LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY
RESEARCH NEWSLETTER

JUNE-AUGUST 2022

VITAMIN C AND COVID: AN UPDATE

In our previous issue of the *LPI Research Newsletter*, we began a series on dietary factors and COVID with a review of the literature on vitamin D and zinc. Here, we continue by examining the scientific literature surrounding vitamin C and COVID.

Vitamin C has a place of prominence within the Linus Pauling Institute. Dr. Linus Pauling and his close supporters established the Institute to explore the roles of vitamin C in health, with the foundation being Dr. Pauling's research on vitamin C and the common cold.

Although the COVID pandemic began more than two years ago, only a limited number of scientific studies on vitamin C and COVID have been published. However, a great deal of misinformation has circulated on this topic. This article aims to clarify the current state of the research.

Vitamin C and the Immune System

Vitamin C plays many roles in a healthy immune system, including acting as a vital antioxidant. Since free radicals are generated by immune cells when combating an infection, a poorly controlled immune response can harm the body's own cells and tissues through excessive inflammation and oxidative damage. Antioxidants like vitamin C help to limit these harmful effects.

A large body of evidence supports the use of vitamin C supplements (at least 250 mg per day) in shortening the duration of common cold symptoms in both children and adults. Vitamin C supplementation may also reduce common cold incidence in individuals undergoing high levels of physical stress.

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Oregon State University
Linus Pauling Institute

Photo credit: Hannah O'Leary

Emily Ho, PhD
Endowed Chair and Director,
Linus Pauling Institute

Dr. Traber's webinar on vitamin E can be viewed at lpi.pub/Traber2022

Dr. Williams' webinar on dietary indoles can be viewed at lpi.pub/Williams2022

FROM THE DIRECTOR

At the Linus Pauling Institute, we are looking forward to summer. Summers in Oregon bring us the best weather of the year, and a quieter OSU campus gives students, staff, and principal investigators at the Institute an opportunity to focus on research. Summer is often our most productive time of the year.

First, I wanted to mention the latest webinars in our 2022 seminar series. On June 23, we presented a webinar featuring our own resident expert on vitamin E, Dr. Maret Traber. In *All You Wanted to Know About Vitamin E But Were Afraid To Ask*, Dr. Traber discussed what vitamin E is, what it does, and why people aren't getting enough in the food that they eat.

Our webinar on dietary indoles is also available on the Linus Pauling Institute YouTube channel. Dr. David Williams answers some of your questions from that webinar on page 6 of this issue.

In late April, the Linus Pauling Institute took part in Dam Proud Day. This fundraising event at Oregon State University was a complete success for the Institute – we raised over $40,000 and placed in the top 15 fundraising units at OSU. Thank you for making this possible!

A special thanks goes out to the Director's Circle members who provided matching gifts (see back cover). And thanks also to everyone who supported us during this annual day of giving.

Sadly, it is also my duty to mention the passing of Dr. Donald Reed (see page 3). As the first interim director of the Institute, Dr. Reed played a critical role in establishing LPI at Oregon State University. He was not only a brilliant scientist but also a responsible caretaker of the Pauling legacy.

In my time as director, I had the privilege of conversing with Dr. Reed many times over. He often wanted to know about the students his fellowship was supporting.

We will all miss Dr. Reed at the Institute. In honor of his life and accomplishments, the Linus Pauling Institute will be co-sponsoring a memorial symposium in Corvallis on September 9, 2022 at the Linus Pauling Science Center. All are invited to attend.

I wish everyone a great summer. Our next newsletter will be a special online-only edition, but if you would like a print copy, let us know by the end of September (write, call, or email).

Talk to you again in the fall,

Emily Ho

ACCOLADES

The American Society for Nutrition (ASN) recently announced its Class of 2022 Fellows, which includes **the Institute's Principal Investigator Dr. Donald Jump**.

To be inducted as a Fellow of the Society is "the highest honor ASN bestows, recognizing individuals for significant discoveries and distinguished careers in the field of nutrition." Congratulations to Dr. Jump on achieving this honor!

Dr. Donald Reed (pictured above) was a prominent figure within Oregon State University. When he was named the first interim director of the Institute, he was concurrently serving as the director of the Environmental Health Sciences Center at OSU – a position he held for 17 years.

IN MEMORIAM:
Dr. Donald J. Reed (1930-2022)

In 1996, the Linus Pauling Institute moved from Palo Alto, California to Corvallis, Oregon. After that move, Dr. Donald Reed led the Institute as its first interim director at Oregon State University.

Dr. Reed's pioneering research on glutathione was a good fit within the Institute. Glutathione is an antioxidant compound produced by the body that is central to protection against oxidative stress and toxins. Dr. Reed's work shaped how today's scientists view the intersection between toxicity, antioxidants, and stress response – with many parallels to how Dr. Linus Pauling viewed vitamin C.

Although Dr. Reed directed the Linus Pauling Institute for only a year, he remained an important part of the Institute. Director Balz Frei asked him to serve on the Institute's Scientific Advisory Committee, a role he maintained even after his retirement from OSU.

Dr. Reed also established the Caron and Donald Reed Fellowship Endowment Fund at the Linus Pauling Institute. This fellowship provides critical support for students in the early years of their doctoral training.

Dr. Reed passed away peacefully on March 10, 2022 at the age of 91. In honor of this great scientist, the Linus Pauling Institute and the Pacific Northwest Center for Translational and Environmental Health Research will hold a joint symposium at the Linus Pauling Science Center in Corvallis on September 9. If you are interested in attending, see **lpi.pub/ReedSymposium** for more information.

The family welcomes a donation to the Caron and Donald Reed Fellowship Endowment Fund in support of graduate students at the Institute. You may select their fund in the drop-down box at **bit.ly/GiveToLPI**

STUDENT FELLOWSHIPS

Every year, the Institute awards fellowships to outstanding graduate students who are being mentored by one of the Institute's investigators. The financial support for these awards comes from endowed funds contributed by our generous donors. These fellowships create a lasting impact on student success and help shape the next generation of nutrition scientists.

The awardees of the 2022 student fellowships are as follows:

Paige Jamieson (Stevens Laboratory)
The Marion T. Tsefalas Graduate Fellowship and the Caron and Donald Reed Fellowship

Daniel Elson (Kolluri Laboratory)
The Mark Sponenburgh Graduate Fellowship

Yi Zhang (Kolluri Laboratory)
The Audrey & George Varseveld LPI Graduate Fellowship

John "Yanni" Bouranis (Ho Laboratory)
The Harvey H. and Donna Morre Basic Cancer Research Fellowship

Lauren Chan (Haendel Laboratory)
The Simone & Balz Frei Graduate Fellowship and the George Bailey Graduate Fellowship

Continued from cover

Intravenous (IV) vitamin C is employed by clinicians in the treatment of viral and bacterial infections, but its efficacy is controversial. Since there is some evidence that IV vitamin C works differently than oral vitamin C, it is prudent to discuss these routes of administration separately.

Trials conducted nearly 50 years ago suggest that oral doses of vitamin C of 2,000 mg per day or more may reduce the incidence of the common cold and pneumonia. However, these findings have not been substantiated by modern clinical trials.

Oral Vitamin C Supplements

Observational studies have found that hospitalized COVID patients tend to have low blood vitamin C levels. While these data focus on those with severe COVID symptoms, they support a relationship between the immune response and blood vitamin C levels.

Do vitamin C supplements prevent COVID? No scientific evidence supports this hypothesis. Observational studies show that people who take vitamin C are equally at risk of contracting COVID as non-supplement users.

Can vitamin C help in the treatment of COVID? Unfortunately, the data are unclear. Four studies have examined the use of vitamin C supplements in COVID patients, but the results were inconsistent.

Only two of the studies reported a benefit of vitamin C supplementation. One randomized controlled trial showed that administering vitamin C supplements (500 mg per day for 14 days) to critically ill COVID patients improved their odds of survival versus a control group. An observational study associated vitamin C supplement use (1,000 mg per day for 7-18 days) with decreased incidence of thrombosis (blood clots blocking blood vessels).

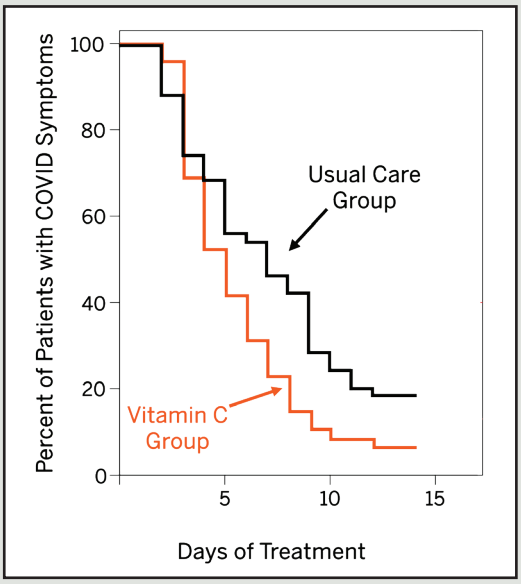
Two other randomized controlled trials did not report any benefits of taking vitamin C supplements when compared to control groups. However, the conclusions of one of these trials were controversial (see **highlight below**).

Current study data are inconclusive in regard to the use of vitamin C supplements in the treatment of COVID. More randomized controlled trials are needed. However, it is worth noting that vitamin C supplement use is widespread in COVID trials, and vitamin C supplements are occasionally given to "placebo" controls in randomized controlled trials for drugs or dietary supplements.

The Cleveland Clinic trial examined the utility of vitamin C and zinc supplements in reducing COVID symptoms. For 10 days, one group of COVID patients took 8 g per day of vitamin C, another group took 50 mg per day of zinc gluconate, and the third group took a combination of zinc and vitamin C. A fourth "usual care" group served as the control.

This trial was terminated "for futility" with less than half of its goal number of participants. Terminating a trial for futility means that an independent review committee elected to stop the trial early since the likelihood of finding a treatment effect is low. After statistical analysis, the authors concluded that zinc and vitamin C were ineffective treatments for COVID.

However, a reanalysis of the Cleveland Clinic data by Dr. Harri Hemilä, Dr. Elizabeth Chalker, and Dr. Anitra Carr suggested that this conclusion was premature. These investigators found that patients taking vitamin C supplements recovered from COVID about 18% faster, on average, than those who did not receive vitamin C, suggesting that vitamin C supplements may offer some benefit (see figure on right, adapted from the supplemental data provided with this reanalysis).



References

Hemilä et al. *Front. Immunol.* **May 10 (2021)** doi: 10.3389/fimmu.2021.674681

Tomas et al. *JAMA Netw. Open.* **4 (2021)** doi: 10.1001/jamanetworkopen.2021.0369

Intravenous Vitamin C

Taking vitamin C orally may have limited effectiveness in severe COVID because blood vitamin C concentrations can decline rapidly, and vitamin C transport proteins in the gut slow the absorption of vitamin C. IV vitamin C has been proposed as a strategy to quickly restore blood vitamin C levels in COVID patients.

In addition, when provided at high doses (25 grams or more), IV vitamin C has both antioxidant and pro-oxidant properties. It is thought that IV vitamin C may produce free radicals that damage pathogens and may help the body fight off infections.

Eight observational studies and six randomized controlled trials have examined the use of IV vitamin C in the treatment of COVID. Although the data from observational studies are mixed, **the randomized trials consistently demonstrate benefits to COVID patients who receive IV vitamin C.** Depending on the trial, patients receiving this treatment showed improved oxygenation parameters, reduced inflammatory markers, faster resolution of COVID symptoms, or decreased risk of poor outcomes, such as cardiac arrest or death.

Although these results are encouraging, the available trials are small and the results are not always consistent across all studies. For instance, a faster resolution of symptoms or improvements in oxygenation parameters were seen in only some of the trials. Ongoing randomized controlled trials will hopefully provide more clarity on the effects of IV vitamin C in COVID patients.

Bottom Line

While it is clear that vitamin C is needed in COVID patients, there is currently no evidence that taking vitamin C supplements will prevent a COVID infection. There is also limited evidence that vitamin C supplements can effectively treat COVID symptoms.

However, IV vitamin C may be a helpful adjuvant to conventional COVID therapies and should not be dismissed. Because there are special precautions for its use, IV vitamin C should only be administered in a medical setting. You cannot achieve the same blood concentrations of vitamin C with any type of oral supplement (including liposomal forms of vitamin C), so there is no way to reproduce the effects of IV vitamin C on your own.

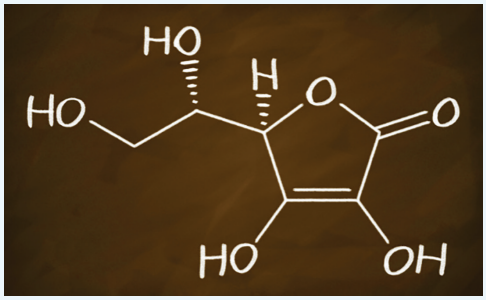
Without additional data, a dose recommendation for vitamin C supplements for the treatment of COVID is premature. At a minimum, the Linus Pauling Institute recommends all adults get 400 mg of vitamin C every day from food and supplements combined.

If you choose to take additional vitamin C supplements during the ongoing pandemic, keep in mind that this could cause an upset stomach, gas, or diarrhea. Smaller doses taken throughout the day may mitigate some of these effects. The National Academy of Medicine set the tolerable upper intake level for vitamin C at 2,000 mg per day for adults due to the risk of these gastrointestinal side effects.

For more about the applications of IV vitamin C, see our article on page 7

Vitamin C and the Common Cold

For more about vitamin C (and zinc) in the common cold, see the Micronutrient Information Center at **lpi.pub/CommonCold**



The citations for all of the scientific publications reviewed here are available on our website at **lpi.pub/COVIDrefs**

In addition, Dr. Anitra Carr from the University of Otago, Christchurch is maintaining an up-to-date repository of published research on vitamin C and COVID. Study summaries and other details can be found on her webpage at **lpi.pub/VitCandCOVID**

Q&A ON DIETARY INDOLES

In April, Dr. David Williams presented a webinar about the anticancer properties of Brussels sprouts, a recording of which is available on the Linus Pauling Institute YouTube channel (for link, see page 2). Dr. Williams focused his presentation on indole-3-carbinol (I3C), a compound formed from glucobrassicin found in cruciferous vegetables, and a beneficial compound called 3,3'-diindolylmethane (DIM), which is produced from I3C in the stomach after consumption or taken directly as a supplement.

This popular webinar inspired many questions from the audience, some of which we have included here with Dr. Williams' answers.

In your trial, Brussels sprouts were steamed. Does this mean that cooking has little effect on the active phytochemicals in these and in broccoli?

Prolonged cooking can degrade beneficial phytochemicals and the enzymes necessary to activate some of them. However, other active enzymes present in raw vegetables can also degrade phytochemicals.

The trick is to find a balance. Light steaming has been suggested as a middle ground between the two, but there may also be benefits to eating them both cooked and raw.

How do other cruciferous vegetables compare in I3C content?

Brussels sprouts have the highest glucobrassicin content of all cruciferous vegetables and thus can produce the most I3C and DIM. At most, broccoli, cauliflower, kale, and cabbage only have 30% of the glucobrassicin content of Brussels sprouts.

Can fermenting cruciferous vegetables preserve these benefits?

During fermentation, I3C is liberated from the glucobrassicin molecule. However, some studies have shown that I3C levels in sauerkraut decline with storage time. This makes it difficult to estimate how much I3C will remain by the time you eat it.

Does the timing make a difference in the protective effect of DIM?

In cancer chemoprevention studies in animals, I3C and DIM work best when given prior to or simultaneously with a carcinogen. Unfortunately, this has not been tested in humans.

DIM has a half-life in human blood of about 4 hours. So, if a carcinogen exposure is 12 hours after DIM dosing, there would only be one-eighth of the original DIM dose left in the blood. It's possible that this is too low to have a beneficial effect.

How much DIM or Brussels sprouts would be needed to treat cancer?

This is an important question, but one that is hard to answer. Many cancers take 20 years or more to progress from initiation (DNA mutations) to malignant tumors, making it difficult to know when to employ an intervention with DIM.

Although there is some evidence that DIM acts through mechanisms that would lend itself to therapeutic interventions, we need to wait for additional trials in cancer patients to know for sure.

Is there a suggested dose of DIM to take?

The Linus Pauling Institute has not evaluated the safety of DIM supplements. However, no adverse effects have been observed in people taking 150-200 mg per day.

Larger doses increase the risk of side effects, such as headache, nausea, vomiting, gas, and diarrhea. If you choose to take DIM supplements, follow the dosing instructions suggested by the manufacturer. It is also important to speak to your primary care provider about possible drug interactions.

BEYOND THE COMMON COLD:

A Recap of the Vitamin C Webinar

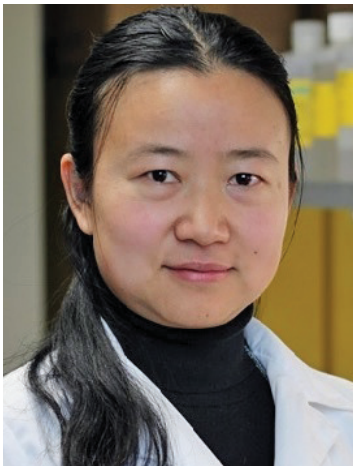
To celebrate Linus Pauling Day on February 28, 2022, the Institute hosted its annual webinar on vitamin C and health in honor of Dr. Pauling. This year, we were joined by Dr. Jeanne Drisko and Dr. Qi Chen from the University of Kansas Medical Center. They both have been investigating the health applications of intravenous (IV) vitamin C, particularly in the treatment of cancer.

Below is a synopsis of the presentations, including some of the information from the Q&A session that followed. You can watch the video recording of the event on The Linus Pauling Institute YouTube Channel at **lpi.pub/VitaminC2022**

Dr. Jeanne Drisko spoke about the distinct effects of oral versus IV vitamin C and how few people appreciate these differences. Most importantly, IV vitamin C behaves like a drug providing anticancer, antiviral, and antibacterial properties that cannot be achieved with oral supplements, *no matter what type of formulation or dose is used*.

Although still in its early stages, there is increasing evidence to support the use of vitamin C for the treatment of various diseases. Randomized controlled trials, including recent studies conducted during the COVID pandemic (see cover article), provide some of the best evidence in support of this therapy. However, it will be a challenge to convince conventional medical practitioners that this is a worthwhile option.

In the Q&A session, Dr. Drisko spoke about the preparation and administration of large doses of vitamin C (25-100 grams at a time). She also commented that doses below 10 grams might not achieve therapeutic benefits, which could be why clinical trials utilizing these lower doses often show no effect of IV vitamin C. She reiterated that IV vitamin C should only be administered by healthcare professionals who have knowledge and experience with this therapy, as serious complications are possible in some individuals.



Dr. Qi Chen spoke about her early work with Dr. Mark Levine at the National Institutes of Health, which explored the properties of IV vitamin C in human volunteers. This work led to studies demonstrating that doses of at least 25 grams of vitamin C are likely to generate hydrogen peroxide, which could explain many of its anticancer, antiviral, and antibacterial properties.

Studies in animal models have clearly shown that IV vitamin C is beneficial in cancer treatment. In humans, the evidence is generally positive, but larger trials are still needed on specific types of cancer. Clinical studies suggest that IV vitamin C reduces tumor growth in some cancer patients. Additional studies have shown that when combined with chemotherapy, IV vitamin C may reduce the associated side effects.

In the Q&A session, Dr. Chen emphasized that the goal of IV vitamin C therapies for cancer is to achieve plasma concentrations of 20 millimolar or higher, roughly 100-500 times higher than those seen after oral supplementation. It is also important that these high blood concentrations remain elevated for hours to achieve the desired effects. This sharply contrasts with oral vitamin C where intestinal absorption is low and peak blood concentrations are not sustained. This is the primary reason why vitamin C supplements are unable to reproduce the anticancer effects of IV vitamin C.

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LINUS PAULING INSTITUTE RESEARCH NEWSLETTER

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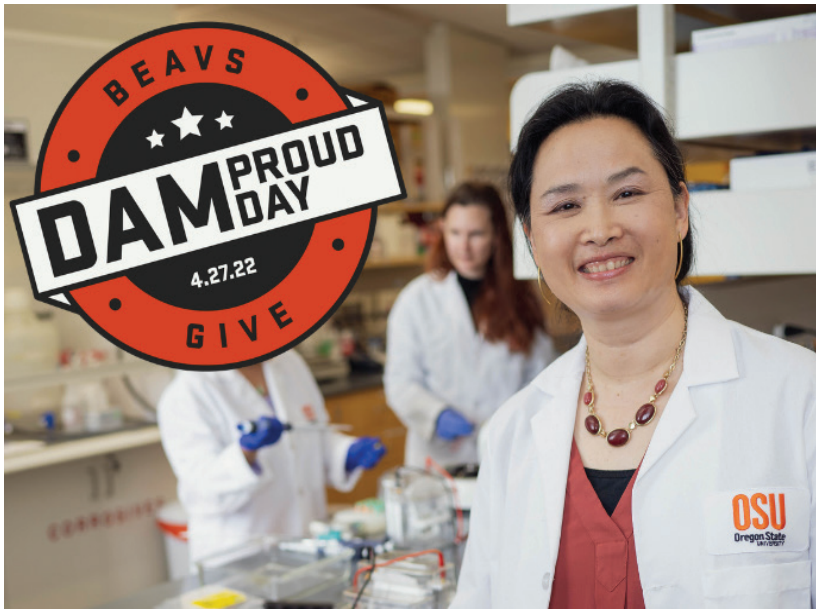
INSIDE: VITAMIN C FOR COVID-19 – THE SCIENTIFIC EVIDENCE



On Dam Proud Day, we raised over $40,000 in support of the Simone & Balz Frei Fellowship and the Micronutrient Information Center!

Our gratitude and appreciation go out to all of our **Director's Circle members** who provided matching gifts on this day of giving:

Dr. Emily Ho
Dr. Balz and Simone Frei
Dr. Maret and Biff Traber
Dr. Mary McCarthy

THANK YOU FOR SUPPORTING OUR WORK!