

The synergistic effect of probiotic bacteria and medicinal plants in Iran

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ABSTRACT

The clinical studies proved the antimicrobial synergistic effect of probiotic bacteria and medicinal plants. In addition, this synergic effect can help to maintain food and prevent food corruption. There are plenty of pharmaceutical-probiotic products in the world and offering the same products in Iran is necessary. As Iran is the origin of variant medicinal plants that are used in Iranian conventional medicine, in this review, the synergistic effects of each one alone and with each other evaluated. The proposed mechanisms demonstrated that the oil essence part of plants and bacteriocins in probiotic bacteria, played the main synergistic role. Also, in this study, the synergistic effects of Iranian medicinal plants and probiotic bacteria assessed. It showed that some medicinal plants and probiotic bacteria would be able to have an adequate synergistic effect. Hence, using them in food and hygiene industries could reduce microbial contamination and improve society health.

Keywords: Probiotic bacteria, medicinal plants, synergistic effect

INTRODUCTION

Human intestinal in about nine meters long. In a healthy colon, there are 100 billion beneficial bacteria per milliliter [1]. The

beneficial microbes in intestinal, compose one-third kilogram of the body. There are harmful microbes in contrast to these microbes as well. The loss of microbial equilibrium in a healthy person is called

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dysbiosis. Using antibiotics is one reason for losing beneficial microbes in the intestine. In this situation, harmful microbes are activated and bring plenty of problems with themselves. One of the most important side effects of dysbiosis, is inflammatory bowel syndrome (IBS). This syndrome is an intestinal malfunction that is accompanied by chronic ailment in the abdomen, feeling pain, bloating and changing in intestinal habits without any other sign in other organs of the body. [2]

Probiotic bacteria can confront pathogens and prohibit their growth and attachment to intestinal mucosal layer by secreting bacteriocins. They also reinforce intercellular attachment and by this, they help the permeability of the intestines [3]. Probiotic bacteria stimulate goblet cells which result in increased production of mucose, rebuild mucosal barrier, and its integrity. They also modulate intestinal movements and reduce gastrointestinal allergy in children and adults. Based on various studies, a lot of probiotic strains such as *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Brevibacterium brevis*, *Brevibacterium langum*, *Brevibacterium lactis* and *Streptococcus thermophilus*, can reduce the symptoms of IBS [4].

On the other side, medicinal plants are used to ameliorate the symptoms of IBS. Since the

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essential oil in some plants has a palliative effect, mint oil coated capsules have proposed for IBS adults and children [5]. Wurm *et.al* in 1988 showed that the anti-inflammatory effect of this mint extract is related to inhibition of prostaglandin synthase and lipoxygenase. Clinical trials demonstrate that mint oil is effective to ameliorate some symptoms of IBS [6]. There is no evidence to prove that mint is harmless in pregnant women, therefore, its use should be with caution [7].

Iran is the origin of variant medicinal plants that are used in Iran's conventional medicine. Regarding the capacity of the country's plants, in this study, the synergistic effect of each one alone and with each other has been evaluated. There are three main mechanisms including 1- immunomodulatory ability, 2- Antioxidant effect, and 3- antibacterial effect. Until now, a lot of mechanisms has proposed for the effect of probiotic bacteria and medicinal plants. However, there are only a few that got great attention.

Evaluation of the adaptor effect of the plant immune system and probiotics

Probiotics and medicinal plants have immunomodulatory effects. Mirzaee *et.al* in 2015 showed that the combinational extract from medicinal plants can reduce the inflammatory cytokines from dendritic cells.

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However, the mechanism of action of this phenomenon is unknown. It is also has been proven that flavonoid compounds from plants like *U. dioica* (nettle), *T. vulgare* (Tansy), *R. canina* are not able to stimulate dendritic cells by themselves but can harness inflammatory cytokines such as IL-6, TNF- α , and IL-12p70 [8]. The immunomodulatory effects of probiotics depend on the strain. Each new probiotic bacterium also can have an immunomodulatory effect on cytokines produced by lymphocytes, or dendritic cells, as well [9].

In addition to probiotics, prebiotics possess beneficial effects as well. Prebiotics are non-digestible compounds that can selectively improve the growth and activity of beneficial bacteria in the gastrointestinal tract. These compounds such as inulin and oligosaccharides like fructooligosaccharide and galactooligosaccharides are more important than others. The reason lies in the fact that lactobacilli and bifidobacteria can degenerate these compounds enzymatically. Prebiotics function as a basement for advantageous bacteria and the short chain fatty acids that are obtained by their fermentation, resulting in the production of IgA and IL-10 and by this way they can for their immunomodulatory and protective effects [10].

Synergistic effect of probiotic bacteria Evaluation of the antioxidant effects of medicinal plants and probiotic bacteria

A frequent chronic disease is manifested as a result of increased oxidation level and metabolic defection. Various studies have shown that probiotic and medicinal plants can increase the antioxidant level and improve body metabolism. Oxidative stress is a potential agent and/or triggering agent of Inflammatory Bowel Disease (IBD) syndrome. The reason for this is the harmful effects of free radicals and their role in inflammation. Also, it seems that IBD patients have more oxidated molecules in their organs such as the gastrointestinal tract, blood, and, respiratory system compared to healthy people. Recent studies have proven that medicinal plants can increase the antioxidant capacity and decrease the symptoms of IBD patients [11]. On the other hand, some studies mentioned the effect of the microbial part in the pathogenesis of IBD. This syndrome occurs in sites of the gastrointestinal tract where has the highest number of bacteria. Normal and non-pathogenic bacteria can cause intestinal chronic inflammation in genetic liable hosts. The inflammations increase the release of oxygen free radicals. Henceforth, the antioxidant effect of probiotics can reduce the inflammations and improve IBD [12].

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Amaretti *et.al* in 2013 evaluated the effect of 7 strains of *Bifidobacterium*, 11 strains of *Lactobacillus*, 6 strains of *Lactococcus* and 10 strains of *Streptococcus thermophilus* on antioxidant effect of ascorbic acid and linoleic acid, Trolox-Equivalent Antioxidant Capacity (TEAC), Intracellular Glutathione (TGSH) and Superoxide Dismutase (SOD). They showed that probiotic strains can limit the account of free radicals inside the body. These findings can lead to control and avert disease which is associated with oxidative stress [13].

Clinical trials showed that disruption of microbial equilibrium can cause oxidative stress and metabolic hindrance. In this way, medicinal plants and probiotic bacteria can improve the metabolism and reduce weight [14].

Evaluation of medicinal plants and probiotics antibacterial effect

Probiotics and therapeutical essence such as cumin, use the same procedure to eradicate pathogenic microbes. Moradi *et.al* in 2012 assessed the effect of green cumin on the growth of *Bacillus cereus* in a food model. They showed that this essence can disrupt the cell wall of the bacteria which ends with antibacterial effect of this compound compared to other similar preservatives [15]. Above studies have been assessed and proved

Synergistic effect of probiotic bacteria by Transmission Electron Microscopy (TEM) [16]. Also, in 2012 Mashak *et.al* determined the combined effect of cinnamon and Origan on the growth of *Bacillus cereus* in a food model. They proved that antimicrobial effect of the combination of these two plants is greater than each of them [17].

Probiotics can produce bacteriocins such as nisin which have antibacterial effects. Nisin can bind to class II lipids, which are the main transporters of peptidoglycans from the cytoplasm to the cell wall, and in this way avert the synthesis of the cell wall. Additionally, they can use lipid II as an adhesive agent to cause transportation in membrane production process and cause cell death by making pores [18].

Regarding that produced bacteriocins by probiotic bacteria can target the cell wall of the bacteria and end to cell death, it can be deduced that synergistic effect of Cumin and probiotics is for the same antibacterial mechanism [19].

Other mechanisms

Probiotic bacteria can use medicinal plants as a basement for growth and even as prebiotic material. Prebiotics are complicated carbohydrates that are non-digestible and can produce energy and short chain fatty acids in

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intestines. They expedite the growth of bifidobacteria and lactobacilli selectively. A large number of herbal products such as root and glands and some fruits are known resources of prebiotic carbohydrates [20].

Simultaneous use of medicinal plants and probiotics is not limited to their synergistic effects. Herbal essence averts the oxidation of cell wall of probiotic bacteria and can increase their maintenance. On the other hand, these compounds can protect probiotic bacteria against stomach acid by microencapsulating those [21].

Synergistic effect of medicinal plants and probiotics

A great number of international articles have been published in the field of effect of medicinal plants and probiotics so far. Reddy *et.al* in 2000 patent using medicinal plants and probiotics in the United States (USA). In this study, the synergistic effect of medicinal plants and probiotics is emphasized. The combination of plants including Fennel and Fenugreek in the ratio of 2:1 to 3:2, with the combination of *Lactococcus*, *Lactobacillus*, *Pediococcus*, *Streptococcus*, *Propionibacterium*, *Brevibacterium*, *Penicillium*, and *Saccharomyces* was evaluated. They had a positive effect on stress symptoms, memory loss, joint erosion, joint

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pain, inflammations, liver disease, rectum bleeding, sexuality impotency in men, loss of sexual appeal, high blood cholesterol, gum bleeding, mouth bad smell, toothache and, intestinal malfunction [22].

Clinical trials proved the synergistic effects of medicinal plants and probiotics to ameliorate the symptoms of IBD and dysbiosis. In Ko *et.al* study in 2011, the simultaneous effect of medicinal plants with probiotics on 60 IBD patients was evaluated. In this study, Chinese medicinal plants were used that some of them are used nowadays as well. It is emphasized that this product is an innovative complement treatment for IBD [23].

In a similar study, Ko *et.al* in 2013 showed the effect of Korea's medicinal plants with probiotic in treating IBS in the two blind-sided and random method. In this study, 53 patients in 4 groups used a conventional combination of 13 medicinal plants and probiotics including *Bifidobacterium brevis*, *B. lactis*, *B. langum*, *Lactobacillus acidophilus*, *L. plantarum*, *L. rhamnosus* and *Streptococcus thermophilus* for 8 weeks. At the end of this experiment, the intestine humidity and qualification of life were evaluated. It was shown that using the combination of medicinal plants and probiotics can ameliorate the symptoms of IBD [24].

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There are numerous studies on conventional medicine and medicinal plants in India. Karmakar *et.al* in 2012, on Ayurveda conventional medicine, showed that the effect of medicinal plants and probiotics can be a useful treatment for intestinal pathogens which lack side effects. They mentioned in their results that the synergistic effect of medicinal plants and probiotics is greater than using each of them alone. Since most of these medicinal plants are edible, their extract does not have any side effect when administered in low dosage. Hence, these products can be beneficial for mankind. However, as the supervising organizations pose strict regulations on using herbal extracts as medicine, there are far more studies needed [25].

Lee *et.al* in 2014 sized up the pharmaceutical effect of conventional plants and probiotics on metabolic obesity. In this study, 25 patients treated for 8 weeks. The change rate of metabolism had a negative relation with reduction of gram-negative bacteria and endotoxin level and had a direct relationship with an increase of bifidobacteria population of the intestine. In the end, it was shown that probiotics have an important effect on the decrease of endotoxin production and may have an effect on increase metabolism in obesity. This study is inscribed in Korea National Hygiene Center [14]. Frequent

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studies of the same kind, depend on medicinal plants in different country's conventional medicine. Considering the history of medicinal plants use in Iran's conventional medicine and biological diversity of medicinal plants in Iran, it is important to produce a product based on conventional plants and improve the taste of it as it conforms to people's taste.

Evaluation the synergistic effect of medicinal plants of Iran and probiotics

Using synergistic effect of food products such as meat chickens is common and can reduce using antibiotics in their food rations [26]. Today herbal supplements are used in order to moderate the intestinal microbiota equilibrium of meat chickens. It has a positive effect on producing poultry without antibiotics [27]. However, the synergistic effect is not used in human products.

The first synergistic studies of endemic plants of Iran was conducted by Pol *et.al* in 1999. In this study, the synergistic effect of nisin and carvacrol on *Bacillus cereus* and *Listeria monocytogenes* was evaluated. Carvacrol can be extracted from Pennyroyal, Thyme, and Marjoram and has severe antibacterial effects. This material is considered as one potent antioxidant. It was shown that microencapsulation and adding

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lysozyme as a third preservative, can increase the synergistic effect of nisin and Carvacrol [28]. One of the most important Iran's endemic plants that have been used with probiotics, is *Zataria multiflora*. The most dominant part of the essence is Thymol. Ettayebi *et.al* in 2000 studied the synergistic effect of nisin and Thymol on *Listeria monocytogenes* and *Bacillus subtilis*. They showed that simultaneous use of Thymol can reduce the concentration of nisin [29].

Moosavy *et.al* in 2009 evaluated the effect of *Zataria multiflora* essence and nisin on the cell membrane of *Salmonella typhimurium* and *Staphylococcus aureus* in a food model. Electron microscopic observations showed that the cell membrane of *S.typhimurium* treated with EO and nisin was more damaged compared to treated cells with nisin. This matter constrains the simultaneous use of probiotics and herbal essence as preservatives [30].

On the other hand, some studies have shown that essential oil of *Zataria multiflora* Inhibited the growth of probiotic bacteria. Shakeri *et.al* in 2011 evaluated the antimicrobial effect of *Zataria multiflora* essence with cheese proteins on pathogenic bacteria and probiotics. They showed that 2% of essence has an effect on all pathogenic bacteria, while gram-negative bacteria were more susceptible to them. The higher

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concentration of the essence inhibited the growth of probiotic bacteria [31].

Lamiaceae is one other important plant as the family members have menthol essence. *Mentha piperita* essence has a synergistic effect with probiotics and also has organoleptic effects. Vosough *et.al* in 2009, evaluated the growth of probiotic bacteria in Doogh and concluded that mint extract can increase the survivability of Doogh's probiotic bacteria [32]. Ehsani *et. al* in 2012 evaluated the effect of *Mentha longifolia* and *Lactobacillus casei* on sentimental traits and growth of *Staphylococcus aureus* and *Listeria monocytogenes*, during manufacturing, ripening and storage of Iranian white cheese. They showed that the synergistic effect of high concentration of essence and probiotic is striking compared to other treatments including essence and probiotic alone. Hence, in case of using essence and this probiotic, we can use lower concentrations of the essence [33].

One of the most important therapeutic endemic plants of Iran is *Cuminum cyminum*. In the majority of studies, the synergistic effect of this plant and probiotics is emphasized. Pajohi *et.al* in 2011 conducted a study on the antibacterial effect of Cumin and nisin in the commercial soup on *Bacillus cereus* and *Bacillus subtilis*. The results of this study confirmed the synergistic effect of

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essence and nisin on the cell membrane and cell wall of bacteria [19].

Probiotic bacteria with therapeutic plants, eradicate the pathogenic microorganisms of the intestinal tract and in this way, they avert the effects of bacterial infections and poisoning. In addition, the simultaneous use of probiotics and therapeutic plants can increase the maintenance of food products and inhibit food corruption. In this regard, Sadeghi *et.al* in 2013 evaluated the prohibitive effect of *Lactobacillus acidophilus* and Cumin essence on *Staphylococcus aureus*. They concluded that bactericidal effect of probiotics and therapeutic plants is far greater than using them alone [34]. Tavakoli *et.al* in 2015 assessed the antibacterial effect of Cumin essence, nisin, and temperature against *Salmonella typhimurium in vitro*. Nisin can disrupt the cell wall of bacteria with the same mechanism as Cumin. Hence, the combination of plant essence and nisin can avert the growth of *Salmonella typhimurium* and *Staphylococcus aureus* and can be a beneficial tool to reduce the microbial contaminations in the food industry [35]. Bazjoo *et.al* in 2016 evaluated the effect of endemic *Bacillus subtilis* JQ61819 and Cumin essence on the reduction of blood sugar in diabetic Wistar male rats. They showed that when the blood sugar increases,

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the cholesterol, and triglycerides in rats will increase as well and using probiotic and cumin, can have an effective function on controlling blood sugar, at most 2.62%. The joint use of these two compounds reduced the cholesterol, and triglycerides in diabetic rats. The final results were indicated that using *Bacillus subtilis* with/without cumin essence can control the blood sugar of diabetic patients [36]. Rohani *et.al* in 2011 measured the effect of oil essence of garlic, *Allium sativum*, and nisin separately and together, on the growth of *Listeria monocytogenes*. In this study, they showed that simultaneous use of essence and nisin, have a greater effect compared to each one alone. The anti-listerial effect of these two compounds at 30°C, pH 5.6 and without NaCl, was striking [37]. Moradi *et.al* in 2013 studied the effect of probiotic cheese and Chicory root extract on lipid profile in volunteer adults. In this study, 180 volunteers divided into three groups with 60 members. The first group, used probiotic cheese and Chicory root extract, the second group used probiotic cheese alone and the third group was considered as control. The rate of amelioration of lipid profile was significant in both groups. However, the rate of change in the first group was more evident which demonstrates the synergistic effect of therapeutic plants and probiotics [38]. Moradi and Sadeghi in 2017 evaluated the

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antimicrobial effect of *Satureja edmondi* essence and nisin on *Staphylococcus aureus* in commercial soup and showed that at 8°C, treatment with nisin and the combination of nisin and essence have the most effect on reduction of bacteria numbers. Nisin using can result in reduced using of the essence and ameliorate the taste of the product [39].

Also, in the study by Moradi and Farahani in 2017, the organoleptic studies on the synergistic effect of therapeutic plants and probiotics were conducted. In this study the first probiotic product based on therapeutic plants in Iran. This product contains seven therapeutic plants and 10 bacterial strains of intestine normal microbiota with probiotic effect. This product named "synergic spoon", is a combination of some endemic Iran plants that normally decrease the symptoms of dysbiosis [40]. The results of studies conducted in this area are shown in Table 1.

CONCLUSION

Regarding the resources of conducted study, experiments in the field of synergistic effect of therapeutic plants and probiotic bacteria, conform in Iran and other parts of the world. Unfortunately, the lack of knowledge of society with functional products, using synergistic effects in food products has faced some difficulties.

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Three main mechanisms justify the synergistic effect of therapeutic plants; 1- Immunomodulatory ability, 2- The antioxidant effect, 3- Antibacterial effect.

Most of the studies in Iran are related to antibacterial effect of *Cuminum cyminum* , *Mentha L.*, *Ziziphora clinopodioids* , *Zataria multiflora* , *Teucrium polium* extract, and *Chicorium intybus* . Among them, *Cuminum cyminum* has had the most use. The most important essence is cumin aldehyde in *Cuminum cyminum*, mint in *Mentha L.* and thymol, in *Zataria multiflora*. Also, the studies show that one of the most important of the effectiveness of probiotics is the production of bacteriocins. So far, in most of the studies nisin has been used to study the synergistic effect. Table 1.

Therapeutic plants can selectively eradicate pathogenic bacteria and maintain the probiotic bacteria because of compatibility with a chemical system of the body. This phenomenon is probably for the high concentration of metal ions such as magnesium and manganese in plant extracts [32].

Frequent numbers of articles justify food products based on the synergistic effect of therapeutic plants and probiotics. The reason for that is that these products can increase the public health and they can also be as a complementary treatment. International

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studies have proved the positive effect of therapeutic plants on the treatment of some disease. Also, by using some plants together, they can have a synergistic effect. The proposed mechanisms show that oil essence in plants and bacteriocins in probiotics have the most dominant role in a synergistic effect. Albeit, the oil essence can eradicate probiotic bacteria and this limit using them in combination. Henceforth, using plant extract can be a simpler and more reliant solution. It is expected that some therapeutic plants and probiotic bacteria can have adequate synergistic effects. So, their use in food and

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hygiene products can have a role in decrease microbial contamination and improve society health. Nevertheless, as drug supervising organizations pose strict regulations on plant extract as drugs, a lot of studies are needed in this field.

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Tabel 1. Experiments in the field of synergistic effect of therapeutic plants and probiotic bacteria in Iran

Plants or herbal extracts	Bacteria or probiotic components	Results	References
Carvacrol	Nisin	Antibactericidal action against <i>Listeria monocytogenes</i> and <i>Bacillus cereus</i>	Pol and Smid, 1999. [28]
Thymol	Nisin Z	Antibacterial activity against <i>Listeria monocytogenes</i> and <i>Bacillus subtilis</i>	Ettayebi et al., 2000. [29]
<i>Zataria multiflora</i> Boiss. essential oil	Nisin	Antibacterial effect against <i>Bacillus cereus</i>	Misaghi and Basti, 2007. [41]
<i>Zataria multiflora</i> Boiss. essential oil	Nisin	Antibacterial effect against <i>Salmonella typhimurium</i> and <i>Staphylococcus aureus</i>	Moosavy et al., 2008. [30]
Mint extract	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium lactis</i>	Survivability of probiotic bacteria	Vosough et al., 2009. [32]
<i>Mentha longifolia</i> L. essential oil	<i>Lactobacillus casei</i>	Antibacterial effect against <i>Staphylococcus aureus</i> and <i>Listeria monocytogenes</i>	Ehsani and Mahmoudi, 2013. [33]
essential oil of <i>Cuminum cyminum</i> L. seed	Nisin	Antibacterial effect against <i>Bacillus cereus</i> and <i>Bacillus subtilis</i>	Pajohi et al. 2011. [19]

<i>Cuminum cyminum</i> L. Essential oil	<i>Lactobacillus acidophilus</i>	Antibacterial effect against <i>Staphylococcus aureus</i>	Sadeghi et al., 2013. [34]
<i>Cuminum cyminum</i> L. essential oil	Nisin	Antimicrobial activity against <i>Salmonella Typhimurium</i> and <i>Staphylococcus aureus</i>	Tavakoli et al., 2015. [35]
<i>Cuminum cyminum</i> L. extract	<i>Bacillus subtilis</i> JQ61819	Effect of reducing blood sugar and improving lipid profile	Bazjoo and Jafari, 2016. [36]
<i>Allium sativum</i> L. essential oil	Nisin	Antibacterial effect against <i>Listeria monocytogenes</i>	Rohani et al., 2011. [37]
<i>Chicorium intybus</i> root extract	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium lactis</i>	in healthy adults Effect on lipid profile	Moradi et al., 2013. [38]
essential oil of <i>Satureja edmondi</i>	Nisin	Antimicrobial effects on <i>Staphylococcus aureus</i>	Moradi and Sadeghi, 2017. [39]
<i>Glycine max</i> extract	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium bifidum</i>	Survivability of probiotic bacteria	Marhamatizadeh et al., 2009. [42]
<i>Teucrium polium</i> Essential Oil	<i>Lactobacillus casei</i>	Survivability of probiotic bacteria	Mahmoudi et al., 2014. [43]
<i>Ziziphora clinopodioids</i> essence	<i>Bifidobacterium lactis</i>	Survivability of probiotic bacteria	Ziaolhagh and Jalali, 2017. [44]
essential oil of <i>Mentha piperita</i> and <i>Ziziphora clinopodioides</i>	<i>Lactobacillus acidophilus</i>	Survivability of probiotic bacteria	Sarabi-Jamab and Niazmand, 2009. [45]
<i>Origanum vulgare</i>	<i>Lactobacillus casei</i> and <i>Lactobacillus paracasei</i>	Survivability of probiotic bacteria	Ghorbani Ranjbary et al., 2014. [46]

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