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Review

Reappraisal of probiotics' safety in human

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ABSTRACT

Contrary to the safe usage of probiotics for years, their threat is still worthy of attention. Several risks have been explained or mentioned in the case reports, clinical trials and experimental studies. Due to a large number of probiotic products worldwide, the certainty of the safety of such products is a matter of concern. Current review appraises all the available information about a range of adverse effects by probiotics in different populations of consumers and almost all qualified investigations and reports, relevant to the adverse effects of probiotics. Furthermore, the effects of basic or original sources of probiotics were studied. The principally noticed adverse effects of probiotics are systemic infections, gastrointestinal side effects, skin complications, inflammation of endocardium, gene transfer from probiotics to the normal microbial flora, metabolic harmful impacts of probiotics, and immune system stimulation. The most at-risk groups consist of infants, elderly people, patients in hospitalized condition, and those with immunodeficiency due to a genetic or acquired disease. The existing evidence suggests careful evaluation of the risk-benefit ratio of probiotics prior to prescription or recommendation to use.

1. Introduction

Probiotics are known as microorganisms effective in the improvement of intestinal flora to warrant health and well-being (Hill et al., 2014; Siu, 2018). The term "Probiotics" originally refers to a body of living microorganisms that have significant influences on other cellular organisms and ensure wellbeing through improving microbial flora (Salminen and Van Loveren, 2012; Hill et al., 2014; Siu, 2018).

The concept of probiotics primarily involves the belief that discharged substances by one microorganism cause the nurture and proliferation of the other one (Rowland et al., 2010). Growing consciousness and market for probiotics has necessitated higher standards and scientific proofs for the mentioned benefits given by all probiotic compounds (Rijkers et al., 2011). While there are so many declared benefits of probiotic products mainly as reducing the discomforts relating to the stomach and intestinal tract, enhancing immune health, such functions have not been adequately explained in terms of mechanisms of action or chronic outcomes (Brown and Valiere, 2004; Durchschein et al., 2016; Rijkers et al., 2011). No types of probiotics have been approved for preventing or treating health problems by the American Food and Drug Administration yet (Mileon-Etuk, 2018). Likewise, food safety control authorities in Europe have refused any requests for the approbation of health claims on probiotics by commercial manufacturers since the lack of research and thus unproved efficiency (EFFSA, 2012). Insufficiency of knowledge about probiotics' mechanism of action has been a hindrance in the way of efforts to make sure about the safety of their applications. As stated by the National Center for Complementary and Integrative Health, "Regardless of some

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probiotics which have been found no-risky in research studies, to support their particular uses for most health conditions, still sufficient evidence is highly lacking" (NCCIH, 2016). Since an increasing number of consumers administer probiotics' products globally, the verification of these products as "safe" is quite a must. This review appraises the adverse effects of probiotics.

2. Search strategy

All information in electronic databases (Scopus, PubMed, Web of Science (WoS) and Google Scholar) regarding the side effects of probiotics in different populations and the effects of different sources of extraction on the side effects of certain probiotics were investigated. The reference lists of retrieved articles were also reviewed. Also, keywords for search were probiotics, adverse effects, side effects, safety, mechanism and source of probiotics. Data were collected up to 2019 and, the search was limited to English and Spanish languages.

3. Results

3.1. Overview

As mentioned before, side effects of probiotics and the influence of different sources of extraction on the side effects were investigated. According to the observed results, immunocompromised patients, critically ill patients, people with cancer, and infants are especially at risk.

3.2. Adverse effects of probiotics and the involved mechanisms

Theoretically, probiotics may be accountable for some types of adverse effects. The WHO has suggested an array of tests such as toxin production, hemolytic potential, antibiotic resistance, and analyzing metabolic activities for safety regards. In the meantime, it emphasized post-market supervision of consumers and study of probiotics applications in immunocompromised animals to determine their infectivity effect (Joint FAO/WHO Working Group, 2002).

The following is a summary of each category of potential adverse effects. A summary of adverse effects is presented in Fig. 1.

3.2.1. Bacteremia

The analysis of the outcomes and predisposing factors to *Lactobacillus* bacteremia has been performed in a clinical trial conducted in the years 1990–2000. Among all the studied *Lactobacillus* strains, *Lactobacillus rhamnosus* had a significant role in suffering from bacteremia. In a patient who had received *Lactobacillus* species, bacteremia was the one observed issue most likely (Salminen et al., 2002, 2004). The presence of *Lactobacillus rhamnosus* in blood was reported in two separated cases. One of these cases was an infant who had received probiotic through gastrostomy tubes, and the other one was a 6-year-old child (Land et al., 2005).

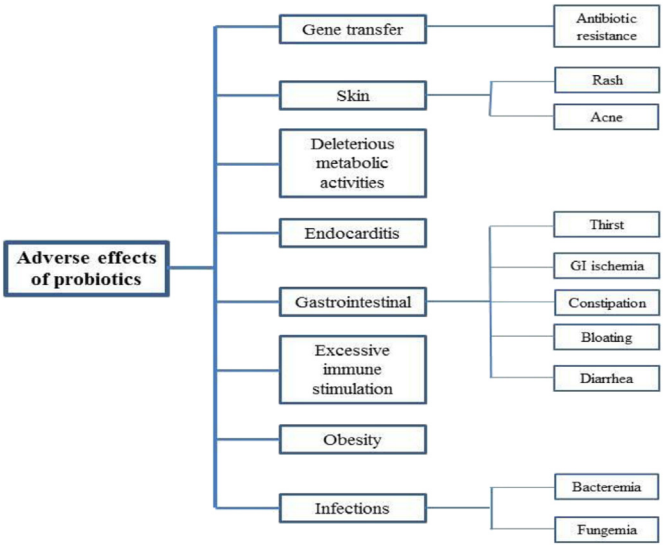

Fig. 1. Adverse effects of probiotics.

The sticking of probiotics to the intestinal mucosa which increases translocation into the bloodstream can be seen as one of the possible mechanisms for such a side effect (Honeycutt et al., 2007). Also, this effect of probiotics illustrates two different mechanisms: one is when probiotics occupy niches completely, so there will be no chance for the pathogen to occupy the niches but if there are some empty and available niches, the pathogen can occupy it and cause infection. The other one is related to the antagonistic nature of a probiotic that decreases pathogen invasion. This effect is clarified through different mechanisms such as lowering the pH by the production of short chain fatty acids and production of small microbial peptides with antibacterial activity and by increasing oxidative stress for pathogen (Vandenplas et al., 2015).

Also, there are many reports that discuss some cases of bacteremia accompanied by three main strains of *Lactobacillus* (*acidophilus*, *casei* and *GG*) (Splichalova et al., 2019; Stroupe et al., 2017; Tommasi et al., 2008; Vahabnezhad et al., 2013). In the meantime, many occasions of overt sepsis have been reported (Land et al., 2005; Ohishi et al., 2010; Salari et al., 2012; Watson and Preedy, 2015; Zein et al., 2008), similar to *Saccharomyces boulardii*, *Lactobacillus GG*, *Bacillus subtilis*, *Bifidobacterium breve*, or group of probiotics.

In two other case reports of critically ill adults (Jain et al., 2004) and children (Honeycutt et al., 2007), indeterminate but possible growth in contagious complications was seen in patients given probiotics.

3.2.2. Fungemia

Fungemia as an adverse effect originated from the use of probiotics has been reported and some types of probiotics such as *Saccharomyces boulardii* or *Saccharomyces cerevisiae* were found in the blood cultures of patients (Apple da Silva et al., 2017; Carter et al., 2016; Costa et al., 2018; Kara et al., 2018; Santino et al., 2014; Trautmann et al., 2008).

As stated in some case reports, fungemia from *Saccharomyces boulardii* produced death as a result. Fungemia was informed in some critically ill patients who had received probiotics such as *Saccharomyces boulardii* in order to stop antibiotic-dependent diarrhea (Cassone et al., 2003).

3.2.3. Gastrointestinal side effects

There have been reports on the gastrointestinal side effects, such as vomiting, nausea, spasms, diarrhea, bloating, thirst, and taste disturbance, happening in cases getting probiotics (Goldenberg et al., 2017; Johnston et al., 2011).

3.2.3.1. Diarrhea or constipation. Current research indicates the effectiveness of probiotic products in improving diarrhea. Having said that, following the consumption of the new probiotic supplements within the first 2–3 days, the digestive tract stimulated and became susceptible to mild diarrhea and soft stools (Goldenberg et al., 2013, 2017; Johnston et al., 2012). The role of *Saccharomyces boulardii* as a cause of constipation was found in a study (Karpa, 2007).

3.2.3.2. Bloating and flatulence. Flatulence and bloating are common undesirable effects of probiotics; however, the reduction of such symptoms and toleration will occur following chronic administration (Karpa, 2007; Goldenberg et al., 2015).

3.2.3.3. Gastrointestinal ischemia. One study evaluated the effect of probiotics to avert infective complications in patients with pancreatitis. There was a higher experience of mortality, attributable

to bowel ischemia, among the subjects who were appointed to the probiotic aim of the survey. Speculating on reasons of bowel ischemia in patients who were given probiotics, the researchers stipulated that maybe the oxygen demand in the intestinal mucosa was due to the administration of probiotics in decreased blood flow condition. As a result of triggered probiotics, there was an opposite inflammatory reaction in the intestine with the decrease of capillary blood flow as yet (Besselink et al., 2008a).

Regarding the impact of probiotics in pancreatitis patients, a biologically prepared combination consisting of *Bifidobacterium* (two strains) and *Lactobacillus* (four strains) was administered to 291 patients with severe pancreatitis per day for about 28 days with 90 days observatory follow-up. Surprisingly, eight out of nine patients who were suffering intestinal ischemia died during therapy (Besselink et al., 2008b).

3.2.4. Skin side effects

According to resulting reports, in patients who received probiotics, moderate problems such as skin rashes or mild acne have been detected. Although, skin rashes might be a symptom resulting from body's activity to eliminate toxins and decrements but on the contrary, not only some probiotics can induce skin rashes and acne but also, they are able to change normal skin microbial flora and result in these skin complications (Salminen et al., 2004).

3.2.5. Harmful metabolic effects

Some metabolic problems such as generating D-lactate metabolite that was produced by specific strains of probiotics were reported in rummaging literature. These issues indicate some cases of D-lactic acidosis in probiotics receiving patients that might be stricken with deconjugation of bile salts (Munakata et al., 2010; Ng et al., 2019; Taylor et al., 2017).

3.2.6. Extreme immune stimulation

Both the intrinsic immune mechanism and the adaptive immune system have been shown to be influenced by probiotics. These include dendritic cell activity and cytokine secretion, and there is a concern about the potentiality to provoke immune system in some people and therefore generating autoimmune disease or inflammation reaction. In some animal studies, its effect on the immune system was completely evaluated such as effects on non-alcoholic steato hepatitis (NASH), Jun N-terminal kinase, and nuclear factor κb. However, there is no report regarding this concern in humans (Braat et al., 2004; Drakes et al., 2004; Vaarala, 2003; Veckman et al., 2004; Wong et al., 2013).

3.2.7. Gene transfer from probiotics to pathogen bacteria

Another matter of concern about the safety of probiotics emerges from the possible conveyance of antibiotic resistance genes from *Lactobacilli* and *Bifidobacterium* to commensals pathogens within the intestinal flora (Magro et al., 2014). Antimicrobial resistance arises on amount of the use of the antimicrobial agent in animals and the transfer of resistant bacteria or genes among animals and the environment and animal products altogether.

There are *Lactobacillales* which transfers genes that giving antibiotic resistance to antibiotics such as tetracycline, erythromycin, chloramphenicol, macrolide, streptomycin, lincosamide, and streptogrammin (Gevers et al., 2003; Lin et al., 1996; Tannock et al., 1994). On the other hand, there are some reports about gene transfer from *Enterococci* to *Lactococci* and *Lactobacilli* in the intestine of animals; however, the transfer to *Lactobacilli* is quite infrequent (Dessart and Steenson, 1991; Morelli et al., 1988).

Full understanding of the resistance to the antimicrobial agent that could be caused by *Bifidobacteria* and *Lactobacilli* and how they could have pathogenic effects, needs further investigations (Fukuda et al., 2012). It is worth noting that resistance to antimicrobial agents may be more common in livestock than it is in humans, because of the administration of antibiotics throughout the whole life of the animal. Furthermore, prophylactic low dose antibiotics are added to animal feeds routinely (Lee et al., 2010; Mañé et al., 2009).

Moreover, some recent *in vitro* and *in vivo* studies were performed in *Lactobacilli* to analyze antibiotic resistance in probiotics within the human gut. Resistance to aminoglycosides such as streptomycin and gentamycin occurred as a result of intrinsic resistant genes *aac(6′)-aph (2”) and ant(6)* and *aph(3’)-IIa*. Furthermore, resistance toward azteronam (a beta-lactam antibiotic) was a result of *blaZ* genes transfer. Also transfer of *van(X)*, *van(E)* brought resistance to vancomycin. These resistances turned out through different mechanisms like gene transfer by conjugation (involving transposons and integrons between the genome and the plasmids), and natural transformation or transduction. Moreover, resistance in probiotics can be detected by analysis of 16S rRNA gene sequences and some biochemical tests using primers and motif-based identification approaches (Wong et al., 2015; Zheng et al., 2017).

As a general rule, added probiotics whether for human or animal food should be checked to be free of transferable antimicrobial resistance determinants.

3.2.8. Endocarditis

There have been reports about the endocarditis, which could be caused by *Streptococcus* and *Lactobacillus* probiotics (Boumis et al., 2018; Mackay et al., 1999; Presterl et al., 2001; Recio et al., 2017). The progress of inflammation of endocardium relevant to *Lactobacillus rhamnosus* was also reported twice in the literature (Conen et al., 2009; Rautio et al., 1999).

3.2.9. Obesity

The role of *Lactobacillus acidophilus* in human weight gain has been shown; however, no positive evidence about such a relationship has been found (Lahtinen et al., 2012).

3.3. Probiotic effects on different consumer populations

3.3.1. Non-patient people

3.3.1.1. Pregnant women. Studies about the benefits of probiotics on pregnant women and their infants are in galore, but simultaneous adverse effects in these populations are pivotal. A meta-analysis over gestational diabetes mellitus patient who also received probiotics, indicated premature delivery and severe intrauterine growth restriction in the arms of newly born. Also, some cases of sense of extreme starvation resulted in severe adverse effects (Rogozińska et al., 2015).

In a randomized controlled study, it was found that most of the adverse effects in pregnant women were the same in all groups, but the risk of nausea, vomiting, and diarrhea increased while probiotics were added to the diet (Mantaring et al., 2018).

3.3.1.2. Healthy people. Some studies of probiotic effects were done to analyze their effects in healthy and mature children who were using probiotics for minor problems. According to a systematic review some adverse effects such as diarrhea, nausea, vomiting, constipation, vaginal discharge, and candidiasis, external genital irritation, itching, moderate abdominal pain, and dysuria in a person with urinary tract infections by using probiotics, were seen (Redman et al., 2014). Moreover, some limited information on harm and mortality probability caused by probiotics was mentioned (Czaja et al., 2007; Reid et al., 2003; Schwenger et al., 2015; Stapleton et al., 2011).

In a study about a healthy case with low defecation frequency and abdominal discomfort who was receiving probiotics, the most adverse effect of probiotics was excessive GI discomfort while the difference with the placebo intervention was very low (Eskesen et al., 2015).

In healthy adults with antibiotic-associated diarrhea treated with probiotics a total of 139 cases of adverse effects of especially

gastrointestinal problems and infections were reported, but the difference between placebo and probiotic's interventions was very partial. The risk of probiotics in this study was reported: “very low” (Evans et al., 2016).

3.3.2. Patient people

3.3.2.1. Infants. Infants are disposed to various risky diseases and controlling risk posing conditions is pivotal. Various cases have been studied to evaluate the effects of probiotics. It seems their administration causes some adverse effects like lack of appetite, taste discomfort, dry skin, abdominal bloating and pain, chest pain, diarrhea, constipation, nausea, vomiting, increased phlegm, and rash (Araujo et al., 2015; Cohen et al., 2013; Kumpu et al., 2012; Łukasik and Szajewska, 2018). Other effects, like cough, rash, vomiting, epitasis, and rhinitis are also reported (Tano et al., 2002).

In a study about antibiotic-associated diarrhea, giving probiotics to healthy children did not cause any severe adverse effects, but in severely debilitated or immune-compromised children, extreme effects such as bacteria or fungemia were observed (Łukasik and Szajewska, 2018).

On the other hand, a randomized controlled study analyzed *Lactobacillus rhamnosus* in children with gastroenteritis proved that using probiotics cause some adverse effects. According to the data and following up the patients, long-term adverse effects such as the risk of developing chronic illnesses increased (Schnadower et al., 2017; Uberos et al., 2017).

In a study of *Saccharomyces boulardii* in infants with *Clostridium difficile* infections, thirst and constipation were detected as adverse effects (Johnston et al., 2012; Uberos et al., 2017).

A survey of pediatric antibiotic diarrhea signified that probiotic treatment does not cause any severe adverse effect, but some effects from mild to moderate ones were found as minor symptoms, such as rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite. Nevertheless, continued assessment of adverse effects is very crucial in the children, and it is better to not consume probiotics in this age group.

Also, a ten-year-old child going through allogeneic hematopoietic stem cell transplantation was treated with *Lactobacilli rhamnosus* Lcr35 and *Lactobacilli rhamnosus* ATCC 53103 and the recurrent episodes of bacteremia occurred as adverse effects of these kinds of probiotics (Di Cerbo et al., 2016a,b).

Other studies also investigated that in children with gastroenteritis there were no better outcomes compared with the control group (placebo) (Schnadower et al., 2019). Further, the group which received probiotics such as *Lactobacillus rhamnosus GG* and *Lactobacillus rhamnosus-L helveticus*, the amount of presence of rotavirus and adenovirus was more and also bacterium such as *Clostridium difficile* and *Shigella* was observed (Basco, 2019).

3.3.2.2. Elderly people. Elderly people are more susceptible to different diseases and risks. A case study reported that using probiotics with *Lactobacilli* may cause some bacteremia and liver abscesses as adverse effects (Sherid et al., 2016).

In a study of *Lactobacilli*, a 73-year-old woman with diabetes mellitus experienced hepatic abscess and bacteremia as adverse effects of probiotics (Di Cerbo et al., 2016a,b).

3.3.2.3. Critically ill patients. In a study aimed to the prevention of pneumonia and endotracheal colonization in critically ill patients by probiotics, some unexpected problems such as the presence of *Lactobacillus* in the blood catheter occurred (Cook et al., 2016).

One other study indicated that using probiotics with other supplements for critically ill adults and children are safe, but adverse effects were seen in critically ill adults who received standard lipid emulsions lead to restriction in use of probiotics (Skillman and Wischmeyer, 2008).

Furthermore, like other cases, GI disorders such as diarrhea were reported in critically ill children with probiotics in their diet (Simakachorn et al., 2011).

Likewise, in a study of hospitalized patients treated with *Lactobacillus rhamnosus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii* and *Lactobacillus paracasei* some adverse effects such as bacteremia were reported and bacteremia caused by *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* may lead to the bloodstream infection (Di Cerbo et al., 2016a,b).

3.3.2.4. Cancer patients. In a study of *lactobacilli*, a man with prostate cancer consuming *Lactobacillus paracasei* as a probiotic, it led to endocarditis. Another case was a 69-year-old man with stage IIIA mantle cell lymphoma that consumed *Lactobacillus* acidophilus, and sepsis occurred as an adverse effect (Di Cerbo et al., 2016a,b). Generally, it is considered that lactobacilli may cause side effects such as sepsis, endocarditis, bacteremia and even death in cancer patients (Fradiani et al., 2010; Kochan et al., 2011; Robin et al., 2010; Søndenaa et al., 2002).

In a study of colorectal cancer, it was found that, contrary to all beneficial effects of probiotics, they could cause many types of adverse effects like increased risk of infections, raised the incidence of allergic sensitization, heightened risk of autoimmune disorders and also finally the DNA damage and chronic diseases (Gratz et al., 2010; Sharma and Shukla, 2016; Snydman, 2008).

Therefore, manipulating the regimen of a cancer patient with probiotics can change the metabolism of anticancer drugs and threat conditions such as sepsis that may lead to death. The effects of probiotics in different populations of consumers have been summarized in Table 1. Also, some case report studies are summarized in Table 2.

3.4. Effect of probiotic source

There are different sources for the extraction of probiotics. At this point, they can be either animal sourced probiotics or human sourced ones. Following some studies, several impacts of probiotics with varied sources have been analyzed. As an example, the potency of probiotics singled out from commercial dairy food products and animal rumen contents was measured. Probiotics that were separated from dairy tolerated better to low pH stress (Jose et al., 2015). However, animal rumen isolated endured better in the presence of bile salts, and its antibiotic impact is much better than the one which is separated from a dairy source. Likewise, in another study bacterial lactic acid isolated of animal manure rendered good performance in survival under-low pH and bile salts and cholesterol lowering (Ilavenil et al., 2015).

As stated earlier, some probiotic strains are sourced from human intestinal flora and breast milk. The type can adhere to the gastrointestinal mucosa, and it can tolerate to gastrointestinal conditions (Mendes et al., 2018). Probiotics can be delivered to the infant's body through vaginal delivery (by the fetus in utero) or specifically while breast feeding. Despite the changes in microbial flora during lifelong occurrence, probiotics that transferred through breast milk, bear positively a life-lasting effect. In animal studies, it is demonstrated that the transferred microbial flora of an obese mouse to another one (twin), resulted in the fat mass increase and the risk of childhood obesity and pediatric obesity, which can directly have an impact on cardiovascular diseases, type 2 diabetes and premature mortality in adults (Lemas et al., 2016; Ridaura et al., 2013). Also, it is found that the microbial flora extracted from bowls in a pregnant woman varies in three trimesters and those in the third trimester was associated with extra inflammation and weight gain. Type 2 diabetes is another problem that can be caused by early diet. Breastfeeding can lead to the mother's microbial flora transfer to the infant's body and mother's type 2 diabetes can directly affect the risk of this problem by inflammation factors (Garcia-Mantrana and Collado, 2016; Mueller et al., 2017; Salek-

Table 1
The adverse effect of probiotics in different population of customers.

Population	Type of study		Administration	Reported adverse effects	Reference
Infants	Review and randomized, controlled trials	General studies	Oral (formula, milk and daily meals	Loss of appetite, taste distribution, dry skin, abdominal bloating, abdominal pain, chest pain, diarrhea, soft stools, constipation, nausea, vomiting, regulation, increased phlegm, and rash	(Cohen et al., 2013; de Araujo et al., 2015; Goldenberg et al., 2015, 2017; Kumpu et al., 2012; Łukasik and Szajewska, 2018)
	Randomized, controlled trials	Immuno-compromised children with AAD [*B. bifidum* W23 and *B. lactis* W51, *L. acidophilus* W37, *L. acidophilus* W55, *L. paracasei* W20, *L. plantarum* W62, *L. rhamnosus* W71 and *L. salivarius* W24]	Oral	Central venous catheter use and disorders associated with bacterial/fungal translocation	(Goldenberg et al., 2015; Łukasik and Szajewska, 2018)
	Review	Children with AAD (mild to moderate ones)	Oral	Rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite	Tano et al. (2002)
	Randomized controlled trials	Using *LGG* in children with gastroenteritis in emergency care [*Lactobacillus rhamnosus* GG (LGG) (ATCC 53103)]	Oral	An increased risk of chronic diseases	(De Araujo et al., 2015)
	Randomized, controlled trials	S. *boulardii* in patients with *C. difficile* infections	Oral	Thirst and consumption	(De Araujo et al., 2015)
	Review	Ten-year-old child undergoing allogeneic hematopoietic stem cell transplantation was treated with *L. rhamnosus Lcr35* and *L. rhamnosus ATCC 53103*	Oral	Recurrent episodes of bacteremia	Sherid et al. (2016)
	Original article	*L. rhamnosus* GG in children with gastroenteritis	Oral	Wheezing	Schnadower et al. (2019)
	Original article	Combination of L. *rhamnosus–L. helveticus* probiotic in children with gastroenteritis [*Lactobacillus rhamnosus*R0011 and *L. helveticus* R0052]	Oral	Febrile seizure (after 6 h of the first dose) and Kawasaki disease (after 3 weeks of consuming)	Freedman et al. (2018)
Healthy people	Randomized controlled trials	Probiotics in UTI [*Lactobacillus rhamnosus GR-1, L. fermentum RC-14*] [*Bifidobacterium animalis* subsp. *lactis*, BB-12]	Oral	Diarrhea, nausea, vomiting, constipation, vaginal discharge, and candidiasis, external genital irritation, itching, moderate abdominal pain, dysuria	(Czaja et al., 2007; Eskesen et al., 2015; Reid et al., 2003; Schwenger et al., 2015; Stapleton et al., 2011)
	Randomized controlled trials	Healthy people with low defecation frequency and abdominal discomfort [*Bifidobacterium animalis* subsp. *lactis*, BB-12]	Oral	GI disorders	Eskesen et al. (2015)
Elderly people	Case report	Using Lactobacilli in a case	Oral	Bacteremia and liver abscesses	Sherid et al. (2016)
	Review	*Lactobacilli* in a 73-year-old woman with the antecedent of diabetes mellitus	Oral	Hepatic abscess and bacteremia	Di Cerbo et al. (2016)
Pregnant women	A Meta-Analysis of Randomized Studies	Probiotics in cases with GDM	Oral	Preterm delivery, severe intrauterine growth restriction in the arms,	Rogozińska et al. (2015)
Critically ill patients	Cohort study	Prevention of pneumonia and endotracheal colonization by probiotics		Presence of Lactobacillus in the blood catheter	Skillman and Wischmeyer (2008)
	Randomized controlled trials	Critically ill children [*Lactobacillus paracasei* NCC 2461 and *Bifidobacterium longum* NCC 3001]	Oral (formula)	GI disorders such as diarrhea	Simakachorn et al. (2011)
	Randomized controlled trials	Hospitalized patients treated with L. rhamnosus, *L. curvatus, L. delbrueckii* subsp *lactis* and *L. paracasei*	Oral	Bacteremia and bloodstream infections	Di Cerbo et al. (2016)
Cancer patients	Review	*L. paracasei in a 73-year-old man with a prostate cancer*	Oral	Endocarditis	Di Cerbo et al. (2016)
	Review	*L. acidophilus in a 69-year-old man with stage IIIA mantle cell lymphoma*	Oral	Sepsis	Di Cerbo et al. (2016)
	Case report And Cohort study	General use of *Lactobacillus* and *Bifidobacterium* in cancer patients	Oral	Change the metabolism of anti-cancer drugs and life-threatening conditions such as sepsis, endocarditis, bacteremia, death	(Ciernikova et al., 2017; Fradiani et al., 2010; Kochan et al., 2011; Robin et al., 2010; Søndenaa et al., 2002)
	Review	Probiotics in cases with colorectal cancer *[Bacillus subtilis* EG-RN and EG-CM, *Lactobacillus delbrueckii* UFV-H2b20 and *Bifidobacterium lactis* Bb12]	Oral	Increased risk of infections, increasing the incidence of allergic sensitization, increasing the risk of autoimmune disorders, DNA damage, different chronic diseases	(Gratz et al., 2010; Sharma and Shukla, 2016; Snydman, 2008)

AAD: antibiotic associated diarrhea.
LGG: Lactobacillus rhamnosus.
UTI: urinary tract infections.
GDM: gestational diabetes mellitus.

Table 2
Some case reports of adverse effect related to probiotics.

Case presentation	Underlying problem/disease	Probiotic	administration	result	Reference
An 82-year-old female	*Clostridium difficile* colitis	*Lactobacillus* (strain identification was not performed)	Oral	Liver abscess and bacteremia	Sherid et al. (2016)
A patient with a graft in the inferior vena cava	Graft in the inferior vena cava	*Lactobacillus rhamnosus*	Oral	Septicemia	Søndenaa et al. (2002)
A 47-year-old immunocompetent patient	Immunocompetent patient	*Lactobacillus jensenii*	Oral	Endocarditis	Fradiani et al. (2010)
A 24-year-old female	After an aortic valve replacement	*Lactobacillus rhamnosus*	Oral	Septicemia	Kochan et al. (2011)

Maghsoudi et al., 2018; Soderborg et al., 2016).

3.5. Ways to reduce the adverse effects

Some studies have suggested ways to reduce some side effects of probiotics, which are being discussed in the following conditions.

3.5.1. Decrease the dosage

Some studies have made it clear that one possible way of minimizing the side effects of probiotics is to reduce the dosage. As the body becomes accustomed to the lower dosage, then it can easily increase the dosage and deal with the higher levels. Conversely, taking too many probiotics at once quickly may give an overdose to probiotic consumption (Lahtinen et al., 2012; Snijder et al., 2007).

3.5.2. Stay hydrated

The effect of water on some side effects of probiotics, such as diarrhea, gas, bloating, cramps, rashes, and acne is certain and can control these adverse impacts (Lahtinen et al., 2012; Snijder et al., 2007).

3.5.3. Ultraviolet radiation

As a solution to mitigate the precarious impacts of probiotics in high-risk populations, use of heat or ultraviolet radiation has been counseled to inactive probiotics. These probiotics hold back their earliest attributes, but they become ineffective regarding their immune-stimulatory functions (Lahtinen et al., 2012; Snijder et al., 2007).

4. Conclusion

Probiotics are used as functional foods or supplements in the prevention or treatment of some diseases but besides the beneficial effects, they may have negative effects if not appropriately used. Receiving probiotics in high-risk populations posed some health complications. Along with the genetic characteristics of intestinal microbiotic in each human case, probiotics and their effects on adults are being influenced by environmental factors, diet, and use of the antibiotics. Hence, viewing non-identical outcomes in different age groups of consumers would be predictable events and therefore, precaution is necessary to be taken just prior to receiving probiotics.

In the current article, we probed the adverse effects of various strains of probiotics in human populations. Current studies are under difficulties due to some restrictions in various factors such as lifestyle of case studies, dissimilarity in the normal flora of humans, gene relevant differences, sex and age of evaluated consumers and difference in the period of treatments or follow-up times that all could lead to different results and a variety of success reports. What is obvious is that the best probiotics in terms of dose, duration of treatment and efficacy requires further study and cannot be underplayed. Our recommendation for the scientists is to focus on effects of sources that probiotics can be extracted, to the host, and safety or adverse effects of probiotics in high-risk consumers.

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Transparency document

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