

## Application of Phytochemicals in Immune Disorders: Their Roles Beyond Antioxidants

Jeffrey S. Bland, PhD, FACN, FACB, Associate Editor

### Abstract

We are witnessing increased global pressure on immune system function as a result of climate change, exposure to xenobiotics, poor quality diets, increased psychosocial stress, and exposure to new infectious agents. Understanding how various phytochemicals and their metabolic byproducts produced by the microbiome

modulate immune-related signal transduction pathways has opened a new chapter in medical nutrition that moves far beyond that of generalized antioxidant effects. Not only is precision nutrition now possible, there is an urgent need for it.

*Jeffrey S. Bland, PhD, FACN, FACB, is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life.*

In the early 1970s, my research group was focused on a phytochemical family of bioactive molecules called the tocopherols (vitamin E). We were exploring the physiological mechanism of action, and we ultimately published a number of cell-based and human clinical studies demonstrating that alpha-tocopherol prevented oxidative changes in membrane-bound cholesterol, which in turn prevented cellular membranes from losing their integrity. One of our observations was that this phenomenon was associated with an extension the cellular longevity of red blood cells in humans under conditions of oxidative stress.<sup>1-4</sup>

Among the general research community of that era, vitamin E was thought to be an antioxidant that protected cells against “rancidity,” in the same sense that antioxidants in food can prevent spoilage. As the 1980s dawned and I transitioned to a new role at the Linus Pauling Institute of Science and Medicine, I continued to explore the antioxidant influence of both vitamin E and vitamin C using cellular and animal models. With a variety of collaborators, I published a number of review papers about the concept of oxidative injury through cellular oxidative damage by free radical species.<sup>5-10</sup> The paradigm that was emerging was that oxidative stress and its associated free radical pathology were major factors in the development of age-related diseases, and that biological antioxidants represented a potential solution.

The phytochemical family of nutrients is vast, and over the last 30 years many studies have been published demonstrating antioxidant influence, with some of the most notable work focused on flavones, flavonoids, flavanols, isoflavones, and anthocyanidins.<sup>11,12</sup> Methods were developed to analyze the relative antioxidant power of specific phytochemicals in foods. These analytical methods are now widely used and include Oxygen Radical Absorbance Capacity (ORAC), Ferric Reducing Ability of Plasma assay (FRAP), Thiobarbituric Acid Reactive Substances (TBARS) assay, and Total Oxidation value (TOTOX), which measures total peroxide and anisidine levels to determine oxidative damage or rancidity.<sup>13-15</sup> The food industry has come to rely on these measuring systems to determine the shelf-stability of products, but they have limited value for understanding the human health effects of phytochemicals in food. This disparity is a consequence of the increasing recognition that phytochemicals play roles in the regulation of metabolic function, but this activity is only partially connected to their antioxidant ability. Recent research has revealed that phytochemicals significantly influence health as modulators of specific cellular signaling processes associated with genetic and epigenetic expression, as well as through a process called signal transduction, which regulates downstream cellular functions.<sup>16-22</sup>

### Role of Phytochemicals as Modulators of Metabolism

In 1992, Edmond H Fischer and Edwin G Krebs were awarded the Nobel Prize in Physiology or Medicine for their discoveries of a fundamental signaling system that controls the function of cells. Their discoveries were focused on protein phosphorylation, a process connected to many essential cellular activities. Phosphorylation dictates how cells grow, divide, and respond to environmental stimuli. It also regulates how cells respond to inflammation and hormones. Drs. Fischer and Krebs