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The Role of Probiotics, Beneficial Microorganisms, In the Treatment and Resistance Against Pathogenic Bacteria.

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KEYWORDS

Probiotic bacteria, Treatment of pathogenic bacteria , Antibiotic-resistant bacteria.

ABSTRACT:

The aim of this research paper is to identify the capability of microorganisms in eliminating antibiotic-resistant bacteria and to find a newer, safer, and more cost-effective technique for treating pathogenic and harmful bacteria to human and animal health. It also seeks to explore new, modern, and effective methods for treating chronic diseases that have harmful side effects on human health and are environmentally polluting, and which result from pathogenic organisms that have high resistance to conventional antibiotics. Furthermore, it aims to produce an effective and safe alternative from beneficial probiotics like Lactobacillus and lactic acid bacteria. To date, several studies have reported an alarming increase in pathogen resistance to current antibiotic therapies and treatments. Therefore, the search for effective alternatives to counter their spread and the onset of infections is becoming increasingly important. In this regard, microorganisms of the former Lactobacillus genus have demonstrated the ability to reduce the virulence of pathogens. lactobacilli have been used as an effective therapy for treatment of several pathological conditions displaying an overall positive safety profile. This review summarises the supporting therapeutic efficacy of lactobacilli. In addition to the production of bioactive substances, self- and coaggregation, and substrate competition, lactic acid bacteria is useful for human healthy such as Applications of lactobacilli include kidney support for renal insufficiency, pancreas health, management of metabolic imbalance, and cancer treatment and prevention. In vitro and in vivo investigations have shown that prolonged lactobacilli administration induces qualitative and quantitative modifications in the human gastrointestinal microbial ecosystem with encouraging perspectives in counteracting pathology-associated physiological and immunological changes. It also highlights the important and vital role in treating diarrhea and some digestive system disorders by using probiotic bacteria, such as lactic acid bacteria found in yogurt, kefir, and some dairy products, which play a significant role in treating and combating harmful and pathogenic bacteria present in the stomach. Thus, with the continuous use of beneficial bacteria, the number of beneficial probiotic bacteria increases, which attack pathogenic bacteria and causes gastrointestinal diseases.

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Introduction:

Bacterial infections have been, and are very likely to continue to be, among the most serious problems in medicine. One of the main reasons for this is that a significant proportion of these infections are endogenous, and the etiologic agents originate from the human bacterial flora. In this context, it must be emphasized that the bacterial microbiota is absolutely essential for human life; on the other hand, however, it represents a source of bacterial pathogens potentially implicated in the development of a wide range of infections (1,2). An integral part of the treatment of bacterial infections is the administration of antibiotics that target etiologic agents. Antibacterial drugs as we know them in today′s medicine have been used for 80 years. Despite the great expansion of antibacterials in the 1960s and 1970s, as documented by the development of a range of new products and their introduction into practice, bacterial infections remain a major issue of increasing importance. Modern medicine is even confronted with the real threat that antibiotics may lose their effect on bacteria and the associated ability to treat bacterial infections. The increasing resistance of bacterial pathogens to antibacterial drugs; for example, the rising prevalence of bacteria producing broad-spectrum beta-lactamases, including metallobeta-lactamases and carbapenems, raises the possibility of a return to a new “antibiotic-free era” in which adequate antibiotics will not be available for the treatment of bacterial infections with an etiological role of multidrug-resistant bacteria (3).Due to their properties, several strains of this group have been identified as probiotics, defined by FAO and WHO as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (4, 5), and their inactivated cells or their cell-free supernatants (CFS) hosting numerous beneficial components are also considered postbiotics, defined as “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” (6). They are also part of the human natural bacterial flora, in which they have a regulatory role in protecting hosts against colonization by pathogens and exert beneficial effects, such as increasing and improving nutrient assimilation during digestion or stimulating host tissues (7). Prolonged consumption of these bacteria leads to modification of the human gastrointestinal microbial flora, thus stimulating the immune system and decreasing pathogen adhesion (8). Herkel et al., reported a statistically significant difference in mortality between patients receiving adequate and inadequate antibiotic treatment for ventilator-associated pneumonia. While the former showed 27% mortality, inadequate antibiotic therapy was associated with a rate of 45%, with bacterial pathogens being resistant to initial antibiotics (9]. Rather alarming is the fact that multidrug-resistant bacteria have also been confirmed as part of the normal microbiota. For example, Arnan et al., found ESBL-positive *Escherichia coli* strains in 29% of patients with neutropenia, compared to only 14% at the time of hospital admission (10). A study conducted in the University Hospital Olomouc, Czech Republic, showed 21% prevalence of ESBL- and AmpC-positive enterobacteria in the gastrointestinal tract of hemato-oncology patients (11). At the same time, it should be emphasized that genetic analysis revealed identical bacterial agents isolated from the urine and blood and from the gastrointestinal tract in two patients with clinically manifested bacterial infection (urinary tract and bloodstream infection). This suggests that multidrug-resistant bacteria present in the intestinal flora caused serious illness (11). It should also be reminded that multidrug-resistant bacteria are found in the environment, as confirmed, for example, by studies published in this Special Issue of *Life* (12,13). The urgency of AMR increases with the requirement for adequate treatment of serious bacterial infections, especially in intensive care patients. In these cases, it is necessary to administer antibacterials as soon as possible, preferably within hours (depending on the diagnosis) (14,15). However, it is not possible to accurately determine the etiologic agent and its susceptibility to antibiotics over such a short period of time. On the other hand, adequate antibiotic treatment can substantially contribute to a positive therapeutic effect in a particular patient. The problem of AMR is clearly multifactorial and must be addressed by an interdisciplinary approach involving many medical specialties. The key prerequisite for its successful solution is close multidisciplinary cooperation and the implementation of bacterial resistance surveillance, an essential part of which must be the determination of the selection of multidrug-resistant bacteria and the pathways and mechanisms of their spread, including their genetic basis as described, for example, in the study by Bogdanova et al., in this Special Issue (16). These data are indispensable for establishing the basic principles of a rational antibiotic policy and adequate hygiene and epidemiological measures. This clearly suggests the need for the practical implementation of antibiotic stewardship, a set of measures leading to rational antibiotic treatment based on appropriate selection of antibacterial drugs, the duration of their administration, as well as the route of administration (17,18,19,20). Such an approach is very comprehensive and includes a range of different activities.The overall solution should also involve strict adherence to hygiene and epidemiological measures, the development of new antibacterial drugs and providing the professional and lay public with information on increasing resistance of bacterial pathogens to antibiotic treatment and the decreasing number of suitable medications. The rational use of antibiotics to treat bacterial diseases is a fundamental requirement of today′s medicine. It must be stressed though that, in many cases, it is not possible to administer antibiotics based on identification of the etiological bacterium and determination of its susceptibility to antibacterial drugs. This is mainly true for acute bacterial infections, where there is a risk of delays. In these cases, it is necessary to use initial (non-targeted) antibiotic therapy.But what is crucial is the indication for antibiotic therapy. The use of antibiotics is a risk factor in terms of the selection of bacterial strains with a higher degree of primary resistance (e.g., strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, or *Burkholderia cepacia* complex), as well as bacteria with secondary, or acquired, resistance (e.g., methicillin-resistant strains of staphylococci, enterobacteria producing broad-spectrum beta-lactamases, or carbapenem-resistant strains of *Pseudomonas aeruginosa*). Therefore, antibiotic treatment should be limited to clinically confirmed or very likely bacterial infections. Administering antibacterials only to “cover the patient” should be rejected as unwarranted and risky. Despite the fact that the use of antibiotics is conditioned by local sources of information, it is necessary to mention other no less important sources of data, namely, the generally valid data on the pathogenesis of bacterial infections and properties of microorganisms, as well as the facts on the properties of antibiotics (pharmacokinetics, excretion, penetration into tissues, etc.), and, last but not least, the results of bacterial resistance surveillance at both national and international levels, such as the EARS-Net database(21). Antitoxic activity Lactobacilli display detoxifying properties and their ability to neutralise toxins (81) or toxic compounds (82). Is important to maintain the host’s health. Antibiotic treatment to treat specific infections has the potential to effectively target the offending microbe as well as other microbes that colonize sites within a host. Antibiotic-associated diarrhea is a classic example resulting from disruption of host microbial communities (122).

1.1. Common microbes used as Probiotics:

The microbes used as Probiotics represent different types such as bacteria, yeast or mold. However, there are more common species of each such as: 1 – Bacteria: (i) *Lactobacillus*: *acidophilus*, *sporogenes*, *plantarum*, *rha mnosum*, *delbrueck*, *reuteri*, *fermentum*, *lactus*, *cellobiosus* , *brevis*, *casei*, *farciminis*, *paracasei*, *gasseri*, *crispatus*;
(ii) *Bifidobacterium*: *bifidum*, *infantis*, *adolescentis*, *longu m*, *thermophilum*, *breve*, *lactis*, *animalis*;
(iii) *Streptococcus*: *lactis*, *cremoris*, *alivarius*, *intermedius*, *thermophilis*, *diacetylactis*; (iv) *Leuconostoc mesenteroides*; (v) *Pediococcus*; (vi) *Propionibacterium*; (vii) *Bacillus*; (viii) *Enterococcus*; (ix) *Enterococcus faecium*; 2 – Yeast and molds: *Saccharomyces cerevisiae*, *Saccharomyces bourlardii*, *Aspergillus niger*, *Aspergillus oryzue*, *Candida pintolopesii*, *Sacaromyces boulardii*.

The type of the microbes used as Probiotics increased due to the increase in the research concerning the subject as well as by the increase of the newly discovered and identified microbes, which could be used as Probiotics. One should update his microbial flora from time to time and follow the research and the published data about Probiotics to gain more knowledge and ideas.

1.2. Probiotic for health improvement:

One of the points described in this review about Probiotics is their role in health improvement. In fact, this is the most important point, where we expected that healthy persons will be the first in need to use Probiotics which will lead to improve their general health and as a result will protect them from different kinds of illness. Improving health will be an intelligent step for protecting us from different types of illness. Nevertheless, how could Probiotics do that? The following paragraphs will highlight the concept of how Probiotics could improve our health directly or indirectly.

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1.3. Good and bad microbes:

Our bodies have groups of microbes each working collectively to perform different functions. The most important ones are those existing in our digestive system (Gismondo et al., 1999; Fioramonti et al., 2003). They improve food digestion and consumption. They are able to complement many deficiencies in our digestive system. They decrease the steps needed in our bodies to change complicated food structures to simpler ones. Alternatively, many bad variants of different microbes will take their positions and will digest our food incorrectly. They will even add some toxins to our food during the digestive process. Hence, each food cycle will lead to a real deterioration to our health (Amara, 2012). Many diseases are diagnosed incorrectly while their main actual elevating purpose is due to the existence of bad microbes in the digestive system, mainly due to the leakage in the feeding processes, the life style or even diseases which will direct the balance toward the bad microbes. The affected ones are humans because they did not follow the correct steps to protect themselves from losing the useful strains and gaining harmful ones. In such cases, Probiotics are needed to be given in higher dosages (Amara, 2012; Reid et al., 2003).

1.4. Probiotic, the good against the bad microbes:

If harmful microbes colonized our digestive system they will ferment food in incorrect ways and toxins, which will affect our health, might be produced. *What could Probiotics do*? Probiotics are able to regenerate our digestive system with good microbes that will neutralize the harmful ones. Useful microbes will ferment our food correctly and improve our health. *Why must we use Probiotics*? During our lives, we are exposed to different types of microbes, which are unsuitable for our health. Antibiotic treatment could destroy our useful microflora. In such cases, Probiotics should be used to regenerate our microflora. If our daily food contains Probiotics, that will be the best and the cheapest way to recover any losses in our digestive system microflora and to improve our health. In olden civilizations, the public used to include food-containing Probiotics in their daily food (Amara, 2012). However, when our microflora has been affected severely due to any reasons, Probiotics should be given in large dosage as tablets or in any other suitable forms (Reid et al., 2003). A healthy intestine is one that maintains a significant balance of bacteria such as lactobacilli, streptococci, clostridia, coliform, and bacteroides. Conditions such as stress, excessive alcohol use, high fat diets, meat, sugar, genetic disorders, chlorine and fluoride in drinking water, antibiotics, inadequate food, exposure to environmental toxins and many others factors could change the balance of our intestinal flora (Hosono, 1992). In fact, our health is affected by many exogenous and endogenous factors that could change our microflora position. Useful microflora guarantees good health. One cannot hear the sound of the daily battles between the good and the bad microbes in our bodies or see how they enter our bodies with each breath, talk and with each food consumed. Actually, they are essential for our health. They build our immune system slowly to be ready for the pathogens (Bandyopadhyay and Das Mohapatra, 2009; Cammarota et al., 2009). Those that live far away from such a lifestyle are more susceptible to infections and diseases (Amara, 2012). Another side of the story, that such microbes and mainly those which are non-pathogenic, are like workers working in a big firm (our body), they do various jobs to support and assist us all the times. Mainly, they do that spontaneously. By doing such work, they save for us energy and power, or they even do what we could not do. Complementing the Lactose digestion deficiency is such an example (Hawrelak, 2003). The existence of harmful bacteria could finding resistance in the body, so their negative effects might not appear directly, but after a considerable time. Alternatively, they are not few in number but produced in considerable amounts, at this point they will be really harmful (Amara, 2012). Bad microbes, even though apparently non existant in a healthy person, actually, exist, but cannot do a lot of harm because of the existence of good bacteria. They are under continuous pressure from good bacteria. Good bacteria, fill in the spaces existing in our body, and prevent bad ones from taking their chances. However, because of our misuse and misunderstanding of their behavior, we change the conditions usually towards the benefit of bad bacteria. By changing the balance toward the bad microbes, we will start to suffer, and our health will start to degrade. To prevent that, the bad microbes should be kept under control (Amara, 2012). Therefore, there is no better solution other than, letting good ones compete with them, take their places and in some cases omit them or decrease them to the minimum safe amount. The intestinal tract is home to one hundred trillion (10^{14}) different types of microbe (Gismondo et al., 1999). Many of the bad microbes like to live in alkaline or natural environment, that is why our stomach is acidic to kill most of them before they pass into the long intestine. Bad microbes produce ammonia that change the intestinal tract pH to becoming more alkaline (Metchnikoff and Mitchell, 1910; Metchnikoff, 2004; Marteau et al., 2001). One might observe that upon drinking fermented milk, which is weakly acidic, he feels good and relaxed. This is because of two factors, that fermented milk contains acids, which kill pathogenic bacteria, and at the same time contains good bacteria, which will directly fill the space of the just killed bacteria (Fernandes et al., 1987; Hilton et al., 1977). Additionally, it still contains proteins that are able to reduce any extra-acidity. One of the most important strains existing naturally in milk products is Lactobacillus. The microflora in our digestive system do crucial jobs, such as filling in digestive system spaces, food digestion, killing of pathogens, and secreting vitamins (e.g. vitamin B) and some essential amino acids, enzymes help in digesting complicated fibers in the food, acid (e.g. lactic acid) helps to prevent pathogenic microflora from exceeding their number limit, and to perform many other vital activities. As well, Probiotic strains found in the colon help in digesting some forms of fiber. One should highlight that Probiotics are also able to some extent activate the immune system (Cammarota et al., 2009).

1.5. The relation of Probiotics to our health could be summarized in the following points and facts :

Probiotics are useful and friendly microbes.

They are able to compete with the bad microbes and colonize our digestive system.

They are able to ferment our food to simpler byproducts and could promote our health by many different mechanisms.

Their amount could be deteriorated due to many factors, such as incorrect diet, alcohol, age and so on. This is why they should be taken through our regular diet.

In particular cases such as after antibiotic treatments, where they are expected to be affected severely, they should be taken orally in considerable amounts or with food.

Probiotics promote health while they:

Remove the side effect of the pathogens or the harmful microbes.

Supply the body with useful byproducts.

Reduce the jobs of our digestive system.

Reduce the effect of the first attack of harmful compounds, instead of our cells, by their biofilm, which protects our digestive system.

Reduce the amount of food needed by our bodies due to the correct digestion and metabolism of any amount of food.

Probiotics in some cases could complement the deficiency in our genetic materials by helping us to borrow the products of their genes (such as in case of the lactose fermentation deficiency).

Here we should highlight that, Probiotics or anything in our lives should not exceed a certain limit and should be used wisely to give the best expected results (Salminen et al., 1998).

1.6. Infection control:

The mechanisms by which Probiotics exert their effects are largely unknown, and there are still many open research points. However, Probiotics are involved in modifying gut pH, antagonizing pathogens through the production of antimicrobial compounds, competing for pathogen binding and receptor sites as well as for available nutrients and growth factors, stimulating immunomodulatory cells, and producing lactase (Table 1). The most important point of Probiotics is that they are proven to be safe, cost effective, and could interfere with the microbial infection. In 1994, the World Health Organization deemed Probiotics to be the next-most important immune defense system when commonly prescribed antibiotics are rendered useless by antibiotic resistance (Kailasapathy and Chin, 2000; Levy, 2000). The use of Probiotics in antibiotic resistance is termed as microbial interference therapy (Botes et al., 2008; Fukao et al., 2009; Zhou et al., 2005).

2. Mechanisms of action:

Outstanding advances have been made in the field of probiotics, but there has yet to be a key breakthrough in the documentation of their mechanism of action. Probiotics possibly exert a positive potential on the human body through these main mechanisms; competitive exclusion of pathogens, improvement in intestinal barrier functions, immunomodulation in the host's body, and production of neurotransmitters (Figure 1; Plaza-Diaz et al., 2019). Probiotics compete with pathogens for nutrients and receptor-binding sites, making their survival difficult in the gut (Plaza-Diaz et al., 2019). Probiotics also act as anti-microbial agents by producing substances; short chain fatty acids (SCFA), organic acids, hydrogen peroxide (Ahire et al., 2021), and bacteriocins (Fantinato et al., 2019) thus decreasing pathogenic bacteria in the gut. Moreover, probiotics improve the intestinal barrier function by stimulating the production of mucin proteins (Chang et al., 2021), regulating the expression of tight junction proteins, including occluding and claudin 1, and regulating the immune response in the gut (Bu et al., 2022; Ma et al., 2022).

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4.Probiotic, the good against the bad microbes:

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TABLE 1 Summary of virulence genes affected by lactobacilli

Bacteria	Gene	Protein	Function	Reference
Salmonella spp.	*avrA*	AvrA	Inhibition of innate immunity	56
	hilA	HilA	Regulation of *Salmonella* pathogenicity island 1 gene expression	48
	hilC *hilD*	HilC, HilD	Transcriptional regulators of *hilA*	48
	spv		Promoter of the virulence genes of nontyphoid *Salmonella* serovars	51
Escherichia coli	*eaeA*	Intimin	Attachment to cell surface	86
	fliC	Flagellin	Motility	96
	hly	Enterohemolysin and α-hemolysin	Toxins with hemolytic activity	87
	ler	LEE1-encoded regulator	Transcriptional activator of LEE genes	94
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	97, 98
Escherichia coli	*stx*	Shiga-like toxin Stx	Toxin causing diarrhea and other disorders	89

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Bacteria	Gene	Protein	Function	Reference
Clostridium spp. *Staphylococcus aureus*	*tir*	Translocated intimin protein	Adhesion to epithelial cells	93
		Adhesins	Adhesion on both abiotic and cell surfaces	91
		Intimin receptor EspE	Type III secretion system that allows attaching and effacing (A/E) lesions	92
	luxS	LuxS enzyme	Production of autoinducer 2 (AI-2)	125
	tcdA	Enterotoxin A	Toxin that causes diarrhea and intestinal damage	119, 120
	tcdB	Toxin B	Toxin with strong cytotoxic effect	119, 120
	txeR	σ factor	Induces RNA polymerase to recognize the promoters of *tdc* genes	121
	agr		QS system that regulates virulence factors	130
	ica		Biofilm formation	137
Helicobacter spp.	*ndvB*		Biofilm formation	157
	pil	Pilin	Type IV pili necessary for twitching motility	158
	rhI/R	RhI/R protein	QS system that regulates virulence factors	162

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