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Overview of Functional Foods

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1.1 Overview of Functional Foods

1.1.1 Foods and Nutrients are Linked to Health and Disease

The Centers for Disease Control and Prevention (CDC) indicates that a healthy lifestyle, including healthy foods, is one strategy to prevent chronic disease (CDC, 2012). Epidemiological studies have shown a diet rich in fruits and vegetables can reduce the risk of inflammatory and age-related chronic diseases, including many cancers, cardiovascular disease, and inflammation (Barbaresco *et al.*, 2013; Esposito and Giugliano, 2006; Heggie *et al.*, 2003; Hu, 2003).

Foods, especially plant foods, contain non-nutrient bioactive compounds that have potential to synergistically and positively impact health. The primary classes are phenolic compounds, carotenoids, alkaloids, nitrogen-containing compounds, organosulfur compounds, and phytosterols (Liu, 2004, 2013a,

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2013b). More than 5000 bioactive components have been identified in plant foods (Liu, 2004, 2013a), but it is thought that more than 25,000 bioactive components are actually present. Most of these components are metabolized to different compounds during and after digestion. Considering these 25,000 bioactives and all of their metabolites, it would be unrealistic to conclude there is a single compound which serves as a “silver bullet” for health promotion. Instead, it is the combination of many dietary compounds consumed from a variety of whole foods that likely confers the greatest health benefits (Liu, 2004). Undoubtedly, there is still much research required in order to fully understand the role of bioactive dietary compounds and their metabolites in human health.

1.1.2 Definition of Functional Foods

Defining functional foods can be difficult. There is no U.S. Food and Drug Administration (FDA) definition of functional foods, and all foods can be considered “functional” because all cause some physiological response. The Academy of Nutrition and Dietetics (AND) defines functional foods 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” (Crowe and Francis, 2013). Similarly, the Institute of Food Technologists (IFT) defines functional foods as “foods and food components that provide a health benefit beyond basic nutrition (for the intended population)” (IFT, 2005). Thus, functional foods can encompass fresh foods, such as tomatoes and broccoli, along with processed or cooked foods, such as tomato juice and broccoli soup. Functional foods also include foods that naturally contain non-nutrient bioactive components, such as flax seeds, as well as foods fortified with bioactive components, such as various nutrition bars.

1.1.3 Functional Foods Market

As reviewed by E. Sloan, the *Nutrition Business Journal* (2013) reports that worldwide sales of functional foods were \$118 billion in 2012. With an increase of 7% from 2011 to 2012, the

United States is the largest market for functional foods (sales of \$43.9 billion), followed by Japan (\$22 billion), the United Kingdom (\$8.1 billion), and Germany (\$6.4 billion) (Sloan, 2014). Also reviewed by E. Sloan, the Multi-Sponsor Surveys' 2012 Gallup Study of Nutrient Knowledge and Consumption reports that 60% of adults in the U.S. consume functional foods or beverages at least occasionally (Sloan, 2014). These statistics confirm that not only is the study of functional foods valuable for consumer health, but also that there is interest by the food and nutrition industries to develop new products for consumers that truly improve health (Pricewaterhouse Coopers, 2009).

1.1.4 How Functional Foods are Studied

Large epidemiological studies are usually used to discover a potential association between a food or group of foods and a health condition. Due to wide variability in various characteristics of epidemiological cohorts (e.g. diet and other environmental exposures, race and other genetic factors), randomized, controlled, human clinical intervention studies are used to identify cause and effect relationships between a specific food and a health condition. These randomized controlled trials are considered the “gold standard”, mandatory to develop health claims, and usually required to develop dietary recommendations. While it is recognized that cellular or other *in vitro* models will never perfectly replicate the complex system of the human body, *in vitro* methods are an essential piece of the puzzle. They can be used to understand the identity and quantity of bioactive components in foods and their metabolites once the food is consumed. In addition, *in vitro* models are used to study mechanisms of action as well as absorption and metabolism. Because even small human clinical intervention studies are very expensive and time intensive, *in vitro* preclinical models are often used to validate epidemiological data, predict the outcome of a human or animal study, justify execution of human clinical trials, and predict human sensory perception of functional foods.

In vitro methodologies are typically used throughout a “crops to the clinic” approach to functional foods research, from growing the plant, producing a food product, analyzing the bioactive components, and predicting the bioavailability and biological

activity of the bioactives, all with the goal of justifying use of the food in a human clinical study (Ferruzzi *et al.*, 2012). These aspects are discussed below.

When growing a plant to be used as a functional ingredient in a food product, *in vitro* methodologies are used to understand genetic and molecular pathways which influence the levels of bioactive components in a plant. For example, genetic mapping techniques can be developed to identify plant varieties that contain higher levels of a specific bioactive component or a form of the bioactive component which is more biologically active or more bioavailable (Battino *et al.*, 2009; Kuzina *et al.*, 2011). In addition, growing conditions such as temperature, light, and soil nutrients can be modulated to optimize levels of a particular bioactive component (Bumgarner *et al.*, 2012). Processing conditions, inclusion of other ingredients, and storage conditions can also impact the stability and biological activity of bioactive compounds, and thus can be monitored using *in vitro* analytical methods to identify and quantify bioactive compounds in food.

The techniques of high performance liquid chromatography (HPLC) in combination with photodiode array (PDA) and/or mass spectrometry (MS) are used for analysis of bioactive compounds in foods. PDA is sufficient to quantify compounds that are adequately detected with UV-Vis absorption, while MS, based on a compound's unique mass-to-charge ratio (m/z), is essential for compounds that require greater selectivity or are at lower concentrations and require greater sensitivity. Tandem MS (MS/MS) and accurate mass measurements provide further confidence in quantitation and identification, respectively. These methods are used to identify and quantify a range of bioactive compounds and their metabolites to help answer a variety of research questions. As above, analytical methods are essential to study the impact of different plant varieties, growing conditions, maturity levels, and plant disease on the type and amount of bioactive components in plants, and the impact of processing, storage, and the presence of other ingredients on the bioactive levels of a functional food product, ultimately predicting the potential health benefits. Bioactive identification and quantification is also critical when evaluating the stability and metabolism of a compound during simulated (*in vitro*) digestion and absorption, in addition to after consumption by animals or humans.

In vitro methods can be used to simulate the bioaccessibility and bioavailability of a functional food or a specific bioactive compound before advancing to a human clinical study. Bioactive components or their active metabolites must reach the target tissue in order to have a health benefit. Thus, bioactives must be released from the food, must remain stable during oral, gastric, and intestinal digestion, and must be delivered to the target tissue (Rein *et al.*, 2013). Digestive stability and bioaccessibility can be predicted using cell-free methods, while absorption and transport across cells can be investigated using Caco-2 intestinal cell methods, saving valuable time and research funds. Many factors can influence stability, digestion, and absorption, such as the chemical properties of the bioactive component, the food source and its matrix, interaction with other components in the food, pH, and temperature (Failla *et al.*, 2008; Rein *et al.*, 2013). Newer multi-compartmental models are also being developed that connect cultures of different cell types (e.g. intestine, liver, and adipose tissue) in order to study metabolism (Vinci *et al.*, 2012).

Biological activity can also be predicted using *in vitro* models. Antioxidant activity is one of the most common *in vitro* screening assessments, but bioactive components have many synergistic mechanisms of action that go beyond antioxidant activity (Liu, 2004). Assessing multiple mechanisms provides a more complete picture of the potential biological activity of a bioactive or food. Therefore, the health benefits of a food or ingredient should not be based on a single antioxidant assay, and it is important that a multi-faceted approach be taken before drawing conclusions. The appropriate *in vitro* model will be dependent on the disease or health condition that is being targeted. For example, when evaluating a food for its potential benefit in reducing risk of cardiovascular disease, *in vitro* markers might include models of platelet function (collagen-induced platelet aggregation, TRAP-induced P-selectin expression as a marker of platelet activation) (Ostertag *et al.*, 2011), inhibition of LDL carbamylation (Ghaffari and Shanaki, 2010), models of carotid injury (Sheu *et al.*, 2013), oxidative stress-induced cardiomyocyte injury (Li *et al.*, 2013), and hemolysis assays (Li *et al.*, 2013).

It is important to note the limitations of *in vitro* methods. It is impossible to replicate the conditions of the human body. For example, with *in vitro* experiments, there is no homeostasis, cell

studies usually only include one type of cell grown in a monolayer, and experiments are usually optimized for maximum cell growth, all conditions which do not occur in the human body (Hartung and Daston, 2009). Thus, *in vitro* studies are only predictive of potential biological activity. In order to validate findings from *in vitro* experiments, animal and human clinical trials are required.

1.2 Functional Foods and their Regulatory Aspects

Around the world, most commercially available products consumed are categorized as food or drugs, with drugs intending to cure, prevent, treat, or mitigate disease, while food is generally consumed for taste, aroma, or nutritive value (Nutrilab v. Schweiker, 1983). Although functional foods may provide benefit beyond standard nutritive value, they must adhere to food regulations. The primary objective of regulatory authorities is to protect the public by ensuring food safety and preventing misleading or false product claims. Many countries do not have specific functional food regulations and often manage these through pre-market evaluation of health benefit/disease risk reduction claims. Japan has one of the most developed regulatory frameworks for functional foods. In Japan, functional foods are officially recognized under a specific “food for specified health use (FOSHU)” which permits claims related to reduction of disease risk (Shimizu, 2012). Japanese regulatory authorities review these foods before they can be placed on the market. The application must include significant scientific evidence that demonstrates the benefit of the health claim, safety, and physical and chemical characterization.

The approach to establishing safety of a functional food does not differ from other foods. Similar to other regulatory bodies (such as the European Union and Canada), the US FDA has published guidance on the studies necessary to support the safety of a new food ingredient (Center for Food Safety and Applied Nutrition, 2007). This guidance helps develop data to demonstrate that a food ingredient is safe for the specific use at a specific use level, including for use as a functional food.

1.3 Nanotechnologies in Functional Foods

Nanotechnology is increasingly being used in functional food products. Nanotechnology is defined by the U.S. National Nanotechnology Initiative as “the understanding and control of matter at dimensions between approximately 1 and 100 nanometers (nm), where unique phenomena enable novel applications not feasible when working with bulk materials or even with single atoms or molecules” (U.S. National Nanotechnology Initiative, 2014). One application of nanotechnology in functional foods and nutraceuticals is to protect a functional ingredient from degradation during production, storage, or digestion (e.g. acidity of stomach) (Ranjan *et al.*, 2014). For example, George Weston Foods (North Ryde, New South Wales, Australia) incorporates tuna fish oil into bread to enhance the bread’s health benefits, but to avoid off odors and flavors, the fish oil is encapsulated within nanoparticles and is released only in the acidic environment of the stomach rather than in the food product (Neethirajan and Jayas, 2011). Nanotechnology is also being used to control the release rate of a functional ingredient, improve bioavailability of a compound, or target delivery to a specific cell type or tissue (Ranjan *et al.*, 2014). For instance, nanotechnology has been used to encapsulate probiotic bacteria to protect it from harsh stomach conditions, allowing controlled release of the bacteria in the neutral environment of the intestine (Neethirajan and Jayas, 2011). Several different types of delivery systems are being evaluated for use in food products, including:

- **Micelles:** Lipid-soluble bioactives, e.g. limonene, lycopene, lutein, omega-3 fatty acids, and essential oils, have very low bioavailability, limiting their use in functional foods (H. Chen, Weiss, and Shahidi, 2006; McClements and Xiao, 2012). Because of their polar head groups and nonpolar tail groups, micelles are being evaluated for encapsulation of nonpolar functional food components to allow incorporation into beverages (H. Chen *et al.*, 2006). This strategy has been used in the pharmaceutical industry to more effectively deliver poorly water-soluble drugs (McClements and Xiao, 2012).

- **Liposomes and cubosomes** are bi- or tri-phasic structures used to encapsulate water-soluble compounds within a hydrophilic component and conversely, to encapsulate lipid-soluble compounds within a lipophilic component. Liposomes and cubosomes are currently being used or evaluated for their ability to encapsulate the proteins lactoferrin and nisin Z to increase the shelf life of dairy products, encapsulate phosvitin (naturally found in egg yolk) to inhibit lipid oxidation in dairy products and ground pork, and encapsulate vitamin C to maintain its activity during long refrigerated storage (H. Chen *et al.*, 2006). Cubosomes can be altered with pH and temperature changes, and can thus be used to control the release of functional compounds (H. Chen *et al.*, 2006).
- **Nanoemulsions:** Because these emulsions are so fine, they are clear to the eye rather than opaque (B. Chen *et al.*, 2013; H. Chen *et al.*, 2006). Nanoemulsions are thermodynamically more stable than regular emulsions, and therefore do not separate over time (Ranjan *et al.*, 2014). Because of these properties, nanoemulsions are commonly used in parenteral nutrition formulations (H. Chen *et al.*, 2006), to add fat-soluble bioactive components to clear beverages (B. Chen *et al.*, 2013), and to obtain a creamy mouthfeel with limited lipid levels (H. Chen *et al.*, 2006).
- **Biopolymeric nanoparticles** are nanopolymers that are linked to form solid particles. A variety of different types of compounds can be encapsulated with biopolymeric nanoparticles, and their use is becoming more popular in functional ingredients. Examples include chitosan (derived from crustacean shells) and the synthetic polymers polylactic acid, polyglycolic acid, and combinations of lactide, galactide, and caprolactone (H. Chen *et al.*, 2006).

New tools also are incorporating biological and chemical ligands that can direct functional compounds within nanoparticles to a specific cell type (H. Chen *et al.*, 2006). The ability to deliver a functional component to a targeted cell or tissue site increases effectiveness and efficiency, allows the compound to be incorporated into the product at lower levels, and therefore can result in fewer adverse effects. For example, if salt could be incorporated in such a way that it is directed only to taste buds

that detect salt, the amount used in the food could be greatly decreased. In the future, there is potential to use nanotechnology to release a bioactive compound only in response to a specific biological trigger, such as a biochemical or genetic marker, leading to possibility of personalized nutrition (H. Chen *et al.*, 2006). Use of nanotechnology in food applications is still in the early stages, and much research is needed to ensure safety, including how nanoparticles are absorbed in the gastrointestinal tract, where nanoparticles are distributed in human body, how long they remain, what concentration they reach, and if the nanoparticles affect unintended biological activity (McClements and Xiao, 2012; Ranjan *et al.*, 2014). As with any new technology, consumers must be educated in order to maintain confidence in the technology and products using the it (Ranjan *et al.*, 2014).

1.4 Sensory Functionalities of Foods

Consumers have expectations regarding the appearance, aroma, flavor, taste and texture of food products and, as such, these sensory properties are key drivers to product acceptance. As a consequence, food companies have traditionally invested heavily in the identification and optimization of important sensory attributes. Emerging evidence, however, suggests that consumers are becoming more savvy and are increasingly looking beyond the sensory attributes to other product characteristics that influence acceptance and choice (Ares, 2011; Wills *et al.*, 2012). In this regard, interest in functional foods has recently burgeoned as consumers are seeking to improve health and wellness by incorporating functional ingredients into their diets. Unfortunately, many bioactive compounds have negative taste and flavor properties and require focused efforts to improve their palatability (Sun-Waterhouse and Wadhwa, 2012). However, for many functional foods, the level of sacrifice that consumers are willing to make in taste and flavor in favor of functionality is unknown. Further research is needed to understand these tradeoffs and to determine their relative importance in different populations (e.g. healthy vs. diseased).

As with all food products, the sensory properties of functional foods should, as much as possible, be optimized to meet or surpass consumer expectations. Prior to executing expensive sensory and consumer testing, instrumental analyses can be completed to gain insight into various physical parameters of the product that influence sensory variables (Kilcast, 2013). Because the human senses are impacted by physiological and psychological factors, it is impossible to replicate human senses with an instrument, which can only provide a discrete measure of a specific property. However, instrumental analyses might be used to reduce the number of samples on which to conduct human sensory assessment. For each product, instrumental analyses should be verified with human sensory panels so that they can be used to predict future results. The superficial appearance and color of food are the first parameters of quality evaluated by consumers. Colorimetry can be used to measure factors contributing to the product's appearance including the chromaticity and radiance, surface reflectance, transmittance and/or translucency (Clydesdale, 1978). Rheological assessments, infrared spectroscopy, water activity measurement and texture analysis can provide understanding of food properties related to perceived texture attributes including viscosity, tenderness, crunchiness, or chewiness, respectively (L. Chen and Opara, 2013; Tunick, 2011). Quantification of volatile and non-volatile compounds enables the detection and identification of chemical species contributing to flavor, odor, and taste. These techniques are particularly important in understanding matrix interactions (e.g. sequestration of hydrophobic compounds into lipids) that impact flavor release and product perception as well as in the identification of taints or other compounds contributing unique sensations. Moreover, real-time chemical analysis with techniques such as proton transfer reaction-mass spectrometry or selected-ion flow tube-mass spectrometry enable correlating concentration of volatile flavor compounds in exhaled air to perception of flavor attributes.

In summary, functional foods have much potential to positively impact human health. Both consumers and the food and nutrition industries are eager to take advantage of these foods with health benefits beyond those imparted by traditional nutrients. A “big picture” crops to the clinic approach to studying

functional foods is essential. *In vitro* methodologies are an important piece of this puzzle, and can be used to identify and quantify bioactive components in foods, identify potential mechanisms of action, and predict bioavailability and metabolism, and thus can be used to justify execution of a human clinical trial.

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