CHAPTER

53

Polyphenolics Evoke Healing Responses

Clinical Evidence and Role of Predictive Biomarkers

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1. INTRODUCTION

Polyphenolics occur by the thousands, giving color and antioxidant protection to plants and animals. Quercetin dihydrate and soluble orthoproanthocyanidins (sOPC) are preferred, safer polyphenolics as supplements. Consumption can be many grams daily, more than all other classes of phytonutrients. Amounts ingested are typically ~10 times higher than the usual dietary intake of vitamin C and 100 times higher than the intake of vitamin E and carotenoids. The primary dietary sources are fruits, colorful vegetables, and plant-derived beverages such as dark chocolate, fruit spritzers, teas, coffees, beers, and wines. Vegetables, cereals, root vegetables, and dry legumes also contribute to the total polyphenolic intake (Table 53.1).[1]

Knowing a person's level of health in terms of oxidative stress and inflammatory repair resilience provides benchmarks of individual needs for enhanced antioxidant supplementation and supplementation. Free radical oxidative stresses and toxin exposures are endemic in today's society, requiring enhanced protective supplementation as detailed below. For many of our patients, it is likely that a good diet is no longer enough to maintain health. The use of global biomarkers referenced to "least risk" or "best outcome" enables us to better determine the level of supplementation that will be sufficient to meet individual needs.

Examples are provided from current research indicating the adaptogenic and effective nature of specific polyphenolics. Polyphenolics are classified first structurally into subgroups and then discussed functionally with emphasis on the evidence supporting safer, more effective flavonoid and flavonol supplementation.

2. FLAVONOIDS AND FLAVONOLS

Flavonoids and flavonols are the major chemical groups of polyphenols, with multiple subgroups. Most polyphenolics have poor bioavailability or toxicity risks that make them inappropriate for health management and promotion. This chapter focuses on the safer exceptions and their effective use. Related reviews are included in the discussion.

Non-toxic forms of polyphenolics with good bioavailability include quercetin dihydrate, sOPC, with or without ellagic acid.

- Flavonoids: quercetin dihydrate, ellagic acid
  - Flavanones: hesperetin, naringenin, eriodictyol
- Flavonols: kaempferol, myricetin, isorhamnetin
  - Flavones: luteolin, apigenin
  - Isoflavones: diedzin
  - Anthocyanidins: orthoproanthocyanidins, cyanidin, delphinidin
  - Malvidin, pelargonidin, peonidin, petunidin
  - Flavan-3-ols: catechins, epicatechins, aflavins, arubigins, quercitrins

3. MEASUREMENTS OF ANTIOXIDANT CAPACITY

Oxidative stress from free radical damage is increasingly associated with the development and progression of such diverse conditions as chronic cardiovascular, degenerative, autoimmune and cancer states. Oxygen radical absorbance capacity (ORAC) and total oxy-radical scavenging capacity (TOSC) assays have been developed to measure antioxidant capacity in foods. A high ORAC value indicates

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TABLE 53.1 Polyphenols: Food Sources and Bioavailability

Compound	Food Source (Serving Size)	Polyphenol Content	
		By wt (or vol) mg/kg Fresh wt (or mg/L)	By Serving mg/Serving
Flavonoids:			
Quercetin dihydrate	Multiple; *Sophora Japonica*	5000	500
Hydroxybenzoate	Blackberry (100 g)	80–270	8–27
Protocatechuate	Raspberry (100 g)	60–100	6–10
Gallate	Blackcurrant (100 g)	40–130	4–13
p-Hydroxybenzoate	Strawberry (200 g)	20–90	4–18
Hydroxycinnamicate	Blueberry (100 g)	2000–2200	200–220
Caffeic acid	Kiwi (100 g)	600–1000	60–100
Chlorogenic acid	Cherry (200 g)	180–1150	36–230
Coumaric acid	Plum (200 g)	140–1150	28–230
Ferulic acid	Egg plant/aubergine (200 g)	600–660	120–132
Sinapic acid	Apple (200 g)	50–600	10–120
	Pear (200 g)	15–600	3–120
	Chicory (200 g)	200–500	40–100
	Artichoke (100 g)	450	45
	Potato (200 g)	100–190	20–38
	Corn flour (75 g)	310	23
	Flour: wheat, rice, oat (75 g)	70–90	5–7
	Cider (200 mL)	10–500	2–100
	Coffee (200 mL)	350–1750	70–350
Flavonols:	Yellow onion (100 g)	350–1200	35–120
Quercitrin	Curly kale (200 g)	300–600	60–120
Kaempferol	Leek (200 g)	30–225	6–45
Myricetin	Cherry tomato (200 g)	15–200	3–40
	Broccoli (200 g)	40–100	8–20
	Blueberry (100 g)	30–160	3–16
	Blackcurrant (100 g)	30–70	3–7
	Apricot (200 g)	25–50	5–10
	Apple (200 g)	20–40	4–8
	Beans, green or white (200 g)	10–50	2–10
	Black grape (200 g)	15–40	3–8
	Tomato (200 g)	2–15	0.4–3.0
	Black tea infusion (200 mL)	30–45	6–9
	Green tea infusion (200 mL)	20–35	4–7
	Red wine (100 mL)	2–30	0.2–3

(*Continued*)

TABLE 53.1 (*Continued*)

Compound	Food Source (Serving Size)	Polyphenol Content	
		By wt (or vol) mg/kg Fresh wt (or mg/L)	By Serving mg/Serving
Flavones	Parsley (5 g)	240–1850	1.2–9.2
Apigenin	Celery (200 g)	20–140	4–28
Luteolin	Capsicum pepper (100 g)	5–10	0.5–1
Flavanones	Orange juice (200 mL)	215–685	40–140
Hesperetin	Grapefruit juice (200 mL)	100–650	20–130
Naringenin	Lemon juice (200 mL)	50–300	10–60
Eriodictyol			
Isoflavones	Soy flour (75 g)	800–1800	60–135
Daidzein	Soybeans, boiled (200 g)	200–900	40–180
Genistein	Miso (100 g)	250–900	25–90
Glycitein	Tofu (100 g)	80–700	8–70
	Tempeh (100 g)	430–530	43–53
	Soy milk (200 mL)	30–175	6–35
Flavanols monomers	Chocolate (50 g)	460–610	23–30
Ellagic acids	Pomegranate	40000	4000
Catechin	Beans (200 g)	350–550	70–110
Epicatechin	Apricot (200 g)	100–250	20–50
	Cherry (200 g)	50–220	10–44
	Grape (200 g)	30–175	6–35
	Peach (200 g)	50–140	10–28
	Blackberry (100 g)	130	13
	Apple (200 g)	20–120	4–24
	Green tea (200 mL)	100–800	20–160
	Black tea (200 mL)	60–500	12–100
	Red wine (100 mL)	80–300	8–30
	Cider (200 mL)	40	8
Anthocyanins	Egg plant/aubergine (200 g)	7500	1500
Orthoproanthocyanidin	Grape Seed or Pine Needles (100 g)	10,000–40,000	1000–4000
Pelargonidin	Blackcurrant (100 g)	1300–4000	130–400
Peonidin	Blueberry (100 g)	250–5000	25–500
Delphinidin	Black grape (200 g)	300–7500	60–1500
Malvidin	Cherry (200 g)	350–4500	70–900
	Rhubarb (100 g)	2000	200
	Strawberry (200 g)	150–750	30–150
	Red wine (100 mL)	200–350	20–35
	Plum (200 g)	20–250	4–50
	Red cabbage (200 g)	250	50

Modified from Manach et al.[41]

increased activity against free radicals and subsequent reduction in reactive oxygen species (ROS) due to high antioxidant content. Both assays are useful in identifying phytochemicals with high antioxidant activity.[2,3]

The US Department of Agriculture published an initial list of ORAC values for more than 100 common foods in 2004, now expanded to 277 foods. The items that contained the highest antioxidant value per serving on the ORAC list were beans (pinto, red kidney, and small red beans) and various types of berries (blueberries, blackcurrants, raspberries, and cranberries).

ORAC reigns as the vitamin industry standard and as one of the easiest ways to compare the antioxidant power of foods and supplements.[4] The ORAC value of a food varies significantly, based on whether dry weight or wet weight of the substance is being measured.

Figure 53.1 shows a comparison of ORAC values among common high antioxidant fruits and vegetables compared to the preferred polyphenolics recommended in this chapter. Basic research and direct clinical experience confirm that high-activity antioxidants are needed to balance the increased oxidative stress and free radical activity that exist commonly today.

4. QUERCETINS

Quercetins are naturally occurring flavonoids that function as active dietary antioxidants. These flavonoids are ubiquitous in foods, including vegetables such as onions, garlic, and ginger; fruit such as apples; and in tea and wine. All quercetins, however, are *not* equal. Certain forms of quercetin such as *quercetin rutinoside* (rutin) are poorly absorbed by the body and are more likely to be irritating or allergenic.[5] Another example is *quercetin chalcone*, a special hesperidin, which has an exceptionally short half-life and is therefore not effective unless it is taken every hour or so.

While quercetin dihydrate is insoluble in water, in physiologic or biological salt solutions it is easily available, especially to first responder phagocytic and dendritic cells. The chemical description of quercetin dihydrate is 3,3′,4′,5,7-pentahydroxy flavone (Figure 53.2).

5. SYNERGISTIC POLYPHENOLS: QUERCETIN DIHYDRATE AND SOLUBLE ORTHOPROANTHOCYANIDIN (sOPC)

Among the various polyphenols, quercetin dihydrate and sOPC are most notable for their safety and functional bioavailability.

Quercetin dihydrate and sOPC combine to achieve an ORAC value of 171,000 units per 100 grams (Figure 53.1). Given this highly protective antioxidant power, it is evident that this flavonoid-flavanol

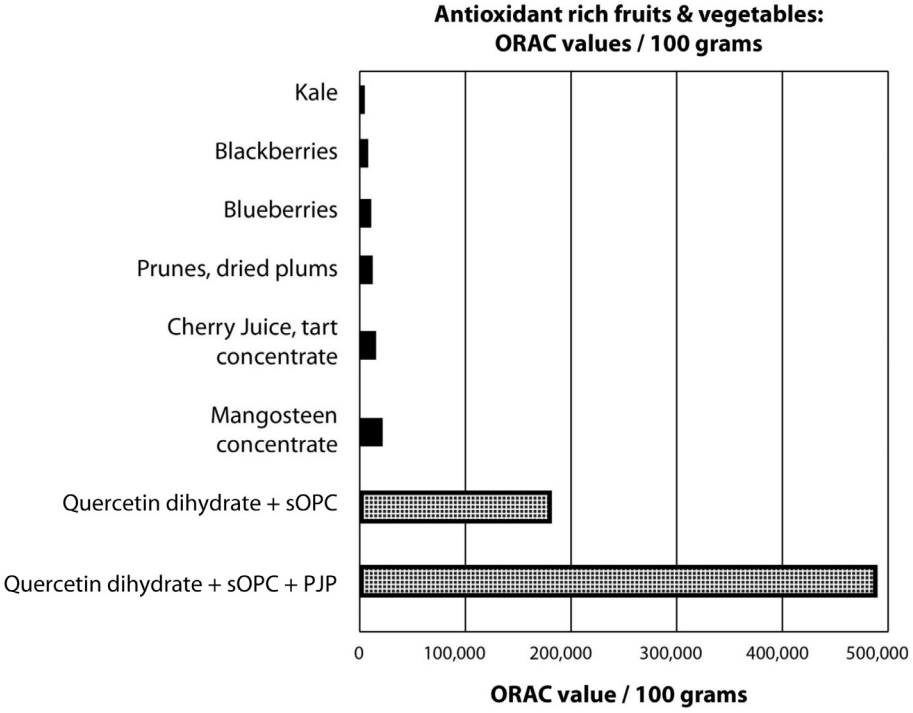

FIGURE 53.1 **ORAC values of antioxidant-rich foods.** sOPC, soluble orthoproanthocyanidin; PJP, pomegranate juice powder (freeze-dried)

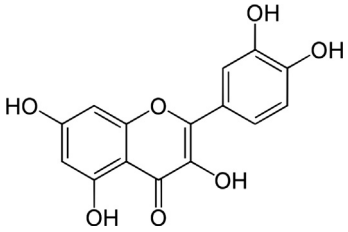

FIGURE 53.2 **Quercetin dihydrate structure**.

combination has a role to play in mitigating inflammation, by reducing oxidative stress and promoting repair processes.

These same polyphenolics also more effectively decrease the need for gene induction of pro-inflammatory, repair-stimulating cytokines because enhanced repair decreases the need to recruit repair cells and chemical 'cries' for help.

Flavonoids such as quercetin dihydrate and flavanols like OPC can benefit connective tissue by promoting repair of injured tissue, improving local circulation, and promoting and maintaining strong collagen, elastin, and basement membrane infrastructure for cells.[6]

Quercetin dihydrate *reduces* IL-12 signaling and Th1 differentiation indicating its potential as therapy for multiple sclerosis and other Th1 cell-mediated autoimmune diseases.[7] We achieve similar results through consumption of 2 capsules containing quercetin dihdyrate with sOPC two or more times daily, sufficient to reduce hsCRP to <0.5 mg/dL or sufficient to convert discomfort into comfortable function.

Synergies between polyphenolics and fully buffered, reduced L-ascorbates make them companions in practice. Ascorbate intake can be based on clinical experience or the 'C Cleanse' self assessment to determine antioxidant needs in proportion to internal oxidative stress.[8]

Quercetin intake has been shown to provide some protection against osteoporosis, pulmonary and cardiovascular diseases and chronic degenerative diseases, including cancers. Quercetin scavenges highly reactive oxygen species such as peroxynitrite and hydroxyl radicals, accounting for the beneficial health effects observed.[9]

5.1 Anti-inflammatory Effects

Oral intake of quercetin dihydrate (160 mg/kg given 5 times a day) decreases pain, confirming quercetin's role as a potent anti-inflammatory agent.[10] Its anti-arthritic properties correlate with a corresponding decrease in pro-inflammatory mediators produced by peritoneal macrophages further solidifying the use of quercetin dihydrate as a potential anti-inflammatory agent. This effect is significant since chronic inflammation can cause connective tissue degradation due to blocked repair processes. Typically, non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids are used to control inflammation. However, long-term use of NSAIDs and other anti-inflammatory medications is associated with adverse effects on the liver, kidney, and gut.[11]

5.2 Decreased Oxidative Stress

Quercetin dihydrate reduces oxidative stress and has been found to inhibit NF-kappa B (NF-κB) activation in an experimental model of portal hypertensive gastropathy.[12]

5.3 Normalized Cholesterol and Fatty Acids

Quercetin dihydrate has a significant cholesterol-lowering action and decreases fatty acid synthesis in the liver better than other polyphenolics. It reduces the activity and mRNA levels of various enzymes involved in hepatic fatty acid synthesis, helping explain its role in lowering blood fats.[13]

5.4 Improved Diabetic Function

Quercetin dihydrate taken at 10 mg/kg dosage improves vascular function in diabetes, reduces blood glucose levels and shows anti-atherogenic effects.[14]

5.5 Reduced Stroke Risk

At higher doses (30 mg/kg), quercetin also protects against cerebral ischemic damage with value in stroke risk reduction and recovery.[15] Quercetin dihydrate has also been shown to reduce lung inflammation, goblet cell metaplasia, and benefit those with chronic obstructive pulmonary disease (COPD).

5.6 Antihistamine Activity

Quercetin dihydrate prevents recruitment of mast cells while stabilizing their membranes and blocking subsequent degranulation.[16] Compounds such as histamine, serotonin, and proteases are prevented from release and the cascade of symptomatic allergic effects is avoided. Quercetin dihydrate also plays a role in the early stages of an allergic reaction, avoiding the activation of the mast cells and by downregulating the imbalance between Th2 and Th1 lymphocytes. Th2 response involves allergic response whereas Th1 is a specific immune defense reaction. By decreasing the

Th2 response, Ig-E production is inhibited and consequently, mast cell, monocyte and macrophage degranulation are reduced and symptoms abate when white cells are rebalanced.[17]

5.7 Anticancer Effects

Quercetin possesses anticancer properties in part by enhanced degradation of NF-κB consistent with a downregulation of the NF-κB binding activity. This activates the AP-1/JNK pathway, important in apoptosis.[18] Quercetin significantly suppresses head and neck cancer-derived tumor initiating cells (HNC-TICs). It also downregulates ALDH1 activity of head and neck cancer cells in a dose-dependent manner and reduces cell production and "stemness signatures expression" in head and neck cancer-derived sphere cells.[19]

The risk of colorectal cancer (CRC) is high in patients with chronic inflammatory disease. Quercetin induces helpful cell cycle arrest and apoptosis, inhibiting excess cell proliferation, stimulating anti-metastatic and anti-angiogenic responses when antioxidant activity and repair ability are available.[20]

Quercetin synergizes with epigallocatechin gallate (EGCG) found in green tea in inhibiting the self-renewal properties of prostate cancer stem cells (CSCs), inducing apoptosis, and blocking CSC's migration and invasion. This complementary action may explain the natural prostate cancer prevention and treatment benefits.[21]

6. ORTHOPROANTHOCYANIDINS (SOLUBLE OPC)

Soluble proanthocyanidins refer to a larger class of polyphenols, termed *flavan-3-ols.* Oligomeric orthoproanthocyanidins (sOPC) are thus classed and are among the safer and more bioavailable of the flavanols. sOPC are powerful antioxidants, in a class of polyphenolic bioflavonoids found common to fruits and vegetables, highly concentrated in the seeds of grapes and the bark of maritime pine trees. Low molecular weight soluble oligomeric proanthocyanidins (LMW sOPC) were first identified by Jacques Masquelier who developed and applied techniques for their extraction. The active fractions of these substances are antioxidant, anti-inflammatory, antidiabetic, and cancer chemopreventive, as well as antimicrobial.

sOPC are made up of proanthocyanidin sub-units termed "monomers." The word "oligomeric" simply means more than one. Thus, oligomeric proanthocyanidins consist of two or more monomers chemically linked together. Strong binding to proteins appears to form the basis of many of their biological actions.[22] Flavanols are distinguished chemically by the hydroxyl group as opposed to the ketone near same position on the pyran ring.

6.1 Adaptogenic and Cytotoxic Effects

sOPC have been reported to possess a broad spectrum of pharmacological and medicinal properties against oxidative stress and have even more free radical scavenging ability than vitamins C, E or beta-carotene. In addition, sOPC have demonstrated significant cytotoxicity towards adenocarcinoma cells affecting the human breast, lung, and stomach, while concurrently enhancing the growth and viability of normal cells.[23] sOPC have an ability to block anti-death signaling mediated through the pro-apoptotic transcription factors and genes such as JNK-1 and c-JUN.

6.2 Cardiovascular Benefits of sOPC

Free radicals and oxidative stress play a crucial role in the pathophysiology of a broad spectrum of cardiovascular diseases including congestive heart failure, vascular heart disease, cardiomyopathy, hypertrophy, atherosclerosis, and ischemic heart disease. Cardioprotective properties and methods of sOPC are varied.[1]

Reduction in foam cells, a biomarker of early stage atherosclerosis, has been observed following supplementation of 50 mg and 100 mg sOPC/kg body weight (with reductions of approximately 49 and 63%, respectively). At 50 mg/kg this means sOPC intake of 4 gm for an 80 kg or 176-pound person and at 100 mg/kg this translated to sOPC intake of 8 g for an 80 kg or 176-pound person. sOPC supplementation has shown significant reduction in oxidized LDL, another important biomarker of cardiovascular diseases. sOPC have also been found to inhibit inducible endothelial CD36 expression, a novel cardio-regulatory gene.

Grape seed extract is one of the most potent sources of sOPC and has demonstrated excellent protection against myocardial ischemia/reperfusion injury and myocardial infarction.[24,25] We suggest this as useful for all patients undergoing angioplasty or heart surgery. In addition, adequate grape seed extract (sOPC) supplementation given to people consuming a high-fat diet has been shown to help normalize body weight, support epididymal tissue, normalize lipid concentrations, and improve carnitine levels by improving lipid metabolism.

6.3 Anti-Aging and Neuro-Protection Functions

sOPC enhance cerebral connectivity by increasing the densities of axons, dendrites, and synapses. In addition, sOPC increase the phosphorylation of vascular endothelial growth factor receptor (VEGFR-2),[26] suggesting a protective role against memory deficit. It also extends the life span of the senescence-accelerated prone mouse (SAMP8) and elevates sirtuin 1 c (SIRT1) expression, a recognized essential factor for life span extension in the brain.[27]

6.4 Nephropathy and sOPC

Studies have shown that sOPC reduce oxidative damage associated with nephropathy and improve renal pathology.[28] Activation of reactive oxygen species and inflammation are implicated in renal ischemia/reperfusion (I/R) injuries. sOPC reduce renal dysfunction and injury caused by renal I/R. Adequate sOPC intake significantly reduces blood urea, creatinine and cystatin C levels, and kidney superoxide dismutase that is upregulated when additional repairs are needed. In addition, glutathione peroxidase levels increase and sOPC reduce malondialdehyde levels indicating more efficient recycling of B vitamins.[29]

6.5 Osteoarthritis and sOPC

Given the anti-inflammatory role of sOPC, it seems fitting that they benefit osteoarthritis. sOPC have been shown to reduce the loss of chondrocytes and proteoglycan and reduce the number of subchondral bone fractures thus promoting bone health.[30]

6.6 Photoprotection and sOPC

Topical application of sOPC has shown significant skin protection from ultraviolet radiation resulting in fewer sunburn cells and promises to evolve into an effective, natural preventive photoprotection agent that works synergistically with natural vitamins E and selenomethionine.[31]

7. ELLAGIC ACID CONTENT: POMEGRANATE JUICE

Pomegranate (*Punica granatum* L, Punicaceae) is a fruit cultivated in many countries and widely consumed. The edible flesh of pomegranate is rich in anthocyanins and polyphenolic compounds including quercetins that possess antioxidant, anti-peroxidative, anti-inflammatory, and pro-repair activities. The most abundant polyphenols in pomegranate juice are the hydrolyzable tannins called ellagitannins formed when ellagic acid binds with a carbohydrate.

Pomegranate's antioxidant capacity is three times that of the popular antioxidant-containing beverages such as red wine and green tea, presumably due to the presence of larger amounts of anthocyanins, quercetin dihydrate, and ellagic acid derivatives.[32] As a result, the activities of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase are enhanced in the liver. Consuming pomegranates exerts repair promoting, anti-inflammatory effects that include:

- Downregulation of COX-2 activity (an enzyme induced when enhanced repair is needed):
- PGE_2 levels are reduced (associated with prostaglandin end-products derived from arachidonic acid and considered pro-inflammatory).
- Nitric oxide (NO), a potent activator in cell functions, is reduced. Mast cells and basophils are known to play a central role in inflammatory and immune events, inducing edema, destroying connective tissue, and supporting lymphocyte chemotaxis, key in the development of an inflammatory condition like rheumatoid arthritis (RA). Research shows that pomegranate juice inhibits the inflammatory activity of activated human mast cells, suggesting its benefit in RA and other pro-inflammatory conditions.[33]

We find the combination of freeze-dried pomegranate juice, quercetin dihydrate, and sOPC a best practice solution for a host of repair-deficient inflammatory conditions promoting remissions in arthritis, cardiovascular diseases, insulin resistance, and diabetes.[34–36] Chronic fatigue and fibromyalgia abate with the restoration of healthful homeostasis, digestive and detoxification competence, neurohormonal balance, and immune tolerance. In addition this combination is clinically well suited to resolve local inflammation, reflected in symptoms from headaches and repair deficits to muscular injuries, sprains, contusions, and bruises.

8. CLINICAL CONSIDERATIONS: WHOLE FRUIT AND FRUIT JUICE

To provide the body comprehensive nutritional support, vegetables, nuts, seeds, and herbs are promoted as good sources of complex carbohydrates and nutrients. Although fruits provide some the highest levels of antioxidants found in nature, their sweetness increases the risk of "sugar overload." Regardless of the fruit and the method used for juicing, the most diverse and intact collection of nutrients comes to us through the whole fruit. Focusing upon two

components of fruit—the skin and the pulp fiber—helps to clarify why there is such a significant difference between whole fruit and fruit juice.

8.1 Nutritional Constituents of Fruit Skins

The edible skins of most fruits are sites of important biological activity in the life of the fruit. The skin is one of the aspects of the plant where the fruit interacts with sunlight, and forms a variety of colored pigments that absorb different wavelengths of light. These pigments include healthy carotenoids and polyphenolics. The skins of whole fruits such as grapes have been studied for their ability to help provide protection from ultraviolet light (a well-recognized source of free radicals) and to help lower risk of cancer. Unfortunately, when fruits are juiced, the fruit's skin may be removed, or their nutritional benefits are lost due to atmospheric oxidation or heating in processing. As a result, the full antioxidant benefits of the whole fruit do not make their way into the juice.

8.2 Pectin Fiber in Fruit Pulp

Orange juice is a good example of the health difference between the fruit and its juice. The white pulpy portion of the orange is a primary source of its flavonoids. The juicy orange-colored flesh of the fruit contains most of its vitamin C. In addition to the skin, the pulp of the fruit is a source of fiber and other nutrients. In the human body, flavonoids and vitamin C often work together, supporting health through their synergistic actions.

When the pulpy white portion of the orange is removed in the processing of orange juice, the flavonoids in the orange are lost. The words "pulp added" on commercial juice product labels indicate an attempt to correct the situation; however, the added pulp may not even be the original pulp found in the whole fruit, and may not adequately restore flavonoid levels.

Another important benefit of fruit fiber is blood sugar regulation. Pectin content in the fiber slows the uptake of sugar into the blood stream, while also nourishing the digestive microbiome.

8.3 Nutritional Issues with Fruit Juices

Commercial fruit juices are fiber poor and simple sugar rich, more easily increasing blood sugar than whole fruit with helpful fiber retained. Fruit juice elevates blood sugar more rapidly than whole fruit, and the level of sugar that can be obtained from fruit juice is substantially higher than the level found in whole fruit. For example, 120 calories' worth of whole apples contains approximately 24 grams of sugar, while 120 calories' worth of apple juice contains about 30% more or 30 grams of sugar. In terms of glycemic effects, a cup of apple juice has a glycemic load of 6, which is twice that of a cup of diced apple with a glycemic load of 3 due to the fiber that slows sugar uptake.

While whole fruit is always a better choice than fruit juice, if the juice is replacing a can of soda then it may be the best option under the circumstances. Making water the beverage of choice is highly recommended. We also encourage the use of herbal beverages, fruit spritzers, diluted fruit juice, and other beverages with minimal sugars and low glycemic effects.

It is important to note that most fruit juices sold in supermarkets contain only a small percentage of actual fruit juice, and usually contain added sweeteners. As a result, it is easy to consume a large amount of calories without getting any actual nutrition. "Over fed and under nourished" are trends that are all too common in the developed world.

Practical tip: Preparing juice at home can allow almost full retention of pulp and skin. The Hurom, Norwalk, and Vitamix juicers are particularly recommended as they extract more of the fiber and polyphenolics.[37,38] Whole fresh fruits and vegetables juiced together fresh can increase total skin and pulp intake, while minimizing the content of natural sugars.

9. PREDICTIVE BIOMARKERS REFERENCED TO GOAL VALUES

The polyphenols elucidated in this chapter prove to be extremely effective for systemic repair especially in the wake of oxidative stress and established inflammation. The issue many clinicians face, is understanding what the true benchmarks of these health states are and the complexity of individual needs. In the clinic, we use independent, primary predictive biomarkers to determine individual needs (Table 53.2). Biochemical individuality has been recognized since Roger Williams' pioneering work in the 1950s.[39] We find the following predictive lab testing to be helpful particularly when referenced to a goal value that reflects the least risk or most gain for a given individual. The basis for the emphasis on these particular evaluations is discussed in more detail elsewhere.[40]

1. Hgb A1c with a goal value of $<5\%$
2. Homocysteine with a goal value of $<6\ \mu mol/L$
3. hsCRP with a goal value of $<0.5\ mg/L$
4. Oxidized HDL/LDL with a goal value of ~ 0
5. 8-oxo-guanine with goal values of $<5.3\ ng/mg$ creatinine
6. Vitamin D (25 OH-D) with a goal value of $50-80\ ng/mL$

TABLE 53.2 Predictive Biomarker Tests to Determine Your Functional Age[1]

Test Name	Test Description	Analysis Laboratory	Specimen Needed	Predictive Goal Values
Hgb A1c (hemoglobin A1c)	Efficiency of sugar/insulin/energy conversion	ZRT Lab: www.ZRTLab.com	Blood spot (self-collected finger prick)	<5%
hsCRP (high sensitivity C reactive protein)	Repair and inflammation immune status	Shiel Medical Laboratory: http://www.shiel.com/specialty_programs/oxidized-ldl	Standard blood draw (1 tube)	<0.5 mg/L
Homocysteine (cardiovascular risk)	Detoxification and epigenetic modulation/methylation status	Quest Diagnostics: http://www.questdiagnostics.com/testcenter/BUOrderInfo.action?tc=31789&labCode=AMD	Blood draw (1 tube)	< 6 μmol/L
Oxidized LDL/HDL (oxidized blood fats)	Oxidative stress and antioxidant status in cell envelope (membrane)	Shiel Medical Laboratory: http://www.shiel.com/specialty_programs/oxidized-ldl	Standard blood draw (requested with hsCRP only 1 tube OK for both tests)	~0
8-Oxo-Guanine (Deoxyguanosine)	Oxidative stress and antioxidant status in cell nucleus	Doctor's Data, Inc.: www.doctorsdata.com	Urine (1st morning sample)	<5.3 ng/mg creatinine
Vitamin D (25-hydroxycholecalciferol)	Vitamin D level for cell communication status	ZRT Lab: www.ZRTLab.com	Blood spot (self-collected finger prick)	50–80 ng/mL
1st AM Urine pH (metabolic acidosis assessment)	Assess mineral need and cell acid/alkaline balance	Self-test. Details available through PERQUE™ Integrative Health: www.PERQUE.com/lifestyle/self-tests/first-morning-ph/	1st morning urine (or after 6 h of rest)	6.5–7.5
LRA by ELISA/ACT™ (immune memory, delayed allergy cell cultures)	Test for immune memory/immune response to up to 491 items	ELISA/ACT Biotechnologies 109 Carpenter Dr Suite 100 Sterling, VA 20164 http://www.elisaact.com/test/nonhc/clinical-successes.asp	Standard Blood Draw (4 tubes)	Healthy immune tolerance means no delayed allergic LRA reactions

[1]*These eight tests measure the major causes of suffering and early death. You can function many years older or younger than your birth age. Life-style choices determine 92% of your lifetime health risk and status. You can add years to life and life to years by bringing or keeping each of these biomarkers at their predictive goal value—the least risk or most gain value for each test.*

7. First urine after 6 hours rest with a goal value pH of 6.5–7.5
8. LRA by ELISA/ACT functional immune memory tests with goal values of no reactions.

These biomarkers provide a revealing snapshot of functional, biochemical health status at a given moment in time. Knowing the client's level of health in terms of oxidative stress and inflammatory processes can alert us to the need for intervention with high ORAC-value supplementation.

10. CONCLUSIONS

Polyphenolics are, collectively, nature's most versatile antioxidant family, essential synergists to ascorbate. Among the polyphenols, flavonoids are the largest group of compounds, with flavanols next in importance in this broad class of plant-derived antioxidants.

This overview highlights safer and more effective choices among the polyphenols, the flavonoid quercetin dihydrate and the flavanol sOPC, with or without freeze-dried pomegranate juice (ellagic acid and other polyphenolic-rich nutrients). In our experience over the last 30 years, use of flavonoids both alone, and in synergistic combination, promote safer, more effective repair and immune competence. Multiple benefits are noted when other antioxidants are also present in physiologic amounts.

It is predictable that the amount of antioxidants required to sustain health has increased, compared to the needs of a generation ago. Many patients experience massive exposures to oxidative free radicals in their food sources, their workplace, and environment associated with high tech urban living. Today, diet alone is rarely enough to provide sufficient protective antioxidants.

With the increase in oxidative stresses and xenobiotic free radical generating toxins to which people are

routinely exposed, it is likely that increased amounts of antioxidants are being utilized by the body and depleted. Supplementation is merited in proportion to the total load of oxidative stresses. Polyphenols such as quercetin dihydrate and sOPC, as well as ascorbates, tocopherols, carotenoids, other vitamins, and buffering minerals may be required in larger amounts to balance and maintain well-being at a time when challenges to health have increased in the environment. While a healthy diet is essential, supplementation is increasingly needed to meet essential nutritional requirements due to dietary deficits, individual stress resilience, and toxin exposures.

We suggest *not* using polyphenols in combination with anti-inflammatory medications such as cyclooxygenase inhibitors because the mechanisms of action compete and do not cooperate. In our experience, supporting repair with a comprehensive, integrative approach provides better clinical outcomes at lower net costs. Since we are taught today not to combine different classes of anti-inflammatory medications, the use of nutrients in place of medications with their potential risks enables us to amplify healing responses without increased toxicity or side effects.

Standardized natural products are available and recommended, particularly when effective polyphenolic protection and repair promotion are sought. We find better outcomes when biochemically individual needs are assessed through the use of predictive biomarker tests, interpreted based on goal values and self assessments used such as the 'C Cleanse'.

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