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Clinical Uses and Survival Study of Free and Encapsulated Probiotic Bacteria in Fruit Juices: A Review

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Abstract

Background and Objective: Probiotics are dietary supplements with potential health benefits for humans when consumed regularly at appropriate quantities. The latest evidence shows possible beneficial effects of probiotics in COVID-19 treatment. Interests in probiotic consumption have led to provide products such as probiotic juices with vitamins, minerals, prebiotics and appropriate levels of probiotics to the market in free and encapsulated forms, which are not fully addressed in scientific literatures. The objective of this review was to investigate effects of probiotics for the management of human health. Other objectives included study on effects of free and encapsulated forms of probiotics when incorporated in fruit juices on their survivability, storage stability and physiological and functional characteristics in host cells under gastric and intestinal conditions.

Results and Conclusion: Studies have shown that lactobacilli strains are verified strains for producing probiotic supplements, including juices. Various methods have been suggested to improve survivability of probiotics. Encapsulation can protect probiotics against physical characteristics of juices and hence bacterial physiological damages under anaerobic conditions. Several methods have been used to encapsulate probiotics, each of them has shown distinct characteristics. However, further studies on the quality control of probiotic juices are necessary.

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1. Introduction

Human gastrointestinal (GIT) is colonized by a complex microbial ecosystem named gut microbiota. Beneficial GIT bacteria include various functions, including production of several nutrients, prevention of infections by pathogens and modulation of immunological responses [1]. Studies have demonstrated that several diseases are associated with dysbiosis of the gut microbiota [2,3]. Therefore, resuming the natural balance of gut microbiota using probiotic-based treatments may protect individuals against diseases, improving their general health [4]. Based on the definition by the Food and Agriculture Organization and World Health Organization (FAO/WHO), "probiotics are live and active microorganisms which upon digested in sufficient amounts exert several health benefits" [5]. Since findings have shown that dead probiotics include health benefits for humans, a novel definition of probiotics has been suggested. In the novel definition, three categories of probiotics are seen, including "true probiotics" (alive/active probiotic cells), "pseudo-probiotics" (viable/inactive cells) and 'ghost probiotics' (dead/nonviable cells) [6]. Based on FAO/WHO

definition, although probiotics need to be alive at the time of ingestion, it has been verified that the physiological effects of lysate cells are preserved. Regular probiotic consumption can lead to promoting lactose digestion, improving bowel function by providing microbial balance, preventing diabetes, cholesterol-related diseases and colon cancers, recovering intestinal flora after receiving antibiotics and inhibiting pathogens by stimulating the immune system and producing hydrogen peroxides, organic acids, lysozymes and bacteriocins [7,8]. Moreover, probiotics are effective in modification of microbiota by producing vitamins, digestive enzymes and short-chain fatty acid (SCFA) metabolites [9].

Consumer interests in consumption of useful products to prevent diseases and maintain health conditions have dramatically affected development of probiotic supplements [10-13]. This has driven industrial interests to produce products containing vitamins, minerals, probiotics and prebiotics. Typically, consumption levels of probiotics depend on several factors such as types of strains and their effects on human health [12,14]. Based on the guidelines by manufacturers, probiotic products should include a proper identification of each probiotic strain. To achieve this goal, characterization of each strain based on its function and safety, determination of its effects on human health and quantitation and truthful shelf-life assessments are needed. The aim of this review was to investigate various health benefits of probiotics on human immunity. These included probiotic strains and their implementation in various fruit juices and comparison of the survivability of probiotics in free and encapsulated forms.

2. Clinical uses of probiotics

Probiotics have been shown to include positive effects on gastrointestinal diseases, allergic diseases and body immunity in clinical trials. In addition, efficiency of probiotics for the treatment of several metabolic diseases such as obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), various types of cancers and complications associated to cancers have been verified [4,15].

2.1. Probiotics and COVID-19

The COVID-19 is a newly-emerged pandemic disease caused by a novel type of coronaviruses, affecting respiratory system and other organs [16]. Since pathophysiological mechanism of the virus has not been described completely, the potential treatments are not well stablished. Although no clinical trial studies have been carried out, there are evidence on possible beneficial effects of the probiotics for the treatment of COVID-19. Emerging evidence suggest connections between gut health and microbiome responses to SARS-CoV-2 [17]. It has been shown that the viral receptors and nucleocapsid proteins exist in epithelial cells of the GIT [17]. Elderly people and those with co-morbidities show the greatest mortality and morbidity rates of COVID-19. Underlying factors have been linked to increased gut permeability and decreased gut microbiome diversity [18]. Based on the prevalence of pulmonary inflammation in SARS-CoV-2 patients, direct suppression of viral infection by the gut microbiome can play critical roles [19]. Theoretically, these findings suggest that treatments with gut microbiota may include widespread antiviral effects on SARS-CoV-2 infections [20-22]. In a recent study, COVID-19 patients included significant changes in their fecal microbiota compared to control group, with increases in opportunistic pathogens and decreases in beneficial commensals [23]. It has been shown that manipulation of gut microbiota represents a promising therapeutic approach for lung diseases [23]. Studies have demonstrated that probiotics include antiviral characteristics against other coronaviruses [24]. Moreover, potentials of probiotics to interact with host receptors of SARS-CoV-2 (ACE2) have been reported [25]. Therefore, further clinical trials are needed to better understand mechanism and efficiency of probiotic-based treatments.

2.2. Gastrointestinal diseases

Beneficial intestine bacteria play essential roles in their host ecosystems, including producing various nutrients, preventing infections triggered by the intestinal pathogens and modulating natural immune responses [26]. Relatively, positive probiotic responses in gastrointestinal diseases have been reported by several clinical trials, including ulcerative colitis reduction, lactose intolerance in irritable bowel syndrome, colorectal cancer, peptic ulcer and various types of diarrhea, especially traveler's diarrhea [4].

2.3. Obesity and metabolic syndrome

Obesity, one of the most serious public health problems, seems to be linked to the development of metabolic syndrome, which is associated to increased risks of several disorders such as cardiovascular disease (CVD), T2DM and NAFLD [27]. Metabolic syndrome is characterized by the presence of central obesity and two of the following conditions, including increased triglyceride (TG > 150 mg dl^{-1}), decreased high-density lipoprotein cholesterol (HDL < 40 mg dl^{-1} in males and HDL < 50 mg dl^{-1} in females), increased blood pressure (systolic blood pressure > 130 mm Hg or diastolic blood pressure > 85 mm Hg) and increased fasting blood sugar (FBS > 100 $mgdl^{-1}$) [28]. Approaches, including behavior therapy, dietary modification, physical activity and drug therapy, can be useful for obesity treatment [29]. In recent years, scientific evidence have revealed that probiotic intervention may lead to novel approaches for the effective treatment of obese people. Clinical trials have indicated that probiotic supplementation can improve clinical aspects of the metabolic syndrome. In

a clinical trial, participants were divided into two groups and received either probiotic yogurt with 300 gd^{-1} *Lactobacillus (L.) acidophilus* and *Bifidobacterium* (*B.*) *lactis* or normal yogurt for two months. Significant improvements were seen in body mass index (BMI), blood sugar, insulin and homeostatic model assessment of insulin resistance (HOMA-IR) of the probiotic yogurt group [30]. Another study reported that consumption of fermented milk with *B. lactis* for 45 days could lead to improvements in lipid profile, glucose metabolism, tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [31]. A recent systematic review of randomized clinical trials (RCTs) on metabolic syndrome patients has revealed that intake of probiotics include several beneficial effects. However, this review has stated necessities for further detailed RCTs in metabolic syndrome patients [32].

2.4. Lipid profile and cardiovascular disease

Nowadays, CVD is one of the most common causes of mortality and morbidity worldwide. Numerous risk factors contributed to CVD, including dyslipidemia, hypertension, smoking, obesity, metabolic syndrome and diabetes [33]. It has been demonstrated that alterations in gut microbiota can increase risk factors of CVD, particularly dyslipidemia. Dyslipidemia refers to high concentrations of total cholesterol (TC), TG and low-density lipoprotein cholesterol (LDL) and low concentrations of HDL [34]. Studies have showed that supplementation with probiotics significantly decreases TC, LDL and TG [31] and increases HDL [31]. A systematic review and meta-analysis reported significant decreases in TC using *L. plantarum* and LDL using *L. plantarum* and *L. reuteri* [35]. Clinical trials have detected improvements in other risk factors of CVD, including inflamematory factors, glycemic controls, BMI and immunological profiles [31]. The most important mechanisms behind the hypolipidemic characteristics of probiotics include suppression of cholesterol absorption, direct assimilation of cholesterol by the bacterial cells and the inhibition of bile acid reabsorption [36]. A recent systematic review of 14 RCT data has recommended that probiotics supplementation can be used as an adjuvant to other treatments of dyslipidemia [37].

2.5. Type 2 diabetes mellitus

In general, T2DM is a progressive, high-prevalence metabolic disease characterized by increases in FBS and glycosylated hemoglobin, which is resulted from insulin resistance and pancreatic β-cell dysfunction [38]. Multiple risk factors are involved in the etiology of T2DM, including genetic background, age, obesity, unhealthy and sedentary lifestyle, smoking and psychological aspects [39]. Recently, evidence have demonstrated that improvement of gut microbiota can help manage T2DM and hence prevent progression of diabetes-linked complications [40]. Recent meta-analysis studies on data of clinical trials have shown that probiotic treatment can decrease glycosylated hemoglobin, FBS and insulin resistance in T2DM patients [39] and improve lipid profile, hypertension and other cardiovascular risk factors in diabetics patients [41,42]. Clinical studies have also revealed that probiotic supplementation can improve oxidative and inflammatory markers as well as the antioxidant status of diabetic patients [40]. Furthermore, probiotic therapy has shown to successfully regulate glycemic and inflammatory statuses of patients with gestational diabetes mellitus [43]. Probiotics can act by increasing fasting insulin levels to boost FBS and lipid profiles, as well as decreasing systolic and diastolic blood pressures to improve hypertension [40]. Altogether, probiotic supplementation has demonstrated promising results in most of the studies to manage diabetes and its complications [34,39,40].

2.6. Non-alcoholic fatty liver disease

In fact, NAFLD is the hepatic manifestation of metabolic syndrome; in which, abnormal quantities of fats are deposited in hepatic cells [27,44]. It has been demonstrated that probiotics can prevent proliferation of harmful bacteria, decrease small bowel bacterial overgrowth, reestablish gastrointestinal barrier function and control the immune system; therefore, probiotics can improve NAFLD [45]. A recent meta-analysis study on clinical trials regarding effects of probiotics on NAFLD patients has revealed that probiotic supplementation restores liver fat infiltration and improves BMI and liver function tests such as liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and alkaline phosphates) as well as other aspects of NAFLD such as lipid profile, FBS and inflammatory profile [45,46]. Accordingly, probiotics are beneficial for hepatic cell protection and can be considered as a promising therapeutics for the NAFLD treatment.

2.7. Cancer

Obesity, low fruit and vegetable intakes, sedentary lifestyle and tobacco and alcohol uses contribute to one-third of all cancer deaths, based on the World Cancer Report [47]. In recent years, anticancer effects of probiotics have been reported frequently. Probiotics have been demonstrated to suppress growth of microbiota involved in production of carcinogens, modify carcinogen metabolism, protect DNA against oxidative damages and regulate immune responses [48]. Therefore, probiotics seem to be successful in stopping, curing and slowing proliferation of cancer cells. A widespread investigation has verified antiproliferative and proapoptotic effects of probiotics in various cancer cells [47]. In addition, results of recent *in vivo* and *in vitro* studies have established beneficial characteristics of the probiotics on cancer cell invasion and

metastasis [48]. Although pre-clinical and clinical studies are not sufficient to decide about probiotic uses in chemotherapy, it seems that probiotic based treatments can include beneficial effects in cancer chemotherapy.

2.8. Other diseases

Probiotic supplementation in RCTs has been shown to affect treatment of allergy or atopic-linked disorders such as atopic dermatitis, allergic rhinitis and asthma [47]. Clinical trial studies have highlighted important effects of probiotics on calcium homeostasis, bone health, chronic kidney disease and urinary tract (UT) infections (Figure 1) [49].

3. Appropriate probiotic strains

Due to various beneficial effects of probiotic strains, it is essential to assess their function and efficacy. Survival rate and physiological and genetic stabilities of the probiotics during food processing and shelf-life and GIT transition are essential issues that must be addressed [50,51]. Survivability of probiotics in adverse conditions of the GIT is one of the critical issues in production of functional foods and beverages. Various methods have been suggested to improve survivability of probiotics, including use of prebiotics such as cellulose, hemicellulose, pectin, inulin, lignin, waxes and guar gum and expose of probiotics to stress conditions that increase their viability and adaptability. Storing products at refrigerator temperatures, incorporating antioxidants to prevent production of reactive oxygen species (ROS) and encapsulating probiotics can protect these microorganisms against acidity of juices and physical damages and provide anaerobic conditions for susceptible microorganisms [52,53]. Lactobacilli and bifidobacteria are the most common types of probiotic bacteria [50,52]. These bacteria play essential roles in prevention of various diseases and improvement of intestinal microbiota. These strains are safe for human use and are good choices in terms of adhesion to GIT and resistance to digestive fluids and antibiotics [50]. Lactobacilli are routinely used in commercial products such as yogurts and fermented milks, depending on the product types. Use of bacteria as probiotics depends on the strain, its metabolic condition and food pH and temperature. The acid resistance property of lactobacilli is essential for the bacterial survivability in gastric juices and acidic foods [54-56].

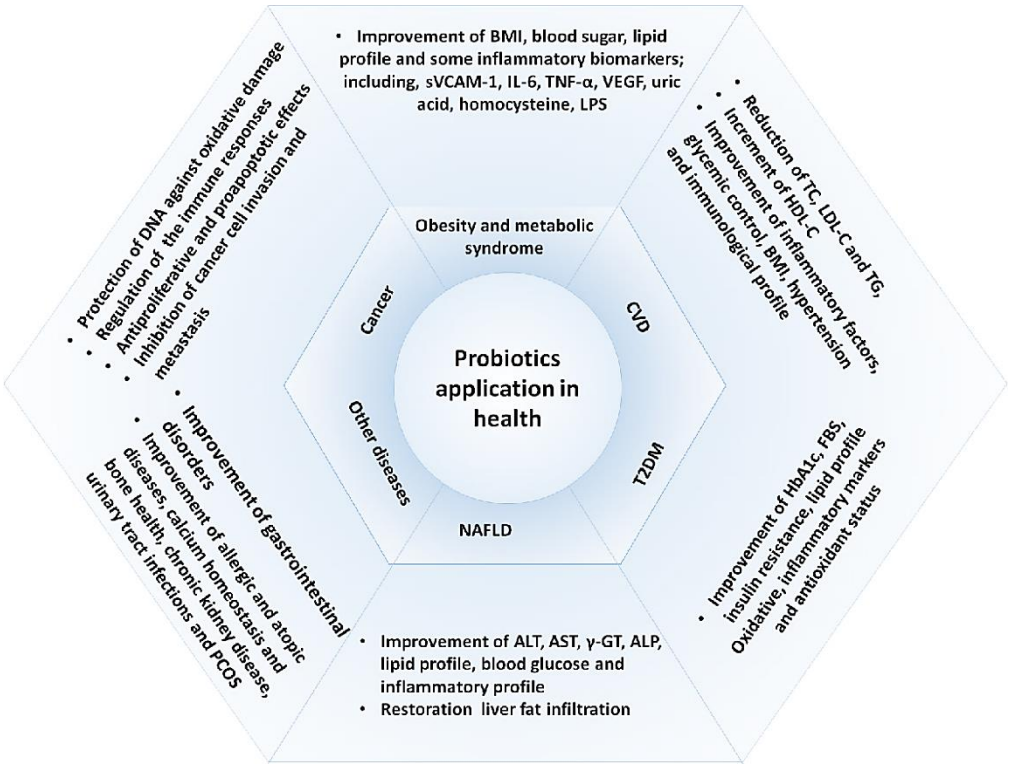

Figure 1. Beneficial effects of probiotics in several diseases. Cardiovascular disease, CVD; type 2 diabetes mellitus, T2DM; non-alcoholic fatty liver diseases, NAFLD; soluble vascular cell adhesion molecule 1, sVCAM-1; interleukine-6, IL-6; tumor necrosis factor α, TNF-α; vascular endothelial growth factor, VEGF; total cholesterol, TC; triglyceride, TG; low-density lipoprotein cholesterol, LDL-C; high density lipoprotein cholesterol, HDL-C; alanine amino transferase, ALT; aspartate amino transferase, AST; gamma-glutamyl transferase, γ-GT; alkaline phosphates, ALP

4. Functional characteristics of probiotic bacteria

Dairy products include two major disadvantages of lactose intolerance and cholesterol content. [57]. Therefore, development of probiotic fruit juices, as an ideal alternative vehicle for probiotic bacteria, has widely been studied [58]. Probiotics must be present in sufficient viable quantities in products without losing their genetic stability during storage. It has been reported that probiotic supplements should contain at least 10^6 CFU g^{-1} or ml of viable bacteria and should be regularly consumed (greater than 100 g d^{-1}) to provide their health-promoting effects [59]. To successfully colonize the host, probiotics should be able to withstand adverse conditions of the GIT such as acidic and enzymatic conditions of the stomach and presence of bile salts and pancreatic enzymes in the small intestine. Moreover, they should be able to grow in the intestines by attaching to the intestinal walls [60]. In the small intestine; however, survivability rate of the probiotic bacteria depends on their resistance to bile salts (e.g., glycocholic acid, glicodeoxycholic acid, taurocholic acid and taurodeoxycholic acid) and acidic conditions [61]. Naturally, bacterial homeostatic disorders occur after exposure to bile salts and decomposition of lipid membranes and cell membrane (CM) proteins cause bacterial content leakage and eventually cell death [62]. Assessing resistance of strains to high concentrations of bile salts is critical from technological and physiological points of view because this assessment is not only a method of selecting probiotic characteristics, it is also unique in particular strains [63].

Survival capability of various strains varies in the GIT. Probiotic bacteria neutralize effects of bile salts by producing dehydrating enzymes. Most studies on the resistance of probiotic strains to bile salts have shown delayed growth of the bacteria in culture media with bile salts [60,61]. A method of assessing survivability of various probiotic strains at low pH includes exposure of these bacteria to acidic buffer solutions and counting of the viable cells when lowering the pH gradually. High resistance of some bacteria to low pH can be due to the production of polysaccharide compounds that inhibit adverse effects of acids on CM [64]. Resistance to acidic conditions in probiotic microorganisms is associated with H^+ ATPase enzyme activity [65]. Therefore, differences in resistance to GIT may be due to the differences in activity of this enzyme in probiotics. Researches have suggested that encapsulation of probiotic bacteria with various biopolymer materials leads to a better cell survivability, compared to free cells in acidic conditions and high concentrations of bile salts. Of various biopolymers, alginate, xanthan gum and carrageenan gum have shown the most protective effects against bile salts. Microencapsulation has been suggested as a promising delivery approach for bioactive nutrients such as probiotics. In a study, probiotic bacteria were encapsulated using various coating biomaterials, including alginate, carrageenan gum, xanthan gum, locust bean gum and guar gum. Results showed gradual losses in bacterial survivability when exposed to acidic conditions [61]. In another study, the survivability rate of *L. acidophilus* in acidic conditions included a similar reduction pattern at pH 4 and 3. Incubating cell cultures at pH 4 and 3 decreased cells by approximately 2 log CFU g^{-1}. At pH 2, cell losses were recorded by nearly 5 log CFU g^{-1}. In contrast, *B. infantis* demonstrated a small decrease at the highlighted pH ranges. The findings suggested that *L. acidophilus* was more sensitive to high acidic conditions, compared to *B. infantis* [66]. Other aspects of probiotic microencapsulation such as various techniques are discussed in the following sections.

Survivability of probiotics is affected by various factors, including types and concentrations of the probiotics, intrinsic food parameters, food additives, processing effects, incubation temperatures and storage conditions [67]. For example, as most probiotics include anaerobic bacteria, viability of the probiotics increases by decreasing quantities of dissolved oxygen in the media. Hydrogen peroxide produced by the probiotic bacteria can decrease the favorable conditions of oxidation and thus decrease the probiotic population. This is accompanied by the absorption of free oxygen and conversion of hydrogen peroxide into water. Addition of thiol-modified compounds such as cysteine can increase growth and survivability of the probiotics by decreasing the oxidation-reduction potential of the matrices [68]. In conclusion, the most important selection assessments of probiotics for producing probiotic supplements are as follows (Figure 2) [60,61]:

- Investigation of the acid tolerance of probiotic bacteria (Mostly).
- Investigation of the bile salt tolerance of probiotic bacteria (Mostly).
- Investigation of the survival rate of probiotic bacteria (Mostly).
- Investigation of the antimicrobial characteristics of probiotic bacteria.
- Investigation of the antibiotic resistance of probiotic bacteria.

5. Probiotic juice

High cholesterol levels in dairy products, lactose intolerance and people interests in using herbal products have led to increased demands for probiotic juices [14,52]. Studies have recommended use of juices in probiotic products [10,12]. Juices are commonly used as sources of calcium and vitamins, which can be much more useful if activated with probiotics. Presence of vitamins such as ascorbic acid simulates anaerobic conditions for several probiotic bacteria due to the oxygen uptake.

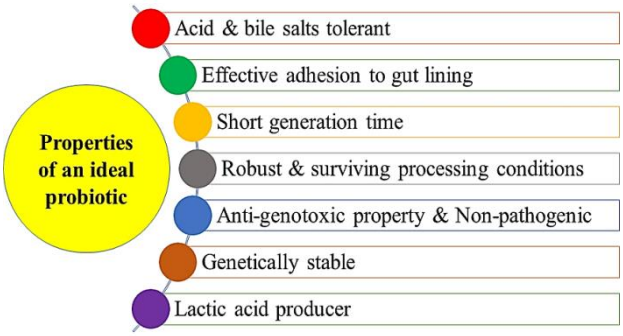

Figure 2. Characteristics of the ideal probiotic strain

Additionally, lack of starters in juices provides further favorable conditions for the bacteria [10]. It has been shown that micronutrients in juices can effectively prevent damages to the genome and combination of juices with probiotics certainly adds values to their health benefits. Criteria that are important in selecting juices include appropriate pH and conditions to preserve bacterial survivability and activity [52]. Most studies on production of probiotic juices have been based on direct addition of probiotics to the products [69,70]. In contrast, other studies have shown that sonicating juices such as pineapple juice can provide acceptable fermentation conditions for *L. casei* B-442 with no addition of supplements. Incorporated bacteria can survive in low-temperature conditions for up to 21 days to acceptable rates. Chemicals such as sodium metabisulfite used to prevent juices from turning brown have been eliminated by sonication. Sonication process as a cheap, environmental-friendly and reliable technology can be used to produce ready-to-drink probiotic juices [10].

Incorporation of *L. casei* T4 in cranberry, pineapple and orange juices showed increases in pH during 21 days of storage. Through the first 14 days, cell counts did not show significant changes but during the last seven days, gradual decreases occurred. It has been shown that pH regulation can significantly affect the bacterial viability. In cornelian cherry juice, pH changes from 2.6 to 3.5 significantly increased the viability of *L. casei* T4 [14]. Vegetable based juices are appropriate carriers for preparing probiotic juices due to their acid tolerance characteristics [52]. The *L. casei* and *L. plantarum* were able to survive and grow in vegetable juices as ideal environments for up to four weeks [11]. Lactic acid bacteria, including *L. plantarum*, *L. casei*, *L. acidophilus*, *L. rhamnosus* and *L. bulgaricus*, are the best candidates for oral vaccines [71]. Usually, *L. plantarum* and *L. casei* respectively are the most common strains used in probiotic products (Table 1) [72].

Table 1. Juices and probiotics used in various studies

Juice	Probiotic strain	Study
Pineapple	*L. casei* NRRL B442	(10)
Cornelian cherry	*L. casei* T4	(14)
Vegetables	*L. casei* PTCC1608 and *L. plantarum* PTCC1058	(11)
Peach	*L. plantarum* DSMZ 20179, *L. delbrueckii* DSMZ 15996, *L. casei* DSMZ 20011	(93)
Cantaloupe	*L. casei* NRRL B-442	(94)
Potato	*L. casei* ATCC 393	(95)
Tomato	*L. plantarum* and *L. casei*	(96)
Pomegranate	*L. acidophilus* DSMZ 20079, *L. plantarum* DSMZ 20174, *L. delbrueckii* DSMZ 20006, *L. paracasei* DSMZ 15996	(97)
Mango	*L. acidophilus* (MTCC10307), *L. delbrueckii* (MTCC911), *L. plantarum* (MTCC9511) and *L. casei*	(98)
Cashew apple	*L. casei* NRRL B-442	(99)
Bitter gourd, bottle gourd and carrot	*L. acidophilus* NCDC 11, *L. plantarum* NCDC 414, *Pediococcus pantosaceus* MTCC 2819	(100)
Noni	*L. casei* subsp. *casei* BCRC 17002, *Bifidobacterium longum* BCRC 14602 and *L. plantarum* BCRC 10069	(101)
Beet	*L. acidophilus* LA 39, *L. casei* A4, *L. delbrueckii* D7 and *L. plantarum* C3	(102)
Cabbage	*L. plantarum* C3, *L. casei* A4 and *L. delbrueckii* D7	(103)

L: Lactobacillus

5.1. Beneficial effects of probiotic juices

To the best of the authors' knowledge, clinical trials using probiotic juices are limited. Effects of synbiotic pomegranate juice on polycystic ovarian syndrome treatment were assessed and results revealed potentials of synbiotic pomegranate juice to improve insulin resistance, insulin and testosterone levels, BMI, weight and waist circumference in polycystic ovarian syndrome in Iranian women [73]. Another study demonstrated that long-term supplementation of microencapsulated probiotics improved bioavailability of the dietary polyphenols of orange juice in healthy humans and thereby increased the potential health benefits of orange juice in the body [74]. In contrast, *Lactobacillus* drink was ineffective on the recurrences of symptomatic UT infections in women [75].

6. Microencapsulation of probiotics

Capability of the microorganisms to persist in GIT strongly shows their probiotic benefits. One of the most effective methods to protect bacterial cells in food industries is encapsulation [76]. Encapsulation is a process to entangle a substance in materials to fabricate particles with sizes of micrometers to millimeters. Bioactive element encapsulation can be used in food processing such as regulating oxidative reactions, concealing tastes, implementing sustained and controlled releases and protecting probiotic microorganisms [77]. In general, numerous methods can be used for the encapsulation of probiotics.

6.1. Spray drying

Spray drying is a low-cost method for drying heat-sensitive products. The major steps in spray drying process include spraying the liquid, regulating contacts of the drying media, vaporizing liquid of the droplets and separating the dry products. Various spray dried probiotic strains have been studied regarding preservation of their distinguishing characteristics such as cholesterol assimilation and acid and bile salt toleration. In one study, *L. reuteri* was cultured in probiotic passion fruit pulps and fermented at 30 °C. Spray drying was used for dehydration and stabilization of the probiotic products. Furthermore, use of gelatin and maltodextrin biocomposites resulted in a higher cellular survivability [78]. Another study assessed effects of spray drying dehydration of cashew apple juice containing *L. casei* as well as storage temperature in long-terms (35 days) on cellular survivability and physical characteristics of the final products. It has been verified that spray dried powders containing maltodextrin included an almost 70% survival rate when stored at 25 °C [79]. Since spray drying causes rapid evaporation of moisture, the product temperature remains reasonably low. Therefore, spray drying process may be used to produce microencapsulated microorganisms with heat-sensitive centers. Characteristics of the microencapsulated results are affected by the composition of materials (bioactive core, encapsulated material, ratio of center), method of processing supplies and system parameters of spray drying such as temperature, feed flow, feed temperature, air flow and nozzle type [80].

6.2. Freeze-drying

Since freeze-drying is normally carried out at low temperatures, this allows for a better protection of volatile components and less degradation of heat-sensitive materials. The most popular industrial process for the composition of dehydrated probiotics includes freeze-drying. It has been used for bioactive microencapsulation, which includes vitamins, polyphenols, omega-3 oils, herbal extracts, citrus extracts and limonene [81]. Recently, protective effects of acerola, cashew and guava tropical fruits on three lactobacilli were assessed during freeze drying process, regarding membrane integrity, membrane potential and efflux activity of the cells. Flow cytometry and colony count assays showed improved stabilization during processing and storage of the foods under refrigeration [82].

6.3. Extrusion

Formation of microbeads is one of the oldest methods for microencapsulation. The method has widely been adopted for microorganism microencapsulation. Since the method includes insignificant damages to microorganisms, long viability of probiotics and high preservation of heat-sensitive materials occur. Alginate is a typical material used as the matrix in extrusion. The necessary steps for using alginate as a matrix include preparing an alginate suspension, combining bioactive cores in the alginate suspension and pouring the suspension into a setting bath through an orifice. Since calcium ions may crosslink the alginate particles forming a gel matrix that traps the loaded components, calcium chloride is widely used as the setting solution [83]. Then, microbeads can be dehydrated to the required moisture contents. Survivability of *L. plantarum* has been investigated during four weeks of storage in orange juice at 4 and 25 °C using encapsulation in alginate-pectin-gelatin biocomposites and extrusion techniques. Results demonstrated that the method of encapsulation did not include adverse effects on survivability of the cells and the biocomposite carrier could enhance the stability of the cells during long-term storage in juices [84]. This process was uncomplicated; however, it could not be used as an industrial method since cumbersome processes were needed during the production of microbeads. Recently, novel methods (e.g., laminar jet break-up) have improved productivity of the method and allowed smaller dimensional scales, increasing encapsulation efficiency [85].

6.4. Emulsion

6.4.1. Simple emulsions

Dispersion of immiscible liquids into various phases is a simple emulsion process. The oil phase is distributed into granular droplets using emulsifier to preserve the oil-water interface, creating an oil-in-water emulsion. The emulsion is made up of tiny droplets produced by microfluidization and high-shear homogenization. Emulsion characteristics and stabilization are affected by the emulsifier, solid content, pH and various formulations and conditions [86]. Emulsion technique was used to microencapsulate *B. animalis* spp. in milk protein matrix and survivability of the encapsulated and unencapsulated cells was assessed during long-term storage in pineapple and strawberry-apple juices. It was verified that the type of juice critical affected stability of the probiotics. Pineapple juice was shown to be more appropriate than strawberry-apple juice after 14 days. Emulsion-based microcapsules in pineapple juice not only protected cells from harsh conditions but also preserved its sensory characteristics [87]. Therefore, emulsion technique can be a promising approach for probiotic juice development.

6.4.2. Multiple emulsions

Multiple emulsions consist of small droplets of water as emulsifiable bioactive molecules dispersed in greater oil droplets and separated in an outer aqueous phase (water-in-oil-in-water emulsions). Of simple emulsions, water-in-oil-in-water can be adjusted to improve encapsulation, stabilization and release characteristics. For example, W/O/W microcapsules with *L. Plantarum* NBRC 3070 have been used to provide physical barriers against harsh environmental conditions to enhance satisfactory parameters and quality of soursop juices. Results demonstrated that high emulsion efficiency, survivability for four weeks and satisfactory level of physical characteristics (color, sensory characteristics and coliform counts) were achieved through the experiment [88]. In the inner water or oil phase, bioactive materials can be integrated. Multiple emulsions may be created using either one-step or two-step emulsification process [86,89].

6.5. Double aerosol method

Metal ions can entrap mixtures in cross-linked alginate gels, resulting in water-insoluble beads; however, certain processes are limited to batch processing and thus cannot be used in industrial scales. The double aerosol method separates impinging aerosols of sodium alginate solution and calcium chloride cross-linking solution is used to produce cross-linked alginate microbeads with diameters less than 40 μm (90,91). A novel dual aerosol technique was used to encapsulate *L. rhamnosus* and *L. acidophilus* to improve their survivability rate and retention during 39 days of storage at 4 and 12 °C in orange juice, respectively. Results showed that viability of the unencapsulated cells decreased significantly. However, viability of the encapsulated cells was quite stable [92]. Encapsulation has been studied for promoting effectiveness of the probiotic microorganism incorporation in juices. Table 2 summarizes the major studies and highlights their strategies for enhancing probiotic survivability and stability during storage.

7. Perspective

The current study addresses clinical uses of probiotics such as improvement of gastrointestinal function and prevention and/or treatment of diseases, including allergic diseases, metabolic syndromes, diabetes, NAFLD, CVD and cancers. Appropriate uses of these products have been shown to play essential roles in inhibition of pathogens by stimulating immune system. Very recent evidence suggest that probiotics may be useful in treatment of COVID-19, which needs further studies. Functional foods containing probiotics mostly include dairy products, which cannot always be used by all the people due to their high cholesterol levels and lactose intolerance. As a result, probiotic juices are further preferable. Juices are commonly used as sources of calcium and vitamins, which can be further nutritious if incorporated with probiotics. Presence of vitamins such as ascorbic acid can cause anaerobic conditions for several probiotic bacteria due to oxygen uptake. Moreover, lack of starters in juices provides further favorable conditions for the probiotic bacteria. Capability of the microorganisms to persist in GIT strongly supports their probiotic benefits. It has been shown that presence of micronutrients in juices effectively prevents genome damages and improves its repair. Furthermore, functionalizing juices with probiotic bacteria significantly adds values to their health benefits. Lactic acid bacteria, including *L. plantarum* and *L. casei*, are two strains of the most common bacteria used in probiotic products. Although various encapsulation techniques have been suggested to improve survivability of the probiotics, further studies are necessary to ensure the optimal conditions. It is also necessary to focus on appropriate materials as well as novel techniques or equipment that provide economic matrices for industrial uses. In conclusion, probiotic juices prepared with appropriate encapsulated probiotic strains can be consumed by various consumers to maintain their health as well as preventing and treating several diseases.

Table 2. Summary of the studies on probiotics encapsulation in juices

Juice Type	Probiotic organism(s)	Encapsulation method	Capsule material	Prebiotic	Coating	Capsule size	Initial Probiotic concentration (log CFU ml^{-1})	Free probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Encapsulated probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Reference
Acerola	*B. animalis*	Spray-drying	Cellulose acetate phthalate	Inulin (in juice)	-	0.11-65.51 µm	9 in 200ml	35 days, 5ºC 5.41 in 200 ml	35 days, 5ºC 7.68 in 200 ml	(104)
Aloe vera	*L.paracasei*	Emulsion	Alginate	-	-	-	9	8 weeks 4 ºC 5.89 8 weeks 25 ºC 5	8 weeks, 4 ºC 6.4 8 weeks, 25 ºC 6	(105)
Ambarella	*L. plantarum*	Co-Extrusion	Alginate	Oligofructose	chitosan	748 µm	9	4 weeks 4 ºC 5.89 4 weeks 25 ºC 0	4 weeks, 4 ºC 7.39 4 weeks, 25 ºC 0	(106)
Apple	*L. rhamnosus*	Extrusion	Chitosan-Alginate	Inulin	-	1.4 mm	-	90 days, 4 ºC 15% survival	90 days, 4 ºC 80% survival (passed the required level = 6)	(107)
		Spray-drying	Resistant Starch / Whey protein (individually and their mixture)	-	-	-	8.8 / 100ml	-	5 weeks, 4 °C 5 in 100 ml 6 weeks, 25 °C 10 in 100ml (best for whey protein alone and their mixture)	(108)
Apple-Strawberry	*B. animalis*	Emulsion	Milk protein	-	-	193 µm	8.8	28days, 8°C 5 28days, 22°C 0	28days, 8°C 6.5 28days, 22°C 0	(87)
Berry	*S.cerevisiae boulardii*	Extrusion	Alginate–Xanthan gum	Inulin	-	1.5 mm	8 (First fermented in 37ºC for 24h)	4 weeks, 4°C 1.5	4 weeks, 4°C 7.58	(109)
Carrot	*L.casei*	Spray-drying	Chitosan-Ca-Alginate	Fructooligosaccharide	-	6.7-12.5 µm	10.5	6 weeks, 4 °C 5.74	6 weeks, 4 °C 8.52	(110)
	L. plantarum P. acidilactci	Extrusion	Alginate	Moringa extract / green tea extract	-	-	9.5	28 days, 4 °C 5.1	28 days, 4 °C 5.4	(111)

Juice Type	Probiotic organism(s)	Encapsulation method	Capsule material	Prebiotic	Coating	Capsule size	Initial Probiotic concentration (log CFU ml^{-1})	Free probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Encapsulated probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Reference
								(Best alginate beads without plant extract)	(Best with moringa extract and *P.acidilacti*)	
	L.plantarum, Lb.fermentumLb. casei, L.sphaericus S.boulardii			-	Chitosan	1.5-1.8 mm	9.7 (first probiotics fermented in juices and then harvested and microencapsulated to use in juice)	5 weeks, 4°C 6 (Best for *Lsphaericus*)	6 weeks, 4°C 6.1 (Best for *Lsphaericus*)	(112)
	L.acidophilus		Alginate-Xanthan	Inulin	-	1.6 mm	free:10.6 encapsulated:12.7 (first fermented in 37 ºC for 48 h)	8 weeks, 4 ºC 8.4	8 weeks, 4 ºC 10.6	(113)
Cranberry	*L.rhamnosus*	Extrusion	Whey protein	-	Apple pectin /Citus pectin / Sodium Alginate / Carrageenan / Inulin	43.1 µm	9	14 days, 25 ºC 3	14 days, 25 ºC 8.9 (Best for apple pectin coated)	(114)
	L. plantarum B. longum		Alginate Pectin	-	Chitosan Gelatin Glucomannan (Single and double coated)	2.6-3.4 mm	9	6 weeks, 4 °C 0	6 weeks, 4 °C 6.5 (best for double gelatin coated pectin beads, both microorganisms had same results)	(59)
Grape	*B.adolescentis*	Emulsion	Alginate	Pea Protein	-	18.4 µm	9.5	6 weeks, 4,22 °C 5.68	6 weeks, 4,22 °C 5.74	(115)
	L.acidophilus B.bifidum			-	-	54.25 µm	9.6	8 weeks, 4°C 7.5	8 weeks, 4°C 8.67 (Best for *L.acidophilus*)	(116)
	L.acidophilus	extrusion		-	-	2 mm	9.3 (then fermented 72h in 37°C)	4 weeks, 4°C 9	4 weeks, 4°C 9.4	(58)
Kiwi	*L.plantarum P.acidilactci*	Extrusion	Alginate	Moringa extract Green tea extract	-	-	9.5	28 days, 4°C 4.8 (Alginate beads without plant extract)	28 days, 4°C 5.27 (Best for moringa extract and *P.acidilacti*)	(111)
Longan	*L.acidophilus L.casei*	Extrusion	Alginate	-	Alginate Poly-lysine-Alginate Gelatin	2.15-2.19 mm	9.1	4 weeks, 4°C 5.7	4 weeks, 4°C 6.7 (Best for alginate recoated)	(117)
	L casei			Cashew flower extract	-	-	9.8	30 days, 4°C	30 days, 4°C	(76)

Juice Type	Probiotic organism(s)	Encapsulation method	Capsule material	Prebiotic	Coating	Capsule size	Initial Probiotic concentration (log CFU ml^{-1})	Free probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Encapsulated probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Reference
	L.acidophilus *B.lactis*			Green tea extract				6.3 (Alginate beads without plant extract)	7.7 (Best for green tea extract and *B.lactis*)	
	L.acidophilus	Emulsion		-	Alginate	-	Aim of the study is the antibacterial activity of encapsulated probiotics			(117)
Maoberry	*L.casei* *L.acidophilus* *B. lactis*	Extrusion	Alginate	Cashew flower extract Green tea extract	-	-	9.6	30days, 4 °C 3.9 (Alginate beads without plant extract)	30 days, 4°C 4.8 (Best for green tea extract and *L.casei*)	(76)
Melon					-	-	9.5	30days, 4 °C 6.6 (Alginate beads without plant extract)	30 days, 4°C 7.5 (Best for green tea extract and *B.lactis*)	
Mulberry					-	-	9.5	30days, 4 °C 4 (Alginate beads without plant extract)	30 days, 4°C 5.8 (Best for green tea extract and *L.casei*)	
Orange	*L.lactis*	Extrusion	Alginate-Persian gum	Fructoolisaccharides Inulin	-	340-1130 µm	9.84	6weeks, 4°C 2.98	6weeks, 4°C 11.5 (Best for Inulin)	(118)
	L.acidophilus *L.casei*		Alginate	Galactooligosaccharide	Chitosan	1.9-1.92 mm	8.4	-	4weeks, 4°C 8.6	(119)
				-	-	2 mm	9.3 (then fermented 72h in 37°C)	4weeks, 4°C 9	4weeks, 4°C 9.25	(58)
	L.paracasei			-	Chitosan Dextran sulfate (single and double coat)	20-120 µm	9.5	50 days, 5°C 9.4	50 days, 5°C 10.3 (Best for uncoated beads)	(120)
	L casei *L.acidophilus*			-	-	-	9.7 (then fermented 72h in 37°C)	-	4weeks, 4°C 8.8 (Best for *L.acidophilus*)	(121)
	L. plantarum		Alginate-Gelatin_Pectin	DHA	-	-	10.5	4weeks, 4°C 7.2 4weeks, 25°C 6.5	4weeks, 4°C 9.2 4weeks, 25°C 8.5	(84)
	B.adolescentis	Emulsion	Alginate	Pea protein	-	18.4 µm	9.5	6weeks, 4,22°C 0	6weeks, 4,22°C 0	(115)
	L.paracasei			-	-	-	9	8weeks, 4°C 5	8weeks, 4°C 6	(122)
	L.acidophilus *L.bulgaricus*			-	-	-	8	4week 4c 4.5	5weeks 4°C 6	(123)

Juice Type	Probiotic organism(s)	Encapsulation method	Capsule material	Prebiotic	Coating	Capsule size	Initial Probiotic concentration (log CFU ml^{-1})	Free probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Encapsulated probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Reference
	L.lactis *B.bifidum* (each one alone and their mixture)							(Best for prebiotics mixture)	(Best for probiotics mixture)	
	L.rhamnosus	Double aerosol method		-	-	10-40 µm	8.5	12 days, 25 °C 8.2 35 days, 4 °C 8	12 days, 25 °C 8.2 35 days, 4 °C 8.1	(92)
	B.longum *B.breve*	Freeze-drying	Poly-γ-glutamic acid	-	-	-	9	39 days 4 °C 0	39 days 4 °C 6.5	(124)
Peach	*L.paracasei*	Extrusion	Alginate	-	Chitosan Dextran sulfate (single and double coat)	20-120 µm	9.5	50 days, 5ºC 9.4	50 days, 5ºC 10.3 (Best for dextran sulfate coated beads)	(120)
	Lacidophilus *Lreuteri* (alone or their mixture)			-	Chitosan	2.06-2.1 mm	9.5	30 days 5ºC 9.5 (Best for alginate-chitosan *Lacidophilus*)	30 days 5ºC 7.5 (Best for alginate-chitosan *Lacidophilus*)	(125)
Pineapple	*B.Longum*	Extrusion	Alginate	Eleutherine americana extract, oligosaccharide, fructo-oligosaccharide	-	1.65-2.05 mm	9	45 days, 4 °C 0	45 days, 4 °C 8.28 (Best alginate-oligosaccharides extract)	(126)
	B.adolescentis	Emulsion		Pea protein	-	18.4 µm	9.5	6 weeks 4,22 ◦C 5.21	6 weeks, 4,22 ◦C 5.33	(115)
	B. animalis		Milk protein	-	-	193 µm	8.8	28 days, 8◦C 7 28 days, 22◦C 7	28 days, 8◦C 7.8 28 days, 22◦C 8.5	(87)
Pomegranate	*L.plantarum*	Extrusion	Alginate	-	Chitosan (single and double coat)	2.5-3.75 mm	8.5	6 weeks, 4 ºC 0	6 weeks, 4 ºC 6.6 (Best double coated)	(127)
	L. plantarum *B. longum*		Alginate Pectin	-	Chitosan Gelatin Glucomannan (Single and double coated)	2.6-3.4 mm	9	6 weeks 4 °C 0	6 weeks 4 °C 8.5 (Best for double gelatin coated pectin beads)	(59)
	B.longum *B.breve*	Freeze-drying	Poly-γ-glutamic acid	-	-	-	9	13 days, 4 ºC 0	13 days, 4 ºC 3.5	(124)
Prickly Pear	*L.plantarum* *P.acidilactci*	Extrusion	Alginate	Moringa extract Green tea extract	-	-	9.5	28 days, 4 ºC 5.3 (Alginate beads without plant extract)	28 days, 4 ºC 5.8 (Best for green tea extract and *P.acidilacti*)	(111)
Sapodilla	*L.acidophilus*	Extrusion	Alginate	-	-	2 mm	9.3	4 weeks 4 °C	4 weeks 4 °C	(58)

Juice Type	Probiotic organism(s)	Encapsulation method	Capsule material	Prebiotic	Coating	Capsule size	Initial Probiotic concentration (log CFU ml^{-1})	Free probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Encapsulated probiotic Survival in juice at the end of shelf life (log CFU ml^{-1})	Reference
								9	9.1	
Tomato	*L.acidophilus*	Extrusion	k-carrageenan	-	-	3 mm	10.7 (first fermented for 80h in 37ºC)	10 weeks, 4 °C 4.8	10 weeks, 4 °C 6.9	(128)
	L.plantarum, Lb.fermentum Lb.casei, L.sphaericus S.boulardii		Alginate	-	Chitosan	1.5-1.8 mm	9.7 (first probiotics fermented in juice and then harvested and microencapsulated)	5 weeks, 4°C 9.1 (Best for *L.casei*)	6 weeks, 4°C 6.3 (Best for *L.sphaericus*)	(112)
Watermelon	*L.acidophilus*	Extrusion	Alginate	-	-	2 mm	9.3 (then fermented 72h in 37 ºC)	4 weeks, 4ºC 9	4 weeks, 4ºC 9.2	(58)

L: Lactobacillus
B. Bifidobacterium

8. Conflicts of interest

The authors declare no conflicts of interest.

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کاربردهای بالینی و بررسی زنده‌مانی باکتری‌های زیست‌یار آزاد و ریزپوشانی‌شده در آب میوه‌ها: مقاله مروری

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چکیده

سابقه و هدف: زیست‌یارها[1] مکمل‌های غذایی هستند، که هنگام مصرف در مقادیر مناسب، فواید بالقوه‌ای برای سلامتی انسان دارند. مشاهدات اخیر امکان اثرات مفید زیست‌یارها را در درمان کرونا (COVID-19) نشان می‌دهد. تمایل به مصرف زیست‌یارها به تولید فرآورده‌هایی مانند آبمیوه‌های زیست‌یار حاوی ویتامین‌ها، مواد معدنی، و مقادیر مناسبی زیست‌یارهای موجود در بازار به اشکال آزاد و ریزپوشانی شده، منجر شده است، که در منابع علمی به‌خوبی به آنها پرداخته نشده است. هدف این مقاله مروری، بررسی اثرات زیست‌یارها بر مدیریت سلامت انسان بوده است. مطالعه بر اثرات آشکال آزاد و ریزپوشانی شده زیست‌یارها، هنگامی‌که به آب میوه اضافه می‌شوند، بر زنده‌مانی، پایداری در زمان انبارمانی و ویژگی‌های فیزیکولوژیکی و فراسودمندی سلول‌های میزبان تحت شرایط معده و روده سایر اهداف این مطالعه می‌باشد.

یافته‌ها و نتیجه‌گیری: مطالعات نشان داده‌اند که سویه‌های لاکتوباسیل، سویه‌های مورد تایید برای تولید مکمل‌های زیست‌یار، از جمله آبمیوه‌ها می‌باشند. روش‌های گوناگونی برای بهبود زنده‌مانی زیست‌یارها پیشنهاد شده‌اند. ریزپوشانی می‌تواند زیست‌یارها را در برابر ویژگی‌های فیزیکی آبمیوه و در نتیجه آسیب‌های فیزیولوژیکی باکتریایی در شرایط بیهوازی محافظت کند. روش‌های گوناگونی برای ریزپوشانی زیست‌یارها مورد استفاده قرار گرفته‌اند، که هریک ویژگی‌های متمایزی نشان داده‌اند. با این حال، انجام مطالعات بیشتر در زمینه کنترل کیفیت آبمیوه‌های زیست‌یار ضرورت دارد.

تعارض منافع: نویسندگان اعلام می‌کنند که هیچ نوع تعارض منافعی مرتبط با انتشار این مقاله ندارند.

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واژگان کلیدی

- زیست‌یار
- ریزپوشانی
- زنده مانی
- آبمیوه زیست‌یار

***نویسنده مسئول**

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[1] Probiotics