

Unsung Herbal Heroes of Immunity

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Disclosures

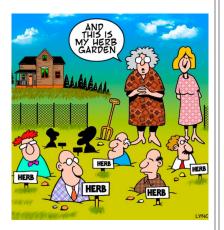
- Compensated occasional industry-sponsored webinars and educational presentations:
- · NutraBioceuticals, Gaia, NFH, Nordic Naturals
- Co-principal for Thrivers, LLC that runs a podcast with commercial support from:
 - Kyowa Hakko, Essential Formulas, Integrative Therapeutics

Topics

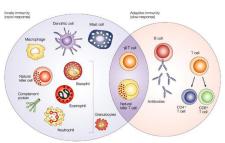
- · A brief review of immunity
- Focus on anti-viral immunity
 Focus on SARS-CoV-2
- Highlighted botanicals:
 - Usnea spp. Spilanthes acmella

 - Hemidesmus indicusCoptis chinensis

 - Andrographis chinensis
 Echinacea spp.
 - Sambucus nigra

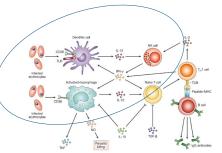


Immunity: Innate and Adaptive



- Not antigen-specific
- First line of defense prior to the initiation of an adaptive immune response against tumor or infection.
- Recruit Immune cells to the sites of infection through the production of cvtokines
- · Activates complement cascade to id bacteria, activate cells and promote clearance of antibody complexes
- · Influences the adaptive immune system.

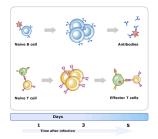
Innate Immunity



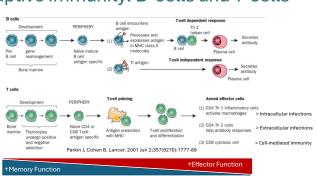
Langers I, et al. Biologics: Targets and Therapy. 2012;6:73-82

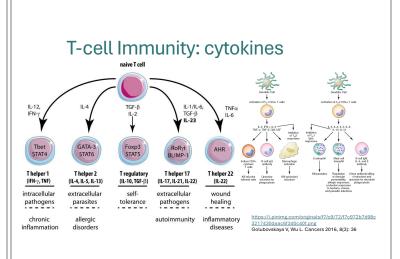
Acquired (Adaptive) Immunity

- Second line of defense
- Protects against re-exposure to the same pathogens
- · Antigen-specific and takes time to react
- Has immunological memory



Adaptive Immunity: B-cells and T-cells



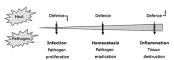


Prevention vs. Disease Management

It is important to separate prevention support from support for mild/moderate symptomatic infection due to the role of inflammation

Inflammation is initially a critical element of immune activation and antiviral peptide production.

However, excessive inflammation (NLRP3 inflammasome activation and continued T_H1 activation) generated underlies the virulence and complications of viral disease, so antiinflammatory strategies are important once infection and/or symptoms are present.

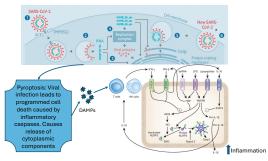


Chen I-Y, et al. Front Microbiol. 2019;10:50

Prevention of viral infections: 3 components, ex. SARS-CoV-2

- Block viral docking to ACE2 receptors
- Prevent viral entry by inhibiting cellular proteases (TMPRSS2) and viral replication (papain-like protease 2, PLP2)
- Increase antigen presenting cell & gamma delta <u>T cell</u> activity, INF-y, secretion and subsequent defensive NLRP3 inflammasome

Echinacea: Anti-viral



Clinically studied dosages

Citations

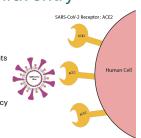
Prevention: 1. Block viral entry

Block ACE2 receptor binding: SARS-CoV-2 S-glycoprotein interacts with ACE2 receptor for viral entry.

Astragalus membranaceus extract has been show in rats to decrease ACE receptor activity.1

Quercetin has been shown to bind to ACE2 and prevent viral binding in a supercomputer-based in-silico study.2

Vitamin D3 reduces ACE2 activation3 and vit D sufficiency is associated with reduced infection and mortality⁴



- Wang Q-Y. Zhongguo Zhong Yao Za Zhi. 2015.40(21):4245 [abstract only]
 Smith M et al. ChemRxiv.2020;v4. [not peer reviewed]
 Cui C, et al. Redox Biol. 2019;26:101295
- Ilie PC, et al. Aging Clinical Exp Res. 2020;32:1195

Sys Rev/Meta-analysis (2019), 29
DBRPCT on URI- overall risk ratio of 0.78° (9.5%CI 0.68-0.88) for URI, however sub-group analysis of children show RR of 0.60 (9.5%CI 0.51-0.69).

*Note: 12% reduction in risk (RR of 0.78) means that @ 4 URI/year, Echinacea x 3 would prevent one URI. DBRCT (2011), of children ages 4-12y, assessing effect of 1.2g Echinaforce® (fresh E purpurea leaves and root tincture) compared to 150mg vit. (controls) x 2 months for prevention of URI. In the intention to treat analysis, Echinacea prevented 22.5% of viral respiratory tract infections, yielding OR = 0.52 (9.5% CI 0.30-0.91, p= 0.021). Further, 76% fewer Echinacea-treated children required antibiotics. 1:2 tincture, 3-7mL/day (20-50 mL/week) 1:5 tincture., 9-15mL/day (60 – 100mL/week) Expressed juice of E. purpurea: 6-10 ml Cohen HA, et al Arch Pediatr Adolesc Med. 2004;158:217 y cytokines esp TNFα and IL-8 Ogal M, Eur J Med Res. 2021;26(1):33

Best Evidence

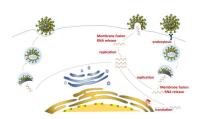
Prevention: 2. Inhibit viral replication

Zinc potently inhibits the enzymatic activity of SARS-CoV PLP2 (viral protease).

This inhibition results in:

Reduction of viral replication

Increased interferon produced by the cell which destroys the virus



Han Y-S, et al. Biochemistry. 2005;44(30):10349 Baez-Santos, YM, Antiviral Res. 2015;115:21. Yuan L, et al. J Biol Chem. 2015;290(5):3172.

Prevention: 2. Inhibit viral replication

Zinc ionophores: Chelators of zinc, increasing its transport into the cytoplasm

Dihydroquercetin1 and quercetin1 Source: onions, apples

Epigallocatechin gallate1 (EGCG) Source: tea leaves, esp. green tea

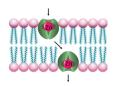
Glycyrrhizin from Glycyrrhiza glabra (licorice plant) Inhibits SARS-CoV virus replication, adsorption and penetration of the virus^{2,3} (more potent than ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid)⁴

Samples derived from patients with SARS admitted for treatment in Germany (2003)

Note: elevated blood pressure and hypokalemia can occur in some individuals after several months of (high dose*) glycyrrhizin. Prevention/early treatment of SARS should only be needed for a short time avoiding this potential adverse effect.

*>50g licorice/day >2 weeks

- Dabbagh-Bazarbachi H, et al. J Agric Food Chem. 2014;62(32):8085
 Cinati J, et al. Lancet. 2003;361(9374):2045
 De Clercq, Expert Rev Anti Infect Ther. 2006;4(2):291
 H. Hoever G, et al. J Med Chem. 2005;48(4):1256.





Prevention: Inhibit viral replication & attachment

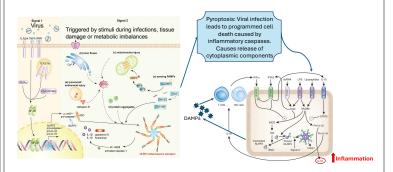
Elderberry (Sambucus nigra):

Inhibits replication and viral attachment of human coronavirus NL63 (HCoV-NL63).



Weng JR, et al. Virus Res. 2019;273:197767

Prevention: 3. NLRP3-induced inflammation



Prevention: Double-edged sword of the NLRP3 inflammasome

- In initial infection, NLRP3 inflammasome activation:1
 - Triggers inflammation-associated cell death
 - Activates neutrophil recruitment to the site to aid in elimination of virally infected cells
- However, in the case of SARS-CoV-2, excessive NLRP3 activation and its associated cytokines (esp. IL-1beta) contribute to extensive pyroptosis (inflammatory cell death from infection) and accentuated inflammation leading to outcomes such as acute respiratory distress.
- Furthermore, in patients with severe Covid-19 symptoms, there are differences in immune responses leading to more inflammation:3
 - Greater quantity of non-virus specific CD4+ T-cells in circulation
 - · Impaired CD4+ T cell responsivity and fewer resident T cells (which are more virally specific)
 - Decreased IFN- γ so greater viral load
 - Neutralizing IgG antibodies are significantly higher with consequent immune impairment
 - Zhao C and Zhao W. Front Immunol. 18 Feb 2020
 Chen I-Y, et al. Front Microbiol. 2019;10:50.

 - 3. Oja A, et al. Eur J Immunol. 2020;50(12):1988

Prevention of COVID-19 illness: Reduce NLRP3 inflammasome activation, animal data

- In a juvenile mouse model of influenza A viral infection, inhibition of the NLRP3 inflammasome starting 3 days after infection <u>ameliorated</u> severe NLRP3 inflammasome-mediated <u>lung injury</u> without impairing viral clearance¹
- NLRP3 inflammasome activation (and associated IL-1beta, and subsequently IL-6 and TNFa) is responsible for pneumonia and acute respiratory distress from avian influenza A H5N1 infection.²
- NFkB activation activates pro-IL-1B transcription and its inhibition improves survival in severe acute respiratory syndrome in coronavirus-infected mice.

 - Coates BM, et al. Front Immunol. 2017;8:782
 Chen YJ, et al. Am J Pathol. 2018;188(4):1031
 DeDeigo ML, et al. J Virol. 2014;88(2):913

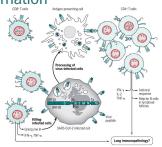
Inflammation, Disease Severity & Immunomodulation

- Severe disease is characterized by ${f decreased}$ CD4+ TH1-cell production of ${f IFN-\gamma}$ and ${f IL-4}$:
 - IFN- γ downregulates cell surface expression of ACE2 and inhibits SARS-CoV-2 replication
 - IL-4 antagonizes TH1 and TH17 responses thereby supporting immune suppressive Treg cells (thus quelling tissue-damaging inflammation)
 - In severely ill individuals, SARS-CoV-2 specific CD4+ TH1 cells do not produce IL-4, thus impairing the ability to prevent a hyperimmune response and Covid-19 cytokine storm.
- Also in severely ill individuals, delayed and insufficient CD4+ T-cell control of viral loads along with decreased innate immune function (common in the elderly) lead to more severe symptoms.
- Failure of a balanced participation of B- and T-cells leads to alveolar epithelial and endothelium inflammation causing vascular leakage. This leads to increased immune cell infiltration of non-SARS-CoV-2-specific immune cells and further pulmonary edema.

Oja A, et al. Eur J Immunol. 2020;50(12):1988

Prevention: 3. Immunoinflammation

- Vitamin D induces cathelicidin, an antiviral peptide secreted by immune cells and respiratory epithelial cells
- Vit. D has immune-modulating actions:
 - Increases macrophage (APC) activation
 - Inhibits APC production of IL-1a, IL-1b, TNF-a
 - · Increases IL-10 (immunosuppressive)
 - · Up and down-regulation of NFkB
- Note, however, that high vit D can potentiate CD4+ T_H1 cell responses – supporting an inflammatory response in the lungs



TCR PHLAI THAIL TPD-1 C038 C04 C08

Cannell JJ, et al. Epidemiol Infect. 2006;134(6):1129. Hughes DA and Norton R. Clin Exp Immunol. 2009;158(1):20.

Prevention of inflammation associated with viral infection



	Mechanisms	Best Evidence	Clinically studied dosages	Level of Evidence & Harm	Citations
Astragalus membranaceus (Huang-Chi)	Polarize macrophages to Mi activation, increase dendritic cell maturation, increase T-cell mediated immunity; downregulate NLRP3 inflammasome signaling	2 week RCT of 82 COPD patients with acute exacerbation, 15mg twice daily of Astragalus extract reduced inflammatory cytokines (TNF α , IL-8, IL-9 β , IL-32) and increased T-helper cells, NK cells, and reduced T regulatory cells	standardized to 40%-0% polysaccharides or 3% astragalosides: 400mg - 2000mg daily. 4-8mL/day; 30-60mL/week of 1:2 tincture Ped: 1-5% adult dose 5-8y = 1/3 th adult dose 109-15y = ½ adult dose	Grade C	Jiang D, Biomed Mater Eng. 2015;26(585):S 2113

Decrease symptoms/severity of infections

	Mechanisms	Best Evidence	Clinically studied dosages	Level of Evidence & Harm	Citations
Sambucus nigra (Elderberry)	Anti-viral; enhances phagocytosis	Meta-analysis (2019), 4 RCT, n=86 found that elderberry reduces duration and severity of URIs, especially influenza (regardless of vaccination status) with weighted effect size of 2.074 (SE: 0.383; 95% CI: 32–2.84; F = <.000, but did not reduce symptoms caused by the common cold weighted effect size of 6.065 (SE: 0.387; 95% CI: -0.096 - 1.421; P = .087) In a RDBPCT of 312 transcontinental air passengers (2006), elderberry extr. taken x 10d before travel, during travel and x 5d after arrival, in those who developed a cold, they experienced a 2-day shorter duration (4.75 days vs. 6.88 days) and lower symptom severity (21 vs. 3.4) in comparison placebo.	Syrup [1 tsp/5mL = 1.9g stnd. liquid extr. 2:1]: Adults: 15 mL 3-4 times daily Children: 5 mL 3-4 times daily	Grade A; uncooked fresh berries are poisonous (d/t cyanogenic glycosides). Insufficient data to recommend during PG	Hawkins J, Complemen t Ther Med. 2019;42:361. Tiralongo E, Nutrients. 2016;8(4):18
Echinacea spp.	Improves sIgA and reduces pro- inflammatory TNFα and IL- 8	Echinacea reduces duration of URI by an average of -45 days (95% Cl 1.85 - 0.94) *did not reach statistical significance		Grade C	Sholto D. Complement Ther Med. 2019;44:18- 26

Decrease symptoms/severity of infections

	Mechanisms	Best Evidence	Clinically studied dosages	Level of Evidence & Harm	Citations
Andrographis paniculata	Andrographolides are antibacterial against Gm- and Gm- by inhibiting biofilm formation and downregulate quorum sensing and adherence, ambiving bit expression thus reducing bacteria adherence, ambiving by inhibiting virul	Systematic review and meta-analysis (2017), 33 RCTs of 7075 participants of all ages with uncomplicated acute respiratory tract infections on common code acute respiratory tract infections on common code acute respiratory tract infections on common code is acute respiratory tractification of the six in blinding participants in most studies due to his in blinding participants found Andrographis was more effective than placeholic overall symptom improvement, cough, sore throat as (Eusey In = 124,7 RR: 1.36, 95/KC!; [1.16, 0.12], and more effective than usual care in overall symptom improvement sore throat, sick leave [in = 124,7 RR: 1.36, 95/KC!; [1.16, 1.27]. Andrographis plus usual care ass more effective in symptom improvement than usual care alone [in = 1900, RR: 1.31, 95/KC!; [1.16, 1.48]. Systematic Rev (2004), 7, DBRCTs, in = 896 for Andrographis for uncomplicated URTIs; average duration of treatment 3 – 7d. Pooled results show Andrographis results is greater improvement in overall symptoms, fewer days of sick leave, greater eradication of sore throat and fewer (compared with paracetamol). No significant adverse events reported, Inote While trails were of good – excellent design, there was a risk of publication bias]	Andrographis stand. Extr.: 90- 600mg daily in Extr.: 90- 600mg daily 20- 100 mg daily 20- 1	Grade A; mild adverse effects (<5%) that include N/V, abdominal discomfort, dizziness, drowsiness, malaise. Adverse effects are more likely when doses reach or exceed 5-to mg/kg body weight of andrographolid e content.	Hu X-Y, PLoS ONE. 2017;21(8):e 0181780 Coon Jan dentrist E. Planta Med. 2004;70:293

Usnea spp.

- Lichen (symbiosis of algae or cyanobacteria and fungi)
- Contains 1-3% by dry weight of usnic acid (soluble in alcohol and to a lesser extent in hot water)
- Lichen acids, i.e. usnic acid (antibiotic), polysaccharides [immunostimulating], mucilage [demulcent], anthraquinones, i.e. endocrocin [laxative], fatty acids, all essential amino acids, vitamins, carotene
 - Antimicrobial against Gm positive bacteria (Staphylococcus aureus and Mycobacterium tuberculosis)
 - Usnic acid is primarily antibiotic, especially against
 Gm. positive organisms such as: Streptococcus,
 Staphylococcus, Mycobacterium tuberculosis and
 other fast-growing species. Usnea spares the gram
 negative bacteria that colonize the intestinal tract
 - Antifungal
 Limited entirely
- Limited anti-viral activity
- Binds free radicals and exert cytotoxic effects
- Vulnerary





- Key indications:
- Gastroenteritis Pharyngitis

 - Fungal skin infections
- Impetigo
- Therapeutic dose: 7 15mL/day; 50-100mL/week of 1:5 tincture
- No known interactions
- Note: isolated usnic acid in dietary supplements (>500mg/day) is hepatotoxic due to uncoupling oxidative phosphorylation (antibacterial MoA) and mitochondrial inhibition
 - [Chen S, J Environ Sci Health C Toxicol Carcinog. 2025;43(1):1-22]



Spilanthes acmella (Toothache plant)

- Herb and flowerhead used
- Contains volatile oils, resins, tannins and alkaloids
- Sialagogue (when chewed)
- · Bitter digestive
- Anti-inflammatory
- Topical analgesic
- Antimicrobial: Spilanthes is a very effective addition to formulas containing Echinacea, as these plants seem to share some of the same medicinal properties.
- Splianthes also appears to have anti-fungal and anti-parasitic properties and combines well with other anti-fungal plants such as Usnea barbata, Hyssopus officinalis, and other plants with a high content of anti-fungal volatile oils.
- 10 -15mL/day; 80-100 mL/week of 1:5 tincture

Hemidesmus inducus (Indian sarsasparilla)

- · Asclepiadaceae family
- Root used

Usnea spp.

- Contains: coumarin, resins, glucosides, tannis, triterpenoid saponins
- Anti-inflammatory, Dupurative, Antioxidant, Mild immunosuppressant, Antibacterial, Antifungal, Proapoptotic, Anti-ulcerogenic, Anti-diabetic
- Indications: Autoimmunity, Chronic inflammation, Bacterial and fungal infections
- · Interrupts bacterial biofilms
- Reduces excessive inflammatory responses giving in primary indication in autoimmune diseases and in severe and chronic viral infections
- Dose: 3 8mL/day; 20-60mL/week of 1:2 tincture





Coptis chinesis

- Ranunculaceae
- Rhizome used
- · Berberine alkaloids
- · Medicinal actions: Antifungal, antibacterial, antidiarrhoeal, anti-inflammatory
- Medicinal indications: IBD, SIBO, Gastroenteritis, Infections, URI, Influenza, Bronchitis¹, Sinusitis, Dermatitis
- Infectious and inflammatory conditions of the mucosa, GI, and skin
- 3 7mL/day; 20-50mL/week of 1:2 tincture

1. Han K, Curr Med Res Opin. 2024;40(7):1235

Decrease COVID-19 inflammasome activation & symptoms

Vitamin C

- Reduces NLRP3 inflammasome activation¹
- Shortens frequency, duration and severity of common cold and the incidence of pneumonia (Sys Rev of human clinical trials)²
- Increases mRNA expression of IFNy genes in macrophages³

Melatonin

- Inhibits NFkB and NLRP3 inflammasome⁴
- Melatonin reduces oxidative lung injury and inflammatory cell recruitment during viral infections⁵
- Induces Sirt1, thereby enhancing the transcription of interferon-producing genes⁶

 - Choe J-Y, Inflammation. 2017;40(3):980 Hemila H, Mil Med. 2004;169(11):90 Suebsaard P. vet Immunol Immunopathol. 2021;235:110231 Hardeland R. J Pineal Res. 2016;65(4):e12525 Silvestri M. Rossi GA. Ital J Pediatr. 2013;39:61 DiNicolantonio J, Open Heart. 2021;8(1):e001568

Decrease COVID-19 inflammasome activation & symptoms

- Plant flavonoids¹ (over 6000 flavonoids in edible plants)
 - Reduce NFkB and NLRP3 inflammasome signaling
- Quercetin^{2,3} (found in onions and apples): in addition to virocidal and improved innate immunity, quercetin has anti-inflammatory effects, potently inhibiting IL-8 (more effective than cromolyn) and IL-6. Quercetin (and isoquercetrin) results in 20x higher plasma concentrations of IFN- γ
- $\textbf{Garlic}^{\textbf{4,5}}\text{: organosulfur compounds activate innate immune cells but also has immunoregulatory and a substitution of the substitution o$ antiinflammatory actions, specifically suppressing inflammatory cytokines such as IL-6, TNF-a.
 - 2g fresh garlic increases the level of interferon- α 4x (produced in virally infected cells) and chronic consumption maintains elevated IFN-lpha
- Epigallocatechin gallate (EGCG)^{5,6} (from green tea) blocks viral attachment and down-regulates proinflammatory cytokines4 including IL-1b5



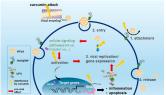


Decrease COVID-19 inflammasome activation & symptoms

Abe Y. Pharmacol Res. 1999;39.41
Jain SK. Antioxid Redox Signal. 2009;11:241
Kedzierski L. PLoS Pathog. 2014;10(5): e1004134
Sordillo F. Helson L. In Vivo. 2015;29(1):1
Yin H. Jimmund. 2018;200(9):2835
Wen CC. J Med Chem. 2007;50(17):4087
Memarzia A. Biofactions. 2021 Feb. doi: 10.1002/biof.1716

Curcumin, a flavonoid found in turmeric root

- Reduces viral attachment, entry, replication, & activation
- Suppresses key cytokines involved in the cytokine storm of SARS-CoV-19: IL-1b, IL-8, TNFa, IL-6^{1,2} and reduces cytokine storm associated with severe viral infections^{3,4}
- Inhibits NLRP3 inflammasome while also inhibiting coronavirus replication through viral protease inhibition^{5,6}
- Increases INF-γ production⁷

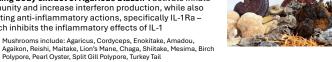


Matthew D. Hsu W-L. J Functional Foods, 2018:40:692



Decrease COVID-19 inflammasome activation & symptoms

Mycelium/fruiting body mushrooms* extract1,2 and fruiting body extract of Agaricus blazeii3: activate innate immunity and increase interferon production, while also exerting anti-inflammatory actions, specifically IL-1Ra – which inhibits the inflammatory effects of IL-1

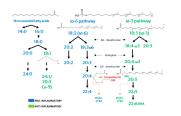


- Davis R, et al. J Inflammation Res. 2020;13:117 Benson KF, et al. MC Complement Alternat Med. 2019;19:342 Tangen J-M. BioMed Res Int. 2015;2015:718539

Decrease COVID-19 inflammasome activation & symptoms

Omega-3 PUFA: suppress proinflammatory cytokines by suppressing gene expression of components of the NLRP3 inflammasome. This results in reduced production of IL-1b.1

Oral supplementation with omega-3 PUFAs (360mg EPA and 240mg DHA) increased INF- γ (~2 pg/mL) (P<0.001) in 40 epileptic patients after 16-weeks of supplementation



- Kumar NG. Nutrients. 2019;11:2974. Ghafouri-Fard S. J Mol Neurosci. 2021 Feb 12. doi: 10.1007/s12031-021-01804-y

Decrease COVID-19 inflammasome activation & symptoms

Andrographis paniculata:

Contains andrographolides that inhibit IL-1b¹ Reduces duration and symptoms of URIs (esp. cough and sore throat) [Sys Rev]2

Astragalus membranaceus:

Contains astragalosides which inhibit IL-1b induced inflammation $^{3,4}\,$

Reduces replication of avian coronavirus⁵

- Chandrasekaran CV. Antiinflamm Antiallergy Agents Med Chem. 2012;11(2):191.
 Hu X-Y. PLoS One. 2017;12(8):e0181780
 He X. Molecules. 2012;17(3):3155
- Li H. Immunopharmacol Immunotoxicol. 2019;421(4):497
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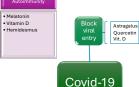
Conclusions















Thank you!

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