

A New Definition for Functional Food by FFC: Creating Functional Food Products Using New Definition

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ABSTRACT:

Functional food science began 30 years ago and has since generated billions of dollars in profits worldwide. Although consumers seek functional food, the concept is hotly debated. Government agencies and scientific organizations have modified the definition for functional food numerous times, leading to global disagreement on the scientific legitimacy and safety of functional food. Furthermore, as consumers buy functional foods to greatly varying degrees, consumers' trust of these products may be based on beliefs rather than on scientific data. As a result, the lack of a formally established definition for "functional food" has damaged the legitimacy of functional food science in the eyes of governments and consumers, preventing functional food from reaching chronically-ill individuals. In this review paper, we introduce a new definition for functional food. Then, we explore how the implementation of this definition would help promote the creation of new functional food products. Finally, we go through the steps involved in creating functional foods and scientific methods that can be used to ensure functional food safety, effectiveness, and legitimacy.

Keywords: Causality; consumers; functional food definition; health claims; legitimacy; market; research

RETRIEVAL OF PUBLISHED STUDIES

Cited research and review papers were electronically retrieved from PubMed and Google Scholar. They were chosen based on their discussion of the functional food definition, health claims legislation, functional food markets, and/or scientific methods. Examples of topics included: the development of the functional food definition, health claim legislation in European countries, consumer attitudes toward functional food, and methods for establishing causality in scientific studies. Keywords for article search included: functional food, nutraceutical, medical foods, definition, health claims, marketing, US, EU, Japan, FDA, FUFUSE, FOSHU, causality, in vitro, in vivo, clinical, causality, and consumer attitudes.

INTRODUCTION

Two thousand years ago, when Hippocrates said "Let food be thy medicine and medicine be thy food," he was on the right path. However, we may now revise this to "Let functional food be thy medicine." Accordingly, since 2006, we at the Functional Food Center (FFC) have incorporated this statement into our functional food-related books.

Functional food science arose out of public need, and is made possible through the collaboration of different sciences. This field of research incorporates food science, nutrition, and medicine to produce

food products that are combinations of food and pharmaceuticals. Specifically, researchers study food components and their potentially-beneficial health effects. They first measure changes in health and homeostatic behavior using biomarkers or indicators in the body. Then, scientists determine the prominent health effects these functional foods have on the body as well as their optimal and safe dosages [1].

But while the steps to developing functional food are more or less consistent across the world, the definition of “functional food” is not [1]. For example, countries like Japan, the EU, and the United States do not have a single legislative definition for functional food, leading to numerous worldwide consequences. The lack of a globally consistent definition has encouraged unregulated publishing of health claims in some nations, restricting of functional food production in other countries, and an overall mistrust or unclear sense of what functional food is among government officials, public health professionals, and consumers [37]. While billions of dollars in sales have been generated through the development of functional food, these setbacks divert functional food scientists from delivering functional food to chronically ill populations.

Consequently, in this review paper, we describe how functional food has been defined in the past, why a standard definition is necessary, and the rationale behind the FFC’s new definition for functional food.

Challenges Due to the Absence of a Proper Definition for Functional Food

A standard definition for functional food is needed to facilitate greater communication between food experts, scientists, government officials, and the public as well as to enable freer exchange of functional food products between countries.

Additionally, there are several consequences of leaving the functional food definition open-ended. These include: the distortion of the meaning of functional food, ambiguous food labels, and the loss of scientific legitimacy among consumers and government officials. As professionals in this field, it is imperative that we clarify what we mean by “functional foods,” “bioactive compounds,” “nutraceuticals,” and other terms.

As researchers discover more bioactive compounds in food, functional food science gains support from the scientific community. Accordingly, government support through research grants and health claim approval will become more crucial to creating new functional food products. The FFC believes that in order to fully inform and educate government officials and others about functional food and bioactive compounds, a new definition for functional food must be established [2, 37]. We predict that a new definition will have several benefits:

First, formalizing a definition for functional food will improve communication between food/nutrition scientists, policymakers, medical researchers and the public [7]. Increased communication will enable the implementation of better policies and food education among non-experts, which will also lead to greater funding for nutrition research and policy initiatives. Second, a definition will legitimize functional food science globally and allow for more progress in food, medical, and policy innovation. Finally, a formal definition will help dispel public misconceptions about functional food [38]. Due to the prevalence of functional food products in the world amongst numerous definitions, people harbor pre-existing notions about the legitimacy of functional food products. Moreover, due to their lack of knowledge or experience with functional food, media and non-experts spread false or misleading information about functional food, thereby planting seeds of doubt in the minds of consumers. Functional food scientists have a responsibility to properly educate the public about functional food because their products are relevant to the future of chronic disease care and prevention. Therefore, this new definition is a step that will, ideally, lead to greater use of functional food by chronically ill consumers. As a result of

their dedicated research, collaboration with fellow functional food scientists, and modern understanding of functional food, the FFC has developed a new definition for functional food.

FUNCTIONAL FOOD: THE CURRENT DEFINITION -OUR CONCEPT(S)

In 2012 at the FFC's 10th International Conference in Santa Barbara, CA, we proposed a new definition for functional food: [3]

“Natural or processed foods that contain known or unknown biologically-active compounds; which provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease.”

Medical, research, and student participants accepted this definition at the conference, which has guided our research and conferences since 2012. At our 17th international conference in 2014, which the U.S. Department of Agriculture (USDA) and Agricultural Research Service (ARS) jointly organized, we organized a Panel Discussion entitled, "The Definition of Functional Foods and Bioactive Compounds." Here, our definition for functional foods was revised to:

“Natural or processed foods that contain known or unknown biologically-active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease.”

In this updated definition, we added the phrase “in effective non-toxic amounts” to highlight the importance of bioactive compound dosage in the consumption of functional food.

What Makes the FFC Definition “Unique?”

To clarify, FFC defines food as components of a normal diet for optimized nutrition. This definition includes conventional foods, such as oranges or bran flakes, not pills or capsules.

Moreover, this definition of functional food highlights the importance of “bioactive compounds” within functional foods. Bioactive compounds are the backbone of functional food effectiveness. For almost 20 years, the FFC has collaborated with scientists who have studied the benefits of bioactive compounds in functional foods. Thanks to modern biochemical technology, food scientists can now separate food substances into fine chemical components and test these food extracts for biological behavior. As a result, researchers can run experiments on these compounds and draw causal relationships between bioactive compounds and health outcomes.

Because the new definition focuses on bioactive compounds, it provides an explanation for functional foods' ability to improve health and treat illness. This definition simplifies and explains how functional foods operate at biochemical and empirical levels. In other words, this definition helps navigate food scientists toward specific goals (e.g. identifying bioactive compounds and where they exist in a food, such as in the skin, pulp, or seeds) and provides directions for future functional food research (e.g. determining the health benefits of all bioactive compounds in a food and the mechanisms by which they produce effects).

According to Dr. Danik Martirosyan, two important concepts within the topic of bioactive compounds are: the amount of bioactive compounds and ratio of bioactive compounds required to convert an ordinary food into a functional food. Different amounts of bioactive compounds are effective in different situations, and sometimes too much of a bioactive compound can be toxic. In general, consuming physiologic levels of bioactive compounds is safe, while higher levels of bioactive compounds (e.g. supra-physiological or therapeutic doses) require testing for health benefits and safety. Therefore, it is crucial to have a thorough discussion on the use and control of bioactive compounds in functional foods. Shown in the FFC's 17th International conference report, we consider the issue of safety to be of the utmost importance. Food safety will also be discussed further at our upcoming 18th and 19th

International conferences at Harvard Medical School on September 15-16, 2015 and Kobe University on November 17-18, 2015 respectively.

Another feature of the current definition is the use of biomarkers in functional food studies. Biomarkers are indicators in the body that give off signals in tissues, organs, or systems. Scientists often use biomarkers to determine the rate or effectiveness of a biological process in its natural state and after functional food administration. Biomarkers can be protein, blood sugar, cholesterol, triglyceride levels, or hormone levels. Like bioactive compounds, biomarkers are a diverse group of compounds and processes. As each and every bodily process triggers countless biological responses, there are numerous ways to measure the rate or effectiveness of a process.

Biomarkers are highly useful in functional food research. Firstly, when scientists theorize that a bioactive compound will have certain benefits, changes in biomarker activity confirm or deny these benefits. Secondly, biomarkers can indicate the mechanism by which bioactive compounds prevent or treat illness. Biological pathways are often long convoluted processes; therefore, researchers may undergo years of research to confirm details about a pathway. Biomarkers are often integral parts of biological pathways. Analyzing these are excellent ways of determining reaction mechanisms, particularly the order of each process and the roles that each enzyme, protein, and molecule play. Thirdly, observing biomarkers in a specific process can clarify the role that a bioactive compound plays in the body on several levels. For example, scientists may measure proteins levels in the liver and hormonal stimulation in the stomach while administering lactose (milk sugar) to a patient. In this case, scientists measure biomarkers involved in disparate processes in order to observe how a bioactive compound (lactose) affects both their activity levels. Functional food scientists try to choose the most efficient, accurate, and easily measured biomarkers in their studies.

In total, with the addition of bioactive compounds and the implicit role of biomarkers, the new functional food definition is complete. While previous definitions simply stated that functional foods improve health and mitigate disease, the current definition provides a reason—activity by bioactive compounds—and implies the use of biomarkers, essential tools for gauging functional food effectiveness.

HOW NEW DEFINITION WILL HELP CREATE NEW FUNCTIONAL FOOD PRODUCTS

Establishing a definitive meaning for functional food will not only bring about a consensus between scientists and governmental officials; it will also help to formally introduce functional foods to global markets.

By 1997, Japan, Europe, and the United States each generated \$3 billion in sales with a projected \$130 billion dollars in global sales by 2015 [4, 5, 9]. However, food industrialists have made claims based on differing definitions. As a result, their health claims are not always based upon strong scientific research and experimentation. Therefore, as more functional food products enter the market, public health risks rise.

Functional food scientists would like to revise this process by establishing a new definition for functional food, which would allow food industrialists to base their health claims on supported research. Bringing legitimate functional foods to markets would benefit billions suffering from chronic disease and general health problems.

Expanding Worldwide Consumer Acceptance

As the functional food market gains momentum, manufacturers increasingly recognize the need for consumer acceptance [6-10]. A 1999 study found that knowledge and beliefs about functional food play significant roles in determining whether individuals purchase or consume functional food [11]. Important beliefs about functional foods include “one’s own impact on personal health, health benefit belief, perception of health claims, belief in the food-disease prevention concept, belief in the disease-

preventative nature of natural foods, and opinions of the relationship between food and health” [13, 12-16].

As of now, consumer attitudes toward functional foods differs greatly between the EU and the United States. While Americans want to eat healthier food and consider themselves capable of doing so, they have, overall, not made that lifestyle shift [17]. More interestingly, while Americans have had a positive perception of functional foods since 1998, they are unfamiliar with the meaning of “functional food” [18]. In contrast to Americans, Northern Europeans are skeptical and Danish consumers consider functional foods to be “unnatural and impure” [19, 20].

Researchers also found that consumers who reported that they had “high knowledge” about functional foods were less likely to accept functional foods. This finding probably resulted from flaws in consumer self-research, and is significant because it suggests that consumers receive misinformation about functional food from unreliable sources, such as the internet, television, and other media sources. In contrast, a standardized definition and professional scientific marketing could properly educate consumers.

Measuring consumer attitudes towards functional foods worldwide is a complex process, taking into consideration consumers’ trust of scientific claims, government agencies, and new foods in general. However, one can deduce that consumers in some Western countries want to pick healthy foods, but have inaccurate information and misplaced biases toward functional food.

Studies have shown that a person’s belief in a food’s health benefits is a powerful motivator towards their acceptance of the new food [8]. Hence, educating consumers about the health benefits of functional food may eradicate doubts in the minds of Western consumers [38]. While a formal standard definition alone cannot resolve all public doubts, functional food scientists, if given the opportunity and legislative legitimacy, can do so.

MAIN STEPS TO BRINGING FUNCTIONAL FOODS TO MARKET

According to the Institute of Food Technologists (IFT), an organization that distributes knowledge about food, nutrition, technology, and policy, bringing functional food to the mass market requires a series of steps involving research, communication with government agencies, and effective public marketing [21, 38].

The FFC agrees with IFT’s general progression from research to marketing. However, we have created our own cycle of steps (Figure 1). In Step 1, we examine the link between a particular food and health benefits. Then, in step 2 we run in vitro and in vivo studies with non-living and animal specimens respectively. We run human studies in step 3. This involves administering human-appropriate dosages of bioactive compounds and testing for adverse side effects. In Step 4, we develop appropriate food vehicles for our bioactive compounds (e.g. fig, celery, or apple with a special yoghurt coating), and in Step 5, we market to the public and educate them about the health benefits of functional food. We run studies on populations to test for long-term effects and overall product effectiveness in step 6. Finally, in Step 7, we measure public attitudes toward functional food. We describe four additional research-related steps toward bringing functional foods to markets below Figure 1.

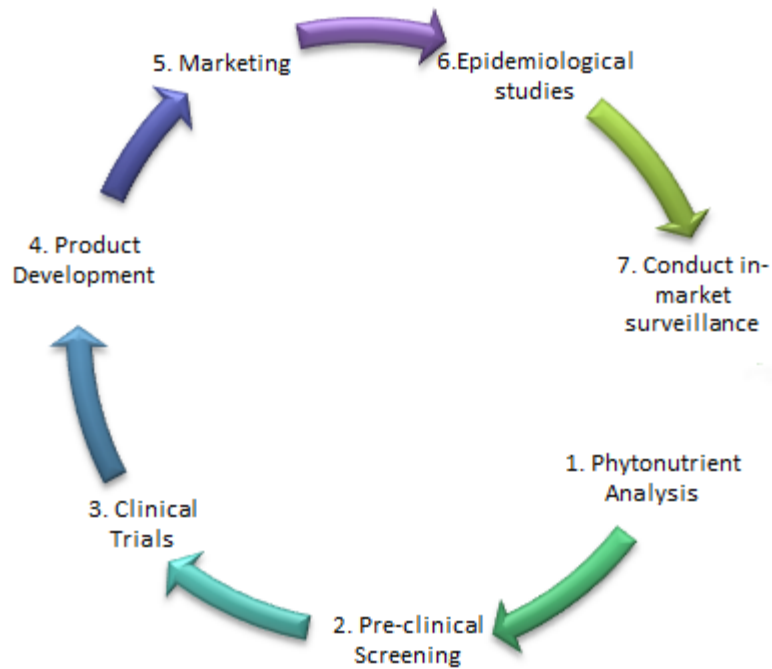


Figure 1. Steps for bringing functional foods to markets (FFC-2015)

Step 1: Identify the relationship between the food component and the health benefit.

First and foremost, scientists must prove their food has some link to health promotion. Functional foods are like drugs in that they can prevent, manage, and treat illness. Because bioactive compounds are vast and diverse, their modes of action fall within a wide range. For instance, compounds can be “mediators, anti-inflammatory agents, modulators of inflammatory cells, cytokines, and gene expression...or free radicals scavengers” [22].

Scientists have also found that phytochemicals can mimic hormones to produce a response or activate non-specific immune cells [23-28].

Some phytochemicals or bioactive compounds in functional foods act in biochemical enzymatic reactions as substrates and cofactors. This phenomenon, often seen in pharmacology, can speed up or slow down chemical reactions by aiding or inhibiting the enzymes involved. Phytochemicals may bind “to specific constituents to enhance absorption, transport or excretion, and scavenging and eliminating reactive or toxic chemicals and species” [21, 29-31]. As a result, bioactive compounds affect biochemical pathways and may alter inflammatory, fat storage, or energy storage processes. These results contain implications toward preventing obesity, cancer, and other chronic diseases.

Overall, bioactive compounds use their biological and chemical attributes, such as: “acidic, basic, chelating, hydrophobic and hydrophilic properties, as well as their amphipathic properties”, to bind to “proteins, enzymes, free radicals, glycolipids and membranes of” microbial cells. Specifically, this binding slows or prevents microbes from replicating their genetic material which thereby slows the movement or progression of an infection. Phytochemicals can help kill microbes by changing or affecting microbial proteins, a process which may inhibit microbial gene replication.

There are innumerable in vitro and clinical studies that illustrate how functional foods benefit health and prevent, manage, or treat illness (21, 32-39).

Studying Bioactive Compounds with Biomarkers

The physiological effects of functional food are varied and are increasing as research progresses. However, certain categories of functional food effects have been identified [38]:

- Physical performance
- Cognitive, behavioral, and psychological function
- Organ or system function (gastrointestinal, genitourinary, bone)
- Chronic disease (heart disease, peripheral vascular disease, diabetes, hypertension, obesity, cancer, degenerative and inflammatory arthritis)

Measuring bioactive compounds activity can be challenging when the chemical structure or identity of the compound is unknown. In that case, researchers must examine the activity of biomarkers, like metabolites or surrogate compounds, in order to assess the health effects of a functional food.

Biomarkers or substitute biomarkers must illuminate the relationship between a functional food (and its bioactive compounds) and one or more biological functions. Ideal biomarkers should remain stable over a long period of time [38]. Below (Table 1) are examples of biomarkers that can be used in functional food studies.

Table 1: Biomarkers for Measuring Physiological Effects

Physiological Category	Biomarker Category	Biomarkers
Gastrointestinal	Digestive symptoms	Release of amylase, peristalsis, stomach churning, absorption
	Digestive rates	Gastric emptying time, intestinal transit times
	Digestive hormones	Insulin, cholecystokinin changes
Bone	Bone density	Bone mineral density by dual x-ray absorptiometry
Genitourinary	Symptom recurrence rates	Rates of fracture
	Levels of osteo compounds in serum/blood	Serum levels of osteocalcin, bone-specific alkaline phosphatase, vitamin D (hydroxyproline, pyridinium cross links, or cross-linked N-telopeptides of type 1 collagen)

Determining Causality

Determining causality, the relationship in which certain events (causes) lead to another set of events (effects), is a premier scientific activity [36]. While establishing causality is difficult (as it requires independent and dependent variables, control for confounding variables, and sufficient participants), the process can generate worthwhile results. For instance, scientists use existing causal relationships to understand new phenomena. Causality is a stronger link than correlation, which merely establishes a relationship between two events or variables. In other words, scientists strive to find causal links in order to better understand worldly phenomena. Functional food science is no different. In fact, the IFT believes that establishing causality is a key process to bringing functional foods to market [37].

There are several existing models of causality. One of the most well-known models was created by Bradford Hill in 1971 [38]. Hill's criteria helps determine the strength of proposed causal relationships [39]:

1. **Strength of Association:** There must be a strong correlation or relationship between the independent and dependent variables.
2. **Temporality:** The cause must precede the proposed effect.
3. **Consistency:** The result must be reproducible with different tests, experimenters, conditions, and instruments.
4. **Theoretical Plausibility:** A hypothesis regarding a particular cause-effect relationship should have some previously established research or theoretical reasoning behind it.
5. **Coherence:** The hypothesis should align somewhat with existing knowledge or theories about the variables of interest. It should not oppose existing knowledge unless the researcher has probable cause to do so.
6. **Specificity in the causes:** Ideally, the effect should only have one cause.
7. **Dose Response Relationship:** The relationship between an independent variable (e.g. amount of bioactive compound ingested) and dependent variable (e.g. cancer cell differentiation) is direct or dose-dependent. In other words, as the amount of bioactive compound ingested increases, the level of cancer cell differentiation also increases.
8. **Experimental Evidence:** Existing experimental or causal studies related to one's study will bolster one's claim.
9. **Analogy:** A researcher may use ideas from other scientific paradigms to formulate hypotheses or interpret results.

Step 2: Demonstrate efficacy, determine the intake level necessary to achieve the desired effect, and demonstrate that the functional food/bioactive compound(s) is not toxic at the efficacy level.

How well do bioactive compounds and functional foods work at promoting health? How much does the average adult need in order to stay healthy or reduce their risk of contracting an illness? These questions are essential to bringing functional foods to mainstream markets.

Researchers know that bioactive compounds and phytochemicals are diverse in their structures and modes of action, although scientists have determined how certain bioactive compounds function. For example, phytochemicals that help relieve symptoms of chronic disease may act as antioxidants. To do this, phytochemicals disrupt free radical reactions by donating their “hydroxyls, methoxylated, carboxylic, and methyl functional groups.” Bioactive compounds could also act as antioxidants using “their hydrophilic, hydrophobic, acidic, basic, and charge to size properties” to inhibit enzymes propagating free radical synthesis. Finally, phytochemicals are capable of slowing bacterial and/or virus replication by blocking microbial invasion into “DNA, RNA, [or] protein synthesis” in cells [22].

When trying to determine the efficacy and/or proper dosage level of a bioactive compound, several factors must be considered, such as the bioactive compound's “class” (e.g. carbohydrates, proteins, lipids, vitamins, minerals, etc.), metabolism (e.g. absorption, transport, metabolism and excretion), analysis (e.g. analytical, chromatographic, genetic, combination, etc.), laboratory and clinical evaluation (e.g. in vivo, in vitro, epidemiological, etc.) and assessment of intake levels (e.g. recommended, upper and lower levels, toxicity) [22].

Thus, evaluating efficacy and intake levels of bioactive compounds requires both level approaches, from cellular to organismal, and multidimensional scientific approaches, from nutrition to genetics.

Measuring efficacy

Traditional medics of various cultures can attest to the success of plants as medicines and herbs. However, in order for these testimonies to be accepted in modern medicine, plants and their bioactive compounds must be tested through rigorous in vitro and in vivo studies [22].

Prior to running either *in vitro* or *in vivo* studies, researchers must decide on appropriate experimental methods. Efficacy testing requires accurate, sensitive, specific, and reliable experimental methods. When choosing testing method(s), scientists should consider the following questions [37]:

1. What is being studied and analyzed? Is it one entity or a collection of entities?
2. Is the entire entity of interest or only the bioactive component?
3. What are the lower and upper amounts of analyte that must be ascertained?
4. Does the compound of interest demonstrate varying levels of effectiveness depending on its chemical form?
5. Does the functional food matrix affect the compound's effectiveness?
6. Does food processing affect the compound of interest and/or experimental analysis?

Testing methods should measure the bioactive or harmful compound at the amount at which a certain effect is expected. Note that different bioactive compounds may have different "peak" levels, which then requires multiple efficacy tests.

***In vitro* studies**

In order to study phytochemical effectiveness at fighting disease, researchers may begin with *in vitro* studies or inanimate lab-based studies. Often fibroblast (connective) or HeLa (cancer) cells are prepared in a pH and temperature-appropriate medium. Cells are usually "incubated at 37°C at 5% CO₂" while researchers measure cell growth with a light microscope. Researchers may also measure cell proliferation by dyeing the cells with trypan blue, adding trypsin, and counting the cells with a cell counter. Researchers can then measure growth by dyeing cells, allowing them to become chromophores, and measuring sample absorbance in a spectrophotometer. Afterwards, researchers prepare bioactive compounds in concentrations that either cause 50%, 90%, and 100% inhibition or cell death. These concentrations help determine a bioactive compound's inhibitory effectiveness.

Finally, researchers add the various concentrations of bioactive compound to cell lines containing microbes. Cell growth can be measured every 24 or 72 hours. Normal biological pathways suggest that parasites will attempt to multiply by infiltrating the healthy cells. The bioactive compound can stop the spread of infection by inhibiting cell growth and killing infected cells.

Using a light microscope, cell counter, or spectrophotometer, researchers can measure the cell growth that follows infection. If bioactive compounds successfully inhibit cell growth, researchers may use "immunological assays, cloning, and PCR techniques" to determine the mechanism(s) or pathway(s) by which the bioactive compound operates.

***In vivo* studies**

In vivo studies involve living subjects, such as animals or humans. If researchers are conducting clinical or human research, they must get informed consent from participants. Participants must understand the experimental procedures; the "potential benefits, adverse effects, outcomes, and handling of the information collected from participants" [22]. Obtaining consent allows for ethical experimentation and protects researchers from legal charges if an experiment is unsuccessful.

Afterwards, researchers screen participants for certain requirements, such as age or symptoms of an illness. Researchers then conduct physical examinations of the participants, such as analyses of "blood, serum, plasma, urine, saliva, and sweat" [22].

Next, researchers prepare various concentrations of the bioactive compound in question in a tablet or syrup form. The bioactive compounds are administered to participants, animal or human, orally or via injection. Oftentimes, participants serve as their own experimental and control groups. For instance, researchers may administer the drug via injection to a participant's one arm or leg (experimental) and

leave the other arm or leg alone (control). In this way, researchers obtain more accurate data and twice the amount of information than if they split the group into two treatments.

Depending on the study, researchers may measure levels of “proteins, lipids, fatty acids, gene expression, and certain enzymes” using “electrophoresis, high performance/thin layer chromatographic, and gas-liquid chromatography or gas chromatography–mass spectrometer (GC-MS)”. Finally, researchers may use immunoassays to measure “antigen-antibody interactions and protein expression” [22]. After one month, researchers should conduct follow-up treatment to test for any adverse effects from the bioactive compound.

To reiterate, when conducting in vivo clinical studies, researchers must get informed consent from all participants and make sure that the condition and concentrations of the administered bioactive compounds are safe.

Use of Epidemiological Studies

Epidemiological studies are useful since they examine how chronic diseases develop in entire populations over long periods of time. In terms of functional food research, epidemiological studies can draw strong conclusions about the relationships between diet, biomarkers, and illness. Researchers should use epidemiological studies to identify populations affected by a certain disease as well as dietary behaviors and/or risk factors that contribute to disease progression [38].

Effects of Bioavailability on Effectiveness

Bioavailability is the quality of food by which its nutrients can be absorbed and reach the necessary tissues. Functional food can vary in its bioavailability based on its physical form, chemical form, and the other foods in an individual’s diet. For example, “when a food component is coated, microencapsulated, emulsified, or altered in some way from its original state, its absorption and utilization may be affected.” Food elements’ chemical state may affect bioavailability. For instance, iron’s ferrous form is better absorbed than its ferric form [40]. Some foods can affect the level of absorption of other foods. “For example, a high level of zinc in the diet decreases copper absorption [41], while dietary vitamin C increases iron absorption [42].” As a result, researchers should carefully document and analyze the form in which they prepare bioactive compounds.

Determining proper intake/dosages

Functional food professionals cannot prescribe bioactive compounds and specific dosages to treat illnesses. However, researchers understand that bioactive compounds have “optimal levels” as well as “upper limits of tolerance” in humans [22].

A bioactive compound’s optimal and upper limits depend on a variety of factors, including the compound’s structure, food source, illness in question, and a patient’s sex, age, height, and weight [43]. Moreover, scientists need to examine the eating behavior of a target population; specifically, how much the target population consumes the bioactive compound naturally. For example, if the proposed food vehicle is a radish and the target population (say American diabetes patients, ages 60-80 do not consume radishes regularly), researchers may find it wise to change their food vehicle to a food consumed to a greater extent by their target population. Likewise, the entire diet of the target population must be examined in order for researchers to balance the amount of nutrients being supplied through their functional food with nutrients supplied through other foods. As previously stated, bioactive compounds consumed at high levels can become toxic.

Absolute and Relative Intake

The first step to determining proper dosages for a bioactive compound involves measuring humans' absolute and relative intake of the compound [44].

The absolute intake of a bioactive compounds measures how much of the compound an average person consumes per day; to do this, researchers must compile nutrition information/content of mass-consumed food and then calculate how much of a particular nutrient an individual consumes.

Relative intake is the amount of a bioactive compound an individual consumes compared to the amount of other nutrients an individual consumes. To measure this, researchers should monitor the breadth of food that their target population consumes and analyze the nutrient levels found in the most commonly consumed foods.

Optimal vs. Toxic Intake levels: Bioactive compounds work best when taken in certain dosages. Researchers attempt to find these optimal levels when comparing experimental dosages with dosages consumed naturally in the world. Conversely, bioactive compounds should not be overused, as they can be dangerous at high levels. Specifically, when compounds are consumed at "toxic levels," they switch from being beneficial antioxidants, to harmful pro-oxidants. As a result, these once-helpful compounds can promote oxidation, leading to the organ/tissue damage and chronic disease [22, 45].

Allergen Safety

A final but important safety consideration is food allergies. Food allergies are medical conditions in which one's immune system reacts abnormally to the ingestion of particular foods [38, 46]. In individuals with food allergies, immune systems react adversely to certain food proteins. These "bad" proteins could either be naturally occurring or added during processing. Regardless, allergic symptoms range from "mild and annoying to severe and life threatening" [38, 47]. Considering the seriousness of food allergies in humans, functional food scientists should screen their products for allergens. There are indexes of existing protein allergens, but new proteins should also be tested for allergenic potential.

Quality of Scientific Evidence

Over time, the scientific community has compiled features of noteworthy literature, indicative of strong experimental evidence:

1. Double-blind experiments controlled for confounds
2. Long-term studies demonstrating consistent results and little to no adverse side-effects
3. Identified dose-response relationship
4. Identified biochemical mechanism and/or relevant biomarkers
5. Statistical significant results (e.g. $p < .05$)
6. Meaningful results to public health and wellness

Experimental contexts can greatly affect results from study to study. Confounding variables may include: "differences in dosage, the form of administration, the population tested, non-dietary factors such as smoking, and environmental contaminants or conditions..." [38]. Regardless, researchers should be able to explain inconsistencies between studies.

Step 3: Make approved health claims

Obtaining approval for food claims in Japan:

Japan, the birthplace of functional foods, acts as a pseudo-model for the FFC's steps for bringing functional foods to market. The Japanese government approves health claims and admission into the legislative category of FOSHU (Foods for Specific Health Uses) using an application process. The FFC supports the overall process by which Japan approves functional food. Japan is also noteworthy because it

has a formal definition for functional food, enables greater understanding amongst its citizens, and acts as a leader in food sales.

Obtaining Approval for Food Claims in the U.S.

In contrast to Japan, the United States has not formally defined “functional food.” While sales are strong in the U.S., functional food manufacturers exploit the concept of functional food for the sake of profit, thereby weakening scientists’ motivation to create good products. This vicious cycle prevents quality functional foods from getting on the market and reaching chronically ill populations.

FDA Functional Food Approval

Currently, the Food and Drug Administration (FDA) evaluates functional foods in the same way they do conventional food. As a result, functional food manufacturers cannot make claims stating functional foods have the ability to prevent, manage, or treat illness, because that would classify functional foods as drugs or pharmaceuticals. Drugs undergo much more scrutiny than foods; FDA drug approval requires the completion a “new drug application,” which involves enormous testing and funding [38].

As for food health claims, the FDA only allows manufacturers to state that their food’s health benefits are derived from the food’s “nutritive value” or growth promotion, replacement of nutrient loss, and energy provision [47]. Besides the definition for “nutritive value” being vague, it does not accurately reflect how functional food provides health benefits, which restricts the range of permissible health claims [38].

Specifically, functional food manufacturers must avoid any language that indicates disease reduction. This leads to claims that are confusing, misleading, or even false. For example, instead of saying that a functional food reduces blood cholesterol (which implies that original blood cholesterol was high), food manufacturers would have to say that their product “maintains normal cholesterol levels,” a false statement if the food did lower cholesterol.

IFT adds that “scientific, regulatory, and business frameworks must be in place” in order to evaluate functional foods for efficacy and safety, prevent regulatory error, and improve consumer understanding of these products [38]. Finally, IFT agrees that “traditional definitions and arbitrary distinctions between food and medicine” is an issue that must be addressed in order to properly educate consumers and increase functional food access in markets [38].

Assessment of Functional Food Scientists

At the FFC, we are aware of the amount of time and resources needed to create safe, effective, and good quality functional foods. Scientists who are professional and invested in functional food creation must undergo:

1. Nutritional and biochemical education
2. Scientific research
3. Product development
4. Marketing and investment in all this steps

This process requires years of studies and multimillion dollar investments. We believe that government agencies, such as the U.S. FDA and EU FUFOSSE should be wary of those seeking to manufacture and market functional foods. In other words, we believe that governments should not only judge a manufacturer’s or scientist’s research findings, but also his or her background and experience in this area [38]. Market research has shown that food manufacturers take advantage of legitimate scientific inquiry by, for example, utilizing a prior approved health claim tested by experienced scientists [38]. This process, of course, generates greater profits but compromises the potency of health claims and food

research. Ideally, functional food researchers and manufacturers should be very experienced, professional, and demonstrate their commitment to creating safe, effective, and quality functional foods. As implied above, creating proper functional food is a highly involved and collaborative process, requiring intense dedication and respect for the scientific process. Therefore, government agencies should carefully weigh the intentions of prospective scientists who hope to market and sell functional foods.

Step 4: Get a special label for functional foods

Japan's functional food regulation is unique because each approved functional food is stamped with a FOSHU label. This designation separates functional food products from ordinary food products, allowing for greater clarity and accessibility to consumers. The FOSHU stamp also allows for greater legitimacy among consumers, because it implies that high quality research, funding, and regulation went into that food product. In this way, functional foods or FOSHU have a higher status in Japan than regular foods. The FFC strives to spread this tradition to improve clarity, accessibility, and legitimacy of functional foods across the world.

How new a definition will help create new functional foods.

Bringing more legitimate functional foods to the market will be difficult. However, we believe that establishing a formal definition for functional foods is an important step. When governments and scientists agree on what makes a food "functional," laws and policies can be put in place that encourage research and greater dissemination of products. If the public (which is often guided by personal beliefs and self-education) is properly educated about functional foods, then it will naturally come to welcome functional foods. A standardized definition and legislative legitimacy will give functional food scientists the right and credibility to educate the public. As a result, we believe the world will exhort functional food production and research into the role of diet on health. Ultimately, we consider a new definition for functional food is the first step to bringing quality functional foods to consumers all over the world.

SUMMARY

- Functional food originated in Japan in the 1980s. Food scientists submitted evidence that their foods had "advantageous physiological effects." Approved foods then acquired special FOSHU, or Food for Specific Health Uses, labels.
- Europe, the United States, other countries and various scientific organizations attempted to create their own definitions of functional food. This led to high sales worldwide, but confusion between countries and among the public on the meaning of functional food.
- The Functional Food Center (FFC) defines "functional food" as natural or processed foods that contains known or unknown biologically-active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease. This definition is unique because of its acknowledgement of "bioactive compounds"; or biochemical molecules that improve health through physiological mechanisms. Also, this definition notes that bioactive compounds must be taken in non-toxic amounts, because bioactive compounds have upper limits before they become dangerous.
- The FFC seeks to standardize the functional food definition in order to legitimize functional food science. We also want to formally bring functional foods to markets, improve international communication, and better population health.

TEST QUESTIONS

1. The following term, created by Dr. Stephen DeFelice, is deemed to be somewhat synonymous with functional food:
 - a. Dietary supplement
 - b. Probiotics
 - c. **Nutraceutical**
 - d. Medical Food

2. A food in a U.S. supermarket contains a claim that “it supports immune function and healthy cholesterol levels.” This claim would be considered a:
 - a. Structure/function claim
 - b. **Health claim**
 - c. Nutrient content claim
 - d. Nutritional claim

3. The main difference between functional food and ordinary food is that:
 - e. Functional food comes in the form of a pill or capsule
 - f. Functional food is genetically modified
 - g. Functional food can be consumed safely at any amount
 - h. **Functional food has some health benefit beyond basic nutrition**

List of Abbreviations: Agricultural Research Service, ARS; Food and Drug Administration, FDA; Functional Food Center, FFC; Food for Specific Health Uses, FOSHU; Functional Food Science in Europe, FUFOS; gas chromatography–mass spectrometer, GC-MS; Institute of Food Technologists, IFT; U.S. Department of Agriculture, USDA

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