Theoretical Article **Open Access**

Functional foods classification system: exemplifying through analysis of bioactive compounds

Danik Martirosyan*1,2, Morgan Ekblad1,3

1Functional Food Center, Dallas, TX, USA; 2Functional Food Institute, San Diego, CA, USA; 3University of South Florida Tampa, Florida, USA

***Corresponding Author**: Danik Martirosyan, PhD, Functional Food Institute, San Diego, CA, USA

Submission Date: March 15th, 2022; **Acceptance Date:** March 25th, 2022; **Publication Date**: April 7th, 2022

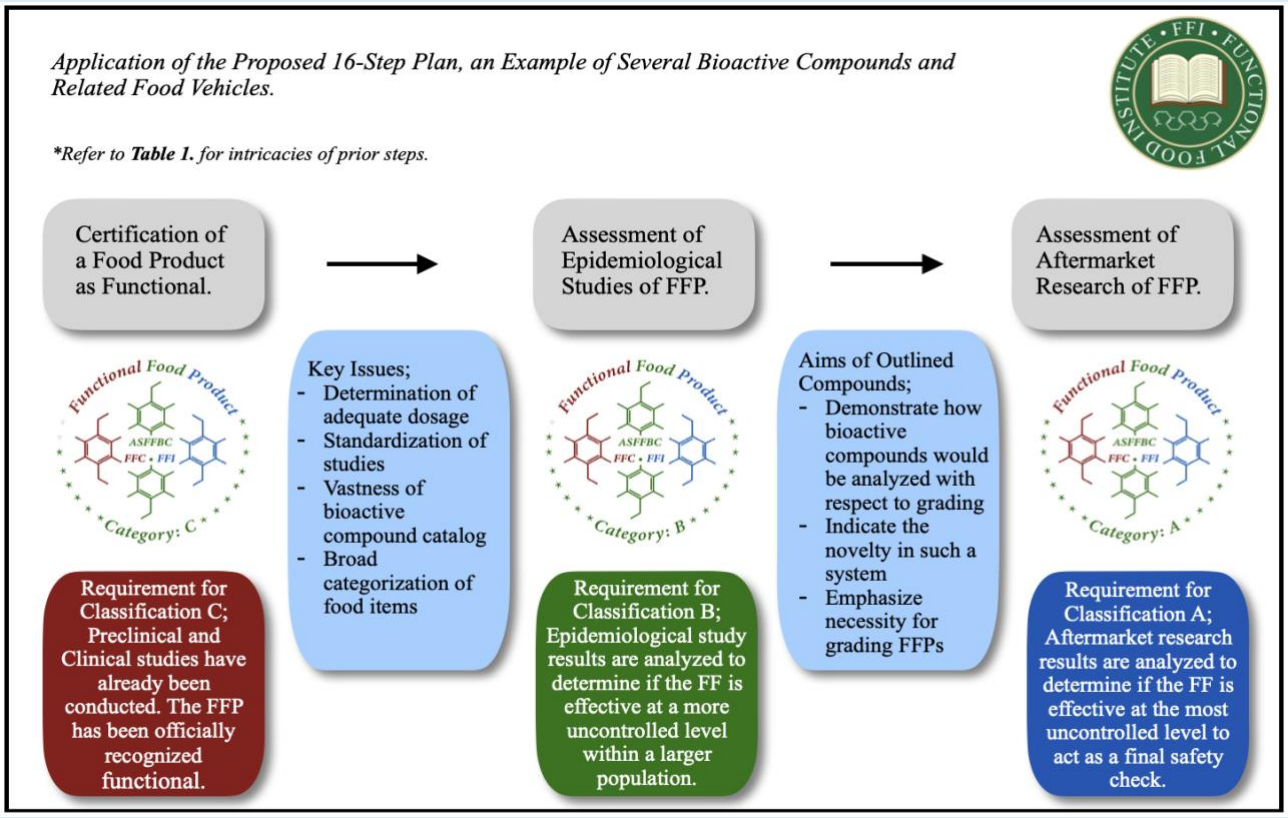
Please cite this article as: Martirosyan D.M., Ekblad M. Functional Foods Classification System: Exemplifying through Analysis of Bioactive Compounds. *Functional Food Science* 2022; 2(4): 94-123. DOI: https://www.doi.org/ffs.v2i4.919

ABSTRACT

The classification of functional foods based on their usefulness in the management of diseases and bodily conditions is currently absent from modern academia. Benefits from a system classifying functional foods by the amount of scholarly research performed on functional foods could be useful in managing diseases, informing the public, and legitimizing functional food as a consistent method for well-being promotion. The purpose of this study is to exemplify a previously proposed 16-step system by which functional foods may be ranked according to which studies have been conducted, highlighting their abilities. Listings would include common chronic diseases affecting first-world individuals; diabetes, obesity, cancer, heart disease, and Alzheimer's/dementia. The proposed system would implement an alphanumeric code of 'A', 'B', or 'C', depending on if foods have undergone epidemiological studies, clinical trials, and aftermarket research, only epidemiological and clinical studies, or have only been certified as a functional food. Current statistics discerning the prevalence of the listed chronic disease are utilized to contextualize the uniqueness of each bioactive compound and demonstrate the variance of effect by functional food products. Additionally, individual bioactive compounds are analyzed, denoting their efficacy in observable trials to better contextualize food function. From the proposed system, many prospective functional food products would not be eligible for classification by standards previously proposed in the 16-step plan. Taking into consideration current literature, the lack of standardized testing and optimal dosage leaves much to be desired in classifying functional food products. This study aims to exemplify a viable system by which functional foods can currently be analyzed and ranked based on empirical research studies. With suitable support from these studies, bioactive compounds and their subsequent food vehicles will be justly classified within an easy-to-

recognize system. As the field of functional food grows, more factors to the analytical process may need to be applied, especially should the definition of functional foods categorize products in a way that aids the FDA's system.

Keywords: Functional Food, Functional Food Classification, Bioactive Compounds, Classification of Bioactive Compounds, Aftermarket research



©FFC 2021. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (http://creativecommons.org/licenses/by/4.0)

INTRODUCTION

Over the past decade, there have been strides made in the field of healthcare specifically pertaining to food. A new branch of dietetics aptly named 'functional food' (FF) has emerged from the field of nutrition, yielding a discipline that focuses on the medical and/or health benefits including the management and risk reduction of disease through food. The definition of functional food has been established already by the Functional Food Center (FFC), however, a classification system for ranking such products is absent from modern knowledge, especially within the United States (U.S.) [1].

To better understand the discrepancies between FFs which may lead to a more holistic analysis, the constituents of such items need to be understood first. FFs are defined by the Functional Food Center/Functional Food Institute as "Natural or processed foods that contain biologically-active compounds; which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [2]. The bioactive compounds in the definition refer to chemicals found in small amounts

within plant/food products that have actions on the body which promote optimal health. In effective doses, these compounds may be able to invoke a positive response within individuals, promoting health in specific conditions [3]. It is important to note that foods containing these bioactive compounds can either occur naturally or be processed. FFs that have been deemed naturally occurring items do not require any industry interference to promote the desired effect, alternatively, processed products do inherently require intervention. Processed FFs most often refer to those which have been chemically modified to either contain a greater or lesser amount of certain bioavailable compounds [4].

The legitimacy of such products is often supported by the use of different trials/studies. Clinical trials, epidemiological studies, and aftermarket studies all may facilitate the establishment of a bioactive compounds placement and validity within the realm of FF. Clinical trials are controlled holistically, where a specific bioactive compound is utilized to manage a set condition within a given population. Epidemiological studies are similar but offer analysis on a more uncontrolled scale. Aftermarket research revolves around how the compounds react within a broad and unfiltered population, providing more realistic data on how food may be accepted on part of the general public [5].

The outlined systems are adequate in determining the legitimacy of FFs on whether they can be certifiably useful or not, however, they do not discern between legitimacy in FFs when compared to each other. As stated previously, there is an inherent lack of classification based on competition and efficacy between FFs. The lack of substantial differentiation between foods categorized as such leads to possible misinformation and communicative issues. This article aims to outline how a prospective bioactive compound would be analyzed by an organization such as the FFC and established as a FF. In doing so, literature can be expanded and steps can be made towards the natural progression of FF utilization. Establishing criteria to classify foods as functionally more beneficial than others with provided examples may allow for a greater understanding of their application [5]. Furthermore, creating a system that legitimizes their role in risk reduction and management plans may cement FFs as a staple in risk reduction and management plans.

Retrieval of Published Studies: Articles found and screened were procured from the Functional Food Center/Functional Food Institute's database, GoogleScholar, PubMed, and FDA listings. Hundreds of articles were viewed for their validity in the study, however, the majority were omitted. The initial content review consisted of upwards of 300 articles. Articles would initially be analyzed for peer review. Should one not have substantial backing, the article would be omitted. Next, articles were analyzed for how current they were. If newer articles studying the same objective were published with reasonable peer review, then older articles would be omitted in favor of more modern data. Finally, articles would be analyzed for their relevance to the study. Upon initial inspection each would seemingly apply to the study, however, they could have contained information that held no academic value to the study. This omitted information is valid, however, did not contribute academically to the contents of the study in a positive or negative respect.

For the articles used in this study, 65, they were stringently viewed and analyzed. To ensure that no articles were duplicated, the transfer and download of each article into a project folder was closely managed, with integrated searches randomly occurring throughout the transfer process. Keywords used to find such articles included the names of chronic conditions, terminology specifically relating to functional food classification,

terminology specifically relating to FOSHU and FDA categorization, and terminology specifically relating to bioactive compounds.

Intricacies of the FFC's 16-step plan

Overview of Proposed System: To create a system in which hierarchy can be easily identified, FFs will be ranked according to an alphanumeric system. The earlier a letter is in the alphabet, the greater the corresponding FFs application is. Differences in research attributed to the food will be denoted by adjustments to the alphanumeric code. A label of 'A' will garner more support than a label of 'B', with this continuing when leveraging 'B' against 'C'. The system will range from 'A', the highest, to 'C', the lowest [5].

There are three key aspects of certifying food as functional that will dictate the classification system. These are clinical, epidemiological, and aftermarket studies. Epidemiological and clinical studies dictate the first two grades in the FFC's 16-step plan for certifying food as functional [5]. On this basis, they are devoted to analyzing the desired bioactive compounds' effects in humans to determine efficacy. In these studies, candidates are chosen due to their afflictions. When attempting to manage a specific disease's symptoms, organisms who are currently affected by the disease need to be observed while ingesting certain amounts of the bioactive compound to discern efficacy. This, however, is not just limited to disease, overall health benefits can be derived from studies such as these, broadening the application for FF use [2]. Other prerogatives include performance enhancement. FFs may offer some intrinsic value for enhancing physical activity. Bioactive compounds, when consumed in certain amounts may offer competitive edges as opposed to organ systems that have not indulged in enhancement. Other forms of testing on bioactive compounds may also include in vivo and in vitro studies [2]. These preliminary excursions will help researchers to determine if consuming these elevated amounts of bioactive compounds is feasible and safe.

Aftermarket classifications of FFs are also important when considering general acceptance of the ranking system. The way by which FFs are assessed through aftermarket evaluation concerning efficacy begs the addition of another form of classification. Studying FF in controlled environments is one thing, but exposing the public to the FF to consume daily with no control over dosage and whether or not a person has the desired condition can lead to varying results. To deem a food as functional, it must exhibit the desired effects in aftermarket research, an uncontrolled environment. This final analysis would be the last part of the 16-step plan, commencing with grade 'A' classification once completed [5].

The basis of the system in ranking foods 'A', 'B', and 'C' will display this characteristic in an easily digestible manner. Foods that have had clinical, epidemiological studies, and aftermarket research will be denoted with the classification of 'A'. This signifies that their use is acceptable and found to promote an overall positive net health outcome. Foods that are lacking in aftermarket research but have undergone epidemiological and clinical studies will be classified as 'B'. This is to display the fact that the food items in question have been observed in particular studies, however, it has not been analyzed in a different environment from the said study. This grade will commonly be observed with foods lacking aftermarket research but having completed epidemiological/clinical studies as there is a chronology to the 16-step plan illustrated in **Table 1**. Foods that have not undergone both epidemiological studies and aftermarket research but have completed clinical studies and been certified as a FF will be classified as 'C'. At this point, the food's

functionality is relatively known. There are links to the positive effects of ingestion, but these remain to be observed in wider settings.

It is important to note that the ranking would be given to the food vehicle, and not the specific bioactive compound itself. This presents a unique opportunity for synthesized FFs to attain desired ranks, however, specificity into components is required for fairness [5]. Furthermore, a system for classifying the efficacy of FFs needs to be based on relevant statistics. Diseases occur in varying rates and prevalence, creating a diverse landscape of management. Despite there being no official classification system for FF in the U.S. as of yet, individuals may seek certain foods for rumored beneficial health effects to aid in pertinent afflictions [1].

A decisive factor in analyzing the efficacy of FFs is bioactive compounds. Bioactive compounds are defined to be non-essential substances present in foods that can regulate metabolic processes towards a net positive health outcome. These are not limited to the three basic macronutrient primary metabolites of carbohydrates, lipids, and proteins. Rather, they can be any compound present in food items. One common umbrella category for these bioactive compounds includes phytochemicals, often found in plants. Other micronutrients to this degree are divided into six categories, namely flavonoids, phenolic acids, alkaloids, saponins, polysaccharides, and others [6]. Each of these chemicals possesses certain valued properties that when applied correctly, deems a food as functional. Contrasting the green portion for bioactive components are those derived from meat, which is rich in bioactive components, primarily taurine, l-carnitine, choline, alpha-lipoic acid, conjugated linoleic acid, glutathione, creatine, coenzyme Q10, and bioactive peptides [7]. Given proper clinical testing, their presence in certain foods may deem those items subsequently as 'functional'. Of course, suitable compounds are not limited to those mentioned above. Specific bioactive compounds that have been analyzed within a clinical setting and deemed appropriate for human consumption can be classified on the list [e].

Current Means for Regulation and Classification: Despite the acknowledgment of the outlined concept, agreement on one single definition for FFs cannot be reached globally. Japan, as a country, affirms FFs placement and legitimacy in diet, however, it seems to be the only nation doing so [1]. The presiding body over 'functional food' in Japan, the Ministry of Health and Welfare, refers to them as 'food for specific health use' (FOSHU). By definition, FOSHU is "foods that are expected to have a specific health effect due to relevant constituents, or foods from which allergens have been removed, and foods where the effect of such an addition or removal has been scientifically evaluated, and permission has been granted to make claims regarding the specific beneficial effects on health expected from their consumption." Albeit, the individual component cannot be certified in singularity [8]. The final food product's efficacy is necessary for the product to be certified as FOSHU. Countries in Europe and the United States's Food and Drug Administration (FDA) both do not have a formal legislative definition for FFs. With the latter more recently relying on the FFC for legitimacy. The common factor either barring or promoting FF production in countries seems to be related to clinical trials. Japan requires that foods deemed to be functional must first go through clinical trials which would reaffirm such. Europe has a similar requirement, however, it is optional, only being required for the food item to receive one of the two claims; health claim [1]. Without a cohesive definition, costly clinical trials may act as a

deterrent for food developers, who could more easily profit from just a nutrition claim.

Healthcare systems and organizations within the U.S. currently understand the implications of FFs, but do not promote them outright for the management of a disease. This is most commonly seen in the difference between the FDA's claim systems and FOSHU. Unlike Japan, the U.S. approves claims based on a disease-food relationship model rather than on an independent product basis [9]. This highlights the primary issue of identification of bioactive compounds within FFs, or rather, the lack thereof. Being that the U.S.'s claim-based system does not require an identification of the specific bioactive compound, this may often create disarray as only the product needs a health label. In contrast, FOSHU identifies the active ingredient. Without proper identification, the healthcare system in the U.S. cannot be expected to utilize FFs to their fullest potential. Mention of such foods are made known by private practices, however, their implementation into the standard procedure is relatively unaccounted for. Due to improper identification methods, it would be difficult to truly assess the efficacy of FFs with the current system, calling for a ranking system's construction.

While the FDA has only two types of health claims, Japan has five subcategory iterations of FOSHU. The FDA breaks down its health claims into two avenues, not including outright rejection, these being authorized and qualified claims. Authorized health claims have been confirmed by researchers and science that they are legitimate in the relationship between food and disease. Alternatively, qualified claims are supported by some evidence but do not meet the agreed standard. These are often accompanied by a disclaimer to not mislead consumers [3]. Contrasting the FDA's labels are the five subcategories of FOSHU; regular, standardized, risk-reduction, reauthorized, and qualified. Regular FOSHU has an apt compound and completes a full evaluation process. Standardized FOSHU only contains compounds that fall in a predetermined dosage range set by the government. Risk-reduction FOSHU refers to compounds that have been proven to reduce the risk of disease. Reauthorized FOSHU are products that have already been confirmed but want to alter a trait of the functional food product (FFP). Qualified FOSHU refers to a product that contains an ingredient with an unknown mechanism but has been observed to promote health benefits [3,5].

Instead of promoting food products, many healthcare providers actively promote pharmaceuticals. By no means are prescribed medications inadequate, however, consuming FFs may only serve to bolster good health in people afraid of developing a chronic condition, viral disease, or simply wanting to promote positive health [2]. There have been recent suggestions of global medical overuse, signifying that FFs may be an adequate form of management when other medications are seemingly redundant [10]. The prospective FFs in junction with their bioactive compounds will be ranked into tiers based on scholarly research applied. A system such as this is meant to provide the U.S. with a classification order to better contextualize food vehicle use concerning bioactive compounds effects in various conditions. The process is meant to provide food manufacturers within the U.S. an outlet to better convey the functionality of their products and create an expedited process to better equip the public with knowledge.

Table 1. 16-step plan for the certification and classification of FFPs [5].

FFC 16-step Plan	
Step Number	**Description of Step to Regulate and Classify FFPs**
1	**Establish goal for the FFP**
2	**Determine relevant BC(s)**
3	**Establish an appropriate dosage for BC(s)**
4	**Determine specific pathways and mechanisms of action**
5	**Establish relevant biomarker(s)**
6	**Choose an appropriate food vehicle to administer BC(s)**
7	**Provide preclinical studies on efficacy and safety**
8	**Provide clinical trials on dosage, efficacy, and safety**
9	**Create a special label detailing consumption of specific FFP**
10	**Publish data in preferably open access journals**
11	**Educate the market and consumer of FFP implications on health**
12	**Send information to credible third parties such as the FDA**
13	**Official establishment of the accredited FFP**
14	**Release FF to market (Classification grade of 'C')**
15	**Provide epidemiological studies (Classification grade of 'B')**
16	**Provide aftermarket research (Classification grade of 'A')**

Contextualization of Chronic Disease Variance: Several infamous chronic conditions seem to appear in great prevalence within the U.S.. The chronic diseases outlined to contextualize issues surrounding health are as follows; cancer, heart disease, Alzheimer's/Dementias, diabetes, and obesity. Some conditions may occur in tandem with others, meaning it is imperative to view chronic diseases both individually and jointly for any correspondences that could be relevant. This is due to the high frequency at which multiple conditions are present in the U.S. In the year 2018, it was reported that roughly 27.2% of all U.S. adults presented with multiple chronic conditions. The presence of multiple chronic conditions may imply a great risk of both mortality and morbidity [11]. Over the past decade, this trend has been increasing incrementally, signaling an inherent issue with health. Thus, a classification system for empirically supported FFPs is imperative.

Cancer has some of the highest metrics in terms of prevalence. As of 2015, cancer afflicts over 1.5 million individuals in the U.S., not including non-melanoma skin cancer. As the population within the U.S. ages, this value is set to increase exponentially. However, this is not associated with the risk of cancer becoming greater, rather as a byproduct of a growing population. It is estimated that by the year 2050, the former value of 1.5 million will increase to roughly 2.2 million individuals diagnosed with cancers [12].

Another notable condition similar in stature to cancer is cardiovascular disease, more specifically, ischemic heart disease. Cardiovascular disease may lead to other fatal complications, such as strokes. In the United States alone, roughly 18.2 million individuals aged 20 and older have been diagnosed with cardiovascular disease. This metric only has room to increase currently as the possibility for individuals going undiagnosed or

misdiagnosed is plausible [13]. These statistics are slightly less worrisome, as their rates are possibly decreasing when leveraged against those of cancer [14]. Regardless, one reason for the appreciation of both values numerically without reference to proportion is due to an aging population. So, while it is positive that rates are decreasing, the pure amount of individuals affected leaves much to be desired.

Alzheimer's and dementia have also been displaying worrying trends. Currently, roughly 46.8 million individuals worldwide are afflicted with dementia. This metric is estimated to increase to 74.7 million by the year 2030 [15]. Alzheimer's only constitutes a small subsection of this figure, with the disease being characterized further by other variants. Multiple FFP's may see benefit on part of the user given how each may utilize different mechanisms of action.

The final two chronic diseases taken into consideration in this initial classification scheme are obesity and diabetes. While individual conditions in their own right, heightened rates of presentation together have spurred the coinage of the term 'diabesity' [16]. Despite this joint term, obesity is a major precursor for many chronic conditions. Globally, approximately one billion adults are overweight, with 300 million of them being clinically obese. High rates of incidence naturally coincide with high rates of mortality. It was noted that at least 2.8 million adults die each year due to complications related to an obesity condition. Excessive weight gain has been attributed to 44% of the diabetes burden, 23% of heart disease, and a range of 7-41% in cancers. Furthermore, its incidence is seemingly on the rise, with it nearly doubling between 1980 and 2008 [17]. While not being directly attributable to obesity, certain deaths due to heart disease or diabetes may be indirectly linked to being clinically obese.

Diabetes, similar in precedence to obesity, currently affects roughly 415 million individuals globally [16]. Like obesity, its implication for other acute conditions is concerning, as these would also be on the rise, naturally, due to increased rates. Trends over the last 50 years signify sustained and continual growth as between 1958 and 2015 there was an over 20 million jump in incidence [18]. In observing the sheer plausible increase of individuals with chronic disease, it is fair to assume a greater need for understanding of foods' functionality. As more people become diagnosed with common diseases, a general uptick in sheer numbers of negative health can be assumed for the coming future overall.

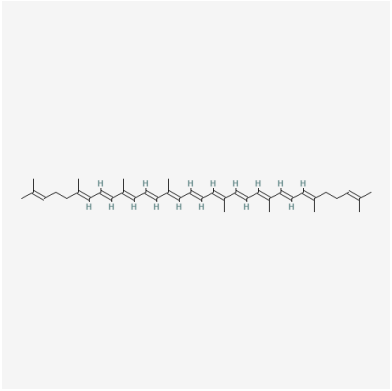
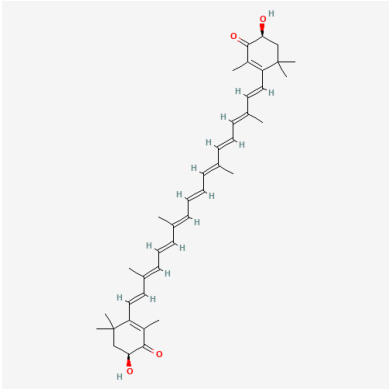
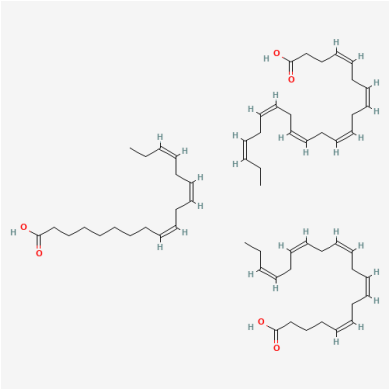
Relevant Bioactive Compounds Present and Dosage Feasibility: While non-essential, bioactive compounds found in foods offer a vast array of health benefits given the correct dosage. They do this by regulating and aiding in metabolic processes towards a net positive health outcome. Most commonly their primary function is interaction within cellular processes, some distinct bioactive compounds may foment binding processes which the body may use to its advantage. Some of which involve the binding to toxins or carcinogens present in the body due to ingestion or other means [19]. Most commonly present in glycosylated, esterified, thiolated, or hydroxylated forms, bioactive compounds serve to promote well-being through intra-bodily interactions.

Overview of Bioactive Compound Food Vehicle Providers: There are two distinct food groups that bioactive components may be derived from, these being plants and animal products. In plants, bioactive compounds are categorized under the umbrella term 'phytochemicals', which are more broadly named secondary metabolites. Currently, there are upwards of 4,000 phytochemicals cataloged, with only about 150

studied vigorously. This indicates that research into this topic is in its infancy, justifying more studies to be conducted to better analyze their effects. Secondary metabolites may be broken down into three distinct categories; terpenes, phenolics, and nitrogen-containing compounds [19]. Each of these subcategories has various other categories outlined beneath them, however, the three listed provide justification for the continual categories listed. It is important to note that phytochemicals are not present in food items in singularity, there is often a mixture of many compounds housed within the food vehicle. Thus, a certain FF high in concentration in several bioactive compounds may exhibit health effects in multiple conditions, however, not equally. Some examples of bioactive compound-rich food items include whole grains, oats, vegetables, and fruits.

In animals, bioactive compounds may be necessary for the internal workings of the host or provide positive effects in those who consume them. These compounds may be observed in their entirety or the form of hydrolysates, a mixture of different peptides and amino acids. Both have been observed to promote various biological activities that may be deemed beneficial to those suffering from a disease. Some examples of animal-derived bioactive compounds are mammalian milk, meats, or other various dairy products [19]. In **Table 2**, there are examples of some known chemical structures for common bioactive compounds. Some of which are found primarily in animals and others in plants, helping to highlight the necessity for a distinction of use due to observable similarity.

Table 2. Exemplary bioactive compounds for contextual purposes [20,21,22].

Exemplary Bioactive Compounds		
Lycopene	**Astaxanthin**	**Omega-3's**
		

Introduction to FDA Food Categories: The FDA has created various food archetypes that marketed products fit within the U.S. [23]. Each classification comes with certain parameters, thus the specificity of how food vehicles fit into FDA classifications is crucial as it will help common markets better assimilate to the FFC's new classification system. The two systems are independent, but contextualizing how bioactive compounds are already present in the market may be beneficial in assigning classifications to FF vehicles. Below is an abridged list table for one published by the FDA displaying each of their food categories and how they are expounded with reference to possible bioactive compounds present.

Table 3. Adapted list of FDA food categories Dairy-Cheese, Mixed Ingredient Dishes, and Other Combination Foods, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Dairy - Cheese			
5, 6, 7, 8, 9, 10	**Soft Cheeses**	**Cream cheese, pasteurized spreadable cheeses, brie, mold-ripened cheeses, mozzarella cheeses, and other Pasta Filata cheeses, Cottage cheese, Feta, and Feta-style cheeses**	**Probiotics**
Mixed Ingredient Dishes			
129	**Grain-based Meals/Entree, Dry-Mix**	**Shelf-stable meals from dry mix which contain grains**	**Fiber**
132	**Grain-based Dishes**	**Prepared noodle, rice, and pasta dishes**	**Fiber**
133	**Vegetable-based Dishes**	**Prepared vegetable-based or vegetarian mixed ingredient dishes and entrees**	**β-carotene, Lutein, Isothiocyanates**
136, 137	**Seafood-based Dishes – With/Without Breading**	**Prepared, seafood-based mixed ingredient dishes and entrees, with/without breading**	**Astaxanthin, Omega-3's**
Other Combination Foods			
147	**Tacos, Burritos and Enchiladas**	**Tacos, burritos, enchiladas, fajitas, taquitos, nachos, quesadillas, etc.**	**Fiber, Astaxanthin, Omega-3's**

Probiotics: Probiotics, differing from many other bioactive compounds listed, comprises live organisms intended to promote health upon consumption. As other bioactive compounds listed are inert, this provides a difficult activity in classifying and regulating FF items containing such organisms. When considered against bioactive compounds like the aforementioned isothiocyanates and flavonoids, each having many subunits, probiotics need to be analyzed on a more specific basis due to each organism having a plausibly different structure. This would afford probiotics many preclinical, clinical, and epidemiological studies as they cannot be generalized to the same extent as other compounds. Probiotics have been noted to promote the health of internal ecosystems, which may prevent chronic diseases such as cancer [24]. They are commonly found in yogurts and soft cheeses. When referenced against the FDA's **Tables 3 and 4**, they may be prevalent in soft cheeses, sauerkraut, pickled vegetables, vegetable juices, and select bread items not using yeast as an ingredient [23]. In preclinical studies, the use of probiotics is different from other bioactive compounds. Firstly, they need to be studied similarly to how bioactive compounds are analyzed in the initial steps of the 16-step

plan. Their mechanisms of action, resistance to antibiotics, and pathogenic properties need to be analyzed first. This may be conducted in alignment with other bioactive compounds in the first six steps of the 16-step process, however, it needs to be more vigilant than normal as these are potentially hazardous microbes. In many species of probiotics in preclinical trials, a dosage range of 20 to 40 mg/kg varying weekly or biweekly has been observed to induce positive effects in reducing the risk of colorectal carcinogenesis. Some of the probiotic species include, but are not limited to, *Clostridium butyricum, Bacillus polyfermenticus,* and *Lactobacillus acidophilus LaVK2* with *Bifidobacterium bifidum BbVK3.* Furthermore, there may be opportunities for single doses measuring between 15 and 100 mg/kg. These would be present in strains similar to *L casei and L rhamnosus IMC501.* Notably, the *L rhamnosus IMC501* was subjected upon the final experimental day, alluding to the notion of prior consistent dosages to be a prerequisite for apt aid [25]. In clinical trials, probiotics have been observed to aid in digestive systems and ease associated symptoms. Specifically, the duration of diarrhea was reduced by an average of 24 hours, indicative of probiotic's fulfillment of both the FFC's definitions when considered against chemoprotective effects noted in preclinical trials [26]. Further supplementation of approximately one billion lactobacilli per day decreases enzyme activity for carcinogenesis. Clinical settings have confirmed that different strains of probiotics can produce different enzymes to be used by the body. Some of which are chemoprotective against adverse events in heart disease [27]. When considering epidemiological data, probiotics' use in studies has been somewhat limited. One such study found that despite high-fat intake, colon cancer was incidentally lower in Finland than in other countries. This was attributed to the high consumption of dairy products [28]. Reaffirming this notion are hypothetical mechanisms by which probiotics may protect against cancer. These include binding to mutagenic compounds, inhibiting the prevalence of procarcinogens, and deactivating carcinogens [29]. Each effect may be dependent on species, meaning overall the bioactive compound field has not been well optimized. In certain instances, probiotics should not be used according to known clinical data. If the patient is undergoing immunosuppressive treatment or happens to be a premature baby, then the use of probiotics is advised against. These factors, amongst others, pose possible increases to risk through previous health compromises [27]. The classification that can be attributed to probiotics as a genre would be a grade of unclassified. Despite epidemiological studies having been conducted, the variability from different genres leaves much to be desired. Each species needs to be considered on an individual basis. This of course would need to be initially outlined in steps one through six, but still poses a daunting task. One aspect that may hinder probiotic FFPs promotion within the 16-steps is the hypothetical mechanisms of action. Step four of the proposed 16-step process states that the mechanism of action must be completely understood to guarantee safety [5]. Should many observable probiotics have only a hypothetical answer for this query, then they may proceed no further in the process until confirmation. Furthermore, the vast range of dosages leaves room for error and cannot be considered standardized unless explicitly stated to induce certain effects. FFPs that contain adequate amounts of a future defined dosage may be subject to a grade of 'C', however, until then it is likely that they will struggle with certification simply due to the field being vast.

Fiber: Fiber is found commonly in beans, cruciferous vegetables, berries, and whole grains. It has been

observed to induce chemoprotective effects against cancer, cardiovascular disease, diabetes, and obesity. When referenced against the FDA-inspired **Tables 3 and 7**, fiber may be found in olives, canned and condensed soup, canned ready-to-eat soup, ready-to-eat cereal flakes, ready-to-eat cereal puffs, rye bread, tortilla wraps, and hard taco shells [23]. Many of these items relate to grains, indicating that to reach a therapeutic threshold, then fiber may be used as an additive to create processed FFPs. The status of fiber within the realm of academia is well explored, however, many models do not fit a classic in vitro/in vivo one desired by the 16-step process. Observational and preclinical studies on fiber's efficacy in the reduction of select cancers have been inconclusive [30]. In clinical studies, dosages of 500 mg administered three times a day induced a mean 1.6% loss in body weight. A natural fiber complex, IQP G-002AS, was utilized to induce such effects [31]. Coinciding with obesity, high fiber intake may also be relevant to the incidence of type 2 diabetes mellitus. A meta-analysis of clinical studies indicates that comparatively, the highest versus lowest dietary fiber intake yielded a statistically significant reduction for relative risk in those who consumed more [32]. Furthermore, a meta-analysis of randomized, controlled clinical trials indicated that increased dietary fiber consumption may provide apt means for blood pressure reduction in patients diagnosed with hypertension. This is indicative of fiber's usefulness in possibly managing symptoms of heart disease, as well as reducing the risk for adverse events. To induce such positive effects, an intervention period would most likely be required, as diastolic and systolic blood pressure both experienced significant changes in clinical trials that had a duration of eight weeks or longer. In trials with a shorter intervention period, the associated effects were less prominent [33]. In epidemiological studies, prior assertions are supported, as diets rich in dietary fiber have been associated with reduced risk of cancer (colon, rectum, and breast), diabetes, and cardiovascular disease [34]. Other meta-analyses have analyzed fiber as a bioactive compound, denoting that dosages ranging from 12 to 28 g/day were observed to diminish carcinogenesis and decrease the risk for intestinal cancer [24]. A key issue with fibers application in FF, is some inconclusive information. As mentioned earlier, preclinical trials were observed to be inconclusive when considering fibers' application in breast cancer. In order to avoid failure in clinical settings, the initial proposals would need to account for already inconclusive data. Further, some fiber complexes that are unnatural compared to IQP G-002AS may exhibit some tendencies of fat malabsorption in obese patients [31]. The first six steps would account for implausible uses at the time and maintain to what is understood from a mechanistic standpoint. Another key issue with fibers used in FFPs is the lack of a definitive amount. The wide variance of dosages associated with products means that health effects cannot be standardized. One condition may see biomarker adjustment while another does not. This lack of standardization would be detrimental to both FFPs and the public, as some may be under the illusion of aid when in reality receiving no benefit. One way to work around this would be the application of different polysaccharides, as fiber is composed of many. Until a standard dose is agreed upon, fiber may see no classification label. But, if one is, then FFPs containing an adequate amount would most likely be given a grade of 'B'. Overwhelming evidence suggests benefit from fiber consumption, meaning that once the initial six-step proposal is completed, FFPs containing fiber would most likely have an easier time being certified than ones pertaining to other bioactive compounds.

Table 4. Adapted list of FDA food categories Fruits, Vegetables, and Legumes, and Salads, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Fruits, Vegetables, and Legumes			
18	**Frozen Vegetables and Legumes**	**Frozen vegetables and legumes in sauces or seasoning**	**α-carotene, β-carotene, Lycopene, Isothiocyanates, and Lutein**
19	**Canned Vegetables**	**Canned and bottled vegetables, legumes, and creamed vegetables**	**α-carotene, β-carotene, Lycopene, Isothiocyanates, and Lutein**
20	**Sauerkraut**	**Refrigerated or canned**	**α-carotene, Isothiocyanates, Probiotics**
21, 22	**Olives, with/without Additions**	**Olives in brine or water**	**Fiber**
23	**Pickled Vegetables**	**Pickled vegetables such as peppers, cucumbers, and beets, excluding olives and sauerkraut.**	**Probiotics**
24	**Vegetable Juice**	**Vegetable-based juices**	**α-carotene, β-carotene, Lutein, Probiotics**
25	**Battered/Breaded Vegetables**	**Fried or baked vegetables**	**Isothiocyanates**
Salads			
138, 139	**Lettuce/Green Salads; With Additions – With/Without Dressing**	**Green salads with additions/toppings containing added sodium, with/without dressing**	**β-carotene, Lutein, Isothiocyanates**
140	**Lettuce/Green Salads: With Additions – Without Dressing**	**Green salads with dressing and without additions/toppings containing added sodium**	**β-carotene, Lutein, Isothiocyanates**
141	**Seafood/Meat-Based Salads**	**Refrigerated, prepared seafood, meat, and poultry-based salads**	**Astaxanthin, Omega-3's, β-carotene, Lutein, Isothiocyanates**
142	**Grain/Vegetable-Based Salads**	**Refrigerated, prepared grain and vegetable-based salads**	**Fiber, β-carotene, Lutein, Isothiocyanates**

Alpha-Carotene: Foods rich in the carotenoid α-carotene have been studied for efficacy within the context of the FFCs definition for FFs. This bioactive compound was chosen due to its commonality in the human diet when referring to the over 700 different carotenoids. In order to better understand the compound's placement within food items, comparing it against chronic diseases such as cardiovascular disease and cancer, namely those of the skin, lung, liver, and colorectal, is fundamental to understanding within the context of the table above [24].

Within clinical studies, α-carotene focuses on risk reduction in the aforementioned chronic diseases aligning with one of the FFC's definitions [35]. Some of the epidemiological studies have been conclusive while others have not, meaning that foods containing this compound are disjointed when classified by the new 16-step plan [5]. The discussion of α-carotene in this context provides a complex example of how ambiguity is managed in this system. Traditionally, for certification of 'C', the FF needs to be certified as such after completion of clinical trials. The absence of many trials denotes issues with classification. Preclinical and clinical studies that have been conducted to date indicate a significant association between α-carotene and the plausible risk reduction of cancer through decreased proliferation. In mice studies, the rate of cancer in those treated with α-carotene and the control dropped from 69% to 25% [24]. This signifies a substantial decrease in risk, suggesting its application in managing cancer yields a plausible indication of use. Furthermore, intake of α-carotene has been observed to decrease the risk of cardiovascular disease in high amounts. For ingestive amounts to reach these desired effects, roughly calculated from murine values, 10.4 mg/60-kg per day should be ample in achieving therapy [36]. It is worth noting that this figure would need to be confirmed and readjusted as the FFs containing such a compound proceed further through the 16 step plan [5]. Foods containing adequate amounts of the bioactive compound include orange vegetables such as carrots, pumpkins, and squashes. When referencing the above FDA-inspired **Tables 4 and 6**, products containing the compound may include those such as canned vegetables, sauerkraut, vegetable juices, canned condensed soups, canned ready-to-eat soups, dry mix soups, vegetable/fruit-based dips, and select bread [23]. Each, provided the FFPs contained an adequate amount of α-carotene, could receive a preliminary classification of 'C'. However, this requires a standardized dosage to be found, if it is not, then no grade can be associated with α-carotene. As the compound has been noted in clinical trials, this grade hinges on the notion of acceptance by the FFC. While epidemiological studies have been conducted, some were inconclusive in findings, denoting some inherent issue with the compound's use that needs to be analyzed [35]. The limitation of the bioactive compounds clinical trial adaptations can be seen in how few studies there are relating it to symptom management. Should no classification be awarded due to more information being necessary, then more clinical trials would be required to better secure dosage and perceived benefits. This is most likely, as the relative absence of α-carotene from trials altogether indicates a further expansion of knowledge pertaining to the compound before its institution within FFPs. Demonstrated in this paragraph is the analysis associated with the grading process, and an example classification being provided. Each bioactive compound and the associated food product requires comprehensive analysis, as studies may be conducted out of order due to the time it will take to implement this system and acceptance of it.

Beta-Carotene: Beta carotene, while similar in structure to α-carotene, is found in both leafy green and orange/yellow vegetables. Some of which include but are not limited to, sweet potatoes, spinach, and carrots. Based on the FDA-inspired **Tables 3, 4, and 6**, there are several food categories in which β-carotene may manifest to a substantial degree. These include canned vegetables, vegetable juices, canned condensed soups, canned ready-to-eat soups, Mexican-style sauces, and condiments [23]. Of course, the provisional grade would be based on a singular product basis, meaning each would need to be observed to have a specific amount of

bioactive compound contained to induce an empirical benefit to the consumer. Beta carotene, like its alpha counterpart, has been observed to exhibit therapeutic tendencies when leveraged against chronic diseases such as cancer and cardiovascular disease. Preclinical studies have already indicated that 200 to 400 nmol of β-carotene may drop the risk of cancer from 69% to 13% [24]. Increasingly in likeness, β-carotene has already undergone epidemiological trials, deemed more conclusive than those committed with α-carotene. In an observational epidemiologic study, high serum levels of total carotene, composed of both alpha and beta, stipulated a reduced risk of cardiovascular disease. Furthermore, in an observational study, lowered serum concentrations of β-carotene on its own were strongly related to an increased risk of cardiovascular disease mortality [37]. From clinical trials associated with β-carotene, a dosage of roughly 5 mg/kg body weight per day, gap junction communication can be observed to significantly increase. A major concern for β-carotene during clinical trials was its possible inhibition of other carotenoids and nutrient uptake by the body [38]. However, there were no recorded results suggesting this to be true. Regardless, it may be unwise to ingest exceedingly high doses of β-carotene as enzymatic functions may be altered with respect to other bioactive compounds [38]. This figure varies greatly from the aforementioned, suggesting that some refinement is required before finding an optimal dose that can be utilized by any individual. Some aftermarket research has been conducted, however, these more pertain to the characteristics of β-carotene's market and not the effects on people. As of current, like α-carotene, products containing suitable amounts of β-carotene can only plausibly be given the classification of 'B' contingent on adhering to a standardized dosage. The presence of epidemiological trials helps to raise its stature as indicated by the previous grade, however, the conflict of dosage leaves much to be desired. No classification is far more likely when scrutinized by the FFC as there is no standardized dosage. The classification of later ranks such as 'A', 'B', and 'C' is contingent on the dosage's legitimacy and standardization.

Isothiocyanates: Isothiocyanates, found in abundance in cruciferous vegetables such as broccoli and cabbage, exhibited chemoprotective effects against numerous conditions such as cancer and diabetes. When referring to its commonality in diet in accordance with the FDA's **Tables 3 and 4**, isothiocyanates may be found in canned vegetables, sauerkraut, and battered/breaded vegetables [23]. The category of isothiocyanates may be broken down even further, as it has many other sub-categories that may have differing effects. Studies committed include pre-clinical, clinical, and limited epidemiological studies. In murine analysis, administration of 10 mg/ml was adequate in inducing apoptosis [24]. Further human clinical trials have been observed to induce positive effects in multiple forms of cancer, diabetes, and heart disease. Dosages ranging from 514 µmol/day isothiocyanates to 250 g/day of food vehicles are found to offer complex administration specifics in cancer alone. Each application of isothiocyanates was observed to differ in response specific to certain cancers. Some such invoked responses were reduction of inflammation and specific biomarkers, as well as increased DNA repair. In diabetes, 150 µmol daily was enough to observe improved fasting in obese participants. Varying this metric, lessening it to 22.5 µmol daily may reduce inflammation biomarkers and serum insulin. Further, in heart disease, dosages ranging from 6 g/day to 400 g/week may improve systolic and diastolic blood pressure [39]. Of the few epidemiological studies conducted, there are high associated correlations with

the consumption of cruciferous vegetables and decreased risk of cancer [40]. A key issue with the studies associated with isothiocyanates is that they can be specified further into sub-categories. This dictates that each study is not equal in its implications when referencing food vehicles. Some may utilize more readily available isothiocyanates than others. Further, each may have a varied therapeutic range in reference to dosage. Select isothiocyanates may prove ineffective in managing conditions characterized by oxidative and inflammatory stress [39]. Each sub-category, once analyzed further, may require different doses, meaning a constant cannot be applied. For the certification of food vehicles containing the bioactive compound to be officiated by governmental agencies, then the dosage needs to be strictly defined in the case of each subcategory. Unless specified, then products containing isothiocyanates may not induce the desired effect. Currently, the highest grade that could be suggested for isothiocyanates by the FFC is 'C'. Although, no grade at all would be better suited as specificity and dosage cannot be assured. More data may become relevant in the future, altering this grade. There are numerous clinical trials supporting efficacy, however, the vastly different isothiocyanates dictate that some form of standardization needs to be instituted. Each would need to be subject, in their proper food vehicles to the 16-step process. While this would be tedious and long, it is important in guaranteeing safety. A classification of 'B' would be unjustifiable, as there have not been many epidemiological trials.

Lutein: Lutein, found in leafy green vegetables and fruits, can also be observed in reference to FDA **Tables 3, 4, and 6** in canned vegetables, vegetable juices, and canned ready-to-eat soups depending on the added ingredients [23]. Again, contextualizing lutein based on chronic diseases is best as comparisons are readily available. In clinical studies, it was observed that 9 to 25 mg/day of lutein can reduce the risk of certain cancers by up to 53% [24]. Furthermore, other studies have been suggestive of the effects of the compound in helping the ocularly impaired. While benefits could not be observed for the average individual, it was suggested that subjects suffering from clinically sub-baseline vision may see benefits [41]. Much of lutein's protective capabilities are thought to focus on the eye, as made evident by the number of studies committed. Murine studies indicate that combining lutein with insulin may prevent the development of cataracts, suggesting use in diabetes symptom management [42]. Straying from the previous list of chronic diseases, a focus on the eye will see the most benefit for lutein's grading as it is a focus of the scientific community. Epidemiological studies have indicated an inverse risk between ingestion of high lutein content foods and the development of age-related macular degeneration. It was observed that individuals within the highest quintile of lutein ingestion were 57% lower in risk compared to those of lower ingestion amounts [43]. Clinical studies into the efficacy of lutein in reference to cardiovascular disease has indicated promise, as those observed to have high serum lutein levels (0.42 µmol/l) would often have less than 80% arterial wall thickening compared to those of lower serum value. Thus indicating some use of lutein in combating heart disease [44]. The dosage of lutein still needs to be confirmed in reference to cancer, diabetes, and eye disorders. Each disease sees a different value within the previously stated range, meaning a set definition is needed to continue. Further, other varieties of antioxidants and carotenoids may not induce the same desired effects as lutein [44]. Should this be established, the FFC can yield products that contain that specific

amount of lutein a classification of 'C'. The prospect of its effects on both risk reduction and symptom management, namely of eye disorders derived from diabetes, gives confidence that lutein can continue through the 16-step process and commit further to epidemiological and aftermarket research. As there are already some epidemiological studies committed, parameters should be easy to reinstate and commit to more within the new set of guidelines once an adequate dosage has been established. Naturally, this would indicate a classification level of 'B', however with conflicting dosage measurements, FFPs cannot be certified until a dose is decided upon by a regulatory body.

Table 5. Adapted list of FDA food categories Nuts and Seeds and Snacks, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Nuts and Seeds			
32	**Nut/Seed Butters and Pastes**	**Nut butters and seed pastes**	**Flavonoids, Omega-3's**
Snacks			
117	**Snack Mixes**	**Multiple component dry snack mix containing cereal, nuts, or dried fruit**	**Flavonoids, Omega-3's**

Flavonoids: Flavonoids, like isothiocyanates, have many derivatives that may pose issues with definitive product creation. Specificity is important, as products can be evaluated on particular constituents, rather than the broad category of flavonoids. Bioactive compounds falling under the umbrella term of flavonoids may be found in a diverse variety of food vehicles such as berries, onion, and dark chocolate. When this information is referenced against FDA **Tables 5, 6, and 7**, many seemingly appear to have prospective amounts of flavonoids. Some categories include nut/seed butters and pastes, canned condensed soup, canned ready-to-eat soup, bean-based dips, ready-to-eat cereal flakes, ready-to-eat cereal puffs, and white bread [23]. There are most likely other categories that flavonoids apply to, dependent on the use of their vehicle as an added ingredient. To discern their usefulness in diet, pre-clinical, clinical, and epidemiological studies have been conducted. In pre-clinical trials, the application of flavonoids was documented to inhibit cell growth and the promotion of apoptosis in treated cells. Doses ranged from 33.3 to 103.3 µg/ml in order to discern these outcomes [24]. Thus, the risk of cancer can be hypothesized to decrease with ingestion. Further in vitro models found dosages ranging from 0.1 to 150 µM were adequate in increasing/decreasing glucose uptake, alluding to modularity in managing insulin within diabetic individuals [45]. Furthermore, many clinical trials have also supported the risk reduction of certain diseases through the ingestion of flavonoid-containing food vehicles. One such indicated that consumption of 65 g dark chocolate was able to increase high-density lipoprotein cholesterol, a biomarker for heart disease. These empirical values however relate to the quantity of

food vehicle necessary and not bioactive compound dosages. In a meta-analysis conducted, polyphenol dosages of 30 mg or more were noted to reduce blood pressure in humans. These, like the previously mentioned clinical trial, were derived from dark chocolates. In the meta-analysis, it was noted that daily doses of 100 g dark chocolate were able to induce such effects [46]. This creates a plausible issue with the analysis of flavonoids, as the 35g discrepancy between each study leaves a large margin of error for ineffective use. A key issue with the broad term flavonoid is that it is composed of many constituents, some of which have been noted to not induce desired chemoprotective effects like its siblings. One such was gallic acid, with little effect on vasodilation [47]. While this is not completely indicative of gallic acid's uselessness, it helps contextualize the necessity for specificity and variance among many polyphenol effects. Epicatechin, a dietary flavonoid, was supplemented in 100 mg/day dosages, inducing positive biomarker effects in the participating individuals. After supplementation through cocoa food vehicles, protein carbonyl and nitrotyrosine residues were observed to stabilize. Thus, the risk of heart failure was hypothesized to reduce [48].

In epidemiological studies, flavonols, a subset of flavonoids, are suggested to reduce the risk of certain cancers, such as those found in the colon. Dosages observed to induce such effects were measured to be a 40 mg even combination of apigenin and epigallocatechin [49]. It is important to account for other constituents of food vehicles containing flavonoids such as excess sugars, fats, and calories when making diet decisions. These may cause other adverse effects such as obesity if not closely monitored [47]. When considering classifications for food vehicles that meet dosage requirements, a grade of 'C' or 'B' would be likely should they be certified as functional. Like many of the other bioactive compounds explored, this is relatively unlikely. Due to many discrepancies in legitimizing a constant dose, further clinical trials are called for. This sets back flavonoids placement in the 16-step process to a preliminary grade of uncertified until an apt definition can be certified. Furthermore, each constituent of flavonoids would need to be studied in their own right contained in respective food vehicles. As seen with gallic acid, this is necessary as some may not produce the desired effects due to differing biomechanics.

Table 6. Adapted list of FDA food categories Soups and Sauces, Gravies, Dips, Condiments, and Seasonings, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Soups			
33	**Canned, Condensed Soup**	**Condensed soup from a can**	**α-carotene, β-carotene, Flavonoids**
34	**Canned, Ready-to-Eat Soup**	**Ready-to-eat soup from a can**	**α-carotene, β-carotene, Lutein, Flavonoids, Fiber**
35	**Dry Mix Soup**	**Dry mixes of soup, includes instant noodles archetype**	**α-carotene**
Sauces, Gravies, Dips, Condiments, and Seasonings			

41	**Mexican-style Sauce**	**Mexican-style sauces and condiments**	**Lycopene, β-carotene**
43	**Tomato-based Sauce**	**Tomato-based sauces with and without additions**	**Lycopene**
47	**Condiments**	**Ketchup, mustard, tartar, barbecue, steak, and hot pepper sauces.**	**Lycopene, β-carotene**
50	**Bean-based Dips**	**Bean-based dips such as hummus and refried**	**Flavonoids, Fiber**
51	**Vegetable/fruit-based Dips**	**Vegetable/fruit-based dips such as salsa and guacamole**	**α-carotene, β-carotene**

Lycopene: Lycopene, found in tomatoes, watermelon, apricots, peaches, and other tomato-based products, is also a carotenoid shown to exhibit therapeutic effects. The compound can readily be found in products such as red fruits and vegetables as indicated by the previous listing. In reference to the FDA-inspired **Tables 4 and 6**, lycopene may be found in canned vegetables, Mexican-style sauces, tomato-based sauces, and other various condiments [23]. Its effects, like the two previous carotenoids, can be best contextualized within the scope of chronic disease as these are where studies are commonly readily available and committed. In several clinical trials, there was an observable correlation between high serum lycopene content and a decreased risk of heart disease. One study suggested that the risk for myocardial infarction was up to 60% lower given the individual met the highest quintile of adipose lycopene concentration [50]. Furthermore, in cancer studies, dosages measuring approximately 30 mg/day were observed to have several benefits, especially in increasing the serum level of lycopene and decreasing the concentration of prostate-specific antigens [51]. These variables are believed to influence the progression of prostate cancer in a negative manner, aligning slightly with the symptom management portion of the FFC's definition. In a meta-analysis of epidemiological studies, high-intakes or high-serum concentration with lycopene is associated with a risk reduction of stroke, mortality, and cardiovascular disease by 26%, 37%, and 14% respectively [52]. Based on its characteristics, lycopene is thought to be more potent than α-carotene and β-carotene in the prevention of cell growth. Thus, lycopene in junction with either of these, specifically β-carotene, may decrease the incidence of cancer substantially. When lycopene is used in tandem with a myriad of other compounds such as S-allylcysteine, other sought-after positive health outcomes may also become evident [24]. While clinical/epidemiological evidence may support a classification of 'C' or 'B' there are some crucial issues that may hinder such assertions. To this extent, the FFC retains the right to overturn decisions based on empirical evidence. One possible means for rejection is adequate dosage amount. If a proper dosage is decided upon, then the previous grade listed can be expected given the best circumstances. However, as with other compounds, this lack of proper dosage may impede study progression within the frames of the 16-step plan, so no grade may be better expected for lycopene overall.

Table 7. Adapted list of FDA food categories Cereals and Bakery Products, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Cereals			
54	**Ready-to-Eat Cereal Flakes**	**Ready-to-eat flaked cereal such as corn and wheat flakes**	**Fiber, Flavonoids**
55	**Ready-to-Eat Cereal Puffs**	**Ready-to-eat puffed cereal such as puffed whole grain, over-puffed, and gun-puffed cereals**	**Fiber, Flavonoids**
Bakery Products			
58	**White bread**	**White bread and rolls, both ready-to-eat and frozen, such as sourdough, potato, and pita bread**	**Flavonoids**
61	**Rye Bread**	**Rye and pumpernickel breads**	**Fiber**
65	**Sweet Rolls**	**Ready-to-eat and frozen sweet rolls, such as cinnamon buns and Danish pastry**	**β-cryptoxanthin**
70	**Tortillas and Wraps**	**Tortillas and wraps made from wheat and flour**	**Fiber**
71	**Hard Taco Shells**	**Hard taco shells made from corn, wheat, and flour**	**Fiber**
75	**Pastries, Pie, and Cobbler**	**Ready-to-eat or frozen pies/other pastries with fruit-based or sweet fillings such as cobbler, tarts, and puff pastry products**	**β-cryptoxanthin**

Beta-cryptoxanthin: Beta cryptoxanthin is found primarily in tangerines, red peppers, and pumpkins is a carotenoid that has several implications on human health. The compound has been associated with risk reduction in certain cancers, degenerative diseases, Alzheimer's, cardiovascular disease, and suggestively osteoporosis. Interestingly, its availability, in select food items, is comparable to that of β-carotene [53]. This suggests a possible correlation or justification for the two to be studied in food items together for efficiency. When compared to the abundance of food items as recognized by the FDA's **Table 7** pastries, pie, and cobblers, sweet rolls as additives, and vegetable/fruit-based dips, β-cryptoxanthin has a limited number of possible FF vehicles that may impede its use due to decreased prevalence [23]. It is important to note that some items containing the compound can be eaten raw, such as tangerines, while others are used as additives of bases to cooked dishes, such as pumpkins [53]. As the FDA does not allocate a category to these raw fruits, it is somewhat

difficult to contextualize their impact with respect to recognition. Studies committed to date include pre-clinical, clinical, and epidemiological trials. In murine studies, dosages of β-cryptoxanthin measuring 25 ppm prevented carcinogenesis. Furthermore, in clinical studies, ingestion of β-cryptoxanthin was observed to significantly decrease c-reactive protein levels [24]. The nature of c-reactive proteins suggests an association with cardiovascular disease and Alzheimer's dictated by elevated levels [54]. Numerous epidemiological studies have also observed dietary use of the compound is associated with lower rates of lung cancer [55]. In humans, dosages measuring approximately 6 mg have been observed to induce desired effects [56]. Further, β-cryptoxanthin has been observed to influence some markers of inflammatory activity, suggesting a role in risk reduction for heart disease [57]. Naturally, dosages would need to be adjusted and tested more, as the broad coverage of the compound may see specific conditions biomarkers not be affected by this dosage. Due to the completed studies outlined, once a refined dosage is decided upon and proper applications have been complete, the grade associated with β-cryptoxanthin could be 'B'. However, it is much more likely that products containing the compound will receive no classification, as studies into the compound are limited. A key issue with this bioactive compound is that it may either be ingested by the consumption of raw or processed goods. Dependent upon the market and the commonality of β-cryptoxanthin in cooking, foods that require its raw constituents to be cooked may have difficulty reaching the proper dosage threshold. A solution to this would be to have a plethora of β-cryptoxanthin processed FF, however, each would need to be subject to the same 16-step process.

Table 8. Adapted list of FDA food categories Meats and Poultry, Fish and Other Seafood, and Sandwiches, their description, and possible bioactive compounds found within them [23].

Abridged FDA Food Categories and Associated Bioactive Compounds			
FDA Food Category ID Reference Number	**Food Category Name**	**Food Category Description**	**Bioactive Compounds**
Meat and Poultry			
90	**Jerky and Prosciutto**	**Meat/poultry/fish jerky and pork prosciutto**	**Astaxanthin, Omega-3's**
Fish and Other Seafood			
105	**Non-Breaded Fish and Other Seafood**	**Frozen, uncooked, and not breaded fish filets and shellfish**	**Astaxanthin, Omega-3's**
106	**Breaded Fish and Other Seafood**	**Frozen, pre-cooked, and breaded fish filets and shellfish**	**Astaxanthin, Omega-3's**
107	**Canned Fish and Seafood**	**Canned fish and shellfish and clams in water, oil, or sauce**	**Astaxanthin, Omega-3's**
Sandwiches			
119	**Poultry/Fish-based Sandwiches**	**Sandwiches and wraps primarily containing poultry, fish and or/seafood. May also include related salads.**	**Astaxanthin, Omega-3's**

Astaxanthin: Astaxanthin is found commonly in marine-oriented foods such as salmon, crab, and green algae and has been observed to possess cardioprotective and anti-cancer effects. When referencing FDA **Tables 3, 4, and 8**, astaxanthin may be prevalent in jerky and prosciutto, non-breaded fish and other seafood, breaded fish and other seafood, canned fish and seafood, poultry/fish-based sandwiches, and seafood-based dishes with and without breading [23]. Each of these categories may be limited in that astaxanthin is not found equally among all seafood items, meaning scrutinous analysis needs to occur in order to justify classification. Food items that astaxanthin can be readily found fit these categories in niche instances, however, there are many more possible constituents that consumers could ingest that are also adequate. Studies demonstrating supportive aspects of the compound include pre-clinical and clinical trials. As of yet, the compound remains relatively unstudied, suggesting many more would be required before classification. However, a suggestive preliminary classification may serve to benefit the FF community and provide an apt representation of astaxanthin in the 16-step process. According to pre-clinical trials, murine studies indicate that 1 mg/kg/day of astaxanthin is enough to observe attenuated promotion of hepatic metastasis induced by restraint stress. Astaxanthin can modify gap junction communication, reducing the risk of cancer [23]. In clinical studies relating to cardiovascular disease, astaxanthin has been described to be more strategic in the cell membrane interactions against oxidative stress. Several trials have cited greatly varied dosage amounts, ranging from 21.6 mg/day to 100 mg in a single dose [58]. This variance in dosage leaves much to be desired. Some studies allude to the notion of a single large dose, while others subscribe to a theory of continuity over time. Furthermore, many of the studies are limited in the number of participants used, calling for even more to be conducted before classification can occur. In alternate clinical trials pertaining to skincare, focus on cosmetic parameters [59]. The FFC's numerous definitions do not typically outline beauty as means for risk reduction, creating an awkward position for astaxanthin. Being that skincare can be argued as an elective instead of necessary maintenance, this presents a gray area for astaxanthin's clinical trials. Regardless, skincare can be argued as optimal health when considering physical and mental effects. Furthermore, healthy skin can be thought of as optimally healthy, fitting with one of the FFC's alternate definitions. In these clinical trials, doses of 6 to 12 mg were enough to maintain moisture in the skin compared to a control without such safeguards [59]. The variability of each of the noted doses leaves much to be desired, as a single food product could not possibly account for such variance unless processed FFs were supplied in tiers. However, this would most likely be inefficient. Studies conducted lack, in that there are simply not very many. Furthermore, few epidemiological trials suitable for 16-step parameters indicate that the classification associated with food products containing a suitable amount of astaxanthin can only, at most, be graded as 'C'. This is provided that a definite dosage can be decided upon first. Realistically, products claiming benefit from this bioactive compound would not be certified as functional if passed along to the FDA for establishment. Due to the variance in dose and application, a preliminary proposal outlining specifically what is intended as well as a scientifically supported dose would be required before any form of classification.

Omega-3's: Omega-3's are found commonly in nuts, seeds, salmon, tuna, and plant oils. When compared to the FDA inspired **Tables 3, 4, 5, and 8**, they may be present in nuts and seeds, nut/seed butter and pastes,

jerky and prosciutto, non-breaded fish and other seafood, breaded fish and other seafood, canned fish and seafood, poultry/fish-based sandwiches, seafood-based dishes with breading, and seafood-based dishes without breading [23]. Ingestion of omega-3's has been linked to positive health effects in chronic conditions such as heart disease and diabetes. Preclinical data indicate that omega-3's slow the progression of atherosclerosis in murine studies. Comparatively, human trials have shown slightly mixed results. Furthermore, omega-3s may also reduce plasma ceramides and reduce differentiation of native T cells, each of which is indicative of effect on the cardiac and immune system respectively [60]. Endpoints for cardiovascular disease have been analyzed through the administration of an 840 mg/d of eicosapentaenoic acid and docosahexaenoic acid. The result of such excursions was the 28% reduction of heart attack risk, 50% reduction of fatal heart attack risk, and 19% reduction of cardiovascular disease death risk [61]. Coinciding with heart disease risk factors, obesity may be altered through ingestion of omega-3s. Dosages of 1.2 g/day for three months observably improved vascular function and lowered the degree of inflammation in obese individuals [62]. Epidemiological studies have advocated for the increased intake of omega-3s within the diet as a practical means of safeguarding health in reference to cardiac events. When supplemented, omega-3s are ingested in doses of 500 mg/day when not affected by heart disease and 1 to 4 g/day when affected by coronary artery disease and hypertriglyceridemia respectively [63]. Further epidemiological data does not assign omega-3s as substantial bioactive compounds in managing related cancers. Specifically, colorectal may see benefit when administered LC-ω3PUFA. Evidence supports exceedingly high doses for risk reduction of breast cancer. Data suggests that dosages of 300 to 500 mg/day and more may produce the desired effect [64]. To certify FFPs containing omega-3s as functional, first, a standardized dose needs to be met. As alluded to in clinical trials, this dose may vary between products, as a processed FF with higher content of omega-3s may be more apt in aiding those already afflicted with coronary artery disease. To reduce risk, FFPs with much lower contents may be utilized. Until that is standardized, however, the highest plausible preliminary classification that can be afforded is that of unclassified. Clinical trials have occurred without refined doses, thus inadequately supporting a grade of 'C'. Furthermore, epidemiological studies taking them into account are relatively absent, denoting that a grade of 'B' would be relatively impossible even if a defined dose was established. Instead of building upon FFPs, they instead look at the implications of just omega-3s. The bioactive compound omega-3 offers much to explore within the range of the FFCs definitions. As outlined in the epidemiological study referenced, they are readily known to reduce risk and manage symptoms. Thus, affording omega-3s confidence within the prospects of the 16-step process.

Variability in Bioactive Compounds Recorded: Many of the bioactive compounds present in food items remain consistent throughout food categories. Variations in the value for bioactive compounds in food items are due to preparation and cooking methods. From the above table, many categories were omitted from the original one published by the FDA due to much overlap. These overlaps could be explained by logistical reasoning that raw, frozen, or uncooked foods would not readily be consumed by the average person. This includes mixes for meats and baked products, as other items would be added in order to create the desired holistic food item for consumption [23].

Furthermore, the bioactive compounds listed are a select few, limited by the current status of research

on the market as well as conciseness. Due to the sheer number of possible compounds present in each item both discovered and undiscovered, limiting the list of possibilities may provide for a more exemplary analysis of the newly proposed 16-step systems application [5]. The chosen analyzed compounds were included due to the commonality of research and overall prevalence in literature. It is worth noting that there are many other compounds that could be added in future analyses.

Issues and Novelty of the 16-step Processes Application:

Many of the food vehicles in question do not have substantial evidence for support as a FFP as they have not been approved through proper channels. This is most directly in reference to plausible FDA recognition of functionality [5]. It is important to understand that the preliminary grades listed are not in any way official. They are simply meant to be used as examples that demonstrate how the 16-step process would work. Those listed take into the consideration of already established research as a basis for results that standardized testing could yield. Furthermore, it is impossible to preliminarily assert a classification grade with accuracy for complete genres of food, as each product would need to be analyzed in its own right for adequate amounts of bioactive compound possession to be considered. Many of the major issues that each bioactive compound and FFP pairing find themselves facing is often a question surrounding dosage. The varying nature of dosage demonstrated by each preclinical, clinical, and epidemiological trial posted creates an issue of definition. The use of optimal dose cannot be facilitated in FFPs until standardized testing ensues and dosage can be officially recognized and defined for implementation in FFPs. Without these standardized tests to discern safety, FFPs cannot be certified. Thus, for advancement through this system, effective bioactive compound dosages need to be established and standardized. Additionally, it is important to recognize that serum levels of a bioactive compound and a food vehicle's attributed value may be different. For example, lycopene, found in tomatoes, and its perceived health benefits may in actuality result from the presence of another compound present in the food vehicle [52]. Therefore it is important to make the distinction and understand that isolation of serum values for specific bioactive compounds need to be analyzed in full before application.

In exemplifying the 16-step process proposed by the FFC, support for the use of FFPs and the methods by which they can be certified can be better understood. This broad but limited overview helps to contextualize the information needed for FFP certification within the realm of chronic disease. As many chronic diseases have readily available studies in great quantity helping to define them, this was chosen as the best alternative instead of more obscure FFPs as mechanisms of action in a specific instance are more easily ascertained than a FF promoting optimal health. Furthermore, the rates of chronic diseases as listed above are common compared to other niche afflictions. This readily available comparison allows for relatiability to ensue, justifying the use of a classification system. Previously, few articles have demonstrated the novelty of a classification system for FF's. The previous 16-step proposal is relatively new, meaning its application is still relatively unknown for both the public and FFP manufacturers [5]. As demonstrated by the 16-step process in conjunction with preliminary bioactive compound literature analysis conducted in this article, manufacturers wishing to have their products certified as FFs should endorse such a progressive system. To use such a system, the manufacturer would submit an application through the FFC, which would be expedited to the FDA for officiation and the result

conferred amongst the FF society. It is important to note that FFP manufacturers cannot claim on their own that their product is a FF. This needs to be confirmed by an official regulatory body so that the consumer can make an honest choice about their health. Inspiration from already utilized systems such as FOSHU cements a steady foundation for the application of FF classification within the U.S. in the future.

Preparation Variance: Food, depending on the ways by which it is prepared, may increase or decrease in its functional efficacy when managing disease risk and symptoms through alteration to bioactive compound bioavailability. Raw foods may have different doses of bioactive compounds than their prepared counterparts varying by the method by which they are cooked.

When considering rice, with already high nutritional content, cooking methods do not significantly alter the glycemic characteristics of many varieties. Five of which, Chiang, Sungyod, Lepnok, and long grain specialties 1 and 2 were tested for glycemic index by using both pressure and rice cookers. Each variety, irrespective of the cooking method, was classified similarly. By rating similarly, it is suggested that cook variance with respect to rice's properties does not affect certain aspects of bioavailability to a major degree. Maintaining the carbohydrate theme, potato tubers, an extremely rich source of antioxidants, were analyzed to determine how methods such as boiling, microwaving, and baking affected total phenolics, flavonoids, flavonols, and other compounds [65]. The slight variance was due to different tubers intrinsically containing higher amounts of bioactive compounds, however, the flesh type of the tuber was accounted for to maintain consistency in tracking these discrepancies. As a result of baking and microwave treatments, total phenolics, flavonoids, flavonols, and the other compounds explored were significantly reduced. Boiling was able to mitigate many of these effects, but overall, baking was seen to cause the most severe loss of antioxidant activity in tubers. This assertion provides context for how nutrients may maintain precedence in baked and microwave environments, or rather a lack thereof [65]. To maintain bioavailability, boiling a product should be a reasonable means to cook an item, which seems to be a beneficial alternative compared to baking.

When referencing vegetables, boiling, steaming, and frying are common cooking methods thought to influence the bioavailability of bioactive compounds. Some compounds in question include polyphenols, carotenoids, and ascorbic acid within carrots, courgettes, and broccoli. Water preparation methods were observed to better preserve carotenoids in all three vegetables and ascorbic acid in carrots and courgettes. Fried vegetables were observed to retain lesser amounts of antioxidant activity, alluding to lesser functionality. Overall, increases could be observed in trolox equivalent antioxidant capacities, total radical-trapping antioxidant parameter, and ferric reducing antioxidant power in all cooked vegetables [66].

Animal products, directly in reference to meats, also have various methods for preparation. In fish products, specifically catfish, baking, grilling, microwaving, and frying may vary mineral contents within select products. Protein contents increase with each level of cooking, while fat contents increase only in fried filets. Vitamin E increases with each given cooking method while vitamin B1 decreases. Grilled fish can be observed to have significant increases in vitamin A, B2, and niacin [67]. Cooking fish products, by these observances, may yield increases in bioavailable compounds as opposed to their raw counterparts. In meats other than marines, such as beef, veal, lamb, and poultry, trace elements of iron, zinc, and copper in conjunction with B vitamins thiamine,

riboflavin, and niacin varied with cut and host species. Furthermore, non-water-based cooking methods allow for higher retention of trace elements and minimize losses of B vitamins. These observances suggest that both cuts and the animal from which said slabs of meat were procured had an effect on the possible ingestion of bioactive compounds [68]. This helps to contextualize that not only different methods of cooking can affect bioavailability, but where products are procured from as well, even if from the same source animal.

CONCLUSION

While this article is not meant to be a strict commentary on FFs as they relate to chronic disease, it does often leverage the two variables against each other to provide context for currently researched benefits. Due to current literature being limited in reference to other portions of the FFCs definition, specifically, performance enhancement, contextualizing proponents with chronic diseases helps to facilitate easier understanding and relatability. Risk reduction associated with common chronic diseases can be easily illustrated through the aforementioned comparison, coinciding with another aspect of the FFCs definition of FFs. At this time, no comprehensive list containing all FFPs officiated within the U.S. can be adjusted, as the rankings in this article can be used solely as plausibilities for certifiability until FFPs are officially recognized by governing bodies such as the FDA. Based on the current literature, the grades associated with the limited list of foods and their bioactive compounds still desire room for expansion as the field of FFs evolves and progresses.

Future studies may want to observe a wider variety of bioactive compound utilization in FFs with reference to the intended use. This process would essentially be another meta-analysis, elongating the classification list exponentially. As the study of bioactive compounds and FFs is in its infancy, this may prove difficult until the fields expand more. With thousands of bioactive compounds derived from plants alone, the prospect of holistic classification calls for an expansion in literature. One possible solution to maintain order amongst a multitude of studies is to formulate a comprehensive database for the storage of information and classification for certified FF recognized by official bodies.

If this classification system is to be built upon in the future, then an initial divergence to signify primary and tertiary prevention may be implemented. By enacting principles of epidemiology, primary and tertiary prevention, more specific classifications can be made for FFs as they relate to unique conditions. Should an FF prove more useful in lowering the risk associated with a disease rather than managing symptoms, it may be better suited for application earlier in the disease pathogenesis and classified as such. Specificity in this way may promote adequate use of FFPs and build resolve towards their application as results should theoretically be more positive.

Generally, the grades proposed and cataloged in this article remain accurate but cannot be preliminarily associated with specific products until officiation can occur. The goal of this article was to provide a suitable foundation for FFs and their classifications to be based upon. Furthermore, this article was meant to exemplify how bioactive compounds and their respective FFPs can expect to be judged in reference to current literature. In analyzing FFPs and bioactive compounds from this respect, it has become obvious that the field still has much room to grow. Information on many compounds is expansive but limited at the same time. Many have been observed to induce positive benefits, however, here seems to be confusion surrounding the intricacies of bioactive compounds, such as dosage, affecting their ethical utilization. It is important to highlight that the

classification system proposed by the FFC is an open one, meaning that upon fundamental discoveries, future research, and expansion of knowledge, each attributed grade that has been finalized may be subject to change based on newly accepted data. This may take the form of slight classification changes in specific instances, or adjustments of the criteria by which FFs are regulated and classified.

Abbreviations: FFC: Functional Food Center, FF: Functional Food, FFP: Functional Food Product, FOSHU: Food for specific health use, FDA: Food and Drug Administration, U.S.: United States

Acknowledgement: We would like to thank Michelle Lee for critical review.

Conflicts of Interest: There are no conflicts of interest associated with this study.

Authors' contribution: The original idea (Functional Foods Classification System: Exemplifying through Analysis of Bioactive Compounds) was conceived by DM and was discussed with ME. ME collected data and wrote the manuscript. DM advised, participated in writing and editing manuscript. All authors read and approved the final version of the manuscript.

REFERENCES:

1. Martirosyan D.M., Singh J. A new definition of functional food by FFC: what makes a new definition unique?. Functional Foods in Health and Disease 2015; 5(6): 209-223. DOI: https://doi.org/10.31989/ffhd.v5i6.183
2. Martirosyan D., Kanya H., Nadalet C. Can functional foods reduce the risk of disease? Advancement of functional food definition and steps to create functional food products. Functional Foods in Health and Disease 2021; 11(5): 213-221. DOI: https://www.doi.org/10.31989/ffhd.v11i5.788
3. Martirosyan D., von Brugger J., Bialow S., Functional food science: Difference and similarities with food science. Functional Foods in Health and Disease 2021; 11(9): 408-430. DOI: https://doi.org/10.31989/ffhd.v11i9.831
4. Henry C.J. Functional Foods. European Journal of Clinical Nutrition 2010; 64(7), 657-659. DOI: https://doi.org/10.1038/ejcn.2010.101
5. Martirosyan D.M., Lampert T., Ekblad M. Classification and regulation of functional food proposed by the functional food center. Functional Food Science 2022; 2(2): 25-46. DOI: https://www.doi.org/10.31989/ ffs.v2i2.890
6. Jiang, L. L., Gong, X., Ji, M. Y., Wang, C. C., Wang, J. H., and Li, M. H. Bioactive compounds from plant-based functional foods: A promising choice for the Prevention and management of hyperuricemia. Foods 2020; 9(8): 973. DOI: https://doi.org/10.3390/foods9080973
7. Kulczyński B., Sidor A., Gramza-Michałowska A. Characteristics of selected antioxidative and bioactive compounds in meat and animal origin products. Antioxidants 2019; *8*(9), 335. DOI: https://doi.org/10.3390/antiox8090335
8. Gibson G. R., Williams C. M. *Functional foods: Concept to product*. Woodhead Publishing 2000.
9. Sadohara R., Martirosyan D. Functional Food Center's vision on functional food definition and science in comparison to FDA's health claim authorization and Japan's Food for Specified Health Uses. Functional Foods in Health and Disease 2010; 10(11): 465-481. DOI: https://doi.org/10.31989/ffhd.v10i11.753
10. Safer D. J. Overprescribed Medications for US Adults: Four Major Examples. Journal of Clinical Medicine Research 2019; 11(9), 617-622. DOI: https://dx.doi.org/10.14740%2Fjocmr3906
11. Boersma P., Black L. I., Ward B. W. Prevalence of Multiple Chronic Conditions Among US Adults, 2018. Prev Chronic Dis 2020; 17:200130. DOI: https://doi.org/10.5888/pcd17.200130.
12. Weir H.K., Thompson T.D., Stewart S.L., White M.C. Cancer Incidence Projections in the United States Between 2015 and 2050. Prev Chronic Dis 2021; 18:210006. DOI: https://doi.org/10.5888/pcd18.210006
13. Fryar C.D., Chen T., Li X. Prevalence of Uncontrolled Risk Factors for Cardiovascular Disease: United States, 1999–2010. NCHS Data Brief 2012: 103
14. Weir H.K., Anderson R.N., Coleman King S.M., Soman A., Thompson T.D., Hong Y., Moller B., Leadbetter S. Heart Disease and Cancer Deaths — Trends and Projections in the United States, 1969–2020. Prev Chronic Dis 2016;13:160211. DOI: https://doi.org/10.5888/pcd13.160211.

15. McAnany B., Martirosyan D. The effects of bioactive compounds on Alzheimer's disease and Mild cognitive impairment. Functional Foods in Health and Disease 2016; 6(6): 329-343. DOI: https://doi.org/10.31989/ffhd.v6i6.257
16. Kalra S. Diabesity. Journal of the Pakistan Medical Association 2013; 63(4):532-534. PMID: 23905459
17. Choudhary M., Grover K. Development of functional food products in relation to obesity. Functional Foods in Health and Disease 2012; 2(6): 188-197. DOI: https://doi.org/10.31989/ffhd.v2i6.90
18. CDC's Division of Diabetes Translation. Long-term Trends in Diabetes. CDC 2017. http://www.cdc.gov/diabetes/data
19. Soumya N.P.P., Mini S., Sivan S.K., Mondal S. Bioactive compounds in functional food and their role as therapeutics. Bioactive Compounds in Health and Disease 2021; 4(3): 24-39. DOI: https://doi.org/10.31989/bchd.v4i3.786
20. National Center for Biotechnology Information. PubChem Compound Summary for CID 446925, Lycopene. https://pubchem.ncbi.nlm.nih.gov/compound/Lycopene. Retrieved on April 7, 2022.
21. National Center for Biotechnology Information. PubChem Compound Summary for CID 5281224, Astaxanthin. https://pubchem.ncbi.nlm.nih.gov/compound/Astaxanthin. Retrieved on April 7, 2022.
22. National Center for Biotechnology Information. PubChem Compound Summary for CID 56842239, omega-3 Fatty acids. https://pubchem.ncbi.nlm.nih.gov/compound/omega-3-Fatty-acids. Retrieved on April 7, 2022.
23. FDA. FDA Food Categories and Voluntary Targets. U.S. Food and Drug Administration 2010; DID: FDA-2014-D-0055
24. Aghajanpour M., Nazer M.R., Obeidavi Z., Akbari M., Ezati P., Kor N.M. Functional foods and their role in cancer prevention and health promotion: a comprehensive review. American Journal of Cancer Research 2017; 7(4): 740-769. ISSN: 2156-6976
25. Cruz B.C., Sarandy M.M., Messias A.C., Gonçalves R.V., Ferreira C.L., Peluzio M.C. Preclinical and clinical relevance of probiotics and synbiotics in colorectal carcinogenesis: A systematic review. Nutrition Reviews 2020; 78(8), 667–687. DOI: https://doi.org/10.1093/nutrit/nuz087
26. Brüssow H. Probiotics and Prebiotics in clinical tests: An update. F1000Research 2019; 8, 1157. DOI: https://doi.org/10.12688/f1000research.19043.1
27. Dudek-Wicher R., Junka A., Paleczny J., Bartoszewicz M. Clinical trials of probiotic strains in selected disease entities. International Journal of Microbiology 2020; 2020, 1–8. DOI: https://doi.org/10.1155/2020/8854119
28. Rafter J. Probiotics and colon cancer. Best Practice and Research Clinical Gastroenterology 2003; 17(5), 849–859. DOI: https://doi.org/10.1016/s1521-6918(03)00056-8
29. Aleta A., Hrvat F., Džuho A. Probiotics review and future aspects. International Journal of Innovative Science and Research Technology 2020; (5), 270, 274. ISSN: -2456-2165
30. Dong J.-Y., He K., Wang P., Qin, L.-Q. Dietary fiber intake and risk of breast cancer: A meta-analysis of prospective cohort studies. American Journal of Clinical Nutrition 2011; 94(3), 900–905. DOI: https://doi.org/10.3945/ajcn.111.015578
31. Grube B., Chong P.W., Lau K.Z., Orzechowski H.D A natural fiber complex reduces body weight in the overweight and obese: A double-blind, randomized, placebo-controlled study. Obesity 2013; 21(1), 58–64. DOI: https://doi.org/10.1002/oby.20244
32. McRae M.P. Dietary fiber intake and type 2 diabetes mellitus: An umbrella review of Meta-analyses. Journal of Chiropractic Medicine 2018; 17(1), 44–53. DOI: https://doi.org/10.1016/j.jcm.2017.11.002
33. Whelton S.P., Hyre A.D., Pedersen B., Yi Y., Whelton P.K., He, J. Effect of dietary fiber intake on blood pressure: A meta-analysis of randomized, controlled clinical trials. Journal of Hypertension 2005; 23(3), 475–481. DOI: https://doi.org/10.1097/01.hjh.0000160199.51158.cf
34. Galisteo M., Duarte J., Zarzuelo, A. Effects of dietary fibers on disturbances clustered in the metabolic syndrome. The Journal of Nutritional Biochemistry 2008; 19(2), 71–84. DOI: https://doi.org/10.1016/j.jnutbio.2007.02.009
35. Tanumihardjo S.A. Hydrocarbon Carotenoid: α-Carotene. Encyclopedia of Human Nutrition, Third Edition 2013. Elsevier Ltd. ISBN: 978-0-12-384885-7
36. Liu Y.Z., Yang, C.M., Chen, J.Y., Liao, J.W., Hu, M.L. Alpha-carotene inhibits metastasis in Lewis lung carcinoma in vitro, and suppresses lung metastasis and tumor growth in combination with taxol in tumor xenografted C57BL/6 mice. The Journal of Nutritional Biochemistry 2015; *26*(6), 607–615. https://doi.org/10.1016/j.jnutbio.2014.12.012
37. Ciccone M.M., Cortese F., Gesualdo M., Carbonara S., Zito A., Ricci G., De Pascalis F., Scicchitano P., Riccioni G. Dietary intake of carotenoids and their antioxidant and anti-inflammatory effects in cardiovascular care. Mediators of Inflammation 2013; *2013*, 1–11. DOI: https://doi.org/10.1155/2013/782137
38. Pryor W.A., Stahl W., Rock C. L. Beta carotene: From biochemistry to clinical trials. Nutrition Reviews 2009; *58*(2), 39–53. DOI: https://doi.org/10.1111/j.1753-4887.2000.tb07810.x

39. Palliyaguru D.L., Yuan J.-M., Kensler T.W., Fahey J.W. Isothiocyanates: Translating the power of plants to people. Molecular Nutrition and Food Research 2018; *62*(18), 1700965. DOI: https://doi.org/10.1002/mnfr.201700965
40. Verhoeven D.T., Goldbohm R.A., van Poppel G., Verhagen H., van den Brandt P.A. Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiology, Biomarkers and Prevention 1996; 5(9): 733-748. ISSN: 1538-7755
41. Scripsema N.K., Hu D.-N., Rosen R.B. Lutein, Zeaxanthin, and meso-zeaxanthin in the clinical management of Eye Disease. Journal of Ophthalmology 2015; *2015*, 1–13.DOI: https://doi.org/10.1155/2015/865179
42. Arnal E., Miranda M., Almansa I., Muriach M., Barcia J.M., Romero F.J., Diaz-Llopis M., Bosch-Morell F. Lutein prevents cataract development and progression in diabetic rats. Graefe's Archive for Clinical and Experimental Ophthalmology 2008; *247*(1), 115–120. DOI: https://doi.org/10.1007/s00417-008-0935-z
43. Koushan K., Rusovici R., Li W., Ferguson L., Chalam K. The role of lutein in eye-related disease. Nutrients 2013; *5*(5), 1823–1839. DOI: https://doi.org/10.3390/nu5051823
44. Alves-Rodrigues A., Thomas B. The role of Lutein in the prevention of atherosclerosis. Journal of the American College of Cardiology 2002; *40*(4), 835. DOI: https://doi.org/10.1016/s0735-1097(02)02023-5
45. Russo B., Picconi F., Malandrucco I., Frontoni S. Flavonoids and insulin-resistance: From molecular evidences to clinical trials. International Journal of Molecular Sciences 2019; *20*(9), 2061. DOI: https://doi.org/10.3390/ijms20092061
46. Singharaj B., Pisarski K., Martirosyan D.M. Managing hypertension: Relevant biomarkers and combating bioactive compounds. Functional Foods in Health and Disease 2017; 7(6), 442. DOI: https://doi.org/10.31989/ffhd.v7i6.324
47. Taubert D., Roesen R., Schömig E. Effect of Cocoa and Tea Intake on Blood Pressure: A Meta-analysis. Archives of Internal Medicine 2007; 167(7):626–634. DOI: https://doi.org/10.1001/archinte.167.7.626
48. Oteiza P.I., Fraga C.G., Galleano M. Linking biomarkers of oxidative stress and disease with flavonoid consumption: From experimental models to humans. Redox Biology 2021; 42, 101914. DOI: https://doi.org/10.1016/j.redox.2021.101914
49. Chang H., Lei L., Zhou Y., Ye F., Zhao G. Dietary flavonoids and the risk of colorectal cancer: An updated meta-analysis of Epidemiological Studies. Nutrients 2018; 10(7), 950. https://doi.org/10.3390/nu10070950
50. Arab L., Steck S. Lycopene and cardiovascular disease. The American Journal of Clinical Nutrition 2000; *71*(6). DOI: https://doi.org/10.1093/ajcn/71.6.1691s
51. Mirahmadi M., Azimi-Hashemi S., Saburi E., Kamali H., Pishbin M., Hadizadeh F. Potential inhibitory effect of lycopene on prostate cancer. Biomedicine and Pharmacotherapy 2020; *129*, 110459. DOI: https://doi.org/10.1016/j.biopha.2020.110459
52. Cheng H.M., Koutsidis G., Lodge J.K., Ashor A.W., Siervo M., Lara, J. Lycopene and Tomato and risk of cardiovascular diseases: A systematic review and meta-analysis of epidemiological evidence. Critical Reviews in Food Science and Nutrition 2017; *59*(1), 141–158. DOI: https://doi.org/10.1080/10408398.2017.1362630
53. Burri B.J., La Frano M.R., Zhu C. Absorption, metabolism, and functions of β-cryptoxanthin. Nutrition Reviews 2016; *74*(2), 69–82. DOI: https://doi.org/10.1093/nutrit/nuv064
54. Luan Y.-yi, Yao Y.-ming. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Frontiers in Immunology 2018; *9*. DOI: https://doi.org/10.3389/fimmu.2018.01302
55. Tanumihardjo S.A. Xanthophyll: *β-Cryptoxanthin*. Encyclopedia of Human Nutrition, Third Edition 2013. Elsevier Ltd. DOI: https://doi.org/10.1016/B978-0-12-375083-9.00045-3
56. Hajizadeh-Sharafabad F., Zahabi E.S., Malekahmadi M., Zarrin R., Alizadeh M. Carotenoids supplementation and inflammation: A systematic review and meta-analysis of randomized clinical trials. Critical Reviews in Food Science and Nutrition 2021; 1–17. DOI: https://doi.org/10.1080/10408398.2021.1925870
57. Maria A.G., Graziano R., Nicolantonio D.O. Carotenoids: Potential allies of cardiovascular health? Food and Nutrition Research 2015; *59*(1), 26762. DOI: https://doi.org/10.3402/fnr.v59.26762
58. Fassett R.G., Coombes J.S. Astaxanthin in cardiovascular health and disease. Molecules 2012; *17*(2), 2030–2048. DOI: https://doi.org/10.3390/molecules17022030
59. Donoso A., González-Durán J., Muñoz A.A., González P.A., Agurto-Muñoz C. "Therapeutic uses of natural astaxanthin: An evidence-based review focused on human clinical trials." Pharmacological Research 2021; *166*, 105479. DOI: https://doi.org/10.1016/j.phrs.2021.105479
60. Sekikawa A., Cui C., Sugiyama D., Fabio A., Harris W.S., Zhang X. Effect of high-dose marine omega-3 fatty acids on atherosclerosis: A systematic review and meta-analysis of randomized clinical trials. Nutrients 2019; 11(11), 2599. DOI: https://doi.org/10.3390/nu11112599
61. Kris-Etherton P.M., Richter C.K., Bowen K.J., Skulas-Ray A.C., Jackson K.H., Petersen K.S., Harris W.S. Recent clinical trials shed

new light on the cardiovascular benefits of omega-3 fatty acids. Methodist DeBakey Cardiovascular Journal 2019; 15(3), 171. DOI: https://doi.org/10.14797/mdcj-15-3-171

62. Dangardt F., Osika W., Chen Y., Nilsson U., Gan L.-M., Gronowitz E., Strandvik B., Friberg P. Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents. Atherosclerosis 2010; 212(2), 580–585. DOI: https://doi.org/10.1016/j.atherosclerosis.2010.06.046
63. Mori T. A. Omega-3 fatty acids and cardiovascular disease: Epidemiology and effects on cardiometabolic risk factors. Food Funct. 2014; 5(9), 2004–2019. DOI: https://doi.org/10.1039/c4fo00393d
64. Gerber M. Omega-3 fatty acids and cancers: A systematic update review of Epidemiological Studies. British Journal of Nutrition 2012; 107(S2). DOI: https://doi.org/10.1017/s0007114512001614
65. Chapagai M.K., Bakar N.A., Jalil R.A., Wan Muda W.A., Karrila T., Ishak W.R., Siwaporn, P. Glycaemic index values and physicochemical properties of five brown rice varieties cooked by different domestic cooking methods. Functional Foods in Health and Disease 2016; 6(8), 506. DOI: https://doi.org/10.31989/ffhd.v6i8.260
66. Miglio C., Chiavaro E., Visconti A., Fogliano V., Pellegrini, N. Effects of different cooking methods on nutritional and physicochemical characteristics of selected vegetables. Journal of Agricultural and Food Chemistry 2007; *56*(1), 139–147. DOI: https://doi.org/10.1021/jf072304b
67. Ersoy B., and Özeren, A. The effect of cooking methods on mineral and vitamin contents of African catfish. Food Chemistry 2009; *115*(2), 419–422. DOI: https://doi.org/10.1016/j.foodchem.2008.12.018
68. Lombardi-Boccia G., Lanzi S., Aguzzi, A. Aspects of meat quality: Trace elements and B vitamins in raw and cooked meats. Journal of Food Composition and Analysis 2005; 18(1), 39–46. DOI: https://doi.org/10.1016/j.jfca.2003.10.007