

Lactobacillus Tritherapy for Cholesterol and Heart Diseases

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Short Commentary

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Abbreviations: Bifido: Bifidobacterium; CH: Cholesterol; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoproteins; L: Lactobacillus; LAB: Lactic-Acid Bacteria; TG: Triglycerides.

SUMMARY

In this research note, we discuss about the idea of using a *Lactobacillus* (L.) cocktail, previously tested in mice, as therapy in hyperlipidemia and obesity conditions in human.

The research note gives new information to the research community, i.e. the cocktail works at tri-therapy, while single bacterial strain treatments are inefficient [1]. Ingestion of probiotic Lactic-acid bacteria (LAB) has been reported to reduce serum cholesterol and many LABs have been suggested as natural candidates for the prevention and treatment of hypercholesterolemia. Our hypothesis is that tritherapy using *L. acidophilus*, *L. casei* and *L. plantarum* works at enhancing beneficial gut flora thereby reducing weight gain, accumulation of fat in tissue, cholesterolemia and lipid blood concentration. In our view, this provides a very promising basis for development of new multi-strain probiotics for heart diseases.

SYNOPSIS

Modern life has led to new food habits (fast food) rather incompatible with human health when used on a daily manner. As generations of all ages become more and more sedentary for work and living, developing habits to fatty food can certainly increase the risk of cardiovascular problems due to overweight gain, high lipid blood concentration and bad cholesterolemia. It is well known that having high blood cholesterol concentration puts organisms at very high risk of central nervous system and heart disease, arteriosclerosis, thrombosis and other vascular problems, the main cause of man and woman death for instance in the US [2,3].

The problem is that most treatment against metabolic diseases (obesity, hyperlipidemia and diabetes) involves drugs, i.e. Simvastatin-like chemicals, which can eventually generate even more deleterious effects than the obese, hyperlipidemic and/or diabetic conditions. Simvastatin (Zocor) is known for many side effects from muscle breakdown to fatigue, diarrhea, memory loss and neuropathy [4]. It is also known that Simvastatin responses and/or responses to any other various drug medications used to control blood cholesterol levels can be influenced by the bacteria that reside in our gut (gut flora) [5]. It is therefore expected that the modulation of gut flora will be particularly helpful to circumvent the problems related to statin drugs [6,7]. Completely new alternative medication to statin drug for hyperlipidemia and/or high cholesterolemia is seriously mandatory for women during pregnancy due to the potential teratogenic effects of the chemical [8,9]. Additionally, application of Simvastatin in treatment of hyperlipidemia can significantly alter the composition of the gut flora as found for antibiotics [10-12], urging to use natural bio-products rather than drugs for human health. It is well established now that obesity seriously alters gut micro-flora (or micro-biome) and is associated with gut microbiome with increased energy harvest from diet [13-15]. If the microbiome can

change rapidly over fat diet intake and/or Simvastatin treatment already negatively impacting health, there is a need to maintain the microbiome including a large amount of beneficial healthful good bacteria to undertake efficient treatment in obese and/or overweight hyperlipidemic patients [16].

Hence, current modern medicinal research about obesity and hypercholesterolemia should favor probiotics in order to develop new efficient curative and preventive strategies against heart diseases and other pathologies related to lipid metabolism. Bio-product drug co-treatments are eventually used as medication. It is expected that certain bio-products will help restore the gut flora altered by statin treatments [17,18]. However, efforts should be made to completely avoid the use of drug chemical such as Simvastatin and replace it by a new type of medicine or treatment therapeutically beneficial without any side effects in cholesterol and obesity control. *Lactobacillus* (L.) and *bifidobacterium* are two of these shy (hidden in the gut) naturally-occurring products already used for treating and preventing infectious types of diarrhea in children, while eventually also used in adults to prevent and treat diarrhea associated with antibiotics intake [19,20]. Thus, Lactic-acid bacteria (LABs) are traditionally seen not only as very beneficial for the balance and maintenance of microbial flora in the intestinal tract, but also as growth and health stimulator by enhancing for instance production of bacteriocins, vitamins, antimicrobial substances and immunological defenses [21-23]. However, although *L.* and *Bifido* are traditionally accepted as natural remedies to various human pathologies by targeting multiple physiological systems, it is still rather debatable whether they are both "scientifically" effective.

The mode of action of LABs is yet to be well characterized indeed, and is rather difficult to study due to the natural aversion of patients for the ingestion of bacterial syrups, pills or stains. This puts a break on the use of probiotics for human health, even as food complement, and on the basic research required to understand how these probiotics have so much beneficial effects on systems as diverse as the digestive and immunological tracts. A yield gap and potential medicinal growth could come from using animal systems as appropriate alternative study models. *Lactobacillus* is largely used in industrial animal farming from birds to cattle due to these numerous curative properties on the indigenous micro-flora [24-27]. However, variability such as weight gain or weight loss over specific *Lactobacillus* treatment usually depends on the animal species and/or the therapeutic *L.* strain in use. While some potential therapeutic effects of *L.* strain such as *L. rhamnosus* have been shown for weight control [28], it could be that other specific *L.* treatments lead to increase gain weight as described not only in birds but also in ruminants, pigs and human [29-32]. It could also be that a bacterial strain beneficial for one species is particularly noxious when used in human or another organism; this may also depend on the bacterial strain and the host individual [32]. The other problem could come from the viability and survival of *L.* bacteria as additive in commercial food products or directly as medicinal potion [33]. By selecting the best way of delivery by oral and/or intestinal ingestion, there should be the guarantee that the potion is efficiently taken up into the digestive tract. By choosing the correct *L.* medications and methods to use them, there should be the potential that the same potion is reliable enough in stimulating beneficial gut flora and thereby health recovery. This leaves a challenge up to us, i.e. to find appropriate LAB or *L.* probiotics for human physiology and then develop the optimal combination of probiotics together with any ingredient that will promote their growth in the intestines (prebiotics). The final mixture (synbiotic) should be the relevant alternative to the growing aversion of patients for drug intake.

CURRENT RESULTS AND PERSPECTIVES

After setting up results in scientific animal models such as lagomorphs or rodents, many further studies are required before to apply a list of candidate synbiotics in practical clinical applications for human health. However, an increasing number of data obtained in rabbits and rats are in favor with the development of specific microbial medicine and/or the optimal combination of various probiotic treatments in obesity and hyperlipidemia [34,35]. This combines with gut microbiota research in mice that allow an in-depth study of the role and functioning of gut flora together with its association with fatty acid-related diseases [36]. Interestingly, in mice, we did not observe any body weight gain or lipid accumulation phenomenon using a mixed composition of *L. acidophilus*, *L. casei* and *L. plantarum* for bio-cocktail product. We observed instead that the healthy mice treated with fat diet complemented with *L.* in step 1 (genesis of hyperlipidemia in mice models) did not gain so much weight and that the hyperlipidemic overweight ill mice finally treated with *L.* in step 2 (healthcare treatment of hyperlipidemic mice models) lost weight in a significant manner, particularly in epididymal and perirenal fat pads. Epididymal and perirenal fat pads both increased over Simvastatin treatment [1]. Using this tri-*Lactobacillus* cocktail (*L. acidophilus*, *L. casei* and *L. plantarum*) is also shown to have strong beneficial effects on cholesterol, triglycerides, HDL and LDL concentration in the blood in addition to anti-oxidant effects, suggesting that it could be a very potent alternative medicine to Simvastatin drugs in various lipid metabolism pathologies (**Figure 1A**).

Finally, analyzing separate effects of the chemical drug Simvastatin and the three *Lactobacillus* mixed-strains in experimental hyperlipidemic mice models shows that Simvastatin intake yields to a completely different fecal bacterial profile compared to control samples from healthy mice and/or mice treated with *L.*, further arguing for the use of *Lactobacillus* syrups rather than Simvastatin tablets in treatment of heart and cardiovascular diseases, in which plaques of cholesterol form in the artery walls thereby constricting blood circulation [1]. **Figure 1** presented in this research note summarizes the valuable information about the effects of our *L.* tritherapy on cholesterol, lipid metabolism and the gut microbiota in mice. Obesity and fat accumulation in human is associated with specific phylum-shift in gut microbiota [37-39]. Applying 3-*L.* in diet-induced hyperlipidemic mice lower CH, HDL/LDL ratio and TG concentration via a phylum-wide shift between Bacteroidetes and Firmicutes as found in genetic ob/ob obese mice (**Figure 1B**) [1 & in preparation, 40]. The molecular effects of such phylum-shift in the mouse gut remain to be investigated. We propose to translate this highly promising basic science research in mouse microbiology into clinical medicinal applications and develop the future for engineering of three specific *L.* strains for biosafety of human health.

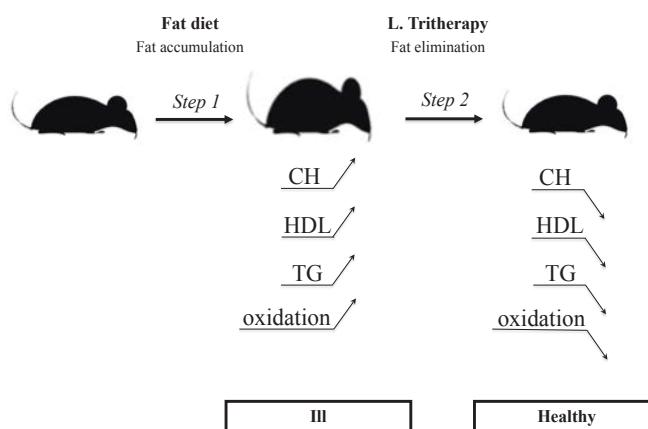
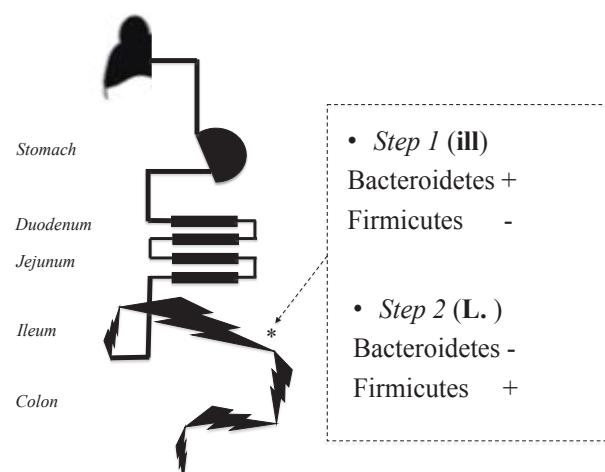
A.**B.**

Figure 1. Beneficial effects of *L. tritherapy* in mice. (A) Metabolic effects. Step 1: Development of hyperlipidemic mice models by constant fat diet intake. Cholesterol (CH), high-density lipoproteins (HDL), triglycerides (TG) and oxidative agents levels increased in overweight mice, leading to specific illness status. Step 2: Addition of *Lactobacillus* cocktail (L.) during diet intake. L. significantly reduced CH, HDL, TG and oxidative agents levels, leading to much more healthy conditions [1]. L. : *Lactobacillus acidophilus SD65 + L. casei SD07 + L. plantarum SD02* (10^9 CFU/ml). Treatment: 0.3 ml of L. administered intra-gastrically. **(B) Effects on gut flora.** Schematic of the mouse digestive tract with the different organs from stomach to large intestine. Through Illumina sequencing, key differences between ill overweight mice and mice subjected to L. tritherapy (*acidophilus + casei + plantarum*) were found in the composition of the gut flora, particularly in amounts of key Bacteroidetes and Firmicutes classes of bacteria mainly abundant in the colon (*). This suggests a beneficial medicinal effect of L. tritherapy on lipid metabolism through main phylum-shift in colon microbiota (Yue et al., in preparation).

CONCLUSION

We discuss about the need to test a specific *L. acidophilus*, *L. casei* and *L. plantarum* three-strain *L.* cocktail developed on hyperlipidemic mouse model system in human health. From the number of beneficial results in mice, it can be expected that such microbial cocktail has also very positive effects in human, particularly on cholesterol and lipid metabolism, via the stimulation of the gut micro-flora. The *L. tritherapy* described here may represent a powerful tool not only as food complement, but also as natural bio-medicinal product against sugar, atherosclerosis and coronary artery diseases.

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