US4.5. RAZVOJ I KLINIČKA VALIDACIJA PROBIOTIKA *LACTOBACILLUS HELVETICUS* BGRA43: INOVATIVNI PRISTUP ZA PODRŠKU TERAPIJI STEATOZE JETRE POVEZANE SA METABOLIČKOM DISFUNKCIJOM

K. Jončić Savić[1], A. Teofilović[2], M. Vratarić[2], B. Bursać[2], Lj. Gligorovska[2], D. Vojnović Milutinović[2], N. Stanisavljević[3], I. Strahinić[3], B. Pavlović[1], C. Aydogan[4], V. Godić[1], D. Pavlović[1], I. Božić Antić[5], D. Miletić[5], I. Jovanović[5], A. Đorđević[2]
[1]Phytonet d.o.o., Beograd, Srbija, [2]Institut za biološka istraživanja "Siniša Stanković"- Institut od nacionalnog značaja za Republiku Srbiju, Univerzitet u Beogradu, Beograd, Srbija, [3]Institut za molekularnu genetiku i genetičko inženjerstvo, Univerzitet u Beogradu, Beograd, Srbija, [4]Phytonet AG, Schindellegi-Feusisberg, Švajcarska, [5]Euromedik zdravstveni sistem, Beograd, Srbija

Steatoza jetre povezana sa metaboličkom disfunkcijom (MASLD) najčešća je hronična bolest jetre u svetu i usko je povezana sa metaboličkim poremećajima kao što su gojaznost, insulinska rezistencija i dislipidemija. Kako se njena učestalost stalno povećava, a trenutne strategije lečenja prvenstveno se zasnivaju na modifikaciji načina života, neophodno je razvijati nove pristupačne i naučno utemeljene intervencije.

Sve više dokaza ukazuje na disbiozu mikrobiote creva i oštećenu funkciju crevne barijere u patogenezi MASLD-a, pozicionirajući probiotike kao obećavajuće terapijske kandidate. Stoga smo istraživali efekte probiotskog soja *Lactobacillus helveticus* BGRA43 (LHBGRA43) u prekliničkom modelu gojaznosti izazvane ishranom. Oralna primena LHBGRA43 značajno je smanjila masu subkutanog masnog tkiva i potpuno sprečila steatozu jetre kod gojaznih miševa, što je potvrđeno histološkom analizom. Ovi efekti praćeni su smanjenom ekspresijom proteina SREBP-1c, transportera masnih kiselina CD36, enzima uključenih u sintezu ceramida i proinflamatornih markera. LHBGRA43 je takođe poboljšao integritet crevne barijere, što je potvrđeno povećanim nivoima proteina ZO-1, i povoljno uticao na sastav mikrobiote creva, uključujući smanjen odnos filuma *Firmicutes/Bacteroidota* i povećano prisustvo rodova *Alistipes*, *Acetatifactor* i *Odoribacter*, kao i smanjene koncentracije metabolita masnih kiselina razgranatog lanca.

Na osnovu ovih nalaza, razvili smo i komercijalizovali probiotičku formulaciju zasnovanu na LHBGRA43 namenjenu podršci lečenju MASLD-a. Translacioni put je napredovao od prekliničke validacije do postmarketinške randomizovane kontrolisane kliničke studije, koja je potvrdila korisne efekte kod pacijenata sa MASLD-om. Ovi nalazi podržavaju LHBGRA43 kao naučno validiran probiotički pristup za poboljšanje zdravlja jetre i nude rešenje za značajnu potrebu u lečenju metaboličkih bolesti.

Zahvalnica

Ovo istraživanje finansirano je kroz Projekat akceleracije inovacija i podsticanja rasta preduzetništva u Republici Srbiji (SAIGE), koji zajednički finansiraju Republika Srbija, Ministarstvo nauke, tehnološkog razvoja i inovacija, Svetska banka i Evropska unija.

US4.5. DEVELOPMENT AND CLINICAL VALIDATION OF LACTOBACILLUS HELVETICUS BGRA43: AN INNOVATIVE PROBIOTIC APPROACH FOR MASLD

K. Jončić Savić[1], A. Teofilović[2], M. Vratarić[2], B. Bursać[2], Lj. Gligorovska[2], D. Vojnović Milutinović[2], N. Stanisavljević[3], I. Strahinić[3], B. Pavlović[1], C. Aydogan[4], V. Godić[1], D. Pavlović[1], I. Božić Antić[5], D. Miletić[5], I. Jovanović[5], A. Đorđević[2]
[1]Phytonet d.o.o., Belgrade, Serbia, [2]Institute for Biological Research "Siniša Stanković"- National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia, [3]Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia, [4]Phytonet AG, Schindellegi-Feusisberg, Switzerland, [5]Euromedik Healthcare System, Belgrade, Serbia

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and is closely associated with metabolic disorders such as obesity, insulin resistance, and dyslipidemia. Its prevalence continues to increase, and current management strategies rely primarily on lifestyle modification, it is necessary to develop new affordable and scientifically based interventions.

Increasing evidence implicates gut microbiota dysbiosis and impaired intestinal barrier function in MASLD pathogenesis, positioning probiotics as promising therapeutic candidates. We investigated the effects of the probiotic strain *Lactobacillus helveticus* BGRA43 (LHBGRA43) in a preclinical diet-induced obesity model. Oral administration of LHBGRA43 significantly reduced subcutaneous adipose tissue mass and completely prevented hepatic steatosis in obese mice, as shown by histological analysis. These effects were accompanied by reduced expression of sterol regulatory element-binding protein-1c (SREBP-1c), the fatty acid transporter CD36, enzymes involved in ceramide synthesis, and pro-inflammatory markers. LHBGRA43 improved intestinal barrier integrity, as indicated by increased ZO-1 protein levels, and favorably modulated gut microbiota composition, including a reduced *Firmicutes/Bacteroidota* ratio, enrichment of the genera *Alistipes*, *Acetatifactor*, and *Odoribacter*, and decreased concentrations of branched-chain fatty acid metabolites.

Based on these findings, we developed and commercialized a probiotic formulation based on LHBGRA43 intended to support MASLD management. The translational pathway progressed from preclinical validation to a post-marketing randomized controlled clinical study, which confirmed beneficial effects in patients with MASLD. Collectively, these findings support LHBGRA43 as a scientifically validated probiotic approach for improving liver health and providing a novel strategy to address a recognized gap in current metabolic disease management.

Acknowledgement

This research was financed through the Project for Accelerating Innovations and Encouraging the Growth of Entrepreneurship in the Republic of Serbia (SAIGE), which is jointly financed by the Republic of Serbia, the Ministry of Science, Technology of Development and Innovation, the World Bank and the European Union.