Methodological Article **Open Access**

Quantum Theory of Functional Food Science: Establishment of dosage of bioactive compounds in functional food products

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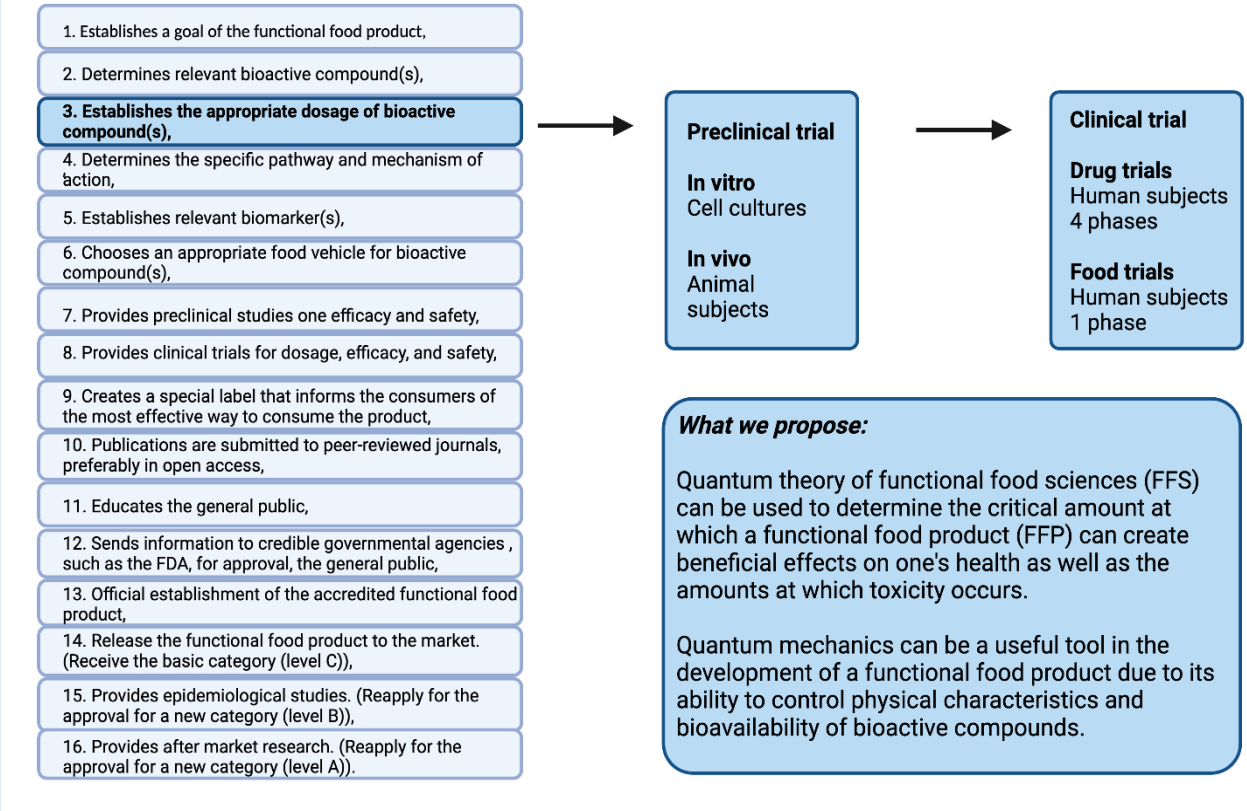
Submission Date: March 8th, 2022; **Acceptance Date:** March 27th, 2022; **Publication Date:** March 29th, 2022

Please cite this article as: Martirosyan D.M., Sanchez S.S. Quantum Theory of Functional Food Science: Establishment of dosage of bioactive compounds in functional food products. *Functional Food Science* 2022; 3(2): 79-93. DOI: https://doi.org/10.31989/ffs.v2i3.915

ABSTRACT

As the prevalence of chronic diseases has increased in the United States there has also been an increase in the need for products that can help prevent, manage, or treat diseases. Functional food products can do this through components within them called bioactive compounds. These compounds can provide multiple health benefits that act on biomarkers of disease. However, there is not a set definition for functional foods, making it hard to classify and regulate them. The Functional Food Center has proposed a definition for functional food as well as a multi-step process for their development. As part of this process a bioactive compound is identified within a functional food product. To understand more about the safety and efficacy of this bioactive compound, an appropriate dose must be established. To find this dose, clinical research is conducted. In preclinical research animal subjects are used to identify the critical amount of a bioactive compound. Researchers also test for safety concerns and adverse effects from the product. After this, clinical trials are performed on human subjects to determine the efficacy of the functional food product. However, these trials are different from trials done on drugs. The quantum theory of functional food science can find the critical amount of a bioactive compound needed to create a chain reaction that leads to the claimed health benefits. This can also help researchers discover possible toxicities of bioactive compounds in doses above the critical amount. The use of quantum mechanics in the food industry could also allow for control of physical characteristics of functional food products as well as bioavailability of bioactive compounds within these products using nanotechnology. However, more research is needed to understand the safety of this technology.

Keywords: functional food products, bioactive compounds, dosage, pre-clinical studies, clinical studies, quantum theory of functional food sciences, quantum mechanics



INTRODUCTION

In the United States, the prevalence of chronic diseases has only been increasing throughout the years [1]. Chronic diseases not only decrease the quality of life, but they also increase the risk of mortality and health costs of the people that suffer from them [1]. Because of this, chronic diseases have become a big issue that need to be addressed. One way that this could be done is using functional foods, which can decrease the risk of disease and by doing so improve health and lower healthcare costs [2]. The way in which FF can do this is through bioactive compounds. Bioactive compounds could be defined as “the constituents of foods, especially functional foods, that provide beneficial health properties” [3]. They are essentially what makes a FF functional.

Although there is not a formal definition for functional foods, the FFC has proposed a definition for FF 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 FFC has proposed a 16-step process to establish a FF and bring it to the market, as can be seen in Table 1 [2]. This process along with the definition of FF allows for the regulation and classification of FFP [2]. As part of this process, a goal must be set in place for a particular FFP, and a bioactive compound must be identified within that FFP to classify it [2]. This includes establishing what disease or population the FFP will target and what the FFP will do to this disease or for this population. Apart from establishing a goal for the functional food and determining the bioactive compound that will help achieve this goal, the appropriate dosage must be established before making the product available. This third step of the 16-step process is highlighted on Table 1

and is important because establishing an appropriate dosage of a bioactive compound can allow a person to trust that the product will allow for them to experience the benefits of the FFP and not cause harmful side effects. To do this, researchers must be able to find the critical amount of a BC. It is also important that they find what amount above the critical amount could cause adverse side effects like toxicity. Critical amount can be defined as the amount needed for a substance to create a chain reaction [4]. Quantum theory of FFS, can be helpful in determining the critical amount of a BC as well as determining amounts in which possible toxicity can occur. Quantum mechanics can be useful in altering physical characteristics of a FFP. Through the use of nanotechnology, it can help researchers control aspects of a BC in a FFP, such as dosage and bioavailability. In this article we will be discussing step three of the multi-step process which establishes the appropriate dosage of bioactive compounds, how clinical research is used to establish it, and how quantum theory of FFS could be useful in the establishment of appropriate and toxic doses.

Table 1. Steps for development of FFP and bringing it to the market [2].

Step Number	Description of Steps to create FF Products
1	Establishes a goal of the functional food product,
2	Determines relevant bioactive compound(s),
3	Establishes the appropriate dosage of bioactive compound(s),
4	Determines the specific pathway and mechanism of action,
5	Establishes relevant biomarker(s),
6	Chooses an appropriate food vehicle for bioactive compound(s),
7	Provides preclinical studies one efficacy and safety,
8	Provides clinical trials for dosage, efficacy, and safety,
9	Creates a special label that informs the consumers of the most effective way to consume the product,
10	Publications are submitted to peer-reviewed journals, preferably in open access,
11	Educates the general public,
12	Sends information to credible governmental agencies , such as the FDA, for approval,
13	Official establishment of the accredited functional food product,
14	Release the functional food product to the market. (Receive the basic category (level C)),
15	Provides epidemiological studies. (Reapply for the approval for a new category (level B)),
16	Provides after market research. (Reapply for the approval for a new category (level A)).

Retrieval of Published Studies: Articles for this review were found through the Functional Food Center website, PubMed, FDA website, NIH website, and google scholar. Multiple articles were viewed and screened, however not all were selected for this article. This is because the information in those articles were not deemed relevant to the topic of this review. In total, only thirty-six papers from the search were used for this article because they had relevant information. It is worth noting that not all of the information from the thirty-six articles was used for this review as not all the information in the articles were relevant. Keywords used to find the references included terminology relating to bioactive compounds, functional food, dosage, chronic disease prevalence in the United States, quantum mechanics, quantum theory of food sciences, upper tolerable intake levels, pre-clinical trials, and clinical trials.

Bioactive Compounds: As previously mentioned, BC are found in FF and are the parts of FF that give them their health promoting properties. They can be defined as "the constituents of foods, especially functional foods, that provide beneficial health properties" [3]. In other words, BC are constituents of foods that provide beneficial health properties that manage, prevent, or treat diseases [3]. BC are primary and secondary metabolites that have antioxidant, anti-inflammatory, and antifungal properties among other beneficial functions [3]. BC can be found in FF and are able to promote health or manage disease by interacting with biological processes in a health promoting matter which can be seen through the presence of or alterations in biomarkers. A great example of a BC is vitamin C which can be found in FFs like citrus fruits [5]. The orange itself is not what brings health benefits, but it is the vitamin C, that has antioxidant and cofactor properties, that allows oranges to be beneficial for health [5].

When ingested, FFs not only interact with different environments within the body, but they also interact with the microbiota. This in turn can affect aspect of the metabolism and bioavailability of the FF [6]. Diet and other factors like method of birth and use of antibiotics can affect the composition of one's microbiome, which in turn can affect a person's health [6]. This is because different types of microbes metabolize undigested foods in intestine in a way that produce different byproducts [6]. The composition of the microbiome also affects how much and what type of short chain fatty acid is absorbed [6]. For example, if a FF is ingested by a person who's microbe is largely composed of *Bacteroides* it is more likely that they will metabolize the FF such that it will be more bioavailable and produce beneficial SCFA's [6]. However, if a FF is ingested by someone who has larger amounts of *Firmicutes* it may be less bioavailable due to H2 producing activities which can stop fermentation from occurring [6].

The proposed 16 step process for the regulation of FFP begins by determining an issue and setting a goal to address it [2]. This is usually done by proposing a FFP that can prevent or manage disease, enhance performance, or promote health [2]. Then, researchers must determine what BC within a FFP will be able to achieve this and specifically help with the issue at hand [2]. The mechanism by which this is done is also determined [2]. However, it is important to understand how much of a BC within a FFP is needed to create these beneficial effects and not be harmful to those using it. Therefore the third step of the multi-step process is important.

Dosage Of Bioactive Compounds: The third step in the multi-step process is crucial in determining the effectiveness and safety of the proposed FFP. Here, the researchers establish the appropriate dosage of the BC [2]. This is done by establishing the therapeutic range at

which it may exhibit an effect to users [2]. When there is an intake of a BC there might be small changes occurring within the body, yet they might not be visible because the critical amount is not present. Which is why researchers must ask the question how much of a BC is able to create chain reactions that result in an effect on one's health? Currently, dosage is established through clinical research, however the quantum theory of FFS can establish the critical amount of a BC, which is discussed later in the article.

A great example of establishing an appropriate dosage of a BC that can exhibit an effect for users is Recommended Daily Intake (RDI) of nutrients. While these do not discuss specific FFP, they do provide appropriate dosage of many BCs for different populations. Going back to the example of vitamin C, its RDI recommends that an intake of 90 mg for men and 75 mg for women should be had daily, however some researchers have proposed that this should be increased to achieve more health benefits [5]. Researchers have found that at these doses, vitamin C is able to take part in the biological processes that require it so that it is able to maintain health and prevent disease. As for FFP, it is important to determine how much and at what range a BC can create an effect on a person's health in a way that allows the FFP to manage or prevent disease. It is also important to determine other aspects of the administration of the FFP. This includes information about how frequently the FFP should be had.

Although a BC may have beneficial effects, it does not mean that having higher amounts of it will increase its effects and benefits. In fact, having doses above what is deemed appropriate could simply lead to the excretion of the excess intake or possibly create adverse effects. Adverse effects can be described as undesired changes in the structure or function of an organism [7]. These adverse effects include toxicity, allergy, and mutagenicity [2]. For example, antioxidants can scavenge free radicals and stabilize them to reduce damage to cells [8]. However, they can also become reactive and have a pro-oxidation effect [8]. One example is lipoic acid which at lower concentrations can be protective, but at higher concentrations can be harmful [8]. As Paracelso stated "All substances are poisonous; without exception. Only the dose can differentiate between poison and a remedy" [10], which is why establishing a dose is very important. Although it does not cause adverse effects when taken in excess, biotin can interfere with lab tests which could indirectly affect a person's health [9]. The bioavailability of BCs affects the dose to which the BC can create an effect on an organism as well as the dose at which it can be toxic [7]. Therefore researchers must ask the questions how much of a bioactive compound must be had in order for it to make a food functional and have an effect on biomarkers, and how much can have adverse effects on a consumer?

As discussed, some BC like vitamin C and antioxidants can produce beneficial effects that can prevent or manage disease, however at high amounts could be more detrimental for one's health. Another example is capsaicinoids which can be found in chili peppers which in appropriate doses can be used for pain management, cancer prevention, and reduced risk of mutagenicity [11]. However, at higher doses can increase the risk of gastric cancer [10]. Resveratrol is a polyphenol that has multiple health promoting benefits and has been found to decrease the risk of many diseases as well as oxidative damage [12]. However, studies done on humans have shown that these benefits are dose dependent. At a dose of 450 mg/day resveratrol can be beneficial however at a dose of 1000 mg/day it was found to increase biomarkers of cardiovascular disease [12]. In

rats, 20 mg/kg/day offered health promoting effects while doses about 1000 mg/kg/day caused health issues in their kidneys [12]. People with certain diseases could experience mild side effects including nausea and diarrhea when they intake higher doses of this BC [12]. A lot of research is needed to determine what dose of a BC can create beneficial effects and not cause side effects or toxicity in its target population.

Another factor that should be taken into account is the form of preparation, which in turn can affect the effectiveness of a FFP. A great example is the use of fermentation which has been used for many years to improve the bioavailability, metabolism, and absorption of foods as well as to change physical characteristics of a product [13]. For example, *Carica Papaya,* is a functional food that is often fermented to increase its health promoting effect [13]. Fermented papaya has been proven to have potent antioxidant and anti-aging effects in rodents [13]. Preparation methods such as fermentation should be considered when determining dosage. By properly preparing a FFP it is possible that a person could be getting larger amounts of BC's, which could optimize their health and further decrease their risk for disease. Other preparation methods include the use of nanotechnology such as liposomes, which are discussed later in the article.

When creating a FFP it should be specified what dose is appropriate for different people. Different groups within a population may react differently to a certain dose [14]. For example, children may require a different dose than adults or a product may not be suitable for children, pregnant women, or people who have a certain condition. It is also possible that a certain dose of a BC can create adverse effects for people who are at an increased risk of a chronic disease. Beta carotene is a phytochemical that is important for the health of eyes, the reproductive system and growth [15]. It has also been shown to reduce the risk of cardiovascular disease and type 2 diabetes [15]. However, beta carotene can be harmful to certain people. One study found that the supplementation of beta carotene for smokers can increase the risk of lung cancer, making it more harmful for this group of people [16]. In smokers, it is probably best to suggest low doses of beta carotene or even for them to avoid supplements. For this reason, researchers must conduct clinical research to determine an appropriate dose and if there are any adverse effects to a BC as well as who this may affect.

Determining Dosage of Bioactive Compounds: Establishing the appropriate dose of a BC in a functional food product requires research. This is often done in the form of preclinical and clinical studies in which animal and human subjects are used, respectively [2]. In these studies, they must test different doses to determine the critical amount at which a BC is able to affect biomarkers of a disease. They must also look for any possible adverse effects that may occur when doses above the critical amount are provided to subjects. In other terms, clinical research is used to determine the appropriate dose of a BC that is needed to test the efficacy and safety of that BC. However, it is not clear how the dose of an animal should be translated to one for a human. As shown in Table 2, there are differences between preclinical and clinical trials. There are also different ways to conduct preclinical and clinical trials. Overall, preclinical and clinical trials are important in the establishment of dosage of BC in FFP.

Table 2. Comparison of in vitro and in vivo preclinical studies and clinical studies of foods and drugs.

Preclinical
Animal subjects or cell cultures
In vitro
Cell cultures
Highly controlled and low cost
Unable to reflect how complex processes of humans will interact with a substance
In vivo
Animal subjects
More costly and less controlled than in vitro
More accurate model
Clinical
Human subjects
Drug trial
Tests drug usually on people who have a disease
Phase 1 (safety and efficacy)
<100 subjects given designated dose for a few months
Phase 2 (efficacy and side effects)
Hundreds of subjects given designated dose for months up to 2 years
Phase 3 (efficacy and adverse reactions)
300-3,000 subjects are given designated dose for up to 4 years
Phase 4 (safety and efficacy)
Substance is FDA approved and in the market, making it available to thousands of subjects
Food trial
Food product is tested on a small group of people that are healthy
One phase testing validity of health claims on participants for a few months

Preclinical: When establishing the dose of a BC, researchers begin by conducting preclinical studies. These studies usually have a small sample size and can provide information on appropriate dosage of a compound as well as any possible side effects and toxicity [17]. This includes in vivo and in vitro studies in which animals (usually rodents) or cell cultures serve as subjects rather than humans [2]. Other than ethical reasons, this is done because animals are easy to control and causal relationships are more easily established [14]. In these studies, researchers aim to determine a dose in which a BC is effective and does not cause harmful effects [2]. They can also learn more about adverse effects of BC and the dose at which this occurs. It is important to note that when retrieving information for this article, articles discussing animal testing proposed that replacing in vivo animal studies with in vitro studies or using high technology should be a step that research should take. This could be due to ethical concerns since in vivo studies can save the lives of animals, but also because they can save time and money [18].

In vitro studies are done on cell cultures and allow us to understand how cells may respond when introduced to a certain substance like a BC [19]. These studies are highly controlled and allow us to understand more about the mechanisms by which a BC can affect a cell while controlling the type of cell and amount of BC introduced [19]. In vitro studies are highly effective and low cost, however living organisms are complex especially at the human level [19, 20]. Because of this, in vitro studies might not be able to accurately reflect how a living human and all of its complex processes might interact with the BC [20].

In vivo preclinical studies usually involve living animals as the subjects of the study. These studies give us a better understanding of the safety and efficacy of a BC [19]. Because these studies are done on living organisms that have more complex biological processes like humans, they can give us a better understanding on the effects of a BC and their interactions with biological processes [20]. However, these studies usually are more costly and require more time and resources [19, 20]. It is also important to consider that animals and humans are different organisms and different sizes. So, researchers must be able to convert the dose for animals to that of humans [20, 21]. Some researchers have made conversions based on body weight [21]. For example, 25 mg/kg is a dose used in rat models that can provide effects on health and that is applied to humans. Allometric scaling is a method that is often used to calculate the appropriate dose for humans [21, 22]. However, this technique can lead to an inaccurate calculation of what the appropriate dose is for humans. It has been suggested that allometric scaling using body surface area can give more accurate results [21]. However, this can often be misunderstood and misused [21]. Researchers should consider if they are using this technique correctly to ensure the safety of human subjects as well as the efficacy of the FFP. To use allometric scaling correctly, pharmacokinetic data should be available for at least two model species [21].

It is very important that researchers maintain good practices when designing and executing their study as well when they are reporting their methods and findings. For this reason, guidelines and regulations have been created. The FDA has provided a set of regulations that must be followed when conducting preclinical studies, which includes good practices for the design, execution, and reporting of the study [23]. Following these guidelines can help researchers create a study that provides and reports results accurately. It can also allow other researchers to recreate their study to see if they can find similar results. Similarly, the UK National Center for the 3 R's has published the ARRIVE guidelines, specifically for animal studies [24]. These guidelines also help researchers create an effective study and help them report information accurately.

Clinical: Once preclinical studies have been performed and have shown that a BC is effective and safe, the BC can

be studied on human subjects. In these studies, the dose can be modified and made appropriate for humans as well as continuing to test for the FFP's safety and efficacy [2]. However, FFPs don't usually have as many adverse effects and safety concerns as drugs, but it is still important to test if the designated dose of the BC is the critical amount needed to make certain health claims [25]. As previously discussed, the dose used in preclinical trials must be converted to the human dose so that it may be tested on humans [21]. Given that these studies are conducted on the target audience of a FFP, they are considered to have the most accurate information on the effectiveness and safety of a BC [14]. They allow us to truly understand the beneficial and harmful effects that can occur when a FFP is given [14]. The information from these studies is most useful in determining the appropriate dosage of a BC in a FFP.

Clinical trials can be done as observational studies or interventional [25]. While observational studies find out more about the relationship between a food or drug with a disease or overall health, interventional studies gather more information about why or how this relationship occurs [25]. For both food and drug clinical studies, it is required that good practices are used and that the protocols clearly define the aims, participants, and measures of the study [25]. This includes protocols conducted when designing, conducting, and reporting on the study. Both studies also require that the factor being tested has gone through preclinical trials and is deemed safe for humans [25]. However, drug and food clinical trials do have different aims, participant characteristics, and designs [25]. Food trials tend to be cheaper, smaller, and have healthy participants or participants at risk who do not necessarily have a disease [25]. Potential issues with this are that FFP are meant to not only prevent, but also treat and manage symptoms of disease. Testing a FFP on healthy people would not allow manufacturers to make a claim regarding the effectiveness of the FFP in treating or ameliorating the effect of a certain disease. Another issue is that testing a FFP on people with a disease could possibly lead to the FFP being classified as a drug and undergo testing and labeling as a drug rather than a food product. Food trials result in the creation of food labels and health claims [25]. Contrary to drug trials that often use subjects that already have a disease [25]. The trials for food must also undergo testing in a way that will not classify it as a drug [25]. Label regulations also differ between food and drugs. Drug labels focus more so on who should use it and how to use it while food labels use evidence to make specific health claims [25]. The FDA requires health claims of food to be tested and have convincing evidence that the food can create certain effects, especially on healthy individuals [25]. Given that drugs may have potential risks for the health of humans, their safety must be reviewed prior to beginning trials, however this is not necessarily true for food products [25]. Drugs and food also require that their results be submitted through different applications to the FDA. Food trials can submit their evidence using an NDI application in which human clinical trials are not required from the products manufacturer [25]. They may also submit evidence using a QHC application which does require clinical trials to assess the efficacy of the food and if its health claims are valid [25]. Food trials also have differences in their methods. Food trials must find a way to deliver the food product of choice and be able to provide a placebo that is not bioactive or noticeable to not create bias in the participants [25]. Food trials have one phase that can take at most a few months [25].

As for drug trials, there are four different phases of clinical trials. Before commencing, however, the safety of the drug in question must be reviewed by the FDA [25]. The first phase gives under a hundred people the designated substance at the designated dose for a few months in order to determine the appropriate dosage and safety of the substance [26]. If eligible, the study moves on to phase two where hundreds of people are given the substance at the appropriate dose for months

up to two years to look at the efficacy and side effects of the substance [26]. The trial can then move to phase three where 300-3,000 people are given the substance for up to four years to determine efficacy and see if there are any adverse reactions [26]. Lastly in phase four, thousands of people are given the substance to determine safety and efficacy of the product once again [26]. In this phase, the substance has received approval from the FDA and is available on the market [27]. It is important to note that not all drugs move on to the next phase. Drug trials tend to be more costly and time consuming compared to food trials [25]. Drug trials also have a different aim which is to establish the efficacy of a drug in treating, curing, or preventing a disease which is why they tend to use subjects who are at high risk or already have the disease [25]. By establishing the appropriate dose of a BC, a FFP can be deemed safe for the market.

Quantum Theory of Functional Food Science: Quantum theory provides information about energy at the atomic and subatomic level. Fission occurs when a neutron is absorbed by an unstable element causing the atom to split, which gives off energy and free neutrons [4]. The neutrons produced by a fission can split other atoms, which can lead to a chain reaction [4]. The critical mass of an atom can determine occurrence of chain reaction events [4]. For example, if there is an amount of an atom present below the critical mass, chain reactions will not continue [4]. However, if there is an amount of an atom at its critical mass then chain reactions will occur at a constant rate [4]. As for amounts above the critical mass, chain reactions will occur at a fast rate [4]. In FFP, it is important to give amounts of a BC at the critical amount as to not create increased chain reactions within the body which could lead to adverse effects. FF can be described 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]. As described, FF should contain enough of a BC so that it creates chain reactions within the body that are able to prevent or manage symptoms of a disease. It should also not have too much that it can be toxic. This could be achieved by determining the critical mass of a BC within a FFP to understand the amount necessary to create an effect on biomarkers of disease, and the amount that can lead to increased chain reactions that can harm consumers. In other words, critical mass of BC should be found to see how much will create steady fission events and how much can create accelerated fission events that can be toxic. The quantum theory of FFS describes a critical amount of a BC within a FF that creates chain reactions in the body that lead to health benefits for those that consume it. It is also able to describe the amount, above the critical amount, at which a BC can have toxic effects. Certain aspects of quantum science like nanotechnology can also be useful in helping researchers control characteristics of a FFP. Other than controlling physical characteristics, nanotechnology can be useful in controlling the dose of a BC that will be delivered and its bioavailability. Once a dose is determined, researchers can add nanocarriers to FFP to carry a BC and deliver a certain amount to a target tissue so that the BC may positively impact that area and help manage or treat disease in that way. It can also be used to fortify or protect the nutrient quality and quantity in a FFP so that it may have the critical amount of a BC to create beneficial effects.

Quantum theory and toxicity: Determining the critical amount of a BC is important for understanding the amount at which a BC is effective and safe. As previously mentioned, vitamin C is a potent antioxidant that has RDIs set in place that give recommendations for daily intake of vitamin C for men and women of different ages

[5]. Although these recommendations are 90 mg for men and 75 mg for women, researchers found that the minimum that a person should ingest is 10 mg a day in order to prevent deficiency [5]. Daily intakes below this amount can affect health and lead to the development of diseases like scurvy [5]. Similarly, researchers have determined that there is a maximum amount of vitamin C that can be had without it causing adverse effects, which is 2 g daily [5]. This can be described as the upper tolerable limit (UL) which is the maximum amount of a nutrient one can take in a day without experiencing adverse effects, and this applies to most people within a population [6]. This can be determined through the no observed adverse effect level (NOAEL) [14], which is the highest amount of a substance that does not create or increase adverse effects in experimental groups compared to controls [28]. Uncertainty factors are usually added to this making the UL lower than the NOAEL [14]. Amounts of vitamin C taken below 2 g/day are considered safe while amounts above this can create adverse effects like gastrointestinal distress and diarrhea [5].

Apart from determining the critical amount of a BC needed to create an effect on health, the quantum theory of FFS can be useful to establish the dose at which a BC can be toxic. This is important information because it can help consumers make better choices about the amount of a FFP they intake. Information about toxicity can be found by conducting preclinical trials in a dose response manner to determine the critical amount at which there are accelerated chain reaction events that cause toxic effects [29]. The amount of time an animal is exposed to the BC should be noted, as it is possible that a toxic effect may not occur in short term trials, but in long term trials show toxic effects [29]. It should also be noted that there are certain foods that may be toxic to some species but not toxic to others [29]. There may be foods that can cause adverse effects in animals but not in humans. An example that could be used is dogs, in which foods like chocolate or grapes could create toxic effects, but in humans these foods do not [30]. Using dose response and the quantum theory of FFS, researchers can expose animal subjects to different doses of a BC and observe any toxic effects. This can help them determine the NOAEL of a BC and critical amount for toxic effects to occur.

Mutagenicity testing can also use quantum theory to determine the critical amount of a BC that causes toxic effects at the cellular level. This includes changes to DNA or genes that can make an organism more susceptible to diseases like cancer [31]. These tests are also done in a dose response manner to assess at what dose a BC can create accelerated chain reactions that lead to a mutation or damage to cells that can promote development of symptoms and possibly even a disease [31]. Rodents are given FFP with different doses of BC for some time and then their tissues are collected to conduct histological analyses [31]. Through this the critical amount for toxicity can be determined so that consumers are warned against taking amounts above this.

Quantum mechanics: With an increasing population and changes in diets, researchers have been searching for a way to use quantum sciences to modify and improve FFP. Researchers at Nestle and the University of California, for example, discovered how water and lipid molecules interact which in turn can allow other scientists to modify these interactions [32]. Using quantum mechanics, researchers are able to create changes in the interactions of water and lipid molecules of foods that can alter its structure and therefore taste and other physical characteristics [32]. Although quantum mechanics does not make a FF, it is able to create modifications that help improve it and make it better for consumers.

Nanotechnology: A way in which this is done is through nanotechnology which is able to alter characteristics of an object at the molecular and atomic level [33]. This can

help the food industry create changes in taste, texture, nutrient bioavailability, and durability of a product [33]. Nanoencapsulation is a method used in food processing that enhances the delivery of certain food compounds [33, 35]. For example, when foods are processed denaturation of certain proteins or BC may occur [33]. This can also occur within the body due to the presence of enzymes and acidic environment in the stomach [35]. Nanoencapsulation prevents this from happening so that consumers can receive these beneficial compounds from foods making them more bioavailable to consumers and saving companies money since they would not have to add more BC to compensate for the amount that is destroyed in digestion. [33, 34]. Nanoscience can allow the food industry to control how much of a BC is bioavailable to consumers. Nanoencapsulation can also be used to protect flavors that may be degraded when food is processed [34]. Nanoparticle use risks are that they are more chemically reactive, can increase risk for toxicity of a BC by making it more bioavailable, and it may have adverse effects on one's immune system and overall health [33]. In the United States, the use of nanoscience in the food industry is currently regulated by the USFDA, but more research must be done on this practice to create regulations that have a better understanding on its safety and efficacy [33].

Although FF can provide enough BCs to create health promoting effects, there is a need for a delivery system. Nanotechnology can be a useful delivery system that can allow FF to have optimal effects on health by ensuring that more of that product is being delivered. The delivery of FF can be improved with the use of carriers like those used in nanotechnology. There are many types of nanocarriers that are used in nanotechnology. These nanocarriers transport BC or other substances to target tissues [34]. Polymeric nanoparticles are biodegradable and allow for better control in the delivery of drugs [34]. Liposomes are composed of lipid bilayers which can make them more stable in certain environments and enhance the delivery of some compounds [34]. Dendrimers contain branches while carbon-based ones contain carbon [34]. Hydrogel ones can absorb water and nanoemulsions are composed of small particles that can be classified as oil in water or water in oil [35]. Quantum dots are another type of nanocarrier that are nanocrystals that can be used as nanosensors that assess the quality of food [34, 35]. Quantum dots can analyze food and detect things like toxins, trace elements, pathogens, flavor, and protein distribution through methods including mass spectrometry, voltammetry, and fluorescence microscopy [35].

It is important to note that nanotechnology is not what makes a food functional. As defined by the FFC, a FF is “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]. A FF is able to create health benefits without the use of quantum mechanics, and is able to create these effects without the use of nanoencapsulation. It is simply a technology that can be used to modify functional foods to make BC more bioavailable and possibly make products more attractive to consumers. It does not affect the function or type of BC within the FFP, just the amount that is available by reducing its destruction in digestion.

Nanoencapsulation can enhance the functionality of FFP. One example is polyphenols, which have antioxidant and anti-inflammatory properties that can reduce the risk of some chronic diseases [36]. Polyphenols can also be degraded by enzymes, acidic environments, and digestion once ingested making them less bioavailable [36]. By using nanocarriers, polyphenols can be encapsulated so that they may not be degraded once ingested making them more bioavailable and able to reduce oxidative damage and inflammation. This has been done on polyphenols like caffeic acid phenethyl

ester so that when ingested, more can be bioavailable allowing it to act on cancer cells to improve health [36]. This type of technology can be used by a vast array of BCs to make their delivery, bioavailability, and function more effective. However, it is important to determine the critical mass of a BC prior to the use of nanotechnology to improve its delivery. There is still more information needed about the safety and effectiveness of quantum sciences on FFP. There is also a need for regulation of its use, specifically of nanotechnology, in the food industry. Future research is needed to understand more about the relationship between quantum physics and its use in the functional food industry.

CONCLUSION

The FFC proposed a 16-step process for creating a FFP and making it available to the market [2]. It should be noted that there are currently only 16 steps in this process, however this could change as more steps could be added in the future. As part of this process, an appropriate dose for a BC within the FFP is established. This is an important step for understanding more about the critical amount needed to create health promoting effects in consumers. It is also important for understanding the safety and possible toxicity of a FFP. Dosage, safety, and efficacy are usually determined by conducting preclinical and clinical trials.

Although clinical research is the main way that dosage is established, quantum sciences can also be useful in the third step of the multi-step process. Quantum theory of FFS can determine the critical amount of a BC needed for chain reactions to occur in the body, ultimately resulting in health benefits and changes in biomarkers of disease. However, more preclinical trials should be conducted in order to get information about how time may be a factor that affects the efficacy of a FFP. For example, although a FFP contains the critical amount of a BC, it may not create significant improvements in health in two months, but at six months of use shows reduced biomarkers of a disease. In other words, the same amount of a BC might not create effects on health with short term usage, but it can if used long term. There might also be cases in which it could be beneficial to use a FFP in cycles where it is used for a time and for another is not used. Through the quantum theory of FFS, researchers will be able to determine the critical amount of a BC that allows a FFP to be functional as well as the amount that can create toxic effects.

Lastly, there needs to be more consideration for labeling of FFP. The Japanese Foods for Specific Health Uses (FOSHU) is a system that evaluates FF and the claims made for their use [2]. FF approved by FOSHU are given a label that provides information about how much BC is present in the FFP, the function of the FFP, and how long the FFP should be had [2]. According to the FFC, FFP should have the dose of a BC established. It is also important that information about this dose is provided to consumers. In the United States, when drugs are made available to the market, they contain information about how much to take, when to take it, who can and can't take it, and possible side effects. Like FOSHU approved products and drugs in the United States, FFP should also have labels providing information on dosage, timing, target and at-risk populations, and possible adverse effects from high intakes. In step 9 of the 16-step process, the FFC has proposed a labeling system for FFP [2].

Prior to bringing a FFP to the market it is important to establish a dose at which a BC can make the FFP effective and guarantee its consumers that it is safe. The methods used to establish a dose were discussed in this article. A FFP must go through preclinical and clinical trials to establish a dose at which a BC can create an effect on health in a safe way. Different methodologies of preclinical trials can be used including in vivo and in vitro. As for clinical studies, there are certain methods used for trials on drug products, however they are not the same for food. Food trials have different objectives than drug trials, so their methodology is different. In this article we

also discussed the relationship between quantum theory and FFS, and proposed a way in which quantum theory and quantum mechanics could be a useful tool in the development of a FFP. Specifically in the establishment of an appropriate dose of a BC within a FFP, which can be established using quantum theory of FFS. Because of the relationship established in this article, future trials establishing the dosage of FFP should consider the use of quantum theory of FFS to understand more about the critical amount of a BC that can produce health promoting effects and the amount that can produce toxicity.

Abbreviations: FF: functional food; FFP: functional food product; FFS: functional food science; FFC: functional food center; BC: bioactive compound

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

Authors' Contribution: The original idea (The concept of quantum theory of functional food science) was conceived by DM and was discussed with SS. SS collected data and wrote the manuscript. DM advised, participated in writing, and editing manuscript.

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