

Probiotic Supplements and Food Products: Comparison for Different Targets

Neda Mollakhalili Meybodi¹, Amir Mohammad Mortazavian^{2*}, Sara Sohrabvandi³, Adriano G da Cruz⁴, Reza Mohammadi⁵

1- Student Research Office, Department of Food Science and Technology, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2- Department of Food Science and Technology, Faculty of Nutrition and Food Sciences, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3- Department of Food Technology Research, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

4- Federal Institute of Rio De Janeiro (IFRJ), Food Department, Rio De Janeiro, Brazil.

5- Department of Food Science and Technology, Faculty of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Abstract

Background and Objective: Currently, probiotics are mainly used in processed foods or nutritional supplements mainly due to their impact on health. The probiotic markets have a considerable share either in food or drug industry. In this article, drug supplements and food products containing probiotic microorganisms are considered in a comparative approach from different aspects including functional, efficacy, hedonistic and economical.

Results and Conclusion: However, the impact of ingesting probiotics via food products or drug supplements is not actually the same from consumer's point of view as well as from clinical efficacy. Consumer attitudes appear to be reflected in expectations on nutritional, functional and health effects side and also from the point of nutrition economics.

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*Corresponding author:

Amir Mohammad Mortazavian,
Faculty of Nutrition and Food Sciences,
Shahid Beheshti University of Medical
Sciences, P.O.Box: 19395-4741, Tehran, Iran.

Tel: +98-912-7114977

Fax: +98 -21-22360657

E-mail: mortazvn@sbmu.ac.ir

1. Introduction

Probiotics are live microorganisms which are healthy to the host when consumed adequately [1]. Thus the important point is the live microorganisms or bacterial cultures ability to endure the gastrointestinal tract conditions and survive to supply beneficial health effects on the host by balancing the gastrointestinal microbiota or by other means [2-4]. Using microorganisms as health improvers has had an increasing trend since the mid-nineteenth century, and probiotics have been well assessed in both clinical and food trials [5-7]. The main commercial probiotic species used in food and drug technologies are presented in Table 1.

The lactobacillus and bifidobacteria species, which were discovered and isolated more than 150 years ago, are the predominant probiotics up to now [8]. Several health benefits are attributed to probiotics; this has increased the commercial attention in the development of different

applications leading to the rapid augment of this market segment [9]. Of these characteristics, the most agreed-upon are modulation of intestinal microflora, immune response enhancement, improved gastrointestinal health, and protection against infections such as acute gastroenteritis illness and inflammatory bowel disease [8,10-15]. A probiotic strain to be used in food matrices and pharmaceutical applications must resist the conditions and interactions when incorporated in foods and drugs and be stable during passing through the gastrointestinal tract [16]. It has been revealed that many strains are not as stable as required. This instability could be overcome by different techniques such as adjusting the compositional and process factors during the manufacture of food and drug products in the favor of strains used, selecting more tolerant strains, and using encapsulation process [2,17].

Table 1. Main probiotic species applied commercially in food and drug (8,9,75)

<i>Lactobacillus acidophilus</i>	<i>pseudocatenulatus</i>	<i>Leuconostoc mesenteroides</i>
<i>johnsonii</i>	<i>catenulatus</i>	<i>Pediococcus acidilactici</i>
<i>plantarum</i>	<i>bifidus</i>	<i>Enterococcus faesium</i>
<i>rhamnosus delbruecki</i>	<i>longum</i>	<i>Lactococcus lactis</i>
<i>reuteri</i>	<i>thermophilus</i>	<i>Saccharomyces boulardii</i>
<i>fermentum</i>	<i>adolescentis</i>	<i>Propionibacterium freudenreichii</i>
<i>Brevis</i>	<i>Streptococcus intermedius</i>	
<i>lactis</i>	<i>salivarius</i>	
<i>cellobiosus</i>	<i>cremoris</i>	
<i>paracasei</i>	<i>lactis</i>	
<i>helveticus</i>	<i>Aspergillus niger</i>	
<i>Bifidobacterium lactis</i>	<i>oryzae</i>	

Commercial probiotics products for use of humans are available in two main forms, including food products and drug supplements. In drug supplements, tablets or capsules, very high amounts of viable probiotic cells (at least 10¹⁰ colony-forming units (CFU ml⁻¹) are carried through the body, while in food products, the cells are added into carrier foods or applied as starter probiotics in fermented foods [18]. A series of complex interactions and interventions is carried out in food matrices that might adversely affect the viability of initially inoculated pro

biotics in food before consumption [19]. Therefore, the matrix and process engineering in food probiotic production is nowadays an advanced and developed

science and technology. However, production and maintenance of probiotic food products are considerably more difficult than the drug ones; it seems that consumers prefer inherently ingesting medicinal additives via food stuffs rather than the drugs. This article reviews the functionality of probiotic food products vs. drug supplements in different aspects such as efficacy and effectiveness, hedonism, price and trade.

2. Probiotic products

Oral consumption of probiotics may take place via drug products, namely supplements and food products. They have their own characteristics and functions (Table 2), which are discussed below:

2.1. Probiotic dietary supplements

A dietary supplement (also might be called food supplement) is an orally administered substance designed to deliver a certain dietary ingredient to complement the diet [20-22]. In other words, they are not substantially applied to treat or cure a specific human disease. They are usually packaged in different forms of capsules, tablets, powders (in sachets) or liquids in measured doses [23-25]. In order to produce a beneficial supplement, probiotics must be able to tolerate the severe conditions of gastrointestinal tract and arrive viable to the site of action [26-28]. This fact must be considered during supplement formulation, production and storage.

Table 2. Advantages of probiotic food products and drug supplements from different aspects, in a comparative approach

concept	Description	
	Supplement	Food
Efficiency (in the product and in GIT)	Transfer of considerably higher numbers of viable probiotics into GIT without considerable loss during the storage. Therefore, they are preferred when specific therapeutic functions are required.	Good to excellent matrix protection for probiotic cells during delivery in GIT.
Hedonism	-	Being consumed for hedonism and comprise sensory attributes.
Product and market development	-	Have higher potential of variation and therefore, product and market development
Simplicity of production (probiotic stability in product during the storage And sensory properties)	Simpler design and formulation from production point of view; namely, the stability of probiotics during the process and storage as well as not having negative effects of added probiotics on sensory properties of final product.	-
Regulatory administration and legislation		Foods are subjected to more difficulties

The manufacturing process of a dietary supplement is similar to medicines; however, the severe courses of action used in medicinal products are not necessary to pursue. Probiotic formulations comprise selecting microorganisms able to subsist throughout the technological process and remain viable subsequently with unaffected properties for long periods of storage [29]. The active element of a probiotic supplement is the resistant probiotic microorganism(s) in a highly enough amount to guarantee precise dosing and good stability [30].

Lyophilizates of microorganisms are usually used to produce probiotic dosage forms. Lyophilization is a process widely used to preserve biological samples. However, the severe environmental conditions that the cells experience during freeze-drying may damage their structure and physiology followed by decrease in their viability [30]. To reduce these adverse effects, shielding agents are usually added to the samples before freezing or freeze-drying [31].

The endurance of probiotics in oral solid dosage forms such as tablets, pellets and capsules have also been inspected in order to formulate a stable oral dosage form. A strong negative correlation between bacterial viability and compression force has been observed, revealing that probiotic survival decreases via increasing the tablet compaction forces [32].

2.2. Probiotic food products

Functional foods, which in Europe and the United States, can mean foods with approved official health claims, are the focus of growing attention nowadays due to the consumers awareness about the importance of food in human health [33,34]. Functional foods containing probiotics as biologically active ingredients create metabolic and physiological health effects more than their nutritional characteristics [35]. In spite of some scientific proofs stating the creation of health benefits due to consumption of some microbial strains, no clear suggestions indicate the effective dose for these strains. It has been accepted that higher numbers of viable bacteria are required to create efficient probiotic foods [30]. Different food matrices have the potential to be used as probiotic delivery systems, which are discussed in the next. Food matrices and processing conditions may also alter the properties of probiotic bacteria; therefore, these should be carefully documented and controlled [36].

2.2.1 Dairy products

Dairy products are the main group of foodstuffs able to transfer and deliver probiotic bacteria [37]. Today, the consumption of probiotic dairy products is recommended considering their effectiveness on human health like reducing the lactose fanaticism, increasing the absorption of minerals, the efficacy against *Helicobacter pylori* infection, and improvement and prevention of diarrhea and

constipation [38,39]. Currently, different kinds of probiotic dairy products are produced and consumed all over the world including pasteurized milk, ice cream, fermented milks, cheese and baby milk powders. milk and dairy products acquire some nutritional properties like high lactose content, which permits the growth of probiotic bacteria [18]. Some dairy products like fermented milks and cheeses are also preferred to be a vehicle for probiotics for their pH, buffering capacity, and fat content, which create an additional protection for the probiotics passing the gastrointestinal tract and improve their maintenance [40-42].

Probiotic microorganisms are added to fermented milks by different methods including: a) as non-starter culture with the main aim of delivering through the gastrointestinal tract, and b) as starter culture [43]. Considering both the complex relationships between probiotic microorganisms and milk components and the inadequacy of probiotics to ferment milk lonely, in the latter method, probiotics are mainly added to the milk with the assistance of lactic starter cultures (mainly, traditional yogurt bacteria) [44]. However, the most accepted probiotic dairy products are fermented products like yogurts and other fermented milks, in which the oxygen exposing may decrease their functionality [45]. Considering the fact that a great number of probiotic bacteria grow in anaerobic conditions, keeping them maintained during the refrigerator storage constitutes a technological challenge. A potential alternative to enhance the survival of probiotic bacteria is using glucose oxidase enzyme to use the infusing oxygen inside of the pot during storage. The existence and viability of probiotic may also be influenced by processing conditions and product environment [41].

2.2.2. Nondairy products

However, dairy products are still the favored products to be used to incorporate probiotic bacteria; their high lactose and cholesterol content, their necessity to be stored at the refrigerator temperature, the consumers demand for vegetarian based probiotic bacteria and even new taste and flavor are the motivation factors to produce nondairy products [46,47]. Accordingly, different types of probiotic-containing non-dairy products such as juices and nondairy beverages, vegetable, cereal-based products [48], chocolate based products and processed meats [49] have been developed and displayed during the past few decades. Production of a new non-dairy probiotic product should accomplish the consumers demand for the products, which are pleasant and healthy [50]. Therefore the development process of a new non-dairy probiotic product would be challenging for both the scientific and applied research [51] because it is necessary to optimize the formulation.

3. Regulatory aspects and legislation of probiotic products

Considering the high growth rate of probiotic markets, the coordination of national and international regulations and rules is going to be extremely important to assess the efficacy and safety of probiotic bacteria [52]. Considering the risk of marketing false and ineffective probiotic products with untrue claims, they must be standardized and essential requirements must be met before being marketed. These necessities differ greatly among different countries regarding their anticipated use, whether as a food, food ingredient, a dietary supplement, and or a drug [53]. In most countries, if a probiotic is going to be used as a drug, it must undertake the regulatory process of a drug same as other new therapeutic agents. In fact, the probiotic drug safety and efficacy must be assessed and approved before marketing. In the case of probiotic dietary supplements, they are recognized as foods, and they do not need to be evaluated or approved before being marketed. However, it is necessary that the regulatory standards on these probiotic bacteria be harmonized at the international level to guarantee their safety and efficacy to be effectively used in different countries around the world [54].

Dietary supplements differ from drugs mainly considering their claims. Drugs are usually claimed to be effective in the treatment, alleviation or cure of a disease, while foods, feed additives and dietary supplements have their general health claims [55]. Probiotics have been used by the customers by considering the fact that no specific health claims on probiotic food labels are allowed by the agency responsible for evaluating the health claim proof in the European Food Safety Authority. The European Commission also points out that the term probiotic has a health claim in itself, consequently, it should not be used for products with the lack of accepted health claims [56-58].

It must be considered that the valuable effect of probiotic microorganisms emerges when they arrive viable and in high enough concentrations after ongoing the gastrointestinal track's (GIT) severe conditions. In order to achieve the beneficial effects of probiotics in consumed food supplements and processed foods, the minimum number of viable cells (CFU g^{-1}) must be consumed in the products. According to the International Dairy Federation, this index is $\geq 10^7$ CFU g^{-1} up to the date of its minimum durability [59]. For bifidobacteria, the viable count of $\geq 10^6$ CFU g^{-1} has been approved in some countries such as Argentina, Prague and Brazil [3]. This standard has been agreed $>10^7$ CFU g^{-1} in Japan [60]. In addition to the viability of probiotics in the product, the amount of product consumed is also influencing on functionality and efficacy. Overall, the recommended daily intake of each

probiotic strain is estimated to be about 10^9 viable cells per day [2].

Suitable labeling and health claims are also the main requirement to provide a well-versed choice for the consumers [61,45]. Therefore, the subsequent information must be exhibited on the food labels:

- a. Genus, species and strain, which should pursue the standard international categorization.
- b. Minimum viable number of each probiotic strain at the end of shelf life.
- c. The serving size that delivers the effective dose of probiotic bacteria related to the health claim.
- d. Appropriate storage conditions including the suitable temperature to be kept.
- e. The recommended conditions to be used.

4. Selecting suitable probiotic cultures for food supplements or processed foods

Carrying foods are effective when the beneficial bacteria are added in sufficient amounts and the conditions are set in a way to maintain their viability [62]. Different parameters affect the survivability of probiotic bacteria and their protection against challenges associated with food and supplement production and the gastrointestinal tract condition. These factors are summarized in Table 3.

The main aspect in formulation of a stable probiotic product is strain selection. Lactic cultures are well recognized for variability of their talents (even within a given species) to grow on food matrices as well as subsist heating, freezing, or storage in acid environments [63]. However, probiotic cultures intended for addition to foods were formerly chosen on the basis of their technological properties [64]; the established health effects are the main factors that must be considered nowadays [30]. Selecting an appropriate condition during fermentation is a critical parameter that must be considered to prevent lethal or sub-lethal hurt to the cells and also higher biomass yield [62]. Changes of processing parameters affect the cell wall and/or the membrane positively or negatively. For example, fermentation temperature alters the fatty acid composition (the ratio of unsaturated to saturated fatty acids) of bacterial membranes [65]. It is also of great importance that survivability of the cultures to subsequent severe conditions will be increased using limited controlled stresses [66]. As an example, the exposure of *Lactobacillus (L.) delbrueckii* ssp. *Bulgaricus* cells to a heat pre-treatment at 50° C or to a hyperosmotic pre-treatment will increase their viability to a lethal temperature challenge (65° C) [67]. Based on these two hypotheses, it is obvious that biomass production parameters will alter the resulting probiotic cells and their viability.

Table 3. Parameters determined the ability of commercial probiotic cultures to survive stress conditions during food/drug preparation or in the gastrointestinal tract (GIT) (36, 63-65)

Parameters	Function
Strain selection	Depending on the nature and quantity of cell components, they are able to withstand stress condition. Probiotic bacteria are selected considering their site of action
Fermentation	Strains structure determined by fermentation condition in a way that any deviation from optimal growth condition could enhance exopolysaccharides production by some species and also change lipid composition of their cell membranes.
Concentration	The damages induced during ultrafiltration and centrifugation is able to decrease the ability of probiotic bacteria to resist the stress.
Encapsulation	Free cells are exposed to stressful condition more rapidly compared to encapsulated ones
Storage	Probiotic bacteria are endangered by different stresses like heat, oxidation, osmotic, acidic and thermal shock, and accumulation of toxic compounds during freezing or drying which possibly lead to cell death.
Delivery	Increasing the temperature enhance the cells damage.

5. Comparison of probiotic delivery supplements and probiotic food products

Probiotic supplements and food products can be compared from different aspects including efficacy hedonism and sensory function, and economical aspect (price and marketing). These characteristics are compared below between the two products:

5.1. Health beneficial efficacy

As mentioned previously, the extent of health benefits related to probiotic products is determined by their abilities to deliver an efficient viable culture at their site of action. This viability will change during processing and storage exposing different conditions, which are separately discussed in the following:

5.1.1. Main factors influencing the efficacy of probiotic delivery by food supplements

Food supplements are naturally rescued in caplets or capsules, which their ability to deliver probiotics is mainly set at the production level. The main factors, influencing the viability of probiotics during storage, are temperature, oxygen and relative humidity [62]. Generally, cultures must be kept refrigerated even if they are dried. It is observed that increasing the cultures temperature from 4 to 25° C during traditional freeze-drying courses results in a ten-fold stability reduction [68]. Some commercial products are able to be kept at room temperature over a few months without losses in their viability greater than 1 log CFU ml⁻¹ [68]. It is to be noted that to achieve such products, the manufacturing setting must be highly specific and controlled [69]. Another problem is the diversity of death rate among different strains during storage. Therefore, the total population in the product should be correct, but the strain ratios might change during storage [70]. Moisture is another important factor, which must be considered. Generally, dried cultures must have a water activity (a_w) around 0.1, and a_w values above 0.3 can decrease their viability [71]. It is obvious that the moisture

of the air increases a_w of the culture powder during storage. In order to prevent the cultures contact with water during storage, two actions are done by food companies: 1) packing in water-resistant bottles or films; and 2) adding small moisture binding agent in bottles. These strategies are valid until the packaging is opened [2]. Oxygen is another harmful factor to the viability of probiotics during storage [62]. In order to overcome the detrimental effects of oxygen and increase the stability of product, companies usually add antioxidants in the drying medium [2]. The protection effects of some oxygen binder agents may decrease when the product is opened.

5.1.2. Main factors influencing the efficacy of probiotic delivery by processed foods

Yogurts are the first foods with probiotic bacteria, and fermented milks are still the most important food vehicles for the delivery of probiotics [47]. However, other foods have now emerged, which transfer probiotic bacteria like chocolate, cheese, sausage and cereal products. An assembly of food products suppresses lactic cultures and is subject to be fortified by probiotic bacteria [72]. There are three critical stages, which may affect the viability of probiotic bacteria in processed foods: a) the state of starter cultures addition to the food matrix; b) processing conditions; and c) storage conditions [62].

Probiotic cultures are usually added to the food matrixes in frozen or dried states. However, this will suppress the probiotics viability, if done improperly. Certainly, the conditions of thawing or hydrating influence the CFU counts [73]. With respect to frozen cultures, thawing temperature is a critical parameter that must be considered, but regarding the dried cultures, different factors are important like the composition of rehydration media, rehydration time and temperature. Hence, inoculation with frozen cultures seems much easier with lower mistakes [62].

Food processing includes different technological steps like addition of starter cultures to the food matrix, blen-

ding, pumping, pasteurization and freezing, which may be damaging to the viability of probiotic bacteria. In order to avoid viability losses during food processing, the two main approaches have been confirmed explicitly as following [62,72,73]:

a) Adjusting the food matrix, for example, by pH adjustment (neutral pH is preferred), adding antioxidants, adding growth factors (prebiotics, plant or yeast extracts), selecting non-toxic ingredients (flavors, preservatives), selecting adjusted and adapted starter cultures, applying higher inoculation rate, and using appropriate enzymes.

b) Adapting the process via, for instance, decreasing the storage temperatures, and using vacuum or nitrogen flushing system in packaging.

While it appears easy to adapt media and processing setting, it is usually not. Processed foods storage conditions will influence the viability of probiotic bacteria as mentioned for food supplements. It warrants to be mentioned that storage not only influences the viability of cells but also the viable cells talent to endure the severe conditions of the gastrointestinal tracts subsequently.

5.2. Probiotics and senses: “How they function?”

Sensory analysis was developed in the mid-19th century and gained greater importance at the end of the 1960s [74]. From a sensory evaluation viewpoint, reliability and validity are the two important issues, which are basic to develop a convincing program, and giving feasible recommendation within the context of a company's business and brand approach [74]. Generally, as a clear principle, people prefer to consume food rather than medicine, because of hedonism from its sensory properties. This hint has been the philosophy of the birth of ‘functional foods’. However, foods are preferable to drugs provided that they do not possess off-flavor, off-texture and off-appeal after adding functional ingredients to the food bases (such as probiotics).

Since sensory characteristics are based on consumer's preference and acceptance, it is required to assess the sensory effect of probiotics in foods. The efficiency of probiotic foods must be as same as the performance of conventional foods [75-77]. Some studies revealed the opportunity of probiotic foods to provide similar or even improved performance compared to conventional ones like functional yogurts with *L. reuteri* RC-14 and *L. rhamnosus* GR-1 added [74]. The ability of probiotic cultures to decrease pentanal and n-hexanal amounts responsible for the beany taste of soya improved its flavor in the case of soy-based probiotic foods [78]. Generally, components produced during the metabolism of probiotic cultures may have negatively effects on the aroma and taste of the food products, which create off-flavor. For example, the acetic acid produced by *bifidobacterium* spp. can create a vinegary flavor in the product [75].

Masking is a technique that has been done by adding new substances to reduce the off-flavors produced by probiotic cultures. It has been revealed that tropical fruit juices addition, mainly pineapple and mango, positively changes the aroma and flavor of the processed foods to prevent the recognition of off-flavors produced by probiotics by the consumers [75]. It is worthy to mention that increasing the frequency of exposure to a food stimulus makes the food stimuli be better liked. Thus, repeated exposing and increased awareness to sensory off-flavors are able to change the consumer's outlook positively to increase their eagerness to use processed foods [79]. Non-sensory techniques are able to increase the sensory quality of products like ensuring consumers by health advantage information related to probiotic cultures. It has been identified that health information is a great motivation to consume probiotic food products. Finally, microcapsules of probiotics may help prevent the off-flavor of cultures [75].

5.3. Economic and trade aspects

Many factors including economical and trade aspects should be considered to design a new product. Increasing in global health knowledge and affinity to take supplements and processed food products is anticipated with the rise in global probiotics market [80]. According to the recorded data, about 10% of the global functional food market is occupied by probiotic industry; more than 84% of it was processed foods (following dietary supplements representing 10 billion Euros) in 2008 [73,80]. It is also documented that the overall probiotic supplement market alone was worth about \$1.5 billion in 2008, and is forecasted to total \$50 billion by 2020 [81]. Recent data reveal that products containing probiotic bacteria have a growth rate of approximately 25% in North America and Eastern Europe, while the highest annual growth rates recorded for Asia and Western Europe are between 5 and 8% [81].

6. Conclusions

The importance of probiotic consumption to increase the quality of life is relatively clearly illustrated by the scientific literature, and the number of food products or drug supplements containing probiotics is growing. Different parameters including the probiotic viability in the product until the time of consumption as well as delivery throughout the gastrointestinal tract (efficiency), sensory characteristic of the product, the natural image of consumers for foods versus drugs, and nutrition economic aspects of the products (cost-benefit analysis) are important factors that determine the customers consumption patterns.

Drug-formulated products are able to transfer high numbers of viable probiotics into the GIT without considerable losses during the storage. In contrast, the

viable number of probiotics in food products, especially fermented types, can considerably decrease, but some foods provide a buffering and protecting matrix on probiotics during the delivery in the GIT, particularly in dense ones such as cheeses. Foods have the advantages of being consumed for need to satisfy hunger or hedonistic reasons while supplements provide a dose of probiotics for specific needs or general wellbeing. Food products have very high potential of variation and development compared to drug supplements, and adding probiotics to them leads to considerable product and market development. Generally, designing the probiotic food formulation is more-to-much complex than drugs considering the stability of probiotics during the process and storage as well as achieving appropriate sensory characteristics, because probiotics might negatively change the sensory characteristics of foods. Also probiotic foods can have more difficulties from regulatory administration and legislation standpoint compared to supplements. Overall, for general usage, probiotic foods with high viability standards are superior to supplements, but for specific therapeutic applications, the latter is more efficient, and therefore, preferred. More human interventions studies are required to demonstrate real health benefits and produce evidence-based recommendations for probiotics use.

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8. Conflict of Interest

The authors declare no conflict of interest

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مکمل‌های پروبیوتیکی و فرآورده‌های غذایی: مقایسه با اهداف گوناگون

ندا ملاخلیلی¹، امیر محمد مرتضویان^{2*}، سارا سهراب‌وندی³، آدریانو جی دی کروز⁴، رضا محمدی⁵

- 1- کمیته پژوهشی دانشجویان، گروه علوم و صنایع غذایی، دانشکده علوم تغذیه و صنایع غذایی، انستیتو تحقیقات تغذیه ای و صنایع غذایی کشور، دانشگاه علوم پزشکی شهید بهشتی، تهران، ایران.
- 2- گروه علوم و صنایع غذایی، دانشکده علوم تغذیه و صنایع غذایی/انستیتو تحقیقات تغذیه ای و صنایع غذایی کشور، دانشگاه علوم پزشکی شهید بهشتی، تهران، ایران.
- 3- گروه تحقیقات صنایع غذایی، دانشکده علوم تغذیه و صنایع غذایی/انستیتو تحقیقات تغذیه ای و صنایع غذایی کشور، دانشگاه علوم پزشکی شهید بهشتی، تهران، ایران.
- 4- انستیتو فدرال ریو دوژانیرو، بخش غذا، ریودوژانیرو، برزیل.
- 5- گروه علوم و صنایع غذایی، دانشکده بهداشت عمومی، دانشگاه علوم پزشکی کرمانشاه، کرمانشاه، ایران.

چکیده

سابقه و هدف: در حال حاضر، پروبیوتیک‌ها به واسطه اثرشان بر سلامتی، در مواد غذایی فرایند شده یا مکمل‌های غذایی مورد استفاده قرار می‌گیرند. بازارهای پروبیوتیک سهم قابل توجهی در صنعت غذا یا دارو دارند. بنابراین در این مقاله، مکمل‌های دارویی و فرآورده‌های غذایی حاوی ریززنده‌های پروبیوتیک از جنبه‌های گوناگون نظیر ویژگی‌های فراسودمندی، کارایی، حسی و اقتصادی بررسی می‌شوند.

یافته‌ها و نتیجه‌گیری: اثر دریافت پروبیوتیک‌ها از طریق فرآورده‌های غذایی یا مکمل‌های دارویی از دو جنبه پذیرش مصرف کننده و کارایی درمان یکسان نیست. به نظر می‌رسد که دیدگاه مصرف کننده در پذیرش یک فرآورده تحت تأثیر اثرات تغذیه‌ای، فراسودمندی، سلامتی بخشی و اقتصاد تغذیه‌ای آن قرار می‌گیرد.

تعارض منافع: نویسندگان اعلام می‌دارند که هیچ تضاد منافی وجود ندارد.

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واژگان کلیدی

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*نویسنده مسئول

امیر محمد مرتضویان، استاد دانشکده علوم تغذیه و صنایع غذایی/انستیتو تحقیقات تغذیه ای و صنایع غذایی کشور، دانشگاه علوم پزشکی شهید بهشتی، صندوق پستی 19395-4741 تهران، ایران.

تلفن: +98-912-7114977

دورنگار: +98-21-22360657

پست الکترونیک: mortazvn@sbmu.ac.ir