FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
VOLUME 03 ISSUE 01 Pages: 39-52
SJIF IMPACT FACTOR (2021: 5.14) (2022: 5.605)
OCLC – 1272874727

Publisher: Frontline Journals


Journal Website: https://frontlinejournals.org/journals/index.php/fmspj



Research Article

# ANTAGONISTIC PROPERTIES OF LACTOBACILLUS STRAINS IN RELATION TO CONDITIONALLY PATHOGENIC BACTERIA, WHICH CAUSE INFLAMMATORY BOWEL DISEASES

**Submission Date:** January 20, 2023, **Accepted Date:** January 25, 2023,
**Published Date:** January 30, 2023
**Crossref doi:** https://doi.org/10.37547/medical-fmspj-03-01-04

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## ABSTRACT

The article presents the findings of the research on the antagonistic properties of lactobacillus strains against conditionally pathogenic clinical isolates that cause intestinal inflammation. Conditionally pathogenic clinical isolates of colon (large intestine) and rectum (straight intestine) were isolated and identified to the described species level. From a variety of dairy products, 28 milk-fermenting lactobacilli were isolated, screened, and their probiotic probiotic properties were studied. From 28 isolates of isolated milk-fermenting bacteria, 7 strains were selected. The selected strains showed high antimicrobial activity against clinical and typical conditional pathogenic isolates causing intestinal inflammatory diseases (ulcerative colitis). For this reason, these strains can be recommended as a means of treatment and prevention of intestinal infections.

## Keywords

Lactobacillus strains, IBD, intestinal infections, MRS.

## Introduction

Ulcerative colitis is characterized by chronic inflammation in the lining of the large intestine (intestinal mucosa). Long-term chronic inflammation of the intestinal mucosa increases the likelihood of developing a dangerous pathological process. In recent decades, the growth trend of inflammatory bowel diseases has been observed throughout the world, including industrialized countries (R. Boyapati, J. Satsangi, 2015).

Probiotics have a multifaceted effect in inflammatory bowel diseases, in particular, they support the digestion process, affect pathogenic bacteria, normalize epithelial cells, and assist the functioning of the local immune system [1]

Probiotics stimulate natural immunity, and they also carry out the followings: suppress the activeness of pathogenic microflora to synthesize bacteriocins and attach to the epithelium (by competition); help to strengthen the barrier functions of the epithelium, stimulate the synthesis of mucin and increase the tight junctions of cells; prevent the production of cytokines that cause inflammation by competing with pathogens for exposure to dendritic cells; increase anti-inflammatory interleukin-10 synthesis; produces short-chain fatty acids, which are an energy source for epitheliocytes, regulate cell growth and differentiation, and have specific anti-inflammatory effects/ яллиғланишга қарши таъсирга [2]. One of the main influencing mechanisms of Probiotics is their competitive interaction with pathogenic microflora, which leads to the modulation of immunity. Entering some types of lactobacilli and bifidobacteria into the intestine reduces the concentration of clostridia and bacteroids, also affects the metabolic activeness of the flora by reducing the production of active substances such as fecal azoreductase, nitroreductase and β-glucuronidase. These substances are produced by probiotic microorganisms and are effective against gram-positive microorganisms [3] and some viruses [4]. In inflammatory bowel diseases, the function of probiotics is to normalize the work of epithelial cells in the existing digestive process, control the functioning of the local immune system to some extent.

Probiotics perform the following functions: 1) stimulate natural immunity, and also synthesize bacteriocins. In addition, they have an antimicrobial effect on pathogenic microflora; 2) strengthen the barrier functions of the epithelium, stimulate the synthesis of mucin; 3) compete with pathogens for their effect on dendritic cells, produce anti-inflammatory cytokines, and also enhance the synthesis of anti-inflammatory interleukins; 4) produce short-chain fatty acids, which are an energy source for epitheliocytes that regulate cell differentiation and growth.

The antimicrobial effect of lactobacilli is based on several mechanisms, such as immune response modulation. Many studies on antagonistic ability have shown that bacteria such as Lactobacillus plantarum, L. acidophilus, L. rhamnosus are effective in the prevention and treatment of infections caused by Morganella morganii, Clostridioides difficile, Helicobacter pylori, Shigella spp., Salmonellalar, Campylobacter spp., Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus mutans, Staphylococcus aureus, Candida albicans ва Candida glabrata [5].

When evaluating probiotics, the antagonistic potential of lactic acid bacteria strains is crucial. The antagonistic capacity includes inhibiting pathogenic bacterial attachment to the intestine, aggregation and co-aggregation, as well as the synthesis of bacteriocins and other antimicrobial compounds [6]. Findings reveal that some representatives of bacteria such as Bacillus subtilis, Bacillus thuringiensis, Bacillus cereus, Bacillus mycoides are antagonistically active against Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis, Proteus vulgaris, Escherichia.coli [7]. One of the key elements affecting the type of antagonistic relationship is the bacilli's capacity to produce compounds with antibiotic properties. Recent studies have found that one of the elements contributing to the manifestation of antagonism is the lytic enzyme complex of bacilli [8]. In recent years, the study of intestinal infections as biological objects and their function in human physiology and pathology is often viewed through the prism of the emergence of infectious diseases, which are currently increasing. These diseases' expanded significance as pathogens is influenced by their antibiotic resistance to a wide range of antibiotics [9].

The scientific work of Hyung-Seok (2019) focuses on the analysis of antagonistic and antioxidant properties of Weissella cibaria (JW15) to determine its functional support in intestinal microflora diseases. For comparison, Lactobacillus plantarum GG (LGG) was selected as a strain which underwent clinical testing. Weissella cibaria JW15 pathogenic bacteria stopped growing of E.coli, Streptococcus salivarius, Klebsiella oxytoca , Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis. Lactobacillus rhamnosus was compared to Weissella cibaria, it was found that Weissella cibaria produces organic acid relatively quickly, and the amount of lactic acid and acetic acid corresponds.

In addition, Ehe direct effect of the epithelium the resistance of Weissella cibaria JW15 pathogens increased microflora on immunity has been studied. Weissella cibaria JW15 has an antioxidant effect by scavenging radicals containing hydroxyl groups and blocking the growth of lipid peroxidation. When compared the tested analysis of Weissella cibaria JW15 with Lactobacillus plantarum GG, and Lactobacillus rhamnosus strains, the results showed antagonistic and antioxidant activeness. The results show that Weissella cibaria JW15 may have potential for improvement of the excitation of pathogenic microorganisms from oxidative stress [10].

With regard to Lactobacillus fermentum BKM B-2793D and Lactobacillus reuteri BKM B-3144D strains isolated from human breast milk, the researcher has studied their antagonistic activity against pathogens causing mastitis during lactation. The author also researched (and found) that the Lactobacillus fermentum BKM B-2793D, Lactobacillus reuteri BKM B-3144D and their consortium are active against indicator microorganisms used in this study (Staphylococcus aureus) and antibiotic-resistant pathogens [11]. Representatives of the Lactobacillaceae family have been found to have antagonism against various types of microorganisms, including gram-negative and gram-positive bacteria, as well as fungi. Fungicidal activeness, hydroxy derivatives of fatty acids, benzoic acid, and cyclic dipeptides were determined in them [12].

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Laboratory strains produce different classes of chemical organic compounds.

Among them, the best studied one the group of bacteriocins. Bacteriocins are toxic to microbes and are the most important metabolites for the development of antibiotic drugs. Bacteriocins are two ribosome-synthesized peptide proteins that inhibit the growth and reproduction of various bacteria [13].

Many researchers have studied the mechanism of this activity. In addition, bacteriocins can also inhibit nucleic acid and protein synthesis [14]. They are divided into two categories. The first are the two lanthionine-containing lantibiotics [15,16]. Polycyclic antibacterial peptides of the lanthionine group from Lactobacillus lactis cause cell damage in gram-positive bacteria [17]. The second class of bacteriocins - L. crispatus and L. helveticus developed by Helveticin M and Helveticin J. Both bacteriocins are used as food preservatives. Recently, Rooney and others proposed bacteriocin-mediated resistance in plants to control bacterial pathogens in commercial crops [18].

## AIM OF THE RESEARCH

Study of antimicrobial activity of local lactobacillus strains against conditionally pathogenic clinical isolates causing inflammation of the colon (large intestine) and rectum (straight intestine).

## RESEARCH MATERIALS AND METHODS

To isolate local lactobacilli strains, the substrate (fermented milk products) was crushed as well as MRC was cultured in liquid nutrient medium and cultured for 48 h at 37 °C for enrichment. Serial dilutions were prepared using enriched nutrient medium and samples were prepared using the method of planting on solid agar surface. Cultivation under aerobic conditions was performed in 2 replicates: the first was placed in the thermostat, the second in the flask, where the air was replaced by gaseous nitrogen (under anaerobic conditions). Cultivated at 37°C for 48 hours. (Foschi and others, 2017) After cultivation, separated colonies were selected from the plates with different morphological characteristics [4]. It was identified by the MALDI-TOF method, studies on probiotic properties were carried out. (Bruker Biotyper system, Bruker Daltonics, Germany) [19]. Determination of the safety of local strains was carried out in accordance with the Instruction of MUK 4.2.2602-10 "Control methods, biological and microbiological factors" and to Guidelines for experimental (preclinical) studies of new pharmacological substances [20, 21].

Regarding conditionally pathogenic clinical isolates, biomaterial samples and surgical and endoscopic materials were collected in a sterile container from patients with chronic inflammatory diseases of the rectum and colon and delivered to the laboratory within 2-4 hours. To isolate bacterial cells from operative material, it homogenized with a sterile pipette before planting it in the nutrient medium: the biopsy was placed in a test tube with physiological solution and homogenized with a pipette for 1 minute. It was directly sown in a dense selective and selective nutrient medium, and immediately placed in an anaerobic container and incubated in a thermostat at 35-37°C. Pure cultures of microorganisms were isolated and isolates were identified based on morphological and biochemical characteristics (Cunha L.R. 2012). The isolated bacteria were identified by MALDI-TOF method (Bruker Daltonik). Isolated clinical isolates: Proteus morganii, Proteus mirabilis, E. coli, Bacillus subtilis, Candida albicans, Klebsiella oxitoca, Staphylococcus aureus, Citrobacter freundii. Antibiotic resistance was assessed by the disc diffusion method (Anisimova & Yarullina, 2019). Antagonistic activity of Lactobacillus strains against clinical isolates and typical strains available in the laboratory was performed by the agar stain method (Zheng & Slavik, 1999. Harries et al).

Obtained results. The author examined the antagonistic activity of 7 strains newly isolated from different dairy products against isolates of clinically conditionally pathogenic microorganism causing intestinal inflammatory diseases, in relation to Lactobacillus plantarum C-3, Lactobacillus plantarum CM, Lactobacillus plantarum OC, Lactobacillus plantarum Б-20, Weissella cibaria WC-1, Weissella cibaria WC-2, Weissella veredescens WV-1 (Saarela et al., 2010).

The antimicrobial zones of lactobacilli strains against clinical isolates are as follows: Lactobacillus plantarum CM strain isolated in cow's milk constituted antimicrobial zones with Proteus mirabilis - 30 mm, Candida albicans - 23 mm, Staphylococcus aureus - 34 mm, Bacillus subtilis - 33 mm; Lactobacillus plantarum OC strain isolated from hard cheese antimicrobial

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zones with Candida albicans and Bacillus subtilis - 32mm; Weissella cibaria WC-1 strain isolated from various cheese products constituted antimicrobial zones with Proteus morganii ва Klebsiella oxitoca - 24 mm, Citrobacter freundii - 30,5 mm, Candida albicans – 40 mm, Staphylococcus aureus - 35 mm, Bacillus subtilis – 36 mm; Weissella cibaria WC-2 strain Proteus mirabilis – 30,5 mm, Candida albicans and Staphylococcus aureus - 38 mm, Bacillus subtilis – 22 mm; Lactobacillus plantarum Б-20 strain separated from bryndza constituted antimicrobial zones with Proteus morganii 39-mm, Proteus mirabilis - 42 mm, Escherichia coli – 29,5 mm; Lactobacillus plantarum C-3 strain separated from camel milk constituted antimicrobial zones with Citrobacter freundii - 25,5 mm, Candida albicans – 37,5 mm, Staphylococcus aureus – 26 mm; Weissella veredescens WV-1 strain Proteus morganii - 27,5 mm, Candida albicans – 33 mm, Staphylococcus aureus - 38 mm, Escherichia coli – 20,5 mmм, Klebsiella oxitoca – 19,5 m (Table 1).

Antimicrobial zones for conditionally pathogenic bacterial strains present in a typical laboratory collection of lactobacilli strains are as follows: Enterococcus faecalis OG1FR – 28 mm, Pseudomonas aeruginosa 003841/114 – 22 mm for Lactobacillus plantarum CM strain; Enterococcus faecalis OG1FR – 20 mm, Pseudomonas aeruginosa 003841/114 – 19 mm for Lactobacillus plantarum OC strain; Serratia marcescens 367 – 34 mm, Listeria monocytogenes ATCC 1911- 24 mm, Enterococcus faecalis OG1FR – 25,5 mm for Weissella cibaria WC-1 strain; Pseudomonas aeruginosa 003841/114 – 34,5 mm, Listeria monocytogenes ATCC 1911- 25,5 mm, Enterococcus faecalis OG1FR – 29 mm for Weissella cibaria WC-2 strain.

**Antimicrobial zones of lactobacilli strains in relation to clinical isolates**

**Table 1**

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| Isolates | | Diameter of antimicrobial zone of indicator strains, mm | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *C. freundii* | *P. morganii* | *P. mirabilis* | *E. coli* | *C. albicans* | *S. aureus* | *B. subtilis* | *K. oxitoca* |
| 1 | *Lactobacillus plantarum CM* | 10.5±1,4 | 20.5±1,2 | 30±1,1 | 0 | 23±0,2 | 34±0,4 | 33±2,1 | 17.5±0,1 |
| 2 | *Lactobacillus plantarum OC* | 20±1,1 | 10±0,2 | 10±0,9 | 15±0,9 | 32±1,4 | 25±2,0 | 32±1,4 | 24±1,4 |
| 3 | *Weiissella cibaria WC-1* | 30,5±0,4 | 24±1,4 | 14±1,6 | 20±2,1 | 40±1,4 | 35±2,1 | 36±0,2 | 24±1,4 |
| 4 | *Weiissella cibaria WC-2* | 20±1,0 | 14.5±1,1 | 30.5±1,1 | 12.5±1,4 | 38±0,8 | 38±0,8 | 22±1,0 | 10±1,6 |
| 5 | *Lactobacillus plantarum Б-20* | 0 | 39±1,4 | 34±2,1 | 29.5±2,1 | 11±1,4 | 22±1,0 | 20±0,9 | 17.8±1,4 |
| 6 | *Lactobacillus plantarum C-3* | 25.5±2,1 | 0 | 13.5±1,4 | 10±0,9 | 37.5±1,4 | 26±0,4 | 24±2,1 | 17±0,4 |
| 7 | *Weiissella viridescens WV* | 14±0,2 | 27.5±1,0 | 10.5±0,4 | 20.5±1,4 | 33±0,4 | 38±1,4 | 15±0,2 | 19.5±1,4 |

**Antimicrobial zones of lactobacilli strains in relation to clinical isolates**

**Diagram 1**

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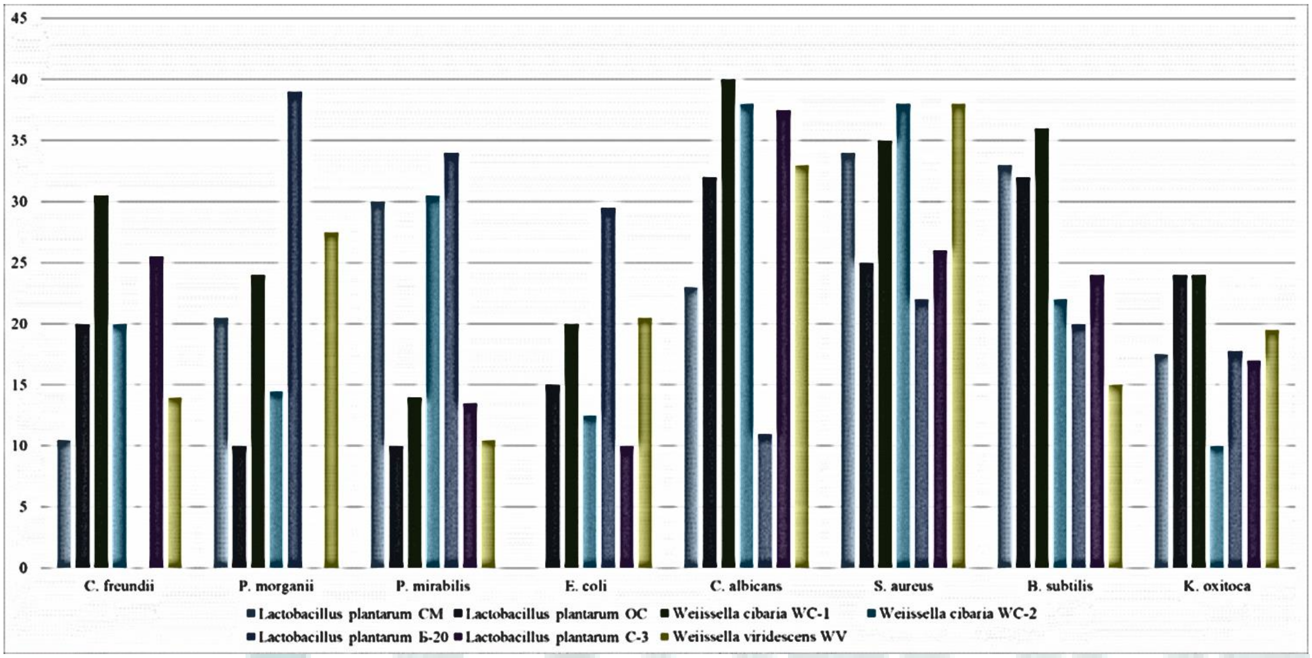


Lactobacillus plantarum B-20 strain showed high indicators of antimicrobial activity such Serratia marcescens 367 – 25 mm, Listeria monocytogenes ATCC 1911- 28 mm; accordingly, Lactobacillus plantarum C-3 strain showed Pseudomonas aeruginosa 003841/114 – 35,5 mm, ATCC 1911- 24,5 mm, Enterococcus faecalis OG1FR – 28,5 mm; Weissella veredescens WV-1 strain showed Pseudomonas aeruginosa 003841/114 – 22,5 mm, Listeria monocytogenes ATCC 1911- 27,5 mm, Enterococcus faecalis OG1FR – 22 mm. (Table 2)

**Antimicrobial zones of lactobacilli strains to conditionally pathogenic bacterial strains present in the research collection**

**Table 2**

| Isolates | Diameter of antimicrobial zone of indicator strains, mm | | | |
|---|---|---|---|---|
| | *P.aeruginosa 003841/114* | *S.marcescens 367* | *L.monocytogenes ATCC 1911* | *E.faecalis OG1FR* |

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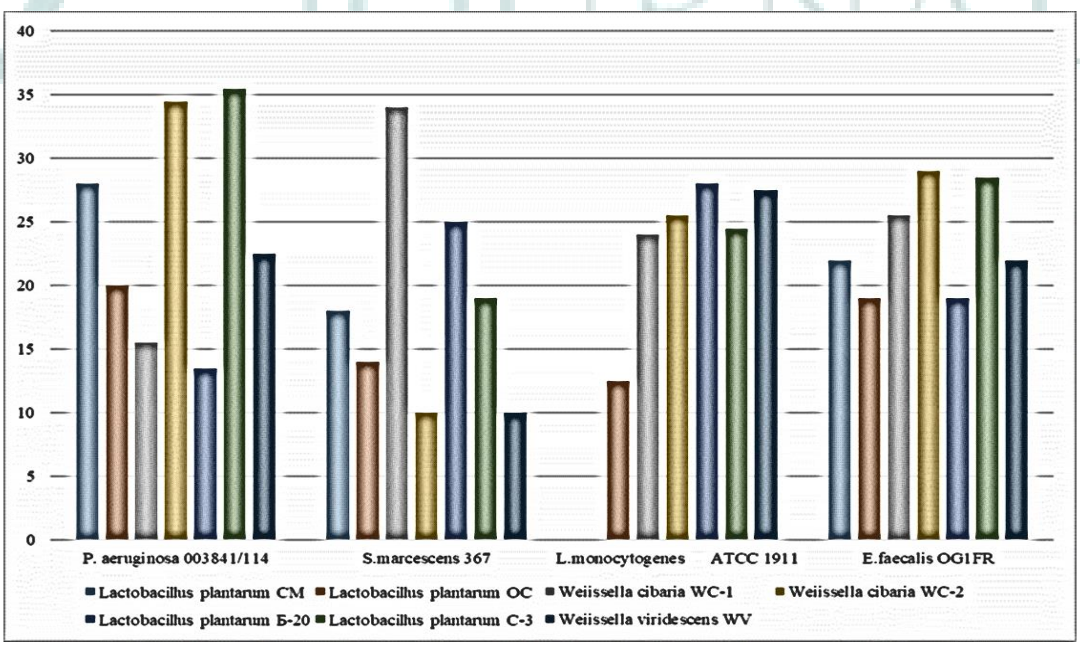
| | | | | | |
|---|---|---|---|---|---|
| 1 | *Lactobacillus plantarum CM* | 28±1,0 | 18±0,4 | 0 | 22±1,1 |
| 2 | *Lactobacillus plantarum OC* | 20±0,8 | 14±0,4 | 12.5±0,4 | 19±0,9 |
| 3 | *Weiissella cibaria WC-1* | 15.5±0,9 | 34±0,2 | 24±1,4 | 25.5 |
| 4 | *Weiissella cibaria WC-2* | 34.5±1,4 | 10±1,1 | 25.5±0,6 | 29±1,0 |
| 5 | *Lactobacillus plantarum Б-20* | 13.5±0,4 | 25±0,2 | 28±1,0 | 19±1,1 |
| 6 | *Lactobacillus plantarum C-3* | 35.5±0,2 | 19±1,1 | 24.5±0,2 | 28.5±0,6 |
| 7 | *Weiissella viridescens WV* | 22.5±1,0 | 10±0,2 | 27.5±0,9 | 22±0,8 |

**Antimicrobial zones of lactobacilli strains to conventionally pathogenic bacterial strains (typical cultures)**

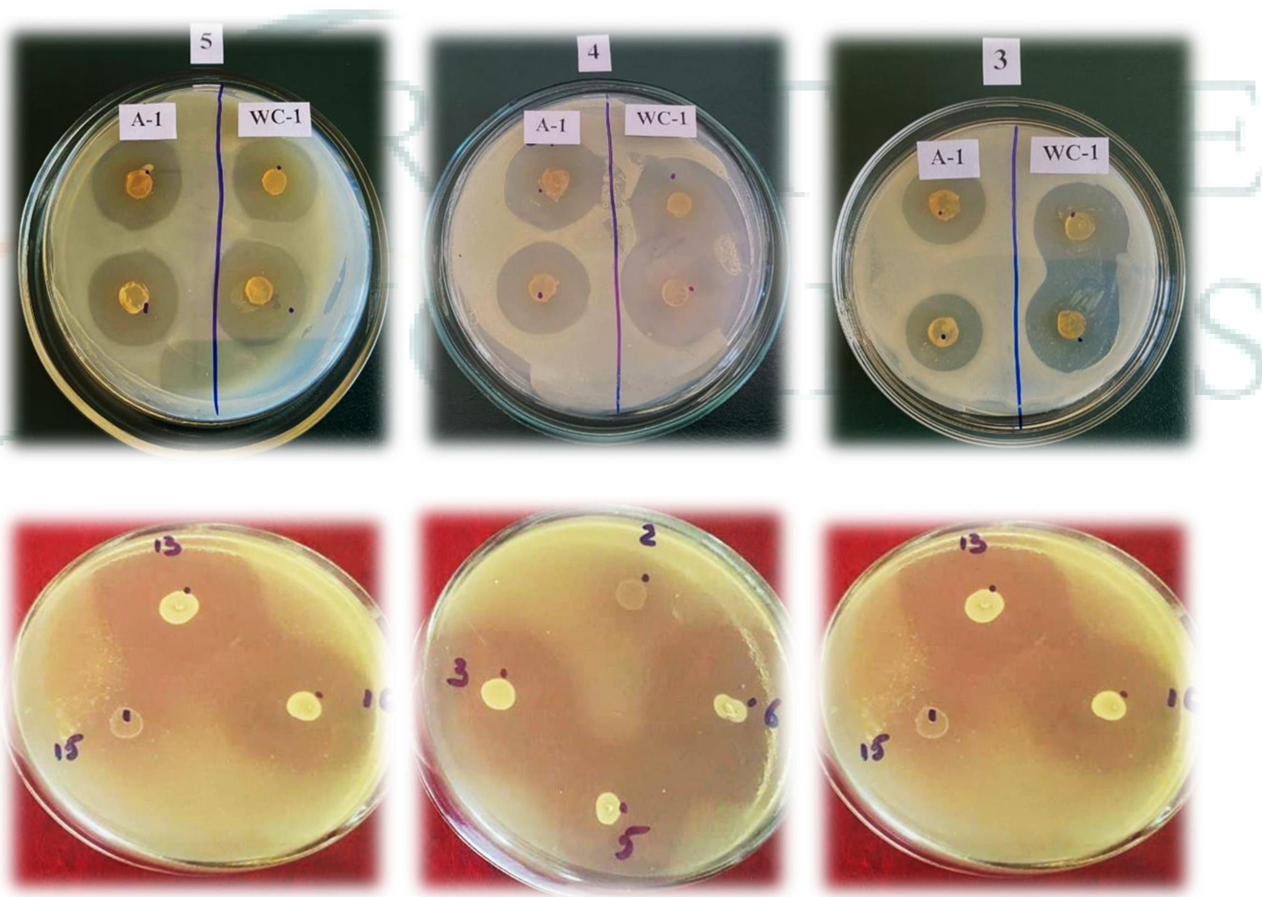
**Diagram 2**



Three repetitions were used for the entire experimental work. Mathematical processing of experimental data was carried out using Microsoft Office and Statistica 10 software in the methods of statistics and regression analysis. A method of planning a mathematical experiment was used in efficient setup of experiments and selection of rational parameters. The reliability of the obtained results was evaluated according to Student's criterion, obtained regression correlations were checked by Fisher's test in consistency of experimental data (Tables 1-2).

**Antimicrobial zones of lactobacilli strains**

**Figure 1**



Antimicrobial activity of Lactobacilli (lactobacilli strains grown on MRS agar plates as spot forms) against Candida albicans, Enterococcus faecalis OG1FR, Klebsiella oxitoca, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis. Conditionally-pathogenic isolates were cultured in coated semi-solid MPB medium (Figure1).

Conclusion. Lactobacilli synthesize metabolites such as organic acids, fatty acids, hydrogen peroxide, bacteriocins. These metabolites prevent the growth and reproduction of conditionally pathogenic bacteria. The strains such as Weissella cibaria WC-1, Lactobacillus plantarum OC, Weissella veredescens WV-1 showed high antimicrobial activity against clinical isolates causing intestinal inflammation. From the above indications, it can be said that these probiotic strains are promising and have the potential to be used as biological drugs for the prevention and treatment of intestinal diseases and related conditions.

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