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Economic implications of functional foods

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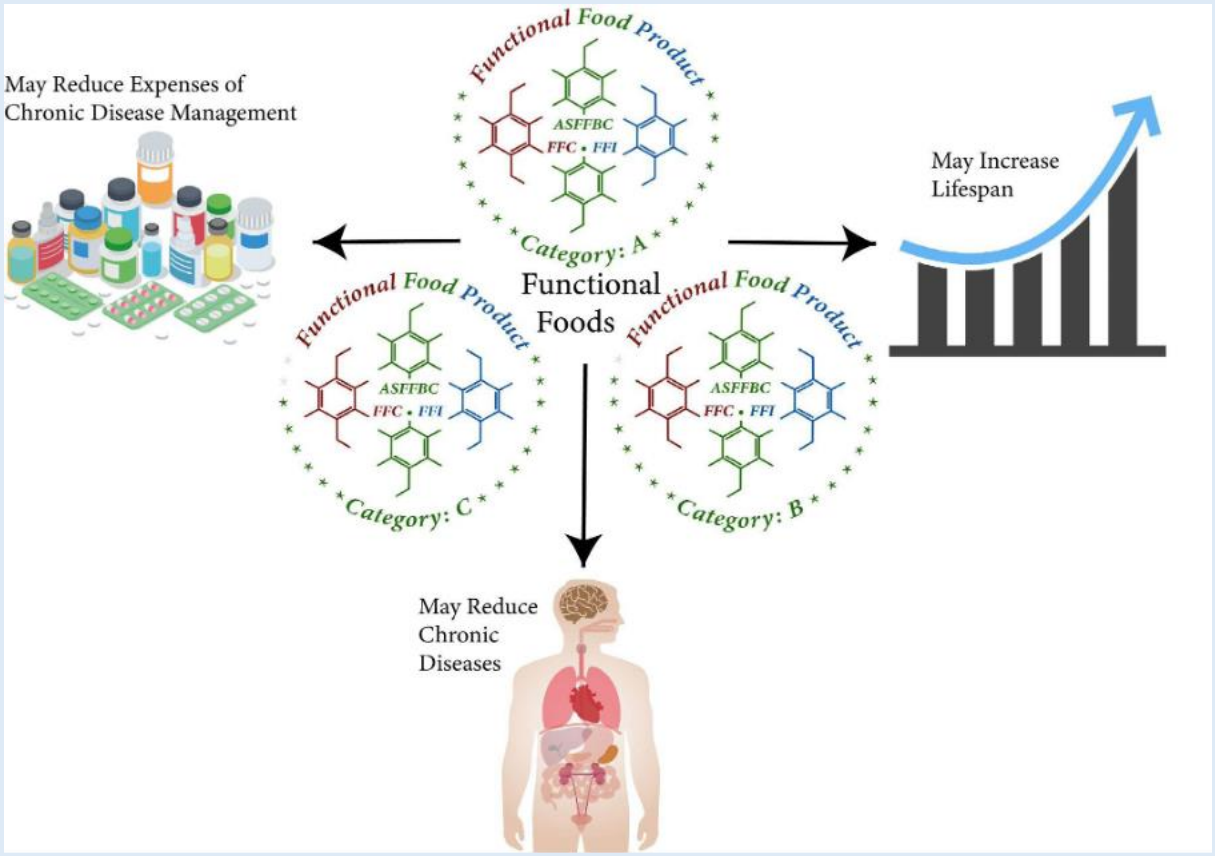
ABSTRACT

Functional food products (FFPs) and their constituents, known as food bioactive compounds (FBCs), possess distinctive properties that may mitigate the risk of specific diseases, offering a potential alternative to conventional medicine. Fruits and vegetables contain specific components such as vitamins, minerals, flavonoids, anthocyanins, and others, which play a role in managing symptoms of chronic diseases. This review explores the impact of functional food products on the economy. The rising costs associated with Western medical treatments for chronic diseases, exacerbated by the side effects of medication, stresses the importance of exploring non-medical alternatives. Furthermore, the absence of a definitive definition for functional food products by the U.S. Food and Drug Administration (FDA) adds to the weakness of the food sector in the United States. On the other hand, Japan has initiated a regulatory system known as Food for Specified Health Uses (FOSHU), which introduces functional foods to the market and educates consumers on their health benefits. Subsequently, they have also introduced a new regulatory system called Foods with Functional Claims. Despite limitations such as the insufficiency of post-market research, clinical studies, and epidemiological studies in both systems, Japan continues to outperform the U.S. in the food industry. Establishing its own regulatory system for functional foods could not only enable the FDA to compete more effectively with Japan but also lead to significant improvements in life expectancy and the economy. By examining regulations in both countries, this review sheds light on how functional food products may contribute to improved public health and economic outcomes.

Keywords: Functional Food Products, Food Bioactive Compounds, Food and Drug Administration, Food for Specified Health Uses, Foods with Functional Claims, Economy



Graphical Abstract:

INTRODUCTION

More than two-thirds of deaths in the United States are attributed to chronic diseases, including heart disease, cancer, stroke, and diabetes [1-2]. It is well known that several food components may elicit certain health benefits that, in return, could reduce the risk of chronic diseases [3]. The treatment of such diseases is projected to cost the U.S. at least $1 trillion dollars every year and is largely attributed to challenges in effectively managing their symptoms [1, 4]. With the growing U.S. population, there is a corresponding increase in the number of Americans affected by at least one chronic disease, subsequently driving up medical expenses [1]. This nationwide economic burden brought about by chronic diseases emphasizes the need to explore nonmedical approaches as potential solutions.

The Functional Food Center (FFC) has defined functional foods 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” [4]. In order to bring these products to market, they must undergo a meticulous and comprehensive process to ensure their safety and efficacy [5]. The food bioactive compounds (FBCs) found within functional food products (FFPs) elicit biological

mechanisms that may reduce the risk of chronic disease [6-9]. Studies on natural FBCs such as anthocyanins, resveratrol, tannins, flavonoids, vitamins, minerals, and dietary fibers suggest a correlation between these compounds and certain molecular pathways, potentially assisting in the management of symptoms associated with cardiovascular diseases, cancer, diabetes, and other conditions [6, 10].

In the United States, the Food and Drug Administration (FDA) is responsible for protecting the public health of its citizens through the regulation of various medical products such as drugs, food, medical devices, and vaccines [11]. However, the World Health Organization (WHO) revealed that the life expectancy and healthy life expectancy at birth and at age 60, are longest in Japan for both males and females [12]. The Consumer Affairs Agency (CAA) is responsible for protecting the rights of consumers in Japan including food safety regulations [13].

This review conducts an analysis of the effects of functional food products on the economy, while also comparing regulations and safety standards for these products in Japan versus the United States.

Methodology: An extensive literature review was conducted to investigate the potential health benefits offered by FFPs, alongside their economic significance, and an examination of the regulatory frameworks in Japan and the United States. The methodology entails an in-depth analysis of secondary data, including peer-reviewed scholarly articles and pertinent information sourced from official health organization websites. This review aims to gather current insights into the potential of functional food products in mitigating disease risk and improving the overall economy. Additionally, it aims to compare the regulatory systems overseeing these products in Japan and the United States, while identifying the strengths and weaknesses inherent in each system.

Research questions: The research began by formulating several pivotal questions to guide the inquiry:

(1) In what ways do functional food products reduce the risk of disease and manage associated symptoms?
(2) What are the key steps involved in the development of a functional food product?
(3) How do functional food products compare with traditional Western medicine?
(4) What economic benefits can functional foods potentially offer?
(5) How do the regulatory frameworks for functional foods in Japan compare to those in the United States, and what are their respective limitations?

Literature search strategy: The search spanned electronic databases such as PubMed, NCBI, MDPI, and the Functional Food Center's journal database [www.ffhdj.com]. These databases were chosen due to their extensive selection of review articles, clinical studies, and randomized controlled trials that are related to our literature review. Information from official health organizations, including the FDA, CAA, and MHLW, was also utilized in the research process.

Selection criteria: To ensure the relevance and quality of selected sources, inclusion criteria were established. A total of 61 articles met these criteria and were included in the review. Selected articles provided objective, scientific perspectives on FFPs and their ability to induce health benefits. Articles that addressed the constituents of functional food products and their corresponding

disease outcomes, the process of developing functional food products, their potential economic impact, as well as the regulatory systems in Japan and the United States were all encompassed within the inclusion criteria. Exclusion criteria consisted of articles that did not primarily concentrate on the implications of functional food products regarding both the economy and health, as well as regulatory systems outside of Japan and the United States. Preference was given to articles that were published within the last 5 years.

Data extraction and analysis: Information retrieved from sources included the risk factors associated with traditional medicine, the components of functional food products, the physiological effects attributed to functional food products, the comparative economic impact of functional foods versus conventional medicine, the functionality of regulatory systems in both Japan and the U.S., as well as the identified weaknesses within these systems. Findings were incorporated into the conclusion and organized into tables for clarity. Keywords used for the search included functional food products, chronic diseases, adverse drug reactions, lifespan, healthcare costs, FDA, and FOSHU.

Economic Impacts of Adverse Drug Reactions: Currently, the primary method of addressing diseases or health-related conditions is through medication, which refers to substances used to cure or alleviate symptoms of illnesses [14]. However, numerous medications carry adverse effects that may pose potential risks, including those that could be life-threatening [15-16]. Adverse drug reactions (ADRs) can result in extended hospital stays or increased hospitalization rates, contributing to escalated costs, amounting to up to $30.1 billion annually in the United States [17-18]. Globally, side effects caused by medical errors account for approximately $42 billion in expenses [19]. The adverse drug reactions causing the most significant economic burden include fevers, bleeding, diarrhea, and irregular heartbeats [17]. Hospitals incur additional expenses on supplies to treat patients, while patients face increased costs due to prolonged hospital stays or outpatient care [20]. Moreover, patients often need to take time off work to manage the side effects, further impacting their financial situation. A study conducted at the University of Gondar Comprehensive Specialized Hospital (UoGCSH) examined the economic implications of ADRs among hospitalized patients [21]. The findings revealed that individuals who experienced ADRs, had a tendency to spend more time in the hospital, required ICU visits, experienced higher in-hospital mortality rates, and incurred significantly higher charges compared to those who did not experience side effects [21]. ADRs initiate a domino effect, wherein new medications are frequently prescribed to address the side effects caused by previous medications, thus perpetuating an endless cycle of financial strain on both patients and the healthcare system [22].

Functional Food Products in Disease Management: Functional food products contain FBCs, which may reduce the risk of diseases [23-24]. FBCs are typically found in fruits and vegetables like blueberries, bananas, pomegranates, spinach, carrots, among others [25]. Abdulqahar et al. conducted a study investigating the impacts of bioactive compounds present in jujube, a Chinese date fruit, through the extraction and analysis of its phytochemicals [26]. The findings indicated that the phytochemicals contained certain neurological properties and the compounds (2,3,6,7-tetramethyl-10-(4-methylphenylsulfonyloxy)- 1,4,4.alpha.,5,8,8a.beta.,9.b) and Andrographolide, which were found in the dates, interacted with molecular targets linked to Alzheimer's and anxiety, thus demonstrating potential anti-Alzheimer's and anti-anxiety effects [26]. Furthermore, Jippo et al. conducted a study assessing the anti-allergic

activity of vegetables, specifically green onions (scallions) [27]. The results revealed that scallions did in fact contain anti-allergic properties and may be used as a potential treatment to allergic diseases such as asthma or food allergies [27]. Additionally, the U.S. FDA has acknowledged certain food compounds for
their potential health benefits related to disease, although it does not recognize functional foods as its own category [3]. Baicalin, a flavonoid naturally occurring in fruits, herbs, and tea leaves, possesses anti-inflammatory and anti-tumor properties [28]. According to a study by Nagarakan et al., oral administration of Baicalin resulted in improved insulin secretion and hemoglobin levels in addition to offering renal tissue protection, thereby alleviating symptoms in type 2 diabetic rats [29]. Also, Hou et al. conducted a study on the impact of health-care foods on altitude hypoxia, finding that natural options such as Chinese senna (Cassia obtusifolia) and red sage (Salvia miltiorrhiza) are more effective than synthetic drugs in preserving normal physiological function at high elevations [30]. FFPs are considered safer than numerous medications and tend to be more cost-efficient due to their minimal incidence of side effects [31]. Given the apparent long-term cost efficiency of FFPs and their potential to effectively manage disease symptoms alongside Western medicine, further research into their therapeutic potential is warranted.

The Economic Impact of Increased Lifespans: Extended lifespans contribute to economic growth because individuals tend to work and contribute to the economy for a longer period [32]. If there are improvements in life expectancy, individuals may decide to retire later in life which will drive up the labor markets [33]. They may also engage more in financial markets as they prepare for retirement. The American Association of Retired Persons has defined longevity economy as the contributions of individuals over the age of 50 years old to the economy [34]. Through a series of data analyses, they have concluded that the 50 plus age group contributes about $8.3 trillion annually and, by 2030, the number will increase by $4.3 trillion [34]. Over time, if people continue to lead long, healthy lives, the economic contributions of this age group will benefit individuals across all age groups or generations [34-35]. Therefore, it is important to make lifestyle adjustments such as regular exercise and adopting a nutrient-rich diet, as these can effectively prolong an individual's lifespan [36-37]. For example, Kinoshita et al., assesses the effects of ubiquinol, a reduced form of ubiquinone found in foods like fatty fish, avocadoes, chicken, and peanuts, on improving the quality of life [38]. The researchers concluded that ubiquinol not only improved mental health, specifically in females, but also did not induce any serious side effects [38]. The consumption of functional food products can help individuals lower the risk of diseases that might affect their health in later years.

In Japan, stroke was the primary cause of death, succeeded by cancer and cardiovascular disease (CVD) [39]. These noncommunicable diseases are labeled as *Adult Diseases* because they typically manifest with age [39]. In 1956, the Japanese government-initiated efforts to prevent the emergence of new diseases, leading to a 70% reduction in stroke mortality rates from 1960 to 1990 [39]. This was achieved through measures such as reducing salt intake to lower blood pressure and ensuring access to fresh food products [39]. A typical Japanese meal comprises a bowl of rice, soup, and three additional dishes featuring a variety of seafood and vegetables, often accompanied by a cup of green tea [39]. Simultaneously, Japan underwent rapid economic growth, leading to an increase in life expectancy, with

projections suggesting a longevity of 91.35 years for females and 84.95 years for males by 2065 [39].

Regulation of health claims in Japan: Functional foods were initially introduced in Japan, with the government granting funds for the exploration of FOSHU [40]. The Ministry of Health, Labour, and Welfare of Japan (MHLW) defines FOSHU: "FOSHU refers to foods containing ingredients with functions for health and officially approved to claim its physiological effects on the human body. FOSHU is intended to be consumed for the maintenance/ promotion of health or special health uses by people who wish to control health conditions, including blood pressure or blood cholesterol" [41]. FOSHU is regulated by the Ministry of Health, Labour, and Welfare of Japan and is identified by a distinctive logo, setting it apart from other foods in the market. The process of developing a FOSHU product involves product planning, conducting in vivo and in vitro clinical trials, and manufacturing [42]. Unlike the United States, Japan maintains a catalog of approved FOSHU products, each endorsed for specific health claims as illustrated in Table 1.

Table 1. List of approved FOSHU products in Japan

Specified Health Uses	Main Ingredients
Gastrointestinal conditions	Oligosaccharides, lactose, bifidobacteria, lactic acid bacteria, dietary fiber 8 ingestible dextrin, polydextrose, guar gum, psyllium seed coat
Blood cholesterol levels	Chitosan, soybean protein, degraded sodium alginate
Blood sugar levels	Indigestible dextrin, wheat albumin, guava tea polyphenol, L -arabinose
Blood pressure	Lactotripeptide, casein decapeptide, geniposidic acid, sardine peptide
Dental hygiene	Palatinose and erythritol
Mineral absorption	Calcium citrate malate, casein phosphopeptide, heme iron, fructooligosaccharide
Osteogenesis	Soybean isoflavone and milk basic protein
Triacylglycerol	Medium-chain fatty acids

Food with Functional Claims: Starting in 2015, Japan implemented a new regulatory system known as Food with Functional Claims, which mandates the inclusion of clinical trials or systematic reviews for acceptance [43]. The Consumer Affairs Agency mandates a six-step approval process for foods before they can be marketed with functional claims [44]. The steps include verifying if the product qualifies under the Foods with Functional Claims category, evaluating product safety, implementing production and quality control systems, developing a system to report information regarding health outcomes, clinical trials, and systematic reviews to evaluate efficacy, and adhering to product labeling guidelines as per CAA regulations [44].

Limitations of Japan's Regulation Systems: A drawback of Japan's regulation systems is that the Japanese government does not thoroughly assess the safety and

effectiveness of functional foods before they are introduced to the market [45]. The Functional Food Center proposes a comprehensive 17-step procedure for the development of functional food products [46]. This includes conducting literature reviews to identify relevant bioactive compounds (BC) and establishing their appropriate dosages, discovering biomarkers associated with molecular mechanisms of the BC, developing a suitable food delivery system, conducting in vivo and in vitro trials, undertaking clinical human trials, and conducting both epidemiological studies and post-market research [46]. Functional food products are classified as A, B, or C based on the stage they have reached in the 17-step development process [46]. If a functional food has completed steps 1-14 and received certification at step 15, it is classified as C. If it has also been investigated in epidemiological studies at step 16, it is classified as B. Finally, if it has completed all the steps, including post-market research at step 17, it receives a classification of A [46]. Conducting studies that specifically focus on the food product in question, while eliminating other potential variables, is crucial for accurately determining the efficacy of the product [47]. Additionally, the absence of aftermarket research represents a major flaw in Japanese regulation systems, as it fails to monitor the product's performance in uncontrolled environments over time [48]. Not to mention the fact that the Food with Functional Claim's notification system contained insufficient information in regard to the sample size and overall results of the study [49]. Masanori Suzuki, a professor at the Faculty of Sport Sciences at Waseda University, emphasizes the need for comprehensive testing under various conditions to ensure the effectiveness of products before they are marketed to consumers by the government [50]. By introducing epidemiological studies after a functional food product is launched to the market, Japan can improve their regulation systems, which, in turn, will improve results from product consumption and advance the emerging field of functional food science.

Regulation of health claims in the United States: Currently, the U.S. FDA does not officially recognize a definition for functional foods [51]. The FDA holds the belief that if certain foods can induce specific biological effects in the body, potentially treating or preventing diseases, then such FFPs would be classified as drugs rather than food items [3]. However, the FDA does assess health claims, which are grounded in scientific evidence and establish a connection between a food component and a health-related condition. Every health claim undergoes a rigorous review process by the FDA, during which there must be significant scientific agreement (SSA) among experts that the claim is supported by public scientific evidence for a specific disease [52].

FDA Regulation of Functional Food Products: Although the FDA has implemented regulatory systems to assess health claims, there are currently none specifically tailored to FFPs [52]. The FDA conducted a public hearing regarding the regulation of conventional foods marketed as functional foods [53]. The Institute of Food Technologists (IFT) suggests that the FDA define and regulate functional foods, recognizing the growing consumer demand [53-54]. However, the FDA feels constrained in its capacity to do so, referencing the Nutrilab v. Schweiker court decision [53, 55]. Given their demonstrated abilities to reduce the risk of diseases, establishing a regulatory system for FFPs in the United States is crucial. Furthermore, the FDA continues to classify functional foods simply as conventional foods rather than medicinal products. This means that

manufacturers incorporating bioactive compounds into their products are not obliged to undergo an extensive drug approval process [56]. In recent years, there has been a rise in health awareness among individuals, leading to a growing emphasis on consuming organic foods [57]. Chronic diseases, along with the associated costs, have risen, adversely impacting quality of life [58]. Functional foods serve as a solution to this problem, offering convenient ways to address health needs that align with the busy schedules of consumers [59]. In Japan, established regulatory frameworks for functional food products have strengthened the public's trust and decreased healthcare costs [60]. By establishing its own regulatory framework, the FDA ensures that U.S. companies will remain competitive in the global market. This fosters the growth of a new market catering to consumer demands as companies invest in the research and development of FFPs. Given the center's extensive years of experience in the field of functional food science, as well as its established 17-step process for developing functional food products, the collaboration between the Functional Food Center and the FDA could be invaluable in developing a system for the regulation and promotion of functional food products in the United States [61].

CONCLUSION

In conclusion, the exploration of functional food products reveals a promising avenue for addressing the limitations of medical treatments on chronic diseases. The treatment of chronic diseases in the United States is currently costing trillions of dollars, especially due to adverse drug reactions, which often result in patients requiring prolonged hospitalization, additional tests, and increased medication. These unplanned hospital visits strain healthcare resources and decrease productivity and wages for patients. Because FFPs do not elicit life-threatening side effects, they not only provide greater benefit to the patient, but also present a more cost-efficient alternative. Furthermore, the correlation between healthier lifestyle choices, increased life expectancy, and economic growth is undeniable. As individuals live longer, they tend to contribute to the economy for a greater portion of their lives, either through engagement in financial markets towards retirement or continued participation in the workforce. The longevity economy, defined by the American Association of Retired Persons, projects that the aging population will contribute trillions of dollars annually to society. Increasing life expectancy and overall quality of life can be done by lifestyle adjustments such as exercise and nutrient-rich diets. FFPs contain many compounds that can manage symptoms of chronic disease and extend healthy aging.

Originally introduced in Japan as Food for Specified Health Uses (FOSHU), functional foods were officially approved by the Ministry of Health, Labour, and Welfare (MHLW) for their physiological benefits. This regulatory framework is limited in its assessment of the safety and efficacy of functional foods before market introduction. The Functional Food Center's 17-step procedure serves as a roadmap for navigating the development and evaluation of functional food products. The procedure underscores key stages such as defining the objectives of the FFP, identifying pertinent BCs, conducting both in vitro and in vivo studies, followed by rigorous clinical trials. Additionally, it advocates for special labeling to educate consumers on optimal product consumption, emphasizes the importance of epidemiological studies, post-market research, and more. However, the absence of meticulous research, encompassing clinical trials, epidemiological studies, and post-market research as outlined in this procedure, reveals a notable flaw in

Japan's current system. This oversight overlooks the long-term performance of products, thus hindering a thorough understanding of their efficacy and safety. Introducing these study methods could enhance Japan's regulatory systems, leading to improved consumer outcomes and contributing to advancements in functional food science.

While the U.S. FDA evaluates health claims grounded in scientific evidence, they do not have an established system designated to functional food products. Establishing a regulatory system, similar to Japan's, is crucial to meet consumer needs, reduce healthcare costs and maintain competitiveness in the global market. The collaboration between the Functional Food Center and the FDA could offer valuable insights in developing a system for FFPs and advancing functional food science in the United States.

This review article provides insights into the health benefits of functional food products and their potential to enhance economic outcomes. Additionally, it conducts a comparative analysis of the regulatory frameworks governing FFPs in Japan and the United States, shedding light on their respective strengths and limitations. Despite the collection of studies demonstrating the effectiveness of FFPs, skepticism persists regarding their ability to genuinely reduce the risk of chronic diseases.

The Novelty of This Work: This review article demonstrates how the positive effects of functional foods on healthy lifespan establish this connection, consequently impacting medical expenses and the overall economy. These effects hold promise for reduced government spending, more cost-effective strategies for insurance companies, and overall decreased expenses.

List of Abbreviations: FFPs: functional food products, FBCs: food bioactive compounds; FDA: Food and Drug Administration; FOSHU: Food for Specified Health Uses, FFC: Functional Food Center, ADRs: adverse drug reactions

Authors' Contributions: All authors discussed and contributed to the final manuscript. DM brought the idea of FF as a factor to reduce the expenses on healthcare costs in US and advised writing this manuscript. AB searched for literature and wrote the article.

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