



# PROSPECTS FOR THE USE OF NANOCRYSTALLINE CERIUM DIOXIDE AS A PREBIOTIC FOR MICROBIOME CORRECTION

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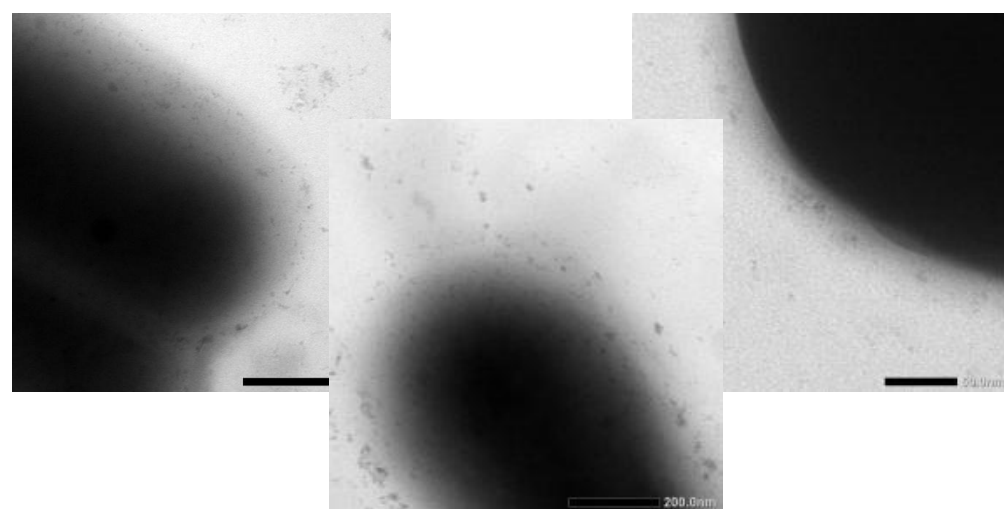
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## Background

Microbiome modulation is a pillar intervention to treat metabolic syndrome and cascade of related pathologies such as atherosclerosis, among others. *Lactobacillus* and *Bifidobacterium* probiotic strains demonstrate efficacy to reduce obesity, dyslipidemia, and improve metabolic health. Novel prebiotic substances composed with known probiotics may strongly synergize health benefits to the host. The aim of this study was to evaluate beneficial effects of *Lactobacillus* and *Bifidobacterium* strains if composed with nanocerium (potential prebiotic) to reduce cholesterol levels and restore gut microbiota in obese mice.



**Nanocerium** (nanocrystalline cerium dioxide, ceria nanoparticles, nCeO<sub>2</sub>) was proved to be able to participate in biological processes as a regulator of reactive oxygen species and free radicals acceptor and its efficacy for number of biomedical applications



Ultrasound during experiment – liver (B), kidney (C)

## Materials and Methods

Two lines of mice were used in the study: BALB/c mice (6–8 weeks, 18–24 g) and CBA mice (11–12 months, 20–26 g); experimental animals were fed by fat-enriched diet 3 weeks before the evaluation. Animals were divided into groups to test probiotic strains and nanocerium. All groups received probiotic strains orally and cerium dioxide orally or intravenously in various composition.

A group of untreated animals was used as a control. Cholesterol level and gut microbiota of mice were studied.

## Results

Cerium dioxide nanoparticles, probiotic strain *L. casei* IMV B-7280, and composition *B. animalis* VKB/*B. animalis* VKL applied separately and in different combinations all reduced at different levels free and bound cholesterol in blood serum of mice fed by fat-enriched diet. The combination of 0.01 M nanocerium and probiotic strain

### The levels of free cholesterol in the serum of young BALB / c mice

Day of study / group of animals	day 4	day 9	day 15	day 21	day 30
	mg/ml				
Intact animals	4.82 ± 0.36	4.34 ± 0.31	4.61 ± 0.18	5.01 ± 0.11	4.46 ± 0.14
Animals on the FED	12.33 ± 0.77	11.27 ± 0.29	9.77 ± 0.37	8.68 ± 0.71	9.21 ± 0.53
FED + 0,1 M CeO <sub>2</sub> orally	11.18 ± 0.08	8.98 ± 0.36	9.88 ± 0.29	9.88 ± 0.19	7.36 ± 0.48
FED + 0,01 M CeO <sub>2</sub> orally	8.40 ± 0.06	5.70 ± 0.17	5.49 ± 0.11	5.04 ± 0.28	4.79 ± 0.35
FED + 0,001 M CeO <sub>2</sub> orally	9.42 ± 0.33	7.50 ± 0.36	7.04 ± 0.18	5.72 ± 0.20	5.31 ± 0.61
FED + 0,1 M CeO <sub>2</sub> + <i>L. casei</i> IMV B-7280 orally	8.36 ± 0.22	8.40 ± 0.28	6.47 ± 0.56	5.31 ± 0.31	6.17 ± 0.34
FED + 0,01 M CeO <sub>2</sub> + <i>L. casei</i> IMV B-7280 orally	6.32 ± 1.11	4.83 ± 0.46	3.01 ± 0.09	2.23 ± 0.48	3.88 ± 0.25
FED + 0,001 M CeO <sub>2</sub> + <i>L. casei</i> IMV B-7280 orally	7.54 ± 0.36	6.40 ± 0.53	5.96 ± 0.74	4.09 ± 0.32	3.52 ± 0.49
FED + 0,1 M CeO <sub>2</sub> + <i>B. animalis</i> VKB / <i>B. animalis</i> VKL orally	10.03 ± 0.43	8.80 ± 0.22	7.98 ± 0.04	6.36 ± 0.30	5.93 ± 0.20
FED + 0,01 M CeO <sub>2</sub> + <i>B. animalis</i> VKB / <i>B. animalis</i> VKL orally	8.65 ± 0.20	8.37 ± 0.10	7.11 ± 0.08	6.38 ± 0.14	5.62 ± 0.11
FED + <i>B. animalis</i> VKB / <i>B. animalis</i> VKL orally	10.03 ± 0.29	8.98 ± 0.24	8.11 ± 0.16	6.93 ± 0.05	7.01 ± 0.15
FED + <i>L. casei</i> IMV B-7280 orally	8.41 ± 0.06	7.19 ± 0.15	5.99 ± 0.25	4.53 ± 0.49	3.15 ± 0.23
FED + <i>B. animalis</i> VKB / <i>B. animalis</i> VKL orally	9.72 ± 0.22	8.54 ± 0.08	6.93 ± 0.19	4.41 ± 0.60	4.19 ± 0.10

## Is nanocerium a prebiotic ?

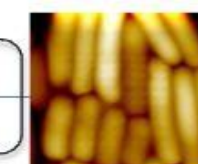
- Nanocerium demonstrate **no suppressive** effects on of the growth of probiotic bacteria strains in size, shape and concentrations used in current experiment (*unpublished data*);
- Nanocerium has strong potential **to modulate metabolism and oxidative stress in the host cells** including intestinal mucosa and beyond gut and to modulate probiotic activity;
- Biological effects to reduce cholesterol levels might effect on **development of favorable conditions for probiotic strains** in particular in the gut;
- The strongest effect of nanocerium was observed when introduced into the vein at a concentration of 0.01M CeO<sub>2</sub>; intravenous administration was more effective vs oral use;
- Effects of nanocerium are size-, shape-, pH-, concentration- and other parameters-dependent;
- Antibacterial activity of cerium oxide nanoparticles is strain-selective and size-dependent, depends on local environment, altering the pH;
- Interaction between nanoparticles and bacterial pili depends on pH;
- Nanocerium can promote growth of bacteria and cells.

The study was conducted with the support of the State Agency on Science, Innovations and Informatization of Ukraine.

*L. casei* IMV B-7280 resulted in the fastest cholesterol level decrease in both young and mature animals. Oral administration of CeO<sub>2</sub> applied alone reduced the number of microscopic fungi in the gut of mice and Gram-positive cocci (staphylococci and/or streptococci). Application of *L. casei* IMV B-7280 as a probiotic strain increased most significantly the number of lactobacilli and bifidobacteria in the gut of mice. The most significant normalization of gut microbiota was observed after oral administration of alternatively either *L. casei* IMV B-7280 + 0.1 M CeO<sub>2</sub> or *L. casei* IMV B-7280 + 0.01 M CeO<sub>2</sub>.

The presented results provide novel insights into mechanisms behind nutritional supplements and open new perspectives for application of probiotics combined with substances demonstrating prebiotic qualities benefiting, therefore, the host health. If validated in a large-scale clinical study, this approach might be instrumental for primary and secondary prevention in obese individual and patients diagnosed with diabetes. To this end, individualized prediction and treatments tailored to the person are strongly recommended to benefit the health condition.

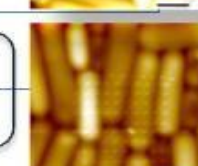
*Lactobacillus casei*  
IMB B-7280



*Lactobacillus acidophilus*  
IMB B-7279



*Bifidobacterium animalis*  
VKL



*Bifidobacterium animalis*  
VKB

