**Berries**
- Berries contain antioxidants responsible for the health of your immune system, as well as your body's ability to destroy invading bacteria and germs. They also contain vitamin C and magnesium, two nutrients that are essential in maintaining the strength and function of your immune system.

**Mushrooms**
- A major source of the immune system-boosting mineral, zinc. If you don't have enough zinc in your diet tend to have fewer white blood cells to help fight off disease, which can lead to a reduced immune response.

**Kale**
- Greens such as kale, spinach, and Swiss chard are immune-boosting foods that contain high levels of vitamin C, which help fight off infection and regenerate other antioxidants in the body, including vitamin E. They also contain folate, another immune booster.

**Watermelon**
- Contains antioxidant Vitamins A and C, which helps to neutralize free radicals than can lead to inflammation, general sickness and chronic illnesses such as stroke and heart attack. It contains beta-carotene, which helps fight cancer, particularly colon cancer. Lycopene, a carotenoid found in watermelon provides additional cancer fighting health benefits.

[http://eatingmywaytobetterhealth.blogspot.com/](http://eatingmywaytobetterhealth.blogspot.com/)
Here is the book on how to live a healthy life

“Quod quid agis, prudenter agas, et respice finem.”

“What you do, please do cautiously, but look to the end.”

**TWELVE WAYS FOR GOOD HEALTH**

Less Meat          More Vegetables
Less Salt          More Vinegar
Less Sugar         More Fruit
Less Worry         More Sleep
Less Hatred        More Love
Less Eating        More Chewing
Less Riding        More Walking
Less Anger         More True Smiles
Less Judgements    More Acceptance
Less Greed         More Giving
Less Talk          More Deeds

Leszz Petti Critaksisms uff Uthors
More Growth of Self
Good Health Starts
with Good Behavior
Must AVOID All High Glycemic Cane or Beet Sugar

If you want to live that is
Stage 1 Exposure

Now we need to deal with the first exposure to a new Virus

On first exposure people who have a strong inflammatory response occurring early during the first infectious exposure seem to not get the disease. This means that the same cytosine chemosine excess late in the Ebola disease that kills the patient, can prevent the disease from developing if it happens early right after exposure. Late in the disease the cytosine chemosine cascade is a last ditch effort of the body to kill the virus and some live, most die. The cascade kills then because of over proliferation of the virus throughout the
body. If we provoke this cascade early when the virus has not proliferated the cascade will stimulate the immune system to eradicate the virus.

This is why Vitamin C works so well at early exposure, because if we take excess Vit C to bowel tolerance it can stimulate an immune surge. I worked with Albert Szent Gyorgyi (the Hungarian scientist who won the Nobel prize for discovering Vit C in 1937) he laughed and said that ascorbic acid is not total vitamin C. he said Vit C was a complex of things and the Bone Marrow was key to its use. He said that there was a bone marrow soup in the old country that was excellent for initial use after exposure to a virus.

"Vitamin C is Much More than Ascorbic Acid"

Albert Szent-Gyorgyi
The best source of Natural Vit C is Green Pepper

CINNAMON STICKS AND GARLIC CLOVES:
HOME REMEDIES AT HAND FOR FIGHTING EBOLA

www.alternative-doctor.com

What to do if Ebola Strikes?
Dose yourself heavily with vitamin C.
At least 10 grams (1000 mg) a day is healthy.

BioFlavenoids, Acerola, Bone Marrow, Glucuronate, minerals are all needed for complete Vit C Utilization

Ascorbic acid is ascorbic acid, the chemical name for what your body likes and needs.
Vitamin C

Citrus fruits, strawberries, tomatoes, green peppers, broccoli and sweet and white potatoes are natural food sources of vitamin C (ascorbic acid).

12 HEALTH BENEFITS OF BONE BROTH

1. Heals the gut lining and relieves intestinal inflammation
2. Supports healthy digestion and nutrient absorption
3. Bolsters the immune system and helps ward off illness
4. Strengthens bones, joints, tendons, ligaments and aids arthritis
5. Promotes healthy, supple skin and strong teeth, improves hair and nails
6. Helps to heal autoimmune disorders
7. Aids in detoxification by supporting the liver
8. Aids digestion by regulating the synthesis of bile salts and the secretion of gastric acid
9. Improves nervous system function and keeps our minds (and moods) in good working order
10. Balances blood sugar, helps maintain muscle, and regulates human growth hormone
11. Helps to reverse heart disease by reducing atherosclerotic plaque build-up
12. Reduced cellulite, stretch marks, and wrinkles (from the collagen content)

The book Bone Broth: A Recipe for Health contains many tips and tricks for preparing bone broth with maximum nutrition. Do not skip this important food, as it is the key to better digestive and thyroid health! Read more at Thyroid blog OutsmartDisease.com
Cytokines & Chemokines

<table>
<thead>
<tr>
<th>Pro-inflammatory cytokines</th>
<th>IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, IL-17, IFN-γ, TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory Cytokines</td>
<td>IL-4, IL-5, IL-10, IL-13, TGF-β</td>
</tr>
<tr>
<td>Pro-inflammatory Chemokines</td>
<td>IL-8, MCP-1, MIP-1β</td>
</tr>
<tr>
<td>Bone Marrow Stimulator</td>
<td>GM-CSF, KC, MIP-2, IL-5</td>
</tr>
</tbody>
</table>

Bone Broth stimulated Cytokines and Chemokines in **RED**

<table>
<thead>
<tr>
<th>TH1 cytokine</th>
<th>TH2 cytokine</th>
<th>TH17 cytokine</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2, IL-12, IFN-γ, TNF-α</td>
<td>IL-4, IL-5, IL-10, IL-13</td>
<td>IL-6, IL-17, TNF-α, TGF-β</td>
</tr>
</tbody>
</table>

**Mix peppers into some Bone Marrow soup and it can kick up cytokines to stop a virus in its early stages. Not for a preventative but use if there is a possible exposure. Also gluten wheat can help. There is a medicinal use for gluten.**
Wheat Gluten Causes Dendritic Cell Maturation and Chemokine Secretion

Marina Nikulina, Christiane Habich, Stefanie B. Flohé, Fraser W. Scott and Hubert Kolb

Abstract

Wheat gluten causes gut inflammation in genetically predisposed individuals. We tested the hypothesis that wheat gluten is not only a target of adaptive immunity, but also modulates the function of APC. Dendritic cells (DC) derived from the bone marrow of BALB/c mice were exposed to chymotrypsin-treated wheat gluten. This induced DC maturation as estimated by all surface markers tested (MHC class II, CD40, CD54, and CD86). The effect was dose dependent, and, at 100 µg/ml gluten matched that caused by 10 ng/ml LPS. A role of endotoxin contamination was ruled out by demonstrating the resistance of wheat gluten effects to LPS antagonist polymyxin B. DC from LPS nonresponder strain C3H/HeJ were affected by wheat gluten, but not by LPS. Proteinase K-digested wheat gluten was unable to stimulate DC maturation. Wheat gluten induced a unique secretion pattern of selected cytokines and chemokines in DC. Classic pro- or anti-inflammatory mediators were not produced, in contrast to LPS. Rather, chemokines MIP-2 and keratinocyte-derived cytokine were secreted in large amounts. We conclude that wheat gluten lowers the threshold for immune responses by causing maturation of APC, by attracting leukocytes and increasing their reactivity state. In the presence of an appropriate genetic predisposition, this is expected to increase the risk of adverse immune reactions to wheat gluten or to other Ags presented.

Received August 6, 2003.
Accepted May 14, 2004.
Ebola weakens Vitamin C -- Utilization

Scurvy -- Vitamin C Deficiency
Water can Wash Away a Virus

When Exposed Drink Drink Drink Water that is

IMUNE
International Medical University for Natural Education
www.imune.net

Evidence Based Natural Energetic Medicine Education
Stage 2 Virus Proliferation

So the virus has not been defeated early and now your symptoms increase what should you do

Ebola virus' typical path through a human being

First symptoms

Day 7-9
Headache, fatigue, fever, muscle soreness

Day 10
Sudden high fever, vomiting, blood, passive behavior

Day 11
Bruising, brain damage, bleeding from nose, mouth, eyes, anus

Day 12
Loss of consciousness, seizures, massive internal bleeding, death

© 2014 MCT
Source: U.S. Centers for Disease and Control, BBC
Graphic: Melina Yingling
You must stop the Bleeding and nothing is better than Cabbage Juice at doing it.

Vitamin K - key to help blood clotting

fat-soluble vitamin

- MAKES PROTEINS FOR BLOOD COTTTING & HEALTHY BONES
- Leafy green vegetables are the best source of Vitamin K
- BUICED PROVIDES 80 MCG which is 100%DV

98% Absorption Rate for LIQUIDS

10-20% Rate for PILLS

SOURCE: Physicians Reference Desk – Page 1542
Here is the natural formula for Tamiflu

It helps the symptoms
Tonic water has quinine which is phosphorescent in UV light to show its Immune enhancing effect, Mix with Anisette to make a powerful anti-Viral to use in early stages of flu or influenza.

Report: National Guard May Be Needed to Enforce Quarantine in Flu Pandemic

WASHINGTON — Military and civilian health facilities will be overwhelmed if a nationwide flu pandemic hits the United States, and the National Guard may have to be called out to provide medical help and even enforce a quarantine, the Defense Department warned in a report released Wednesday.

As the Pentagon fights criticism from...
Ebola hemorrhagic fever (Ebola HF) is one of numerous Viral Hemorrhagic Fevers. It is a severe, often fatal disease in humans and nonhuman primates (such as monkeys, gorillas, and chimpanzees).

Ebola HF is caused by infection with a virus of the family Filoviridae, genus Ebolavirus.

**PREVENTION**

Wearing of protective clothing (such as masks, gloves, gowns, and goggles)

The use of infection-control measures (such as complete equipment sterilization and routine use of disinfectant)

Isolation of Ebola HF patients from contact with unprotected persons.

**SIGN AND SYMPTOMS**

- A Rash
- Red Eyes
- Hiccups
- Cough
- Sore throat
- Chest pain
- Difficulty breathing
- Difficulty swallowing
- Bleeding inside and outside of the body

- Fever
- Headache
- Joint and muscle aches
- Weakness
- Diarrhea
- Vomiting
- Stomach pain
- Lack of appetite

**TRANSMISSION**

Direct contact with the blood or secretions of an infected person

Exposure to objects (such as needles) that have been contaminated with infected secretions

Source: cdc.gov

*INQUIRER.net* Infographics by Bernard Esquerra
**Mashed Malanga, Yuca, Taro with Bone Broth to fight virus**

The tropical roots malanga, taro, and yuca all make excellent savory, starchy mashed potato substitutes. These are a great way to incorporate more bone broth into your diet!

**Prep time:** 5 minutes

**Cook time:** 25.35 minutes

**Total time:** 30-40 minutes

**Ingredients**

- 1 lb malanga, taro, or yuca, peeled and coarsely chopped
- 3/4 to 1 cup beef or chicken bone broth
- 2 tbsp fat of choice (olive oil, lard, ghee, butter, palm shortening)
- salt and black pepper to taste

**Cooking Directions**

1. Begin by rinsing your root well under running water. Then, use a kitchen peeler to peel taro or malanga. Use a sharp knife to peel yuca. In all 3, look for any soft or discolored parts and cut those out.
2. Chop into chunks about 2” long and add to a pot filled with filtered water.
3. Bring to a boil, then cover and reduce heat to a simmer.
4. Cook for 25 minutes or until very tender and easily pierced with a fork.
5. If using yuca, remove the stringy, tough, fibrous center from each piece.
6. Strain in a colander, then add to a large bowl.
7. Mash with a potato masher. Add bone broth and oil to desired consistency (may require more or less than what is suggested here).
8. If you like, use a hand mixer to whip your mashed starch.
9. Serve immediately and enjoy!
10. You may also use any of these mashed starches as a topping for shepherd’s pie.

---

**Creamy Mashed Malanga, Taro, or Yuca**

---

**Cure for Ebola Virus**
WHAT IS **Anti-Viral Coffee?**
+ The Benefits of Grass-Fed Butter & Coconut Oil in Your Coffee

**coconut oil & coffee**

Add 1 tablespoon of Butter or Coconut Oil and 20 to 30 drops of Sunflower oil or Essential Fatty Acid formula to your Morning coffee cup.

**IMUNE**

International Medical University for Natural Education

**Evidence Based Natural Energetic Medicine Education**
Stage 3 Crisis Cytosine Storm

What to do if the virus gets critical and your life is in danger
Sambucca Nigra

Herbal Indications-----Homeopathic Indications

Acts on Respiratory organs, fever, sweats sniffles, extreme Flu symptoms, purgative

Acts on Respiratory organs, fever, sweats sniffles, extreme Flu symptoms, dry coryza

Sambucca (Elderberry) can stop a Cytosine cascade---DO NOT USE in the EARLY stages SAVE THIS FOR an EXTREME Emergency
ELDERBERRY WINE

- 10 lbs fresh, ripe elderberries
- Remove insects, wash lightly
- 1 lbs finely granulated fructose
- 4-1/2 to 5 pints RO water
- 1 tsp acid blend
- 1 tsp yeast nutrient
- 1 tsp pectic enzyme
- Montrachet wine yeast

Wash, destem and inspect the berries for ripeness and soundness. Put berries in a stainless steel or enameled pot with 1/2 pound of fructose sugar and half the water. Slowly bring to boil while stirring occasionally and turn off heat. Cover and set aside to cool to room temperature. Strain berries over primary through a nylon straining bag and hang bag over primary to drip drain for two hours. Very gently press pulp to extract a little more juice, but do not overdo this. Stir in remaining fructose sugar and dry ingredients (except yeast) and stir well to dissolve. Add enough water to bring to one gallon and add yeast. Cover primary and wait for active fermentation. Ferment 2 weeks and siphon off sediments into secondary. Top up and fit airlock. Ferment two months, rack, top up, and refit airlock. Repeat after additional two months. Stabilize, wait 10 days, rack, sweeten to taste, and bottle. Age one year before tasting.
Reduce Stress of all kinds

The Desi-astrous Sign of STRESS ANXIETY

LACK OF CONCENTRATION
SLEEPLESSNESS
IRRITABLE
OVERREACTING
STOMACH PROBLEMS
ANTSY

FEAR
MUSCLE TENSION
FATIGUE
RACING HEART
HEADACHE

STRESS IS CAUSED BY THE DESIRE FOR THINGS TO BE DIFFERENT

RELAX
BREATHE FULLY
YOGA & EXERCISE
REDUCE DISTRACTION

SIMPLIFY
PLAN & ORGANIZE
REDUCE CLUTTER
SET LIMITS

IDENTIFY TRIGGERS
THOUGHTS
FEELINGS
FOOD

SHARE
THOUGHTS
FEELINGS
FEARS

NOURISH SPIRIT & INTELLECT
LIVE IN THE PRESENT
JOURNAL
IDENTIFY SPIRITUAL BELIEFS

AVOID
PROCRASTINATION
NEGATIVE THINKING
CATASTROPHIZING

Learn to ACCEPT the things you can’t change &
Change the things you can...
...and find the Wisdom to
Know the Difference

37
Nelson Method of Medicine

1. Reduce causes of disease

2. Rebuild organs and tissue destroyed by causes

3. Unblock the blockages of flow

4. Treat symptoms NATURALLY

5. Metabolic and Constitutional Treatment of the individuality of the Patient
Ebola what to do if exposed

Always Avoid Antibiotics, Processed Sugar, Tobacco, Stress, Trans Fats, High glycemic foods and any SINthetic chemicals

Use High doses of Vitamin C, Pepper Bone Marrow Soup, Do Not Use During stage 3
Ginger and Garlic  Lots of water, Cinnamon

Cabbage Juice, Deep Muscle Relaxation, Immune building foods, lots of water, Cruciferous foods, Tonic+Anisette, Yuca, Taro

Do NOT USE During Stage 1
Sambuca, Elderberry,
Cloves, Cardamon Coconut Oil, Immune building oils, Sunflower Oil, Olive Oil

Cabbage Juice, Deep Muscle Relaxation, Immune building foods, lots of water, Cruciferous foods, Tonic+Anisette, Yuca, Taro

Prayer
Feel free to pray at any time or stage
Ebola what to do if exposed

BECAREFUL - TIMING IS EVERYTHING

EARLY USE HERBS TO STIMULATE IMMUNO CASCADE

Use High doses of Vitamin C, Pepper Bone Marrow Soup, Echinacea, Capsicum, Astragalus, Ligusticum, Unicaria and Schizandrae, High Dose of Garlic

The Body uses a cytokine storm or inflammatory chemosine cascade to help reject virus. If this happens at first it can reject the virus and stop the progression of the disease early. If it happens late when the body is full of virus this same cascade can kill the patient, so herbs that cause and help sustain the cascade are helpful in the beginning and these same herbs are harmful later. Later in the disease we must use anti-inflammatory herbs to stop the cascade here is a list of herbs that can be used early and not late and a list that can be used late not early. Timing is everything.

Late stage herbs include moderate Vit C and Garlic, Sambuca, Curcumin, Tumeric, Paeonia, Devil's claw, Fever Few, Cilantro, Chamomile, Cardamon, Basil, Licorice, Cloves, Fennel, Parsely, Rosemary

Prayer

Feel free to pray at any time or stage
“There is good scientific evidence that cannabinoids, and in particular Cannabidiol (CBD), may offer control of the immune system and in turn provide protection from viral infections (4). Cannabis has already been recognized to inhibit fungus and bacteria and can be considered a new class of antimicrobial because of the different mechanism of action from other antimicrobials. (1) Ebola is a complex RNA viral organism that causes the cell to engulf it by pinocytosis, and then the virus hijacks the cell to replicate itself. This replication can involve many mutations in the RNA code that make it difficult to impossible to create an effective vaccine. There are U.S. Patents showing evidence that Cannabinoids have significant anti-viral activity. (3) (4) Normally any virus infected cells will produce surface proteins that are identified as foreign. The Immune system attacks these cells when the surface protein is identified as foreign. The Ebola virus infection causes the cell to produce proteins that hide the virus from the immune system. The viral proteins are sterically shielded, i.e. “hidden” from view, thereby hindering cellular (and thus viral) destruction by the immune system. This mechanism allows the RNA virus to hide the infected cell by shielding it from view from the immune system.

The cause of death by this virus is the body’s own immune response to the viral infection. This is what causes the mortality and morbidity of this infection. Subsequently, the virus triggers the immune killer cells to release
the enzymes (cytokines) they hold. This release of enzymes causes other lymphocyte to release even more Cytokines in a Storm of release. This is properly termed a Cytokine Storm.
Causes small blood clots to form in all arterioles, called; DIC or Disseminated Intravascular Coagulation.
Causes a massive Coagulopathy where the blood will not to clot properly simultaneously with the DIC (Bleeding and clotting occur at the same time.) Toxic Shock Syndrome occurs when the cytokines release causes the blood vessels to dilate to such an extent that a shock state exists.
Cannabinoids are proven to reduce and prevent Toxic Shock and DIC (2)
“The Ebola virus also attacks the adhesions between cells caused by the immune Killer cells to release of VEGF (Vascular Endothelial Growth Factor) which result in the destruction of the Tight Junction between cells and causes a fluid leakage between cells until bleeding occurs. The inhibition of VEGF by cannabinoids prevent the cellular junctions from haemorrhage.
Cannabinoids Inhibit VEGF and inhibit Glioma brain tumors growth by this mechanism. (6) It is reasonable to predict that inhibition of VEGF and other Cytokines by Cannabinoids during an Ebola infection will help the survival of this deadly disease. (6 and 7) Stopping the release of Cytokines will be a key feature of treatment of this deadly disease.
The discovery and application of the Endocannabinoid Signalling System is proving to be the control of virtually all diseases of mankind. Cannabinoids are emerging as a new class of drugs that treat infections of bacteria, fungi and virus by different mechanisms of action not found in any other class of drug. (1) Cannabinoids are proving to have significant cidal (killer) activity to many viruses, including hepatitis C and the HIV virus. Cannabinoids down-regulate (inhibit) the immune response to the infection (2) (3). The cited U.S. Patents (3 and 4) are proof that cannabinoids inhibit many different virus strains from replicating. These patents also prove cannabinoids decreases the body’s immune over stimulated response to the viral infection. Claims that are made in these U.S. Patents include the following:
(refer to patent for exact quote.)
- A method of treating HIV disease by the direct inhibition of viral replication using a cannabinol derivative of claim 2. (see patent)
- The cannabinol derivatives of claim 10 wherein the cannabinol derivative of claim is used to treat HIV disease by the direct inhibition of viral replication. (see patent)
- A method of treating diseases of immune dysfunction which are the result of infectious origin such as Simian Immunodeficiency Virus, Feline Immunodeficiency Virus, Herpes Simplex virus, Epstein-Barr virus, Cytomegalovirus, hepatitis B and C, influenza virus, rhinovirus and mycobacterial infections using the cannabinol derivatives of claim 2. (see patent)
- This United States Patent, proves cannabinoids treats this immune dysfunction that becomes what is known as a Cytokine Storm caused by different viral infections. (4)
In Summation: The US Patents prove down regulation of the immune system by cannabinoids may be a key in survival of HIV and may indeed translate into survival for Ebola patients. The direct Killing or Cidal effect of Cannabinoids is proven in HIV infections,(4) but not yet in Ebola. Inhibition of VEGF is crucial to prevent endothelial leakage and haemorrhage.
Because cannabis is so very safe especially under doctor supervision, I believe it is crucial for the medical community to start human trials on survivability of Ebola infected patients regardless of the political restraints.

David B. Allen M.D.
retired Cardiothoracic and Vascular Surgeon
Medical Director, Cannabis Sativa, Inc. (Cali215doc@gmail.com)

References
1) Antibacterial Cannabinoids from Cannabis sativa: A Structure−Activity Study Antibacterial Cannabinoids from Cannabis sativa: A Structure−Activity Study; Giovanni Appendino et al. The School of Pharmacy, University of London
2) Protection Against Septic Shock and Suppression of Tumor Necrosis Factor α and Nitric Oxide Production by Dexamabinol (HU-211), a Nonpsychotropic Cannabinoid Ruth Gallily1, Aviva Yamin1. Departments of Immunology The Hebrew University, Faculty of Medicine, Jerusalem, Rehovot, Israel.
3) Cannabinoid derivatives US patent 20070179135 A1
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6) Cancer Res August 15, 2004 64; 5617 Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas Cristina Blázquez HYPERLINK “http://cancerres.aacrjournals.org/content/64/16/5617.full”1,
7) How Cannabis Might Keep Coronary Stents Open Longer
www.cbds.com/.../how-cannabis-might-keep-coronary-stents-open-longer
Jun 10, 2014 David Allen M.D.
Bone Broth for Autoimmune Support

David Peterson, DC, DCCN, FAAIM / January 19, 2014

Bone Broth & Folklore Nutrition

Based on the assumption that immune system needs stimulation no matter what the condition is. Bone broth provides our bodies with bio-available (very easy to consume, digest and absorb) forms of calcium, magnesium, phosphorus and other trace minerals that are so lacking in our diets today. While we can also use vegetable-only broths to obtain certain minerals, without bones in the mix, we won’t get some of the other fantastic benefits from the gelatin and collagen they provide.

Bone Broth & Alternative Medicine (Green Allopathy)

Based on the assumption that immune system needs stimulation no matter what the condition is. Bone broths are extraordinarily rich in nutrients – particularly minerals and amino acids. Bone broths are a good source of amino acids – particularly arginine, glycine and proline. Glycine supports the body’s detoxification process and is used in the synthesis of hemoglobin, bile salts and other naturally-occurring chemicals within the body. Glycine also supports digestion and the secretion of gastric acids. Proline, especially when paired with vitamin C, supports good skin health. Bone broths are also rich in gelatin which improves collagen status, thus supporting skin health. Gelatin also supports digestive health, which is why it plays a critical role in the GAPS diet. And, lastly, if you’ve ever wondering why chicken soup is good for a cold, there’s science behind that, too. Chicken stock inhibits neutrophil migration; that is, it helps mitigate the side effects of colds, flus and upper respiratory infections.
Calcium is the raw material for bone production and fortification, and bone stock might be one of the best sources of calcium around, especially for those who avoid dairy and don’t eat enough leafy greens.

**Inhibits Neutrophil Migration**

It aids in digestion, helps with achy joints, heals the lining of your gut to help boost your immune system and prevent diseases, sickness, leaky gut, and has many other benefits.

Let’s look at it from another perspective – “inhibits neutrophil migration” – describes how the immune system is held back from responding to an infection. Yet, neutrophil migration is necessary to eliminate the infection. Another view is that anything that “inhibits” your immune system “suppresses” your immune system.

**Bone Broth & Functional Medicine**

While bone broth is an immune stimulator. Is it a good idea to stimulate the immune system with autoimmune, immune stimulated, immunosuppressed, immune-compromised or cancer patients? Granted immunosuppressed may feel better for a short time but constant provocation/stimulation of the chemokine and cytokines of TH1, TH2 & TH17 systems can have adverse consequences. It is generally believed that immune over-activation is a major contributor to multiple organ dysfunction.

The gastrointestinal tract is an extremely effective route for the induction of both systemic and mucosal immune responses. Peritoneal exudate cells (PEC) located in the gut lining are primarily for the prevention of local or systemic disease, and serve as an immunologic barrier against a wide range of infectious agents.

### Cytokines & Chemokines

<table>
<thead>
<tr>
<th>Pro-inflammatory cytokines</th>
<th>IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, IL-17, IFN-γ, TNF-α</th>
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<tr>
<td><strong>Anti-inflammatory Cytokines</strong></td>
<td>IL-4, IL-5, IL-10, IL-13, TGF-β</td>
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<td><strong>Pro-inflammatory Chemokines</strong></td>
<td>IL-8, MCP-1, MIP-1β</td>
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<tr>
<td><strong>Bone Marrow Stimulator</strong></td>
<td>GM-CSF, KC, MIP-2, IL-5</td>
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**Bone Broth stimulated Cytokines and Chemokines in RED**

<table>
<thead>
<tr>
<th>TH1 cytokine</th>
<th>TH2 cytokine</th>
<th>TH17 cytokine</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2, IL-12, IFN-γ, TNF-α</td>
<td>IL-4, IL-5, IL-10, IL-13</td>
<td>IL-6, IL-17, TNF-α, TGF-β</td>
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</tbody>
</table>

Bone Broth Stimulate Cytokine & Chemokine Release
Bone broth stimulates the immune system. A breakdown shows bone broth stimulates gastrointestinal PEC to secrete cytokines interleukin (IL)-12, TNF-alpha, and IL-6. In addition, bone broth activates the secretion of chemokines KC, MIP-2, MCP-1, RANTES, and MIP-1a as well as IL-6.

**Pro-Inflammatory**: IL-12 (TH1); TNF-alpha, and IL-6 (TH17); MIP-1 (TH1 & IgG stimulant); MCP-1

**Chemokine**: KC is a potent neutrophil attractant found on endothelial surfaces. Chemokines acting on MIP-2, including IL-8, may have direct pathogenic effects in Central Nervous System diseases, independent of the induction of leukocyte migration.

**RANTES** (regulated upon activation, normal T-cell expressed and secreted): RANTES/CCL5 is released by many cell types such as platelets or smooth muscle cells and is report in the involvement of the angiogenic process.

(Cancer is angiogenic)

**Summary**: Bone broth provides concentrated nutrients and immune stimulants to the gastrointestinal tract. Making any meal with bone in the soup, stock, stew or grilling enhances the flavor. For those with a minor illness, i.e. common cold or flu, the occasional use of broth made with bone is beneficial. For those with autoimmune conditions, concentrating bone broth will lead to further immune stimulation in an uncontrolled immune system.

- Increased calcium in the body triggers neurotransmitter release resulting in sympathetic stimulation.
- Bone broths are a good source of amino acids – particularly arginine, glycine and proline. Increased concentrations of arginine further potentiate Inducible NOS (iNOS). Arginine is associated with an increase in the release of T cells and Memory T cells.
- The cytokines stimulate the rapid mobilization of white blood cells (WBC). Within the gastrointestinal tract, chemokines leads to a significant increase of circulating WBC numbers and Memory T cell movement into the gastrointestinal tract

Those with an autoimmune condition are unlikely to eat their way out of it. Though there is benefit to the autoimmune diet. Raw vegans exposure to lectins will have a severe detrimental stimulatory effect on the immune system. In autoimmunity, **Probiotics** only maintain the disease process. Autoimmunity does not discriminate and exempt the gastrointestinal from its effects. Digestion of food requires a properly functioning gastrointestinal tract capable of producing digestive chemistry in the correct amounts, sequence and order. Autoimmune conditions prevent this from occurring. Even organic food requires digestive chemistry to extract nutrition.

In Dr. Kharrazian’s latest newsletter listing the “Top 10 reasons Hashimoto’s patients don’t get well” Number 9. Taking Immune Enhancing Supplements

Nutritional supplements can either help or flare up your autoimmunity based on an individual’s T-helper dominance (whether you have a TH-1 or TH-2 dominance).

Unfortunately there is no mention of TH17 but as mentioned above Bone broth is a TH1 and TH17 stimulator.
I look at inflammation and the immune system; the way firemen look at fires. What type of fire is it – Combustible, grease, electrical, chemical? Next where is it located – crown, surface, ground? What is the immune status, **TH1, TH2, and/or TH17** – stimulated, suppressed, and/or deficient of the individual, (Fig. 1). What is the status of the gastrointestinal tract? Then develop a nutritional supplement plan to calm and restore control over the immune response. Once this is done, a person can maintain themselves through diet and lifestyle.

**How Does Functional Medicine View Bone Broth?**

The immune system is designed to protect the body from infection and injury, but an overactive immune response can damage organs or lead to inflammatory diseases.

The immune system is not working properly in autoimmune and many other conditions. The loss of regulatory mechanisms are the reason autoimmune conditions occur. The Immune status must be viewed in context with the NEI Supersystem cytokine, chemokine, immunoglobulins and the immune status.

**Inflammation is a general term describing the effects of too many inflammatory cytokines and stimulating neurotransmitters unopposed by too few anti-inflammatory cytokines and inhibitory neurotransmitters.**

When health deteriorates the immune system and the ability to produce immunoglobulins, cytokines and chemokines falters. Bacteria, parasites, and mold actively hack into the NEI Supersystem for their own benefit. In addition, many nutritional supplements or dietary habits also shift the NEI Supersystem balance, i.e. bone broth, lectins, etc. PEC responds in a similar fashion to lectins as they do to bone broth. The cytokine, chemokines and immunoglobulins of the NEI supersystem should respond with the appropriate controlled response to the situation. Our immune system should function like a team of samurai warriors wielding a variety of different inflammatory weapons, wiping out foreign invaders with precision, accuracy, and with deadly force when necessary, but then quickly returning to a calm of an enlightened master blending into the background – unobserved and inconspicuous.

Cytokine levels differ dramatically in acute and chronic pathological conditions. In many disease states, marked local inflammatory responses cause cytokines to spill into general circulation. Changes in the circulating levels of these cytokines and chemokines have been linked to many disease states, making them valuable as functional biomarkers. Excessive or diminished cytokine levels are associated with many clinical conditions and diseases, including:

- **Central Nervous System (Brain) Disorders – Thyroid – Allergies**
- **Autoimmunity – Cytokine Induced Sickness – Asthma**
- **Endometriosis – Fibromyalgia – Toxicity – Diabetes**
- **Bacterial infections – Viral infections – Parasitic infections**

The immune system is ever vigilant with responses from the sniffles of the common cold to the **cytokine storm** reaction to the peanut. The common thread I observe in all Folklore Nutrition, the Green Allopathy of Alternative Medicine and even the Functional Medicine practitioners is stimulation of the immune system. Some
recommend doing the TH1/TH2 challenge or the elimination – provocation diet. Doing a challenge or a provocation of the immune system incurs the same risk as using a match to check for a gas leak. When the TH1/TH2 challenge was developed, TH17 was a glimmer in the distance, with only a few immunologists aware on the possible implications of a TH17 response. But TH17 is the system to watch out for. A bad experience with the **TH1/TH2 challenge** is likely TH17 dominance.

A good defense against most illness is a healthy immune system. We have been conditioned to think of external microbes as our enemy during a time of infection or inflammation. But our own immune systems are potentially more lethal. When the body detects foreign microorganisms or substances, it can respond by overprotecting the site of that irritation. In its hurry to get antibodies to the infection site, the body may dispatch so many that the level of cytokines becomes highly elevated, creating a **Cytokine Storm**.

Many take the cavalier attitude that – water will not wet them & fire will not burn them – based on their intentions that nutritional support will always do good and never do any harm.

Another thread is they treat the condition and not the person. Figure 1 is a Stimulated Cytokine test results from four *Hashimoto's* patients. Each bar represents a different cytokine. Low levels (**Immunosuppression**) are read from top to bottom (blue). High levels (**Immunostimulation**) are read from bottom to top (red). Neutral levels are shown as white.

1) *Hashimoto's*  
- General/PHA TH2 Immune Activation  
- LPS TH17 Immune Activation  
- PHA/LPS – TH1 Suppression

2) *Hashimoto's*  
- PHA/LPS TH17 Immune Activation  
- General/PHA TH2 Immune Activation  
- LPS TH1 Suppression

3) *Hashimoto's*  
- PHA/LPS TH17 Immune Activation  
- General Low Immune Activity  
- General/PHA/LPS TH1 Suppression  
- General/PHA/LPS Chemokines Suppression

4) *Hashimoto's*  
- General/PHA/LPS TH17 Immune Activation  
- General/PHA TH2 Immune Activation  
- General TH1 Immune Activation  
- PHA TH2 Suppression  
- LPS Chemokines Suppression
All have of the patients in Fig. 1 have TH17 Immune Activation. Stimulation of an already stimulated immune system does not restore health. Instead, this would induce cytokine-induce sickness behavior with frequent cytokine storms. A Cytokine storm is more of a symptomatic condition which occurs in varying forms and involves a number of different mechanisms. The primary symptoms of a cytokine storm are extreme fatigue, low mood, anxiousness, anxiety, insomnia, high fever (intermittent hot flashes), swelling and redness, and nausea. (You may be more familiar with a cytokine storm known as Septic Shock, which is another example of the immune system gone berserk.) “Storm” may be an appropriate metaphor, acknowledging a variety of mechanisms in a variety of circumstances.

After the storm is done: Cytokine-Induce Sickness Behavior

After the cytokine storm has subsided, sick individuals have common symptoms of sickness, little motivation to eat, withdrawal from normal social activities, fever, burning muscles, aching joints and fatigue and have significant changes in sleep patterns. They display an inability to experience pleasure, have exaggerated responses to pain and brain fog. Proinflammatory cytokines acting in the brain cause sickness behaviors. Although Functional Medicine has defined proinflammatory cytokines as the central mediators of sickness behavior, for your unique circumstances a much better understanding of how the cytokines and neurotransmitters are communicating with each other is best done through lab testing.

How sensitive is the Immune System?

Some individuals can have a life-threatening event simply by having a peanut touch them. Functional Medicine asks questions beyond the obvious allergic response. What must have occurred in the context of the NEI Supersystem for this to taken place? The normal checks and balances are not present in anaphylactic cases. The same could be said for those suffering from autoimmune or chronic health conditions.

Bone Broth Provides Nutrients and Immune Stimulating Cytokines and Chemokines

Calcium

When the level of calcium in the body fluids rises above normal, the nervous system is depressed and reflex activities of the central nervous system become sluggish. Also increased calcium ion concentration decreases the QT interval of the heart, and it causes constipation and lack of appetite, probably because of depressed contractility of the muscle walls of the gastrointestinal tract. Nerves rely on calcium to properly regulate the release of neurotransmitters. Increased calcium in the body triggers neurotransmitter release resulting in sympathetic stimulation.
Sympathetic stimulation causes: stimulates heartbeat, raises blood pressure, dilates the pupils, dilates the trachea and bronchi, stimulates the conversion of liver glycogen into glucose, while shunting blood away from the skin and viscera to the skeletal muscles, brain, and heart, inhibits peristalsis in the gastrointestinal (GI) tract, and inhibits contraction of the bladder and rectum.

**Symptoms of Excess Sympathetic / Deficient Parasympathetic**

- Anxiety-like response
- Enlarged pupils
- High blood pressure
- Infrequent bowel movements
- Nervous strain
- Tension headaches
- Irritability
- Indigestion
- Rapid heartbeat with palpitations or weak pulse
- Nightmares
- Muscle tension

**Arginine**

Bone broths are a good source of amino acids – particularly arginine, glycine and proline. Dietary supplementation with arginine can improve immune responses in various inflammatory models. However, increased concentrations of arginine further potentiate Inducible NOS (iNOS)-dependent \( \text{O}_2^- \) formation in inflammatory macrophages. Arginine is associated with an increase in the release of T cells from the thymus. In addition, arginine has a direct effect on T-cell activity.

Persistent inflammation and the generation of nitric oxide play key roles in tissue injury during onset of disease and as a reaction to toxicant exposures. The associated oxidative and nitrative stress promotes diverse pathologic reactions including neurodegenerative disorders, atherosclerosis, chronic inflammation, cancer, and premature labor and stillbirth. These effects occur via sustained inflammation, cellular proliferation and cytotoxicity and via induction of a proangiogenic environment. Oxidative and nitrative stress is also thought to play a role in creating the proinflammatory microenvironment associated with the aggressive phenotype of inflammatory breast cancer.

Inducible NOS is expressed following stimulation by a variety of inflammatory cytokines such as TNF-\( \alpha \) or by lipopolysaccharide (LPS). Persistent vasodilation characteristic of [cytokine storms](#) may result from overproduction of nitric oxide.

TNF-\( \alpha \) tilts the metabolism of connective tissue fibroblasts toward proteolysis and enhances expression of iNOS, which was highly upregulated in unrestrained proinflammatory macrophages. iNOS in turn stimulates macrophage generation of \( \text{NO}^- \), which, together with \( \text{O}_2^- \), forms \( \text{ONOO}^- \) and leads to nitrative tissue damage.

Pro-inflamatory cytokines IL-1, TNF-\( \alpha \), IFN-\( \gamma \), and IL-2 also induce iNOS. The activation of iNOS depends on the type of inflammatory response to a specific disease process. T lymphocytes depend on arginine for multiple key biological processes, including proliferation, of the T-Cell receptors responsible for recognizing antigens and the development of memory T cells.
Memory T cells are characterized based on what tissues of the body they enter. The body is subdivided into different immunologic zones, and T cells that encounter antigen first in a particular tissue tend to recirculate through that tissue in the future. This tissue-specific migration is controlled by chemokines, AKA homing beacons, on the surface of memory T cells. The homing chemokines guides T cells to the tissue, and specifically to the gut. This selective recirculation allows T cells to focus their attention on sites where this antigen is most likely to be encountered in the future.

**Bone Marrow and Immune Stimulation**

Chemokines and cytokines act systemically to mobilize neutrophils. Neutrophils are the most abundant (40 to 75%) type of white blood cells. Chemokines are generated locally at sites of inflammation, and orchestrate the local recruitment of neutrophils from the blood into tissues by promoting neutrophil movement into tissues.

Mature neutrophils are present in the bone marrow where they wait to be mobilized. Upon reaching the bone marrow, chemokines in the blood stimulate neutrophil migration out of the bone marrow into the blood. The rapid mobilization of neutrophils from the bone marrow is driven by the coordinated actions of the chemokines, KC and MIP-2, and the cytokine G-CSF acting via different means. Increased plasma concentrations of pro-inflammatory (IL-6, TNF, IL-1β, KC, MIP-2, MCP-1), have been associated with systemic inflammatory response (**cytokine storms**).

The chemokines KC and MIP-2 stimulate the rapid mobilization of neutrophils. Within the gastrointestinal tract, MIP-2 leads to a significant increase of circulating neutrophil numbers and neutrophil movement into the gastrointestinal tract. MIP-2 acts both systemically to increase circulating neutrophil numbers and locally to promote neutrophil recruitment into the tissue. In this regard, it is interesting that the same chemokine can stimulate mobilization and act as a homing beacon.

The chemokines MCP-1 and MCP-3 generated at sites of inflammation act to remotely mobilize leukocytes from the bone marrow. Monocyte chemo-attractant protein 1 (MCP-1) is a chemokine that attracts monocytes, memory T lymphocytes, and natural killer cells. MCP-1 influences TH2 responses. MCP-1 is required for elicit a full complement of white blood cells in a delayed hypersensitivity response. MCP-1 can attract dendritic cells.

**Bone Marrow Fatigue**

Elevated levels of specific cytokines, e.g., type I IFN, have been linked to low white blood cells, which by itself is an important predictor of poor outcomes of systemic bacterial infections. Innate immune stimulation worsens the outcome of bacterial infection by exhausting the Bone Marrow neutrophil supply. Systemic innate immune stimulation causes bone marrow neutrophil exhaustion, which negatively influences the outcome of bacterial infections. The systemic presence of bacterial compounds deriving from the infection exhaust the Bone Marrow neutrophil reservoir through a combination of increased demand and increased cell death.

**Bone Broth References**


Ley K. Integration of inflammatory signals by rolling neutrophils. Immunol Rev. 2002;186:8–18.


Can Vitamin C Cure Ebola?

Orthomolecular.org reports in their article: Can Vitamin C Cure Ebola? that:

"People need to know that vitamin C is an option for fighting Ebola, and how it works. [...] Get the illness and, it is said, you have at best 50-50 chance of surviving without vitamin C-based therapy. [...] The clinical reports of vitamin C in viral infection are that if you get the dose right, you will survive. Vitamin C is known experimentally to inactivate viruses."

Steve Hickey and Hilary Roberts report on the same article:

- Taking a gram or so of Vitamin C daily will not protect you from anything except acute scurvy. [Presumably it only protects you from scurvy if you are otherwise healthy.]

- "Clinical reports suggest that taking vitamin C almost to bowel tolerance every day (in divided doses) will help to protect you against all viruses." But the dose and the way you take it must be right or it will not work.

- "Massive doses [of Vitamin C] have been reported to have helped against every virus it has been pitched against", including Polio, Dengue and AIDS.

- Vitamin C is the primary antioxidant in the diet and most people don’t take enough to be healthy. "Ignore governments telling you that you only need about 100mg a day and can get this amount from food."

- "A normal adult in perfect health may need only a small intake, say 500 mg per day, but more is needed when someone is even slightly under the weather. Similarly, to prevent illness, the intake needs to be increased."
**EBOLA: KILLER VIRUS**

An outbreak of the deadly Ebola virus is spread by close contact and kills between 25 and 90 percent of victims. There is no cure or vaccine.

**SYMPTOMS**
- Headache
- Fever
- Fatigue
- Bleeding from eyes, nose and mouth
- Muscle pain
- Sore throat
- Impaired liver and kidney
- Diarrhoea
- Vomiting
- Rash
- Internal and external bleeding

**Preventative measures**
- Stop contact with infected animals and the consumption of their meat
- Isolate the sick
- Prompt disposal of victims’ bodies
- Disinfect homes of dead and infected
- Protective clothing for healthcare workers

*Source: WHO*
Ebola is nasty
But not everyone gets it,
Not everyone is Killed by it

It depends on the strength of your IMMUNE System
Viruses
(including Ebola)
are no match for

Young Living
ESSENTIAL OILS

Are you prepped for the season?

The Oil Dropper

Top Oil Choices for Viruses

Top on my list is Thieves. Thieves is highly anti-microbial. It can even fight against airborne carried germs (now Ebola we are told is not airborne) but I don't think they know everything about this rapidly mutating virus, so it wouldn't hurt to be protected from airborne transmission. This blend helped protect people against the Black Plague endemic in France many years ago. I would be willing to bet it could help against Ebola. I tend to want to "be sure" if you know what I mean, so I would use a variety of oils to cover the bases.
Wheat Gluten Causes Dendritic Cell Maturation and Chemokine Secretion

Marina Nikulina, Christiane Habich, Stefanie B. Flohé, Fraser W. Scott and Hubert Kolb

Abstract

Wheat gluten causes gut inflammation in genetically predisposed individuals. We tested the hypothesis that wheat gluten is not only a target of adaptive immunity, but also modulates the function of APC. Dendritic cells (DC) derived from the bone marrow of BALB/c mice were exposed to chymotrypsin-treated wheat gluten. This induced DC maturation as estimated by all surface markers tested (MHC class II, CD40, CD54, and CD86). The effect was dose dependent, and, at 100 µg/ml gluten matched that caused by 10 ng/ml LPS. A role of endotoxin contamination was ruled out by demonstrating the resistance of wheat gluten effects to LPS antagonist polymyxin B. DC from LPS nonresponder strain C3H/HeJ were affected by wheat gluten, but not by LPS. Proteinase K-digested wheat gluten was unable to stimulate DC maturation. Wheat gluten induced a unique secretion pattern of selected cytokines and chemokines in DC. Classic pro- or anti-inflammatory mediators were not produced, in contrast to LPS. Rather, chemokines MIP-2 and keratinocyte-derived cytokine were secreted in large amounts. We conclude that wheat gluten lowers the threshold for immune responses by causing maturation of APC, by attracting leukocytes and increasing their reactivity state. In the presence of an appropriate genetic predisposition, this is expected to increase the risk of adverse immune reactions to wheat gluten or to other Ags presented.

Received August 6, 2003.
Accepted May 14, 2004.
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<tr>
<td>- Low Libido</td>
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<td>- Indigestion</td>
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SweetBeetAndGreenBean.net
Symptoms of Ebola

- Headache
- Red Eyes
- Pharynx and lungs
  - Hiccups
  - Sore throat
  - Difficulty breathing
  - Difficulty swallowing
- Systemic
  - Fever
  - Lack of appetite
  - Internal bleeding
- Muscular
  - Aches
  - Weakness
- Joints
  - Aches
- Intestines
  - Diarrhea
- Chest pain
- Stomach
  - Pain
  - Vomiting
- Skin
  - Rash
  - Bleeding
Human asymptomatic Ebola infection and strong inflammatory response

Summary

Background

Ebola virus is one of the most virulent pathogens, killing a very high proportion of patients within 5–7 days. Two outbreaks of fulminating hemorrhagic fever occurred in northern Gabon in 1996, with a 70% case-fatality rate. During both outbreaks we identified some individuals in direct contact with sick patients who never developed symptoms. We aimed to determine whether these individuals were indeed infected with Ebola virus, and how they maintained asymptomatic status.

Methods

Blood was collected from 24 close contacts of symptomatic patients. These asymptomatic individuals were sampled 2, 3, or 4 times during a 1-month period after the first exposure to symptomatic patients. Serum samples were analyzed for the presence of Ebola antigens, virus-specific IgM and IgG (by ELISA and western blot), and different cytokines and chemokines. RNA was extracted from peripheral blood mononuclear cells, and reverse-transcriptase-PCR assays were done to amplify RNA of Ebola virus. PCR products were then sequenced.

Findings

11 of 24 asymptomatic individuals developed both IgM and IgG responses to Ebola antigens, indicating viral infection. Western-blot analysis showed that IgG responses were directed to nucleoprotein and viral protein of 40 kDa. The glycoprotein and viral protein of 24 kDa genes showed no nucleotide
differences between symptomatic and asymptomatic individuals. Asymptomatic individuals had a strong inflammatory response characterized by high circulating concentrations of cytokines and chemokines.

**Interpretation**

This study showed that asymptomatic, replicative Ebola infection can and does occur in human beings. The lack of genetic differences between symptomatic and asymptomatic individuals suggest that asymptomatic Ebola infection did not result from viral mutations. Elucidation of the factors related to the genesis of the strong inflammatory response occurring early during the infectious process in these asymptomatic individuals could increase our understanding of the disease.

**Introduction**

Ebola virus belongs to the Filoviridae family and is subdivided into four subtypes: Zaire, Sudan, Côte d’Ivoire, and Reston.\(^1\) Ebola virus is one of the most virulent pathogens, killing a very high proportion of patients within 5–7 days.\(^2\) The virus is endemic in central Africa, where it occasionally causes fulminating haemorrhagic disease in human and non-human primates.\(^3\) The genome is composed of linearly arranged genes on a single negative-stranded RNA molecule that encodes the seven structural proteins: nucleoprotein, virion structural proteins VP35, VP40, glycoprotein (GP), VP30 and VP24, and RNA-dependent RNA polymerase (L).\(^4\) The organisation and transcription of the GP gene is unusual and involves transcriptional editing before it can be expressed.\(^5,\, 6\)\n
We have found that immunological events very early in an Ebola-virus infection determine the control of viral replication and recovery or catastrophic illness and death.\(^7\) Recovery from infection is related to orderly and well-regulated humoral and cellular immune responses, characterised by the early appearance of IgM and IgG, followed by activation of cytotoxic cells at the time of antigen clearance from blood. By contrast, fatal outcome is associated with impaired humoral responses and an early activation of T cells unable to control virus replication, followed by considerable intravascular apoptosis.\(^7\)

Two outbreaks of Ebola virus occurred in northern Gabon in early and late 1996, resulting in case-fatality rates of 66% and 75% among 59 and 60 symptomatic patients with laboratory-confirmed infections.\(^8\) Most patients developed high fever, headache, diarrhoea, vomiting, and haemorrhagic manifestations. The virus was transmitted from a dead chimpanzee in the first outbreak and from person to person in the second outbreak, via infected body fluids\(^8\) (faeces, vomit, saliva, sweat, or blood). From the beginning to the end of both outbreaks, we identified 24 individuals who were directly exposed to infected materials from fatal and non-fatal cases, but who did not develop
symptoms. These individuals were family members of symptomatic patients who lived continuously with them, and took care of them without any physical protection such as gloves. Throughout the study, these individuals were sampled several times, from the time of first exposure to a sick patient. We report a description of asymptomatic and replicative Ebola infection in human beings.

**Methods**

**Detection of specific IgM and IgG**

We used the standard IgM capture assay (carried out by Special Pathogens Branch, CDC, Atlanta, GA, USA). IgM from the serum sample of the infected patients were first captured with antibody to human IgM. Viral antigens were then added to the captured IgM and were exposed to a polyclonal hyperimmune rabbit serum containing antibodies to Ebola virus. Bound antibodies to Ebola virus were detected by antibody to rabbit IgG conjugated to peroxidase.

The IgG assay we used was an ELISA in which plates were coated with Ebola Z antigen, diluted 1:1000 in phosphate buffered saline (PBS), and incubated overnight at 4°C. Plates were coated with uninfected vero cell culture antigens under the same conditions. Serum samples were then diluted 1:400, 1:1600, 1:3200, 1:6400 in 5% non-fat milk in PBS-Tween 20 and incubated overnight at 4°C. Binding was visualised with peroxidase-labelled antibody to human IgG (Sigma, L’Isle d’Abeau, France) and the TMB detector system (Dynex Technologies, Issy-les-Moulineaux, France). Optical density was measured at 450 nm, on an ELISA plate reader (Diagnostics Pasteur, Marne la Coquette, France).

Results were interpreted as previously described. A panel of ten endemic normal serum samples was run each time the assay was used. Adjusted optical densities were calculated by subtracting the optical density of uninfected antigen-coated well from its corresponding antigen-coated well. The cut-off value was given as the mean adjusted optical density for the ten normal serum samples (+350). All samples were handled according to WHO guidelines on viral haemorrhagic fever in Africa (WHO recommendations for management of viral haemorrhagic fevers in Africa, Sierra Leone, 1985).

**Western-blot analysis**

Purified Ebola virus from tissue culture medium was loaded on 10% sodium dodecyl sulfate-polyacrylamide gel and transferred onto a polyvinylidene fluoride membrane at 55 V for 3 h at 4°C. Protein immunoblotting analysis was done with serum samples diluted in a ratio of 1:500, and a secondary antibody (goat antibody to human IgG peroxidase conjugate) in a dilution of 1:30 000. All incubations were done for 1 h at room temperature. Immune complexes were visualised by
chemiluminescence detection with Super Signal Substrate reagents (Pierce, Rockford, IL, USA) according to the manufacturer’s instructions.

Detection of Ebola-specific RNA

Peripheral blood mononuclear cells were separated from whole blood by Ficoll-diatrizoate density-gradient centrifugation. Total RNA was extracted with a kit (Qiagen, Courtaboeuf, France). The first-strand complementary (cDNA) was synthesised by the superscript II kit (Gibco BRL, Eragny, France), a dNTP mix (Amersham, Orsay, France), random hexamer primers (PCR1, PCR2; Boehringer, Mannheim, Germany), primers specific for positive-strand RNA, or primers specific for negative-strand RNA. Half of the reaction product was used as a template for PCR with Taq DNA polymerase (Appligene-Oncor, Illkirch, France) for 40 cycles (94°C for 30 s, 55°C for 30 s, and 72°C for 90 s). The reaction was run in a Perkin-Elmer 480 thermocycler (Perkin Elmer, Rotkreuz, Switzerland) with designed primers from a conserved region of the L gene (coding for RNA-dependent RNA polymerase), as described elsewhere. The amplification products were analysed on 1.5% agarose gels. After the first round of amplification, the products of interest were identified by southern hybridisation. The 420 bp reverse transcriptase PCR products were purified and labelled with a digoxigenin labelling kit (Boehringer). The PCR products were then run in 1.5% agarose gel and transferred overnight to a positively charged nylon membrane with 1 M sodium hydroxide. Hybridisation and chemiluminescence detection were done using the Dig kit (Boehringer). For nested PCR, 5 μL of the first-round reaction product was used as a template, and the reaction was run in the same conditions as first-round PCR. The 298 bp products from the nested PCR (PCR2) were also run in 1.5% agarose gel.

Sequencing of PCR products

The PCR fragment of 298 bp from the L gene was purified and sequenced with the Sequenase II kit (Amersham). Reverse transcription and first and second round PCR amplification of VP24 and GP were done for the L gene. For VP24 we used 5′-ACATCACTTTGAGCGCCCTCA-3′ and 5′-AGCTGGCTTACAGTGAGGATT-3′ as primers for the first round and 5′-CGCAAGGTTTCAAGGTTGAA-3′ and 5′-TTGAGT CAGCATATATGAGTT-3′ as primers for the second round of PCR. For amplification of GP, we needed to divide it into two overlapping parts of equal size which represent together the complete open reading frame. Primers for the first part were: 5′-GATGAAGATTAAGCCGACAGTGAGCG-3′ and 5′-GTTGCTCTGTTCGGTGATCTTG-3′ for the first round of PCR and 5′-GTGAGCTTAACTTGCAACAGTGAGCG-3′ and 5′-GTGTCTGGTCTGCTTGGTATCTTG-3′ for the second round. Primers for the second part were: 5′-TGCAATGGTTCAAGTGCACAGTC-3′ and 5′-AAGAGATAACTAGAT GTGATGTTTAAACC-3′ for the first round and 5′-CAAGGAAGGGAAGCTGCAGTGCG-3′ and 5′-GAATCACATTGCGCTATGTTTAAAGC-3′ and 5′-AGCTGGCTTACAGTGAGGATT-3′.
3′ as primers for the second round. The different amplification products were electrophoresed on 1·5% agarose gels, stained with ethidium bromide, excised from the gel, and extracted with a QIA quickgel extraction kit (Qiagen, Courtaboeuf, France). Sequencing of VP24 fragments was run on an ALF express DNA sequencer (Pharmacia Biotech, Uppsala, Sweden) with an Autocycle 200 sequencing kit (Pharmacia). Analysis was done with the OS/2 computer system. Sequencing of GP fragments was done by ACTgene laboratory (ACTgene, Evry, France).

Detection of cytokines in plasma

Plasma concentrations of interleukin-1β (IL-1β), interferon alpha (IFNα), I, IL-12, IL-13, tumour necrosis factor (TNF), macrophage inflammatory protein-1α (MIP-1α), and MIP-18 were measured with commercial kits (R&D Systems Europe, Abingdon, UK). Plasma concentrations of IL-10 and interferon gamma (IFNγ) were each measured at the same time with two different kits (IL-10: Amersham and Immunotec, Orsay and Marseille, France; IFNγ: R&D Systems Europe and Immunotec). Plasma concentrations of the other cytokines were measured with a two-site ELISA, with specific capture and biotinylated antibodies against IL-2 or IL-6 (Genzyme, Cergy-St-Christophe, France), IL-4, IL-5 (Pharmingen, CA, USA). To confirm the results, plasma concentrations of IL-2, IL-4, and IL-6 were also measured with commercial kits (Immunotec). Optical density was measured at 492 nm on an ELISA plate reader (Diagnostics Pasteur). Cytokine concentrations were calculated from standard curves.

Samples from all patients were taken, treated, and stored in exactly the same conditions. In patients who displayed symptoms, the mean time from infection was assessed on the basis of the time of the earliest samples after the onset of symptoms, and the mean incubation period. Because the incubation period is between 5–8 days and that the earliest samples were taken within 3 days after the onset of symptoms, the samples from symptomatic patients were from 8–11 days after the putative infection.

Results

Humoral responses

We investigated these apparently protected individuals by measuring viral-specific IgM and IgG in serum samples collected serially at various times during the two outbreaks, with Ebola Zaire antigens (figure 1). The first samples from each individual were without antibody, excluding prior immunity. 11 of the 24 patients tested later developed both IgM and IgG responses to viral antigens. Concentrations of specific IgM started to increase 15–18 days after the first identified potentially infectious contact, and about 10 days after the last such contact (figure 1). 1 month after the last exposure, Ebola-specific IgM was found in all 11 individuals. Virus-specific IgG appeared 1 week after IgM, and reached lower titres
than IgM. When serum samples from IgG-positive asymptomatic individuals were analysed by western blotting in denaturing conditions with purified Ebola virus, reactivity was mainly directed against the nucleoprotein (NP) or VP40 proteins (figure 1).

**Figure 1 Full-size image (58K) Download to PowerPoint**

Humoral responses in asymptomatic individuals

A Specific IgM and IgG antibody responses to Ebola Zaire, as determined by ELISA. Each point represents one contact individual who was sampled several times. B Antibody responses analysed by western blotting for one symptomatic patient who recovered (T+), two negative endemic controls (EC), and five IgG-positive asymptomatic individuals. Identity of each band from symptomatic case was confirmed previously with antibody to Zaire hyperimmune goat serum.

Detection and isolation of Ebola virus

By contrast with the symptomatic patients, circulating Ebola antigen was never detected by an antigen capture assay in serum samples from antibody-positive patients. Similarly, we did not isolate virus on vero-E6 cells, without blind passages, from serum from the seven individuals.

Viral RNA detection

We developed a reverse-transcriptase PCR assay to detect viral RNA fragment in the L gene in peripheral blood mononuclear cells with primers. The PCR assay was negative in all these individuals, whereas the appropriate 420 bp fragment was detected in all symptomatic patients infected with Ebola virus (figure 2). By contrast, second-round PCR yielded DNA products of the expected size (298 bp) in seven of 11 asymptomatic individuals tested but in none of the 13 of the exposed antibody-negative individuals and in none of the negative control individuals (figure 2). Southern-blot hybridisation of the first-round PCR products was also positive (figure 2). The viral specificity of the nested PCR assay was confirmed by sequencing the amplicon (data not shown).
Reverse transcriptase PCR detection of Ebola-specific RNA

A Results for seven asymptomatic individuals are shown. They were sampled between 7 and 16 days after the first exposure to a sick patient. The 420 bp product obtained from the first round of PCR (PCR 1) and the 298 bp product obtained after two steps of PCR (PCR 2) represent cDNA fragments of the Ebola-virus polymerase gene. The first-strand cDNA was synthesised by random hexamer primers (PCR1, PCR2) or primers specific for positively-stranded RNA (PCR2+) or primers specific for negative-stranded RNA (PCR2-). (+) is a positive symptomatic patient during the acute phase of the disease. (-) is a healthy negative endemic control. (M-) is PCR mix without cDNA. These controls were included in each run. Ten negative controls were tested but only one is shown in the figure. B Detection of Ebola RNA during infection. The cDNA was constructed with a primer set specific for negative-stranded RNA (PCR-) or positive-stranded RNA (PCR+). Peripheral-blood mononuclear cells were collected from two asymptomatic individuals (asymptomatic 1 and 2), 7, 9, 16, and 23 days after the first exposure to a sick patient.

To find out how long viral RNA could be detected in asymptomatic individuals, we sampled two of the seven such individuals on four occasions (figure 2). We detected viral genomic RNA for up to 2 weeks after the last known exposure to infected materials, suggesting that the virus replicated in the patients’ mononuclear cells. To confirm this, we used reverse transcriptase PCR with primer specific for positive-strand RNA. As described in figure 2, four of the seven asymptomatic patients were positive, confirming virus replication because Ebola virus (EBOV) is a negative-strand virus. Interestingly, the positive-strand RNA signal disappeared between 9 and 16 days after the first infectious contactie, 1 week before the detection of specific antibodies, indicating transient virus replication that lasted about 2 weeks.

Amplicons of 853 bp (VP24) and 2445 bp (GP) were obtained in three fatal cases, three non-fatal symptomatic cases, and three asymptomatic individuals. Only second-round PCR yielded the fragments of the expected size in samples from asymptomatic individuals, whereas in symptomatic patients one-step PCR was sufficient, indicating once again that viral RNA is present in low copy numbers in asymptomatic individuals. Comparative sequence analysis of the GP gene showed 36 nucleotide substitutions that led to 15 switches in the predicted aminoacid sequences in Gabon-96 Ebola virus relative to Zaire Mayinga 76. By contrast, analysis of VP24 showed only eight nucleotide substitutions in
Gabon-96 relative to Zaire Mayinga 76, but none of these changes led to switches in the deduced VP24 aminoacid sequences. Isolates from all nine patients tested had identical VP24 and Gp nucleotide sequences.

**Cellular immune responses**

High concentrations of pro-inflammatory cytokines IL-6, IL-1β, and TNF and chemokines MCP-1, MIP-1α, and MIP-1β were detected 1 week after the first potentially infectious contact, whereas concentrations were below the detection limit in uninfected controls, indicating a strong inflammatory response triggered 4—6 days after infection (figure 3). The inflammatory responses in the asymptomatic individuals disappeared rapidly within just 2—3 days, thereby avoiding fever and other physiological disturbances indicating tissue or organ damage.

**Figure 3** Full-size image (14K) Download to PowerPoint

Inflamatory responses

Concentrations of pro-inflammatory cytokines (IL-1β, TNF, and IL-6, expressed in ng/L) and chemokines (MCP-1, MIP-1α, and MIP-1β, in μg/L) were measured in plasma by ELISA. Individual values for the seven PCR-positive asymptomatic individuals are shown between 7 and 23 days after the first potentially infectious contact. Each asymptomatic individual is represented by a point.

By contrast, no IFNα, no IL-12, and no T-cell-derived cytokines (IL-2, IL-4, IL-5, or IFNγ) were detected in the plasma of asymptomatic individuals at any time during the sampling period.

**Discussion**

Despite our inability to isolate Ebola virus on vero E6 cells from stored serum from the seven asymptomatic individuals, these data do show that asymptomatic, replicative Ebola-virus infection occurs in human beings.

First, these individuals mounted Ebola-specific humoral responses, mainly directed against the proteins NP and VP40, indicating either true infection or antigenic stimulation. Concentrations of IgM and IgG started to rise between 10 and 18 days and between 17 and 25 days, respectively, after the infectious contact, indicating no prior immunity. The appearance of IgM and IgG when viral RNA disappeared may suggest that humoral responses can have a protective role in asymptomatic infection. These findings
also confirmed the immunogenicity of NP and VP40 and were consistent with results obtained in
symptomatic human beings who survived the disease\textsuperscript{7} and with other results obtained in animal
studies.\textsuperscript{11} The appearance of antibodies came somewhat later in asymptomatic patients than in
symptomatic patients who recovered\textsuperscript{7} (day 3 following disease onset, about 8–11 days after presumed
exposure assuming a 5–8 day incubation period).

Despite seroconversion, circulating Ebola antigen was never detected in asymptomatic individuals.
Then, to lower the detection threshold and to distinguish passive immunisation from true infection in
the asymptomatic individuals, we developed a reverse-transcriptase PCR assay to detect viral RNA
fragment in the L gene in peripheral-blood mononuclear cells with primers described previously.\textsuperscript{10} We
tested circulating white blood cells rather than serum because filoviruses replicate in cells of the
monocyte and macrophage lineage both in vitro\textsuperscript{12} and in vivo.\textsuperscript{13–14} Ebola RNA was detected in
samples from asymptomatic individuals after two rounds of amplification. The need to apply nested
PCR to detect viral RNA in these asymptomatic individuals compared with a direct PCR in symptomatic
cases\textsuperscript{15} is suggestive of a very low viral load, consistent with the absence of detectable circulating
antigens. Moreover, detection of viral genomic RNA in peripheral-blood mononuclear cells for 2 weeks
after exposure together with detection of positive-stranded viral RNA indicate viral replication. In fact,
it has been shown that the Ebola genome is transcribed into monocistronic RNA (mRNA), which is
complementary to viral genomic RNA. Replication works via a full-length positive-strand antigenome
that serves as the template for synthesis of the negative-strand genome.\textsuperscript{1}

These findings show that some individuals were infected with the virus without developing symptoms.
Results from previous outbreaks had only indicated that such an asymptomatic infection was possible.
During the first three outbreaks of Ebola virus in Sudan and Zaire in 1976 and 1979, WHO teams noticed
that individuals had symptoms that ranged in severity, from mild (and probably asymptomatic) to
rapidly fatal.\textsuperscript{16} Moreover, the immunofluorescence showed higher antibody prevalence among
asymptomatic family members who had had physical contact with clinical cases than among the
general population who had no contact with symptomatic patients.\textsuperscript{17, 18} More recently, a cohort of
152 household contacts of convalescents was studied for up to 21 months during the Kikwit outbreak in
Republic Democratic of the Congo.\textsuperscript{19} Blood samples of only five such individuals were IgM and IgG
positive. Although the authors could not exclude the possibility of false positive (5 [3\%] of 152), they
suggested that mild cases may occur.

Interestingly, guinea pigs and mice develop a very mild or subclinical infection when inoculated with
wild-type Ebola virus, but serial passage leads to increasing pathogenicity and high
lethality.\textsuperscript{14, 20} Genomic sequence analysis of the entire genome of guinea-pig-adapted Ebola virus
showed several nucleotide substitutions, mainly in the VP24 gene; only changes in VP24 led to switches
in the predicted aminoacid sequence, suggesting a direct link between VP24 mutations and appearance of pathogenicity of the virus (Volchkov, unpublished data). Furthermore, the GP protein is known to be involved in the virus binding to cellular receptors and entry into cells, and is suspected to inhibit innate immunity to the virus, facilitating virus replication and symptoms. Thus, the complete open reading frame of these two genes was sequenced by nested-PCR amplification.

The nucleotide divergence between GP and VP24 occurring in Yambuku (Mayinga strain) and Ebola in Gabon was found to be 1.5% and 0.5%, respectively, despite the fact that they were isolated more than 20 years and almost 2000 km apart. This confirms the genetic stability of the virus. Moreover, isolates from all nine patients tested had identical GP and VP24 nucleotide sequences. These findings suggest genetic variability between symptomatic (survivors and deceased patients) and asymptomatic individuals, and are consistent with the lack of changes seen in the most variable region of GP during repeated human-to-human passages and during prolonged virus persistence within the same patients in the Kikwit outbreak in 1995. These data suggest that asymptomatic Ebola infection in human beings does not result from viral mutations, and that no different virus variants cocirculated during the Gabon outbreak.

The seven asymptomatic individuals in our study had an early and strong inflammatory response with high circulating levels of IL-1β, TNF, IL-6, MCP-1, MIP-1α, MIP-1β (figure 3). IL-1β, IL-6, and TNF have been shown to be major triggers and regulators of inflammatory responses to microbial pathogens, inducing further cytokine release, endothelial cell activation, acute-phase proteins synthesis, and fever. MCP-1, MIP-1α, and MIP-1β have a role in the recruitment of immune cells to the site of infection (being potent chemoattractants for monocytes and lymphocyte effector cells), and also enhance the capacity of these cells to adhere to the vascular endothelium. The pro-inflammatory cytokine response in the asymptomatic individuals might have directly or indirectly inhibited viral repliation in its target cells, probably at the site of infection. Indeed, the cytokines involved have been shown to inhibit virus replication either directly or indirectly by stimulating immunological functions such as antigen presentation, cytokine production, inflammation, phagocytosis, and cytotoxic activity.

We estimate that our earliest samples from symptomatic patients are between 8 and 12 days after infection, that is 2–3 days after the onset of symptoms. At this time-point, in the infectious process in patients who died, proinflammatory cytokines (IL-1β, TNF, IL-6, MIP-1α, and MIP-1β) were not detected in any samples, whereas patients who recovered from symptomatic disease had intermediate to low plasma concentrations of these same cytokines (data not shown). Comparison between patients has the limitation that symptomatic patients were sampled a few days later than the asymptomatic ones (8–11 versus 7 days after infection in asymptomatic individuals). However, given the fact that symptomatic
patients have a continuous infection, inflammatory cytokines should still be detectable between 8 and 11 days after infection if they were present at high concentrations a few days earlier. These observations are consistent with studies showing a close correlation between the severity of Ebola disease in guinea pigs and mice during serial passage as well as the loss of inflammatory cell infiltration around infected loci. In the same way, light microscopic examination of liver and skin tissues from 13 fatal and one non-fatal human case during the Kikwit outbreak showed that perivascular infiltrates of inflammatory cells were absent or mild. These observations suggest a link between clinical status and inflammatory responses. Although it is possible that some individuals mount a local cellular mechanism that inhibits replication, or that the infectious dose in these individuals was so small that even a modest inflammatory response could clear virus, this response may be involved in some way in the rapid control of virus and absence of symptoms. The public-health impact of Ebola infection needs also to be reassessed in light of these new findings. The risk of transmission via blood products donated by such individuals or via semen should be taken into consideration in public-health policy since infectious filovirus have already been found in semen from symptomatic patients 2–3 months after symptoms.

Contributors

E M Leroy and S Baize designed the scientific project, did the technical studies, and wrote the paper. E M Leroy and S Baize contributed equally to this work. A J Georges and M-C Georges-Courbot were responsible for epidemiological investigations during all Gabonese Ebola outbreaks, and for instigating this research project at CIRMF. J Lansoud-Soukate was responsible for coordinating the activities of the Gabonese public-health authorities during these outbreaks as co-director of the national Epidemic Control Committee. J Lansoud-Soukate contributed also to epidemiological investigations. S Fisher-Hoch and J McCormick contributed to the design of the study, and gave advice on the paper. P Debré and M Capron gave advice on the paper. V E Volchkov advised on sequencing the VP24 gene and on the paper and gave us the purified Ebola antigens.

Acknowledgments

We thank C Y Lu for technical advice; T G Ksiazek and P E Rollin (Special Pathogens Branch, CDC, Atlanta, GA, USA) for their assistance with the IgM assay and for providing Ebola-specific reagents; A Pendy, P Obiang, and B Pambo for providing access to their patients; and C Tevi-Benissan, P Tshipamba, and I Bedjebaga for their assistance with the fieldwork. CIRMF is supported by the State of Gabon, ELF-Gabon and the Ministère de la Coopération Francaise. This study was supported also by grants from the Duetsche Forschungsgemeinschaft (SFB 286 and SFB 535).
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Modulation of Cytokine Expression by Traditional Medicines: A Review of Herbal Immunomodulators

Kevin Spelman, MS; JJ Burns, ND; Douglas Nichols, ND; Nasha Winters, ND; Steve Ottersberg, MS; Mark Tenborg, ND

Abstract
INTRODUCTION: Modulation of cytokine secretion may offer novel approaches in the treatment of a variety of diseases. One strategy in the modulation of cytokine expression may be through the use of herbal medicines. A class of herbal medicines, known as immunomodulators, alters the activity of immune function through the dynamic regulation of informational molecules such as cytokines. This may offer an explanation of the effects of herbs on the immune system and other tissues. For this informal review, the authors surveyed the primary literature on medicinal plants and their effects on cytokine expression, taking special care to analyze research that utilized the multi-component extracts equivalent to or similar to what are used in traditional medicine, clinical phytotherapy, or in the marketplace.

METHODOLOGY: MEDLINE, EBSCO, and BIOSIS were used to identify research on botanical medicines, in whole or standardized form, that act on cytokine activity through different models, i.e., in vivo (human and animal), ex vivo, or in vitro. RESULTS: Many medicinal plant extracts had effects on at least one cytokine. The most frequently studied cytokines were IL-1, IL-6, TNF, and IFN. Acalypha wilkesiana, Acanthopanax gracilistylus, Allium sativum, Ananus comosus, Cissampelos sympodialis, Coriolus versicolor, Curcuma longa, Echinacea purpurea, Grifola frondosa, Harpagophytum procumbens, Panax ginseng, Polygala tenuifolia, Poria cocos, Silybum marianum, Smilax glabra, Tinospora cordifolia, Uncaria tomentosa, and Withania somnifera demonstrate modulation of multiple cytokines. CONCLUSION: The in vitro and in vivo research demonstrates that the reviewed botanical medicines modulate the secretion of multiple cytokines. The reported therapeutic success of these plants by traditional cultures and modern clinicians may be partially due to their effects on cytokines. Phytotherapy offers a potential therapeutic modality for the treatment of many differing conditions involving cytokines. Given the activity demonstrated by many of the reviewed herbal medicines and the increasing awareness of the broad-spectrum effects of cytokines on autoimmune conditions and chronic degenerative processes, further study of phytotherapy for cytokine-related diseases and syndromes is warranted. (Altern Med Rev 2006;11(2):128-150)
**Introduction**

Cytokines, a large group of soluble extracellular proteins or glycoproteins, are key intercellular regulators and mobilizers. Classified into family groups (e.g., interleukins, interferons, and chemokines) based on the structural homologies of their receptors, these proteins were initially believed to act primarily as antiviral or antineoplastic agents. They are now seen to be crucial to innate and adaptive inflammatory responses, cell growth and differentiation, cell death, angiogenesis, and developmental as well as repair processes. Their secretion, by virtually every nucleated cell type, is usually an inducible response to injurious stimuli. In addition, cytokines provide a link between organ systems, providing molecular cues for maintaining physiological stability. Medical literature of the last several decades reveals an array of conditions, from cardiovascular disease to frailty, whose onset and course may be influenced by cytokines.

The diverse and far-reaching influences of these proteins can be seen in the central nervous system (CNS); cytokines cause the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioral shifts. Abnormal cytokine production has been demonstrated in neuropsychiatric disorders such as attention deficit hyperactivity disorder, obsessive-compulsive disorder, and anorexia nervosa. Cytokines also appear to play a role in depression, schizophrenia, and Alzheimer’s disease, and may be a common link between insomnia and depression.

In addition, there appears to be an involvement of cytokines in anhedonia (the inability to experience pleasure) and learned helplessness.

The understanding of stimuli that invoke cytokine secretion has expanded. Besides chronic infections, negative emotions and stressful experiences have been shown to stimulate production of proinflammatory cytokines. In addition to involvement in neuropsychiatric disorders, these diverse glycoproteins have activity in all body systems. As models of physiology continue to develop beyond compartmentalized organ systems, elucidation of the global activity of cytokines offers further support to an expanding understanding of cell-to-cell communication. The inflammatory processes of cardiovascular disease are one such example. Beyond leukocytes, the liver, heart, vessel walls, and adipose tissue are known to produce cytokines; thus any of these tissues may potentially contribute to the inflammatory nature of cardiovascular disease.

As a result of the growing recognition of cytokine activities, altering cytokine expression and targeting their receptors may offer therapeutic potential. Current pharmacological strategies include cytokine antagonist, agonist, inhibition, and stimulation models. Therapeutic application of cytokines in clinical medicine has rapidly surpassed the FDA’s 1986 approval of an interferon (IFN) agonist for the treatment of hairy cell leukemia. In 2001, an antagonist to tumor necrosis factor (TNF), a pivotal cytokine in the pathogenesis of rheumatoid arthritis (RA), was described as one of the most important advances in RA treatment. In addition, interleukin-1β (IL-1β) and TNF antagonists offer options for the treatment of periodontal disease. A novel approach in the treatment of asthma is the inhibition of T-helper 2 (TH2) derived cytokine expression, resulting in downstream effects on IgE and eosinophils. Interleukin-10 (IL-10) demonstrates modulation of brain inflammation, which may have application for conditions such as Alzheimer’s disease. In additional, interleukin-2 (IL-2) and interleukin-12 (IL-12) in combination may provide a potential therapeutic approach for neuroblastomas.

Due to their diverse and pleiotropic activities, cytokine treatments may prove promising for disorders seemingly unrelated to immune function. However, much of their therapeutic effect relies on direct influence of immune activity. For example, in the field of oncology, progress has been made in the therapeutic use of several interleukins, including IL-4, -6, -11 and -12. In combination with surgery, pre-treatment with IL-2 may enhance survival rates in patients with renal cell carcinoma. IL-18 demonstrates antitumor effects in leukemia. The interferons are used in the treatment of hepatitis B and C, malignant melanoma, follicular lymphoma, and AIDS-related Kaposi’s sarcoma.

However, as with the development of many nascent pharmacological strategies, the occurrence of adverse events generates barriers to successful therapeutic applications. Such obstacles have delayed progress in the use of several synthetic cytokines.
Treatment with recombinant cytokines has yielded a number of adverse effects, such as transient lymphopenias induced by IFN, IL-2, and TNF. Monocytopenia has been reported with the use of interferon-gamma (IFN-γ) and TNF, while IL-2, IFN-α, and TNF induce neutrophilia. Patient experience of flu-like symptoms with the use of interferons makes adherence to a therapeutic protocol a challenge. Both IL-2 and IFN-α, used for the treatment of hepatitis C and some cancers, are known to evoke depression, fatigue, sleepiness, irritability, and loss of appetite. These toxic side effects have limited the clinical value of such therapies.

In light of the adverse events experienced with cytokine-targeted therapy, it could prove useful to consider the use of phytotherapy in the modulation of cytokine expression. Immune-related illnesses have long been treated with herbal medicines. The primary literature suggests many of the effects of botanicals may be via cytokine modulation. The term immunomodulator has been used in the phytotherapy literature to describe botanical medicines believed to influence immunity. In regard to phytotherapy, immunomodulators may be defined as botanical medicines that alter the activities of the immune system via the dynamic regulation of informational molecules – cytokines, hormones, neurotransmitters, and other peptides.

This article provides an informal review of the scientific literature regarding the effects of botanical medicines on cytokines. Islam and Carter point out that therapy based on medicinal plants, such as the immunomodulators, is based on diverse constituents or groups of constituents and therefore, researching isolated constituents to reveal modes of activity disregards the principles of phytotherapy. In addition, when clinicians use medicinal plant preparations in practice, they often do not treat with isolated constituents. Therefore, in order to maintain relevance for clinical phytotherapy, this informal survey was limited to herbal medicines available in the marketplace or preparations that represent multi-component botanical medicines.

Methodology

Search Strategy

The databases MEDLINE, EBSCO, and BIOSIS were searched for appropriate studies. Titles were screened for all hits to the terms “herbs and cytokines” and “Chinese medicine and cytokines” and “Ayurveda and cytokines.” A language restriction of English was observed.

Criteria for Inclusion

The following parameters were necessary for study inclusion:

- Investigations on whole herbs (e.g., seed, leaf, root, stem, flower, or entire plant), standardized extracts, or extractions of whole herbs not reduced to one constituent were accepted. Research on isolated constituents or multiple herbal formulations were generally rejected. Fungi, although technically not plants, were included as they are commonly used in phytotherapy.

- All study model types were accepted – in vitro, ex vivo, and in vivo (both animal and human) models were accepted.

- Information on methods of herbal preparation, concentration of the plant preparation, and dose/exposure time were required.

- Only studies demonstrating activity with regard to cytokines were included.

One hundred thirty-nine titles and abstracts were reviewed for inclusion criteria. Ninety-five studies were eliminated due to single constituent-based research or insignificant results. Forty-nine papers met the criteria.

Results

Information collected as a result of searches is listed in Tables 1-5. The majority of the research used in vitro models, but in vivo animal models were also utilized. Data in Tables 1A and 1B catalog in vivo results, noting the genus and species of the plants, the
### Table 1A. In vivo Effects of Botanicals on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe secundiflora</td>
<td>Sap</td>
<td>Aqueous</td>
<td>200 mg/kg (pre), 400 mg/kg (post) infection</td>
<td>2 weeks (pre) + 7 days (post)</td>
<td>In vivo, Fowl</td>
<td>IL-6</td>
<td>(Waihenya et al, 2002)</td>
</tr>
<tr>
<td>Angelica sylvestris</td>
<td>Root</td>
<td>Aqueous</td>
<td>640 mg/kg PO</td>
<td>2 weeks</td>
<td>In vivo, Murine</td>
<td>IL-1α, TNF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Asparagus racemosus</td>
<td>Root</td>
<td>80% Ethanol</td>
<td>100 mg/kg OD PO</td>
<td>17 weeks</td>
<td>In vivo, Murine</td>
<td>TF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Bupleurum falcatum</td>
<td>Root</td>
<td>Aqueous</td>
<td>640 mg/kg PO</td>
<td>2 weeks</td>
<td>In vivo, Murine</td>
<td>TNF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Cinnamomum cassia</td>
<td>Bark</td>
<td>Aqueous</td>
<td>560 mg/kg PO</td>
<td>2 weeks</td>
<td>In vivo, Murine</td>
<td>TNF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Cnidium monnieri</td>
<td>Rhizome</td>
<td>Aqueous</td>
<td>560 mg/kg PO</td>
<td>2 weeks</td>
<td>In vivo, Murine</td>
<td>TNF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Coptis spp.</td>
<td>Rhizome</td>
<td>1% Coptis pwd in standard mouse diet</td>
<td>7 days</td>
<td>In vivo, Murine</td>
<td></td>
<td>IL-6</td>
<td>(Iizuka et al, 2000)</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Root</td>
<td>40% Ethanol</td>
<td>150 mg/kg OD injection</td>
<td>7 days</td>
<td>In vivo, Murine</td>
<td>IL-4, IFN-γ</td>
<td>(Song et al, 2002)</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Root</td>
<td>40% Ethanol</td>
<td>150 mg/kg OD injection</td>
<td>21 days</td>
<td>In vivo, Murine</td>
<td>IL-4, IFN-γ</td>
<td>(Song et al, 2002)</td>
</tr>
<tr>
<td>Genus species</td>
<td>Plant Part</td>
<td>Preparation Used</td>
<td>Dose</td>
<td>Duration of Exposure</td>
<td>Model</td>
<td>Cytokines Affected</td>
<td>Author/Date</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>-----------------------------</td>
<td>----------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><em>Perilla frutescens</em></td>
<td>Leaf</td>
<td>Aqueous</td>
<td>0.4 mL/murine x2 PO</td>
<td>18 hrs+1 hr</td>
<td>In vivo, Murine</td>
<td>TNF, IL-1α, IL-4</td>
<td>(Ueda and Yamazaki, 1997)</td>
</tr>
<tr>
<td><em>Picrorhiza kurroa</em></td>
<td>Rhizome</td>
<td>Aqueous</td>
<td>100 mg/Kg QD PO</td>
<td>17 weeks</td>
<td>In vivo, Murine</td>
<td>IL-1β, IL-6</td>
<td>(Dhuley, 1997)</td>
</tr>
<tr>
<td><em>Polygala tenuifolia</em></td>
<td>Root</td>
<td>80% Ethanol</td>
<td>2x10¹² mg/Kg QD PO</td>
<td>9 days</td>
<td>In vivo, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Hong et al, 2002)</td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>Seed and Fruit</td>
<td>Silymarin</td>
<td>250 mg/Kg QD IP Injection</td>
<td>5 days</td>
<td>In vivo, Murine</td>
<td>IL-1, -2</td>
<td>(Johnson et al, 2003)</td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>Seed</td>
<td>Silymarin</td>
<td>250 mg/Kg QD IP Injection</td>
<td>5 days</td>
<td>In vivo, Murine</td>
<td>IL-2</td>
<td>(Johnson et al, 2002)</td>
</tr>
<tr>
<td><em>Smilax glabra</em></td>
<td>Rhizome</td>
<td>Aqueous</td>
<td>400 mg/Kg QD PO</td>
<td>14 days</td>
<td>Ex vivo, Murine</td>
<td>IL-1α, IL-1α</td>
<td>(Johnson et al, 2003)</td>
</tr>
<tr>
<td><em>Tinospora cordifolia</em></td>
<td>Root and Herb</td>
<td>Silymarin</td>
<td>100 mg/Kg QD IP</td>
<td>17 weeks</td>
<td>In vivo, Murine</td>
<td>IL-1, -2, IFN-γ</td>
<td>(Jiang and Xu, 2006)</td>
</tr>
<tr>
<td><em>Withania somnifera</em></td>
<td>Root</td>
<td>70% Methanol</td>
<td>20 mg QD IP</td>
<td>10 days</td>
<td>In vivo, Murine</td>
<td>IL-2, IL-2</td>
<td>(Davis and Kuttan, 1999)</td>
</tr>
<tr>
<td><em>Withania somnifera</em></td>
<td>Root</td>
<td>70% Methanol</td>
<td>20 mg QD IP</td>
<td>10 days</td>
<td>In vivo, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Davis and Kuttan, 1999)</td>
</tr>
</tbody>
</table>
Table 2A. *In vitro* (human cell) Effects of Aqueous Botanical Extracts on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthopanax gracilistylus</td>
<td>Bark</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Acanthopanax gracilistylus</td>
<td>Bark</td>
<td>Aqueous</td>
<td>$20 \mu g/mL$ incubation</td>
<td>3 days</td>
<td><em>In vitro, Human</em></td>
<td>IL-1, -6 IFN-$\gamma$, TNF</td>
<td>(Shan et al, 1999)(^{40})</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
<td>Root</td>
<td>Aqueous</td>
<td>$1.5 \times 10^5 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-6</td>
<td>(Shon et al, 2002)(^{41})</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
<td>Root</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Cinnamomum cassia</td>
<td>Bark</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Codonopsis pilosula</td>
<td>Root</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Derris scandens</td>
<td>Stem</td>
<td>Aqueous</td>
<td>$10 \mu g/mL$ incubation</td>
<td>5 days</td>
<td><em>In vitro, Human</em></td>
<td>IL-2</td>
<td>(Srivanthana and Chavalitmunrong, 2001)(^{42})</td>
</tr>
<tr>
<td>Epimedium brevicomunum</td>
<td>Herb</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Oldenlandia diffusa</td>
<td>Herb</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Rauwolfia serpentina</td>
<td>Root</td>
<td>Aqueous</td>
<td>$5 \mu g/mL$ incubation</td>
<td>42 hours</td>
<td><em>In vitro, Human</em></td>
<td>TNF</td>
<td>(Jin et al., 2002)(^{43})</td>
</tr>
<tr>
<td>Rauwolfia serpentina</td>
<td>Root</td>
<td>Aqueous</td>
<td>$10 \mu g/mL$ incubation</td>
<td>42 hours</td>
<td><em>In vitro, Human</em></td>
<td>IFN-$\gamma$</td>
<td>(Jin et al., 2002)(^{43})</td>
</tr>
<tr>
<td>Schisandra chinensis</td>
<td>Fruit</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
<tr>
<td>Sinomenium acutum</td>
<td>Stem</td>
<td>Aqueous</td>
<td>$0.1 \mu g/mL$ incubation</td>
<td>1 hour</td>
<td><em>In vitro, Murine</em></td>
<td>TNF</td>
<td>(Kim et al, 1999)(^{44})</td>
</tr>
<tr>
<td>Smilax glabra</td>
<td>Rhizome</td>
<td>Aqueous</td>
<td>400 mg/kg QD PO</td>
<td>14 days</td>
<td><em>Ex vivo, Murine</em></td>
<td>IL-1, -2 TNF</td>
<td>(Jiang and Xu, 2003)(^{37})</td>
</tr>
<tr>
<td>Typhonium sp.</td>
<td>Rhizome</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>24 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Shan et al, 1999)(^{39})</td>
</tr>
</tbody>
</table>
Table 2B. *In vitro* (human cell) Effects of Ethanolic Botanical Extracts on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Curcuma longa</em></td>
<td>Rhizome</td>
<td>Acetone or Ethanol, % unspecified</td>
<td>1.8 µg/mL incubation</td>
<td>4 hours</td>
<td><em>In vitro, Human</em></td>
<td>TNF</td>
<td>(Chan, 1995)⁴⁵</td>
</tr>
<tr>
<td><em>Curcuma longa</em></td>
<td>Rhizome</td>
<td>Acetone or Ethanol, % unspecified</td>
<td>1.8 µg/mL incubation</td>
<td>18 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1</td>
<td>(Chan, 1995)⁴⁵</td>
</tr>
<tr>
<td><em>Harpagophytum procumbens</em></td>
<td>Root</td>
<td>60% Ethanol</td>
<td>&gt;100 µg/mL incubation</td>
<td>0.5 hour</td>
<td><em>In vitro, Human</em></td>
<td>IL-1β, -6</td>
<td>(Fiebich et al, 2001)⁴⁶</td>
</tr>
<tr>
<td><em>Harpagophytum procumbens</em></td>
<td>Root</td>
<td>60% Ethanol</td>
<td>100 µg/mL incubation</td>
<td>0.5 hour</td>
<td><em>In vitro, Human</em></td>
<td>TNF</td>
<td>(Fiebich et al, 2001)⁴⁶</td>
</tr>
<tr>
<td><em>Sparassis crispa</em></td>
<td>Fruit</td>
<td>Defatted by Ethanol, Aqueous</td>
<td>100 µg/mL incubation</td>
<td>48 hours</td>
<td><em>In vitro, Murine</em></td>
<td>IL-6</td>
<td>(Harada et al, 2002)⁴⁷</td>
</tr>
<tr>
<td><em>Tripterygium wilfordii</em></td>
<td>Bark</td>
<td>50% Hot Ethanol</td>
<td>0.6 µg/mL incubation</td>
<td>48 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-2</td>
<td>(Chou and Chang, 1998)⁴⁸</td>
</tr>
<tr>
<td><em>Zingiber officinale</em></td>
<td>Rhizome</td>
<td>50% Ethanol</td>
<td>2x10⁴ µg/mL incubation</td>
<td>18 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-1β, GM-CSF*</td>
<td>(Chang et al, 1995)⁴⁹</td>
</tr>
<tr>
<td><em>Zingiber officinale</em></td>
<td>Rhizome</td>
<td>50% Ethanol</td>
<td>1x10⁴ µg/mL incubation</td>
<td>18 hours</td>
<td><em>In vitro, Human</em></td>
<td>IL-6</td>
<td>(Chang et al, 1995)⁴⁹</td>
</tr>
</tbody>
</table>

* granulocyte/macrophage-colony stimulating factor
### Table 2C. *In vitro* (human cell) Effects of Other Botanical Extracts on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acalypha wilkesiana</em></td>
<td>Seed</td>
<td>6.8% Ethanol, 5.9% Water, 42.5% Hexane</td>
<td>10 µg/mL incubation</td>
<td>2 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-5, -6, IFN-γ, TNF</td>
<td>(Bussing et al, 1999)</td>
</tr>
<tr>
<td><em>Allium sativum</em></td>
<td>Bulb</td>
<td>Crushed extract</td>
<td>≥0.1 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-12</td>
<td>(Hodge et al, 2002)</td>
</tr>
<tr>
<td><em>Allium sativum</em></td>
<td>Bulb</td>
<td>Crushed extract</td>
<td>≥104 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1α, -2, -6, -8, -10, IFN-γ, TNF</td>
<td>(Hodge et al, 2002)</td>
</tr>
<tr>
<td><em>Ampelopsis brevipedunculata</em></td>
<td>Unspecified</td>
<td>Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>3 days</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1β TNF</td>
<td>(Kuo et al, 1999)</td>
</tr>
<tr>
<td><em>Curcuma longa</em></td>
<td>Rhizome</td>
<td>Curcumin in DMSO 0.1%</td>
<td>18 µg/mL incubation</td>
<td>2 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-8</td>
<td>(Hidaka et al, 2002)</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Rower and Herb</td>
<td>Dried or fresh juice in 20% ethanol</td>
<td>0.012 µg/mL incubation</td>
<td>18 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1</td>
<td>(Burger et al, 1997)</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Rower and Herb</td>
<td>Dried or fresh juice in 20% ethanol</td>
<td>0.012 µg/mL incubation</td>
<td>72 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-6</td>
<td>(Burger et al, 1997)</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Rower and Herb</td>
<td>Dried or fresh juice in 20% ethanol</td>
<td>0.025 µg/mL incubation</td>
<td>36 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-10</td>
<td>(Burger et al, 1997)</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Rower and Herb</td>
<td>Fresh juice in 20% ethanol</td>
<td>0.012 µg/mL incubation</td>
<td>36 hours</td>
<td><em>In vitro</em>, Human</td>
<td>TNF</td>
<td>(Burger et al, 1997)</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Rower and Herb</td>
<td>Dried juice in 20% ethanol</td>
<td>0.025 µg/mL incubation</td>
<td>36 hours</td>
<td><em>In vitro</em>, Human</td>
<td>TNF</td>
<td>(Burger et al, 1997)</td>
</tr>
<tr>
<td><em>Ludwigia octovalvis</em></td>
<td>Unspecified</td>
<td>Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>3 days</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1β TNF</td>
<td>(Kuo et al, 1999)</td>
</tr>
<tr>
<td><em>Rhus semialata</em></td>
<td>Unspecified</td>
<td>Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>48 hours</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1β TNF</td>
<td>(Kuo et al, 1999)</td>
</tr>
<tr>
<td><em>Tabernaemontana divaricata</em></td>
<td>Unspecified</td>
<td>Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>3 days</td>
<td><em>In vitro</em>, Human</td>
<td>IL-1β TNF</td>
<td>(Kuo et al, 1999)</td>
</tr>
</tbody>
</table>
Tables 3A-C, similar to Tables 2A-C, list the in vitro results utilizing animal cells, categorized by solvents used for the medicinal plant extractions (A, aqueous; B, ethanolic; and C, other extractions). Table 4 illustrates the

<table>
<thead>
<tr>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Model</th>
<th>Duration of Exposure</th>
<th>Dose</th>
<th>Genus species</th>
<th>Part</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seed</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>0.5 hour</td>
<td>10^3 µg/mL</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Yi et al, 2002)</td>
</tr>
<tr>
<td>Flower</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>260 µg/mL</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Fujiki et al, 2003)</td>
</tr>
<tr>
<td>Rhizome</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>2 weeks</td>
<td>560x10^3 µg/kg</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Haranaka et al, 1985)</td>
</tr>
<tr>
<td>Root</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>20 hours</td>
<td>500 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Kim et al, 2000)</td>
</tr>
<tr>
<td>Whole plant</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>24 hours</td>
<td>100 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Chung et al, 2002)</td>
</tr>
<tr>
<td>Root</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>20 hours</td>
<td>100 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Root</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>18 hours</td>
<td>1 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>IL-1</td>
<td>(Kim et al, 1998)</td>
</tr>
<tr>
<td>Root</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>16 hours</td>
<td>100 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Kim et al, 1998)</td>
</tr>
<tr>
<td>Root</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>14 days</td>
<td>0.1 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Root</td>
<td>TNF</td>
<td>(Kim et al, 2000)</td>
</tr>
<tr>
<td>Fruit</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>400 mg/kg PO</td>
<td>Acanthopanax senticosus</td>
<td>Stem</td>
<td>IL-1</td>
<td>(Jiang and Xu, 2003)</td>
</tr>
<tr>
<td>Stem</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>14.1x10^3 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Stem</td>
<td>TNF</td>
<td>(Sandoval et al, 2002)</td>
</tr>
<tr>
<td>Stem</td>
<td>Aqueous</td>
<td>Ex vivo, Murine</td>
<td>1 hour</td>
<td>9.5x10^3 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Stem</td>
<td>TNF</td>
<td>(Sandoval et al, 2002)</td>
</tr>
<tr>
<td>Bark</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>19 hours</td>
<td>1x10^3 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Bark</td>
<td>TNF</td>
<td>(Sandoval et al, 2002)</td>
</tr>
<tr>
<td>Bark</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>24 hours</td>
<td>100 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Bark</td>
<td>TNF</td>
<td>(Sandoval et al, 2002)</td>
</tr>
<tr>
<td>Bark</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>2 hours</td>
<td>14x10^3 µg/mL incubation</td>
<td>Acanthopanax senticosus</td>
<td>Bark</td>
<td>TNF</td>
<td>(Sandoval et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>555 µg/mL PO</td>
<td>Polygala tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>100 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>0.1 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>14 days</td>
<td>400 mg/kg PO</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>9.5x10^3 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>1x10^3 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>19 hours</td>
<td>100 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>24 hours</td>
<td>14x10^3 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>2 hours</td>
<td>14x10^3 µg/mL incubation</td>
<td>Polygala tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>555 µg/mL PO</td>
<td>Uncaria tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>100 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>0.1 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Root</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>14 days</td>
<td>400 mg/kg PO</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>9.5x10^3 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>1x10^3 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>19 hours</td>
<td>100 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>24 hours</td>
<td>14x10^3 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>2 hours</td>
<td>14x10^3 µg/mL incubation</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
<tr>
<td>Plant part</td>
<td>Aqueous</td>
<td>In vitro, Murine</td>
<td>1 hour</td>
<td>555 µg/mL PO</td>
<td>Uncaria tomentosa</td>
<td>Stem</td>
<td>TNF</td>
<td>(Assis et al, 2002)</td>
</tr>
</tbody>
</table>
research conducted on medicinal mushrooms. Tables 5A-E are categorized by cytokine, matching the cytokine and the direction of effect (upregulation or downregulation) exerted by the particular plant.

A large volume of research was disregarded due to the inclusion criteria. Much of the rejected research was based on isolated constituents. Some research on semi-purified compounds, such as curcumin or bromelain, was included due to their frequent use and availability in commerce.

**Discussion**

The majority of the research presented in this review relies on *in vitro* and/or animal models; the authors acknowledge the inadequacies of information derived from such research. Both *in vitro* and animal models may be misleading and often prove to be poor representations of human physiology. The lack of pharmacokinetics in an *in vitro* model brings up questions of the relevance of data gathered from such methodology. In addition, animal models often are misrepresentative of human physiology. Nevertheless, data drawn from such sources, coupled with empirical data from traditional uses of botanical medicines, may provide an insight, however limited, to the mode of activity for many of these herbs. *In vivo* and *in vitro* studies for the listed herbs do suggest that the immunomodulating effects of the botanical medicines reviewed may be due, at least in part, to cytokine modulation. Furthermore, given the broad-spectrum effect of cytokines on cell-to-cell communication, it seems likely some of the other organ systems and tissue effects of these herbal immunomodulators are due to modulation of cytokine expression.

**Astragalus membranaceus**

The root of *Astragalus membranaceus* is traditionally used in Chinese medicine as a “spleen tonic” and for various deficiency and wasting conditions. A. membranaceus, in an *in vitro* human model, has been shown to lower IL-6. IL-6 is implicated in a number of inflammatory disorders and as a global marker of impending deterioration. The decrease of IL-6 activity provides a possible rationale for thousands of years of use of this plant in deficiency and wasting diseases. In addition, Astragalus is also indicated in shortness of breath and edema.
Table 3C. *In vitro* (animal cell) Effects of Other Botanical Extracts on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ananas comosus</em></td>
<td>Stem</td>
<td>Bromelain</td>
<td>50 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>TNF</td>
<td>(Engwerda et al, 2001)<em>66</em></td>
</tr>
<tr>
<td><em>Ananas comosus</em></td>
<td>Stem</td>
<td>Bromelain</td>
<td>50 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IFN-γ</td>
<td>(Engwerda et al, 2001)<em>66</em></td>
</tr>
<tr>
<td><em>Anonas comosus</em></td>
<td>Stem</td>
<td>Bromelain</td>
<td>80 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IL-1α, IL-1β</td>
<td>(Rininger et al, 2000)<em>67</em></td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Unspecified</td>
<td>Simulated digestion</td>
<td>320 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IL-6</td>
<td>(Rininger et al, 2000)<em>67</em></td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Unspecified</td>
<td>Simulated digestion</td>
<td>320 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>TNF</td>
<td>(Rininger et al, 2000)<em>67</em></td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Unspecified</td>
<td>Simulated digestion</td>
<td>320 µg/mL incubation</td>
<td>1 hour</td>
<td><em>In vitro</em>, Bovine</td>
<td>IL-8</td>
<td>(Oh et al, 2001)<em>68</em></td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Unspecified</td>
<td>Simulated digestion</td>
<td>5 µg/mL incubation</td>
<td>6 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IL-1α, IL-1β</td>
<td>(Choi et al, 2001)<em>69</em></td>
</tr>
<tr>
<td><em>Paeonia suffruticosa</em></td>
<td>Bark</td>
<td>Simulated digestion</td>
<td>50 µg/mL incubation</td>
<td>24 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IL-8</td>
<td>(Kim et al, 2001)<em>70</em></td>
</tr>
<tr>
<td><em>Pinus maritima</em></td>
<td>Root</td>
<td>70% Methanol</td>
<td>10 µg/mL incubation</td>
<td>60 hours</td>
<td><em>In vitro</em>, Murine</td>
<td>IL-1α, -10, IFN-γ</td>
<td>(Waserussmeier et al, 2002)<em>71</em></td>
</tr>
<tr>
<td><em>Scutellaria baicalensis</em></td>
<td>Seed and Fruit</td>
<td>Methanol, then Hexane</td>
<td>25 or 250 µg/mL</td>
<td>6 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IL-4, TNF</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>Seed and Fruit</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-1β, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>Seed</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Terminalia chebula</em></td>
<td>Seed</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Tylophora asthmatica</em></td>
<td>Fruit</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Vatica parviflora</em></td>
<td>Leaf</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
<tr>
<td><em>Vatica parviflora</em></td>
<td>Leaf</td>
<td>Methanol</td>
<td>1.0 mg/mL incubation</td>
<td>5 days</td>
<td><em>In vivo</em>, Murine</td>
<td>IL-2, IFN-γ</td>
<td>(Johnson et al, 2003)<em>75</em></td>
</tr>
</tbody>
</table>

Symptoms that could be suggestive of cardiovascular effects. Notably, increased levels of IL-6 and C-reactive protein are associated with a significant increase in cardiovascular-related death.\(^5,11\) Thus, a possible mechanism for the cardiovascular effects of *A. membranaceus* could be due to its reduction of IL-6.
Table 4. The Effect of Medicinal Mushrooms on Cytokine Expression

<table>
<thead>
<tr>
<th>Genus species</th>
<th>Plant Part</th>
<th>Preparation Used</th>
<th>Dose</th>
<th>Duration of Exposure</th>
<th>Model</th>
<th>Cytokines Affected</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordyceps cicadae</td>
<td>Fruiting body</td>
<td>50% Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-2, IFN-γ</td>
<td>(Weng et al, 2002)</td>
</tr>
<tr>
<td></td>
<td>Larvae</td>
<td>50% Methanol, then DMSO</td>
<td>100 µg/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-2, IFN-γ</td>
<td>(Weng et al, 2002)</td>
</tr>
<tr>
<td>Coriolus versicolor</td>
<td>Mycelia</td>
<td>70% Ethanol</td>
<td>5 µL/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-1β</td>
<td>(Hsieh et al, 2002)</td>
</tr>
<tr>
<td>Coriolus versicolor</td>
<td>Mycelia</td>
<td>70% Ethanol</td>
<td>3 µL/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-6</td>
<td>(Hsieh et al, 2002)</td>
</tr>
<tr>
<td>Coriolus versicolor</td>
<td>Mycelia</td>
<td>Aqueous</td>
<td>5 µL/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-1β, -8</td>
<td>(Hsieh et al, 2002)</td>
</tr>
<tr>
<td>Coriolus versicolor</td>
<td>Mycelia</td>
<td>Aqueous</td>
<td>3 µL/mL incubation</td>
<td>3 days</td>
<td>In vitro, Human</td>
<td>IL-6</td>
<td>(Hsieh et al, 2002)</td>
</tr>
<tr>
<td>Ganoderma lucidum</td>
<td>Fruiting body</td>
<td>Aqueous, Ethanolic precipitation</td>
<td>12.8 µg/mL incubation</td>
<td>48 hours</td>
<td>In vitro, Murine</td>
<td>IL-12</td>
<td>(Cao and Lin, 2002)</td>
</tr>
<tr>
<td>Grifola frondosa</td>
<td>Fruiting body</td>
<td>Ethanol</td>
<td>1x10³ µg/mL incubation</td>
<td>18 hours</td>
<td>In vitro, Murine</td>
<td>IL-12</td>
<td>(Kodama et al, 2002)</td>
</tr>
<tr>
<td>Grifola frondosa</td>
<td>Fruiting body</td>
<td>Ethanol</td>
<td>5x10³ µg/kg body wt</td>
<td>14 days</td>
<td>In vivo, Murine</td>
<td>TNF, IFN-γ</td>
<td>(Kodama et al, 2002)</td>
</tr>
<tr>
<td>Poria cocos</td>
<td>Sclerotium</td>
<td>50% Hot Ethanol</td>
<td>800 µg/mL incubation</td>
<td>6 or 24 hours</td>
<td>In vitro, Human</td>
<td>IL-1β</td>
<td>(Yu and Tseng, 1996)</td>
</tr>
<tr>
<td>Poria cocos</td>
<td>Sclerotium</td>
<td>50% Hot Ethanol</td>
<td>400 µg/mL incubation</td>
<td>6 or 24 hours</td>
<td>In vitro, Human</td>
<td>IL-6</td>
<td>(Yu and Tseng, 1996)</td>
</tr>
<tr>
<td>Poria cocos</td>
<td>Sclerotium</td>
<td>50% Hot Ethanol</td>
<td>400 µg/mL incubation</td>
<td>3, 6 or 12 hours</td>
<td>In vitro, Human</td>
<td>TNF</td>
<td>(Yu and Tseng, 1996)</td>
</tr>
<tr>
<td>Poria cocos</td>
<td>Sclerotium</td>
<td>50% Hot Ethanol</td>
<td>200 µg/mL incubation</td>
<td>3, 6 or 24 hours</td>
<td>In vitro, Human</td>
<td>TGF-β</td>
<td>(Yu and Tseng, 1996)</td>
</tr>
</tbody>
</table>
Table 5A. Botanical Influences on IL-1

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Plant</th>
<th>Model</th>
<th>Direction of Effect</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Acanthopanax gracilistylus</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
</tr>
<tr>
<td></td>
<td>Astragalus membranaceus</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
</tr>
<tr>
<td></td>
<td>Cinnamomum cassia</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
</tr>
<tr>
<td></td>
<td>Codonopsis pilosula</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
</tr>
<tr>
<td></td>
<td>Curcuma longa</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
</tr>
<tr>
<td></td>
<td>Echinacea purpurea</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Chen, 1995)45</td>
</tr>
<tr>
<td></td>
<td>Epimedium brevicornum</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Burger et al, 1997)54</td>
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<td>Increase</td>
<td>(Shan et al, 1999)39</td>
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<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)39</td>
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<td>Decrease</td>
<td>(Shan et al, 1999)39</td>
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<td>Increase</td>
<td>(Jiang and Xu, 2003)37</td>
</tr>
<tr>
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<td>Tylophora asthmatica</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Ganguly et al, 2001)73</td>
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<td>Decrease</td>
<td>(Shan et al, 1999)39</td>
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<td>Decrease</td>
<td>(Lemaire et al, 1999)63</td>
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<td>IL-1α</td>
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<td>In vitro, Human</td>
<td>Increase</td>
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<td>Allium sativum</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Hodge et al, 2002)51</td>
</tr>
<tr>
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<td>Echinacea purpurea</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Rininger et al, 2000)67</td>
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<td></td>
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<td>(Dhuley, 1997)30</td>
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<td>Increase</td>
<td>(Dhuley, 1997)30</td>
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<td></td>
<td>Withania somnifera</td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Dhuley, 1997)30</td>
</tr>
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<td>IL-1β</td>
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<td>(Kuo et al, 1999)52</td>
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<td>Coriolus versicolor</td>
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<td>Increase</td>
<td>(Hsieh et al, 2002)75</td>
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<td>Harpagophytum procumbens</td>
<td>In vitro, Human</td>
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<td>(Fiebich et al, 2001)46</td>
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<td>Ludwigia octovalvis</td>
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<td>Decrease</td>
<td>(Kuo et al, 1999)52</td>
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<td>Decrease</td>
<td>(Cho et al, 2001)69</td>
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<td></td>
<td>Poria cocos</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Yu and Tseng, 1996)78</td>
</tr>
<tr>
<td></td>
<td>Rhus semialata</td>
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<td>Decrease</td>
<td>(Kuo et al, 1999)52</td>
</tr>
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<td></td>
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<td>(Johnson et al, 2003)35</td>
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<td>(Kuo et al, 1999)52</td>
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<td>Zingiber officinale</td>
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<td>Decrease</td>
<td>(Chang et al, 1995)49</td>
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### Table 5B. Botanical Influences on IL-2, -4, and -5

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<th>Model</th>
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<td><em>Cordyceps cicadae</em> (Fruit body)</td>
<td>In vitro, Human</td>
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<td>(Weng et al, 2002)⁷⁴</td>
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<tr>
<td></td>
<td><em>Cordyceps cicadae</em></td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Weng et al, 2002)⁷⁴</td>
</tr>
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<td></td>
<td><em>Derris scandens</em></td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Sriwanthana and Chavalitumrong, 2001)⁴²</td>
</tr>
<tr>
<td></td>
<td><em>Pinus maritima</em></td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Cho et al, 2001)⁶⁹</td>
</tr>
<tr>
<td></td>
<td><em>Silybum marianum</em></td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Johnson et al, 2003)³⁵</td>
</tr>
<tr>
<td></td>
<td><em>Silybum marianum</em></td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Johnson et al, 2002)³⁶</td>
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<td></td>
<td><em>Smilax glabra</em></td>
<td>Ex vivo, Murine</td>
<td>Decrease</td>
<td>(Jiang and Xu, 2003)³⁷</td>
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<td></td>
<td><em>Tripterium wilfordii</em></td>
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<td>Increase</td>
<td>(Chou and Chang, 1998)⁴⁸</td>
</tr>
<tr>
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<td><em>Tylophora asthmatica</em></td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Ganguly et al, 2001)⁷³</td>
</tr>
<tr>
<td></td>
<td><em>Tylophora asthmatica</em></td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Ganguly et al, 2001)⁷³</td>
</tr>
<tr>
<td></td>
<td><em>Withania somnifera</em></td>
<td>In vitro, Murine</td>
<td>Increase</td>
<td>(Davis and Kuttan, 1999)³⁸</td>
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<td>IL-4</td>
<td><em>Cissampelos sympodialis</em></td>
<td>In vitro, Murine</td>
<td>Increase</td>
<td>(Piuvezam et al, 1999)⁶⁴</td>
</tr>
<tr>
<td></td>
<td><em>Polygala tenuifolia</em></td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Hong et al, 2002)³⁴</td>
</tr>
<tr>
<td></td>
<td><em>Panax ginseng</em></td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Song et al, 2002)³²</td>
</tr>
<tr>
<td></td>
<td><em>Panax ginseng</em></td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Song et al, 2002)³²</td>
</tr>
<tr>
<td></td>
<td><em>Silybum marianum</em></td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Johnson et al, 2003)³⁵</td>
</tr>
<tr>
<td></td>
<td><em>Silybum marianum</em></td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Johnson et al, 2002)³⁶</td>
</tr>
<tr>
<td></td>
<td><em>Silybum marianum</em></td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Wilasrusmee et al, 2002)⁷¹</td>
</tr>
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<td>IL-5</td>
<td><em>Acalypha wilkesiana</em></td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Bussing et al, 1999)⁵⁰</td>
</tr>
</tbody>
</table>

**Allium sativum**

*Allium sativum* (garlic), like many of the plants highlighted in this review, demonstrates effects on multiple cytokines. Garlic lowered IL-6 in an *in vitro* human model.⁵¹ Besides the hypcholesterolemic, antioxidant, and ACE-inhibition activity of garlic,⁸⁰ the effect on IL-6 may offer further insight into garlic’s well-known cardiovascular activity.

In the same model, garlic also lowered the proinflammatory cytokine IL-1. IL-1 has been postulated to be involved in the destruction of pancreatic β-cells⁸⁰ and garlic demonstrates hypoglycemic action and amelioration of alloxan-induced diabetes in murine models.⁵¹ IL-1 inhibition may be partially responsible for this activity.

Because of the potential for garlic to reduce the proinflammatory cytokines IL-1, TNF, and IL-8, and stimulate IL-10 secretion (an antagonist of proinflammatory cytokines), Hodge et al⁵¹ concluded that this effect, along with garlic’s antimicrobial activity, may provide potential mechanisms for garlic’s use in inflammatory bowel disease.⁸⁰ IL-10 demonstrates modulation of the immunopathology of brain inflammatory diseases such as Alzheimer’s disease, providing another potential use for garlic as a cytokine modulator.¹⁶
Table 5C. Botanical Influences on IL-6, -8, -10, and -12

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Plant</th>
<th>Model</th>
<th>Direction of Effect</th>
<th>Author/Date</th>
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<td>Acanthopanax graciifolius</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shan et al, 1999)⁴⁰</td>
</tr>
<tr>
<td></td>
<td>Allium sativum</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Shon et al, 2002)⁴¹</td>
</tr>
<tr>
<td></td>
<td>Aloe secundiflora</td>
<td>In vitro, Murine</td>
<td>Increase</td>
<td>(Iizuka et al, 2000)³¹</td>
</tr>
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<td>Astragalus membranaceus</td>
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<td>Decrease</td>
<td>(Hsieh et al, 2002)⁷⁵</td>
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<td>Coptis spp.</td>
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<td>Decrease</td>
<td>(Hsieh et al, 2002)⁷⁵</td>
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<tr>
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<td>Coriolus versicolor</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Burger et al, 1997)⁵⁴</td>
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<tr>
<td></td>
<td>Coriolus versicolor</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Rininger et al, 2000)⁶⁷</td>
</tr>
<tr>
<td></td>
<td>Echinacea purpurea</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Fiebich et al, 2001)⁴⁶</td>
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<td>Echinacea purpurea</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Yu and Tseng, 1996)⁷⁸</td>
</tr>
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<td>Harpagophytum procumbens</td>
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<td>Increase</td>
<td>(Johnson et al, 2003)³⁵</td>
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<td>(Harada et al, 2002)⁴⁷</td>
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<td>Increase</td>
<td>(Lemaire et al, 1999)⁶³</td>
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<td>Increase</td>
<td>(Chang et al, 1995)⁴⁹</td>
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<td>Uncaria tomentosa</td>
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<td>Increase</td>
<td>(Hsieh et al, 2002)⁷⁵</td>
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<td>Zingiber officinale</td>
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<td>Decrease</td>
<td>(Shon et al, 2002)⁴¹</td>
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<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Hsieh et al, 2002)⁷⁵</td>
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<td>Curcuma longa (Curcumin)</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Burger et al, 1997)⁵⁴</td>
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<td>Paeonia suffruticosa</td>
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<td>Decrease</td>
<td>(Johnson et al, 2003)³⁵</td>
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<td>IL-8</td>
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<td>Decrease</td>
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<td>Increase</td>
<td>(Burger et al, 1997)⁵⁴</td>
</tr>
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<td>(Wilasrusmee et al, 2002)⁷¹</td>
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<td>Increase</td>
<td>(Kodama et al, 2002)⁷⁷</td>
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</table>

The Case for Multi-Component Remedies: A Hypothesis

One of the criticisms of botanical medicines is they are “crude drugs” representing a dilute mixture consisting of hundreds of compounds, not concentrated to contain any single active constituent. Laboratory studies clearly elucidate that the overall pharmacological effects and therapeutic efficacies of medicinal plants often do not derive from a single compound, but from several compounds generating synergic activity.⁸²-⁸⁶ A number of researchers have proposed that multi-component pharmacological agents that hit multiple targets impact the complex
Table 5D. Botanical Influences on TNF

<table>
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<th>Model</th>
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<td>Increase</td>
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<td>(Fujiki et al, 2003)⁵⁶</td>
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<td>Decrease</td>
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<td>(Chan, 1995)⁴⁵</td>
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<td>(Burger et al, 1997)⁵⁴</td>
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<td>Increase</td>
<td>(Chung et al, 2002)⁵⁸</td>
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<td>Perilla frutescens</td>
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<td>Picrorhiza kurroa</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Dhuley, 1997)³⁰</td>
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<td>(Hong et al, 2002)³⁴</td>
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<td>Decrease</td>
<td>(Kim et al, 1998)⁶⁰</td>
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<td>Poria cocos</td>
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<td>Increase</td>
<td>(Yu and Tseng, 1996)⁷⁸</td>
</tr>
<tr>
<td></td>
<td>Rauwolfia serpentina</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Jin et al, 2002)⁴³</td>
</tr>
<tr>
<td></td>
<td>Rhus semialata</td>
<td>In vitro, Human</td>
<td>Decrease</td>
<td>(Kuo et al, 1999)⁵²</td>
</tr>
<tr>
<td></td>
<td>Rosa davurica</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Kim et al, 1999)⁴⁴</td>
</tr>
<tr>
<td></td>
<td>Scutellaria baicalensis</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Kim et al, 2001)⁷⁰</td>
</tr>
<tr>
<td></td>
<td>Silybum marianum</td>
<td>In vitro, Murine</td>
<td>Increase</td>
<td>(Johnson et al, 2003)³⁵</td>
</tr>
<tr>
<td></td>
<td>Silybum marianum</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Wilasrusmee et al, 2002)⁷¹</td>
</tr>
<tr>
<td></td>
<td>Sinomenium acutum</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Kim et al, 1999)⁴⁴</td>
</tr>
<tr>
<td></td>
<td>Smilax glabra</td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Jiang and Xu, 2003)³⁷</td>
</tr>
<tr>
<td></td>
<td>Tabernaemontana divaricata</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Kuo et al, 1999)⁵²</td>
</tr>
<tr>
<td></td>
<td>Terminalia chebula</td>
<td>In vitro, Human</td>
<td>Increase</td>
<td>(Shin et al, 2001)⁷²</td>
</tr>
<tr>
<td></td>
<td>Tinospora cordifolia</td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Dhuley, 1997)³⁰</td>
</tr>
<tr>
<td></td>
<td>Uncaria tomentosa</td>
<td>In vitro, Murine</td>
<td>Decrease</td>
<td>(Sandoval et al, 2002)⁶²</td>
</tr>
<tr>
<td></td>
<td>Withania somnifera</td>
<td>In vivo, Murine</td>
<td>Increase</td>
<td>(Dhuley, 1997)³⁰</td>
</tr>
<tr>
<td></td>
<td>Withania somnifera</td>
<td>In vivo, Murine</td>
<td>Decrease</td>
<td>(Davis and Kuttan, 1999)³⁸</td>
</tr>
</tbody>
</table>
### Table 5E. Botanical Influences on TGF-β, IFN-γ, and GM-CSF

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Plant</th>
<th>Model</th>
<th>Direction of Effect</th>
<th>Author/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β</td>
<td><em>Poria cocos</em></td>
<td><em>In vitro, Human</em></td>
<td>Decrease</td>
<td>(Yu and Tseng, 1996)78</td>
</tr>
</tbody>
</table>
| IFN-γ    | *Acalypha wilkesiana*  
*Annanus comosus* (Bromelain)  
*Cordyceps cicada* (Fruit Body)  
*Cordyceps cicada* (Larvae)  
*Emblica officinalis*  
*Grifola frondosa*  
*Panax ginseng*  
*Polygala tenuifolia*  
*Rauwolfia serpentina*  
*Withania somnifera* | *In vitro, Human*  
*In vitro, Human*  
*In vitro, Murine*  
*In vitro, Human*  
*In vitro, Human*  
*In vitro, Murine*  
*In vitro, Murine*  
*In vitro, Murine*  
*In vitro, Murine* | Increase  
Increase  
Decrease  
Decrease  
Increase  
Increase  
Decrease  
Decrease  | (Bussing et al, 1999)50  
(Shan et al, 1999)40  
(Hodge et al, 2002)51  
(Engwerda et al, 2001)66  
(Pluvezam et al, 1999)64  
(Weng et al, 2002)74  
(Weng et al, 2002)74  
(Sai Ram et al, 2003)65  
(Kodama et al, 2002)77  
(Song et al, 2002)62  
(Hong et al, 2002)34  
(Jin et al, 2002)43  
(Davis and Kuttan, 1999)38 |
| GM-CSF*  | *Zingiber officinalis* | *In vitro, Human* | Increase | (Chang, 1995)49 |

* granulocyte/macrophage-colony stimulating factor

Substantial historical, empirical, and scientific evidence demonstrates that whole plants, not just isolated constituents, have immunomodulating activity. Combinations of phytochemicals and cytokines may also provide a novel approach to clinical medicine. Engwerda et al. demonstrated the potential for combination therapy using bromelain, a mixture of cysteine proteases from the stems of pineapple plants. In this model, bromelain alone showed limited activity on cytokine secretions. However, if combined with cytokines, a synergic effect was observed. Bromelain with IFN-γ significantly enhanced TNF production beyond the effect of IFN-γ alone. In addition, when bromelain was combined with IL-12, a significant increase of IFN-γ was demonstrated compared to that of only IL-12. Since such responses could enhance acquired immune responses in addition to innate immune responses, critical for first-line defense against many infectious agents, such combinations are likely important. For example, combination therapies could act as vaccine adjuvants, enhancing their efficacy.

Equilibrium of whole cellular networks more favorably than drugs that act on a single target. Keith and Zimmerman suggest many genes might need complementary action to modify disease processes. In other words, efficacious therapy might depend on perturbing more than one target. In addition, multitarget agents need affect their targets only partially, which corresponds well with the presumed low-affinity, substrate/enzyme interactions of medicinal plants. The partial “perturbations” of medicinal plants on a pharmacological network may accurately mimic physiological scenarios where hundreds of different enzyme systems and receptor types and subtypes are triggered simultaneously. This is compared to the complete elimination of a single network node (enzyme or receptor system), which is a rather unusual phenomenon not typically found in a physiological scenario. Clinicians have historically overcome such single target insufficiency by using combination drug therapy; for example, therapeutic application of drug cocktails are increasingly utilized in AIDS, cancer, and resistant infections.
The combination of medicinal plants with one another or other pharmacological agents fits well into a phytotherapeutic paradigm. Commonly, many of these constituents have additive or synergic activity, while a class of constituents or a single constituent may potentiate a single pharmacologically active molecule.83,98

Csermely89 suggests that a pharmacological strategy directed toward multiple targets could result in more efficient therapeutic outcomes. Broader specificity, lower affinity, multi-component compounds, as found in botanical medicines, can be more efficient than high affinity, high specificity compounds.87 Moreover, the use of whole plants, instead of isolated chemicals, may offer a safer clinical strategy in the treatment of many diseases.85,99 Network models of pharmacology, which view human physiology as a complex web of molecular interactions, strongly imply that herbal remedies serve clinical therapy efficaciously, efficiently, and safely.

Equally, this web-like nature is reflected in the immune system by the concerted signaling of cytokines. Cytokines operate both as a cascade and as a network, regulating the production of other cytokines and cytokine receptors, while stimulating the production of acute-phase proteins.100 Endogenous levels of cytokines are in the nanomolar to picomolar range, suggesting that dilute mixtures of biologically active compounds may provide therapeutic benefit. Illustrating the therapeutic potential for dilute mixtures of biologically active compounds, a group of researchers found subclinical doses of oral IFN-α can provide powerful, broad-spectrum benefits.1

In another study, when cytokine levels were compared to symptoms in individuals with cardiovascular disease, Testa et al101 demonstrated that circulating levels of cytokines increased with severity of symptoms. Considering the variety of adverse events listed for recombinant cytokine therapies, perhaps subtle perturbations of the cytokine network should be considered. The dilute nature of botanical immunomodulators may offer a reasonable strategy for subtle induction of a variety of cytokines.

Most likely, cells are seldom exposed to only a single cytokine. Rather, combinations of cytokines and other messenger molecules generate biologically relevant informational cues.102 This is demonstrated by the synergic antitumor effects observed from combining IL-12 gene therapy with other cytokines, chemokines, or co-stimulatory molecules.22 The effects of cytokines on their target cells and tissues may be inhibited or enhanced by other cytokines, hormones, and cytokine-receptor antagonists and circulating receptors. Just as pharmacological activity by specific plant constituents is suggested to be affected by combinations of constituents,83,98,102 combinations of cytokines have been found to have additive, inhibitory, or synergic effects.100 Further research may find that the herbal immunomodulators affecting multiple cytokines can each generate a unique signature of immune perturbation dependent on the concerted effect on arrays of cytokines.

**Biphasic Effects**

Both exogenous and endogenous compounds can have opposing, dose-dependent biological effects. For example, Calabrese and Baldwin discuss biphasic aortic smooth muscle response to an adrenergic agonist; low doses of isoproterenol bind β-adrenergic receptors, inducing relaxation of aortic smooth muscle. However, at higher doses, where the β-receptors are saturated and the α-receptors are also bound, isoproterenol induces aortic constriction.103 Similarly, Sapolsky104 discusses the effects of glucocorticoids (GCs) on performance of hippocampal-dependent memory, suggesting low-to-moderate levels of endogenous GCs, saturating mineralocorticoid receptors (and some GC receptors), could enhance this process, while higher doses of GCs impair memory.

This biphasic effect can be noted in Table 5D. For example, *Withania somnifera* (ashwagandha) has been found to influence the expression of TNF. Dhuley et al30 found *W. somnifera* increased TNF expression, while Davis and Khutan38 showed it decreased TNF.

The models used in these two laboratory investigations are disparate. Dhuley30 used the carcinogen ochratoxin A (OTA) against murine macrophages to suppress chemotactic activity induced by IL-1 and TNF. Ashwagandha, at an oral dose of 100 mg/kg daily, countered the immunosuppressive effects of OTA, raising TNF expression and theoretically restoring chemotactic activity.
In contrast, Davis and Khutan, using a dose of 20 mg/animal daily by IP injection, found TNF was lowered in the W. somnifera group without an inducer. Although the two models are unrelated by dose, duration of exposure, and method of administration, the question still arises as to the paradoxical effects on TNF secretion. The inconsistency in the TNF results could lie in the utilization of divergent models, although these authors suggest the possibility of a biphasic dose response.

TNF is believed to be a key factor in cancer anorexia-cachexia syndrome. Ashwagandha has a history of thousands of years of use in the treatment of wasting syndromes and general debility, and is often currently used clinically as an adjuvant to cancer treatments.

Known as anthrapachaka in the Ayurvedic system, Tylophora asthmatica is traditionally used in the treatment of asthma, allergies, and autoimmune disorders. Tylophora demonstrates a biphasic effect on IL-2 secretion. Ganguly et al demonstrated this effect in an in vitro model. Using the same model throughout their investigations, a lower dose of T. asthmatica increased IL-2 levels, while more than a thousand-fold increase in dose reduced IL-2 levels, demonstrating a paradoxical response to the same exogenous stimulus.

**Conclusion**

Although many of the plants listed in this review appear to affect only a few cytokines, it is the lead author’s opinion that future research will further demonstrate the broad-spectrum activity of herbal medicine. Currently, the research on the influence of botanical medicines on cytokines and other messenger molecules is limited. Informational molecules and many of their receptors may likely turn out to be modulated by plants, both herbal medicines and foods, providing potential for future therapeutics.

Despite the fact that the majority of research in this review was performed with in vitro or animal models, there is substantial historical, empirical, and scientific evidence that whole plants, not just isolated constituents, have immunomodulating activity. The in vitro and in vivo research suggests that the reviewed botanical medicines modulate cytokines, and that such modulation may provide the mechanism of action for many of their therapeutic effects. Further research (particularly clinical studies) is indicated to elucidate the effects of botanical medicines and to support or refute the hypotheses presented in this article.

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