THE PATH AHEAD

"Unimportant" Molecules?—Part 2

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Abstract

"Unimportant" Molecules?—Part 1 reviewed the research on how the loss from the food supply of molecules that are not considered required nutrients has substantially contributed to the chronic disease epidemic. In Part 2, I present more research on the clinical benefits of dietary and supplemental carotenoids, flavonoids, and other important plant molecules. The research is clear that regularly eating colorful, organically grown foods is required for health.

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Introduction

In Part 1 of my editorial on "Unimportant" Molecules?-Part 1[1] I presented considerable research on the dramatic loss of molecule diversity in the food supply. This loss of diversity happened because the core nutrition research that determined what was important in food was incomplete. The vast majority of the work was performed a century ago when our understanding of physiology, and the laboratory equipment of the time, were relatively primitive. This resulted in the erroneous belief that the 40 to 50 vitamins, minerals, fatty acids, etc, were the only important molecules and elements in food. This limited perspective seemed to rationalize growing food chemically rather than organically since most of the "important" nutrients were retained even though the rest of the up to 50 000 molecules in food were reduced, some dramatically. This was aggravated by the synthesis of vitamins (such as folic acid) which are not identical to the natural forms, resulting in unexpected problems and the mistaken belief that vitamins are single molecules that can be synthesized and prescribed, rather than families of vitamers that work both independently *and* synergistically in the complex matrix of physiology. The net result has been a dramatic decrease in human ingestion of a huge number of molecules which may not technically be required for life but are definitely required for health and for disease resistance.

In Part 2 of this editorial, I delve more deeply into the research showing the clinical benefits of these "unimportant" molecules and the health improvement, and even disease reversal, that occurs when these are added back into the diet. While many of these "unimportant" molecules are now being marketed as "miracle" *phytonutrients*, they should have been in the food supply to begin with.

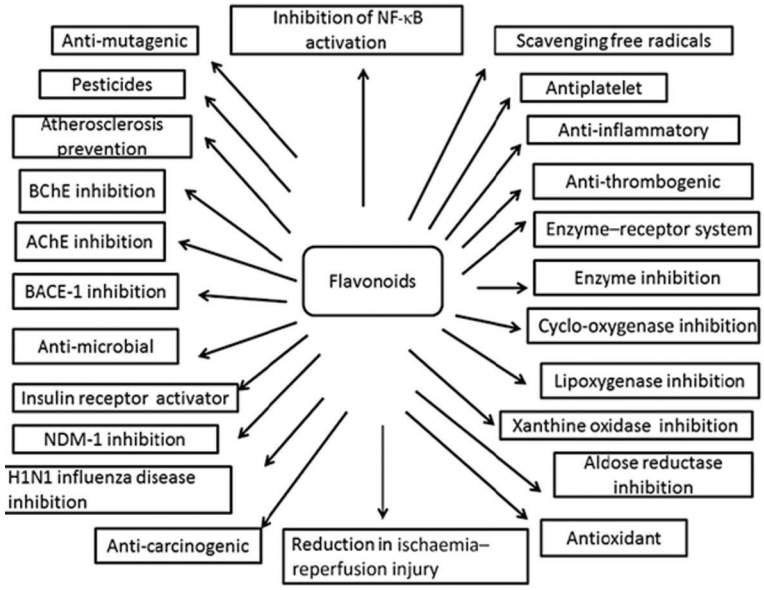
Flavonoids

The obvious reason I've focused so much on flavonoids is the huge body of research demonstrating their clinical significance and their reduction in the food supply over the past few decades. Figure 1 provides a nice overview of the remarkably diverse physiological benefits of the many flavonoid classes.

A simple search of PubMed yields thousands of studies documenting an inverse correlation between flavonoid—and virtually every chronic disease.

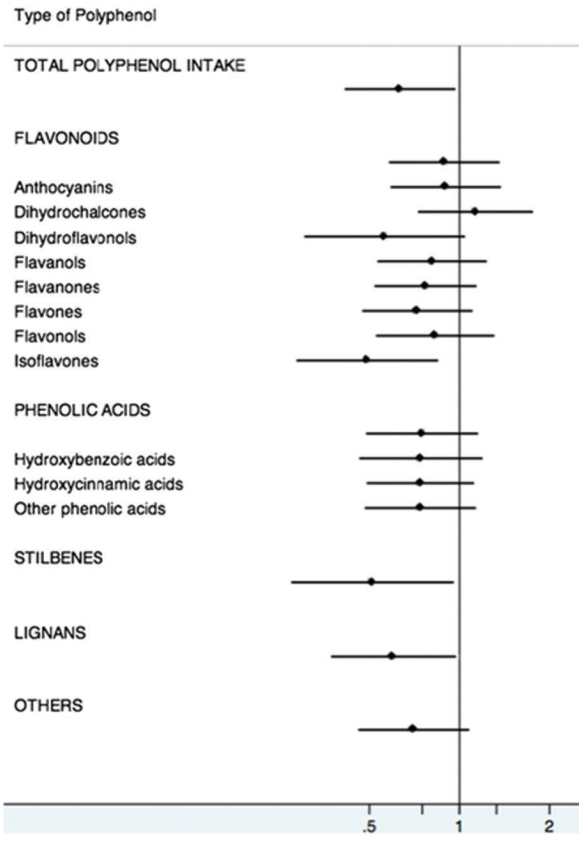
Many studies have shown that supplemental flavonoids improve many measures of health and decrease risk of many diseases. For example, a search of PubMed for clinical trials on quercetin yielded 303 hits. Supplementation with quercetin lowers uric acid in hyperuricemic males, improves outcomes in COVID-19, improves neuromuscular function after muscle damage, lowers blood pressure, and helps heal diabetic foot ulcers; the list is long and is continuing to expand.[2-6] Note that I intentionally did not include in this list common diseases like diabetes, cancer, and cardiovascular disease because most readers are aware of the voluminous research in these areas. Rather, I am showing the remarkably diverse health benefits of flavonoids.

Figure 1. The Diverse Physiological Effects of Flavonoids[7]



Abbreviations: AChE, acetylcholinesterase; BACE-1, β active site cleavage enzyme-1; BChE, butyrylcholinesterase; H1N1, hemagglutinin type 1 and neuraminidase type 1; NDM-1, New Delhi metallo-β-lactamase-1; NF-κB, nuclear factor kappa light chain enhancer of B cells.

Figure 2. Polyphenol Intake Inversely Correlates With Risk of Death[8]



The graph shows hazard ratios (95% CI) of total mortality for the highest vs lowest quintiles of polyphenol intake.

But of greater interest for my unimportant molecules thesis is the correlation between dietary intake of flavonoids and disease risk, not just the benefits of supplementation. I think Figure 2 is quite illustrative. As can be seen, all but one polyphenol is inversely correlated with all-cause mortality.

Note that stilbenes show a remarkable 52% (multivariate adjusted) reduction in risk of death. Lignans show a 40% reduction. These are not small effects!

Another aspect of flavonoids that is important to understand is their short half-life in humans. For example, the half-life of quercetin is only about 12 hours.[9] This implies that flavonoids likely need to be in the diet every day to achieve their optimal benefits. This is discussed more thoroughly below.

Loss of Flavonoids

While the decrease in flavonoid levels in commonly eaten foods is easy to demonstrate, assessing blood levels (typically measured in plasma) over time has proven beyond my ability to document. Unfortunately, NHANES (National Health and Nutrition Examination Survey) has not tracked flavonoids. I believe body levels of flavonoids have decreased for several reasons, including loss of flavonoids from foods due to changing food choices, chemical-agriculture, cultivar choices, processing (commercial as well as at home), and storage. While there are a few instances where food processing can free some flavonoids from the food matrix making them more bioavailable, the typical net impact of processing is a substantial loss, as shown in Table 1. Please note that the

study cited provides a lot more detail for those who want to pursue this further. Those processing methods listed are my best effort to highlight the key findings.

Table 1. Examples of Loss of Food Flavonoid Content by Processing[10]

Method	Time (minutes)	Loss
Commercial		
Water (50°C)	1.5	22%
Roasting (120°C)	20	12%
Steam	40	25%
Blanching (100°C)	4	None
Domestic		
Boiling	60	20.5%-43.9%
Frying	5-15 min	23%-29%
Microwaving	Various	None
Sautéing	3	21%

As can be seen, a substantial portion of the flavonoids are lost during both commercial and in-home processing. A key challenge with this data is the huge variation in flavonoid stability depending upon the flavonoid type and the food where it is located. For example, heat pasteurization (90°C, 60 seconds) of strawberry juice has no effect on quercetin and kaempferol, while the same procedure greatly reduces naringin, narirutin, quercetin, and naringenin content for grapefruit juice.[10] The clearest takeaway is that microwaving is least damaging to flavonoids.

Storage also decreases flavonoid content, but inconsistently between foods and the type of flavonoid. For example, storing **uncut** vegetables **at 4°C** in the **dark** results in no significant loss of flavonoids. In contrast, cutting the food and/or storing under light, even if cold, results in significant loss. In other words, once a food is processed (cutting, cooking, etc) flavonoids become much more fragile and decline during storage. There are a few examples where a few flavonoids increase in a food with time during storage, but these are not common.

The bottom line is that to optimize flavonoid content of food it needs to be as unprocessed as possible and eaten soon after harvest.

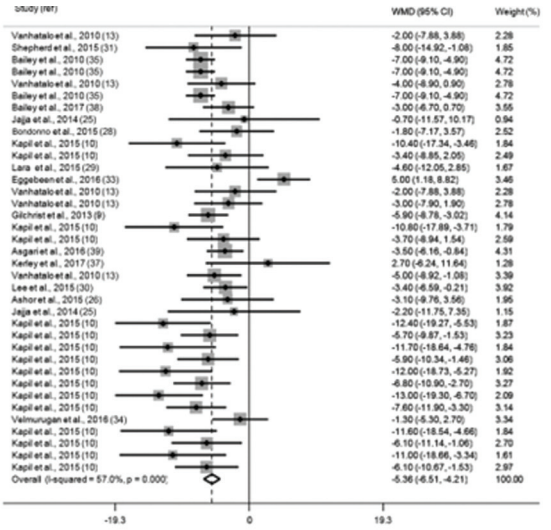
Carotenoids

Similar to flavonoids, there is also considerable research showing efficacy of dietary and supplemental carotenoids. Space limitations do not allow me to cover this in much detail. One example is illustrative: lycopene intake is inversely correlated with prostate cancer. Those consuming adequate levels of lycopene experience a remarkable 60% reduction in prostate cancer risk.[11]

Clinical Implications

As noted above, many studies have looked at the impact of dietary and supplemental flavonoid and carotenoid intake on multiple diseases. The research is very clear: virtually every disease is inversely correlated with body levels of "unimportant" molecules. As near as I can determine, the best way to increase dietary intake of the needed diverse flavonoids, carotenoids, and many other "unimportant" molecules is green drinks and eating organically. Figure 3 shows how beetroot juice decreases blood pressure (other benefits like improving kidney function are summarized in my editorial, The Kidney Dysfunction Epidemic, Part 2: Intervention.[12]

Figure 3. Beetroot Juice Decreases Blood Pressure[13]



Note: Forest plot of trials that investigated the effects of beetroot juice supplementation on diastolic blood pressure in relation to baseline values

Abbreviations: ref, reference; WMD, weighted mean difference.

Interestingly, this meta-analysis of 22 studies showed that beetroot juice was more effective the longer it was consumed (benefits most strongly show up after 14 days) and was most effective in those who were least healthy.

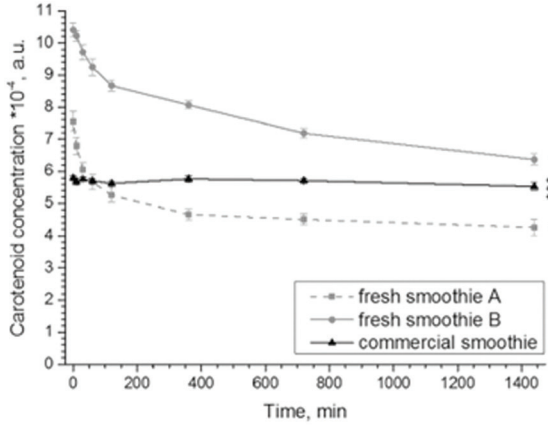
Similar benefits are shown with fruit juices high in polyphenols, such as pomegranate. Table 2 shows the improvements in many measures of inflammation.

Table 2. Pomegranate Juice Decreases Inflammation[14]

hs-CRP:	↓ 6.57 mg/L
CRP:	↓ 2.19 mg/dL
TNF-α:	↓ 2.37 pg/mL
IL-6:	↓ 1.68 pg/mL
MDA:	NS

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; MDA, malondialdehyde; NS, not significant; TNF-α, tumor necrosis factor-alpha.

Figure 4. Carotenoids Degrade Quickly at Typical Refrigeration Temperatures[15]



Abbreviation: a.u., arbitrary units.

Obviously, I could cite many more studies. The message is clear—dietary intake of unimportant molecules promotes health and reduces disease risk. However, green drinks should be consumed as quickly after juicing as possible. As shown in Figure 4, even at 4°C carotenoid levels decrease rapidly—after 1 hour, levels for the fresh smoothies have decreased about 15% to 30%.

Conclusion

While not necessary for life, "unimportant" molecules are critical for optimal health and disease resistance. Many studies have shown an inverse correlation between consumption of these food molecules and all-cause mortality and virtually every chronic disease. For optimal health, everyone should primarily eat organically grown foods and consume a green drink at least once a week.

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