Antioxidant Polyphenols and the Microbiome

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The word “antioxidants” is a familiar one; most people with even a passing interest in nutrition are aware of the benefits of compounds like vitamin C and vitamin E. However, how many of us really understand what antioxidants do and why they are so important to our health? This paper will explain the basics of how antioxidants work, with a special focus on an important class of antioxidants from the nutritional point of view: the polyphenols. We will also consider how some polyphenols may exert their effects without ever being absorbed into our bloodstream, through direct effects in the gut; in particular, through support of our microbiome.

Oxygen: Friend and Foe

Oxygen is our best friend; without it, it would be impossible to survive as the complex living beings we are. It may come as some surprise, therefore, that oxygen is also one of the most toxic substances we are exposed to in our everyday environment. In fact, oxygen is so dangerous that our bodies have developed elaborate systems with the sole purpose of protecting against damage wrought by this very life-giving element.

To understand this paradox, it is helpful to take a step back in time, to the first years of life on planet Earth. The atmosphere during those early years had little to no oxygen gas (Pavlov and Kasting, 2002). The early life forms that existed at that time (bacteria-like cells called archaeans) had no use for O_2, and happily lived without it. All life forms were anaerobes—microbes that live without oxygen. Then, around 2.5 billion years ago, some bacteria evolved the ability to use sunlight to create food and began to emit large amounts of oxygen as a waste product of this new process of photosynthesis. Eventually, as the amount of oxygen produced exceeded the amount removed through reaction with minerals or gases, oxygen became established as a gas in the earth’s atmosphere and continued to accumulate until a different type of bacterium—the ancestor of our own cells’ powerhouse organelles, the mitochondria—evolved the means to harness this highly reactive substance.

Today, this same system is seen throughout the world. It is essential for almost all animals, plants, and fungi, as well as much unicellular life (the aerobes, which require oxygen, and the facultative anaerobes, which can “turn on” the oxygen-harnessing system in the presence of oxygen). However, when oxygen gas first began to cover the earth, the result was not a flourishing of evolution, but rather death on a massive scale. Oxygen was a toxic pollutant, and the mass extinction it caused--called the Oxygen Catastrophe and Oxygen Crisis, alongside forwardlooking terms like Oxygen Revolution and Great Oxygenation Event—killed almost all life on earth at the time (Dorado et al. 2010).

Oxygen—or, more precisely, its derivatives, reactive oxygen species (ROS)—is highly toxic because it is highly powerful, with a large amount of easily accessible energy stored in the O_2 bond. You can see this in the form of fire—the destructive power of fire stems from the release of the immense power when these bonds are broken in a process called oxidation. When living systems gained the ability to release this power in tiny steps instead of all at once, they were able to harness an enormous amount of energy—enough to power the numerous and complex reactions that eventually allowed modern life, including humans, to evolve. However, alongside the power of harnessed oxygen is the ever-present danger of unharnessed oxygen. Just as the energy of broken O_2 bonds combined with an organic substance like wood can lead to fire, this same oxidative energy can lead to destruction of the organic molecules that makes up our bodies. For this reason, alongside the harnessing of the great energy of O_2, aerobic biological organisms need a system of protection against this energy when it is not harnessed.

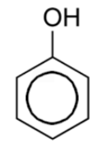
Unharnessed oxygen in our bodies takes the form of reactive oxygen species (ROS, also known as free radicals), which form when O_2 is broken but the energy of the bond is retained in a molecule that can, in turn, harm our bodies through oxidation of important biomolecules. ROS are unstable because they have unpaired electrons; an energy state that drives them to react with other molecules. Some examples are the hydroxyl radical (OH-) and peroxide (O_2^{-2}). Essentially, ROS are molecules with extra or “loose” electrons that are ready to fly off and stick to other molecules (like our DNA) resulting in a reaction that changes the biomolecules. If this happens, the damage can lead to cancer, accelerated aging, and a host of other health problems.

Antioxidants: Biological Defense via Nutrition

Antioxidants protect the body from damage by reacting with oxidants, especially strong oxidants like ROS. Whereas ROS have “loose” electrons ready to fly off, antioxidants are structured to catch those electrons, reacting with and absorbing the ROS before the ROS can react with important cellular biomolecules. These electron scavengers circulate through the blood, ready to react with and neutralize any ROS they encounter.

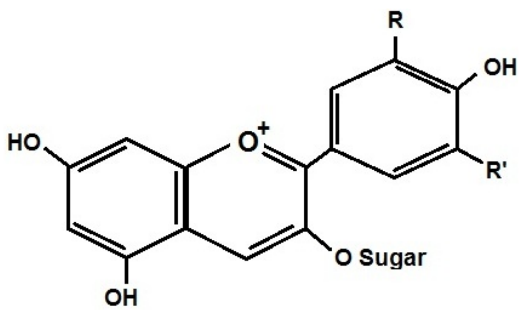
Since plants are bombarded with oxygen-splitting UV rays from the very source of their own energy, antioxidants are even more important for plants than animals, especially in their reproduction-related organs—for example, seeds, berries, beans, and tree fruit. Although our bodies have developed several built-in systems for detoxifying ROS, we can also take advantage of the fact that plants produce their own antioxidants. Some of these antioxidants may be familiar:

Vitamins A, E, and C are all antioxidants that plants produce and we consume in a healthy diet.



Phenol

Plant antioxidants have structures containing one or more phenol groups and so are often called **polyphenols**, meaning many phenols. Phenols are chemicals that contain a benzene group attached to a hydroxyl group, a structure which confers antioxidant ability. They are found throughout the world, and particularly in plants. Some polyphenols are colorful, such as the anthocyanins which give blueberries their dark color and red cabbage its red-purple color. As some of the most powerful antioxidants, anthocyanins are an important part of a healthy diet (Hidalgo et al., 2012). In addition to blueberries and red cabbage, natural sources of anthocyanins include elderberries, purple corn, cranberries, bilberries, black raspberries, blackberries, blackcurrants, cherries, strawberries, purple grapes, red wine, and eggplant.



Anthocyanin, a polyphenol found in blueberries

To reach our cells, the polyphenol antioxidants that we eat must be absorbed in our small intestine into the blood and then pumped by the heart to each cell. The ease of entry of a substance from the gut into the blood where it can reach its target is called **bioavailability**. Bioavailability is no small issue. There are many barriers to overcome. First, the antioxidant must survive digestive processes from the mouth to the small intestine itself, including the harsh, acidic environment of the stomach. Then, it must pass through the cells lining the intestine and the cells of a capillary blood vessel to enter the bloodstream. Finally, it must survive chemical processes taking place in the liver, since almost all molecules absorbed by the intestine travel through the liver on the way to the heart. The liver has an enormous capacity to change the nature of an antioxidant.

If an antioxidant is changed by digestion or processes in the liver, it may no longer be able to neutralize ROS. This is, in fact, what happens with the majority of polyphenols, and this loss of bioavailability means that these antioxidants—while powerful ROS absorbers in the test tube—will not be capturing ROS in the cells of the person who ate them. Yet, there is strong evidence supporting many health benefits of eating these very antioxidants. So, is it necessary for a nutrient to be bioavailable to be helpful? And, if not, how and where can these antioxidants be working?

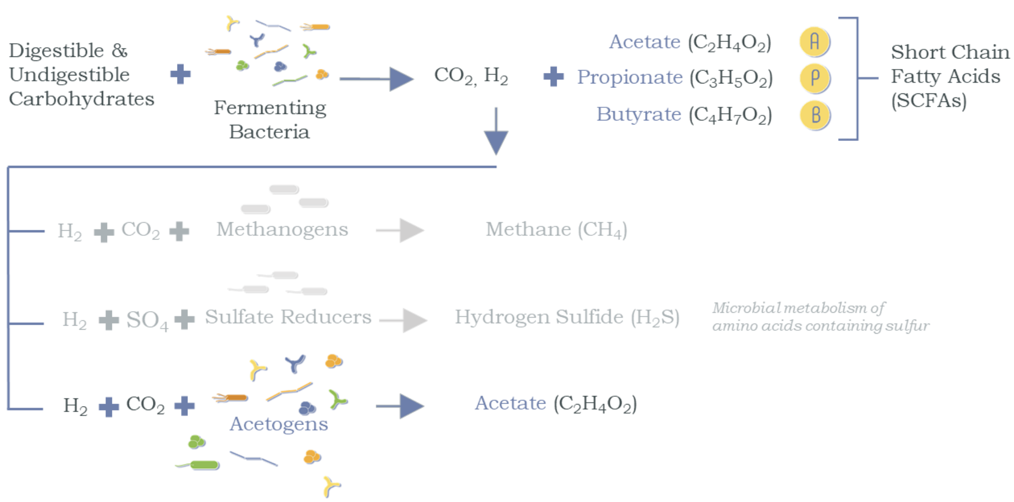
Antioxidants and the Microbiome

An emerging explanation for the health benefits seen with polyphenols that have great antioxidant activity in the lab but low bioavailability may lie with the gut microbiome, the personal population of microbes that lives in our gastrointestinal system. Instead of entering the blood stream, the antioxidants could be reacting with ROS generated by digestion of nutrients right there in the gut—neutralizing the ROS before they have a chance to get absorbed into the body.

Importantly, new research (Cardona et al., 2013) suggests that polyphenols serve as key nutrients for bacteria in our GI microbiome. Some bacteria forage on polyphenols to generate vitamins such as vitamin B12 and vitamin K. Some bacteria appear to use polyphenols to generate molecules that function as natural antibiotics for potentially pathogenic bacteria. Some bacteria that thrive on polyphenols generate acetate, a useful short-chain fatty acid.

Hydrogen Production and Balance

One metabolic waste product of many intestinal microbes is hydrogen gas (H_2), which is in turn fermented into one of three compounds: methane (CH_4; produced by microbes known as methanogens), hydrogen sulfide (H_2S; produced by microbes known as sulfate reducers), or acetate ($C_2H_4O_2$; produced by microbes known as acetogens). Of these, acetate is by far the healthiest. Methane has been associated with weight gain and obesity, and hydrogen sulfide gas has been associated with GI diseases such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and leaky gut (Tomasova et al., 2016). The methanogens, sulfate reducers, and acetogens are all in dynamic competition for the available hydrogen.



To shift production away from hydrogen sulfide and methane and towards the creation of more acetate, the healthy fermentation product, the environment of the gut should be optimized for encouraging the metabolic activity and growth of the acetogens. This is where polyphenols again come in to the picture: only the acetogens can use polyphenols as a nutrient. So, eating polyphenols supports the acetogens, promoting the production of healthy acetate instead of unhealthy hydrogen sulfide and methane. This is an example of a process called cross-feeding, in which a particular nutrient benefits one subgroup of biota to create particular metabolites.

Through the properties of ROS scavenging in the gut and support of beneficial gut microbes, polyphenols can benefit overall health in a myriad of ways, including maintenance of healthy blood glucose levels, protection against cancer, and aid in maintaining a healthy weight. For this purpose, however, we want polyphenols that will get to the microbe population in the large intestine. The best polyphenols for this are therefore those that have low bioavailability or are not bioavailable; in other words, those that stay in the gut. A great food source fitting that requirement is blueberry. However, since polyphenols are destroyed during the reaction with ROS–each polyphenol molecule sacrifices itself in order to neutralize one ROS molecule--they cannot be reused. Therefore, while high-polyphenol fruits like blueberries can influence the gut population in favor of the beneficial acetogens, they must be consumed in high enough quantities to do so. In other words, both quality and quantity matter—for ideal gut health, it's not enough to just eat blueberries; you have to eat a *lot* of blueberries.

Unfortunately, constraints of modern life, such as budget and time, can make it difficult to get an optimal level of polyphenols in our diet. Further, in addition to practical difficulties, eating enough polyphenol-containing fruits—for example, several cups of blueberries each day—can place a strain on the bodies of individuals trying to manage diabetes, pre-diabetes, or obesity, through the extra sugar in that much fruit. Here at Microbiome Therapeutics, we have developed methods to safely extract polyphenols from blueberry, while removing most of the sugars. The result is that BiomeBliss contains significant levels of these GI-directed antioxidant polyphenols, without all the calories of the whole fruit, in a convenient and delicious drink mix. Feeding your microbiome has never been this easy!

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