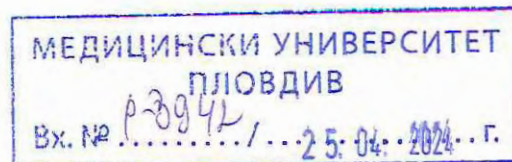


REVIEW



by Prof. Yoana Dimitrova Kiselova-Kaneva, PhD

Department of Biochemistry, Molecular Medicine and Nutrigenomics

Faculty of Pharmacy, Medical University "Prof. D-r Paraskev Stoyanov", Varna

Заличено на основание Чл. 5 ст. 6 "В" Регламент (ЕС) 2016/679

Member of scientific jury, defined with Order No P-1045/04.04.2024 r of the Rector of Medical University of Plovdiv

Subject: review in regard to awarding of the educational and research degree "Philosophy Doctor, PhD" to Maria Atanasova Choneva, PhD student and Professor Assistant at the Department of Medical Biochemistry, self-preparation form of PhD studentship that has been finalized with an Order No P-1021/01.04.2024 z. of the Rector of Medical University of Plovdiv

For this Review I was provided with a PhD thesis entitled "*Effects of prebiotic oligosaccharides and aerobic training on metabolic and behavioral impairments in an experimental model of type 1 diabetes*".

1. Biographical data and work experience

Maria Atanasova Choneva graduated with honors in Pharmacy in 2018 at the Medical University - Plovdiv, where she is currently specializing in Biochemistry at the Department of Medical Biochemistry, the Faculty of Pharmacy. In the period 2016-2019 she worked as a technician in "Protea 2000" pharmacy, and since 2020 she has been appointed as an professor assistant at the Department of Medical Biochemistry, the same university. As an professor assistant, Maria Choneva has been participating in teaching of biochemistry to students in "Medicine", "Dental Medicine" and "Pharmacy" courses, in Bulgarian and English, as well as in knowledge evaluation process during colloquia and exam sessions.

2. PhD thesis structure

Provided PhD thesis, entitled «*Effects of prebiotic oligosaccharides and aerobic training on metabolic and behavioral impairments in an experimental model of type 1 diabetes*» contains 147 pages, 26 illustrations and figures, and 4 tables. It is structured according to the established standards for such scientific work and contains the following sections: Introduction - 2 pages; Literature review - 33 pages; Aim and Tasks - 1 page; Materials and Methods – 16 pages; Results and Discussion – 54 pages; Conclusions - 2 pages and Contributions - 1 page. References are presented on 28 pages and the list contains a total of 307 citations. A list of frequently used abbreviations is provided, which is in favor of reading and orientation in the

PhD thesis. A list of research articles, noted citations and participation in conferences has been provided, as well.

3. Scientific relevance of the PhD thesis

The relevance of the topic of the PhD thesis is clearly emphasized by the data that the doctoral student herself indicates, citing sufficiently authoritative sources, namely: The World Health Organization - more than 400 million people or 7.3% of the world's population suffer from diabetes, as 10-15% of patients have type 1 diabetes (T1D); International Diabetes Federation - by 2021, approximately 537 million people in the elderly population (20- to 79-year-olds) suffer from diabetes, and the number is expected to increase to 783 million by 2045. The overall percentage annual increase in T1D cases in Europe and the world in recent years is about 3.4%, and the rate is expected to double in the next two decades.

The implementation of various strategies to control and reduce the complications of T1D are crucial for improving the quality of life of patients and reducing the social burden of the disease. Prebiotics as functional products are increasingly important as elements of supportive and complementary therapy in a number of pathologies, including the complex treatment of diabetic patients. Oligosaccharides are potential prebiotics with a proven positive effect on the composition and activity of the intestinal microbiome, improve glycemic control, lower intestinal permeability and modulate the immune and inflammatory response.

Lifestyle, with its variables, is also considered an important factor in the onset and course of T1D. Physical activity is a non-pharmacological approach to the control of diabetes and its complications. Sports and physical exercises improve the physical and mental condition of patients with diabetes, have a beneficial effect on weight and impaired metabolic function, improve muscle strength and endurance, respiratory function, pulse and heart activity. Aerobic exercise improves cognitive function as well as some psychiatric disorders such as depressive symptoms and anxiety in diabetic patients. Exercise is also thought to have a beneficial effect on the gut microbiome, increasing the number of beneficial bacterial species.

Having in mind abovementioned and as the PhD student herself justifies, it is clear that the study of the individual and combined action of prebiotic oligosaccharides and aerobic training in animal models of T1D would contribute to expanding our knowledge of their metabolic and physiological effects and of their potential for application in treatment and the prevention of diabetes and its complications.

4. Assessment of research rationale and literature review

This section is well structured and contains comprehensive information on type 1 diabetes mellitus (nature and epidemiology, diagnosis, environmental factors in the etiology of T1D, complications), gut microbiota (composition, microbiota-macroorganism interaction, role of gut microbiota in T1D), prebiotics (essence, intestinal metabolism and significance in T1D) and aerobic exercise (effect on immunity, intestinal metabolism, metabolic disorders and cognitive and behavioral disorders).

The section is excellently illustrated with summarizing figures and schemes. At the end of this section, a short and clear conclusion is provided, where the PhD student argues for the need to study the effects of prebiotic oligosaccharides and aerobic training on metabolic and behavioral disorders in an experimental model of T1D. From the conclusions made from the literature review, the aim and the tasks of the PhD thesis follow logically and are formulated briefly, clearly and precisely.

5. *Assessment of used materials and methods*

Description of materials and methods used is detailed and clear. Selected analytical techniques are informative and in accordance with the tasks set. Statistical processing of the obtained results was with appropriate methods. The section is well illustrated with relevant figures, diagrams and tables.

6. *Assessment of the results and discussion*

Results are described and discussed comprehensively. Figures and tables in this section are neat, clear and informative. At the end, there is a conclusion, which in a synthesized form presents the essence and the most significant results achieved in the course of the research.

In the conducted study, it was proven that administered galactooligosaccharides reduced blood sugar levels in rats with induced T1D. The effect of xylooligosaccharides is similar, but in healthy animals.

Aerobic training exerts a significant hypocholesterolemic effect in diabetic rats. Although less pronounced, the effect of administered prebiotics on blood cholesterol levels is similar. No significant effect of oligosaccharides and aerobic exercise on serum levels of triglycerides, HDL and lipoprotein a, Lp(a), nor of aerobic exercise on blood glucose levels was found.

Some markers of oxidative stress (malondialdehyde, MDA) in the blood of T1D rats were favorably affected by the administration of galacto- and xylooligosaccharides, while in healthy rats such an effect was achieved only by galactooligosaccharides. Here it is striking that the combination of xylooligosaccharides and aerobic training have a beneficial effect on serum MDA concentrations, while other indicators of oxidative stress appear not to be affected by the applied interventions – oligosaccharides and training alone or in combination.

Prebiotic supplementation and aerobic training also show beneficial effects on some neurological and behavioral indicators. For example, they reduce the degree of anxiety and have a positive effect on the locomotor activity of diabetic rats. The combination of prebiotics and exercise overcomes cognitive deficits by improving passive learning, short-term and long-term memory, as well as spatial and recognition memory.

Microbiological analyzes show preserved species diversity in the conditions of oligosaccharide therapy and aerobic training.

Based on the obtained results, the PhD student makes the conclusion that oligosaccharides and aerobic training would be a useful part of the complex strategy for the prevention and treatment of diabetes and its complications.

7. Assessment of the Conclusions and Contributions

Based on the data from the conducted research, PhD student has formulated 7 conclusions, corresponding to the set tasks and reflecting the actual data from the obtained results.

Contributions are divided into two categories – original contributions and of scientific-applied nature, thus emphasizing the importance of the dissertation work.

I accept thus presented conclusions and contributions of the PhD thesis.

8. Related to the PhD thesis research articles and participation in scientific forums

Scientific output of Maria Choneva corresponds to the quantitative and qualitative criteria for obtaining the PhD degree according to the Regulations for Academic Development at the MU-Plovdiv, namely:

- Availability of three research publications, two of which in journals indexed in Web of Science and/or Scopus;
- 30 points from research publications

In addition, research articles of Maria Choneva have been already cited, and the results of the research conducted have been reported in six scientific forums.

9. Research activity and training

Maria Choneva has active research activity, taking part in a number of scientific projects. She has been attending training courses with the aim to improve her expertise in the field.

10. Conclusion

This PhD thesis entitled “*Effects of prebiotic oligosaccharides and aerobic training on metabolic and behavioral impairments in an experimental model of type 1 diabetes*” that has been submitted to me for a Review is a completed scientific work on a relevant and important problem, and the data obtained are of immediate fundamental and applied importance for pharmacy and medicine.

As a Member of the Scientific Jury, determined with Order No P-1045/04.04.2024 of the Rector of the Medical University - Plovdiv, I state a definite **positive** opinion regarding awarding of the PhD degree to Maria Atanasova Choneva.

Заличено на основание
Чл.5 §1, б. "В" Регламент (ЕС)2016/679

22.04.2024 г.
Varna

Prepared:.....
(Prof. Yoana Dimitrova Kiselova-Kaneva, PhD)