

## news



# COVID-19: Functional Medicine Resources

## **The Functional Medicine Approach to COVID-19: Virus-Specific Nutraceutical and Botanical Agents**

Published April 1, 2020

### **Background and Introduction**

Health professionals and the public must be well informed about the COVID-19 virus, the disease it causes, and how it spreads. This information is readily available and not within the scope of this document. At this time, there are no specific vaccines or uniformly successful treatments for COVID-19. In this context of insufficient evidence, the scope of this document will be to assess the scientific plausibility of promising prevention approaches and therapeutic (nutraceutical and botanical) interventions and then to offer clinical recommendations.

With respect to interventions, the practice of Functional Medicine emphasizes the primacy of safety, validity, and effectiveness. In the novel context of COVID-19, validity in the form of published evidence is lacking. Therefore, “validity” relies upon inferences from the mechanisms of action of individual agents and/or published outcomes data supporting their mitigating effects on illness from other viral strains. Likewise, data for the “effectiveness” of interventions targeting the viral mechanisms of COVID-19 are nascent and rapidly emerging. In this context, the following recommendations represent the Functional Medicine approach to the COVID-19 crisis:

- Adherence to all health recommendations from official sources to decrease viral transmission.

- Optimizing modifiable lifestyle factors in order to improve overall immune function (an introductory document on ‘Boosting Immunity’ is available [here](#)):
  - Reduces progression from colonization to illness.
- Personalized consideration of therapeutic agents that may:
  - Favorably modulate cellular defense and repair mechanisms.
  - Favorably modulate viral-induced pathological cellular processes.
  - Promote viral eradication or inactivation.
  - Mitigate collateral damage from other therapeutic agents.
  - Promote resolution of collateral damage and restoration of function.
- Treatment of confirmed COVID-19 illness (as per conventional standards and practice):
  - May reduce the severity and duration of acute symptoms and complications.
  - May support recovery and reduce long-term morbidity and sequelae.

Additional references are being collated and will be made available in the future.

## **Clinical Recommendations and Mechanisms of Action**

### **Background and Mechanisms of Action**

We encourage practitioners to learn about the mechanism of invasion, replication, and pathophysiology of the COVID-19 virus. Much of what we know has been extrapolated from basic science research on SARS-CoV-2. Excellent resources are available online, including the free [YouTube lectures through Dr. Roger Seheult](#):

This document discusses the mechanisms of action of a number of different botanical and nutraceutical agents. These agents can be considered as immunoadjuvants, defined as substances that act to accelerate, prolong, or enhance antigen-specific immune responses by potentiating or modulating the immune response.<sup>[1]</sup>

A coronavirus such as SARS-CoV-2 can be deadly because of its ability to stimulate a part of the innate immune response called the inflammasome, which can cause uncontrolled release of pro-inflammatory cytokines, leading to cytokine storm and severe, sometimes irreversible, damage to respiratory epithelium.<sup>[2]</sup> The SARS-CoV-2 virus has been shown to activate the NLRP3 inflammasome.<sup>[3,4]</sup> A 2016 review article<sup>[5]</sup> entitled “Natural compounds as regulators of NLRP3 inflammasome-mediated IL-1 $\beta$  production” notes that “resveratrol, curcumin, EGCG [epigallocatechin gallate], and quercetin are potent inhibitors of NLRP3 inflammasome-mediated IL-1 $\beta$  production, typically acting at more than one element of the involved pathways. However, it should be noted that these polyphenols have an even much broader biological effect, as they influence a variety of pathways.” For example, these polyphenols modulate NF- $\kappa$ B upregulation, which is useful to counteract the COVID-19 ‘hyper-inflammation.’<sup>[6]</sup>

A preprint released on March 23, 2020, identified the ability of plant bioactive compounds to inhibit the COVID-19 main protease (M<sup>pro</sup>),<sup>[7]</sup> which is necessary for viral replication. There is much excitement surrounding the recent identification of M<sup>pro</sup>, and it is a current potential pharmaceutical drug target. Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate were the natural compounds that appeared to have the best potential to act as COVID-19

M<sup>pro</sup> inhibitors. Though further research is necessary to prove their efficacy, this study provides the biologic plausibility and mechanistic support (COVID-19 protease inhibition) to justify their use.

For these reasons, we recommend the following compounds, at standard dosages, to **prevent** activation of the NLRP3 inflammasome, to decrease NF-κB activation, and to potentially inhibit COVID-19 replication. There is no literature to support a regimen of a single vs. multiple agents. Our recommendation is to use higher dosing and/or multiple agents when patient contextual factors (e.g., patient desire, pre-existing inflammation, multiple co-morbidities, higher risk, etc.) and/or therapeutic decision-making warrant such use.

In the recommendations below, the following criteria are used to identify strength of evidence and risk of harm.



## Recommended Interventions

### QUERCETIN

Quercetin has been shown to have antiviral effects against both RNA (e.g., influenza and coronavirus) and DNA viruses (e.g., herpesvirus). Quercetin has a pleiotropic role as an antioxidant and anti-inflammatory, modulating signaling pathways that are associated with post-transcriptional modulators affecting post-viral healing.<sup>[8]</sup>

Intervention	Quercetin
Suggested Dose	<b>Regular 1 gm po bid, phytosome 250-500 mg bid</b>
Mechanism(s) of action against non-COVID-19 viruses	<p><i>Promote viral eradication or inactivation:</i><sup>[9],[10],[11],[12],[13]</sup></p> <ul style="list-style-type: none"> <li>•Inhibition of viral replication</li> </ul> <p><i>Favorably modulate viral-induced pathological cellular processes:</i></p> <ul style="list-style-type: none"> <li>•Modulation of NLRP3 inflammasome activation<sup>[5],[14],[15]</sup></li> </ul> <p><i>Mechanistically promote resolution of collateral damage and restoration of function:</i></p> <ul style="list-style-type: none"> <li>•Modulation of mast cell stabilization (anti-fibrotic)</li> </ul>
Outcomes data supporting their mitigating	Reduction of symptoms
Strength of evidence	Moderate
Risk of harm: <sup>[16],[17]</sup>	Mild

### CURCUMIN

Curcumin has been shown to modulate the NLRP3 inflammasome,<sup>[5]</sup> and a preprint suggests that curcumin can target the COVID-19 main protease to reduce viral replication.<sup>[18]</sup>

Intervention	<b>Curcumin</b>
Suggested Dose	<b>500-1,000 mg po bid (of absorption-enhanced curcumin)</b>
Mechanism(s) of action against non-COVID-19 viruses	<i>Favorably modulate viral-induced pathological cellular processes:</i> •Modulation of NLRP3 inflammasome activation <sup>[5],[19],[20],[21]</sup>
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm: <sup>[22],[23],[24],[25],[26],[27]</sup>	Mild

### **EPIGALLOCATECHIN GALLATE (EGCG)**

Green tea, in addition to modulating the NLRP3 inflammasome and, based on a preprint, potentially targeting the COVID-19 main protease (M<sup>pro</sup>)<sup>[31]</sup> to reduce viral replication, has also been shown to prevent influenza in healthcare workers.<sup>[28]</sup>

Intervention	<b>Epigallocatechin gallate (EGCG)</b>
Suggested Dose	<b>4 cups daily or 225 mg po qd</b>
Mechanism(s) of action against non-COVID-19 viruses	<i>Favorably modulate viral-induced pathological cellular processes:</i> •Modulation of NLRP3 inflammasome activation <sup>[5],[28],[29]</sup>
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm: <sup>[30],[31],[32],[33],[34],[35]</sup>	Significant (rare) - Hepatotoxicity

## N-ACETYLCYSTEINE (NAC)

N-acetylcysteine promotes glutathione production, which has been shown to be protective in rodents infected with influenza. In a little-noticed six-month controlled clinical study enrolling 262 primarily elderly subjects, those receiving 600 mg NAC twice daily, as opposed to those receiving placebo, experienced significantly fewer influenza-like episodes and days of bed confinement.<sup>[36]</sup>

Intervention	<b>N-Acetylcysteine (NAC)</b>
Suggested Dose	<b>600-900 mg po bid</b>
Mechanism(s) of action against non-COVID-19 viruses: <sup>[36]</sup>	<i>Favorably modulate cellular defense and repair mechanisms:</i> •Hypothetical: repletion of glutathione and cysteine
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms
Strength of evidence	Limited
Risk of harm: <sup>[37],[38],[39],[40],[41]</sup>	Mild

## RESVERATROL

Resveratrol, a naturally occurring polyphenol, shows many beneficial health effects. It has been shown to modulate the NLRP3 inflammasome.<sup>[5]</sup> In addition, resveratrol was shown to have in vitro activity against MERS-CoV.<sup>[43]</sup>

Intervention	<b>Resveratrol</b>
Suggested Dose	<b>100-150 mg po qd</b>
Mechanism(s) of action against non-COVID-19 viruses	<i>Favorably modulate viral-induced pathological cellular processes</i> •Modulation of NLRP3 inflammasome activation <sup>[5]</sup>
Outcomes data supporting their mitigating effects on illness from other viral strains	MERS-CoV <sup>[43]</sup> Influenza <sup>[44],[45]</sup>
Strength of evidence	Conditional
Risk of harm: <sup>[46],[47],[48],[49],[50],[51],[52],[53]</sup>	Mild

## VITAMIN D

Activated vitamin D, 1,25(OH) D, a steroid hormone, is an immune system modulator that reduces the expression of inflammatory cytokines and increases macrophage function. Vitamin D also stimulates the expression of potent antimicrobial peptides (AMPs), which exist in neutrophils, monocytes, natural killer cells, and epithelial cells of the respiratory tract.<sup>[54]</sup> Vitamin D increases anti-pathogen peptides through defensins and has a dual effect due to suppressing superinfection. Evidence suggests vitamin D supplementation may prevent upper respiratory infections.<sup>[55]</sup> However, there is some controversy as to whether it should be used and the laboratory value that should be achieved. Research suggests that concerns about vitamin D (increased IL-1beta in cell culture) are not seen clinically. The guidance we suggest is that a laboratory range of >50 and < 80ng/mL serum 25-hydroxy vitamin D may help to mitigate morbidity from COVID-19 infection.

Intervention	<b>Vitamin D</b>
Suggested Dose	<b>5,000 IU po qd in the absence of serum levels</b>
Mechanism(s) of action against non-COVID-19 viruses <sup>[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78]</sup>	<p><i>Favorably modulate cellular defense and repair mechanisms:</i></p> <ul style="list-style-type: none"> <li>•Activation of macrophages Stimulation of anti-microbial peptides</li> <li>•Stimulation of anti-microbial peptides</li> <li>•Modulation of defensins</li> <li>•Modulation of TH17 cells</li> </ul> <p><i>Favorably modulate viral-induced pathological cellular processes:</i></p> <ul style="list-style-type: none"> <li>•Reduction in cytokine expression</li> <li>•Modulation of TGF beta</li> </ul>
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms and complications
Strength of evidence	Limited
Risk of harm: <sup>[79],[80],[81],[82]</sup>	Mild

## MELATONIN

Melatonin has been shown to have an inhibitory effect on the NLRP3 inflammasome.<sup>[94]</sup> This has not gone unnoticed by the COVID-19 research community, with two recent published papers proposing the use of melatonin as a therapeutic agent in the treatment of patients with COVID-19.<sup>[84],[85]</sup>

Intervention	<b>Melatonin</b>
Suggested Dose	<b>5-20 mg qd</b>

Mechanism(s) of action against non-COVID-19 viruses .[83],[84]	<i>Favorably modulate viral-induced pathological cellular processes</i> • Modulation of NLRP3 inflammasome activation .[83],[84]
Outcomes data supporting their mitigating effects on illness from other viral strains	Research in progress
Strength of evidence	Conditional
Risk of harm:[86],[87],[88],[89],[90],[91],[92],[93],[94]	Mild

## VITAMIN A

Vitamin A is a micronutrient that is crucial for maintaining vision, promoting growth and development, and protecting epithelium and mucus integrity in the body. Vitamin A is known as an anti-inflammation vitamin because of its critical role in enhancing immune function. Vitamin A is involved in the development of the immune system and plays regulatory roles in cellular immune responses and humoral immune processes through the modulation of T helper cells, sIgA, and cytokine production. Vitamin A has demonstrated a therapeutic effect in the treatment of various infectious diseases.[95]

Intervention	<b>Vitamin A</b>
Suggested Dose	<b>Up to 10,000-25,000 IU/d</b>
Mechanism(s) of action against non-COVID-19 viruses [95],[96]	<i>Favorably modulate cellular defense and repair mechanisms:</i> • Modulation of T helper cells • Modulation of sIgA <i>Favorably modulate viral-induced pathological cellular processes:</i> • Modulation of cytokine production
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm:[97],[98],[99],[100],[101],[102]	Mild if does not exceed this dose; caution: pregnancy

## ELDERBERRY

Elderberry (*Sambucus nigra*) is seen in many medicinal preparations and has widespread historical use as an anti-viral herb.[103] Based on animal research, elderberry is likely most effective in the prevention of and early infection with respiratory viruses.[104] One in-vitro study reported an increase in TNF-alpha levels related to a specific commercial preparation of elderberry[105] leading some to caution that its use could initiate a “cytokine storm.” However, these data were not confirmed when the same group performed similar studies, which were

published in 2002.<sup>[106]</sup> Therefore, these data suggest it is highly implausible that consumption of properly prepared elderberry products (from berries or flowers) would contribute to an adverse outcome related to overproduction of cytokines or lead to an adverse response in someone infected with COVID-19.

Intervention	<b>Elderberry</b>
Suggested Dose	<b>500 mg po qd (of USP standard of 17% anthocyanosides)</b>
Mechanism(s) of action against non-COVID-19 viruses <sup>[103],[107],[108],[109],[110],[111],[112]</sup>	<i>Favorably modulate cellular defense and repair mechanisms</i> <i>Favorably modulate viral-induced pathological cellular processes</i>
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm: <sup>[103],[107],[113],[114]</sup>	Mild; caution w/autoimmune disease; uncooked/unripe plant parts toxic; USDA GRAS

### **PALMITOYLETHANOLAMIDE (PEA)**

PEA is a naturally occurring anti-inflammatory palmitic acid derivative that interfaces with the endocannabinoid system. There was a significantly favorable outcome in five of six double blind placebo-controlled trials looking at acute respiratory disease due to influenza.<sup>[115]</sup> Dosing was generally 600 mg three times daily for up to three weeks. There are multiple mechanisms of action associated with PEA, from inhibition of TNF-alpha and NF-kB to mast cell stabilization. In influenza, it is thought that PEA works by attenuating the potentially fatal cytokine storm.

Intervention	<b>Palmitoylethanolamide (PEA)</b>
Suggested Dose	<b>300 mg po bid to prevent infection, 600 mg po tid x two weeks to treat infection</b>
Mechanism(s) of action against non-COVID-19 viruses <sup>[115]</sup>	<i>Favorably modulate cellular defense and repair mechanisms</i> <i>Favorably modulate viral-induced pathological cellular processes</i>
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional (treatment) Strong (prevention)
Risk of harm: <sup>[116],[117],[118],[119]</sup>	Mild

### **VITAMIN C**

Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. Supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections.<sup>[120]</sup> Vitamin C has been used in hospital ICUs to treat COVID-19 infection.

Intervention	<b>Vitamin C</b>
Suggested Dose	<b>1-3 grams po qd</b>
Mechanism(s) of action against non-COVID-19 viruses <sup>[120]</sup>	<i>Favorably modulate cellular defense and repair mechanisms</i> <i>Favorably modulate viral-induced pathological cellular processes</i>
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm <sup>[121]</sup>	Mild

### Evaluative Criteria

In the recommendations above, the following criteria are used to identify strength of evidence and risk of harm.

Strength of Evidence	Risk of Harm
Strength of Evidence Conditional Clinical experience and/or expert opinion and/or conflicting studies; biological mechanism at least partly explained.	Risk of Harm Mild Risk of self-limited symptoms; no risk of loss of function or corrective intervention anticipated; observation only.
Strength of Evidence Limited One study showing correlation between intervention and outcome; compelling ATMs and/or PCFs; biological mechanism at least partly explained.	Risk of Harm Moderate Risk of symptoms; no risk of loss of function or quality of life; minor evaluative and/or therapeutic intervention needed.
Strength of Evidence Moderate Two independent studies (one of which is LOE = 1 or 2) showing correlation between intervention and outcome; biological mechanism at least partly explained.	Risk of Harm Significant Risk of temporary loss of function or quality of life; significant evaluative and/or therapeutic intervention needed.
Strength of Evidence Strong Two independent studies (both LOE = 1 or 2) showing correlation between intervention and outcome; biological mechanism fully explained or partly explained and having one additional correlative study.	Risk of Harm Severe Risk of permanent symptoms, loss of function, quality of life, or death; long-term evaluative and/or therapeutic intervention needed.

## special thanks to

[Joel Evans, MD \(Lead\)](#), [Robert Rountree, MD](#), Tom Williams, PhD, [Michael Stone, MD](#), [Robert Luby, MD](#), [Patrick Hanaway, MD](#), Kirsten Ramsdell, MS, CN, [Sam Yanuck, DC](#), [Helen Messier, MD](#), and [Dan Lukaczer, ND](#),

[Click here to see all references](#)

## References

1. Hotchkiss RS, Opal SM. Activating immunity to fight a foe – a new path. *N Engl J Med*. 2020;382(13):1270-1272. doi:[10.1056/NEJMcibr1917242](#)
2. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34(2):1. doi:[10.23812/CONTI-E](#)
3. Ding S, Xu S, Ma Y, Liu G, Jang H, Fang J. Modulatory mechanisms of the NLRP3 inflammasomes in diabetes. *Biomolecules*. 2019;9(12):E850. doi:[10.3390/biom9120850](#)
4. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Front Microbiol*. 2019;10:50. doi:[10.3389/fmicb.2019.00050](#)
5. T?zsér J, Benk? S. Natural compounds as regulators of NLRP3 inflammasome-mediated IL-1? production. *Mediators Inflamm*. 2016;2016:5460302. doi:[10.1155/2016/5460302](#)
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. doi:[10.1016/S0140-6736\(20\)30628-0](#)
7. Adem S, Eyupoglu V, Sarfraz I, Rasul A, Ali M. Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: an in silico strategy unveils a hope against CORONA. *Preprints*. Published online March 23, 2020. doi:[10.20944/preprints202003.0333.v1](#)
8. Dostal Z, Modriansky M. The effect of quercetin on microRNA expression: a critical review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2019;163(2):95-106. doi:[10.5507/bp.2019.030](#)
9. Wu W, Li R, Li X, et al. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses*. 2015;8(1):E6. doi:[10.3390/v8010006](#)
10. Kinker B, Comstock AT, Sajjan US. Quercetin: a promising treatment for the common cold. *J Anc Dis Prev Rem*. 2014;2:2:1000111. doi:[10.4172/2329-8731.1000111](#)
11. Somerville VS, Braakhuis AJ, Hopkins WG. Effect of flavonoids on upper respiratory tract infections and immune function: a systematic review and meta-analysis. *Adv Nutr*. 2016;7(3):488-497. doi:[10.3945/an.115.010538](#)
12. Qiu X, Kroeker A, He S, et al. Prophylactic efficacy of quercetin 3-?-O-D-glucoside against Ebola virus infection. *Antimicrob Agents Chemother*. 2016;60(9):5182-5188. doi:[10.1128/AAC.00307-16](#)
13. Wong G, He S, Siragam V, et al. Antiviral activity of quercetin-3-?-O-D-glucoside against Zika virus infection. *Virol Sin*. 2017;32(6):545-547. doi:[10.1007/s12250-017-4057-9](#)

14. Yi YS. Regulatory roles of flavonoids on inflammasome activation during inflammatory responses. *Mol Nutr Food Res*. 2018;62(13):e1800147. doi:[10.1002/mnfr.201800147](https://doi.org/10.1002/mnfr.201800147)
15. Sun Y, Liu W, Zhang H, et al. Curcumin prevents osteoarthritis by inhibiting the activation of inflammasome NLRP3. *J Interferon Cytokine Res*. 2017;37(10):449-455. doi:[10.1089/jir.2017.0069](https://doi.org/10.1089/jir.2017.0069)
16. Andres S, Pevny S, Ziegenhagen R, et al. Safety aspects of the use of quercetin as a dietary supplement. *Mol Nutr Food Res*. 2018;62(1). doi:[10.1002/mnfr.201700447](https://doi.org/10.1002/mnfr.201700447)
17. O?arowski M, Miko?ajczak P?, Kujawski R, et al. Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: review of *in vitro*, *in vivo*, and clinical studies. *Evid Based Complement Alternat Med*. 2018;2018:7421489. doi:[10.1155/2018/7421489](https://doi.org/10.1155/2018/7421489)
18. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 main protease (M<sup>pro</sup>) from several medicinal plant compounds by molecular docking study. *Preprints*. Published online March 13, 2020. doi:[10.20944/preprints202003.0226.v1](https://doi.org/10.20944/preprints202003.0226.v1)
19. Yin H, Guo Q, Li X, et al. Curcumin suppresses IL-1? secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. *J Immunol*. 2018;200(8):2835-2846. doi:[10.4049/jimmunol.1701495](https://doi.org/10.4049/jimmunol.1701495)
20. Gong Z, Zhao S, Zhou J, et al. Curcumin alleviates DSS-induced colitis via inhibiting NLRP3 inflammsome activation and IL-1? production. *Mol Immunol*. 2018;104:11-19. doi:[10.1016/j.molimm.2018.09.004](https://doi.org/10.1016/j.molimm.2018.09.004)
21. Zhao J, Wang J, Zhou M, Li M, Li M, Tan H. Curcumin attenuates murine lupus via inhibiting NLRP3 inflammasome. *Int Immunopharmacol*. 2019;69:213-216. doi:[10.1016/j.intimp.2019.01.046](https://doi.org/10.1016/j.intimp.2019.01.046)
22. Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol*. 2017;174(11):1325-1348. doi:[10.1111/bph.13621](https://doi.org/10.1111/bph.13621)
23. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*). *J Altern Complement Med*. 2003;9(1):161-168. doi:[10.1089/107555303321223035](https://doi.org/10.1089/107555303321223035)
24. Ng QX, Koh SSH, Chan HW, Ho CYX. Clinical use of curcumin in depression: a meta-analysis. *J Am Med Dir Assoc*. 2017;18(6):503-508. doi:[10.1016/j.jamda.2016.12.071](https://doi.org/10.1016/j.jamda.2016.12.071)
25. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. A meta-analysis of the clinical use of curcumin for irritable bowel syndrome (IBS). *J Clin Med*. 2018;7(10):E298. doi:[10.3390/jcm7100298](https://doi.org/10.3390/jcm7100298)
26. Bahramsoltani R, Rahimi R, Farzaei MH. Pharmacokinetic interactions of curcuminoids with conventional drugs: a review. *J Ethnopharmacol*. 2017;209:1-12. doi:[10.1016/j.jep.2017.07.022](https://doi.org/10.1016/j.jep.2017.07.022)
27. Xu J, Qiu JC, Ji X, et al. Potential pharmacokinetic herb-drug interactions: have we overlooked the importance of human carboxylesterases 1 and 2? *Curr Drug Metab*. 2019;20(2):130-137. doi:[10.2174/1389200219666180330124050](https://doi.org/10.2174/1389200219666180330124050)
28. Matsumoto K, Yamada H, Takuma N, Niino H, Sagesaka YM. Effects of green tea catechins and theanine on preventing influenza infection among healthcare workers: a randomized controlled trial. *BMC Complement Altern Med*. 2011;11:15. doi:[10.1186/1472-6882-11-15](https://doi.org/10.1186/1472-6882-11-15)

29. Lee HE, Yang G, Park YB, et al. Epigallocatechin-3-gallate prevents acute gout by suppressing NLRP3 inflammasome activation and mitochondrial DNA synthesis. *Molecules*. 2019;24(11):E2138. doi:[10.3390/molecules24112138](https://doi.org/10.3390/molecules24112138)
30. Mereles D, Hunstein W. Epigallocatechin-3-gallate (EGCG) for clinical trials: more pitfalls than promises? *Int J Mol Sci*. 2011;12(9):5592-5603. doi:[10.3390/ijms12095592](https://doi.org/10.3390/ijms12095592)
31. Chow HH, Cai Y, Hakim IA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res*. 2003;9(9):3312-3319.
32. Isomura T, Suzuki S, Origasa H, et al. Liver-related safety assessment of green tea extracts in humans: a systematic review of randomized controlled trials [published correction appears in *Eur J Clin Nutr*. 2016;70(11):1221-1229]. *Eur J Clin Nutr*. 2016;70(11):1340. doi:[10.1038/ejcn.2016.78](https://doi.org/10.1038/ejcn.2016.78)
33. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf*. 2008;31(6):469-484. doi:[10.2165/00002018-200831060-00003](https://doi.org/10.2165/00002018-200831060-00003)
34. Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol Rep*. 2020;7:386-402. doi:[10.1016/j.toxrep.2020.02.008](https://doi.org/10.1016/j.toxrep.2020.02.008)
35. Younes M, Aggett P, Aguilar F, et al. Scientific opinion on the safety of green tea catechins. *EFSA J*. 2018;16(4):e05239. doi:[10.2903/j.efsa.2018.5239](https://doi.org/10.2903/j.efsa.2018.5239)
36. McCarty MF, DiNicolantonio JJ. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. *Prog Cardiovasc Dis*. Published online February 12, 2020. doi:[10.1016/j.pcad.2020.02.007](https://doi.org/10.1016/j.pcad.2020.02.007)
37. Mokhtari V, Afsharian P, Shahhoseini M, Kalantar SM, Moini A. A review on various uses of N-acetyl cysteine. *Cell J*. 2017;19(1):11-17. doi:[10.22074/cellj.2016.4872](https://doi.org/10.22074/cellj.2016.4872)
38. Bauer IE, Green C, Colpo GD, et al. A double-blind, randomized, placebo-controlled study of aspirin and N-acetylcysteine as adjunctive treatments for bipolar depression. *J Clin Psychiatry*. 2018;80(1):18m12200. doi:[10.4088/JCP.18m12200](https://doi.org/10.4088/JCP.18m12200)
39. Berk M, Turner A, Malhi GS, et al. A randomised controlled trial of a mitochondrial therapeutic target for bipolar depression: mitochondrial agents, N-acetylcysteine, and placebo [published correction appears in *BMC Med*. 2019;17(1):35]. *BMC Med*. 2019;17(1):18. doi:[10.1186/s12916-019-1257-1](https://doi.org/10.1186/s12916-019-1257-1)
40. Clark RSB, Empey PE, Bay?r H, et al. Phase I randomized clinical trial of N-acetylcysteine in combination with an adjuvant probenecid for treatment of severe traumatic brain injury in children. *PLoS One*. 2017;12(7):e0180280. doi:[10.1371/journal.pone.0180280](https://doi.org/10.1371/journal.pone.0180280)
41. Bhatti J, Nascimento B, Akhtar U, et al. Systematic review of human and animal studies examining the efficacy and safety of N-acetylcysteine (NAC) and N-acetylcysteine amide (NACA) in traumatic brain injury: impact on neurofunctional outcome and biomarkers of oxidative stress and inflammation. *Front Neurol*. 2018;8:744. doi:[10.3389/fneur.2017.00744](https://doi.org/10.3389/fneur.2017.00744)
42. Brisdelli F, D'Andrea G, Bozzi A. Resveratrol: a natural polyphenol with multiple chemopreventive properties. *Curr Drug Metab*. 2009;10(6):530-546. doi:[10.2174/138920009789375423](https://doi.org/10.2174/138920009789375423)

43. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis*. 2017;17(1):144. doi:[10.1186/s12879-017-2253-8](https://doi.org/10.1186/s12879-017-2253-8)
44. Palamara AT, Nencioni L, Aquilano K, et al. Inhibition of influenza A virus replication by resveratrol. *J Infect Dis*. 2005;191(10):1719-1729. doi:[10.1086/429694](https://doi.org/10.1086/429694)
45. Euba B, López-López N, Rodríguez-Arce I, et al. Resveratrol therapeutics combines both antimicrobial and immunomodulatory properties against respiratory infection by nontypeable *Haemophilus influenzae*. *Sci Rep*. 2017;7(1):12860. doi:[10.1038/s41598-017-13034-7](https://doi.org/10.1038/s41598-017-13034-7)
46. Mendes da Silva D, Gross LA, Neto EPG, Lessey BA, Savaris RF. The use of resveratrol as an adjuvant treatment of pain in endometriosis: a randomized clinical trial. *J Endocr Soc*. 2017;1(4):359-369. doi:[10.1210/js.2017-00053](https://doi.org/10.1210/js.2017-00053)
47. Zhu CW, Grossman H, Neugroschl J, et al. A randomized, double-blind, placebo-controlled trial of resveratrol with glucose and malate (RGM) to slow the progression of Alzheimer's disease: a pilot study. *Alzheimers Dement (N Y)*. 2018;4:609-616. doi:[10.1016/j.trci.2018.09.009](https://doi.org/10.1016/j.trci.2018.09.009)
48. Roberts VH, Pound LD, Thorn SR, et al. Beneficial and cautionary outcomes of resveratrol supplementation in pregnant nonhuman primates. *FASEB J*. 2014;28(6):2466-2477. doi:[10.1096/fj.13-245472](https://doi.org/10.1096/fj.13-245472)
49. Klink JC, Tewari AK, Masko EM, et al. Resveratrol worsens survival in SCID mice with prostate cancer xenografts in a cell-line specific manner, through paradoxical effects on oncogenic pathways. *Prostate*. 2013;73(7):754-762. doi:[10.1002/pros.22619](https://doi.org/10.1002/pros.22619)
50. Shaito A, Posadino AM, Younes N, et al. Potential adverse effects of resveratrol: a literature review. *Int J Mol Sci*. 2020;21(6):E2084. doi:[10.3390/ijms21062084](https://doi.org/10.3390/ijms21062084)
51. Salehi B, Mishra AP, Nigam M, et al. Resveratrol: a double-edged sword in health benefits. *Biomedicines*. 2018;6(3):E91. doi:[10.3390/biomedicines6030091](https://doi.org/10.3390/biomedicines6030091)
52. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. Clinical trials of resveratrol. *Ann N Y Acad Sci*. 2011;1215:161-169. doi:[10.1111/j.1749-6632.2010.05853.x](https://doi.org/10.1111/j.1749-6632.2010.05853.x)
53. Brantley SJ, Argikar AA, Lin YS, Nagar S, Paine MF. Herb-drug interactions: challenges and opportunities for improved predictions. *Drug Metab Dispos*. 2014;42(3):301-317. doi:[10.1124/dmd.113.055236](https://doi.org/10.1124/dmd.113.055236)
54. Mawson AR. Role of fat-soluble vitamins A and D in the pathogenesis of influenza: a new perspective. 2013;2013:246737. *Int Sch Res Notices*. doi:[10.5402/2013/246737](https://doi.org/10.5402/2013/246737)
55. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess*. 2019;23(2):1-44. doi:[10.3310/hta23020](https://doi.org/10.3310/hta23020)
56. Zhou J, Du J, Huang L, Wang Y, Shi Y, Lin H. Preventive effects of vitamin D on seasonal influenza A in infants: multicenter, randomized, open, controlled clinical trial. *Pediatr Infect Dis J*. 2018;37(8):749-754. doi:[10.1097/INF.0000000000001890](https://doi.org/10.1097/INF.0000000000001890)
57. Tzilias V, Bouros E, Barbayianni I, et al. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther*. 2019;55:17-24. doi:[10.1016/j.pupt.2019.01.003](https://doi.org/10.1016/j.pupt.2019.01.003)
58. Ricca C, Aillon A, Viano M, Bergandi L, Aldieri E, Silvagno F. Vitamin D inhibits the epithelial-mesenchymal transition by a negative feedback regulation of TGF- $\beta$  activity. *J Steroid Biochem Mol Biol*. 2019;187:97-105. doi:[10.1016/j.jsbmb.2018.11.006](https://doi.org/10.1016/j.jsbmb.2018.11.006)

59. Fischer KD, Agrawal DK. Vitamin D regulating TGF- $\beta$  induced epithelial-mesenchymal transition [published correction appears in *Respir Res.* 2015;16:139]. *Respir Res.* 2014;15:146. doi:[10.1186/s12931-014-0146-6](https://doi.org/10.1186/s12931-014-0146-6)
60. Schrupf JA, Ninaber DK, van der Does AM, Hiemstra PS. TGF- $\beta$ 1 impairs vitamin D-induced and constitutive airway epithelial host defense mechanisms. *J Innate Immun.* 2020;12(1):74-89. doi:[10.1159/000497415](https://doi.org/10.1159/000497415)
61. Liu RM, Gaston Pravia KA. Oxidative stress and glutathione in TGF-beta-mediated fibrogenesis. *Free Radic Biol Med.* 2010;48(1):1-15. doi:[10.1016/j.freeradbiomed.2009.09.026](https://doi.org/10.1016/j.freeradbiomed.2009.09.026)
62. Lu L, Lu Q, Chen W, Li J, Li C, Zheng Z. Vitamin D<sub>3</sub> protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. *J Diabetes Res.* 2018;2018:8193523. doi:[10.1155/2018/8193523](https://doi.org/10.1155/2018/8193523)
63. Rao Z, Chen X, Wu J, et al. Vitamin D receptor inhibits NLRP3 activation by impeding its BRCC3-mediated deubiquitination. *Front Immunol.* 2019;10:2783. doi:[10.3389/fimmu.2019.02783](https://doi.org/10.3389/fimmu.2019.02783)
64. Hewison M. Vitamin D and immune function: an overview. *Proc Nutr Soc.* 2012;71(1):50-61. doi:[10.1017/S0029665111001650](https://doi.org/10.1017/S0029665111001650)
65. Fitch N, Becker AB, HayGlass KT. Vitamin D [1,25(OH)2D3] differentially regulates human innate cytokine responses to bacterial versus viral pattern recognition receptor stimuli. *J Immunol.* 2016;196(7):2965-2972. doi:[10.4049/jimmunol.1500460](https://doi.org/10.4049/jimmunol.1500460)
66. Zdrengeha MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol.* 2017;27(1). doi:[10.1002/rmv.1909](https://doi.org/10.1002/rmv.1909)
67. Verway M, Bouttier M, Wang TT, et al. Vitamin D induces interleukin-1 $\beta$  expression: paracrine macrophage epithelial signaling controls *M. tuberculosis* infection. *PLoS Pathog.* 2013;9(6):e1003407. doi:[10.1371/journal.ppat.1003407](https://doi.org/10.1371/journal.ppat.1003407)
68. Tulk SE, Liao KC, Muruve DA, Li Y, Beck PL, MacDonald JA. Vitamin D<sub>3</sub> metabolites enhance the NLRP3-dependent secretion of IL-1 $\beta$  from human THP-1 monocytic cells. *J Cell Biochem.* 2015;116(5):711-720. doi:[10.1002/jcb.24985](https://doi.org/10.1002/jcb.24985)
69. Lee MT, Kattan M, Fennoy I, et al. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. *Blood Adv.* 2018;2(9):969-978. doi:[10.1182/bloodadvances.2017013979](https://doi.org/10.1182/bloodadvances.2017013979)
70. Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol.* 2017;5(12):986-1004. doi:[10.1016/S2213-8587\(17\)30357-1](https://doi.org/10.1016/S2213-8587(17)30357-1)
71. Sluyter JD, Camargo CA, Waayer D, et al. Effect of monthly, high-dose, long-term vitamin D on lung function: a randomized controlled trial. *Nutrients.* 2017;9(12):E1353. doi:[10.3390/nu9121353](https://doi.org/10.3390/nu9121353)
72. Scragg R. The vitamin D assessment (ViDA) study – design and main findings. *J Steroid Biochem Mol Biol.* 2020;198:105562. doi:[10.1016/j.jsbmb.2019.105562](https://doi.org/10.1016/j.jsbmb.2019.105562)
73. Turin A, Bax JJ, Doukas D, et al. Interactions among vitamin D, atrial fibrillation, and the renin-angiotensin-aldosterone system. *Am J Cardiol.* 2018;122(5):780-784. doi:[10.1016/j.amjcard.2018.05.013](https://doi.org/10.1016/j.amjcard.2018.05.013)
74. Zaheer S, Taquechel K, Brown JM, Adler GK, Williams JS, Vaidya A. A randomized intervention study to evaluate the effect of calcitriol therapy on the renin-angiotensin

- system in diabetes. *J Renin Angiotensin Aldosterone Syst.* 2018;19(1): 1470320317754178. doi:[10.1177/1470320317754178](https://doi.org/10.1177/1470320317754178)
75. Cremer A, Tambosco C, Corcuff JB, et al. Investigating the association of vitamin D with blood pressure and the renin-angiotensin-aldosterone system in hypertensive subjects: a cross-sectional prospective study. *J Hum Hypertens.* 2018;32(2):114-121. doi:[10.1038/s41371-017-0005-2](https://doi.org/10.1038/s41371-017-0005-2)
  76. Zittermann A, Ernst JB, Prokop S, et al. Effects of vitamin D supplementation on renin and aldosterone concentrations in patients with advanced heart failure: the EVITA trial. *Int J Endocrinol.* 2018;2018:5015417. doi:[10.1155/2018/5015417](https://doi.org/10.1155/2018/5015417)
  77. Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep.* 2014;4:7027. doi:[10.1038/srep07027](https://doi.org/10.1038/srep07027)
  78. Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep.* 2017;16(5):7432-7438. doi:[10.3892/mmr.2017.7546](https://doi.org/10.3892/mmr.2017.7546)
  79. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA.* 2010;303(18): 1815-1822. doi:[10.1001/jama.2010.594](https://doi.org/10.1001/jama.2010.594)
  80. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med.* 2016;176(2):175-183. doi:[10.1001/jamainternmed.2015.7148](https://doi.org/10.1001/jamainternmed.2015.7148)
  81. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. *Clin Pharmacol Ther.* 2009;85(2): 198-203. doi:[10.1038/clpt.2008.165](https://doi.org/10.1038/clpt.2008.165)
  82. Žofková I. Hypercalcemia. Pathophysiological aspects. *Physiol Res.* 2016;65(1):1-10. doi:[10.33549/physiolres.933059](https://doi.org/10.33549/physiolres.933059)
  83. Favero G, Franceschetti L, Bonomini F, Rodella LF, Rezzani R. Melatonin as an anti-inflammatory agent modulating inflammasome activation. *Int J Endocrinol.* 2017;2017:1835195. doi:[10.1155/2017/1835195](https://doi.org/10.1155/2017/1835195)
  84. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov.* 2020;6:14. doi:[10.1038/s41421-020-0153-3](https://doi.org/10.1038/s41421-020-0153-3)
  85. Zhang R, Wang X, Ni L, et al. COVID-19: melatonin as a potential adjuvant treatment. *Life Sci.* Published online March 23, 2020. doi:[10.1016/j.lfs.2020.117583](https://doi.org/10.1016/j.lfs.2020.117583)
  86. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: a critical systematic review of clinical evidence. *Complement Ther Med.* 2019;42:65-81. doi:[10.1016/j.ctim.2018.11.003](https://doi.org/10.1016/j.ctim.2018.11.003)
  87. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. *Clin Drug Investig.* 2016;36(3):169-175. doi:[10.1007/s40261-015-0368-5](https://doi.org/10.1007/s40261-015-0368-5)
  88. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev.* 2002;2:CD001520. doi:[10.1002/14651858.CD001520](https://doi.org/10.1002/14651858.CD001520)
  89. Leite Pacheco R, de Oliveira Cruz Latorraca C, Adriano Leal Freitas da Costa A, Luiza Cabrera Martimbianco A, Vianna Pachito D, Riera R. Melatonin for preventing primary headache: a systematic review. *Int J Clin Pract.* 2018;72(7):e13203. doi:[10.1111/ijcp.13203](https://doi.org/10.1111/ijcp.13203)

90. Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. *Arch Dis Child*. 2018;103(12):1155-1162. doi:[10.1136/archdischild-2017-314181](https://doi.org/10.1136/archdischild-2017-314181)
91. Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a systematic review. *CNS Drugs*. 2019;33(12):1167-1186. doi:[10.1007/s40263-019-00680-w](https://doi.org/10.1007/s40263-019-00680-w)
92. Harpsøe NG, Andersen LP, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. *Eur J Clin Pharmacol*. 2015;71(8):901-909. doi:[10.1007/s00228-015-1873-4](https://doi.org/10.1007/s00228-015-1873-4)
93. Wirtz PH, Spillmann M, Bärtschi C, Ehlert U, von Känel R. Oral melatonin reduces blood coagulation activity: a placebo-controlled study in healthy young men. *J Pineal Res*. 2008;44(2):127-133. doi:[10.1111/j.1600-079X.2007.00499.x](https://doi.org/10.1111/j.1600-079X.2007.00499.x)
94. McGlashan EM, Nandam LS, Vidafar P, Mansfield DR, Rajaratnam SMW, Cain SW. The SSRI citalopram increases the sensitivity of the human circadian system to light in an acute dose. *Psychopharmacology (Berl)*. 2018;235(11):3201-3209. doi:[10.1007/s00213-018-5019-0](https://doi.org/10.1007/s00213-018-5019-0)
95. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. *J Clin Med*. 2018;7(9):E258. doi:[10.3390/jcm7090258](https://doi.org/10.3390/jcm7090258)
96. Cui D, Moldoveanu Z, Stephensen CB. High-level dietary vitamin A enhances T-helper type 2 cytokine production and secretory immunoglobulin A response to influenza A virus infection in BALB/c mice. *J Nutr*. 2000;130(5):1132-1139. doi:[10.1093/jn/130.5.1132](https://doi.org/10.1093/jn/130.5.1132)
97. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. *N Engl J Med*. 1995;333(21):1369-1373. doi:[10.1056/NEJM199511233332101](https://doi.org/10.1056/NEJM199511233332101)
98. Bartlett H, Eperjesi F. Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements. *Ophthalmic Physiol Opt*. 2005;25(3):179-194. doi:[10.1111/j.1475-1313.2005.00294.x](https://doi.org/10.1111/j.1475-1313.2005.00294.x)
99. Bendich A, Langseth L. Safety of vitamin A. *Am J Clin Nutr*. 1989;49(2):358-371. doi:[10.1093/ajcn/49.2.358](https://doi.org/10.1093/ajcn/49.2.358)
100. Cruz S, da Cruz SP, Ramalho A. Impact of vitamin A supplementation on pregnant women and on women who have just given birth: a systematic review. *J Am Coll Nutr*. 2018;37(3):243-250. doi:[10.1080/07315724.2017.1364182](https://doi.org/10.1080/07315724.2017.1364182)
101. Oliveira JM, Allert R, East CE. Vitamin A supplementation for postpartum women. *Cochrane Database Syst Rev*. 2016;3:CD005944. doi:[10.1002/14651858.CD005944.pub3](https://doi.org/10.1002/14651858.CD005944.pub3)
102. García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. *Int J Mol Sci*. 2016;17(4):537. doi:[10.3390/ijms17040537](https://doi.org/10.3390/ijms17040537)
103. Porter RS, Bode RF. A review of the antiviral properties of black elder (*Sambucus nigra* L.) products. *Phytother Res*. 2017;31(4):533-554. doi:[10.1002/ptr.5782](https://doi.org/10.1002/ptr.5782)
104. Chen C, Zuckerman DM, Brantley S, et al. *Sambucus nigra* extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res*. 2014;10:24. doi:[10.1186/1746-6148-10-24](https://doi.org/10.1186/1746-6148-10-24)
105. Barak V, Halperin T, Kalickman I. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. *Eur Cytokine Netw*. 2001;12(2):290-296.

106. Barak V, Birkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J*. 2002;4(11 Suppl):919-922.
107. Ulbricht C, Basch E, Cheung L, et al. An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. *J Diet Suppl*. 2014;11(1):80-120. doi:[10.3109/19390211.2013.859852](https://doi.org/10.3109/19390211.2013.859852)
108. Frank T, Janssen M, Netzet G, Christian B, Bitsch I, Netzel M. Absorption and excretion of elderberry (*Sambucus nigra* L.) anthocyanins in healthy humans. *Methods Find Exp Clin Pharmacol*. 2007;29(8):525-533. doi:[10.1358/mf.2007.29.8.1116309](https://doi.org/10.1358/mf.2007.29.8.1116309)
109. Badescu M, Badulescu O, Badescu L, Ciocoiu M. Effects of *Sambucus nigra* and *Aronia melanocarpa* extracts on immune system disorders within diabetes mellitus. *Pharm Biol*. 2015;53(4):533-539. doi:[10.3109/13880209.2014.931441](https://doi.org/10.3109/13880209.2014.931441)
110. Curtis PJ, Kroon PA, Hollands WJ, et al. Cardiovascular disease risk biomarkers and liver and kidney function are not altered in postmenopausal women after ingesting an elderberry extract rich in anthocyanins for 12 weeks. *J Nutr*. 2009;139(12):2266-2271. doi:[10.3945/jn.109.113126](https://doi.org/10.3945/jn.109.113126)
111. Fallah AA, Sarmast E, Fatehi P, Jafari T. Impact of dietary anthocyanins on systemic and vascular inflammation: systematic review and meta-analysis on randomised clinical trials. *Food Chem Toxicol*. 2020;135:110922. doi:[10.1016/j.fct.2019.110922](https://doi.org/10.1016/j.fct.2019.110922)
112. Li S, Wu B, Fu W, Reddivari L. The anti-inflammatory effects of dietary anthocyanins against ulcerative colitis. *Int J Mol Sci*. 2019;20(10):E2588. doi:[10.3390/ijms20102588](https://doi.org/10.3390/ijms20102588)
113. Elderberry for influenza. *Med Lett Drugs Ther*. 2019;61(1566):32. [<https://secure.medicalletter.org/w1566f>]
114. Hawkins J, Baker C, Cherry L, Dunne E. Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials. *Complement Ther Med*. 2019;42:361-365. doi:[10.1016/j.ctim.2018.12.004](https://doi.org/10.1016/j.ctim.2018.12.004)
115. Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. *Int J Inflam*. 2013;2013:151028. doi:[10.1155/2013/151028](https://doi.org/10.1155/2013/151028)
116. Cordaro M, Cuzzocrea S, Crupi R. An update of palmitoylethanolamide and luteolin effects in preclinical and clinical studies of neuroinflammatory events. *Antioxidants (Basel)*. 2020;9(3):E216. doi:[10.3390/antiox9030216](https://doi.org/10.3390/antiox9030216)
117. Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. *Am J Hosp Palliat Care*. 2019;36(12):1134-1154. doi:[10.1177/1049909119850807](https://doi.org/10.1177/1049909119850807)
118. Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. *Br J Clin Pharmacol*. 2016;82(4):932-942. doi:[10.1111/bcp.13020](https://doi.org/10.1111/bcp.13020)
119. Natural Medicines Database. Palmitoylethanolamide (PEA). Accessed March 30, 2020. <https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1596>
120. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*. 2017;9(11):E1211. doi:[10.3390/nu9111211](https://doi.org/10.3390/nu9111211)
121. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. *Nutrients*. 2019;11(4):708. doi:[10.3390/nu11040708](https://doi.org/10.3390/nu11040708)

