DISCUSSION

The human gut microbiota is a dynamic system that is influenced by its host lifestyle, genetics and epigenetics. The human genome and gut microbiome networking within metabolic pathways directly influence both normal physiology and disease processes[29]. SPIs and galactooligosaccharides exhibit prebiotic effects, which have beneficial immune, metabolic and cognitive functions [23]. The short chain fatty acids (SCFAs) produced by the gut microbiota are known to inhibit class I Histone deacetylases (HDACs) and also activate the UCP2-AMPK-acetyl-CoA carboxylase (ACC) pathway with decreased *PPARγ* gene expression, thus resulting in decreased lipogenesis and increased AMP: ATP ratio. Latter induces AMP-activated protein kinase (AMPK) and sirtuins (SIRT) activation, having multiple beneficial effects on human health [23][30].

Improved digestion was reported by the participants after SIRTFOOD®SHOT supplementation. Kwon et al. investigated the effect of GM on defecation and concluded the increasing amount of *Bifidobacterium* is associated with increased stool frequency and better defecation [31]. This means increasing the amount of *Bifidobacterium*, which we observed after the active supplementation, might be helpful for people with obstipation.

Almost half of the participants from our study mentioned to feel healthier, having more energy, and better sleep after SIRTFOOD®SHOT treatment. Although, these results reflect subjective well-being, SPI and GM metabolites are known to exhibit anti-inflammatory, cardio- and neuroprotective properties and influence metabolism [23]. Via methoxyindole pathway, the gastrointestinal tract is responsible for 95% of bodies serotonin synthesis from dietary tryptophan and is transported via the blood-brain barrier [23]. Because microbial composition is individual, metabolism and health effect can differ within individuals. Due to their prebiotic effect and modulation of GM, SPI supports tryptophan synthesis, the precursor of serotonin [23]. SPI favor the growth of beneficial GM, like *Bifidobacterium*, which we observed after SIRTFOOD®SHOT treatment but not in the control [17]. *Bifidobacterium* acts probiotic and Tian et al. [32] reported serotonin enhancement via modulating tryptophan biosynthesis pathways after *Bifidobacterium* supplementation [33][32]. Additionally, GM and its metabolites influence the sleep duration and quality of its host by influencing clock gene expression. *Bifidobacterium* has been found to improve the subject's sleep, both factors increased in our study [34]. Short sleep and bad quality are associated with GM dysbalance and counteract age-related diseases and increased mortality [34].

GM and its modulation by SPI play an important role in mood and gut health. Nevertheless, the host body is a fine-tuning network of many factors and epigenetic mechanisms play an essential role in gene expression thus human health. Thus, participants self-reported better well-being and sleep, this might also be explained by the increased *miR16- 5p* expression in the SIRTFOOD®SHOT group compared to the placebo group. MiR16-5p can be modulated by SPIs [13][35] and regulates not only gut health by targeting claudin 2, which latter is predominantly expressed in leaky epithelia and upregulated in participants with bowel dysfunction [36]. Additionally, host miRNA can enter bacterial cells and regulate growth behavior and certain bacterial gene transcripts [37]. MiR16-5p, which decreases within age [38] is also an important regulator of the cell cycle, but also of serotonin thus regulating mood,

satiety and sleep, factors protective against depression, eating disorders, and aging [39].

SPIs also impact *miR34a- 5p,* involved in the regulation of senescence. Additionally, overexpression is known to silence *SIRT1* mRNA expression [40][41]. Obesity is associated with elevated miR34a -5p levels thus resulting in decreased SIRT1 expression. SIRT1 and SIRT3 enhance mitochondrial function, oxidative metabolism and counteract obesity [42]. Interestingly, the SIRTFOOD®SHOT group showed increased mitochondrial DNA amount compared to the control group. Weight loss (data not shown) was the same in both groups with an average -0.5 kg after three months, thus more studies are needed to investigate sirtuins counteract obesity via weight loss in humans.

SIRT can also be expressed in human gut epithelial cells. Khalili et al. [19] reported a significant increase of SIRT1 expression after probiotic supplementation with *Lactobacillus casei* in participants with type 2 diabetes [19]. The same connections were seen in our study. A higher amount of SIRT3 expressed were seen with increased amount of Actinobacteria, especially *Bifidobacterium*. All three biomarkers were elevated after SIRTFOOD®SHOT treatment but not with the placebo. Interestingly, Chen et al [43] demonstrate, mice lacking SIRT3 leads to gut dysbiosis, intestinal permeability and inflammation following a high fat diet [43]. Additionally, Natividad et al. [44] reported increased amount of *Bilophilia* after high fat diet in mice, contributing to intestinal barrier dysfunction, inflammation, and metabolic syndrome. After SIRTFOOD®SHOT supplementation, we saw lower *Bilophilia* amount correlated with *SIRT3* expression, implicating protective properties against metabolic syndrome.

Veillonellaceae increased in the active study population, but not in the control group. This specific group of microbiotas is known to metabolite lactate for energy production, a substrate contributing to fatigue during a physical performance and produced by *Bifidobacterium* [45][46]. Thus, an increase in the amount of *Veillonellaceae* may contribute to better physical performance, thus more energy, which the subjects reported. In addition, we observed a correlation between *Veillonellaceae* and MutL homolog 1 (MLH1). Latter belongs to DNA mismatch repairs and persons hypermethylated of one allele in *MLH1*, which contributes to lower *MLH1* expression, having a predisposition to developing colorectal cancer [47] [48].

Veillonellaceae contribute to hosts adaptive immune system. Gut microbial dysbiosis can release toxins that induce human DNA damage, concurring its mutability, tumor induction and progression in gastrointestinal cancer [49]. EGCG, the polyphenol of green tea can reverse DNA damage [48]. Moreover, SPI can modulate the abundance of *Veillonellaceae* [50]

SIRTs are mostly known for their longevity related properties, which are all protecting against the hallmarks of aging [51][52] [4]. Based on this knowledge SIRTS are getting more attention to slowing down skin aging processes and develop cosmetics including natural STATs, although bioavailability and skin permeability are restricting factors for use of many potential active substances [25].

Premature skin aging is manifested by accelerated induction of wrinkling, scaling, roughness, dryness, laxity, and hyperpigmentation. After SIRTFOOD®SHOT supplementation up to 10% of the participants reported improved skin appearance, less dryness, finer pores and fewer wrinkles [53]. Even

here the tight network between SPI, GM and Skin aging needs to be highlighted, thus an imbalance in GM leads to dermatological manifestations [54]. This communication is not only via the skin gut axis but also more directly via metastasis of GM and their metabolites in cases of disrupted intestinal barriers, which can be detected in patients' bloodstream [55] [29]. Besides being antioxidative and prebiotic, SPIs protect against skin aging via several mechanisms, including via SIRT activating, thus reducing inflammation and limit oxidative damage in tissues via SIRT3/SOD pathway in the mitochondria [56]. Additionally, SPI, like EGCG and resveratrol inhibit the collagen degradation enzyme MMP1, leading to wrinkles and tyrosinase, which leads to Hyperpigmentation [53][25].

More than one-third of the active gup reported faster hair and nail growth. Kubo et al. investigated the effect of several polyphenols regarding hair growth in mice. The results show resveratrol and fisetin as the strongest compound promoting hair growth mainly keeping hair follicles in the anagen phase via telomerase reverse transcription[57]. Several other studies investigated the hair growth potential of SPI, like cyanidins or EGCG [58][59] [60].

Many polyphenol-rich botanicals are considered to be adaptogenic: stress-modifying phytochemicals that increase organisms' nonspecific resistance to stress by increasing their ability to adapt and survive to external stressors and stimuli.

Thus, being one of the first studies investigating the possibility of SIRT activation by a combination of SPI and GOS in human and some outcomes reflect subjective wellbeing via FFQ this study needs to be considered as a pilot study and further interventions would be interesting to prove causality regarding specific mechanisms for a specific aspect.

CONCLUSION

Microbial dysbiosis or SIRT depletion leading to different pathologies, namely e.g. obesity, Alzheimer disease, Cancer, Diabetes type 2, Liver stenosis, depression, skin diseases. The results of the study demonstrating a broad range of beneficial effects in humans by supplementing a synergistic combination of prebiotics. Secondary plant ingredients not only elevate SIRT expression, it modulates gut microbiota and improved subjective wellbeing.

List of Abbreviation: SIRTs: sirtuins, STACs: sirtuin-activating compounds, SPI: secondary plant ingredients, mtDNA: mitochondrial DNA, NAD+: nicotinamide adenine dinucleotide, HDAC: histone deacetylases, AMP: adenosine monophosphate, ATP: adenosine triphosphate, NAMPT: nicotinamide phosphoribosyltransferase, miRNA: micro RNAs, GM: gut microbiota, SCFAs: short chain fatty acids, SD: standard deviation, MLH1: MutL homolog 1**Author Contributions:** S.L., A.H designed the research. S.L., H.B., C.S., conducted the research. S.L., H.B, T.D., A.M and B.H. performed clinical analysis. S.L., H.B., C.S. performed statistical analyses. S.L., A.P and A.H. wrote the manuscript. A.H. had primary responsibility for the final content. All authors read and approved the final version of the manuscript.

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence their work in this paper.

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