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

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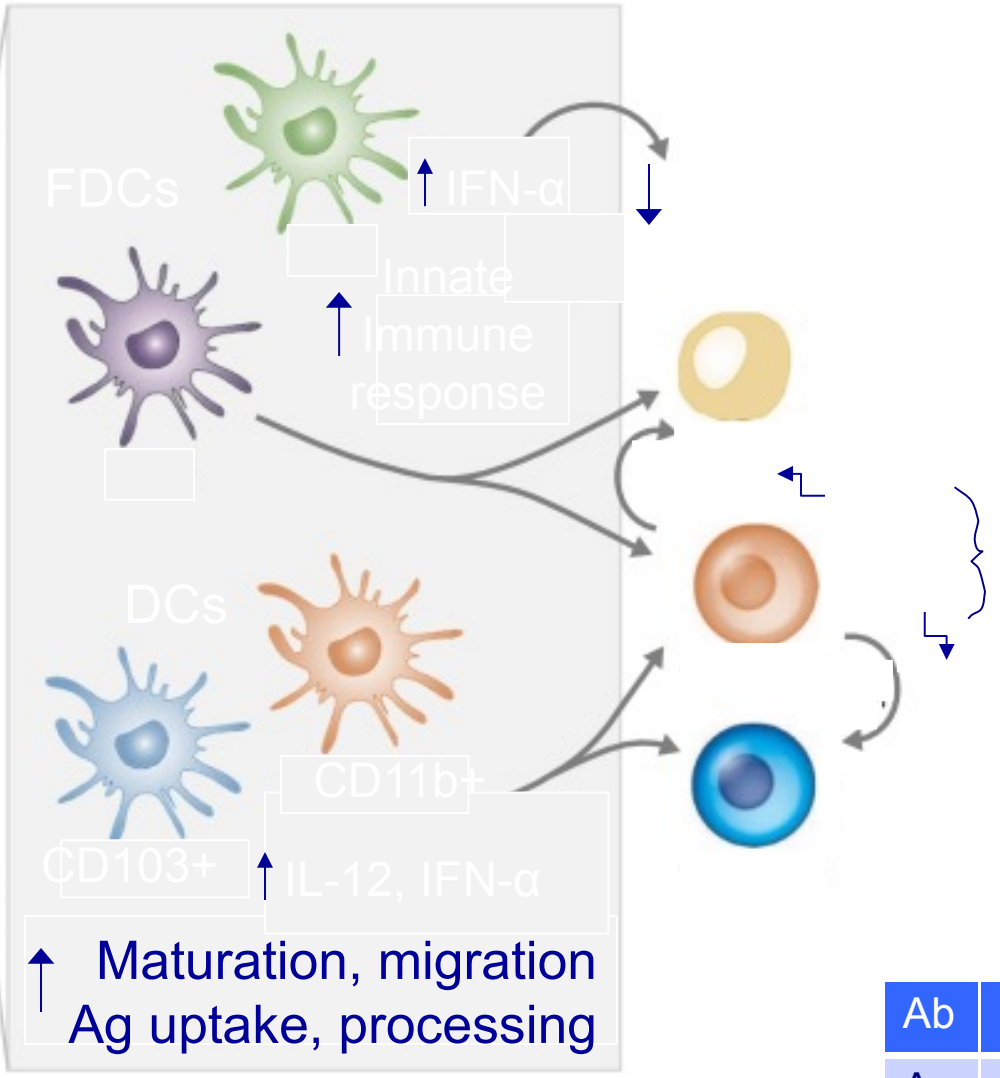
Elements required for an optimal anti-viral immune response against respiratory viruses

Optimal antigens + TLR agonists + non-TLR agonists

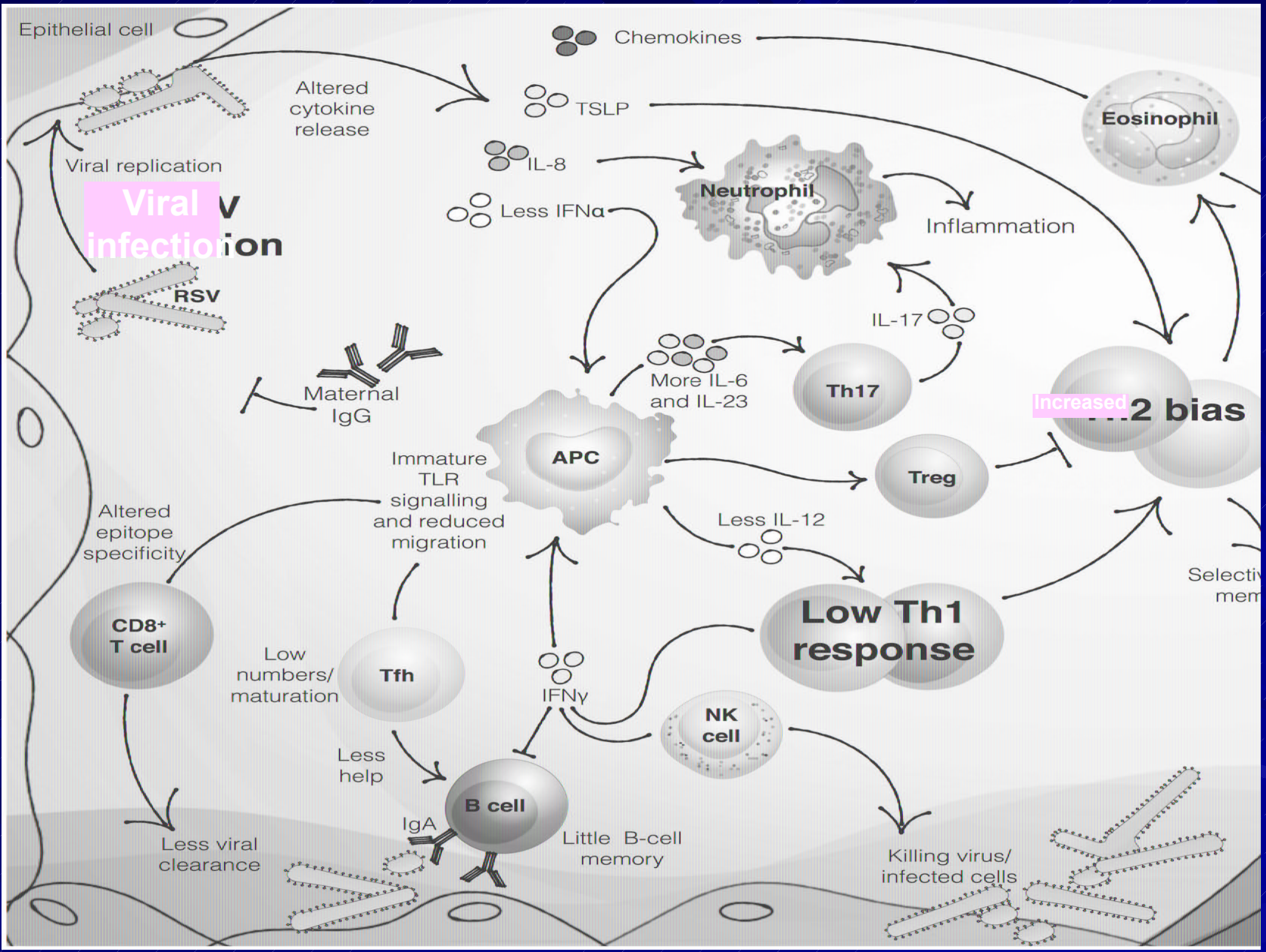


Term	Definition
TLR	*Toll-like* receptor
FDC	Follicular dendritic cell
DC	Dendritic cell
CTL	Cytotoxic T cell

Ab	Antibody
Ag	Antigen

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

Elements involved in weak response to respiratory viruses



Adapted from 71Lambert et al. Front Imm, 2014; 5:1-14

Botanical & mushroom extracts used in treating respiratory infections

Botanical Extracts
Echinacea spp.
Andrographis paniculata
Eleutherococcus senticosus
Sambucus nigra
Glycyrrhiza glabra
Allium sativa
Thymus vulgaris
Populus spp.
Lomatium dissectum
Astragalus membranaceus

Mushroom/fungal Extracts
Lentinus edodes (Shiitake)
Agaricus blazeii
Pleurotus ostreatus
Ganoderma lucidum (Reishi)
Cordyceps sinensis
Crytoporus volvatus
Phellinus igniarius
Trametes versicolor

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: 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:

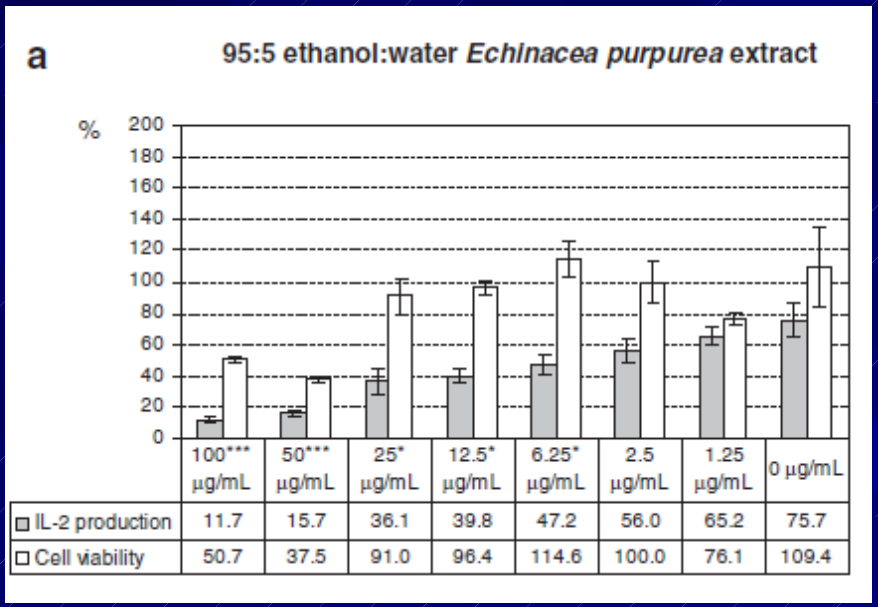
- Throat spray of Echinacea whole plant extract with sage every 2 hr up to 10 times daily for 5 days relieves sore throat due to tonsillitis or pharyngitis
- Echinacea root extract with thuja and wild indigo used TID up to 2wk in combination with antibiotic

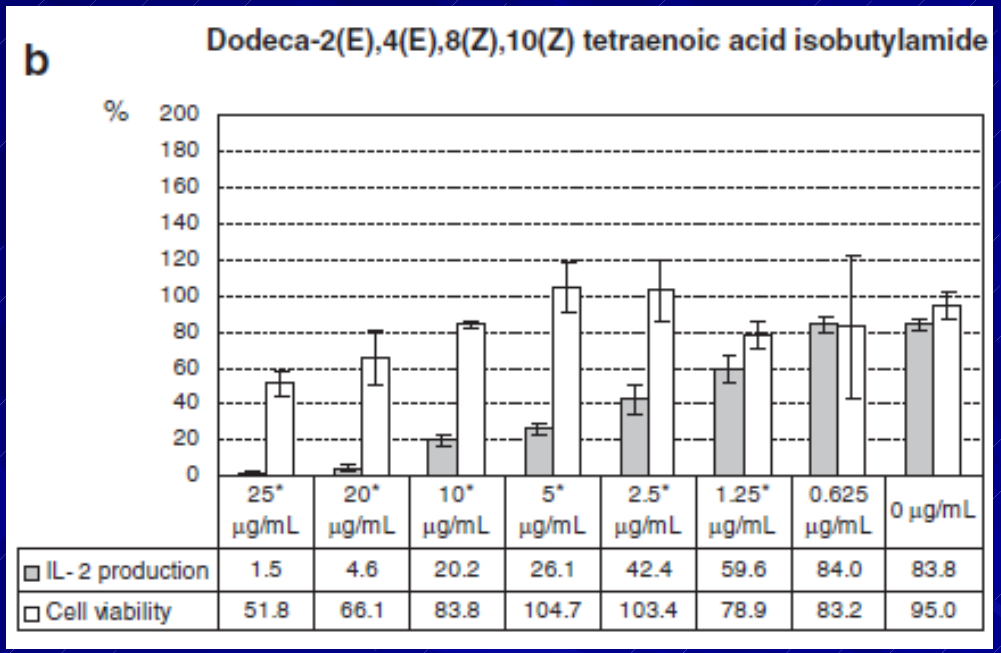
Echinacea-derived constituents have distinct immune modulatory properties

- 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 constiutents.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

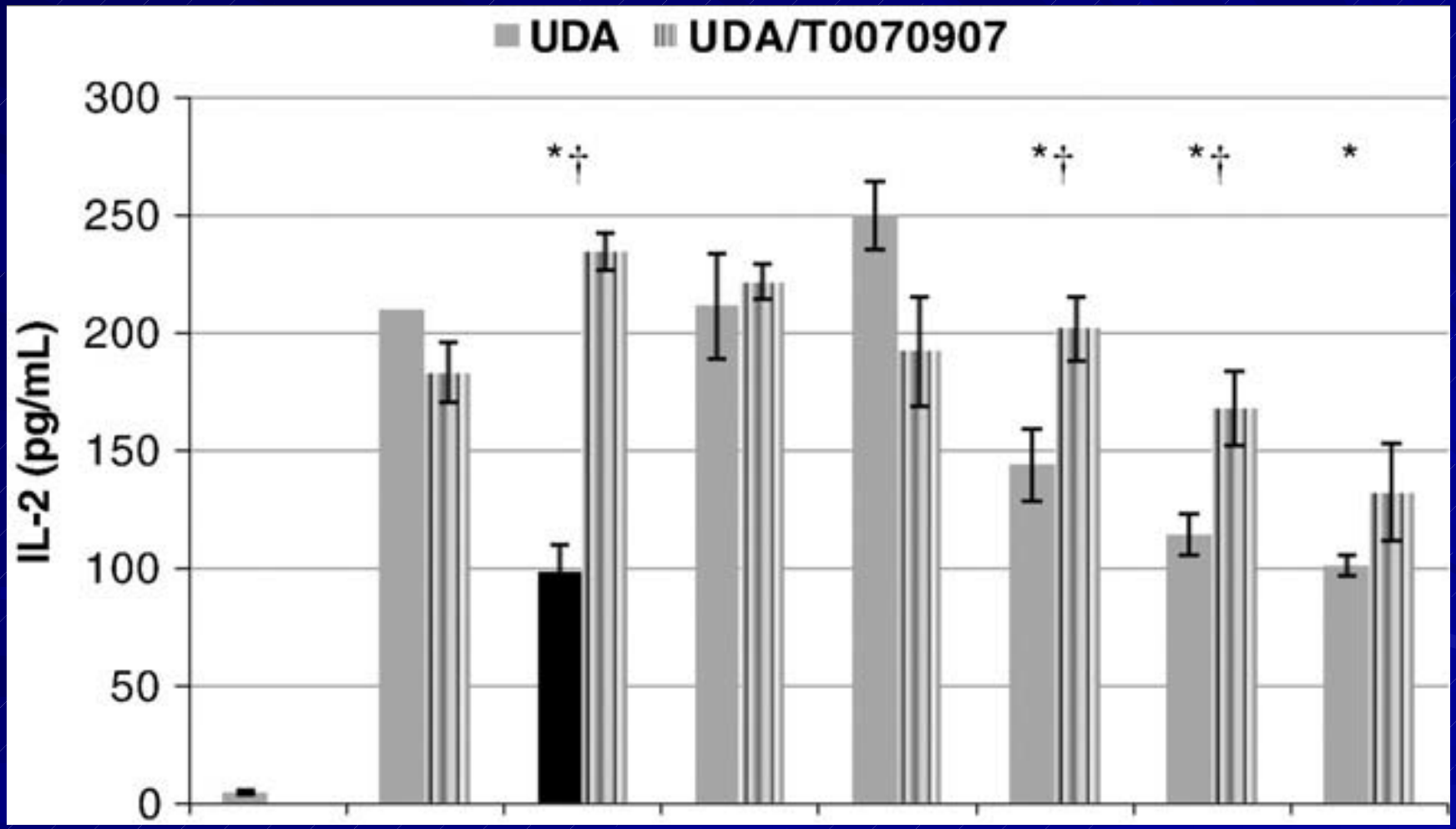




E. Purpurea ethanolic extract and alkylamide isolates dose-dependently inhibit IL-2 production in activated human Jurkat T cells46

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 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 3-5days
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-□ 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 vitro45*
  - Elderberry extract dose-dependently inhibits H1N1 virus infection
  - Elderberry extract reduces *S. pyogenes* proliferation upon contact33
- Increases inflammatory cytokines (IL-1β, 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

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

- Constituents show antibacterial activity against respiratory bacteria*51*
  - 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
  - Glycyrrhyzin-treated DCs increased proliferation of allogenic T cells
  - T cells showed increased IFN-□ and decreased IL-4 production3

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. pyogenes22*
- Allicin (9 mg/kg) immune enhancing:
  - increases IFN-□ 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 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. pyogenes48, H.influenza25, Klebsiella pneumonia*
- Thymol, carvacrol reduce IL-2, IFN□ 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; also used topically in throat sprays or tinctures
- Indications: Common cold, H1N1 influenza, bacterial URIs

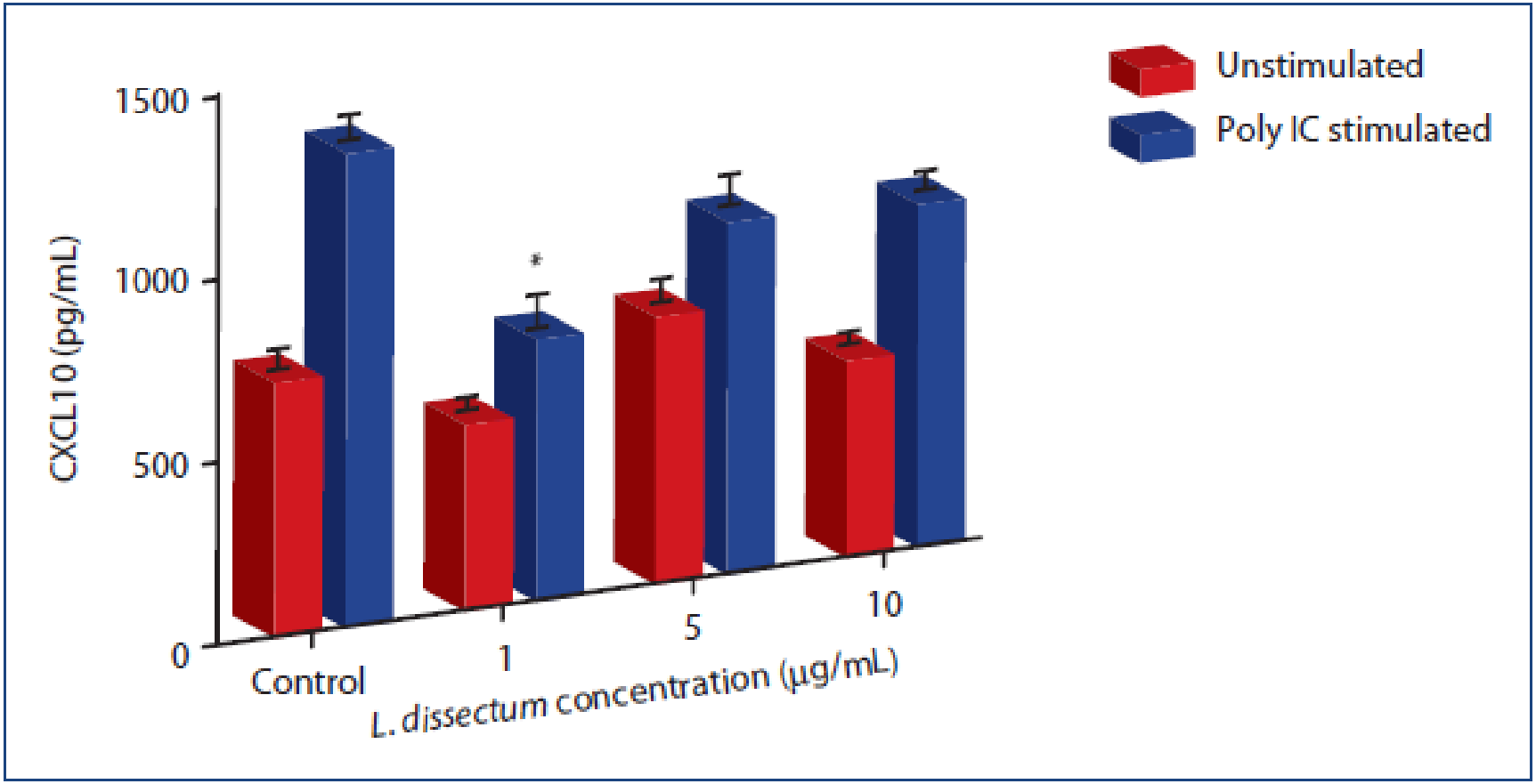
- Hydroethanolic extract bactericidal and antiviral4,9
  - Inhibits *S. pyogenes, H. influenzae*, adenovirus, influenza virus
- Immune-stimulatory effects
  - Caffeic acid ophenethyl ester, cinnamic acids and artepilin-C activate macrophages *in vitro* and *in vivo*40,6,9,30
- Clinical evidence supporting 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 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 response64,66,39
  - Enhances IL-12, IFNγ and NO production
  - IncreasesTH1 response
  - Stimulates maturation of dendritic cells
  - Increases activity of neutrophils and NK cells

Proposed antiviral actions for lentinan

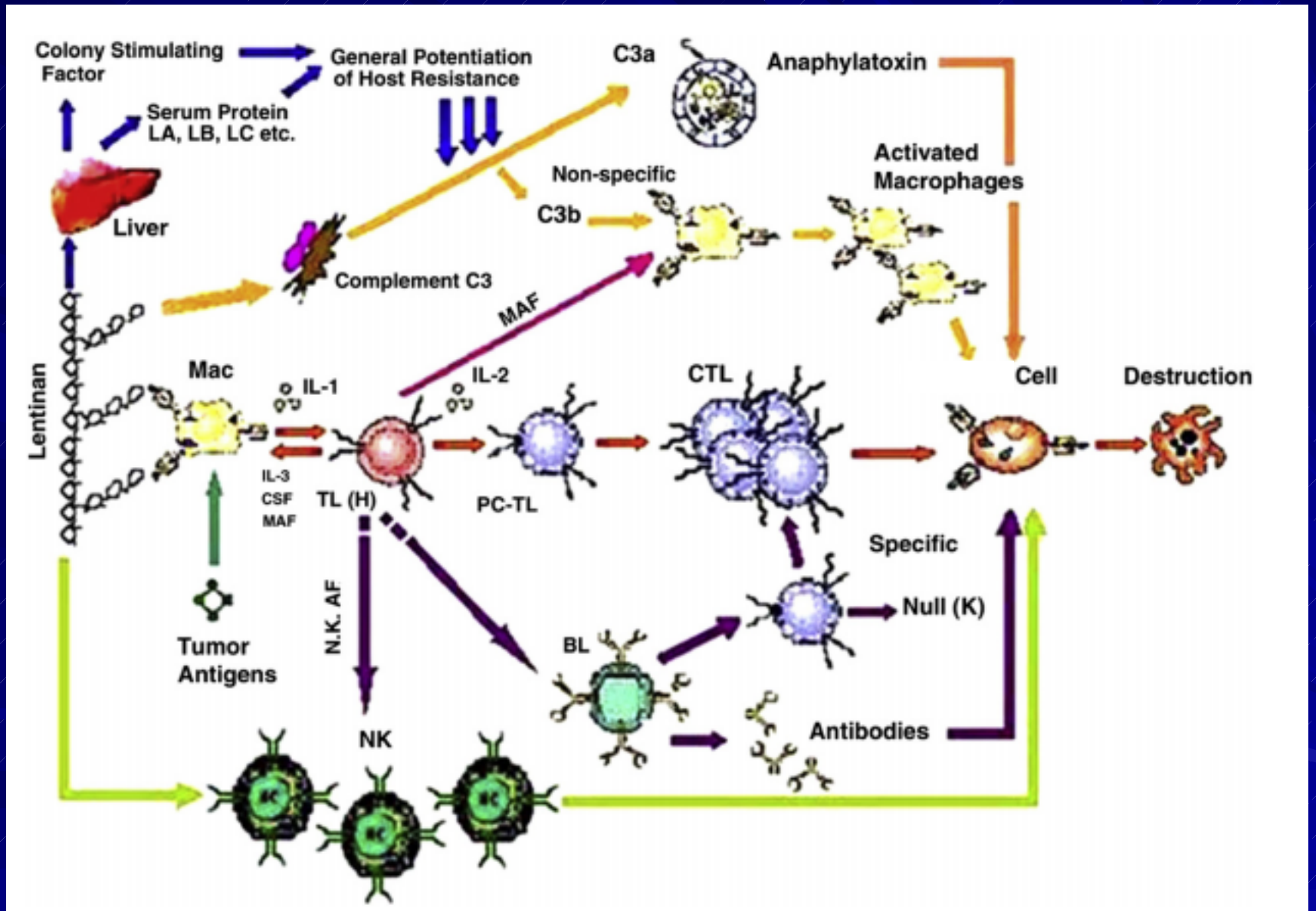


Fig. 7. Mechanisms of antitumor activity of lentinan as a β-D-glucan. Taken from Moradali et al., 2007.

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) production2

- 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*61
- 8 week hot water extract increased IFN□, 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 IFN□ and IL-1036

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 cells34
  - Extract abrogates inhibitory effect of Group A Streptococcal (GAS) virulence factor SPE B on phagocytosis34
  - Extract also Increases expression of cytokines IFN-□, 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 (Coriolus; Turkey Tail)

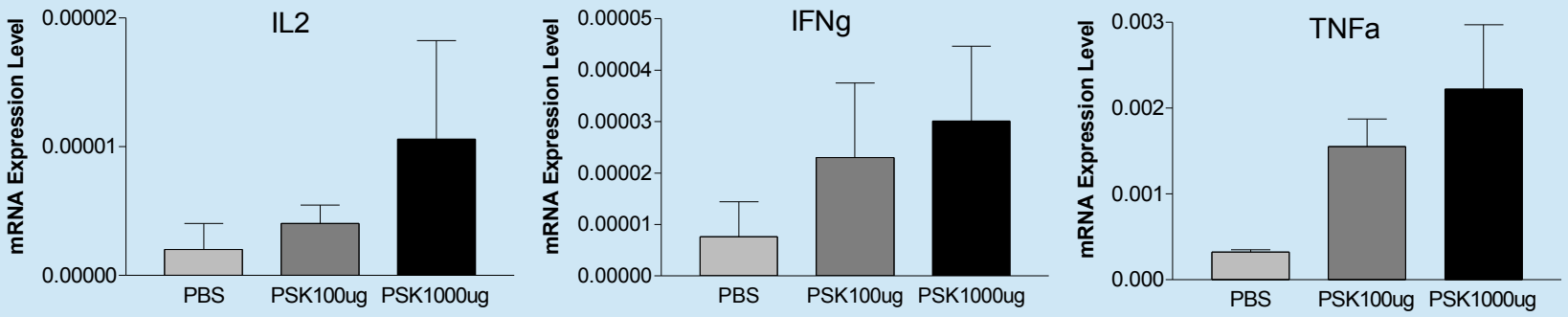
- Fungi Class: Basidiomycetes
- Common Name: Turkey Tail
- Fruiting body and mycelium extracts
- PSK: pharmaceutical grade hot water mycelium extract
- Typical dosing: 1,5g BID
- Indications: URIs, pulmonary disorders, cancer treatment adjuvant

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

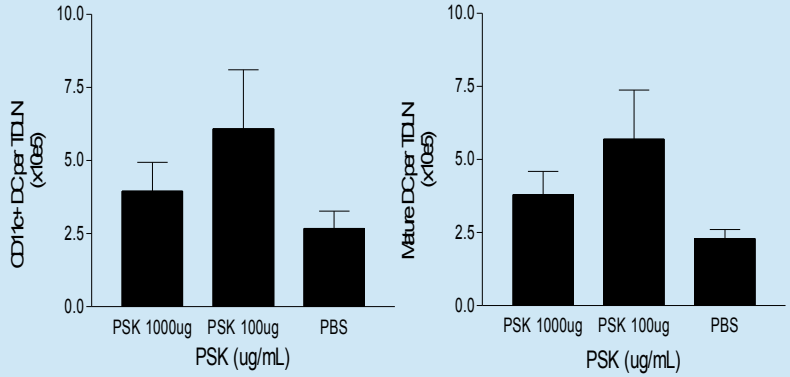
- PSK induces TH1-dependent antitumor and antiviral immune responses37
  - TLR2 agonist actions prime strong dendritic cell activity
  - Induces TH1 cytokines, CTL and NK cell responses
- Active constituents proposed to be beta-1,3-D-glucans, shown to be bioavailable after oral ingestion57, 69

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

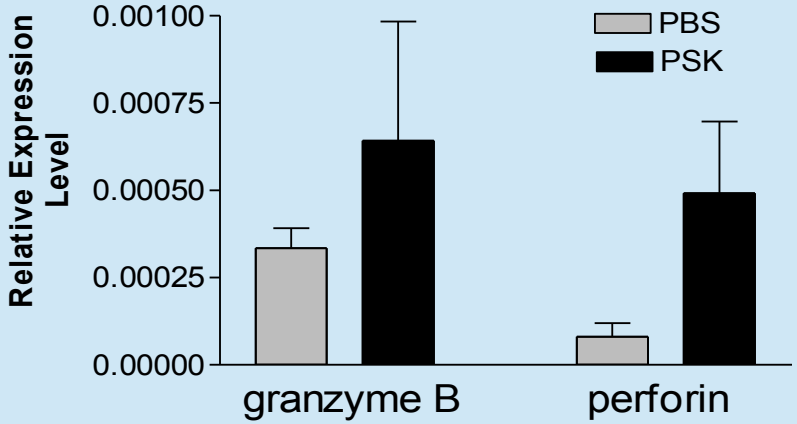


PSK dose-dependently increases Th1 cytokines after oral gavage in Her2/neu tumor bearing mice

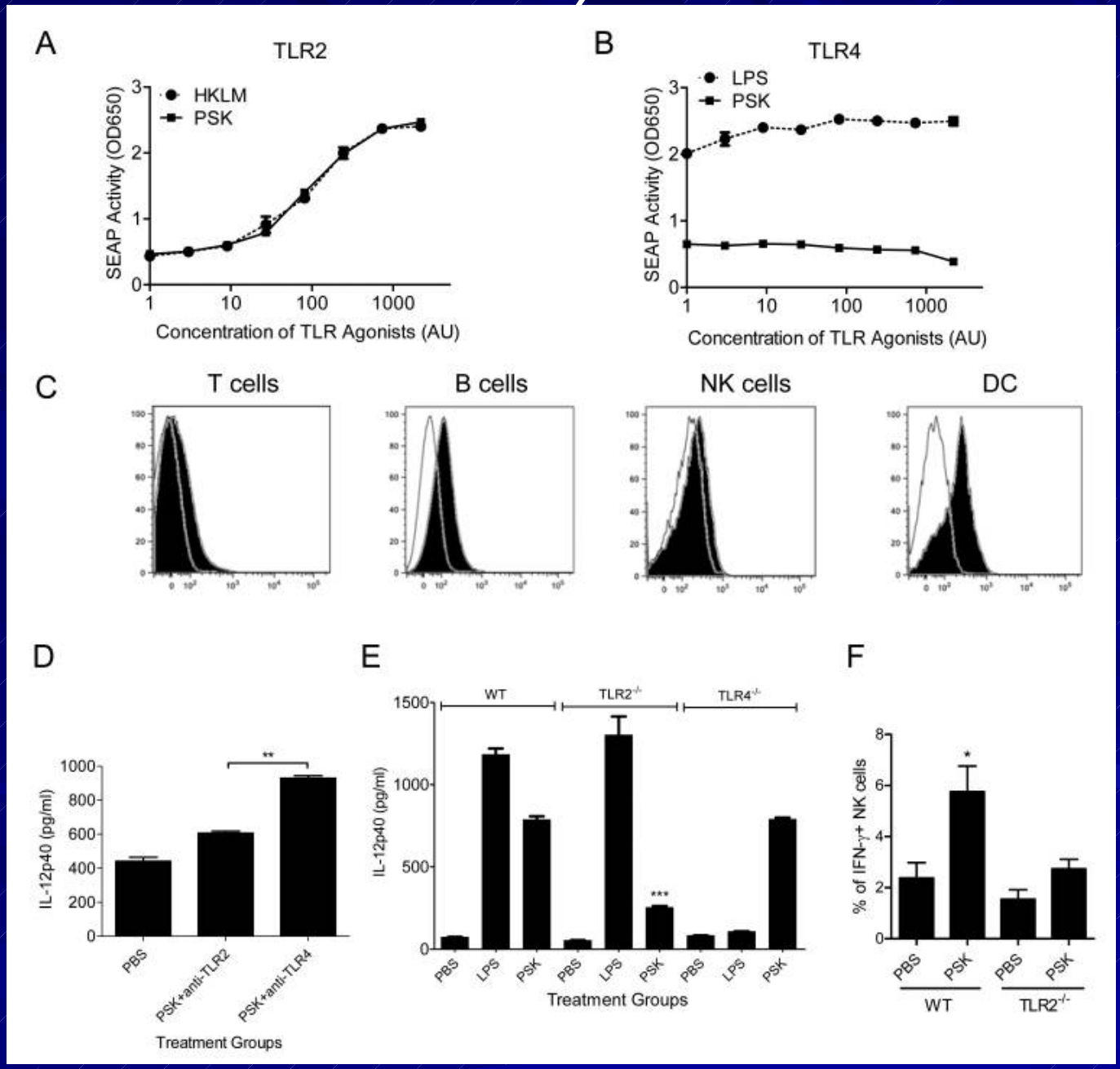
PSK increases DCs in tumor draining lymph nodes (TDLN)



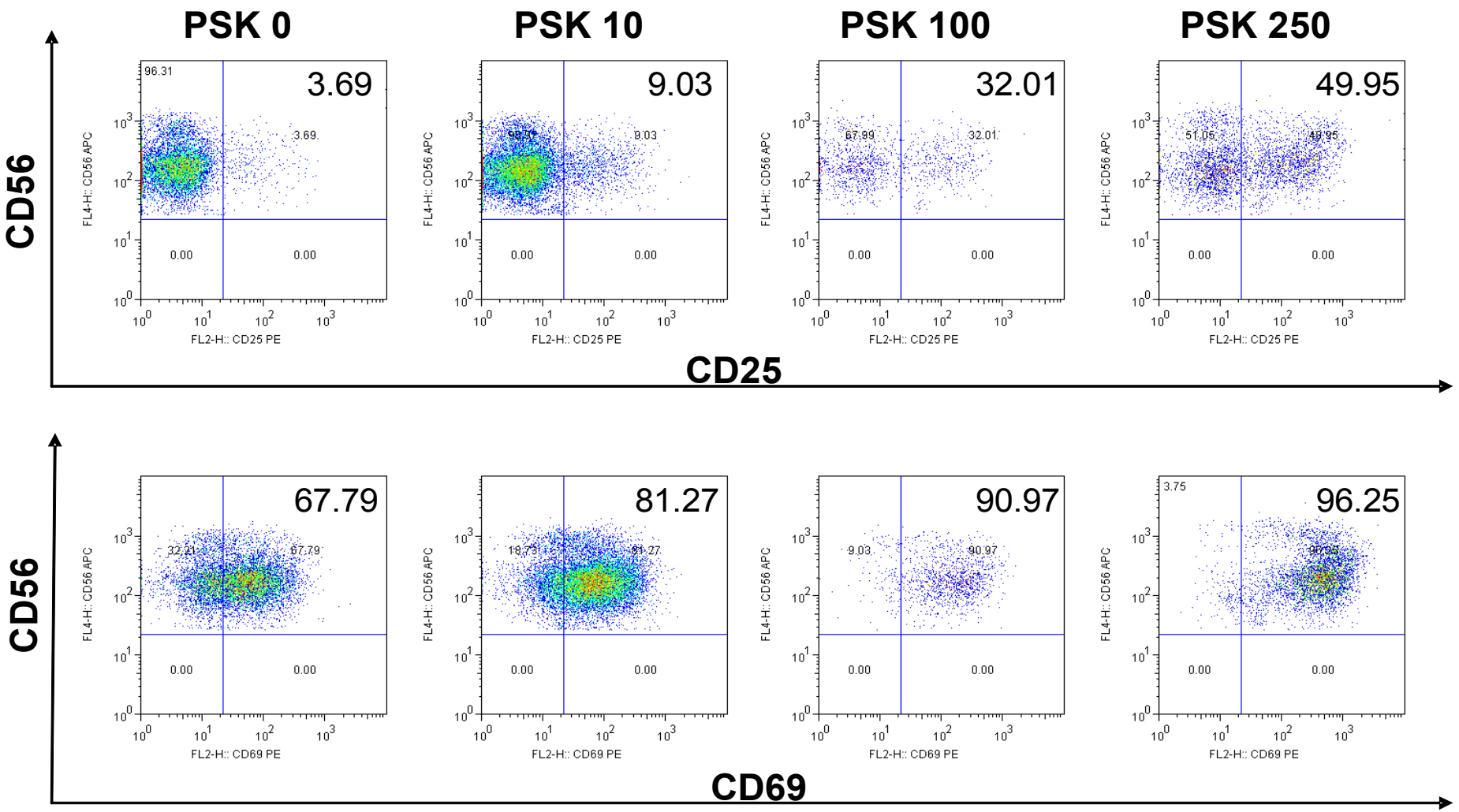
PSK increases cytotoxic effector molecules in tumor target cells



PSK acts as a TLR2 agonist to activate DCs

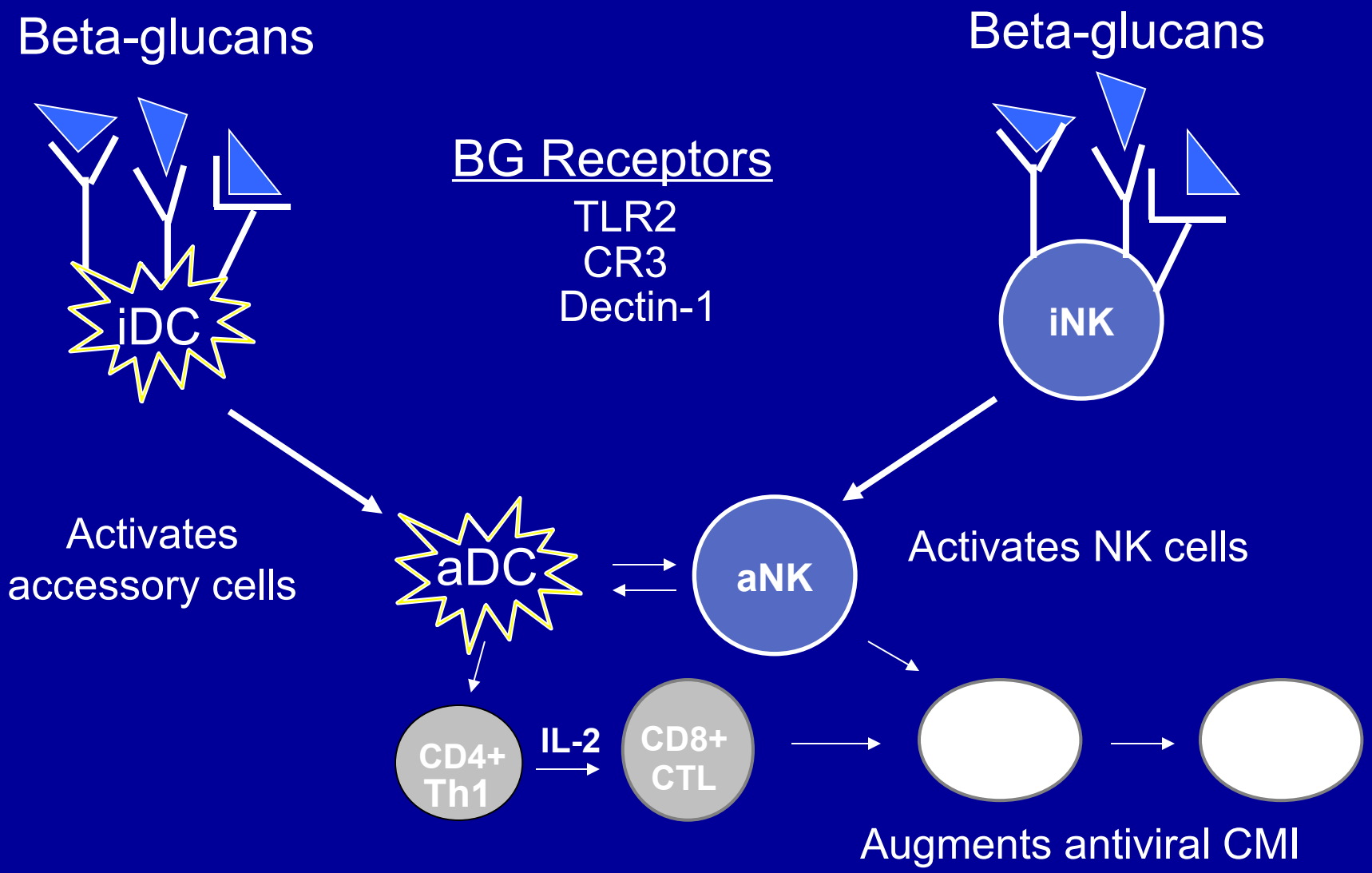


PSK dose-dependently enhances NK cell activation



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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