CHAPTER

29

Polyphenolics Evoke Healing Responses: Clinical Evidence and Role of Predictive Biomarkers

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A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiological function in humans. ***Kevers et al. [1].***

Polyphenols give color and protection to plants and, in adequate amounts, promote animal health as synergistic antioxidants. Flavanoids and flavanols are the two major categories of polyphenols (polyphenolics). Tens of thousands of polyphenols have been identified, confirming them as abundant and beneficial antioxidants in nature. This review examines the virtues of various polyphenols and documents that the literature recognizes quercetin dihydrate flavanoid and soluble oligomeric/orthoproanthocyanidin (OPC) flavanol, with or without ellagic acid, as the "dream team" that supports safer, more effective protection from free radical excess. Free radical excess induces repair deficits known as inflammation when inadequate antioxidants are available at the times needed. Examples are provided from the research literature indicating the adaptogenic and efficacious nature of specific polyphenolics.

Assessing a person's level of health in terms of oxidative stress and inflammatory repair resilience provides individual biomarker benchmarks of need for high ORAC-value diet and supplementation. ORAC is an acronym for *oxygen radical absorbance capacity*. Given the ubiquitous free radical and toxic exposures intrinsic to industrial society today (allostatic load), the question of supplementation has high relevance both in the clinic and in the community. Absent of biodynamic and organic sources, it is likely that a sensible diet no longer provides enough of the needed essentials to maintain health. The use of global predictive biomarkers referenced to "least risk" or "best outcome" enables more accurate determination of the level of supplementation sufficient to meet individual needs. As discussed in following sections, laboratory tests are reframed from having statistical meaning to having individually predictive meaning.

Polyphenolics are classified first structurally into subgroups and then discussed functionally with emphasis on the evidence supporting safer, more effective flavanoid and flavonol supplementation to meet 21st century oxidative total burden.

1 POLYPHENOLIC CONSUMPTION

The average person consumes several grams of polyphenols daily. This is much more than for all other classes of phytonutrients and known dietary protectants. Amounts ingested are typically approximately 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, 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 polyphenolic intake [2].

Several hundred polyphenolics are found in commonly consumed food. These molecules are secondary

metabolites of plants and are generally involved in protection from ultraviolet radiation or defense against aggression by pathogens (both examples of oxidative stress that the polyphenolics are designed to resist or repel).

2 FLAVANOIDS AND FLAVONOLS

Flavanoids 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. Nontoxic forms of polyphenolics with good bioavailability indicated in the following list include quercetin dihydrate and orthoproanthocyanidins (OPC), with or without ellagic acid (see Table 29.1).

- Flavanoids (higher bioavailability; lower risks): quercetin dihydrate, ellagic acid
  - Flavanones (lower bioavailability; higher risks): hesperetin, naringenin, eriodictyol
- Flavonols: kaempferol, myricetin, isorhamnetin
  - Flavones (lower bioavailability): luteolin, apigenin
  - Isoflavones (lower bioavailability): diedzin
  - Anthocyanidins (higher bioavailability): orthoproanthocyanidins (OPC), cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin
  - Flavan-3-ols (lower bioavailability): catechin, epicatechin, aflavin, arubigin, quercitrin

3 MEASUREMENTS OF ANTIOXIDANT CAPACITY

Oxidative stress from free radical damage is increasingly associated with the development and progression of chronic, degenerative, and autoimmune diseases. **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 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 [3].

The ORAC assay measures the degree of inhibition of peroxy-radical-induced oxidation by the compounds of interest in a chemical milieu. It measures the value as Trolox equivalents and includes both inhibition time and the extent of inhibition of oxidation. In addition to the ORAC assay, other common measures of antioxidant capacity

TABLE 29.1 Polyphenols: Food Sources and Bioavailability

		Polyphenol content	
Compound	**Source (serving size)**	**By wt or vol mg/kg fresh wt (or mg/L)**	**By serving mg/serving**
Hydroxybenzoic acids	Blackberry (100 g)	80–270	8–27
Protocatechuic acid	Raspberry (100 g)	60–100	6–10
Gallic acid	Black currant (100 g)	40–130	4–13
p-Hydroxybenzoic acid	Strawberry (200 g)	20–90	4–18
Hydroxycinnamic acids	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	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
Anthocyanins	Aubergine (200 g)	7500	1500
Cyanidin	Blackberry (100 g)	1000–4000	100–400
Pelargonidin	Black currant (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

TABLE 29.1 Polyphenols: Food Sources and Bioavailability—cont'd

Compound	Source (serving size)	Polyphenol content	
		By wt or vol mg/kg fresh wt (or mg/L)	By serving mg/ serving
	Red cabbage (200 g)	250	50
Flavonols	Yellow onion (100 g)	350–1200	35–120
Quercetin	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
	Black currant (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
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
Monomeric flavanols	Chocolate (50 g)	460–610	23–30
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

Source: Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79(5):727–747.

(AC) include ferric ion reducing antioxidant power (FRAP) and Trolox equivalence antioxidant capacity (TEAC) assays [4,5]. These assays are based on discrete underlying mechanisms that use different radical or oxidant sources and therefore generate distinct values and cannot be compared directly. The ORAC assay is therefore considered to be a preferable method because of its biological relevance to the in vivo antioxidant efficacy.

The U.S. Department of Agriculture published an initial list of ORAC values for more than 100 common foods in 2004, expanded to 277 foods, and most recently in 2010, this list has grown to 326 foods. The items that contain the highest antioxidant value per serving on the ORAC list are beans (pinto, red kidney, and small red beans) and various types of berries (blueberries, black currants, raspberries, and cranberries) [6].

ORAC reigns as the vitamin-industry standard and as one of the easiest ways to compare the antioxidant power of foods and supplements [7]. The ORAC value of a food

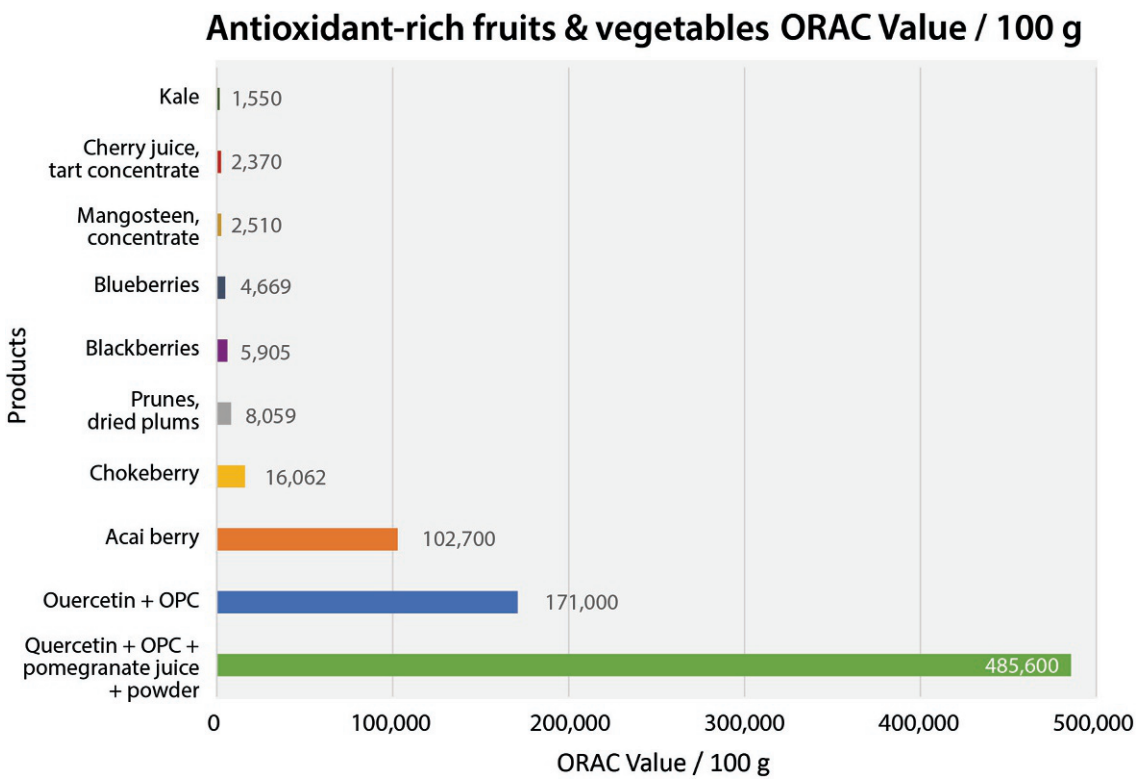

FIG. 29.1 ORAC values of antioxidant-rich foods. *sOPC*, soluble orthoproanthocyanidin; pomegranate juice powder (freeze-dried).

varies significantly, based on whether dry weight or wet weight of the substance is being measured.

Fig. 29.1 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.

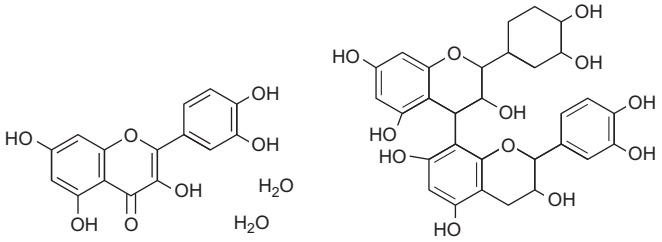

FIG. 29.2 Structure of quercetin dihydrate and oligomeric/orthoproanthocyanidins (OPC).

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 [8]. 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. Quercetin *dihydrate* therefore seems to have the apparent best bioavailability followed by *glycosides*, *aglycone*, and finally *rutinoside* [9]. The chemical description of quercetin dihydrate is *3,3′4′, 5,7-pentahydroxy flavone* (Fig. 29.2).

5 SYNERGISTIC POLYPHENOLS: QUERCETIN DIHYDRATE AND SOLUBLE ORTHOPROANTHOCYANIDIN

Among the various polyphenols, quercetin dihydrate and soluble orthoproanthocyanidin (OPC) are most notable for their safety and functional bioavailability.

Quercetin dihydrate and soluble OPC combine to achieve an ORAC value of 171,000 units per 100 g (Fig. 29.1). Given this highly protective antioxidant

power, it is evident that this flavonoid-flavanol 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 proinflammatory, repair-stimulating cytokines.

Flavanoids 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 [10].

Quercetin dihydrate *reduces* IL-12 signaling and Th1 differentiation, indicating its potential as therapy for multiple sclerosis and other Th1 cell-mediated autoimmune diseases. We achieve similar results on a twice-daily regimen of two to four 500 mg quercetin dihydrate capsules taken with 5 mg OPC.

When warranted, higher doses are used in conjunction with fully buffered, fully reduced L-ascorbates whose need is determined by a vitamin C cleanse protocol (systematic use of buffered vitamin C as the next generation beyond bowel tolerance to determine need from time to time) [11].

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 [12].

5.1 Antiinflammatory Effects

Oral intake of quercetin dihydrate (160 mg/kg given five times a day) decreases pain, confirming quercetin's role as a potent antiinflammatory agent [13]. Its antiarthritic properties correlate with a corresponding decrease in proinflammatory mediators produced by peritoneal macrophages, further solidifying the use of quercetin dihydrate as a potential antiinflammatory agent. This effect is significant since chronic inflammation can cause connective tissue degradation due to blocked repair processes. Typically, nonsteroidal antiinflammatory drugs (NSAIDs) and/or corticosteroids are used to control inflammation. However, long-term use of NSAIDs and other antiinflammatory medications is associated with adverse effects on the liver, kidney, and gut [14].

While there are some who suggest avoidance of all items that influence CYP family/cytochrome function, our experience over the last 30 years is that specifically quercetin dihydrate has been safer and helpful. This means that people find they need less of OTC antihistamines or antiinflammatory products. Indeed, many find they can discontinue the repair dampening effects of OTC products when they enhance the innate immune defense and repair system abilities. Quercetin dihydrate, fully reduced and buffered L-ascorbate, and enhanced uptake magnesium are among the team that overcomes oxidative distress by enhancing repair cell energetics and capacities.

5.2 Decreased Oxidative Stress

Quercetin dihydrate reduces oxidative stress and has been found to inhibit NF-kappa B activation in an experimental model of portal hypertensive gastropathy [15].

5.3 Normalized Cholesterol and Fatty Acid Levels

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 to explain its role in lowering blood fats [16].

5.4 Improved Diabetic Function

Quercetin dihydrate taken at 10 mg/kg dosage improves vascular function in diabetes, reduces blood glucose levels, and shows antiatherogenic effects [17].

5.5 Reduces Obesity

Oxidative stress suppresses the endocrine functions of adipose tissue by disrupting the secretion of adipokines such as adiponectin. Preliminary studies have shown that quercetin can reduce body weight (almost 40%) and suppress expression of adipogenic, lipogenic, and inflammation-related cytokines. The potential to inhibit lipid accumulation and obesity-induced inflammation in the cell is achieved by quercetin's ability to down-regulate MAPK signaling [18].

5.6 Reduced Stroke Risk

At higher doses (30 mg/kg, i.p.), quercetin also protects against cerebral ischemic damage with value in stroke risk reduction and recovery [19]. Quercetin dihydrate has also been shown to reduce lung inflammation, goblet cell metaplasia, and benefit those with chronic obstructive pulmonary disease (COPD).

5.7 Antihistamine Activity

Quercetin dihydrate prevents recruitment of mast cells while stabilizing their membranes and blocking

subsequent degranulation [20]. 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 down-regulating 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 [21].

5.8 Anticancer Effects

Quercetin possesses anticancer properties in part by enhanced degradation of NF-kappa B consistent with a down-regulation of the NF-kappa B binding activity. This activates the AP-1/JNK pathway, important in apoptosis. Quercetin significantly suppresses head and neck cancer-derived tumor initiating cells (HNC-TICs). It also down-regulates 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 [22].

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 and stimulating antimetastatic and anti-angiogenic responses when antioxidant activity and repair ability are available [23].

Quercetin synergizes with epigallocathechin 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 [24].

6 ORTHOPROANTHOCYANIDINS (SOLUBLE OPCs)

Soluble proanthocyanidins refer to a larger class of polyphenols, termed *flavan-3-ols.* Oligomeric orthoproanthocyanidins (OPCs) are thus classed and are among the safer and more bioavailable of the flavanols. OPCs are powerful antioxidants, in a class of polyphenolic bioflavonoids found commonly in fruits and vegetables, and highly concentrated in the seeds of grapes and the bark of maritime pine trees. Low-molecular-weight soluble oligomeric proanthocyanidins (LMW OPCs) were first identified by Jack Masquelier, who developed and applied techniques for their extraction [25]. The active fractions of these substances are antioxidant, antiinflammatory, antidiabetic, and cancer chemopreventive, as well as antimicrobial.

OPCs are made up of proanthocyanidin subunits termed "monomers." "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 [26]. Flavanols are distinguished chemically by the hydroxyl group as opposed to the ketone near the same position on the pyran ring.

6.1 Adaptogenic and Cytotoxic Effects

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

6.2 Cardiovascular Benefits of OPC

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. Cardio-protective properties and mode of action of OPCs are varied.

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

Grape seed extract is one of the most potent sources of OPC and has demonstrated excellent protection against myocardial ischemia-reperfusion injury and myocardial infarction [27]. We suggest this as useful for all patients undergoing angioplasty or heart surgery. In addition, adequate grape seed extract (OPC) 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 Antiaging and Neuroprotection Functions

OPCs enhance cerebral connectivity by increasing the densities of axons, dendrites, and synapses. In addition, OPCs increase the phosphorylation of vascular endothelial growth factor receptor (VEGFR-2), suggesting a protective role against memory deficit. It also extends the lifespan of the senescence-accelerated prone mouse (SAMP8) and elevates sirtuin 1 c (SIRT1) expression, a recognized essential factor for lifespan extension in the brain [28].

6.4 Nephropathy and Soluble OPC

Studies have shown that OPCs reduce oxidative damage associated with nephropathy and improve renal pathology [29]. Activation of reactive oxygen species and inflammation are implicated in renal ischemia/reperfusion (I/R) injuries. OPCs reduce renal dysfunction and injury caused by renal I/R. Adequate OPC intake significantly reduces blood urea, creatinine, and cystatin C levels, and kidney superoxide dismutase, which are up-regulated when additional repairs are needed. In addition, glutathione peroxidase levels increase and OPCs reduce malondialdehyde levels, indicating more efficient recycling of B vitamins [30].

6.5 Osteoarthritis and OPC

Given the antiinflammatory role of OPCs, it seems fitting that they benefit osteoarthritis. OPCs have been shown to reduce the loss of chondrocytes and proteoglycan and reduce the number of subchondral bone fractures, thus promoting bone
health [31].

6.6 Photo-Protection and OPC

Topical application of OPCs has shown significant skin protection from ultraviolet radiation, resulting in fewer sunburn cells and promising to evolve into an effective, natural preventative photo-protection agent that works synergistically with natural vitamins E and selenomethionine [32].

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, antiperoxidative, antiinflammatory, and prorepair 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 [33]. As a result, the activities of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase are enhanced in the liver. Consuming pomegranates exerts repair-promoting, antiinflammatory effects that include:

- Down-regulation of COX-2 activity (an enzyme induced when enhanced repair is needed);
- PGE2 levels are reduced (associated with prostaglandin end-products derived from arachidonic acid and considered proinflammatory);
- 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 proinflammatory conditions [34].

We find the combination of freeze-dried pomegranate juice, quercetin dihydrate, and OPCs a best-practice solution for a host of repair-deficient inflammatory conditions, promoting remissions in arthritis, cardiovascular diseases, insulin resistance, and diabetes. Chronic fatigue and fibromyalgia abate with the restoration of healthful homeostasis, digestive and detoxification competence, neurohormonal balance, and immune tolerance [35]. 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 with 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 components 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

Fruit juice that has been robbed of its fiber and nutrients is basically just a concentrated source of sugar that lacks most of the supportive nutrients necessary to aid in digestion and metabolism. 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 g of sugar, while 120 calories' worth of apple juice contains about 30% more or 30 g 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. "Overfed and undernourished" 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. 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: PERSONALIZED CARE

We transition into an overview of eight key predictive biomarkers (PBs) that were developed on the premise that epigenetics influence 92% and genetics influence the remaining 8% of health. Biochemical individuality supports supplement use in physiologically meaningful amounts for each individual, monitored through predictive biomarker lab tests to determine individual need.

The polyphenols elucidated earlier in this chapter prove to be extremely effective for systemic repair, especially in response to oxidative stress and repair deficit commonly known as inflammation. The issue many clinicians face is understanding what the true benchmarks of these health states are and the complexity of individual needs. The primary predictive biomarkers described here are different from most laboratory tests physicians would generally order. They are an interdependent suite of tests referenced to best outcome goal values rather than usual or normal statistical ranges. PBs can be used as valuable tools in individual clinical assessment of risk and resilience, of need and of sufficiency.

Biochemical individuality has been recognized since Roger Williams's pioneering work in the 1950s [36]. 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. These PBs were developed on the premise that epigenetics influences 92% and genetics influences the remaining 8% of health [37] and selected on the basis that they have a variance of 5% or less, which is desirable. The less the variance, the more predictive is the observed value.

Additional basis for the emphasis on these particular evaluations is discussed in more detail elsewhere [38–41].

1. Hgb A1c with a goal value of <5%
2. hsCRP with a goal value of <0.5 mg/L
3. Homocysteine with a goal value of <6 μmol
4. LRA by ELISA/ACT functional immune memory tests with goal values of no delayed allergies
5. First urine after 6 h rest with a goal value pH of 6.5–7.5
6. Vitamin D (25 OH-D) with a goal value of 50–80 ng/mL
7. Omega-3 index with a goal value of >8%
8. 8-oxo-guanine (8 OHdG) with goal values of <5 g/ng creatinine

10 CONCLUSIONS

Polyphenolics are, collectively, nature's most versatile antioxidant botanical family and essential synergists to ascorbate in mammalian cells.

This overview highlights safer, more effective choices among polyphenols: the flavonoid quercetin dihydrate and the flavanol soluble OPC, 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 physiologic benefits are noted when the full team of antioxidants are also present in physiologic balance that includes nature's preferred antiinflammatory prorepair molecules. Among the polyphenols, flavanoids are the largest group of compounds, with flavonols next in importance in this broad class of colorful plant-derived antioxidants.

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. Polyphenols such as quercetin dihydrate and soluble OPC's, as well as ascorbates, tocopherols, carotenoids, B complex, and other vitamins, and buffering minerals may be required in larger amounts to balance and maintain well-being at a time when most challenges to health have increased substantially. While a healthy diet is essential, supplementation is increasingly needed to meet essential nutritional requirements due to dietary deficits, individual learned responses, and toxin exposures. 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 warranted in proportion to the total allostatic and homeostatic oxidative load.

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

Standardized natural, professional products are now available and recommended—the polyphenols described here are notable for their safety, efficacy, and lack of toxicity when present in their native, forms.

We find better outcomes when biochemically individual needs are assessed through the use of predictive biomarker tests, and interpreted or referenced to best outcome goal values. With the predictive biomarkers discussed in this chapter we provide a timely solution to the increasing number of health care consumers who are interested in predictive, proactive, personalized primary prevention practices. Each biomarker has an epigenetic meaning and elucidates metabolic pathways. Scientists evaluate biomarkers to evaluate a suspected disturbance in particular pathways. Four strongly validated predictive biomarkers are HgbA1c, homocysteine, hs-CRP and Lymphocyte Response Assay (Table 29.2). These biomarkers provide the practitioner with a window into individual glucose, inflammation, repair methylation, and immune status. Evidence-based clinicians can utilize this valuable set of tools to provide a higher level of health.

Life for most people contains increasing external distress and allostatic, oxidative, and acid-rich metabolic dysfunctions. This report builds on the evidence that personalized, proactive, predictive, primary prevention practices saves lives and can reduce total cost of care more than 20% while improving quality of care and quality of life. We can choose life. In the 21st century this requires more personalized, proactive, predictive primary prevention practices and products.

TABLE 29.2 Predictive Biomarkers, Healthier Goal Values, Personalized Care

Predictive Biomarker test (PB)	Best outcome goal value	Measures	Significance
Hgb A1c, HbA1c (Hemoglobin A1c)	<5%	Blood sugar, diabetic risk and insulin resistance	Highly predictive of certain aspects of physiology having to do with sugar metabolism and insulin functions, which in turn are linked to cell energy status, metabolism, weight and related chronic health conditions such as metabolic syndrome, diabetes, cardiovascular disease, and bone and collagen related conditions
hsCRP (high sensitivity C-Reactive Protein)	<0.5 mg/L	Repair and inflammation status	Highly predictive of repair deficits
Homocysteine (high sensitivity homocysteine)	<6 μmol/L	Methylation, detoxification, cardiovascular risk	Helps to measure adequate methylation, sulfur metabolism, detoxification, and epigenetic modulation
hsLRA by ELISA/ACT	No delayed allergies	Immune tolerance to foods and chemicals	*LRA* measures immune defense and repair tolerance and intolerance across all delayed allergy pathways
First AM Urine pH	6.5–7.5	Mineral need assessment and cellular acid/alkaline balance	Measurement after 6 h rest reflects net acid excess and metabolic acidosis. Consequences of metabolic acidosis include hormonal changes, insulin resistance, loss of bone and muscle protein degradation
Vitamin D (25-OH cholecalciferol)	50–80 ng/mL	Cellular equilibrium and communication	Vitamin D pleiotropic functions dictate cellular function, physiology and proliferation—crucial for immune health, bone metabolism, neurological and cognitive function
Omega-3 index	>8%	Omega-3 level of oxidative stress	Reflects the relative amount of omega-3 fatty acids within red blood cell membranes and expressed as percentage of total fatty acids, useful in predicting oxidative stress
DNA oxidative stress (8-OHdG)	<5 ng/mg creatinine	Oxidative stress and nuclear antioxidant status	DNA oxidative stress marker that can be a predictor of repair deficit and risk of conditions like diabetes and atherosclerosis

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 such as the hsCRP and 8-OHdG among others can alert us to the need for intervention with high ORAC-value supplementation.

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