1 Nutraceuticals and Functional Foods

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1.1 INTRODUCTION

Interest in nutraceuticals and functional foods continues to grow, powered by progressive research
efforts to identify properties and potential applications of nutraceutical substances, and coupled
with public interest and consumer demand. Estimates vary; global market size for functional food
ingredients is projected to exceed 250 billion by 2025. Among the principal reasons for the growth
of the functional food market are current population and health trends. Across the globe, populations
are aging. For instance, in 2015, the average projected life expectancy globally for those born that
year was 71.4 years. Moreover, about 30 countries recorded average life expectancy at 80 years or
above, including Japan, Singapore, and Switzerland, all above 83 years.¹

Meanwhile, obesity is now recognized as a global epidemic as its incidence continues to climb in
countries throughout the world. According to reports of the World Health Organization (WHO) in
2016, more than 1.9 billion adults aged 18 years and older were overweight, with over 650 million
adults obese. In 2016, 39% of adults aged 18 years and over were overweight. Overall, about 13%
of the world’s adult population (11% of men and 15% of women) were obese in 2016.² In the United
States of America in 2017, nearly 38% of adults were obese. Nearly 8% are extremely obese.³ Global
trends show stability or favor an increased incidence of obesity versus a reduction. Meanwhile, heart
disease continues to be a primary cause of death, responsible for one out of every four deaths in the
U.S., and cancer, osteoporosis, and arthritis remain highly prevalent.

Although genetics play a major role in the development of the diseases mentioned above, by
and large most are considered preventable or could be minimized by a health-promoting diet and
physical activity, weight management, and a healthier lifestyle, including environment. Additionally,
people can optimize the health-promoting capabilities of their diet by way of supplementation and by consuming foods that have been formulated or fortified to include health-promoting factors.

Another reason for the growing trend in functional foods is public education. People today are more nutrition savvy than ever before, the interest in health-related information being met by many informational resources. Every day people are exposed to media articles, blogs, and social media posts devoted to the relationship between diet and health. Numerous websites have been developed by government agencies such as the U.S. Department of Agriculture (USDA; www.nal.usda.gov) and organizations such as the American Heart Association (www.americanheart.org) and the American Cancer Society (www.cancer.org). Last, information-based entities abound on the Internet, including WebMD.com and TheNutritionDr.com.

1.2 DEFINING NUTRACEUTICALS AND FUNCTIONAL FOODS

The term *nutraceutical* is a hybrid or contraction of *nutrition* and *pharmaceutical*. Reportedly, it was coined in 1989 by DeFelice and the Foundation for Innovation in Medicine.⁴ Restated and clarified in a press release in 1994, its definition was “any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and diets to genetically engineered ‘designer’ foods, herbal products, and processed foods such as cereals, soups, and beverages.”⁵ At present there are no universally accepted definitions for nutraceuticals and functional foods, although commonality exists between the definitions offered by different health-oriented professional organizations.

According to the International Food Information Council (IFIC), functional foods are foods or dietary components that may provide a health benefit beyond basic nutrition.⁶ The International Life Sciences Institute of North America (ILSI) has defined functional foods as “foods that by virtue of physiologically active food components provide health benefits beyond basic nutrition.”⁷ Meanwhile, Health Canada defines functional foods as “similar in appearance to a conventional food, consumed as part of the usual diet, with demonstrated physiological benefits, and/or to reduce the risk of chronic disease beyond basic nutritional functions.”⁸ The *Nutrition Business Journal* classified functional food as “food fortified with added or concentrated ingredients to functional levels, which improves health or performance. Functional foods include enriched cereals, breads, sport drinks, bars, fortified snack foods, baby foods, prepared meals, and more.”⁹

In the 2013 Academy of Nutrition and Dietetics (AND) position paper on nutraceuticals and functional foods, the authors state: “It is the position of the Academy of Nutrition and Dietetics to recognize that although all foods provide some level of physiological function, the term functional foods is defined as whole foods along with fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis at effective levels based on significant standards of evidence. The Academy supports Food and Drug Administration (FDA)-approved health claims on food labels when based on rigorous scientific substantiation.”¹⁰

Based on these statements, one can surmise that functional foods include everything from natural foods, such as fruits and vegetables endowed with antioxidants and fiber, to fortified and enriched foods, such as orange juice with added calcium or additional carotenoids, to formulated ready-to-drink beverages containing protein, amino acids, vitamins, minerals, antioxidants, immune-supporting factors, etc.

Regarding the term “nutraceutical,” the *Nutrition Business Journal* states that it uses the term nutraceutical for anything that is consumed primarily or particularly for health reasons. Based on that definition, a functional food would be a kind of nutraceutical.⁹ On the other hand, Health Canada states that nutraceuticals are a product that is “prepared from foods but sold in the form of pills or powders (potions), or in other medicinal forms not usually associated with foods. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease.”⁸ Based on this definition and how functional foods are characterized, as noted previously, nutraceuticals would be distinct from functional foods.
The potential functions of nutraceutical/functional food ingredients are so often related to the maintenance or improvement of health that it is necessary to distinguish between a food ingredient that has function and a drug. The core definition of a drug is any article that is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” (21 U.S.C. 321(g)(1)(B)). At the same time, certain health claims can be made for foods and ingredients that are associated with health conditions.

In the U.S., such health claims are defined and regulated by the U.S. Food and Drug Administration (FDA). Health claims related to foods and ingredients include an implied or explicit statement about the relationship of a food substance to a disease or health-related condition (21 U.S.C. 343(r)(1)(B) and 21 C.F.R.101.14(a)(1)). The major categories of health claims are listed in Table 1.1 with examples of each.

### Table 1.1

<table>
<thead>
<tr>
<th>Claim</th>
<th>Purpose</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrient content claim</td>
<td>Describe content of certain nutrients.</td>
<td>“Fat-free,” “low sodium.”</td>
</tr>
<tr>
<td>Qualified health claim</td>
<td>Describe the relationship between food, food component, or dietary supplement and reduced risk of a disease or health related condition. This claim uses qualifying language because the evidence for this relationship is emerging and is not yet strong enough to meet the standard of significant scientific advancement set by the FDA.</td>
<td>“Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive.”</td>
</tr>
<tr>
<td>NLEA authorized health claims</td>
<td>Characterize a relationship between a food, a food component, dietary ingredient, or dietary supplement and risk of a disease.</td>
<td>“Diets high in calcium may reduce the risk of osteoporosis.”</td>
</tr>
<tr>
<td>Structure/function claim</td>
<td>Describes role of nutrient or ingredient intended to affect normal structure or function in humans. May characterize the means by which the nutrient or ingredient affects the structure or function. May describe a benefit related to a deficiency. Must be accompanied by a disclaimer stating that FDA has not reviewed the claim and that the product is not intended to “diagnose, treat, cure, or prevent any disease.”</td>
<td>“Calcium builds strong bones.”</td>
</tr>
</tbody>
</table>


1.3 **CLASSIFYING NUTRACEUTICAL FACTORS**

The number of purported nutraceutical substances is in the hundreds, and some of the more recognizable substances include isoflavones, tocotrienols, allyl sulfur compounds, fiber, and carotenoids. Considering a long and growing list of nutraceutical substances, organization systems are needed to allow for easier understanding and application. This is particularly true for academic instruction, as well as product formulation by food companies.

Depending upon one’s interest and/or background, the appropriate organizational scheme for nutraceuticals can vary. For example, cardiologists may be most interested in those nutraceutical substances that are associated with reducing the risk factors of heart disease. Specifically, their interest may lie in substances purported to positively influence hypertension and hypercholesterolemia.
and to reduce free radical or platelet-dependent thrombotic activity. Accordingly, nutraceutical factors such as certain fibers, omega-3 fatty acids, phytosterols, quercetin, and grape flavonoids would be of interest. Meanwhile, oncologists may be more interested in those substances that target anticarcinogenic activities. These substances may be associated with augmentations of microsomal detoxification systems and antioxidant defenses, or they may slow the progression of existing cancer. Thus, their interest may lie in both chemoprevention or potential adjunctive therapy.

On the other hand, the nutraceutical interest of food scientists working on the development of a functional food product will not only include physiological properties, but also stability and sensory properties, as well as issues of cost efficiency. To demonstrate this point, the anticarcinogenic triterpene limonin is lipid-soluble and intensely bitter, somewhat limiting its commercial use as a functional food ingredient. However, the glucoside derivative of limonin, which shares some of the potential anticarcinogenic activity of limonin, is water soluble and virtually tasteless, thereby enhancing its potential use as an ingredient.

Whether it is for academic instruction, clinical trial design, functional food development, or dietary recommendations, nutraceutical factors can be organized in several ways. Cited below are a few ways of organizing nutraceuticals based upon food source, mechanism of action, and chemical nature.

### 1.4 FOOD AND NONFOOD SOURCES OF NUTRACEUTICAL FACTORS

One of the broader models of organization for nutraceuticals is based upon their potential as a food source to humans. Here nutraceuticals may be separated into plant, animal, and microbial (i.e., bacteria and yeast) groups. Grouping nutraceutical factors in this manner has numerous merits and can be a valuable tool for diet planning, as well as classroom and seminar instruction.

One interesting consideration with this organization system is that the food source may not necessarily be the point of origin for one or more substances. An obvious example is conjugated linoleic acid (CLA), which is part of the human diet, mostly as a component of beef and dairy foods. However, it is made by bacteria in the rumen of the cow. Therefore, issues involving the food chain or symbiotic relationships may have to be considered for some individuals working with this organization scheme.

Because of conserved biochemical aspects across species, many nutraceutical substances are found in both plants and animals, and sometimes in microbes. For example, microbes, plants, and animals contain choline and phosphatidylcholine. This is also true for sphingolipids; however, plants and animals are better sources. Also, linolenic acid (18:3ω-3 fatty acid) can be found in a variety of food resources, including animal flesh, even though it is primarily synthesized in plants and other lower members of the food chain. Table 1.2 presents some of the more recognizable nutraceutical substances grouped according to food-source providers.

Nonfood sources of nutraceutical factors have been sourced by the development of modern fermentation methods. For example, amino acids and their derivatives have been produced by bacteria grown in fermentation systems. The emergence of recombinant-genetic techniques has enabled new avenues for obtaining nutraceutical compounds. These techniques and their products are being evaluated in the arenas of the marketplace and regulatory concerns around the world. An example is the production of eicosapentaenoic acid (EPA) by bacteria, which is normally produced by some algae and bacteria. The EPA derived from salmon are produced by algae and are later incorporated in the salmon that consume the algae. Meanwhile, there is the potential to produce EPA by non–EPA-producing bacteria by importing the appropriate DNA through recombinant methods. The ability to transfer the production of nutraceutical molecules into organisms that allows for economically feasible production is cause for both optimism and discussion concerning regulatory and popular acceptance.

### 1.5 NUTRACEUTICAL FACTORS IN SPECIFIC FOODS

In an organization model related to the one above, nutraceuticals can be grouped based upon relatively concentrated foods. This model is more appropriate when there is interest in a nutraceutical
compound or related compounds, or when there is interest in a specific food for agricultural/geographic reasons or functional food-development purposes. For example, the interest may be in the nutraceutical qualities of a local crop or a traditionally consumed food in a geographic region, such as pepper fruits in the southwestern United States, olive oil in Mediterranean regions, and red wine in western Europe and Northern California.

There are several nutraceutical substances that are found in higher concentrations in specific foods or food families. These include capsaicinoids, which are found primarily in pepper fruit, and allyl sulfur (organosulfur) compounds, which are particularly concentrated in onions and garlic.

Table 1.3 provides a listing of certain nutraceuticals that are considered unique to certain foods or food families. One consideration for this model is that for several substances, such as those just named, there is a relatively short list of foods that are concentrated sources. However, the list of food sources for other nutraceutical substances can be much longer and can include numerous seemingly unrelated foods. For instance, citrus fruit contain the isoflavone quercetin, as do onions, a plant food seemingly unrelated. Citrus fruit grow on trees, whereas the edible bulb of the onion plant (an herb)
develops at ground level. Other plant foods with higher quercetin content are red grapes—but not white grapes—broccoli (which is a cruciferous vegetable), and the Italian yellow squash. Again, these foods appear to bear very little resemblance to citrus fruit, or onions for that matter. On the other hand, there are no guarantees that closely related or seemingly similar foods contain the same nutraceutical compounds. For example, both the onion plant and the garlic plant are perennial herbs arising from a rooted bulb and are also cousins in the lily family. However, although onions are loaded with quercetin, with some varieties containing up to 10% of their dry weight of this flavonoid, garlic is quercetin void.

### 1.6 MECHANISM OF ACTION

Another means of classifying nutraceuticals is by their mechanism of action. This system groups nutraceutical factors together, regardless of food source, based upon their proven or purported physiological properties. Among the classes would be antioxidant, antibacterial, antihypertensive, anti-hypercholesterolemic, anti-aggregate, anti-inflammatory, anti-carcinogenic, osteoprotective, and so on. Like the scheme just discussed, credible Internet resources may prove invaluable to this
TABLE 1.4
Examples of Nutraceuticals Grouped by Mechanisms of Action

<table>
<thead>
<tr>
<th>Anticancer</th>
<th>Positive Influence on Blood Lipid Profile</th>
<th>Antioxidant Activity</th>
<th>Antiinflammatory</th>
<th>Osteogenic or Bone Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin</td>
<td>β-Glucan</td>
<td>CLA</td>
<td>Linolenic acid</td>
<td>CLA</td>
</tr>
<tr>
<td>Genistein</td>
<td>γ-Tocotrienol</td>
<td>Ascorbic acid</td>
<td>EPA</td>
<td>Soy protein</td>
</tr>
<tr>
<td>Daidzein</td>
<td>δ-Tocotrienol</td>
<td>β-Carotene</td>
<td>DHA</td>
<td>Genistein</td>
</tr>
<tr>
<td>α-Tocotrienol</td>
<td>MUFAs</td>
<td>Polyphenolics</td>
<td>GLA</td>
<td>Daidzein</td>
</tr>
<tr>
<td>γ-Tocotrienol</td>
<td>Quercetin</td>
<td>Tocopherols</td>
<td>(gamma-linolenic acid)</td>
<td>Calcium</td>
</tr>
<tr>
<td>CLA</td>
<td>ω-3 PUFAs</td>
<td>Tocotrienols</td>
<td>Capsaicin</td>
<td>Casein phosphopeptides</td>
</tr>
<tr>
<td>Lactobacillus acidophilus</td>
<td>Resveratrol</td>
<td>Indole-3-carbonol</td>
<td>Quercetin</td>
<td>FOS</td>
</tr>
<tr>
<td>Spingolipids</td>
<td>Tannins</td>
<td>α-Tocopherol</td>
<td>Curcumin</td>
<td>(fructooligosaccharides)</td>
</tr>
<tr>
<td>Limonene</td>
<td>β-Sitosterol</td>
<td>Ellagic acid</td>
<td></td>
<td>Inulin</td>
</tr>
<tr>
<td>Dialyl sulfide</td>
<td>Saponins</td>
<td>Lycopene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ajoene</td>
<td>Guar</td>
<td>Lutein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Pectin</td>
<td>Glutathione</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterolactone</td>
<td></td>
<td>Hydroxytyrosol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycyrrhizine</td>
<td></td>
<td>Luteolin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equol</td>
<td></td>
<td>Oleuropein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curcumin</td>
<td></td>
<td>Catechins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellagic acid</td>
<td></td>
<td>Gingerol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutein</td>
<td></td>
<td>Chlorogenic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnosol</td>
<td></td>
<td>Tannins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. bulgaricus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The substances listed in this table include those that are either accepted or purported nutraceutical substances.

approach. Examples are presented in Table 1.4. This model would also be helpful to an individual who is genetically predisposed to a medical condition or to scientists trying to develop powerful functional foods for just such a person.

The information in this model would then be helpful in diet planning in conjunction with the organization scheme just discussed and presented in Table 1.3. It would also be helpful to a product developer trying to develop a new functional food, perhaps for heart health. This developer might consider the ingredients listed in several categories to develop a product that would reduce blood pressure, total and LDL-cholesterol levels, and inflammation.

Some nutraceutical ingredients or mixtures are marketed on the basis that they have been used for many years in the practice of traditional or cultural medicine, that is, treatments for medical illness that have developed in cultural tradition because of trial and error. This rationale for use can be both compelling and a cause for concern. The plant and animal kingdoms contain many compounds that offer therapeutic benefit or danger; often the same compound offers both, with the difference being dependent upon the dose. While traditional medicines are assumed low risk for the most part, one 5-year study that followed over 1000 cases reported a possible or confirmed association between use and toxicity in nearly 61% of the cases. Thus, whereas a statement regarding traditional use seems to offer a sense of safety by virtue of use by many individuals over time, there always need to be systematic regulatory efforts to determine and document safety over time.

What may be of interest is that there are several nutraceuticals that can be listed as having more than one mechanism of action. One of the seemingly most versatile nutraceutical families is the omega-3 polyunsaturated fatty acids (PUFAs). Their nutraceutical properties can be related to direct effects as well as to some indirect effects. For example, these fatty acids are used as precursors
for eicosanoid substances that locally vasodilate, bronchodilate, and deter platelet aggregation and clot formation. These roles can be prophylactic for asthma and heart disease. Omega-3 PUFA may also reduce the activities of protein kinase C and tyrosine kinase, both of which are involved in a cell-growth-signaling mechanism. Here, the direct effects of these fatty acids may reduce cardiac hypertrophy and cancer-cell proliferation. Omega-3 PUFA also appears to inhibit the synthesis of fatty acid synthase (FAS), which is a principal enzyme complex involved in de novo fatty acid synthesis. Here the nutraceutical effect may be considered indirect, as chronic consumption of these PUFAs may theoretically lead to decreased quantities of body fat over time and slow the development of obesity. The obesity might then lead to the development of hyperinsulinemia and related physiological aberrations such as hypertension and hyperlipidemia.

### 1.7 CLASSIFYING NUTRACEUTICAL FACTORS BASED ON CHEMICAL NATURE

Another method of grouping nutraceuticals is based upon their chemical nature. This approach allows nutraceuticals to be categorized under molecular/elemental groups. This preliminary model includes several large groups, which then provide a basis for subclassification or subgroups, and so on. One way to group nutraceuticals grossly is as follows:

- Isoprenoid derivatives
- Phenolic substances
- Fatty acids and structural lipids
- Carbohydrates and derivatives
- Amino acid–based substances
- Microbes
- Minerals

As scientific investigation continues, several hundred substances will probably be deemed nutraceuticals. As many of these nutraceutical compounds appear to be related in synthetic origin or molecular nature, there is the potential to broadly group many of the substances together (Figure 1.1). This scheme is by no means perfect, and it is offered “in pencil,” as opposed to being “etched in stone.” It is expected that scientists will ponder this organization system, find flaws, and suggest ways to evolve the scheme, or disregard it completely in favor of a better concept. Even at this point,
several “gray” areas are apparent. For instance, mixtures of different classes can exist, such as mixed isoprenoids, prenylated coumarins, and flavonoids. Also, phenolic compounds could arguably be grouped under a very large “amino acid and derivatives” category. Although most phenolic molecules arise from phenylalanine as part of the shikimic acid metabolic pathway, other phenolic compounds are formed via the malonic acid pathway, thereby circumventing phenylalanine as an intermediate. Thus, phenolics stand alone in their own group, whose most salient characteristic is chemical structure, not necessarily synthetic pathway.

1.7.1 ISOPRENOID DERIVATIVES (TERPENOIDS)

*Isoprenoids* and *terpenoids* are terms used to refer to the same class of molecules. These substances are without question one of the largest groups of plant secondary metabolites. In accordance with this ranking, they are also the basis of many plant-derived nutraceuticals. Under this large umbrella are many popular nutraceutical families such as carotenoids, tocopherols, tocotrienols, and saponins. This group is also referred to as isoprenoid derivatives because the principal building block molecule is isoprene (Figure 1.2). Isoprene itself is synthesized from acetyl coenzyme A (CoA), in the well-researched mevalonic acid pathway (Figure 1.3), and the glycolysis-associated molecules pyruvate and 3-phosphoglycerate in a less-understood metabolic pathway. In both pathways, the product is isopentenyl phosphate (IPP), and IPP is often regarded as the pivotal molecule in the formation of larger isoprenoid structures.

Once IPP is formed, it can reversibly isomerize to dimethylallyl pyrophosphate (DMAPP) as presented in Figure 1.4. Both five-carbon structures are then used to form geranyl pyrophosphate (GPP), which can give rise to monoterpenes. Among the monoterpenes are limonene and perillyl alcohol. GPP can also react with IPP to form the 15-carbon structure farnesyl pyrophosphate (FPP), which then can give rise to the sesquiterpenes. FPP can react with IPP or another FPP to produce either the 20-carbon geranylgeranyl pyrophosphate (GGPP) or the 30-carbon squalene molecule, respectively. GGPP can give rise to diterpenes, while squalene can give rise to triterpenes and steroids. Lastly, GGPP and GPP can condense to form the 40-carbon phytoene structure, which then can give rise to tetraterpenes.

Most plants contain so-called essential oils, which contain a mixture of volatile monoterpenes and sesquiterpenes. Limonene is found in the essential oils of citrus peels, whereas menthol is the chief monoterpene in peppermint essential oil (Figure 1.5). Two potentially nutraceutical diterpenes in coffee beans are kahweol and cafestol. Both of these diterpenes contain a furan ring. As discussed by Miller and colleagues, the furan-ring component might be very important in yielding some of the potential antineoplastic activity of these compounds.

Several triterpenes (examples in Figure 1.6) have been reported to have nutraceutical properties. These compounds include plant sterols; however, some of these structures may have been modified to contain fewer than 30 carbons. One of the most recognizable triterpene families is the limonoids. These triterpenes are found in citrus fruit and impart most of their bitter flavor. Limonin and nomilin are two triterpenoids that may have nutraceutical application, limonin more so than nomilin. Both of these molecules contain a furan component. In citrus fruit, limonoids can also be found with an attached glucose, forming a limonoid glycoside. As discussed above, the addition of the sugar group reduces the bitter taste tremendously and makes the molecule more water soluble. These properties

![Figure 1.2: Isoprene.](image-url)
FIGURE 1.3  The mevalonic acid pathway.
may make it more attractive as a functional food ingredient. Saponins are also triterpene derivatives, and their nutraceutical potential is attracting interest.\textsuperscript{22,23}

The carotenoids (carotenes and xanthophils), whose name is derived from carrots (\textit{Daucus carota}), are perhaps the most recognizable form of coloring pigment within the isoprenoid class.

Carotenes and xanthophils differ only slightly, in that true carotenes are purely hydrocarbon molecules (i.e., lycopene, \(\alpha\)-carotene, \(\beta\)-carotene, \(\gamma\)-carotene); the xanthophils (i.e., lutein, capsanthin, cryptoxanthin, zeaxanthin, astaxanthin) contain oxygen in the form of hydroxyl, methoxyl, carboxyl, keto, and epoxy groups. With the exception of crocin and bixin, naturally occurring carotenoids are tetraterpenoids, and thus have a basic structure of 40 carbons with unique
modifications. The carotenoids are pigments that generally produce colors of yellow, orange, and red. Carotenoids are also very important in photosynthesis and photoprotection.

Different foods have different kinds and relative amounts of carotenoids. Also, the carotenoid content can vary seasonally and during the ripening process. For example, peaches contain violaxanthin, cryptoxanthin, \( \beta \)-carotene, persicaxanthin, neoxanthin, and as many as 25 other carotenoids; apricots
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contain mostly α-carotene, β-carotene, and lycopene; and carrots contain about 50–55 parts per million of carotene in total, mostly α-carotene, β-carotene, and γ-carotene, as well as lycopene. Many vegetable oils also contain carotenoids, with palm oil containing the most. For example, crude palm oil contains up to 0.2% carotenoids. Meanwhile, there are a few synthetic carotenoids, including β-apo-8′-carotenal (apocarotenal), and canthaxanthin. Beta-Apo-8′-carotenal (apocarotenal) imparts a light reddish-orange color, and canthaxanthin imparts an orange-red to red color.

1.7.2 Phenolic Compounds

Like the terpenoids, phenolic compounds are also considered secondary metabolites. The base for this very diverse family of molecules is a phenol structure, which is a hydroxyl group on an aromatic ring. From this structure, larger and interesting molecules are formed such as anthocyanins, coumarins, phenylpropamides, flavonoids, tannins, and lignin. Phenolic compounds perform a variety of functions for plants, including defending against herbivores and pathogens, absorbing light, attracting pollinators, reducing the growth of competitive plants, and promoting symbiotic relationships with nitrogen-fixing bacteria.

There are a couple of biosynthetic pathways that form phenolic compounds. The predominant pathways are the shikimic acid pathway and the malonic acid pathway. The shikimic pathway is more significant in higher plants, although the malonic acid pathway is also present. Actually, the malonic pathway is the predominant source of secondary metabolites in lower plants, fungi, and bacteria. The shikimic pathway is so named because an intermediate of the pathway is shikimic acid. Inhibition of this pathway is the purpose of a commercially available herbicide (Roundup).

The malonic acid pathway begins with acetyl CoA. Meanwhile, in the shikimic pathway, simple carbohydrate intermediates of glycolysis and the pentose phosphate pathway (PPP) are used to form the aromatic amino acids phenylalanine and tyrosine. A third aromatic amino acid, tryptophan, is also a derivative of this pathway. As animals do not possess the shikimic acid pathway, these aromatic amino acids are diet essentials. Obviously, these amino acids are considered primary metabolites or products. Thus, it is the reactions beyond the formation of these amino acids that are of greater importance to the production of secondary metabolites. Once formed, phenylalanine can be used to generate flavonoids (Figure 1.7). The reaction that generates cinnamic acid from phenylalanine is catalyzed by one of the most-studied enzymes associated with secondary metabolites, phenylalanine ammonia lyase (PAL). The expression of PAL is increased during fungal infestation and other stimuli, which may be critical to the plant.

From trans-cinnamic acid, several simple phenolic compounds can be made. These include the benzoic acid derivatives vanillin and salicylic acid (Figure 1.8). Also, trans-cinnamic acid can be converted to para-coumaric acid. Simple phenolic derivatives of para-coumaric acid include caffeic acid and ferulic acid. CoA can be attached to para-coumaric acid to form para-coumaryl CoA. Both para-coumaric acid and para-coumaryl CoA can also be used to form lignin-building blocks, para-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol. After cellulose, lignin is the most abundant organic molecule in plants. To continue the formation of other phenolic classes, para-coumaryl CoA can undergo further enzymatic modification, involving three malonyl CoA molecules, to create polyphenolic molecules such as chalcones and then flavonones. The basic flavonone structure is then the precursor for the flavones, isoflavones, and flavonols. Also, flavonones can be used to make anthocyanins and tannins via dihydroflavonols (Figures 1.7, 1.9, and 1.10).

The flavonoids are one of the largest classes of phenolic compounds in plants. The basic carbon structure of flavonoids contains 15 carbons and is endowed with two aromatic rings linked by a 3-carbon bridge (Figure 1.11). The rings are labeled A and B. Whereas the simpler phenolic compounds and lignin-building blocks result from the shikimic pathway and are phenylalanine derivatives, formation of the flavonoids requires some assistance from both the shikimic pathway and the malonic acid pathway. Ring A is derived from acetic acid (acetyl CoA) and the malonic acid pathway (see the use of 3 malonyl CoA to form chalcones in Figure 1.7). Meanwhile, ring B and the
Figure 1.7  Production of plant phenolic molecules via phenylalanine.
3-carbon bridge are derived from the shikimic acid pathway. The flavonoids are subclassified based primarily on the degree of oxidation of the 3-carbon bridge. Also, hydroxyl groups are typically found at carbon positions 4, 5, and 7, as well as other locations.

The majority of naturally occurring flavonoids are actually glycosides, meaning a sugar moiety is attached. The attachment of hydroxyl groups and sugars will increase the hydrophilic properties of the flavonoid molecule, while attachment of methyl esters or modified isopentyl units will increase the lipophilic character. Anthocyanins and anthocyanidins (Figure 1.9) are produced by plants and function largely as coloring pigments. Basically, anthocyanins are anthocyanidins with sugar moieties attached at position 3 of the 3-carbon bridge between rings A and B. These molecules help attract animals for pollination and seed dispersal. They are responsible for the red, pink, blue, and violet coloring of many fruits and vegetables, including blueberries, apples, red cabbage, cherries, grapes, oranges, peaches, plums, radishes, raspberries, and strawberries. Only about 16 anthocyanidins have been identified in plants and include pelargonidin, cyanidin, delphinidin, peonidin, malvidin, and petunidin.

Although the flavonols and flavones are structurally like their close cousin anthocyanidins and the anthocyanin-glycoside derivatives anthocyanins, they absorb light at shorter wavelengths and thus are not perceived as color to the human eye. However, they may be detected by insects and help direct them to areas of pollination. Because flavones and flavonols do absorb UV–B light energy (280–320 nm), they are believed to serve a protective role in plants. Also, certain flavonoids promote the formation of a symbiotic relationship between plant roots and nitrogen-fixing bacteria. The primary structural feature that separates the isoflavones from the other flavonoids is a shift in the position of the B ring. Perhaps the most ubiquitous flavonoid is quercetin. Hesperidin is also a common flavonoid, especially in citrus fruit.

**1.7.3 Carbohydrates and Derivatives**

The glucose derivative ascorbic acid (vitamin C) is perhaps one of the most recognizable nutraceutical substances and is a very popular supplement. Ascorbic acid functions as a nutraceutical compound, primarily as an antioxidant. Meanwhile, plants produce some oligosaccharides that appear to function as prebiotic substances.
Several plant polysaccharide families are not readily available energy sources for humans, as they are resistant to secreted digestive enzymes. These polysaccharides are grouped together along with the phenolic polymer compound lignin to form one of the most recognizable nutraceutical families—fibers. By and large the role of fibers is structural for plants. For example, cellulose and hemicellulose are major structural polysaccharides found within plant cell walls. Beyond providing structural characteristics to plant tissue, another interesting role of certain fibers is in tissue repair after trauma, somewhat analogous to scar tissue in animals.

The non-starch polysaccharides can be divided into homogeneous and heterogeneous polysaccharides, as well as into soluble and insoluble substances. Cellulose is a homogeneous non-starch polysaccharide, as it consists of repeating units of glucose monomers. The links between the glucose monomers are $\beta$-1-4 in nature. These polysaccharides are found in plant cell walls as microfibril bundles. Hemicellulose is found in association with cellulose within plant-cell walls and is composed of a mixture of both straight-chain and highly branched polysaccharides containing pentoses, hexoses, and uronic acids. Pentoses such as xyloans, mannans, galactans, and arabicans are found in relatively higher abundance. Hemicelluloses are somewhat different from cellulose in that they are not limited to glucose, and they are also vulnerable to hydrolysis by bacterial degradation.

Another homopolysaccharide is pectin, where the repeating subunits are largely methylgalacturonic acid units. It is a jelly-like material that acts as a cellular cement in plants. The linkage between the subunits is also $\beta$-1-4 bonds. The carboxyl groups become methylated in a seemingly random
Chemically related to pectin is chitin. Chitin is not a plant polysaccharide but is found within the animal kingdom, although not necessarily in humans. It is a $\beta_1$-4 homopolymer of N-acetyl-glucosamine found in shells or exoskeletons of insects and crustacea. Chitin has been positioned as a dietary ingredient for weight loss.

Another family of polysaccharides that is worthy of discussion is glycosaminoglycans (GAGs). While these compounds are found in animal connective tissue, they are important to this discussion,
as they are potential components of functional foods. At present, GAG and chondroitin sulfate are popular nutrition supplements being used by individuals recovering from joint injuries and suffering joint inflammatory disorders. Glycosaminoglycans are often referred to as mucopolysaccharides. They are characterized by their content of amino sugars and uronic acids, which occur in combination with proteins in secretions and structures.

GAGs are responsible for the viscosity of body-mucus secretions and are components of extracellular amorphous ground substances surrounding collagen and elastin fibers, and cells of connective tissues and bone. Some examples of glycosaminoglycans are hyaluronic acid and chondroitin sulfate. Hyaluronic acid is a component of the ground substance found in most connective tissue, including the synovial fluid of joints. It is a jelly-like substance composed of repeating disaccharides of β-glucuronic acid and N-acetyl-d-glucosamine. Hyaluronic acid can contain several thousand disaccharide residues and is unique from the other glycosaminoglycans in that it will not interact with proteins to form proteoglycans. Chondroitin sulfate is composed of β-glucuronic acid and N-acetylgalactosamine sulfate.

This molecule has a relatively high viscosity and ability to bind water. It is the major organic component of the ground substance of cartilage and bone. Both polysaccharides have β1-3 linkage between uronic acid and acetylated amino sugars but are linked by β1-4 covalent bonds to other polysaccharide units. Unlike hyaluronic acid, chondroitin sulfate will bind to proteins to form proteoglycans.

1.7.4 Fatty Acids and Structural Lipids

At present, there are several fatty acids and/or their derivatives that have piqued the interests of researchers for their functional potential. These include the omega-3 PUFA found in higher concentrations in plants, fish, and other marine animals, and conjugated linoleic acid (CLA) produced by bacteria in the rumen of grazing animals such as cattle. The formation of CLA probably serves to help control the vitality of the released bacterial population in the rumen, whereas plants and fish use omega-3 fatty acids for their properties in membranes. Some plants also use omega-3 PUFA in a second messenger system to form jasmonic acid when plant tissue is under attack (i.e., by insect feeding). The CLA precursor, linoleic acid, and omega-3 PUFA are produced largely in plants. In processes very similar to those found in humans, plants construct fatty acids using two-carbon units derived from acetyl CoA. In humans and other animals, the reactions involved in fatty acid synthesis occur in the cytosol, whereas in plants they occur in the plastids. In both situations, FAS, acetyl CoA carboxylase enzymes, and acyl carrier protein (ACP) are major players. Plants primarily produce fatty acids to become components of triglycerides in energy stores (oils), as well as components of cell membrane glycerophospholipids and glyceroglycolipids, which serve roles similar to the phospholipids in humans. In fact, several of the plant glycerophospholipids are generally the same as phospholipids. Some of the major fatty acids produced include palmitic acid (16:0), oleic acid (18:1ω-9), linoleic acid (18:2ω-6), and linolenic acid (18:3ω-3). Grazing animals ingest linoleic acid, which is then metabolized to CLA by rumen bacteria. Herbivorous fish also ingest these fatty acids when they consume algae and other seaweeds and phytoplankton. Carnivorous fish and marine animals then acquire these PUFA and derivatives from the tissue of other fish and marine life. Fish will further metabolize the PUFA to produce longer and more unsaturated fatty acids such as DHA (docosahexaenoic acid, 22:6ω-3) and EPA (eicosapentaenoic acid, 20:5ω-3). The elongation and further unsaturation yield cell-membrane fatty acids more appropriately suited for colder temperatures and higher hydrostatic pressures, usually associated with deeper water environments.

CLA is distinct from typical linoleic acid in that CLA is not necessarily a single structure. There seem to be as many as nine different isomers of CLA. However, the primary forms are mainly 9-cis, 11-trans, and 10-trans, 12-cis. From these positions, it is clear that the locations of the double bonds are unique. The double bonds are conjugated and not interrupted by methylene. Said another way, the double bonds are not separated by a saturated carbon but are adjacent. CLA is found mostly in the fat and milk of ruminant animals, which indicates that beef, dairy foods, and lamb are major dietary sources.
Two other types of lipids in food products are structured lipids and diglycerides. Structured lipids are triglycerides that have undergone hydrolysis and re-esterification under conditions that resulted in triglycerides with new combinations of fatty acids. For example, a mixture of medium-chain triglycerides and fish oil taken through this process results in triglycerides that can contain medium-chain fatty acids and EPA, and DHA. The basic process results in the free fatty acids being randomly re-esterified to the glycerol backbones. However, the process can be manipulated to place specific fatty acids in preferred positions on the glycerol molecule. This option is quite expensive and thus has not been adopted by the food industry to any degree. However, the random re-esterification process has been used to produce structured triglycerides designed to facilitate the absorption of both medium-chain and long-chain omega-3 fatty acids.

Diglycerides have been used as emulsifying agents in manufactured food products for many years. More recently, more specialized diglycerides, termed diacylglycerols (DAGs), have been produced by limited hydrolysis of triglycerides. This process results in a mixture of 1,2-diglycerides and 1,3-diglycerides. These diglycerides have absorption and metabolism characteristics like those of medium-chain triglycerides; that is, some of the fatty acids escape re-esterification within the cells of the small intestine and subsequent delivery to adipose tissue via the lymphatic system. Instead, they are delivered to the liver, where they are oxidized to produce energy and possibly to produce ketones. The result is an apparent caloric content that is somewhat less than the 9 kcal/g associated with most fats.

1.7.5 AMINO ACID–BASED

This group has the potential to include intact protein (i.e., soy protein), polypeptides, amino acids, and nitrogenous and sulfur amino acid derivatives. Today, a few amino acids are also being investigated for their nutraceutical potential. Among these amino acids are arginine, ornithine, taurine, and aspartic acid. Arginine has been speculated to be cardioprotective in that it is a precursor molecule for the vasodilating substance nitric oxide (NO). Also, arginine may reduce atherogenesis.

The non-proteogenic amino acid taurine may have blood pressure–lowering properties as well as antioxidant roles. However, the research in these areas is still inconclusive, and the effects of supplementation of these amino acids on other aspects of human physiology is unclear. Several plant molecules are formed via amino acids. A few of the most striking examples are isothiocyanates, indole-3-carbinol, allyl sulfur compounds, and capsaicinoids. Another nutraceutical amino acid–derived molecule is folic acid, which is believed to be cardioprotective in its role of minimizing homocysteine levels. Other members of this group would include the tripeptide glutathione and choline.

Several amino acid–derived molecules have nutraceutical potential as well. These include creatine, which is derived from three amino acids and found in meats. Creatine is an important short-term anaerobic energy reserve in muscle tissue, brain, kidneys, and other tissue. Higher intakes via supplementation can support gains and/or retention of strength and power and provide cellular protection during transient anoxia. In addition, carnitine might have application in supporting healthier blood glucose and lipid levels.

1.7.6 MICROBES (PROBIOTICS)

Where the other groupings of nutraceuticals involve molecules or elements, probiotics involve intact microorganisms. This group largely includes bacteria, and its criteria are that a microbe must be resistant to: Acid conditions of the stomach, bile, and digestive enzymes normally found in the human gastrointestinal tract; able to colonize the human intestine; be safe for human consumption; and, lastly, have scientifically proven efficacy. Among the bacterial species recognized as having functional food potential are Lactobacillus acidophilus, L. plantarum, L. casei, Bifidobacterium bifidum, B. infantis, and Streptococcus salarius subspecies thermophilus. Some yeasts have been noted as well, including Saccharomyces boulardii.
1.7.7 MINERALS

Several minerals have been recognized for their nutraceutical potential and thus become candidates for functional food recipes. Among the most obvious is calcium with relation to bone health, colon cancer, and perhaps hypertension and cardiovascular disease. Potassium has also been purported to reduce hypertension and thus improve cardiovascular health. A couple of trace minerals have also been found to have nutraceutical potential. These include copper, selenium, manganese, and zinc. Their nutraceutical potential is usually discussed in relation to antioxidation. Copper, zinc, and manganese are components of superoxide dismutase (SOD) enzymes, whereas selenium is a component of glutathione peroxidase. Certainly, more investigation is required in trace elements considering their metabolic relationships to other nutrients and the potential for toxicity.

REFERENCES

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