Botanical Medicine and Medicinal Mushroom Therapies for Colds and Flu: Optimizing the Immune Response to Prevent and Treat Respiratory Infections

Cynthia A. Wenner, PhD
Anna Sitkoff, ND 2020

Primary research on PSK was funded by Grant No. 5 U19-AT001998 from the National Center for Complementary and Integrative Health (NCCIH), NIH, USA. The authors are solely responsible for the contents, which do not necessarily represent the official views of the NCCIH, or the NIH.
Elements required for an optimal anti-viral immune response against respiratory viruses

Adapted from Ruckwardt et al. Curr Opin Virol, 2016; 16:151–157

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td><em>Toll-like</em> receptor</td>
</tr>
<tr>
<td>FDC</td>
<td>Follicular dendritic cell</td>
</tr>
<tr>
<td>DC</td>
<td>Dendritic cell</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic T cell</td>
</tr>
</tbody>
</table>

Optimal antigens + TLR agonists + non-TLR agonists

**Table:**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TLR</strong></td>
<td><em>Toll-like</em> receptor</td>
</tr>
<tr>
<td><strong>FDC</strong></td>
<td>Follicular dendritic cell</td>
</tr>
<tr>
<td><strong>DC</strong></td>
<td>Dendritic cell</td>
</tr>
<tr>
<td><strong>CTL</strong></td>
<td>Cytotoxic T cell</td>
</tr>
<tr>
<td><strong>Ab</strong></td>
<td>Antibody</td>
</tr>
<tr>
<td><strong>Ag</strong></td>
<td>Antigen</td>
</tr>
</tbody>
</table>

**Diagram:**

- FDCs
- DCs
- Maturation, migration
- Ag uptake, processing
- IFN-α
- Innate immune response
- IL-12, IFN-α
- CD11b+
- CD103+
- CD4+
- TH1
- TFH
- IL-21
- IFN-γ
- IFN-α
- Innate immune response
- CD8+ CTL
- Neutralizing Ab
- B cell memory
- Affinity maturation
- CTL response
- Viral clearance
- Ab
Elements involved in weak response to respiratory viruses

Adapted from Lambert et al. Front Imm, 2014; 5:1-14
Botanical & mushroom extracts used in treating respiratory infections

<table>
<thead>
<tr>
<th>Botanical Extracts</th>
<th>Mushroom/fungal Extracts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echinacea spp.</strong></td>
<td><strong>Lentinus edodes</strong> (Shiitake)</td>
</tr>
<tr>
<td><strong>Andrographis paniculata</strong></td>
<td><strong>Agaricus blazeii</strong></td>
</tr>
<tr>
<td><strong>Eleutherococcus senticosus</strong></td>
<td><strong>Pleurotus ostreatus</strong></td>
</tr>
<tr>
<td><strong>Sambucus nigra</strong></td>
<td><strong>Ganoderma lucidum</strong> (Reishi)</td>
</tr>
<tr>
<td><strong>Glycyrrhiza glabra</strong></td>
<td><strong>Cordyceps sinensis</strong></td>
</tr>
<tr>
<td><strong>Allium sativa</strong></td>
<td><strong>Crytoporus volvatus</strong></td>
</tr>
<tr>
<td><strong>Thymus vulgaris</strong></td>
<td><strong>Phellinus igniarius</strong></td>
</tr>
<tr>
<td><strong>Populus spp.</strong></td>
<td><strong>Trametes versicolor</strong></td>
</tr>
<tr>
<td><strong>Lomatium dissectum</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Astragalus membranaceus</strong></td>
<td></td>
</tr>
</tbody>
</table>
Echinacea spp.

Part used: Flowers and Roots
Types of extracts used:
- Ethanol-water extracts with alkylamides: **anti-inflammatory**
- Fresh pressed flower juice high in polysaccharides: **pro-inflammatory**

Indications: URIs including colds & viral influenza; tonsillitis; strep throat

Distinct Echinacea extracts show varying results in URI trials:
- *E. purpurea* given at first URI: no difference in URI severity and duration in children but URI recurrence significantly decreased vs. placebo.
- *E. pallida* extract reduced the length of URI infection from 13 to 9.8 days for bacterial infection and 13 to 9.1 days for viral infection.
- 60% ethanolic *E. angustifolia* extract given TID (1.5mL tincture with 300g equivalent of root) showed no effect vs. placebo in URI occurrence or severity after forced rhinoviral exposure.
Common Dosing Regimens for Echinacea

For treatment of common colds:

- **Fresh pressed juice:**
  - Children: BID up to 10 days (3.75 mL in 2-5 yr olds, 7.5 mL in 6-11 yr olds)
  - Adults: 5 mL BID up to 10 days
- Alcoholic extract: 20 drops in water every 2 hr on first day of symptoms, then TID up to 10 days
- Whole plant extract: 3-4 mL taken 8-10 times on first day, then 3-4 times daily for up to 6 days

For prevention of common colds:

- Alcoholic extract: 0.9 mL TID up to 4 months; increased to 0.9 ml 5 times daily at first sign of a cold.

For treatment of tonsillitis:

- Throat spray of Echinacea whole plant extract with sage every 2 hr up to 10 times daily for 5 days relieves sore throat due to tonsillitis or pharyngitis
- Echinacea root extract with thuja and wild indigo used TID up to 2wk in combination with antibiotic
Echinacea-derived constituents have distinct immune modulatory properties

• Immune-modulatory activities of Echinacea-derived constituents:
  - *E. purpurea* alkylamides have IL-2 suppressive effects
  - Alkylamide-induced IL-2 suppression decreased by CytP450 metabolism; may suppress alkylamide affinity for CB2 receptors on immune cells.46,5
  - Echinacea-derived alkylamides act as agonists of CB2 receptors58 and PPARγ receptors47 to inhibit cytokine production by immune cells.
  - Endophytic bacterial compounds in Echinacea induce immune modulatory effects at lower concentrations than required for immune modulation by other constituents.44,53

• Different Echinacea treatment conditions influence biological effects:
  - 75% ethanolic *E. purpurea* root extract alone stimulated production of TNF
  - Treatment with same *E. purpurea* extract during LPS stimulation suppressed TNF production.53
*E. purpurea* alkylamides inhibit IL-2 secretion in activated human T cells

*E. Purpurea* ethanolic extract and alkylamide isolates dose-dependently inhibit IL-2 production in activated human Jurkat T cells

IL-2 inhibitory effects not due to ethanolic extract cytotoxicity
IL-2 suppression induced by Echinacea-derived alkylamide is reduced by PPAR-γ antagonist
Andrographis paniculata & Eleutherococcus senticosus

Part used: whole herb
Extracts & adult dose:
  3-6g daily in 3-4 doses for 4-10 days (48-500mg andrographolides)
Children’s dose: 3-6g daily in 3-4 doses for up to 7 days
For prevention of URIs: 200 mg daily for up to 3 months

Indications: URIs including colds & flu, bronchitis, tonsillitis, pharyngitis pneumonia; URI prevention

Common name: Siberian ginseng
Part used: root
Extracts & adult daily dose:
  2-3g crude extract powder
  300-400mg concentrate
For flu: 20-30 mg with standardized Andrographis extract TID for 3-5 days
Children: Insufficient evidence for use under 12; safe in 12-17 yr olds

Standardized to Eleutherosides B & E
Concentrated extract: 10mg =120mg crude
Indications: influenza, swine flu, bronchitis; URI prevention
A. paniculata and E. senticosus for URIs

Evidence of efficacy:

- A. paniculata alone or combined w/ E. senticosus: more effective than placebo for treatment of uncomplicated URI7,16,41,43
- Combination significantly improved common cold symptoms compared to Echinacea or placebo

Mechanisms of action:

- A. paniculata alone is not antibacterial, but acts on immune cells
  - decreases neutrophil migration & inflammatory mediators (e.g., NO)
  - Inhibits NFkB binding to DNA promoters of inflammatory genes
- E. Senticosus alone may be antibacterial, and is antiviral (vs. RNA viruses)
  - Stimulates macrophages, Complement, Ab production, Tcell proliferation
- A. paniculata and E. Senticosus combination:
  - Induce peripheral blood lymphocyte & IFN-γ and TNF production
  - Increase activation markers: neopterin, β-2-microglobulin and IL-2R41
- These actions indicate ↑ in TH1 and ↓ in TH17 responses induced by combination extract
Sambucus nigra

- Part used: Berries
- Extract types: Syrup of elderberry juice, lozenge
- Dosing: within 24-48 hr of symptom onset:
  - Adults: 15 mL QID 3-5 days
  - Children: 15 mL BID for 3 days
- Indications: influenza A & B; H1N1 swine flu; *Streptococcus pyogenes* (*S. pyogenes*) infection

  - Sambucus extracts and constituents inhibit influenza virus and *S. pyogenes*
    - Elderberry extract inhibits several strains of influenza virus *in vitro*.
      - Flavonoids from elderberry extract bind to H1N1 virion and block ability of virus to infect host cells *in vitro*.
    - Elderberry extract dose-dependently inhibits H1N1 virus infection
    - Elderberry extract reduces *S. pyogenes* proliferation upon contact.

  - Increases inflammatory cytokines (IL-1β, TNF, IL-6, IL-8) compared to LPS

  - Suppresses virus replication & induces neutralizing Ab In influenza A infected mice

  - 15 mL QID syrup within 48 hr of onset reduced symptoms & duration of influenza A and B infections in double blind, placebo-controlled RCT.
Glycyrrhiza glabra / uralensis

- Part used: Root
- Extract type: hot water extract
- Dosing: typically used in combination formulas, optimally standardized to 4% glycyrrhizin per European Pharmacopoeia
- Indications: bacterial and viral URIs, sore throat, bronchitis

Has both direct antimicrobial actions and TH1-inducing immunological actions:

- Constituents show antibacterial activity against respiratory bacteria
  - licoricidin and glycocoumarin inhibited *S. pyogenes* and *H. influenzae*
- Active against human RSV in human respiratory tract cell lines
  - prevented viral attachment & internalization, and induced IFN-β secretion
- Glycyrrhizin induced T cell differentiation toward Thelper 1 (TH1) response
  - Glycyrrhizin-treated DCs increased proliferation of allogenic T cells
  - T cells showed increased IFN-β and decreased IL-4 production
Culinary Herbs: *Allium sativa* and *Thymus vulgaris*

- **Common name:** garlic  
  - **Part used:** bulb  
  - Powder or extract standardized to allicin (1-2.5 mg) in 200-400 mg  
  - Indications: colds and flu, bronchitis

- **Bactericidal:** *H. influenza, S. pyogenes*  
  - Allicin (9 mg/kg) immune enhancing:  
    - increases IFN-γ and TNF
  - promotes expansion of mature DCs after oral treatment in mice

- **Common name:** thyme  
  - **Part used:** Aerial parts and volatile oils  
  - Ethanolic extract; steam inhalant  
  - Dosing for URI: 1-2g dry herb in 150mL boiling water steeped 10 min; drink several times daily; 20-40 drops tincture up to TID; also in cough syrup

  - Indications: bronchitis, cough, sore throat; topically for tonsillitis & laryngitis

- **Thymol bactericidal:** *S. pyogenes*, *H. influenza*, *Klebsiella pneumonia*

- **Thymol, carvacrol reduce IL-2, IFN-γ secretion in stimulated Jurkat T cells**
Propolis

- Part used: Conifer & *Populus spp.* bud resin made by bees
- Extract type: powder, ethanolic extract
- Typical dose: 2 x 250mg capsules TID 3 days; also used topically in throat sprays or tinctures
- Indications: Common cold, H1N1 influenza, bacterial URIs

- Hydroethanolic extract bactericidal and antiviral4,9
  - Inhibits *S. pyogenes, H. influenzae*, adenovirus, influenza virus

- Immune-stimulatory effects
  - Caffeic acid ophenethyl ester, cinnamic acids and artemisinin-C activate macrophages *in vitro* and *in vivo*40,6,9,30

- Clinical evidence supporting use in treating URIs:
  - Propolis treatment decreases duration of rhinovirus infection (common cold) by 2.5 times vs. placebo68
  - Propolis combined with Echinacea and vitamin C for 12 wk treatment decreased URI incidence, number and duration of infection in children
Local botanical used in respiratory infections: *Lomatium dissectum*

- Part used: Root
- Aqueous extract, added to steam bath
- Dosing: insufficient data available
- Indications: colds, cough, influenza, pneumonia

- Okanagan-Colville Native Americans of British Columbia traditionally use Lomatium root in treatment of respiratory infection

- May resolve lower respiratory symptoms in influenza virus infection
  - Lomatium extract treatment decreased CXCL10 secretion by BEAS-2B human bronchial epithelial cells
Lomatium inhibits chemokine secretion

$L. \text{ dissectum}$ decreases CXCL10 production by poly i:c stimulated BEAS-2B human bronchial epithelial cells. Zamechek and Wenner, 201465
Astragalus membranaceus

- Part used: Root
- Aqueous extract, powder, decoction, tincture
- Typical dosing: 20-500mg extract TID or QID; 1-30g of dried powder daily; 500-1,000mg capsules TID; 3-5mL of a tincture (1:5) in 30% EtOH TID
- Indications: common cold, upper respiratory infections, H1N1 swine flu

- Prevents acute URIs49
- Induces T cell-dependent immune response
  - Promotes proliferation of human peripheral blood immune cells
  - Elevates CTL activity
  - Enhances phagocytosis and increases TNF and IL-6 production in vitro56
- Astragalus with G. glabra and E. purpurea enhances T cell response
  - Induces CD8 and CD4 T cell activation within 24 hr of ingestion56
  - Effect continued for at least 7 days with twice daily dose of tincture
  - T cell-enhancing effects could improve immune response to URI
**Lentinus edodes**: Shiitake

- Part used: Fruiting body and mycelium
- Extract used: Hot water extract; lentinan
- Typical dosing: 6-16g whole, dried mushroom, 4g powder or 1-3g mycelium BID or TID
- Indications: influenza and other viral infections, including common cold, strep throat

• *L. edodes* extracts and lentinan have direct antimicrobial actions:
  - Culture fluid of mycelium was active against *S. pyogenes*\(^{23}\)
  - Lentinan active against adenovirus
• Lentinan induces strong antiviral immune response\(^{64,66,39}\):
  - Enhances IL-12, IFNγ and NO production
  - Increases TH1 response
  - Stimulates maturation of dendritic cells
  - Increases activity of neutrophils and NK cells
Proposed antiviral actions for lentinan
Other edible gilled mushrooms: 
*Agaricus blazeii* & *Pleurotus ostreatus*

- Common names: almond mushroom; himematsutaki
- Part used: Fruiting body extract
- Typical dosing: 500 mg TID
- Indications: immune stimulant and antioxidant
  - Extract protective against lethal *S. pneumonia* infection in mice
  - Stimulates TNF and chemokine CXCL8 (IL-8) production

- Common name: oyster mushroom
- Part used: Fruiting body
- Dosing: insufficient data available
- Indications: immune stimulant; directly bactericidal
  - Extract inhibits *K. pneumonia* and *S. pyogenes* in vitro
  - 8 week hot water extract increased IFNγ, IL-12, and NK cell activity
Polypore mushrooms: 
*Ganoderma lucidum* (Reishi)

- Part used: Carpophores
- Raw powder, decoction, encapsulated powder, ethanol and aqueous extracts
- Dosing: 2-6g or equivalent dosage of concentrated extract
- Indications: influenza, bronchial diseases

Ganoderma constituents have antimicrobial and immune-stimulatory effects

- Triterpenoids ganoderic acid TQ and TR inhibited activity of different influenza neuraminidase subtypes
- Effects ranged from 55.4% to 96.5% inhibition for different NA subtypes
- *G. lucidum* isolates showed inhibitory effects against Influenza A13
- Treatment of dendritic cells with *G. lucidum*-derived polysaccharide:
  - Enhanced cell-surface expression of CD80, CD86, CD40, CD54
  - Increased T cell stimulatory capacity and secretion of IFN-γ and IL-10
- Ganoderic acid enhances NK and IL-2 activity in vivo
Cordyceps sinensis and other Cordyceps spp.

- Entomopathogenic fungi
- Part Used: Mycelium
- Dried aqueous extract of mycelium
- Traditional dosing: 3-9g daily in tea or meal; 1g TID of CS-4 strain
- Used up to 40 days for chronic bronchitis
- Indications: coughs, chronic bronchitis, respiratory disorders

- Cordyceps extracts induce strong antimicrobial immune responses
  - Aqueous extract of mycelium increases phagocytic activity of human monocytic U937 cells
  - Extract abrogates inhibitory effect of Group A Streptococcal (GAS) virulence factor SPE B on phagocytosis
  - Extract also increases expression of cytokines IFN-γ, IL-12 and TNF, involved in augmenting phagocytosis
  - C. militaris extract enhances NK cell activity, lymphocyte proliferation and partially increases TH1 cytokine secretion in vivo.
**Crytoporus volvatus & Phellinus igniarius**

- **Common names:** Pouch Fungus, Cryptic Globe, Veiled Polypore
- **Part Used:** Fruiting body
- **Aqueous extract**
- **Dosing:** insufficient data available
- **Indications:** influenza and other URIs; immune-stimulating
  - Inhibited Influenza A *in vivo* & *in vitro*17
  - Immune-modulatory polysaccharides:
    - Reduce LPS-induced expression of TLR2 mRNA60
    - May help prevent LPS-induced lung injury in respiratory infections
  - Interferes with influenza virus replication cycle:
    - Inhibits viral attachment to cells35
    - Enhances antiviral responses

- **Common name:** Willow Bracket
- **Part Used:** Fruiting Body
- **Aqueous extract**
- **Dosing:** insufficient data available
- **Indications:** influenza and other URIs; immune-stimulating
Trametes versicolor (Coriolus; Turkey Tail)

- Fungi Class: Basidiomycetes
- Common Name: Turkey Tail
- Fruiting body and mycelium extracts
- PSK: pharmaceutical grade hot water mycelium extract
- Typical dosing: 1.5g BID
- Indications: URIs, pulmonary disorders, cancer treatment adjuvant

Adjunctive treatment for several cancer types:

- Stomach cancer: 16 RCTs in 6462 patients
- Colorectal cancer: 8 RCTs in 1374 patients
- Esophageal cancer: 4 RCTs in 279 patients
- Breast cancer: 3 RCTs in 1517 patients

- PSK induces TH1-dependent antitumor and antiviral immune responses
- TLR2 agonist actions prime strong dendritic cell activity
- Induces TH1 cytokines, CTL and NK cell responses
- Active constituents proposed to be beta-1,3-D-glucans, shown to be bioavailable after oral ingestion

Adjunctive treatment for several cancer types:
PSK induces TH1 response needed for effective antitumor and antiviral immune responses

PSK dose-dependently increases Th1 cytokines after oral gavage in Her2/neu tumor bearing mice

PSK increases DCs in tumor draining lymph nodes (TDLN)

PSK increases cytotoxic effector molecules in tumor target cells
PSK acts as a TLR2 agonist to activate DCs.
PSK dose-dependently enhances NK cell activation

Figure 5b: PSK dose-dependently enhances CD25 and CD69 expression by CD56^+ NK cells in an IL-2 treated human primary NK cell culture

PSK dose-dependently induces CD69 activation marker in human NK cells
Proposed mechanism for mushroom-derived beta-glucans enhancing antiviral immune responses

Beta-glucans

- Activates accessory cells
- Activates NK cells

BG Receptors
- TLR2
- CR3
- Dectin-1

Augments antiviral CMI

CD4+ Th1 → IL-2 → CD8+ CTL

Dead target cell

Augments antiviral CMI
Limitations & future research

Most studies conducted in human cell lines *in vitro*
- More clinical trials needed to determine optimal parameters (e.g., dosing regimen) for treating and preventing respiratory infections

Need to ensure modulatory effects observed *in vitro* are not due to bacterial endotoxin contamination
- Several studies report cytokine-suppressive actions, not caused by bacterial endotoxins which induce inflammatory cytokines
- Bacterial endotoxin testing is requirement for *in vitro* assay

Quality control of botanical and mushroom extracts needed
- Ensuring product quality and stability are key to accurately assessing botanical and medicinal mushroom extracts for safety and efficacy

Some immune-enhancing effects may be due to endophytic bacterial compounds in botanical and mushroom extracts
- Further research needed to identify actions of constituents in bioactive extracts and correlate levels with growth and extraction conditions.
The authors would like to thank Sarah Acosta, ND for reviewing and providing additional information on clinical dosing and usages.


