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Antimutagenic Activity as a Criterion of Potential Probiotic Properties

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Abstract

The antimutagenic activity of probiotic strains has been reported over several decades of studying the effects of probiotics. However, this activity is rarely considered an important criterion when choosing strains to produce probiotic preparations and functional food. Meanwhile, the association of antimutagenic activity with the prevention of oncological diseases, as well as with a decrease in the spread of resistant forms in the microbiota, indicates its importance for the selection of probiotics. Besides, an antimutagenic activity can be associated with probiotics' broader systemic effects, such as geroprotective activity. The main mechanisms of such effects are considered to be the binding of mutagens, the transformation of mutagens, and inhibition of the transformation of promutagens into antimutagens. Besides, we should consider the possibility of interaction of the microbiota with regulatory processes in eukaryotic cells, in particular, through the effect on mitochondria. This work aims to systematize data on the antimutagenic activity of probiotics and emphasize antimutagenic activity as a significant criterion for the selection of probiotic strains.

Keywords Probiotics · Antimutagenic agents · Antioxidants · Bacteria · Bbifidobacterium · Lactobacillus · Bacillus

Introduction

In the modern anthropogenic environment, humans and animals are regularly exposed to various mutagens, in amounts that significantly exceed natural ones. Some of the widely used drugs can have a mutagenic effect [1], including those acting on the human microbiota, increasing the likelihood of antibiotic resistance. Anticancer drugs [2, 3] or antibiotics [4] are examples of such preparations. Moreover, mutagens are formed even during heat treatment of food [2]. Reactive oxygen species produced by both body cells and microbiota can also be considered promutagens, so probiotics' antioxidant potential should also be considered [3].

In addition to exogenous mutagens that enter the human body from the environment, there are also endogenous mutagens. Reactive oxygen species (ROS), produced in mitochondria, are an integral part of cellular metabolism. ROS take part in signaling pathways in the cell, but they can lead to oxidative stress and damage cellular molecules: lipids, proteins, and DNA, thereby causing mutations [5, 6].

A high mutational burden leads to an increase in the level of several diseases and systemic effects. Also, the accumulation of mutations at critical points of the genome is considered one of the most likely mechanisms of aging. And even though now it is believed that the accumulation of mutations by cells to a greater extent affects the likelihood of malignization than the general fitness, over time there is more and more evidence that healthy cells accumulate many somatic mutations with age. That is, among others, associated with the risk of age-related diseases [7].

Antimutagens, or substances and structures capable of inactivating mutagens or reducing their effect on the body, have been found in various natural sources, including probiotic microorganisms.

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However, in the search for new probiotic strains and screening and selection of components for complex probiotic preparations, little attention is paid to the criterion of antimutagenicity. The antimutagenic activity of probiotic strains is rarely considered an important criterion when choosing strains to produce probiotic preparations and functional food. Meanwhile, the association of antimutagenic activity with the prevention of oncological diseases, as well as with a decrease in the spread of resistant forms in the microbiota, indicates its importance for the selection of probiotics.

Besides, an antimutagenic activity can be associated with probiotics' broader systemic effects, such as geroprotective activity.

Mostly, the positive effect of probiotics on the host organism is explained by the following mechanisms:

1. Probiotic microorganisms are in an antagonistic relationship with pathogenic fungi and bacteria.
2. Probiotics release metabolites that have a positive effect on the host organism.
3. Probiotics can metabolize hazardous and toxic compounds coming from the external environment into less toxic ones.
4. Probiotics release substances that can interfere with the regulatory processes in the host's body.
5. There are also cases of specific interactions, such as some strains' ability to suppress tumor cells' growth.

However, a variety of systemic effects can also be observed. Some studies indicate that probiotics affect the mental state of the host [8], interfere with the regulation of metabolism, the work of hormonal systems [9], gene expression [10], and other regulatory mechanisms. Gradually, numerous facts have accumulated about the ability of probiotic microorganisms to effectively correct pathological manifestations of diseases not associated with infections, particularly allergies, toxicosis of various natures, etc. [11]. This nonspecific stimulating activity may be associated with the release of metabolites that protect host cells from the most destructive effects of stress — the generation of reactive oxygen species and DNA damage.

It is also known that probiotics play an immunomodulatory role, have anticancer effects, and help lower cholesterol levels. These functions are associated with the release of metabolites such as bacteriocins, biosurfactants, exopolysaccharides, and siderophores [12].

The antimutagenic activity of probiotics is generally viewed primarily in the context of the mechanism of anticancer action. A search for reviews focusing on the antimutagenic effects of probiotics reveals that no review has emerged that specifically addresses the antimutagenic effects of probiotics. The most recent review on a related topic, containing a mention of the antimutagenic activity of probiotics, also focuses on the anticancer effect of exopolysaccharides of lactic acid bacteria [13].

Indeed, it is the antimutagenic activity that allows some probiotic strains to reduce cancer incidence in hosts, which has been shown in various mammalian models. Thus, it has been shown that the administration of lactobacilli and *Bifidobacterium* effectively reduces DNA damage caused by chemical carcinogens in the gastric and colon mucosa in rats [14]. Lyophilized cultures of *Bifidobacterium longum*, introduced into the diet of rats, inhibited tumors of the liver, colon, and mammary gland caused by food mutagens [15]. Several spore-forming probiotics, such as *Bacillus subtilis* var. *natto*, also exhibit anticancer properties [16, 17].

Nevertheless, an antimutagenic activity can be the basis for other systemic effects, such as, for example, slowing down aging processes, including reproductive aging. It has been shown that the stabilization of mitochondrial DNA observed under the action of probiotic *Bacillus* preparations may be associated with the prolongation of reproductive age in chickens [18]. It should also be noted that metabolites of probiotic bacteria exhibit the ability to suppress the SOS response [19], which can also be attributed to antimutagenic effects.

This work aimed to systematize data on the antimutagenic activity of probiotics and emphasize antimutagenic activity as a significant criterion for selecting potential probiotic strains. The novelty of this work is that for the first time, antimutagenic activity is considered as an independent criterion for screening probiotics. We believe that putting together the available data on antimutagenic activity in a form of a critical review, with emphasis on the importance of this criterion for the future selection of probiotic candidates, may inspire researchers to use the criterion of antimutagenic activity in the selection of probiotics.

Probiotics with Antimutagenic Activity

Among all genera of probiotic bacteria, representatives of lactic acid bacteria (LAB) and *Bifidobacterium* are most often mentioned as sources of antimutagenic compounds. Several studies showed antimutagenic activity against heterocyclic amines, N-nitroso compounds, benzo (a) pyrene, and aflatoxin B [20–22]. Both live cultures of LAB and their fermentation products demonstrate antimutagenic and anticarcinogenic activity [23, 24].

Probiotics strains with antimutagenic activity are also found in other groups of microorganisms. For example, the *Escherichia coli* Nissle 1917 (EcN) strain is one of the oldest probiotics [25] that exhibits antimutagenic activity. Presumably, 4-nitroquinoline-1-oxide (4-NQO) is deactivated by the *E. coli* cell's metabolic systems with the formation of decay products of 4-aminoquinoline. However, the exact

mechanisms of deactivation of benzo(a)pyrene have not yet been established [26]. This kind of activity is quite typical for probiotics, for example, *Lacticaseibacillus* (formerly *Lactobacillus*) *rhamnosus* IMC501 can also convert 4-NQO into a non-genotoxic metabolite [27].

LAB with Antimutagenic Properties

It was stated that probiotic bacteria characteristic of the microbiota of goats, isolated from healthy goat feces and belonging to the genera *Lactobacillus*, *Enterococcus*, and *Bifidobacterium*, could reduce the mutagenicity of sodium azide and benzopyrene in the Ames test and reduce the risk of gastrointestinal cancer [28]. Among the substances whose mutagenic effects can be reduced by probiotic lactobacilli, heterocyclic aromatic amines should also be noted [29].

Lactobacillus and *Bifidobacterium* produce extracellular bioactive compounds with antimutagenic properties against benzo[a]pyrene (BaP) and sodium azide (SA). Interestingly, the common antimutagenic effects in exponential and stationary growth phases were different. *Lactobacillus* exhibit this activity mainly in the stationary growth phase [30].

Lactobacillus acidophilus (isolated from commercially available yogurt), *Lactobacillus gasseri* (P79), *Weissela confusa* (formerly *Lactobacillus confusus*) (DSM20196), *Streptococcus thermophilus* (NCIM 50,083), *Bifidobacterium breve*, and *Bifidobacterium longum* (isolated from child stools) reduced the DNA-damaging effect of methylnitronitrosoguanidine (MNNG) in rat intestinal cells. It is peptidoglycan fraction from lactobacilli that exhibit antimutagenic effects [14].

It has been shown that six strains of *L. acidophilus* and nine strains of *Bifidobacteria* show antimutagenic activity against the following mutagenic compounds: MNNG; 4-nitro-O-phenylenediamine; 4-nitroquinoline-N-oxide; Aflatoxin B; 2-amino-3-methyl-3H-imidazoquinoline; PhIP, и 2-Amino-3-methyl-9H-pyrido[2,3-b]indole. The effect strongly depends on strains [22]. *L. acidophilus* LA 106 fermented milk significantly decreased mutagenic effects by MNNG (by 77%) [31].

Lactiplantibacillus (formerly *Lactobacillus*) *plantarum* and *Staphylococcus xylosus* reduced the mutagenic activity of biogenic amines in the production of sausages [32].

Streptococcus thermophilus and *Lactobacillus bulgaricus* fermented milk reduced the effects of 4-nitroquinoline-N-oxide (a direct-acting mutagen) and 2-aminofluorene (a mutagen requiring S9 activation) [33].

There is evidence that palmitic acid produced by *Lactobacillus delbrueckii* ssp. *bulgaricus* and *Streptococcus salivarius* ssp. *thermophilus* in yogurt has antimutagenic effects on MNNG [34].

The possible mechanism of *Lacticaseibacillus* (formerly *Lactobacillus*) *casei* ATCC 393 antimutagenic effect can be connected with involvement and support in polyamines metabolism (putrescine, spermidine, and spermine) in host-organism cells [35].

It should be noted that not all LAB have antimutagenic activity. Moreover, Sharma M. et al. (2020) have shown that out of 60 LAB isolated from various sources, only 10 isolates showed antigenotoxicity of more than 30%, and four showed cytotoxicity of 70–80% [36]. In another research, only 4 strains from 25 isolates exhibited a pronounced antimutagenic activity [37].

Bifidobacterium with Antimutagenic Properties

Bifidobacterium bifidum, Bifidobacterium lactis, and *Bifidobacterium longum* showed significantly higher antimutagenic potential against benzo(a)pyrene than *Bifidobacterium adolescentis*, *Bifidobacterium breve*, and *Bifidobacterium infantis*. In particular, the activity of bifidobacteria on benzo [a] pyrene was noted by Lo et al. [21]. *Bifidobacterium pseudocatenulatum* G4 and *B. longum* are able to directly bind heterocyclic amines [38]. *Bifidobacterium longum* exhibited anti-mutagenic properties in fermented milk [20] and have shown the ability to bind *dietary carcinogens* [39].

Bacillus with Antimutagenic Properties

As for the representatives of the genus *Bacillus*, there is less research reported on their antioxidant and antimutagenic activity, although this is gradually changing. However, it should be noted that bacteria of this genus began to be considered as probiotic bacteria later than LAB.

Caldini et al. studied the effect of 16 *Bacillus* strains from pharmaceutical probiotic preparations and laboratory collections (*B. subtilis*, *Bacillus firmus*, *Bacillus megaterium*, *Bacillus pumilus*) on genotoxicity caused by the standard mutagen 4-nitroquinoline-1-oxide (4-NQO) using the SOS chromotest, with *E. coli* PQ37 as a test organism [40]. It was found that the activity of 0.1 mm 4-NQO decreased after co-incubation with *Bacillus* suspension with a titer of 10^8 CFU/mL. All isolates showed the ability to deactivate 4-NQO, with genotoxicity inhibition ranging from 92.9 to 100%. The authors associate the observed effect with the modification of the 4-NQO molecule.

In a later work [41], the inhibitory effect of 21 bacilli strains on four genotoxins was investigated in vitro using the same method. All strains exhibited high inhibitory activity against 4-nitroquinoline-1-oxide and N-methyl-N′-nitro-nitro-nitrosoguanidine (direct genotoxic agents), while against 2-amino-3,4-dimethylimidazo [4,5-f]-quinoline and aflatoxin B1 (indirect genotoxic agents), inhibitory activity was high or moderate. Antigenotoxicity was observed in vegetative cells but not in heat-treated cells or spore suspensions. The spectroscopy showed that the properties of

genotoxin molecules were changed after incubation with cells, and all strains retained high viability after exposure to genotoxins.

It has been shown that the *Bacillus coagulans* strain GKN316 can efficiently metabolize furfural, 5-hydroxymethylfurfural (HMF), vanillin, syringaldehyde, and p-hydroxybenzaldehyde (pHBal), converting them into less toxic corresponding alcohols in situ [42].

Other Gut Bacteria with Antimutagenic Properties

Cell extracts and *Streptococcus faecalis* cells reduce the mutagenic effect of 2-nitrofluorene in the *Salmonella* Typhimurium TA1538 strain. This is manifested through several mechanisms involving extracellular and intracellular factors. Presumably, thiol compounds are extracellular factors. Desmutagens affecting the biotransformation of a mutagen within a cell include thermally stable compounds, possibly of proteinaceous nature, with a molecular weight of less than 12 kDa [43].

Another intestinal microorganism *Enterococcus faecium* M-74 had a more significant antimutagenic effect under similar conditions in a live state and when selenium was added to the medium [44].

Most of the above studies have some methodological drawbacks. The researchers choose xenobiotics as genotoxic substances (such as MNNG and NQO, rather exotic for living organisms) that must be inactivated by probiotics. Meanwhile, living organisms do not encounter these compounds that often. Even if considering the anthropogenic environment, among all the most frequently used experimental models of promutagens and mutagens, benz(a)pyrene is the only compound that humans and animals have to deal with. If we consider probiotics as a factor in preventive therapy against diseases caused by mutagenic factors, models based on more typical substances that threaten the human body in the modern world should be used for screening and selection of promising targeted probiotic strains. As stated earlier in the "Introduction" section, many drugs are mutagens and therefore can be used for similar models.

Probiotic strains with antimutagenic activity and their sources were summarized in Table 1.

Analyzing the data summarized in Table 1, we can conclude that among all references to probiotics with antimutagenic activity, representatives of lactobacilli are in the lead. According to our meta-analysis, reports of them represent about 43% of all mentions of antimutagenic probiotics. In 23% of cases, bifidobacteria are mentioned; 20% of papers mention representatives of the genus *Bacillus*; 9%, *Streptococcus* sp.; and in 5% of cases, other bacteria.

Antioxidant Activity of Probiotics

Antioxidant activity, although part of antimutagenic activity, requires separate consideration. The mechanisms responsible for it are usually more specific than those that provide antimutagenic activity.

Antioxidant activity of probiotics is shown for many strains, among which *Lactobacillus* species are most studied and used in medicine and the food industry.

Lactobacillus with Antioxidant Properties

Chooruk et al. showed that in a series of 201 strains of lactobacilli isolated from the human oral cavity, antioxidant activity is, to some extent, inherent in all of the isolated strains, and in a large number of strains, it was significant. The most prominent strains belonged to *L. fermentum*, *L. paracasei*, and *L. rhamnosus* [52]. It was shown that *L. plantarum* ATCC14917 enhanced the antioxidant activity of apple juice [53], and the *Levilactobacillus* (formerly *Lactobacillus*) *brevis* KCCM 12203P strain possessed both antioxidant and immunomodulatory activity [54].

Bifidobacterium with Antioxidant Properties

Bifidobacterium probiotic species are less studied due to the difficulty of their cultivation in the laboratory. However, there is evidence of the antioxidant activity of their representatives. It was shown that *B. longum* LTBL16 has high antioxidant activity [55]. *B. lactis* strain HN019 reduced the level of oxidative stress in patients with metabolic syndrome and reduced the level of inflammation [56]. The intake of *Bifidobacterium bifidum* ATCC 29,521 had a beneficial effect on the structure of the intestinal microbiota, in addition to antioxidant effects [57].

Other Gut Bacteria with Antioxidant Properties

Among genera that are less clearly (or, perhaps, more controversially) associated with probiotic activity, there are also probiotic species with antioxidant properties. For instance, *Ent. faecium* strains isolated from various fermented foods were reported as having antioxidant properties [58]. *Streptococcus salivarius* ssp. *thermophillus* strain exhibited high antioxidant activity and caused a significant decrease in the level of markers of oxidative stress in liver cells of mice [59]. Representatives of the genus *Bacillus* also demonstrated high antioxidant activity levels, both in vitro and in vivo [60, 61].

Table 1 Probiotics species and strains with antimutagenic activity

Probiotic species with antimutagenic activity	Source of identification
Bifidobacterium longum [14, 15, 20], *Bifidobacterium breve* [14], *Bifidobacterium lactis* Bb-12 [21], *Bifidobacterium adolescentis* [22], *Bifidobacterium bifidum* [22], *Bifidobacterium infantis* [22], *Bifidobacterium pseudocatenulatum G4* [38]	Dairy products, human feces
Lactobacillus acidophilus [14, 22, 31]	Yogurt, fermented milk
Lactobacillus gasseri (P79) [14], *Lactobacillus confusus* (DSM 20,196) [14], *Streptococcus thermophilus* (NCIM 50,083) [14, 33]	Dairy products
Bacillus subtilis KATMIRA1933 [19]	Fermented dairy product YoguFarm (catalog no. 74699–02,905; JSL Foods, Los Angeles, CA, USA)
Bacillus amyloliquefaciens B-1895 [19, 45], *Bacillus amyloliquefaciens* CBSYD1 [46]	Soil
Escherichia coli Nissle 1917 [26]	Human feces
Lactobacillus rhamnosus (IMC501) [27, 46], *Lactobacillus rhamnosus* 231 [51]	Human feces
Lactobacillus reuteri DDL 19 [28], *Lactobacillus alimentarius* DDL 48 [28], *Enterococcus faecium* DDE 39 [44], *Bifidobacterium bifidum* DDBA [28]	Goat feces
Bacillus subtilis [40, 41], *Bacillus megaterium* [40, 41], *Bacillus firmus* [40, 41], *Bacillus pumilus* [40, 41]	Pharmaceutical preparations
Lactobacillus helveticus [47], *Streptococcus thermophilus* [47], *Lactobacillus kefir* [47], *Lactobacillus plantarum* [47]	Dairy products
Lactobacillus helveticus CH65 [48], *Lactobacillus acidophilus* BG2F04 [48], *Streptococcus salivarius* ssp. *thermophilus* CH3 [34, 48], *Lactobacillus delbrueckii* ssp. *bulgaricus* 191R [34, 48]	Dairy products
Lactobacillus acidophilus KFRI342 [49]	Kimchi
Lactobacillus acidophilus [50], *Lactobacillus casei* [35, 50], *Lactococcus lactis biovar. diacetylactis* DRC-1 [50]	Probiotic curd
Lactobacillus rhamnosus 231 [51]	Human feces
Streptococcus faecalis [43]	Human intestine samples

Bacterial Consortia with Antioxidant Properties

Antioxidant activity is observed not only in individual strains but also in microbial consortia. For instance, the kefir grains consortium's bacteria exhibit antioxidant properties, and their beneficial effect on the condition of patients with Alzheimer's disease (AD) has been shown to be connected with such activity. Moreover, in this study antioxidant defense mechanisms were involved in improving physiological and cognitive functions, and probiotics were able to reduce the ROS-mediated pro-inflammatory response, which is part of the pathogenesis of AD [62].

Antioxidant activity can overlap with antimutagenic activity since a decrease in ROS levels will reduce the total number of mutations in the genome. However, there are methods to consider them separately. Such an approach, in particular, can be the use of bacterial biosensors — a method that we used and was shown to be successful for the stage of primary screening of probiotics for veterinary medicine (see Table 3 and the corresponding links). In this case, the marker is the expression of bacterial genes responsible for responding to specific ROS (superoxide anion radical, hydrogen peroxide) or DNA damage (individual genes of the SOS response system).

Possible Mechanisms of Action

The mechanisms of antimutagenic action of probiotics are still the subject of discussion. It should be noted that the antimutagenic properties of probiotics can benefit the host not only through direct interaction of metabolites of probiotic bacteria with host cells but also indirectly by reducing the intensity of mutational processes in the microbiota. As shown earlier [3], this process slows down the emergence and spread of antibiotic resistance factors in the microbiota, reducing possible complications after antibiotic therapy.

At the molecular level, two groups of mechanisms can be distinguished:

1. Direct binding to mutagens.
2. Mutagens transformation [28]

   On the cellular level, there are also two ways to fight mutagens:
3. Production and/or excretion of antimutagenic metabolites.
4. Production of antimutagenic substances via fermentative transformation of a substrate.

   The latter two mechanisms are not necessarily ways of dealing with dangerous mutagens for themselves but could also arise as a side effect of other processes and gain a foothold as an advantage in symbiotic relationships.

   On a systemic level:
5. Indirect influence on the level of spontaneous mutagenesis and the expression of genes of the host defense systems.

Binding of Mutagens

The correlation between lactobacilli's ability to bind mutagens and their antimutagenic activity has been persuasively shown by Stidl et al. [47].

The cell wall components can also play a significant role in binding and deactivating mutagens [29, 63]. Specifically, such a mechanism should be characteristic of the inactivation of amines [29]. Morotomi and Mutai found that the ability of probiotic *Lactobacillus* to bind to mutagenic products of tryptophan pyrolysis is pH-dependent and decreases with the addition of metal salts [64]. The authors concluded that the effect of amine binding by the bacterium *L. casei* appears to be related to cation-exchange mechanisms.

Studies comparing Gram-positive and Gram-negative bacteria's ability to bind the pyrolysis products of tryptophan have shown that Gram-positive strains are consistently more effective [65]. This fact can be taken as an indication of the cell wall structure's important role in the inactivation of mutagens. Subsequent studies have shown that the binding of amines with Gram-positive and Gram-negative bacteria occurs in the peptidoglycan layer and the outer membrane, respectively [48]. Sreekumar and Hosono suggested that the HA binding receptors are carbohydrate fragments of the cell wall and that glucose molecules play a crucial role in the binding reaction [20].

Transformation of Mutagens

The possibility of inhibiting certain stages of the transformation of promutagens into mutagens is also considered as a possible mechanism of probiotics' action. It has been found, for example, that *L. delbrueckii* ssp. *bulgaricus* 191R releases hydrophobic metabolites with antimutagenic activity against MNNG and 3,2′-dimethyl-4- aminobiphenyl (DMAB). The exact mechanism or active substance has not been identified, but the authors consider the inhibition of cytochrome P450 1A2, inhibition of subsequent activating enzymes such as acetylase, reaction with N-hydroxy DMAB or other already activated forms of DMAB, or increased DNA repair as mechanisms of its activity [61].

In some studies, the effects of temperature-inactivated cells were compared with those of living cells, and it was found that the latter has a consistently higher antimutagenic activity [22, 66]. This observation suggests that living bacteria can produce metabolites or catalyze reactions that detoxify amines. Another study investigated the potential antimutagenic effects of various organic acids (lactic acid, butyric acid, and acetic acid) on IQ, PhIP, and Trp-P-1 and some non-amine carcinogens [20]. These acids are products of microbial fermentation of fibers and other polysaccharides [67]. Butyric acid inhibited the mutagenic effects of amines in the *Salmonella enterica* serovar Typhimurium TA98 test, while no such effects were observed with other acids.

It was shown that *L. rhamnosus* 231 has several mechanisms of antimutagenic action: adsorption (for example, acridine orange) and biotransformation with subsequent detoxification (for example, MNNG and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline) [51].

Production and/or Excretion of Antimutagenic Metabolites

Considering the release of effector molecules, one can assume two possibilities: probiotics can release antimutagenic metabolites or transform the substrate so that antimutagen compounds are obtained. Methodologically, it can be quite difficult to differentiate these two mechanisms by studying the effects of a particular strain.

Thus, it has been shown that the main contribution to the antimutagenic activity of sour milk fermented by the probiotic strain *L. plantarum* is made by peptides less than 3 kDa and 3–10 kDa in size. However, it is unknown whether they are produced by the bacterium or obtained during the proteolysis of milk proteins [68].

The study of antimutagenic metabolites of the probiotic strain *L. rhamnosus* MD 14 showed that they belong to thermosensitive protein compounds and organic acids [35]. However, on the other hand, *Bacillus* metabolites, which have antimutagenic activity and can inhibit the SOS response in *E. coli*, exhibited thermal stability [19].

Fermentation of soy milk by lactic acid bacteria (*Strep. thermophilus*, *L. acidophilus*) and bifidobacteria (*B. infantis*, *B. longum*) significantly increased its antimutagenic properties against 4-nitroquinoline-N′-dimethyl -biphenyl (DMAB). The mutagenic effect of these compounds was also reduced by pretreating *S.* Typhimurium TA 100 cells with fermented soy milk [69, 70].

The degree of proteolysis of proteins in yogurt by *Lact. acidophilus* (ATCC® 4356 ™), *L. casei* (ATCC® 393 ™), and *Lacticaseibacillus* (formerly *Lactobacillus*) *paracasei* subsp. *paracasei* (ATCC® BAA52 ™) correlated with its antimutagenic activity. The released peptides showed high activity in trapping radicals with 1,1-diphenyl-2-picrylhydrazyl and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) [71]. It is known, *L. plantarum* KLAB21 produces glycoproteins with antimutagenic activity [72].

The differentiation of the mechanisms of cell-mediated antimutagenic activity from that of metabolite-mediated can be performed via testing cell-free preparations together with probiotic strain's cells.

Systemic Effects

One more direction for implementing the antimutagenic effects of probiotics could be pointed out: these effects can be achieved by indirectly influencing the level of spontaneous mutagenesis. Recently, increasing information has appeared that probiotics can influence the expression of host genes, interfering with the work of its regulatory cascades, such as, the p38 MAP kinase pathway [73, 74]. It should be noted that these effects were observed both under the action of living cells and under the influence of cell-free preparations [74]. Such a change in the host's cellular homeostasis may be associated, among other things, with the level of mutagenesis in the cells.

Maintaining the balance of prooxidants/antioxidants in the cell can also be one of the indirect pathways.

Mechanisms of Antioxidant Activity

As mentioned above, antioxidant activity can be considered a special case of antimutagenic activity, usually provided by different mechanisms that vary from strain to strain.

In general, we can describe antioxidant mechanisms by the binding or transformation of prooxidants/ROS, the release of antioxidants or the conversion of substrate molecules into antioxidants, as well as the regulation of the host defense systems.

Prooxidants/ROS Binding and Transformation

Another possible mechanism for the antioxidant action of probiotic bacteria is metal chelation. For example, *Lactobacillus helveticus* CD6 can produce substances that bind Fe^{2+} ions into chelates [75].

Bacteria have their own Fe-SOD and Mn-SOD enzyme systems to protect against free radicals [76], while Mn-SOD is similar to the Mn-SOD of eukaryotic cells mitochondria. These enzymes can reduce the number of prooxidant molecules in the environment. It has been shown that two strains of *L. fermentum*, which has a high production of glutathione peroxidase (GPx), also had significant antioxidant properties [77, 78]. There are genetically modified strains of lactobacilli that carry catalase genes, and their use has been shown to reduce the severity of Crohn's disease in mice [79].

Producing of Antioxidant Metabolites or Substrate Transformation

A significant part of the antioxidant properties of food products, for example, milk and dairy products, is provided by protein substances: casein fraction and albumin [80] and short peptides [81]. Probiotic bacteria, which are used to produce fermented dairy products, can increase the number of antioxidant peptides in products due to their proteolytic activity. It has been shown for different genera of LAB, for example, for the symbiotic cultures of *L. delbrueckii* ssp. *bulgaricus* and *Strep. thermophilus*, as well as monocultures of *L. acidophilus*, *L. casei*, and *B. bifidum* [82]. At the same time, it is noted that the addition of probiotic strains increases the antioxidant properties of the fermented product compared to the unfermented one [83]. There is a correlation between the level of the strain's proteolytic activity and the final product's antioxidant properties, as was shown by the example of various *Lactobacillus* species [71, 83]. Solieri et al. compared the proteolytic and antioxidant activity of 39 non-starter lactobacilli from different cheeses [83]. Sah showed the same effect on *L. acidophilus* (ATCC4356), *L. casei* (ATCC 393), and *L. paracasei* ssp. *paracasei* (ATCC BAA52). Furthermore, even if there was no difference in antioxidant activity between the fermented and non-fermented products, there was a better bioavailability of antioxidants from the fermented product [47] as demonstrated with five strains of *Bifidobacterium longum* ssp. *Longum* [84]. We should note the synergistic effect of co-cultivation of different strains, as was shown for *Lact. acidophilus* (ATCC4356), *L. casei* (ATCC 393), and *L. paracasei* ssp. *paracasei* (ATCC BAA52) [71].

The other way is the production of low-molecular antioxidant molecules such as glutathione [85], butyrate [86, 87], and folate [75]. It has been shown that probiotic bacteria have enzyme complexes to produce antioxidant molecules, such as glutathione-producing *L. fermentum* ME-3 enzymatic system [85]. These molecules can be absorbed by the host and exhibit their properties in the host's cells and tissues, for example, reducing the effects of oxidative stress in the liver [87–89].

Considering extracellular metabolites, some specific qualities should be mentioned, specifically: small size (associated with the ability to penetrate membranes); resistance to proteinases and other environmental factors; existence in a variety of isoforms; and the ability to reform the structure quickly. In particular, bacterial oligopeptides and

lipopeptides synthesized both ribosomally and nonribosomally usually correspond to those criteria. It is known that the non-ribosomal synthesis of oligopeptides occupies a more significant share in the metabolism of *Bacillus*. Its products do not exceed several kDa in size, and a significant number of them are thermostable and are not hydrolyzed by proteinase K. Such resistance is provided by the atypical amino acids and stereoisomers in the structure of nonribosomally synthesized bacilli peptides [90]. These peptides are often considered to be antimicrobial and antifungal agents; however, recent data indicate their participation in regulatory processes [91]. For *Lactobacillus, Enterococcus*, or *Bifidobacterium* probiotic strains, the synthesis of ribosomal peptides with a broad spectrum of activities is more typical.

It is known that endogenous eukaryotic peptides that regulate the prooxidant/antioxidant balance are involved in the body's response to oxidative stress that occurs during pathological processes and stressful conditions [92]. In addition to the signaling effect that allows peptides to normalize the cell's oxidative status, they have antioxidant properties [93].

Besides, peptides of various origins (including synthetic peptides) can regulate the processes of cell proliferation and apoptosis [94], as well as penetrate the nucleus and nucleolus and bind there with DNA and histone proteins, affecting gene expression [91, 95]. Thus, peptides released by the microbiota should not be disregarded as they may have similar effects.

Systemic Effects

Presently, the influence of probiotic bacteria on the host organisms signaling pathways is an actively studied topic. For instance, *Lactobacillus* spp. influence the Nrf2-Keap1-AREA pathway. Nrf2 activates many genes, including those involved in the detoxification of xenobiotics and ROS [96]. An extracellular polysaccharide from the *Bacillus* sp. LBP32 inhibits NFκB production, preventing macrophage inflammatory responses, and ROS production [97]. *L. rhamnosus* GG improved the state of intestinal epithelial cells under severe oxidative stress through the production of soluble proteins p40 and p75, which acted through the mechanism of activation of mitogen-activated protein kinases (MAPKs), as well as inhibition of protein kinase C (PKC) [98]. However, specific mechanisms and specific signaling molecules that regulate these pathways are often not described in published reports.

It is proved that YD1 peptide, isolated from *Bacillus amyloliquefaciens* CBSYD1, has antioxidant activity and an effect on the host organism, similar to NF-E2-related factor-2 (Nrf-2) [46]. *B. amyloliquefaciens* SC06 strain reduced the level of damage to pig intestinal epithelial cells by modulating the Nrf2/Keap1 pathway and ROS production [60]. *B. megaterium* SF185 also protected CACO-2 intestinal epithelial cells from the effects of hydrogen peroxide [99]. However, in general, the antioxidant effect of bacillary probiotics is described much less than that of probiotics based on LAB and bifidobacteria.

The search for metabolites that provide these and other effects listed above seems to be a promising topic for further research.

However, the relationship between the antimutagenic activity of probiotic bacteria and the production of antioxidants is currently at the initial stage of the study. The ability of lacto- and bifidobacteria to produce substances that inactivate ROS has been reliably confirmed by experiments [100, 101], but for spore-forming probiotics, such activity has so far been described in very fragmentary terms.

Postbiotics as Antioxidants and Antimutagens

In recent years, researchers have been using the term "postbiotics" for the products of the probiotic microorganism's activity that can positively affect the host organism, even in the absence of living cells. Among the representatives of this group, compounds with antioxidant immunomodulatory and anticancer properties have been identified.

Postbiotics are functional bioactive compounds generated in a matrix during fermentation. Postbiotics can include many different components, such as metabolites, short-chain fatty acids (SCFA), microbial cell fractions, functional proteins, extracellular polysaccharides (EPS), cell lysates, teichoic acid, peptidoglycan derived muropeptides, and pili-like structures [102].

As the variety of substances included in this group, the properties of postbiotics are diverse. They are able to exert immunomodulatory effects; for example, postbiotics obtained from *Bifidobacterium breve* C50 and *Strep. thermophilus* 065 induce high IL-10 production through TLR-2 and also stimulate Th1 responses [103, 104]. The use of *L. paracasei* CBA L74 postbiotics in infants led to a change in the levels of immune biomarkers in the blood and amelioration of the disease's progression [105].

The cell-free supernatants of *L. acidophilus*, *L. casei*, *Lactococcus lactis*, *Limosilactobacillus* (formerly *Lactobacillus*) *reuteri*, and *Saccharomyces boulardii* demonstrate an antioxidant activity in addition to immunomodulatory effect [106]. Postbiotic exopolysaccharides from *L. plantarum* 70,810 have antitumor properties, inhibiting the proliferation of HepG-2, BGC-823, and HT-29 tumor cells [107]. Exopolysaccharides from *L. helveticus* MB2 showed the ability to bind ferrous ions, which provides one of the well-known mechanisms of antioxidant activity [108]. Exopolysaccharides of several wild lactobacilli strains also showed antioxidant properties [109].

As mentioned above, the production of folate, glutathione, and other antioxidant molecules is one of the mechanisms of probiotics' antioxidant activity. Moreover, such products

can be considered postbiotics [75, 85]. For example, folate-producing *L. helveticus* CD6 cell-free supernatants demonstrate antioxidant properties [75].

Some of the more specific properties of postbiotics are presented in Table 2.

Antimutagenic Effect of Probiotics in Mitochondria

In recent years, there was increasing evidence indicating that mitochondria can, in addition to a well-studied energy function, also serve as a kind of a "regulatory center" for eukaryotic cells [110–113]. Changes in mitochondrial function affect many processes, ranging from aging to diabetes [114, 115], and many of the proteins that play a crucial role in signaling cascades are found in mitochondria. It is especially relevant for systems regulating oxidative status, which provide an accurate balance of pro- and antioxidant activity [116]. For example, regulation of the nfe2l2/AP1 pathway that controls the antioxidant system can be directly initiated by changes in the mitochondrial membrane state. The same works for a number of other cascade processes and regulators: the antioxidant defense pathway regulated by MAPK10 kinase and the NFE2L2/AP1 pathway in general, the thioredoxin 2/peroxiredoxin 3 system, etc. [117–119].

This set of data could lead to an interesting hypothesis that the antimutagenic effect of probiotics can be realized indirectly. Namely, it can be carried out through the influence on redox homeostasis through interaction with mitochondria. Stefanaki et al. showed that the intestinal microbiota and its secreted metabolites could interact with mitochondria [120]. The prokaryotic origin of mitochondria is likely to contribute to such interactions [121].

The possibility of interaction of probiotics with host mitochondria is supported, for example, by the following studies. In Nakagawa et al. experiments, the *L. gasseri* SBT2055 probiotic increased the lifespan of *Caenorhabditis elegans* [73]. It was noted that the number of mitochondria significantly increased when the host was fed with the LG2055 strain, as compared to the control. The probiotic intake slowed down the age-related decline in mitochondrial function that is characteristic of aging. The transmembrane potential of the mitochondrial membrane was significantly higher in old worms fed with LG2055 than in their peers fed with the standard *E. coli* OP50. At the same time, life extension was observed both when feeding with live and dead LG2055 cells.

Emerging data indicate the role of ROS, nitric oxide, short-chain fatty acids, and hydrogen sulfide in cross-linking between microbiota-mitochondria and redox signaling [122]. Several studies show that the microbiota modulates mitochondrial activity and enhances the interaction between the host and the microbiota. Moreover, the effects can be both positive and negative, depending on which strain is involved — pathogenic or probiotic [123, 124]. Apparently, the microbiota can control mitochondrial activity and redox homeostasis [122].

We have previously shown the effect of probiotic *Bacillus* strains on mitochondrial DNA stability in birds [18]. It was shown that *B. subtilis* strains caused an increase in the expression of the genes associated with antioxidant activity in the liver and mitochondria compared as compared to the control group [62]. Biogenic selenium nanoparticles synthesized by *L. casei* ATCC 393 can protect the barrier function of the intestinal epithelium from oxidative damage by alleviating ROS-mediated mitochondrial dysfunction via the Nrf2 signaling pathway [125]; the positive effect of probiotics in Alzheimer's disease also appears to be associated with effects on redox homeostasis, DNA damage levels, and mitochondrial activity [62].

There are three main mechanisms for the implementation of these effects that are being discussed in related publications:

Table 2 Postbiotics and their effects on eukaryotic hosts

Source	Effects	References
Supernatants *Bifidobacterium breve* C50 and *Strep. thermophilus* 065	Inducing high production of IL-10 through the TLR-2 and stimulating Th1 response	[103, 104]
Postbiotics based on *Lact. paracasei* CBA L74	Altering of immune biomarkers levels in blood and relief the course of diseases in infants	[105]
Cell-free supernatants *Lact. acidophilus, Lact. casei*, *Lact. reuteri*, *L. lactis,* and *Saccharomyces boulardii*	Immunostimulatory and antioxidant effects	[106]
Postbiotics-exopolysaccharides from *Lact. plantarum* 70,810	Antitumor properties through inhibition of HepG2, BGC823 and HT-29 tumor cell proliferation	[107]
Exopolysaccharides from *Lact. helveticus* MB2	Ability to bind ferrous ions	[108]
Exopolysaccharides several wild strains of *Lactobacillus*	Antioxidant properties	[109]
Cell-free supernatants *Lact. helveticus* CD6	Antioxidant properties due to folate production	[75]

1. Microbiota can control mitochondrial activity and redox homeostasis.
2. Microbiota can influence the expression of nuclear genes by stimulating the insertion of bacterial DNA.
3. Mitochondrial DNA insertions occur in the host's somatic cells and may be triggered by microbiota activity.

Concerning point one, apparently, the mediator molecules secreted by the microbiota modulate mitochondrial activity and biogenesis. Depending on their concentration, these molecules affect mitochondrial homeostasis, which controls various cellular functions, in particular, ROS signaling, innate immune response, and energy metabolism [122]

The theory of endosymbiosis, according to which mitochondria originate from bacterial endosymbionts, also suggests that mitochondria may have signaling pathways that respond to bacterial signals [126, 127].

Thus, the antioxidant/antimutagenic effect on mitochondria should be considered one of the criteria for bacterial strains' probiotic potential. Such a test might be difficult to perform at a stage of initial screening, but at the stage of animal tests, it is possible to measure the level of mutagenesis in mitochondria using the Comet Assay, PCR and any other available method.

The Effect of Complex Preparations

It is interesting to note that antimutagenic activity increases with the use of a complex of strains compared with a monoculture. Several studies report that probiotic bacteria work better in combination than individually. For example, a complex of four strains isolated from goats showed better activity than the same strains separately [28]. Given this, another way of realizing the antimutagenic properties of probiotic *Bacillus* strains seems to be possible: since probiotic

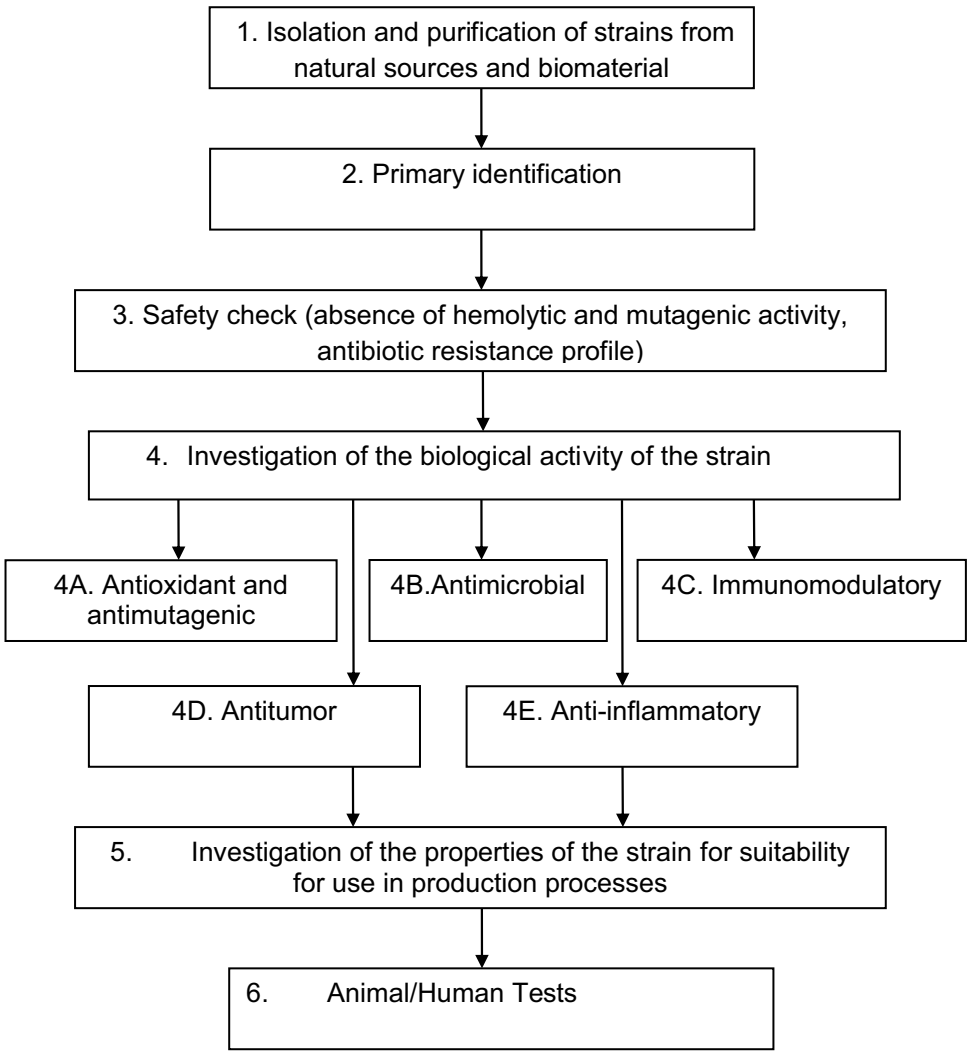

Fig. 1 Scheme of potential probiotic screening and selection

Table 3 Techniques used for screening to assess antimutagenic activity of probiotic strains

Method	Advantages	Disadvantages	References
Ames method (pre-incubation method)	1) Relatively inexpensive; 2) easy to perform; 3) easy to understand by people not trained in genetics or mutagenesis; 4) the most common method	No selectivity for the type of genetic damage	[51, 131–133]
Measuring the concentration of mutagens by physicochemical methods	Measurement accuracy	(1) Indirect measurement; (2) high cost and complexity; (3) no selectivity for the type of genetic damage	[36, 51]
Comet assay	1) Speed; (2) simplicity; (3) selectivity for the type of genetic damage	Inability to detect other types of mutations, except for breaks	[26, 49, 50]
Biosensor test	1) Relative simplicity; (2) selectivity for the type of genetic damage; (3) genotoxicity in prokaryotes correlates with the same effect in eukaryotic cells	1) The ability to measure the SOS response; 2) fully relevant only for prokaryotes	[3, 19, 40, 41]

Bacillus, in particular *B. subtilis*, improves the viability of normal intestinal microbiota, such as representatives of *Lactobacillus* and *Bifidobacterium*; this may, in turn, lead to active production of antimutagenic metabolites by the latter and, thus, improve the antimutagenic potential of microbiota in general. It was found that the viability of lactobacilli when combined with bacilli is increased significantly. The authors speculate that this effect may be due to the release of catalase and subtilisin from *B. subtilis* [128, 129].

The fact that often complex probiotic preparations can be more effective also makes sense in the context of the diversity of the spectrum of metabolites secreted by different groups of probiotics, since different groups of microorganisms secrete different antimutagenic metabolites, apparently, complementing each other's activity (see, for example, [111, 112]).

Antimutagenic Action as a Criterion for Screening

The current approach to selecting potential probiotics can be summarized in the following scheme (Fig. 1).

After isolation of strains from natural sources and their preliminary identification, they are checked for several criteria, such as safety (hemolytic activity, ability to adhere to mammalian cells, production of lytic enzymes, toxins, biogenic amines), biological activity, and ability to colonize the host and survive in the internal environment (such parameters as hydrophobicity of the cell surface, ability to adhere to mucin, to the intestinal epithelium, and autoaggregation screening are considered) [130]. These studies can be performed in a different order or simultaneously. However, they always precede the study of the effects of a probiotic directly on the host organism.

All screening procedures preceding animal and/or human testing are naturally aimed at predicting the strain's probiotic properties before it is introduced into the host. There are various model systems based on cell cultures, single-cell biosensors, and in vitro tests. Biological activity, which is most often evaluated at stage 4, is understood very broadly in different studies. The main effects include antimicrobial, immunomodulatory (for example, in models of co-cultivation of bacteria with epithelial cells and immune cells that mimic in vivo interactions), anti-inflammatory, antitumor properties (this section sometimes includes antimutagenic), and the ability to interact with certain specific metabolites or produce them. All these tests are conducted quite randomly, making it difficult to compare the results of different studies [130].

We consider it essential to distinguish antimutagenic and antioxidant activity as a mandatory criterion for screening probiotic strains in vivo (Point 4A of Fig. 1) since it can be associated with many systemic effects.

The most common methods used to assess antimutagenic activity are summarized in Table 3.

Conclusion

Thus, we can conclude that antimutagenic activity is an important property of probiotic strains. Many data obtained based on in vitro experiments using model mutagens shows that many probiotic strains can inactivate these substances or reduce their effect, exhibiting, in particular, anticarcinogenic properties. The mechanisms of antimutagenic activity of probiotics can be associated with (a) binding of mutagens, (b) transformation of mutagens, and (c) inhibition of the transformation of promutagens into antimutagens. Effector molecules that carry out these processes can be part of cell structures, be secreted extracellularly, or be obtained due to the transformation of the substrate by bacteria. The possibility of an indirect decrease in the level of

mutagenesis in cells due to the interaction of metabolites of probiotics with the host's regulatory cascades requires separate consideration. Antimutagenic activity may be associated with the broader systemic effects of probiotics, such as geroprotective activity, and should be considered an essential criterion in selecting probiotic strains.

Also, it is interesting to study the effect of probiotics on mitochondria. The evolutionary relationship between bacteria and mitochondria suggests that mitochondria may have previously unknown signaling pathways that respond to bacterial signals. Besides, mitochondria play a significant role in the production and control of ROS in the cell. It means the pathways of probiotics' systemic antioxidant effects can be implemented through them.

Probiotics with antimutagenic properties can be used as adjunctive therapy in the treatment of genotoxic drugs, as well as to prevent the mutagenic effect of environmental pollutants on humans and animals. However, the use of these strains should not be limited only to this area, since antimutagenic properties can lead to wider systemic effects that still require further study.

Author Contribution Evgeniya V. Prazdnova conceived the original idea and performed the overall analysis. Maria S. Mazanko performed the analysis on antioxidant activity of probiotics. Vladimir A. Chistyakov supervised the project. Anna A. Bogdanova prepared figures and schemes and systematized the list of references. Aleksandr G.Refeld performed the analyses of recent reviews. Evgeniya Y.Kharchenko performed meta-analysis. Michael L. Chikindas was in charge of the overall direction and planning.

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Availability of Data and Material All data generated or analyzed during this study are included in this published article.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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