

EFFECT OF *LACTOBACILLUS PLANTARUM* LS/07 ON INTESTINAL BACTERIAL ENZYME ACTIVITIES IN THE PREVENTION OF CANCER, ATHEROSCLEROSIS AND DYSBIOSIS

HIJOVÁ Emília*, KUZMA Jozef, STROJNÝ Ladislav, BOMBA Alojz, BERTKOVÁ Izabela, CHMELÁROVÁ Anna, HERTELYOVÁ Zdena, KULIKOVÁ Lucia, ŠTOFILOVÁ Jana, AMBRO Ľuboš

Institute of Experimental Medicine, Medical Faculty, University of P. J. Šafárik, Košice, Slovak Republic

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The effect of the probiotic strain *Lactobacillus plantarum* LS/07 on intestinal bacterial enzyme activities – β -glucuronidase (β -GLUCUR), β -galactosidase (β -GAL), and β -glucosidase (β -GLU) in the prevention of cancer, atherosclerosis and dysbiosis was investigated. Male Sprague-Dawley rats were randomly divided into 12 experimental groups: C (control group), AT (atherosclerotic group), CC (carcinogenic group), and then each group in combination with antibiotics and probiotics individually and each group in double combination on antibiotic and probiotic. In the control group the β -glucuronidase activity did not change throughout the experiment. High fat diet in the atherosclerotic group significantly increased the activity of β -glucuronidase ($p < 0.001$) and β -glucosidase ($p < 0.01$). Azoxymethane application in the carcinogenic group significantly increased β -glucuronidase ($p < 0.01$), but reduced β -glucosidase ($p < 0.01$). Daily application of probiotics individually and in double combination with antibiotics increased the activity of β -galactosidase, and β -glucosidase, and positively decreased the level of β -glucuronidase. In the control antibiotic group β -glucuronidase was significantly increased ($p < 0.05$), and β -glucosidase decreased ($p < 0.01$) which can be caused by a change of microflora in favor of coliform bacteria. These findings indicate the positive effects of probiotic *Lactobacillus plantarum* LS/07 which allows its use in disease prevention in human and veterinary medicine.

Key words: Sprague-Dawley rats, Bacterial enzyme, Cancer, Atherosclerosis, Dysbiosis

INTRODUCTION

The gut microbiota acts as a real organ. The symbiotic interactions between resident microorganisms and the digestive tract highly contribute to maintain gut homeostasis. However, alterations to the microbiome caused by environmental changes in humans and animals (e.g. diet, antibiotics, xenobiotics, stress, viruses, bacteria, parasites, and age) can cause significant changes in the composition of intestinal microflora [1].

*Corresponding author: e-mail: emilia.hijova@upjs.sk

Disturbance of intestinal microflora - dysbiosis may increase individual's susceptibility to infections and diseases. Different patterns of microbial colonization associated with disease state compared to healthy controls have been documented, although a causal relationship has not been established. However, the patterns of microbial colonization associated with health are more difficult to define. A definition of healthy microbiota would provide a target for interventions aimed at sustaining health in the generally healthy populations and improving the health status of people exhibiting disrupted microbiota and diseases associated with these disruptions. A definition of healthy microbiome is not yet defined. Dysbiosis negatively affects the host organism by means of qualitative and quantitative changes in the composition of intestinal microflora, changing its metabolic activity and local distribution and plays an extremely important role in the pathogenesis of chronic diseases. Consequently, in the gastrointestinal tract occurs a disruption in intestinal permeability, increased transfer of lipopolysaccharides derived from a gram-negative bacterium into the blood stream, endotoxemia and form a slowly progressive inflammation, leading to metabolic disorders and chronic diseases [2].

The production of bioactive carcinogenic compounds from environmental factors (diet, chemical agents) may be obtained through enzyme activation. The assessment of intestinal bacterial enzymes activities is often used to demonstrate changes in the colon and may provide complementary information on the effect of dietary intervention on the modulation of the gut microbiota [3-5]. In the present study, the influence of long-term administration of probiotic *Lactobacillus plantarum* LS/07 in the prevention of atherosclerosis induced by high fat diet, prevention of chemically induced colon cancer and in prevention of dysbiosis induced by antibiotic treatment on activity of β -glucuronidase, β -glucosidase and β -galactosidase was evaluated.

MATERIAL AND METHODS

Animals and experimental design

Animal experiments were carried out in two stages – 1. stage (dysbiotic) and 2. stage (probiotic) in accordance with the principles outlined in Law No. 377/2012 and No. 436/2012 of the Slovak Republic for the Care and Use of Laboratory Animals, and were approved by the Ethical Committee of the Faculty of Medicine of P. J. Šafárik University and State Veterinary and Food Administration of the Slovak Republic. Male Sprague-Dawley rats (n=120, 60 per stage, 10 per group in each stage, 6 weeks old) with mean initial body weight in 1. stage $177\text{g} \pm 17\text{g}$ (min. 167g - max. 192g) and in 2. stage with mean initial body weight $143\text{g} \pm 14\text{g}$ (min. 141g - max. 147g) were placed in Laboratory of Research Bio-models of the Faculty of Medicine, P. J. Šafárik University, Slovak Republic (SK PC4013) with a 12-h light/dark cycle. The room was maintained at $21^{\circ}\text{C} \pm 1^{\circ}\text{C}$ with 50% to 60% humidity.

The rats were randomly assigned to the following groups (Table 1): in 1. stage were **C** (control group), **AT** (atherosclerotic group), **CC** (carcinogenic group), **C+ATB** (control antibiotic group), **AT+ATB** (atherosclerotic group in combination with antibiotic), and **CC+ATB** (carcinogenic group in combination with antibiotic). In 2. stage were **C+PRO** (control probiotic group), **AT+PRO** (atherosclerotic group in combination with probiotic), **CC+PRO** (carcinogenic group in combination with probiotic), **C+ATB+PRO** (control group with antibiotic and probiotic), **AT+ATB+PRO** (atherosclerotic group in combination with antibiotic and probiotic), and **CC+ATB+PRO** (carcinogenic group in combination with antibiotic and probiotic).

Table 1. Experimental design

| Stage (dysbiotic) | Stage (probiotic) |
|--|---|
| C control group | C+PRO Control probiotic group |
| AT atherosclerotic group | AT+PRO Atherosclerotic group with probiotic |
| CC carcinogenic group | CC+PRO Carcinogenic group with probiotic |
| C+ATB control antibiotic group | C+ATB+PRO Control group with ATB and PRO |
| AT+ATB atherosclerotic group with antibiotic | AT+ATB+PRO Atherosclerotic group with ATB and PRO |
| CC+ATB carcinogenic group with antibiotic | CC+ATB+PRO Carcinogenic group with ATB and PRO |

The duration of the experiment was 25 weeks, animal weights, feed consumption, water, antibiotic and probiotic were recorded daily. All animals had free access to water and feed intake. C group received the conventional feed (Snina, Slovak Republic). AT groups (individual and in combination) received conventional feed enriched with 10% of fat (pork fat 100 g per 1 kg conventional feed) and 0.5% of cholesterol (cholesterol 5 g per 1 kg conventional feed).

After 25 weeks the animals were euthanized under anesthesia Zoletil (Virbac S.A., France) administered at a dose of 50 mg/kg body weight with Xylazin (Riemsers, Germany) at a dose of 15 mg/kg body weight, intramuscular). Caecal samples from the colon were used for analysis.

Induction of colon cancer

CC groups (individuals and in combination) two weeks after started feeding with conventional diet were treated with azoxymetan (Sigma Aldrich, USA), at a dose of 15

mg/kg i.p., at a two times a week interval, dietary treatments were continued during the entire experiment.

Development of dysbiosis

Dysbiosis was induced by daily administration of antibiotics in combination of metronidazolom (Medana Pharma SA, Poland) in a dose of 60-350 mg/L and amoxicilin (Sandoz GmbH, Austria) in dose 140-500 mg/L. The daily dose of antibiotics was calculated based on the analysis of total microbial counts of coliform bacteria.

Probiotic strain. The probiotic strain of *Lactobacillus plantarum* LS/07 was isolated from rectal human swabs reported by Strojny and coworkers [6]. The strain was cultured in MRS broth (Merck, Germany) prepared as night cultures at 37°C aerobically. Each rat received approximately 7.5×10^8 CFU lactobacilli in 75 µL volume by the oral route daily. In vitro tests revealed that the administered probiotic strain *Lactobacillus plantarum* LS/07 does not exhibit the activity of β-glucuronidase activity but exhibits β-galactosidase and β-glucosidase activity.

Measurement of bacterial enzyme activity

The activity of bacterial enzymes was measured in fresh caecal digesta taken after completion of the experiment by determining the rate of *p*- or *o*-nitrophenol as previously described by the Juskiwicz et al. [7]. The reaction contained 0.3 mL a substrate solution (5 mM, Sigma Aldrich, USA) *p*-nitrophenyl-β-D-glucuronide for β-glucuronidase (β-GLUCUR), *o*-nitrophenyl-β-D-galactopyranoside for β-galactosidase (β-GAL), *p*-nitrophenyl-β-D-glucopyranoside for β-glucosidase (β-GLU) and 0.2 mL of 1:10 (v/v) dilution of the caecal digesta in 100 mM phosphate buffer (pH 7.0) centrifuged at 10,000 g for 15 min at 4 °C. Incubation was carried out at 37 °C for 10 min, and *p*- or *o*-nitrophenol was quantified after addition of 0.25 M cold sodium carbonate and measured absorbation at 400 nm. A measurement unit of enzymatic activity is expressed as µmol of *p*-nitrophenol per min per gram digesta.

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Statistical analysis was performed using analysis of variance (ANOVA) with *p* values (*p*<0.05) were considered to be statistically significant.

RESULTS

No clinical changes observed in rats did lead to death during the experimental trial. The mean body weight of the rats at the beginning of the experiment and at the end of the experiment in 1. stage increased from $177\text{g} \pm 17\text{g}$ to $572\text{g} \pm 63\text{g}$ (min. 544g in CC+ATB group; max. 597g in CC group) and in 2. stage was increased from $143\text{g} \pm 14\text{g}$ to $501\text{g} \pm 53\text{g}$ (min. 491g in AT+PRO group; max. 514g in CC+PRO group). The

average daily feed consumption in 1. stage was 26.37 ± 1.26 g (min. 24.82 ± 0.96 g in AT+ATB group; max. 28.74 ± 0.65 g in CC group), and in 2. stage was 23.63 ± 2.19 g (min. 21.60 ± 2.46 in AT+ATB+PRO; max. 24.73 ± 2.17 g in CC+PRO). Intake of antibiotic was in 1.stage on average 26.62 mL/rat/day and in 2. stage on average 28.55 mL/rat/day. In all experimental groups studied in the 1. stage (Table 2) there was a decrease in β -galactosidase, which is produced mainly by lactobacilli and bifidobacteria indicating a transition diet of milk formula at the time of entering rats into the experiment on solid food at the time the experiment. In the C group the β -glucuronidase activity did not change throughout the experiment. In the AT group after applying the high fat diet significantly increased the activity of β -glucuronidase ($p < 0.001$) and β -glucosidase ($p < 0.01$) indicating a potential for increased aglycone production from food and plant glycosides. Azoxymethane application in CC group significantly increased the activity of β -glucuronidase ($p < 0.01$) but the reduced β -glucosidase ($p < 0.01$). In the control antibiotic group C+ATB significantly increased β -glucuronidase ($p < 0.05$), and β -glucosidase decreased ($p < 0.01$) which can be caused by a change of microflora in favor of coliform bacteria. Antibiotic treatment in combination with high fat diet (AT+ATB) and azoxymethane (CC+ATB) increased β -glucuronidase activity (nonsignificantly versus $p < 0.01$). In all experimental groups studied in 2. stage (Table 3) the application of probiotics has increased the activity of the enzyme β -galactosidase with the exception of the CC+PRO+ATB. Similarly, the activity of β -GLU was increased in groups with probiotic administered. A significant decrease in β -glucuronidase ($p < 0.01$) was in group CC+PRO as a positive effect of probiotics. The groups wherein the probiotic was combined with the antibiotic activity of β -glucuronidase was significantly reduced, with the exception of CC+PRO+ATB where the activity of β -glucuronidase increased indicating a predominance of antibiotic versus probiotic.

Table 2. Changes of intestinal bacterial enzyme activity in experimental group of 1. stage

| Experimental group | | β -GAL $\mu\text{mol/g/min}$ | β -GLUCUR $\mu\text{mol/g/min}$ | β -GLU $\mu\text{mol/g/min}$ |
|--------------------|--------|---------------------------------------|--|---------------------------------------|
| C | before | 0.035 ± 0.01 | 0.074 ± 0.02 | 0.059 ± 0.012 |
| | after | $0.029 \pm 0.01^{**}$ | 0.084 ± 0.03 | 0.068 ± 0.03 |
| AT | before | 0.050 ± 0.004 | 0.081 ± 0.003 | 0.037 ± 0.01 |
| | after | 0.033 ± 0.007 | $0.104 \pm 0.01^{***}$ | $0.065 \pm 0.01^{**}$ |
| CC | before | 0.039 ± 0.01 | 0.077 ± 0.01 | 0.057 ± 0.02 |
| | after | 0.018 ± 0.002 | $0.103 \pm 0.01^{**}$ | $0.033 \pm 0.01^{**}$ |
| C+ATB | before | 0.078 ± 0.03 | 0.070 ± 0.006 | 0.072 ± 0.03 |
| | after | 0.045 ± 0.01 | $0.108 \pm 0.05^*$ | $0.036 \pm 0.02^{**}$ |
| AT+ATB | before | 0.070 ± 0.02 | 0.044 ± 0.02 | 0.039 ± 0.02 |
| | after | 0.058 ± 0.01 | 0.045 ± 0.02 | 0.047 ± 0.02 |
| CC+ATB | before | 0.029 ± 0.003 | 0.043 ± 0.01 | 0.032 ± 0.01 |
| | after | 0.020 ± 0.006 | $0.058 \pm 0.01^{**}$ | 0.020 ± 0.001 |

Values are expressed as mean \pm SD. Statistical significance is in different experimental groups before and after experimental period : * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 3. Changes of intestinal bacterial enzyme activity in experimental group of 2. stage

| Experimental group 2. stage | | β -GAL $\mu\text{mol/g/min}$ | β -GLUCUR $\mu\text{mol/g/min}$ | β -GLU $\mu\text{mol/g/min}$ |
|--------------------------------|--------|---------------------------------------|--|---------------------------------------|
| C+PRO | before | 0.031 \pm 0.01 | 0.169 \pm 0.09 | 0.039 \pm 0.006 |
| | after | 0.070 \pm 0.01 *** | 0.149 \pm 0.02 | 0.114 \pm 0.02*** |
| AT+PRO | before | 0.031 \pm 0.01 | 0.169 \pm 0.09 | 0.039 \pm 0.006 |
| | after | 0.048 \pm 0.01** | 0.113 \pm 0.02 | 0.067 \pm 0.02*** |
| CC+PRO | before | 0.031 \pm 0.01 | 0.169 \pm 0.09 | 0.039 \pm 0.006 |
| | after | 0.044 \pm 0.009 | 0.089 \pm 0.02** | 0.043 \pm 0.007 |
| C+PRO +ATB | before | 0.027 \pm 0.005 | 0.194 \pm 0.08 | 0.028 \pm 0.006 |
| | after | 0.048 \pm 0.01*** | 0.113 \pm 0.02** | 0.068 \pm 0.02*** |
| AT+PRO +ATB | before | 0.019 \pm 0.007 | 0.231 \pm 0.08 | 0.025 \pm 0.005 |
| | after | 0.045 \pm 0.01*** | 0.069 \pm 0.02*** | 0.103 \pm 0.03*** |
| CC+PRO +ATB | before | 0.029 \pm 0.003 | 0.043 \pm 0.01 | 0.032 \pm 0.01 |
| | after | 0.019 \pm 0.007*** | 0.099 \pm 0.05*** | 0.037 \pm 0.01 |

Values are expressed as mean \pm SD. Statistical significance is in different experimental groups before and after experimental period: ** $p < 0.01$; *** $p < 0.001$

DISCUSSION

The human microbiota has identified three enteric microbial biotransformations of particular relevance for human health [8]. First, selective bacteria can reverse beneficial hepatic hydroxylation to produce toxic secondary bile acids, especially deoxycholic acid. Second, numerous bacterial species can reverse hepatic detoxification - in a sense, retoxify hormones and xenobiotics - by deglucuronidation. Third, numerous enteric bacteria can effect a very positive biotransformation through the production of butyrate, a small chain fatty acid with anti-cancer activity. Members of the gut microbiota in the human large intestine exhibit a variety of enzymatic activities with a potential impact on human health through biotransformation of secondary plant products and xenobiotic compounds [9,10]. Modulation of intestinal bacterial enzyme activity has been described as one of the mechanisms through which pro- and prebiotics exert their beneficial effects [11,12]. Lactobacilli and bifidobacteria the most widely studied probiotic genera, have low activities of enzymes involved in the conversion of procarcinogens into potentially carcinogenic compounds and show their protective effects *in vitro* and *in vivo* [13,14].

β -Glucuronidases liberate toxins and mutagens that have been glucuronated in the liver and excreted into the gut with the bile. This can lead to high local concentrations of carcinogenic compounds within the gut, thus increasing the risk of carcinogenesis [15]. Furthermore, re-uptake of the deconjugated compound from the gut and reglucuronidation in the liver leads to an enterohepatic circulation of xenobiotic compounds, which increases their retention time in the body. β -Glucosidases can exert either beneficial or harmful effects, as they form aglycones from a range of different

plant glucosides, which might exhibit either toxic/mutagenic or health-promoting effects [16-18]. Some plant glucosides are also subject to deconjugation by host β -glucosidases in the upper gut and may subsequently be glucuronated by the host, making them a substrate for bacterial β -glucuronidases when they reach the colon with the bile. The resulting aglycones of plant polyphenols may be subject to further degradation and biotransformation by the gut microbiota. Bacterial β -galactosidase could also be involved in the hydrolysis of any undigested lactose reaching the large intestine. This enzyme is mainly produced by bifidobacteria and lactobacilli and its increase in large intestine substantiates a stimulatory effect of lactic acid bacteria. *Lactobacillus plantarum* LS/07 application increased activities of β -galactosidase in all experimental groups studied in 2.stage except CC+PRO+ATB indicating a predominance of antibiotic versus probiotic which is in agreements with the results of β -glucuronidase activity in the same group.

Azoxymethane is first hydrolyzed in the liver to methylazoxymethanol and conjugated with glucuronic acid before it is transported to the intestine through bile secretion of glucuronic acid-conjugated methylazoxymethanol where the β -glucuronidase captures the highly methyl carbonium ion, a carcinogenic form from azoxymethane, while the inhibition of β -glucuronidase reduces the ability of azoxymethane to induce tumors in rats [19,20]. Azoxymethane application in CC group significantly increased the activity of β -glucuronidase ($p < 0.01$) but the reduced β -glucosidase ($p < 0.01$). Similar tendency was in CC+ATB group where activity of β -glucuronidase was increased ($p < 0.01$) and reduced β -glucosidase activity. *Lactobacillus plantarum* LS/07 in CC+PRO increased activity of β -galactosidase and β -glucosidase, reduced activity of β -glucuronidase ($p < 0.01$). CC+PRO+ATB group show increased activity of the β -glucuronidase ($p < 0.001$) indicating a predominance of antibiotic versus probiotic. High fat diet intervention in our experiment increased activity of β -glucuronidase ($p < 0.001$) and β -glucosidase ($p < 0.01$) similar as in the work by An et al. [21]. *Lactobacillus plantarum* LS/07 in AT+PRO group decreased the activity of β -glucuronidase and increased β -glucosidase ($p < 0.001$) as well is in AT+PRO+ATB group where probiotic was in predominance against antibiotic.

CONCLUSION

In conclusion, our results indicate that changes in fecal bulk intestinal bacterial enzymes activities in response to changes in dietary intake are likely to be due to both, changes in the number of bacteria carrying those activities and regulatory changes within certain strains. Modulation of the activity of bacterial enzymes is described as one of the mechanisms through which probiotics *Lactobacillus plantarum* exhibit their beneficial effect.

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Authors' contributions

Author's contribution were substantially to the article and herein describe their contributions: EH and AB conception and design of the study, JK and ZH statistical analysis and interpretation data, LS animal welfare, application of azoxymetan, IB and JŠ animal welfare, analysis and interpretation data, AC, LK and LA animal welfare, probiotic application.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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EFEKTI *LACTOBACILLUS PLANTARUM* LS/07 NA AKTIVNOSTI ENZIMA CREVNIH BAKTERIJA U PREVENIRANJU KANCERA, ATEROSKLEROZE I DISBIOZE

HIJOVÁ Emília, KUZMA Jozef, STROJNÝ Ladislav, BOMBA Alojz, BERTKOVÁ Izabela, CHMELÁROVÁ Anna, HERTELYOVÁ Zdena, KULIKOVÁ Lucia, ŠTOFILOVÁ Jana, AMBRO Ľuboš

Ispitivani su efekti probiotičkog soja *Lactobacillus plantarum* LS/07 na aktivnosti bakterijskih enzima – β -glukuronidaze (β -GLUCUR), β -galaktozidaze (β -GAL) i β -glukozidaze (β -GLU) u prevenciji kancera, ateroskleroze i disbioze. Sprague-Dawley muški pacovi su metodom slučajnog izbora, podeljeni u 12 eksperimentalnih grupa: C (kontrolna grupa), AT (grupa ateroskleroze), CC (karcinogena grupa), svaka grupa

u kombinaciji samo sa antibioticima ili probioticima kao i svaka grupa sa dvostrukom kombinacijom antibiotika i probiotika. U kontrolnoj grupi, aktivnost β -GLUCUR nije se menjala tokom trajanja ogleada. Ishrana sa velikom količinom masti u AT grupi, uslovlila je značajno povećanje aktivnosti β -GLUCUR ($p < 0,001$) i β -GLU ($p < 0,01$). Aplikacija azoksimetana u CC grupi, značajno je povećala aktivnost β -GLUCUR ($p < 0,01$) ali je smanjila β -GLU ($p < 0,01$). Svakodnevna aplikacija probiotika, individualno i u kombinaciji sa antibioticima, povećala je aktivnost β -GAL, kao i β -GLU, uz pozitivno smanjivanje nivoa β -GLUCUR. U kontrolnoj antibiotskoj grupi, β -GLUCUR aktivnost se značano povećala ($p < 0,05$) uz smanjenje β -GLU ($p < 0,01$). Ovo može da bude posledica promene mikroflore u korist koliformnih bakterija. Rezultati pokazuju da postoji pozitivan efekat *Lactobacillus plantarum* LS/07, što nadalje ukazuje na moguću upotrebu ove bakterije u prevenciji oboljenja u humano i veterinarskoj medicini.