LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY RESEARCH NEWSLETTER

FALL 2021

Photo credit: Hannah O'Leary

LIVING LONGER & BETTER:

Exploring Dietary Factors and Healthspan

For nearly half a century, the Linus Pauling Institute has focused on how dietary factors can help you reach your optimum health. Instead of focusing on extending lifespan, however, our researchers seek new ways to increase our years free from disease and disability. This is a concept known as *healthspan*. Or, to paraphrase Dr. Pauling: to live better, longer.

In this article, we explore the basics of healthspan and why it is a driving factor behind the Institute's research on aging. Ultimately, research has revealed that a quality diet is one of the major determinants of healthspan. And while meeting our basic micronutrient needs is an essential part of health, the key to healthy aging may include micronutrients and other dietary components that go beyond these basic needs in order to support optimal health.

Lifespan versus Healthspan

The term *lifespan* is typically used to reflect the health and longevity of a population. While it can vary among individuals, lifespan is the maximum number of years that any species can live.

Changes in human lifespan are often used as a gauge of wellness. The average lifespan in the United States has nearly doubled in the last century from 45 to just short of 80 years. Largely due to public health initiatives, infants and children today are less likely to die, and adults are more likely to survive into old age.

But are we living healthier lives? Unfortunately, lifespan does not reflect quality of life – it tells us how long people usually live, not how well they are living.

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Oregon State University
Linus Pauling Institute

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

FROM THE DIRECTOR

Looking back over the past year makes me feel immensely grateful to all of the friends of the Linus Pauling Institute. As we continue to celebrate our 25th anniversary at Oregon State University this year, your support means more to us than words can convey.

As I mentioned in our last issue, we are continuing our anniversary webinar series. In July, Dr. Kathy Magnusson presented her webinar on the aging brain. In August, Dr. Tory Hagen presented a webinar dedicated to a healthspan approach to successful aging. Concepts from these two webinars form the foundation of our cover article on healthspan in this issue of this newsletter.

September was the first month of *Diet and Optimum Health Online,* the virtual version of our biennial scientific conference. By the time you read this, we will have just completed our final session: *Dietary Factors for a Healthy Immune System.* We plan on bringing you some of the key messages from these sessions in the winter edition of this newsletter.

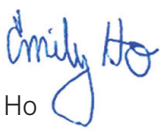
I also wanted to let you know that we have one more webinar left in our 25th anniversary series. On December 7, 2021, I will present *Cancer Fighter: Harnessing the Power of Broccoli* (see back cover). This webinar will explore how vegetables modify cancer risk with a special focus on broccoli. I hope you are able to attend.

And there is more to come! Linus Pauling Day (February 28, 2022) is fast approaching, and there will be special events leading up to that day.

Also, this next year will reveal new offerings for our donors. I don't want to spoil the surprise, so look for details coming soon.

Thank you for celebrating with us this year – it certainly has been one for the history books. Your support has meant everything to us.

Hope you have a great holiday season!



Emily Ho

READER QUESTION

Q. In Dr. Linus Pauling's books, he talks about "ascorbic acid" being vitamin C. However, there are other websites that say ascorbic acid is not vitamin C because it is synthetic!

Did Dr. Pauling want people to take natural vitamin C? What is the difference?

— D.M. by email

A. Ascorbic acid is produced in many plants and animals. There is no difference between the ascorbic acid created in a laboratory and the ascorbic acid found in plants. Their chemical structures are identical.

Ascorbic acid – regardless of the source – is vitamin C. We know this because if you give either natural or synthetic ascorbic acid to someone with scurvy, it will cure them. That's the definition of a vitamin.

Dr. Pauling supported the use of synthetic vitamin C. He took synthetic vitamin C supplements and supported the companies that produced them. Experiments in his laboratory (and in many other laboratories around the world) defining the health benefits of vitamin C were conducted with the synthetic form of the vitamin.

Unfortunately, the superiority of "naturally derived vitamin C" is a myth often repeated in the marketing of dietary supplements. This misbelief is exacerbated by the fact that the synthetic and natural forms do differ for other vitamins, such as vitamin E.

While there are no known additional benefits of taking natural-source vitamin C versus synthetic, eating a diet rich in fruit and vegetables has numerous health benefits.

— Alexander Michels, PhD

ACCOLADES

MARET TRABER NAMED AS A 2021 ASN FELLOW

In June, the American Society for Nutrition (ASN) inducted 15 individuals into its Class of 2021 Fellows. Included on this year's list is the Linus Pauling Institute's own **Dr. Maret Traber** for her pioneering work on vitamin E.

With this award, the ASN acknowledges Dr. Traber's trailblazing research and pivotal contributions to understanding the role of vitamin E in human health. In addition, the Society formally recognizes Dr. Traber's legacy in vitamin research and thanks her for inspiring the next generation of nutrition scientists worldwide.

RICHARD VAN BREEMEN IS PART OF THE POWER LIST

Each year, *The Analytical Scientist* publishes its "Power List" – a list of the world's most influential analytical scientists. To develop the Power List, this industry publication held open nominations for candidates. A panel of independent judges then selected the top 100 scientists in the field.

For the second year in a row, the Linus Pauling Institute's **Dr. Richard van Breemen** has been included as one of the top 100 analytical scientists on this list. This recognizes Dr. van Breemen's talent, ingenuity, and leadership in the field of analytical chemistry, particularly in natural products chemistry.

THE FUTURE IS BETTER HEALTH

NOW MORE THAN EVER, people all over the world are focused on maintaining good health. The Linus Pauling Institute has been discovering the pathways to optimal health for nearly 50 years.

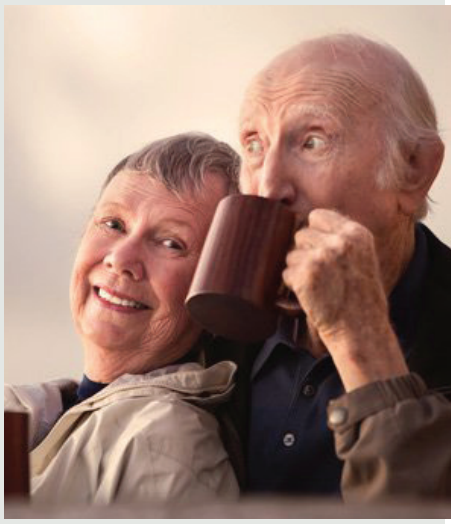
We know that there is power in science-based information – knowing more about the food you eat and supplements you take will not only empower you to make better decisions about health, but it will shape the healthspan of generations to come.

The future of health starts today. Will you join us?

Making a donation in support of the Linus Pauling Institute today will allow you to:

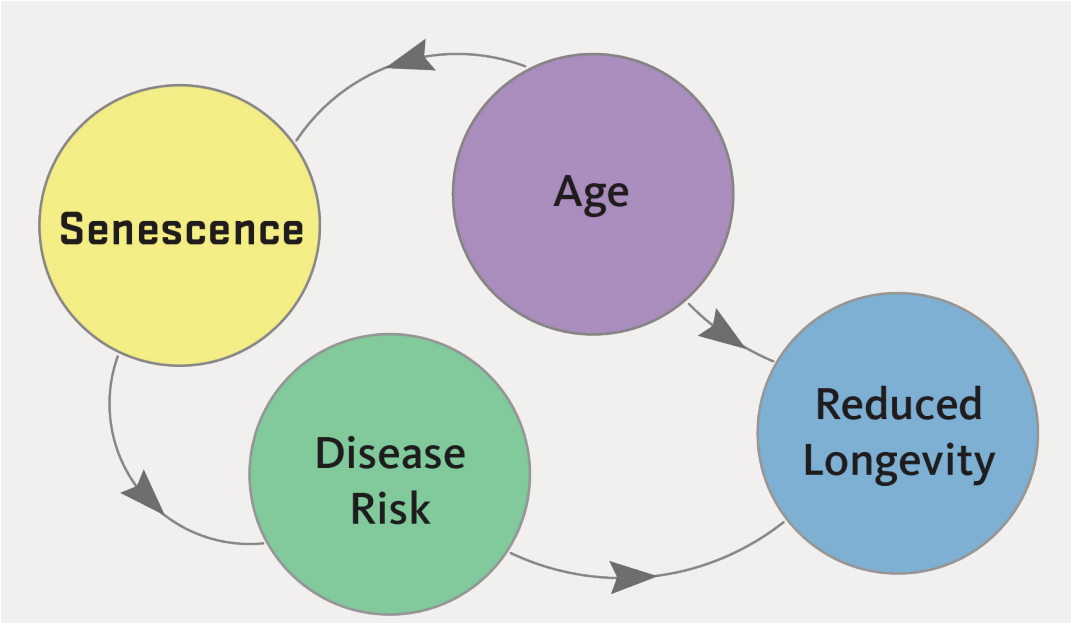
- Support research at the Institute that matters to you
- Sustain our outreach and education programs
- Empower students to learn from the Institute
- Explore possible tax benefits of charitable giving

Don't wait! Contact Andrew Norwood to learn more about the ways you can support the LPI mission!
Andrew.Norwood@osufoundation.org



Oregon State University
Linus Pauling Institute | 25 years

Senescence is the natural, progressive, and irreversible process of biological aging at the cellular level. As cells get older, they progress into a senescent state. As the number of senescent cells increase with aging, this increases the risk for disease, reducing overall health and longevity for the entire organism.



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Thus, researchers in the field of aging developed the concept of healthspan. Although in its strict definition, healthspan refers to the number of years one spends free of disease, it can also include years of living with a high quality of life despite chronic health conditions.

Basic Biology of Aging

No matter what we do, the cells in our body have a finite limit – they simply cease to function at some point. Ideally, everyone would live free of disease until the moment of death, and many people would be able to live until a healthy old age.

In reality, many people develop chronic diseases decades before they die, translating to many years of declining health, potential suffering, and poor quality of life. Lifespan is almost always longer than healthspan. However, the gap between lifespan and healthspan does not have to be as wide as it is today.

Extending our healthspan requires knowledge of the underlying causes of age-related diseases. Researchers often refer to this as the "basic biology of aging." For the last few decades, scientists have been characterizing a cellular process called *senescence*, which seems to hold the key to the aging process.

During senescence, cells enter a different metabolic state where they cease to divide and communicate this change to surrounding cells.

This change is not always harmful, but studies of senescence demonstrate that some of these senescent cells are behaving badly. The presence of senescent cells can irritate neighboring healthy cells, initiating unwanted inflammation.

Senescence is an irreversible and natural change that occurs more frequently as we get older. This increasing number of senescent cells is often associated with a decline in physiological function that ultimately increases the risk of developing disease.

Therefore, in order for our healthspan to match our lifespan, we need to minimize the impact of senescence. Delaying the onset of cellular senescence is one strategy that is generally believed to be effective.

Alternatively, targeting and destroying senescent cells in the body has already demonstrated clinical benefits. There are indications that some markers of age-related disease can be reversed through the use of these "senolytics," which is the name for these compounds that target senescent cells.

How to Address Healthspan

Long before the term healthspan was coined, Dr. Linus Pauling addressed this concept in his book *How to Live Longer and Feel Better.* His recommendations for good health still hold true today and are echoed in many of the current recommendations of the National Institute on Aging.

While genetics and environment do play a role in determining our healthspan, diet may be a greater factor than both of these combined. Therefore, the Linus Pauling Institute is uniquely positioned to address healthspan research with its focus on diet, dietary compounds, and healthy aging.

One area of active research at the Linus Pauling Institute is the role that micronutrients (vitamins and minerals) play in health. This includes understanding when and how micronutrient deficiencies occur and who is more prone to micronutrient shortfalls.

Adequate micronutrient intake is directly related to healthy aging. The health consequences of not consuming the necessary vitamins and minerals include premature aging and an increased risk of developing age-related diseases. There are also indications that micronutrient deficiencies may promote the formation of senescent cells.

Several lines of research at the Institute focus on the potential challenges of obtaining adequate micronutrients, as well as the changing micronutrient requirements throughout life, especially in older age.

In a recent clinical trial, Dr. Adrian Gombart showed that multivitamin supplement use reduced the severity of respiratory illness symptoms in older adults, suggesting effects on immune function. Drs. Tory Hagen and Kathy Magnusson are currently examining the effect of multivitamin supplements on the nutritional status of older men in an ongoing trial.

Other dietary compounds are an additional area of interest for healthspan research at the Institute, as many have the potential to influence the course of age-related disease. One area of focus is purified phytochemicals, or plant compounds, which can be used as dietary supplements. Although many are found in foods, both animal and clinical trials often use these compounds at levels much higher than what would be obtained by consuming the plant.

Current phytochemical research at the Institute looks to combat age-related disease. For instance, Dr. Emily Ho is examining the role of isothiocyanates, especially sulforaphane, in reducing cancer risk. Drs. Fred Stevens and Adrian Gombart are investigating the biological effects of xanthohumol – a flavonoid from the hops plant – and evaluating its potential in combating metabolic syndrome (see pages 6 and 7 for more details on this research).

Aging research at the Institute also includes seeking applications for other natural compounds, such as lipoic acid, acetyl-L-carnitine, and N-acetylcysteine. These compounds provide metabolites that decline with age and/or bolster the stress response of aging cells.

Many of the compounds mentioned above have shown promise in animal models, and this lays the groundwork for clinical trials. While research in these areas is exciting, we have a long road ahead before any recommendations for humans can be made.

For More Information

The Linus Pauling Institute's Healthy Aging Program has been making strides in understanding the basic biology of aging while searching for how diet and dietary factors might improve our chances of living a longer, healthier life.

Many of the concepts discussed here were presented in a webinar in August 2021 by Dr. Tory Hagen: ***Keeping Life in Your Years: Dietary Factors Affecting Healthspan and Longevity***.

Dr. Hagen's webinar can be viewed at: lpi.pub/HagenWebinar

The basic biology of brain aging and the effects of diet and lifestyle on cognitive function were presented in a webinar in July 2021 by Dr. Kathy Magnusson: ***Why You and Your Dog Can't Find Your Keys: This is Your Brain on Aging***.

Dr. Magnusson's webinar can be viewed at: lpi.pub/MagnussonWebinar

For more of the basics about senescence, see our highlight of Dr. Viviana Pérez's research in our **Fall-Winter 2017 Research Newsletter**, available on our website.

LPI STUDENT HIGHLIGHT: TWO NEW PHDS!

Graduate students at the Linus Pauling Institute must complete and successfully defend their dissertation to fulfill the requirements of a PhD program. Their success is not only that of the Institute but of all who supported their work.

We feature research projects of graduate students supported by Linus Pauling Institute fellowships, which are supported by generous donations. In this issue, we highlight two recent graduates from the Institute: the newly hooded Drs. Isabelle Logan and Ines Paraiso.

Working with Drs. Fred Stevens (Paraiso) and Adrian Gombart (Logan), both students completed their dissertations on xanthohumol, a compound from hops that is found in beer. Their success is a reflection of the long-term collaboration between Drs. Stevens and Gombart to explore the health benefits of xanthohumol.

Isabelle Logan, PhD
Formerly of the Gombart Laboratory

Xanthohumol & Health: The Role of Gut Microbes

Previous studies showed that animals fed a high-fat diet experience some degree of insulin resistance and elevated blood sugar levels. Adding xanthohumol to their diet reversed some of these changes, but it was not understood how this worked.

Working with Dr. Gombart, Isabelle Logan started looking deeper into the metabolic effects of xanthohumol as part of her PhD dissertation project.

Isabelle's research was funded by both the George and Audrey Varseveld and the Mark Sponenburgh Endowed Fellowships at the Linus Pauling Institute

Isabelle first examined the role that microbes played in the guts of these animals. This was a logical starting point, as diets high in saturated fat are known to change the population of microorganisms in the intestine and could contribute to metabolic syndrome in animal models.

To determine the influence of gut bacteria in xanthohumol's biological effects, Isabelle needed to work with mice with absolutely no gut bacteria, known as **"germ-free mice."**

For more about germ-free mice and how they are used in microbiome research, see our Fall-Winter 2019 newsletter.

To test the effects of xanthohumol, animals were fed a normal (low-fat) diet, a diet high in saturated fat, or this same high-fat diet with xanthohumol. Half of the animals in this study were germ-free mice, and the other half had normal gut bacteria.

As expected, the animals eating a high-fat diet developed insulin resistance and elevated blood sugar levels compared to animals on the normal diet. These changes happened in both the germ-free mice and those with normal gut bacteria.

However, when xanthohumol was included with the high-fat diet, it prevented the insulin and blood sugar issues – but only in animals with normal gut bacteria. Germ-free mice still developed insulin resistance and elevated blood sugar levels despite the xanthohumol added to the diet.

Isabelle's findings show that xanthohumol's health benefits are somehow related to gut bacteria. This supports the idea that gut bacteria chemically transform xanthohumol into something else – perhaps a beneficial compound that acts in the intestine or can enter the bloodstream.

There are also indications that xanthohumol changes the composition of gut bacteria. While it is too soon to say if xanthohumol can completely reverse the changes induced by a diet high in saturated fat, this is an exciting avenue for future research.

In the spring of 2021, Isabelle defended her dissertation with Dr. Gombart and earned her PhD in Biochemistry and Biophysics. Dr. Logan is now working with Dr. Maria Clara Franco at Oregon State University, looking at the effects of protein nitration in the immune system.

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Logan et al. *Mol Nutr Food Res* **(2021); e-publication ahead of print**
doi: 10.1002/mnfr.202100389

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doi: 10.3390/microorganisms8040520

Bile Receptors: The Key to Xanthohumol's Actions?

When rodents eat a diet high in fat, they quickly gain weight. However, if xanthohumol is included with that high-fat diet, the animals gain less weight. Because of this, xanthohumol is being explored as a possible treatment for obesity.

Current research in this area focuses on uncovering the mechanisms of action of xanthohumol. One protein that has emerged as a possible target for xanthohumol is called the Farnesoid X Receptor – or FXR for short.

FXR is a receptor protein that exists in many organs throughout the body. In the intestine and liver, it binds to and regulates the production of bile acids. FXR is so important to the function of bile acids that it was originally called the "Bile Acid Receptor."

Working in Dr. Stevens' laboratory, Ines Paraiso focused her research on determining whether xanthohumol's effect was due to changes in FXR activity. Since FXR regulates some aspects of lipid and glucose metabolism, it was a good target for xanthohumol's activity.

But activating FXR can have different effects based on the organ in which it is working. Compounds that stimulate FXR in the liver help improve the metabolism of fat. On the other hand, activating FXR in the intestine could promote weight gain.

In order to be considered an effective weight loss treatment, xanthohumol would need to stimulate FXR in the liver and also inhibit its activity in the intestine.

Ines first looked at the effect of xanthohumol in the liver. As expected, xanthohumol increased FXR's activity, resulting in a decreased activity of genes involved in fat synthesis and stimulation of genes involved in bile acid production.

However, in the intestine, something different was occurring. As Isabelle Logan discovered (page 6), xanthohumol can induce changes in the composition of gut bacteria. As was seen in Isabelle's work, Ines observed that the altered population of the gut bacteria changed bile acids into new compounds that seemed to inhibit FXR activity in the intestine.

So it appears that xanthohumol is pulling double duty: stimulating FXR in the liver directly and inhibiting FXR in the intestine through bile acid metabolism via gut bacteria. Combined, these effects lead to an overall change in fat metabolism that could explain reduced weight gain in animals.

In the spring of 2021, Ines defended her dissertation with Dr. Stevens and earned her PhD in Medicinal and Pharmaceutical Chemistry. Dr. Paraiso is now working with Dr. Nika Danial at the Dana-Farber Cancer Institute, part of the Harvard Medical School in Boston.

Ines Paraiso, PhD
Formerly of the Stevens Laboratory

References

Paraiso et al. *Front Pharmacol* **12 (2021);** doi: 10.3389/fphar.2021.643857

Paraiso et al. *Mol Nutr Food Res* **64 (2020);** doi: 10.1002/mnfr.202000341

Xanthohumol is normally found in the flowers of the hops plant (also known as "cones"). While this compound is found in beer in varying amounts depending on style, these research studies used amounts of xanthohumol that dwarf those found in beer.

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INSIDE: NEW DISCOVERIES BY LINUS PAULING INSTITUTE GRADUATE STUDENTS!