

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

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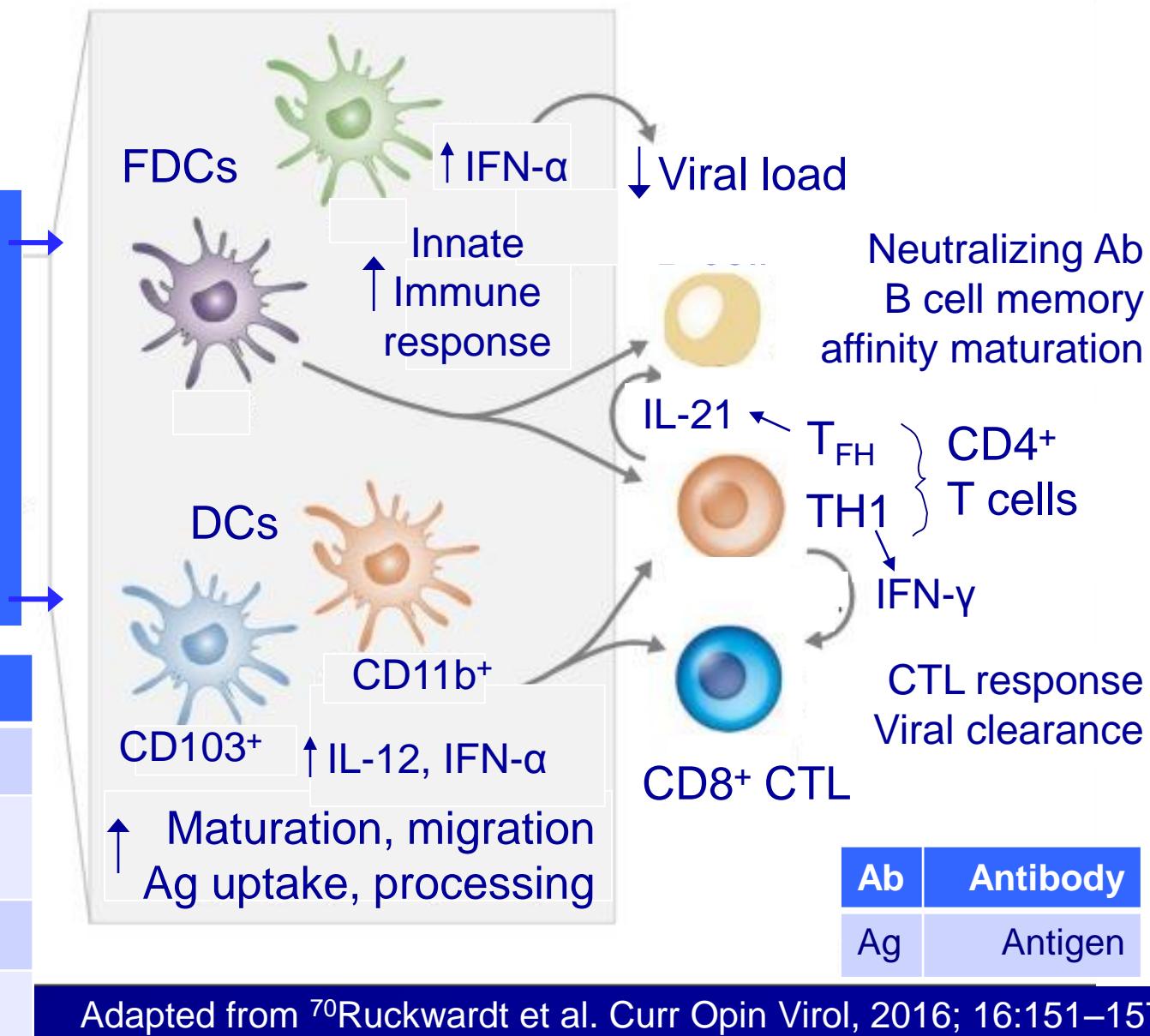


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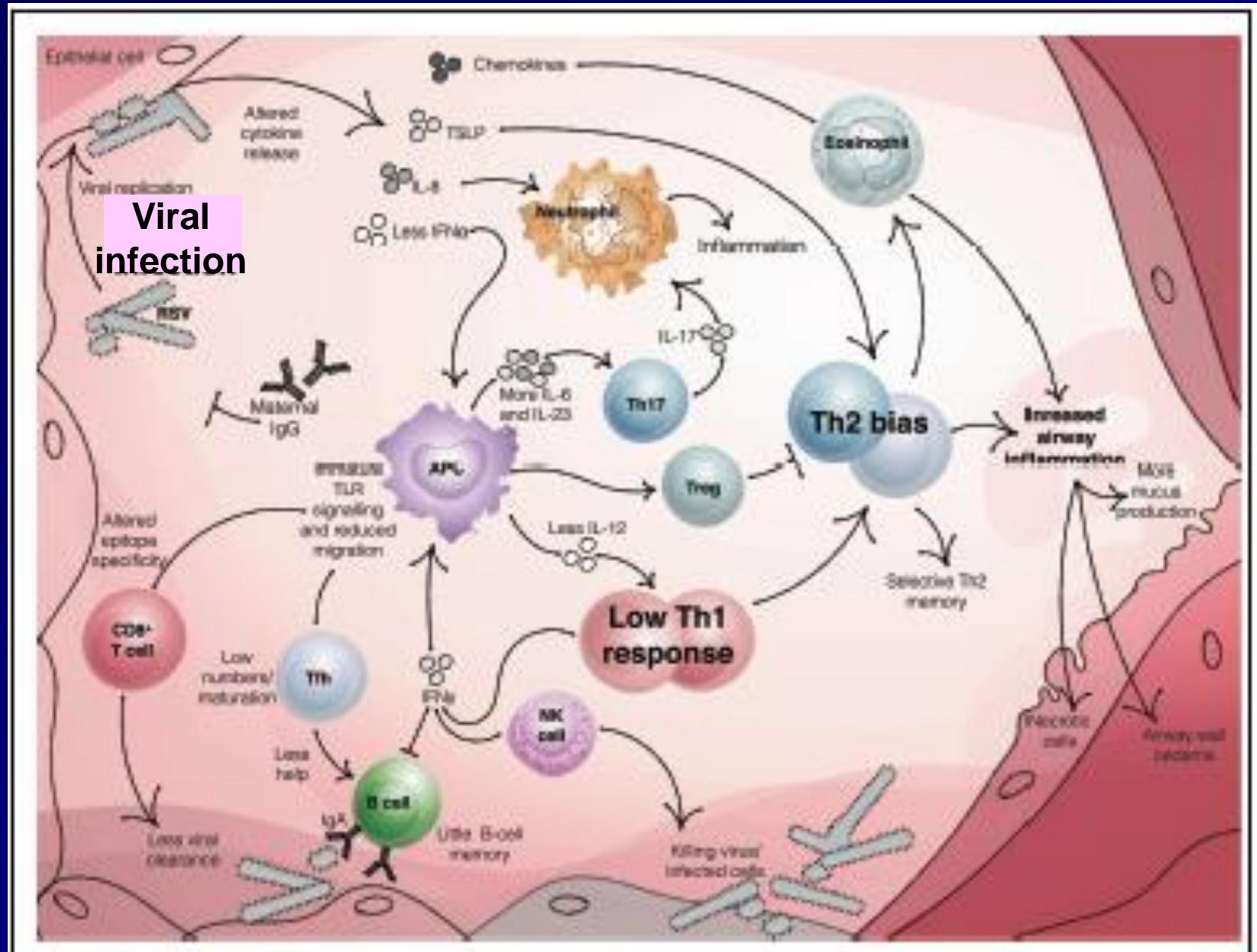
Elements required for an optimal anti-viral immune response against respiratory viruses

Optimal antigens
+
TLR agonists
+
non-TLR
agonists



Adapted from ⁷⁰Ruckwardt et al. Curr Opin Virol, 2016; 16:151–157

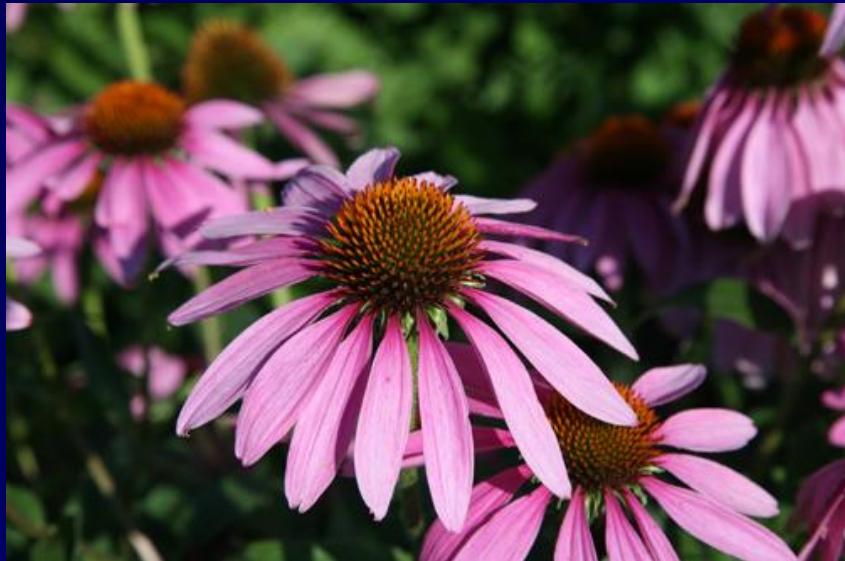
Elements involved in weak response to respiratory viruses



Botanical & mushroom extracts used in treating respiratory infections

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

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 duration⁵² in children but URI recurrence significantly decreased vs. placebo⁵⁹
 - *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 infection¹⁰
 - 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.⁵⁴

Common Dosing Regimens for Echinacea

For treatment of common colds:

- Fresh pressed juice:
 - Children: used safely BID at 3.75 mL for 2-5 yr olds, 7.5 mL 6-11 yr olds
 - Adults: used safely BID at 5 mL per day
- 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

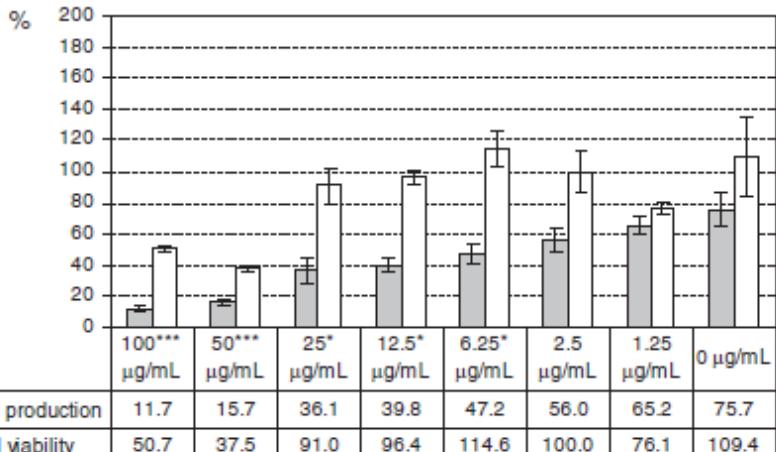
Echinacea-derived constituents have distinct immune modulatory properties

- 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 PPAR γ 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

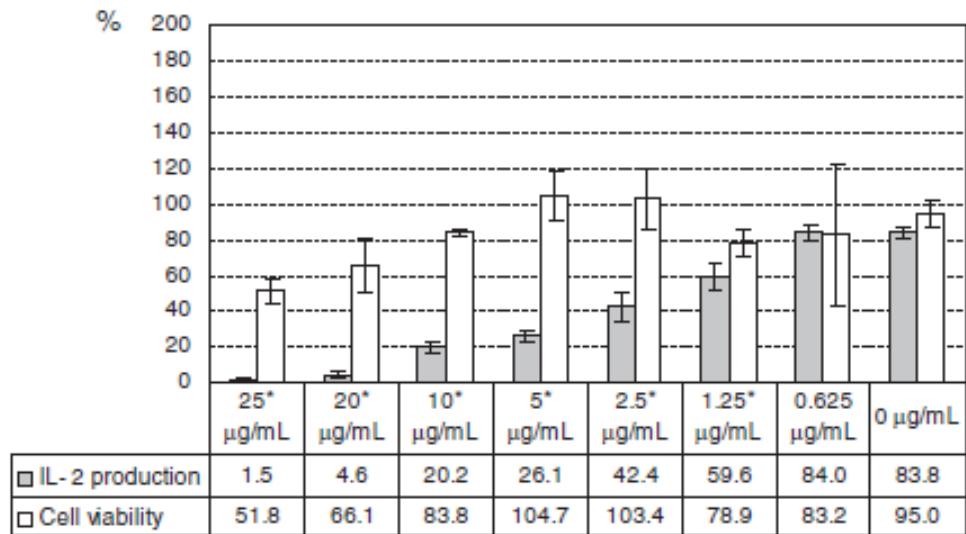
a

95:5 ethanol:water *Echinacea purpurea* extract



b

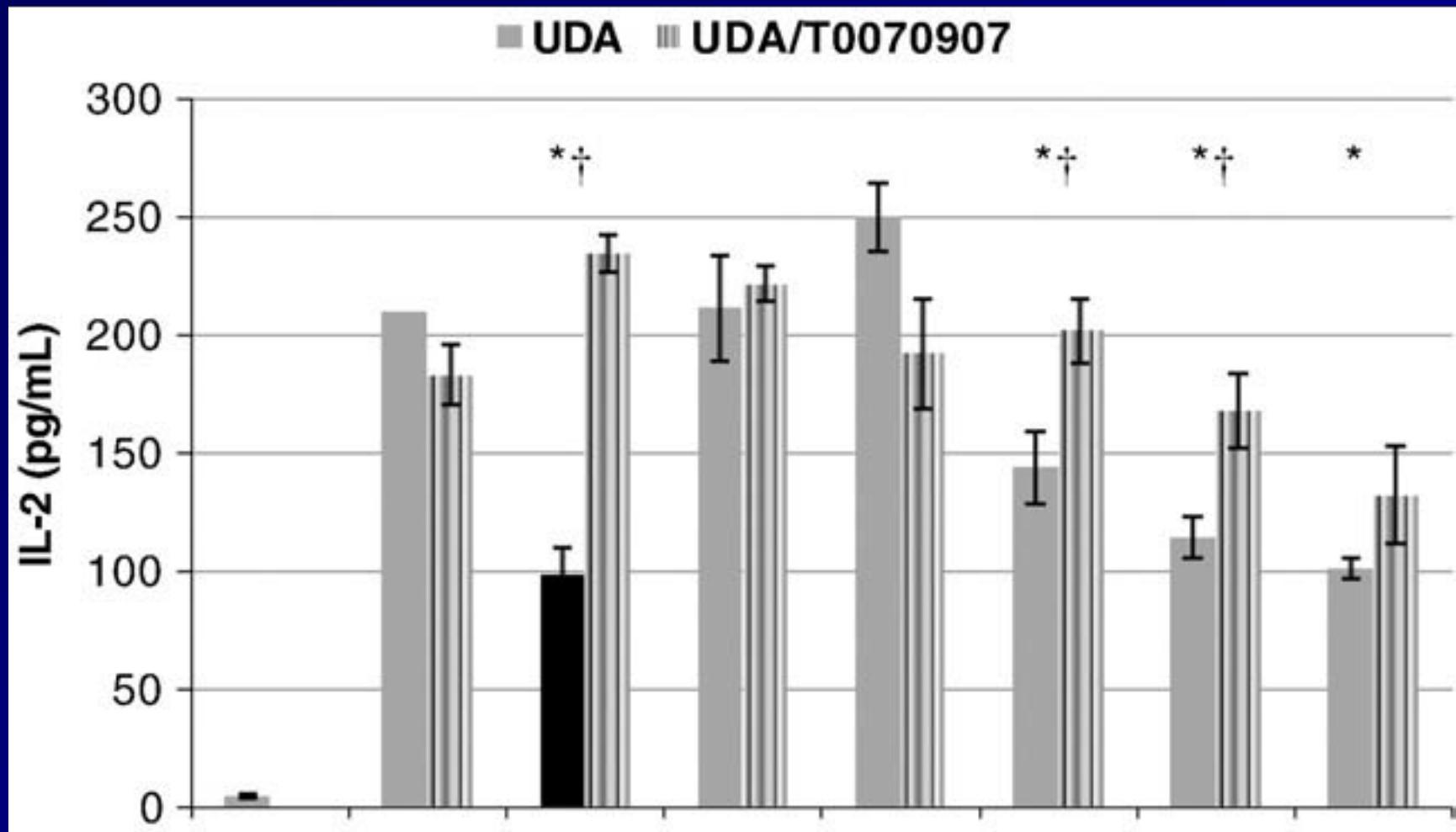
Dodeca-2(E),4(E),8(Z),10(Z) tetraenoic acid isobutylamide



E. Purpurea ethanolic extract and alkylamide isolates dose-dependently inhibit IL-2 production in activated human Jurkat T cells⁴⁶

IL-2 inhibitory effects not due to ethanolic extract cytotoxicity

IL-2 suppression induced by Echinacea-derived alkylamide is reduced by PPAR- γ antagonist⁴⁹



Andrographis paniculata & *Eleutherococcus senticosus*



Part used: whole herb

Extracts & adult daily dose:

500-3,000mg TID

300mg tablet QID

4% andrographolides/tablet = 48mg

Children's dose: 1-2g TID or QID

Standardized extract equivalent
to 4-6 mg andrographolides

Indications: URIs including colds &
flu, bronchitis, tonsillitis, pharyngitis
pneumonia, tuberculosis; also used
for URI prevention

Common name: Siberian ginseng

Part used: root

Extracts & adult daily dose:

9-20g powder in tea

2-3g crude extract powder

300-400mg concentrate

Tablet dose ~ 3g powder

Standardized to Eleutherosides B and E

Concentrated extract: 10mg = 120mg crude

Indications: influenza, swine flu, bronchitis,
tuberculosis; also used for 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 URI^{7,16,41,43}
- 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*³³
Flavonoids from elderberry extract bind to H1N1 virion and block ability of virus to infect host cells *in vitro*⁴⁵
 - Elderberry extract dose-dependently inhibits H1N1 virus infection
 - Elderberry extract reduces *S. pyogenes* proliferation upon contact³³
- Increases inflammatory cytokines (IL-1 β , TNF, IL-6, IL-8) compared to LPS¹
- Suppresses virus replication & induces neutralizing Ab In influenza A infected mice³¹
- 15 mL QID syrup within 48 hr of onset reduced symptoms & duration of influenza A and B infections in double blind, placebo-controlled RCT⁶²



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, tuberculosis

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

- Constituents show antibacterial activity against respiratory bacteria⁵¹
 - licoricidin and glycocoumarin inhibited *S. pyogenes* and *H. influenzae*
- Active against human RSV in human respiratory tract cell lines¹⁴
 - 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-γ and decreased IL-4 production³
- 18-β-glycyrrhetic acid induced TH1 response and IFN-γ production *in vivo*²⁹

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, whooping cough, tuberculosis, bronchitis
- Bactericidal: *H. influenza*, *S. pyogenes*²²
- Allicin (9 mg/kg) immune enhancing:
 - increases IFN- γ and TNF
 - promotes expansion of mature DCs after oral treatment in mice¹⁵
- Common name: thyme
- Part used: Aerial parts and volatile oils
- Ethanolic extract; steam inhalant
- Dosing: insufficient data available
- Indications: Bronchitis, cough
 - Thymol bactericidal: *S. pyogenes*⁴⁸, *H. influenza*²⁵, *Klebsiella pneumonia*
 - Thymol, carvacrol reduce IL-2, IFN γ secretion in stimulated Jurkat T cells¹⁹

Propolis



- Part used: Conifer & *Populus spp.* bud resin made by bees
- Extract type: powder, ethanolic extract
- Typical dose: 2 x250mg capsules TID 3 days
- Indications: Common cold, H1N1 influenza, bacterial URIs, tuberculosis
- Hydroethanolic extract bactericidal and antiviral^{4,9}
 - Inhibits *S. pyogenes*, *H. influenzae*, adenovirus, influenza virus
- Immune-stimulatory effects
 - Caffeic acid ophenethyl ester, cinnamic acids and artepillin-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

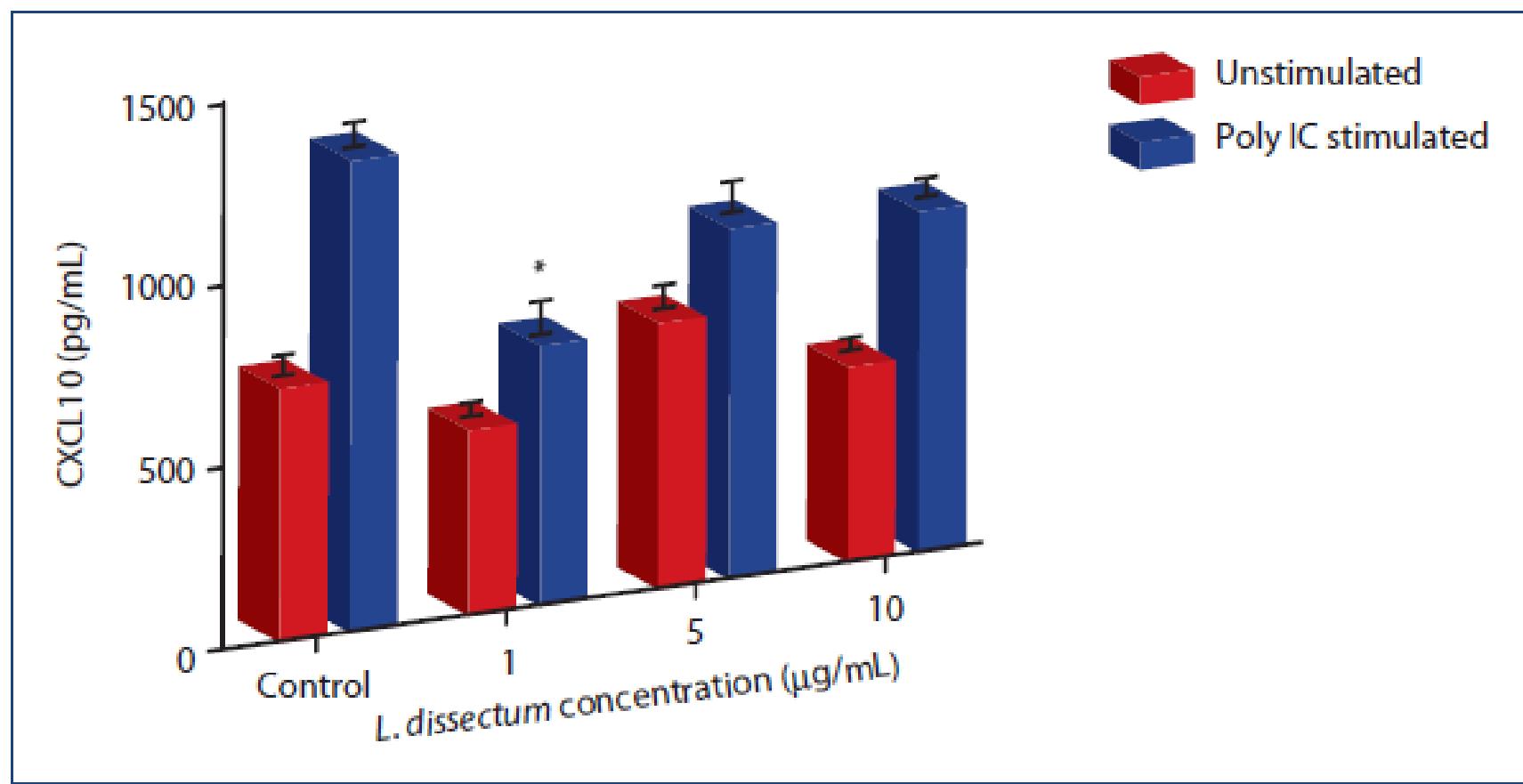
Local botanical used in respiratory infections: *Lomatium dissectum*



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

- Okanagan-Colville Native Americans of British Columbia traditionally use Lomatium root in treatment of respiratory infection³⁸
- May resolve lower respiratory symptoms in influenza virus infection
 - Lomatium extract treatment decreased CXCL10 secretion by BEAS-2B human bronchial epithelial cells⁶³

Lomatium inhibits chemokine secretion



L. 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 vitro*⁵⁶
- 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

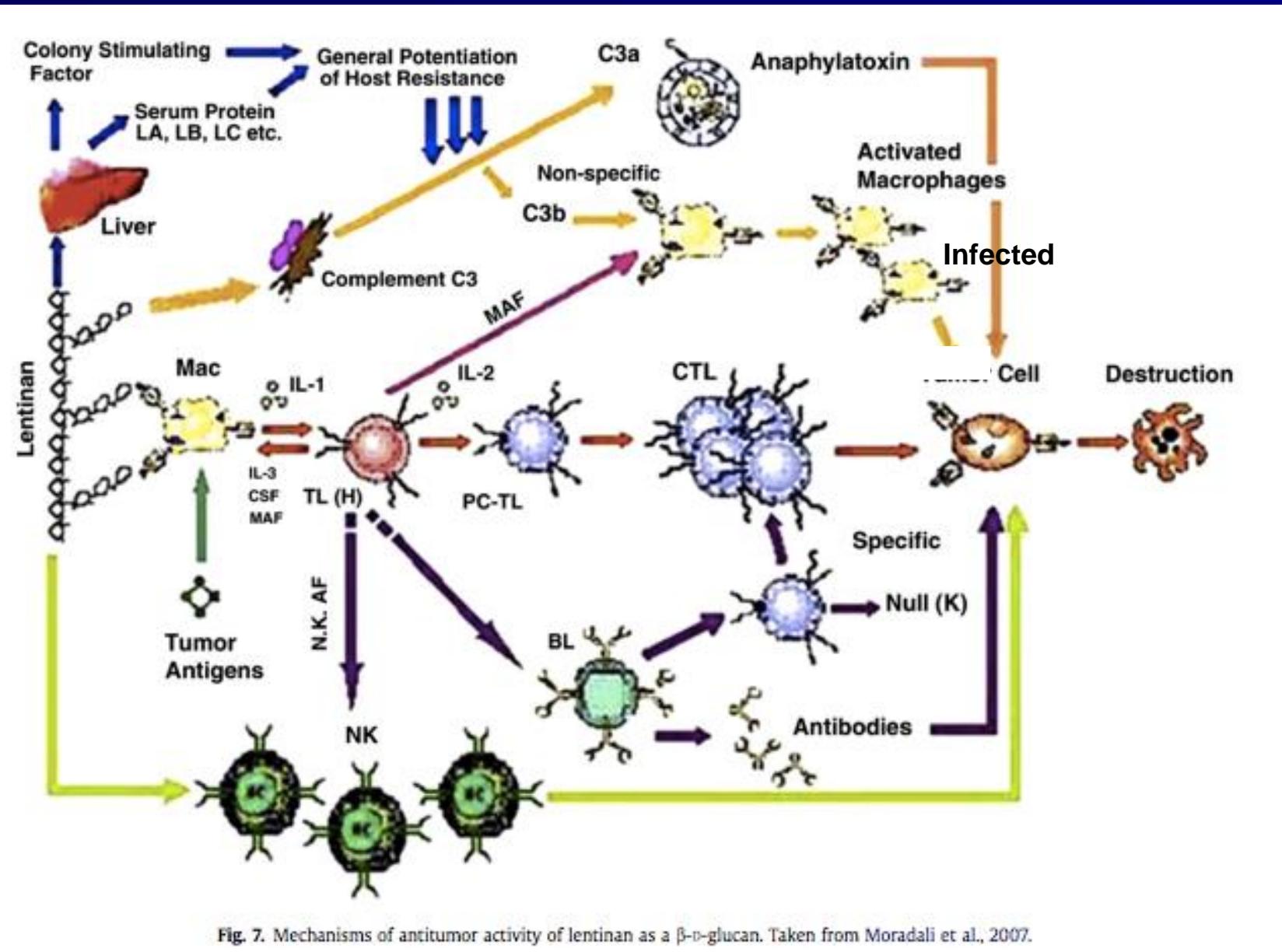
Lentinus edodes: Shiitake



- 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. pneumoniae* infection in mice
 - Stimulates TNF and chemokine CXCL8 (IL-8) production²
- Common name: oyster mushroom
- Part used: Fruiting body
- Dosing: insufficient data available
- Indications: immune stimulant; directly bactericidal
 - Extract inhibits *K. pneumoniae* and *S. pyogenes* *in vitro*⁶¹
 - 8 week hot water extract increased IFN γ , IL-12, and NK cell activity⁵⁰

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 subtypes⁶⁷
 - 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 polysaccharide³⁶:
 - Enhanced cell-surface expression of CD80, CD86, CD40, CD54
 - Increased T cell stimulatory capacity and secretion of IFNγ and IL-10³⁶
 - Ganoderic acid enhances NK and IL-2 activity in vivo⁵⁵

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
- Indications: coughs, chronic bronchitis, respiratory disorders

- Cordyceps extracts induce strong antimicrobial immune responses
 - Aqueous extract of mycelium increases phagocytic activity of human monocytic U937 cells³⁴
 - Extract abrogates inhibitory effect of Group A Streptococcal (GAS) virulence factor SPE B on phagocytosis³⁴
 - Extract also Increases expression of cytokines IFN- γ , IL-12 and TNF, involved in augmenting phagocytosis³⁴
 - *C. militaris* extract enhances NK cell activity, lymphocyte proliferation and partially increases TH1 cytokine secretion *in vivo*.²⁸

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
- Common name: Willow Bracket
- Part Used: Fruiting Body
- Aqueous extract
- Dosing: insufficient data available
- Indications: influenza and other URIs; immune-stimulating
- Interferes with influenza virus replication cycle:
 - Inhibits viral attachment to cells³⁵
- Enhances antiviral responses
 - Increases CD8 T cells and NK cell activity *in vivo*⁶⁵

Trametes versicolor (Turkey Tail)



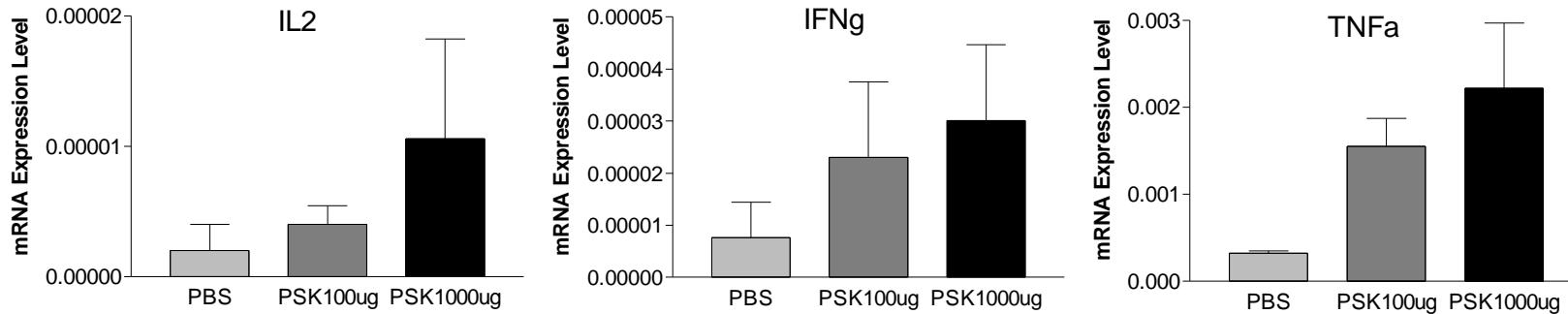
- Fungi Class: Basidiomycetes
- Common Name: Turkey Tail
- Fruiting body and mycelium extracts
- PSK: pharmaceutical grade hot water mycelium extract
- Typical dosing: 1,5g BID
- Indications: URIs, pulmonary disorders, cancer treatment adjuvant

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 responses³⁷
 - 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^{57, 69}

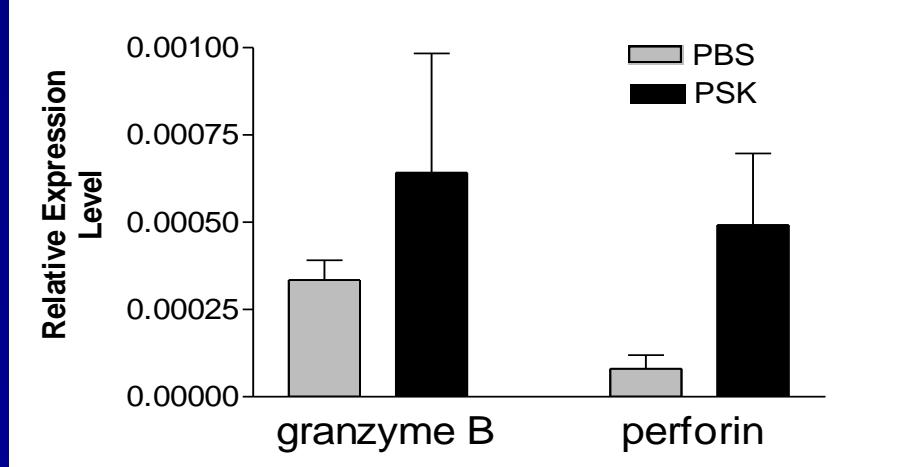
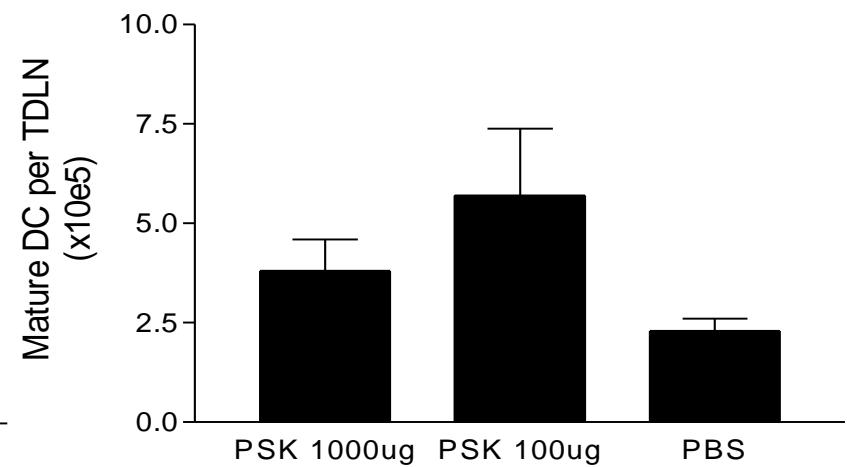
PSK induces TH1 response needed for effective antitumor and antiviral immune responses



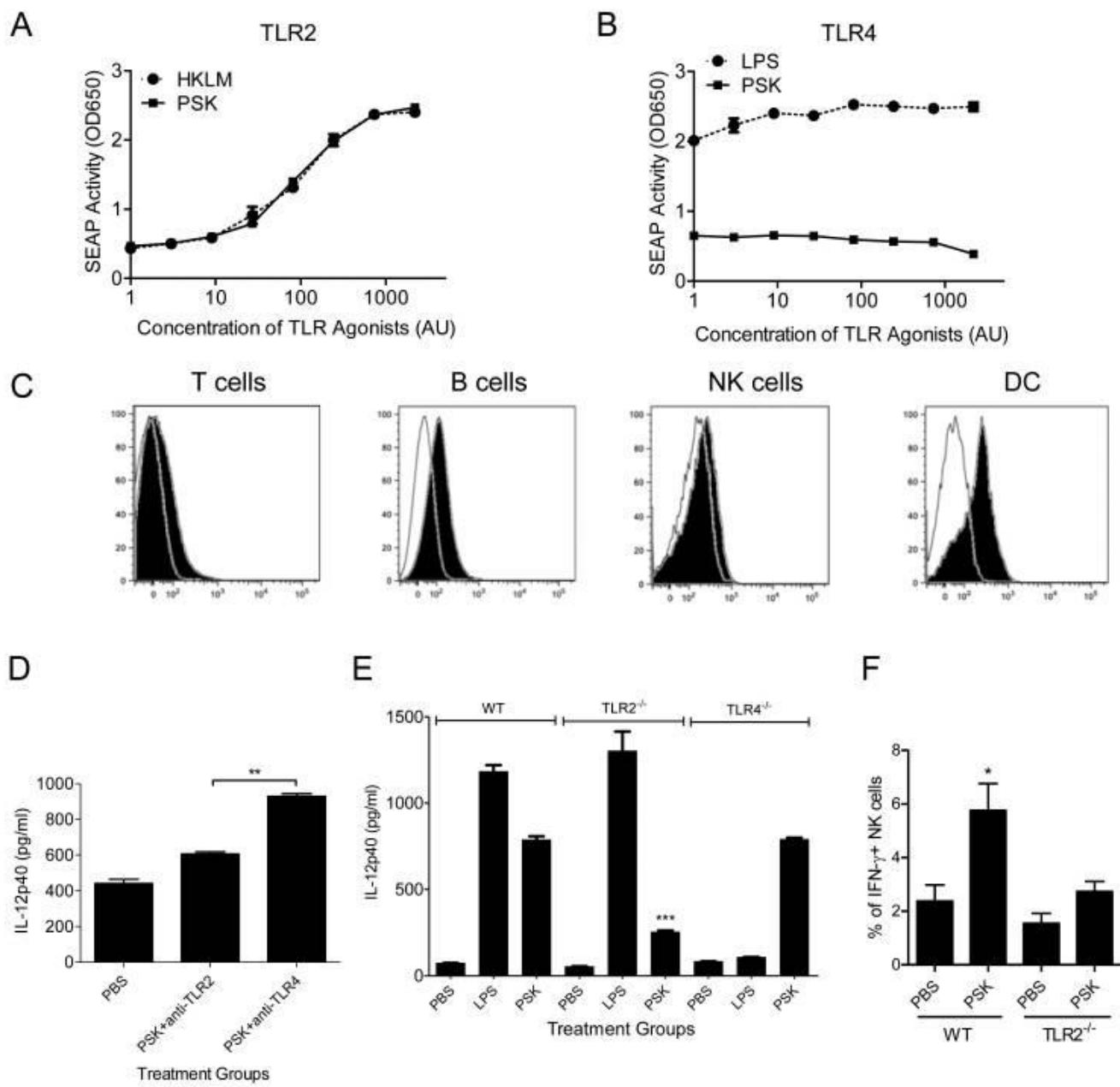
PSK dose-dependently increases Th1 cytokines after oral gavage in Her2/neu tumor bearing mice

PSK increases DCs in tumor draining lymph nodes (TDLN)

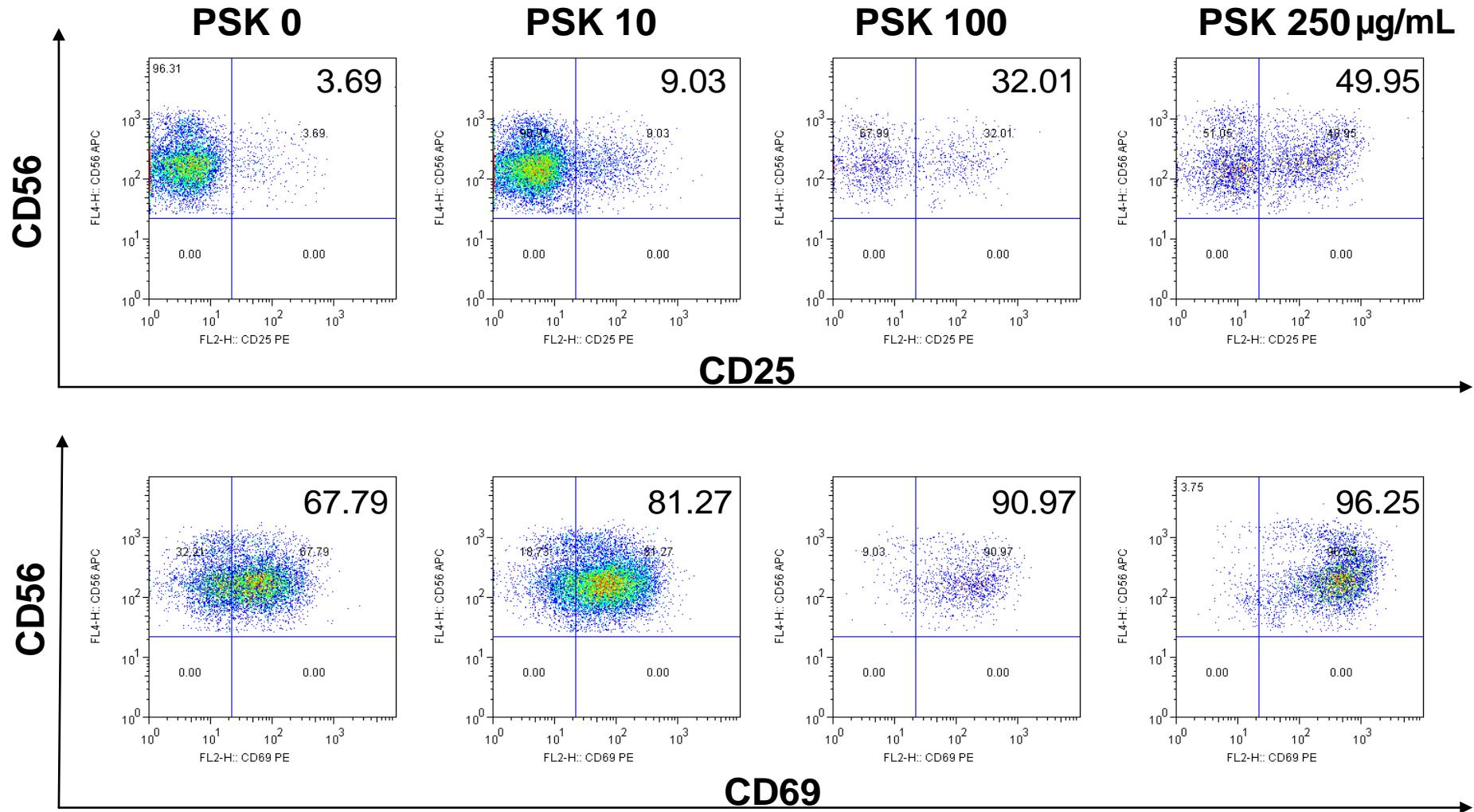
PSK increases cytotoxic effector molecules in tumor target cells



PSK acts as a TLR2 agonist to activate DCs⁷

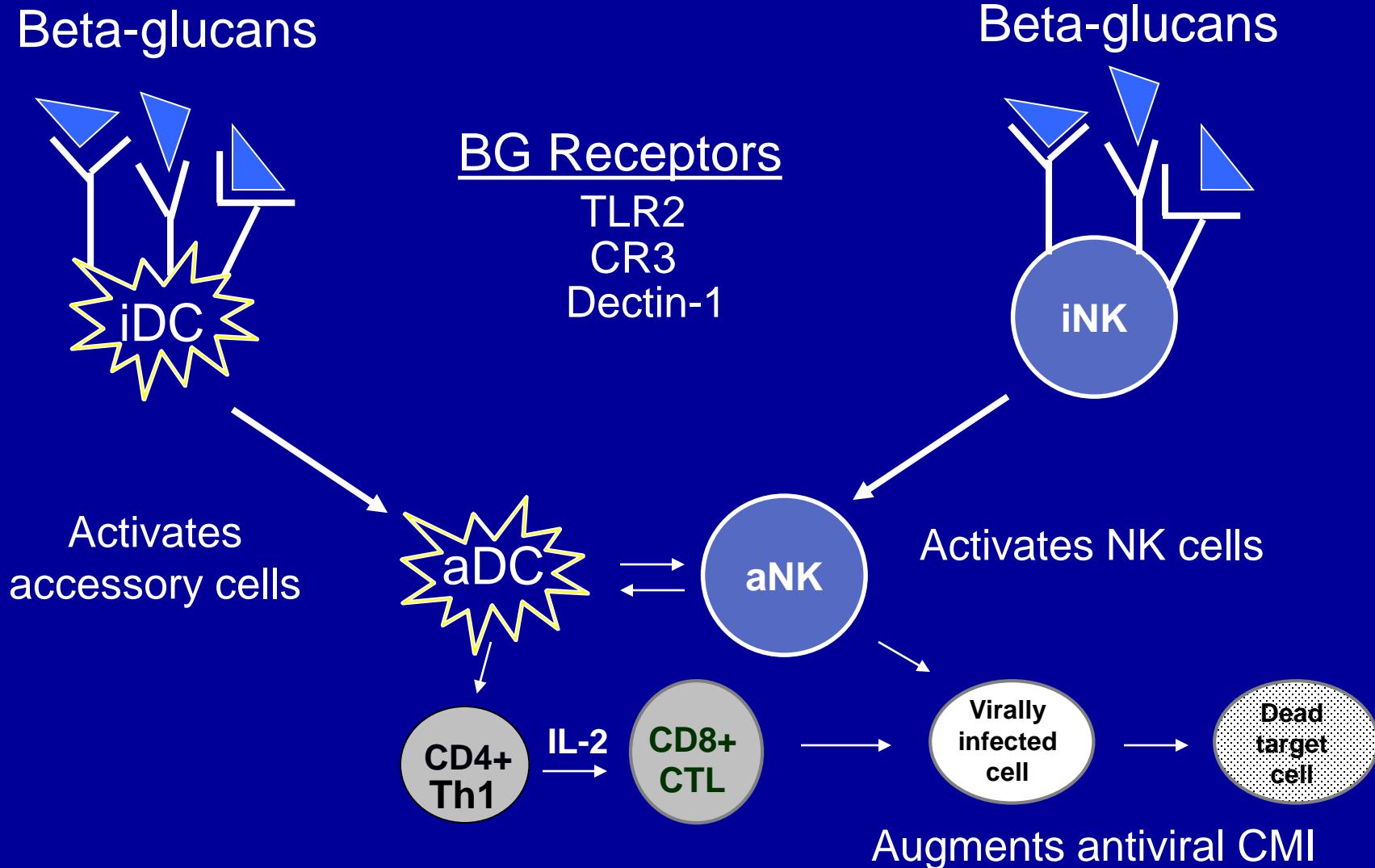


PSK dose-dependently enhances NK cell activation



PSK dose-dependently induces CD69 activation marker in human NK cells

Proposed mechanism for mushroom-derived beta-glucans enhancing antiviral immune responses



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.

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