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Locally sourced probiotics, the next opportunity for developing countries?

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We describe factors promoting the exploration of locally sourced probiotics, targeting local populations to balance human needs and market opportunities. This would be particularly beneficial for people in developing countries, who generally lack access to affordable probiotics and are often exposed to poor hygiene conditions, toxic compounds, malnutrition, and chronic enteric infections.

Probiotics on the world market

The world market for probiotics was worth USD 27.9 billion in 2011 and is expected to reach USD 44.9 billion in 2018 [1]. Since the late 1980s the market has been dominated by only a few probiotic bacteria, including the well-known *Lactobacillus rhamnosus* GG, *Lactobacillus casei* Shirota, and *Bifidobacterium animalis* lactis (BB12). Although probiotic products are globally marketed, and their benefits are generally claimed for people of different genders, race, age, geographic location, and health status, access to these products is often limited to people from more-developed countries who can afford to buy the premium probiotic products.

We contend that five factors will direct the development of, and increase accessibility to, a new generation of so-called locally sourced probiotics (Figure 1). These microbes will especially be beneficial for people in developing countries who generally have limited buying power and restricted access to probiotic products, but are often exposed to poor hygiene conditions, toxic compounds, malnutrition, and chronic enteric infections [2]. The described opportunities could justify and stimulate further funding for research around locally sourced probiotics.

Differences in composition of gut microbiota of people from different geographical regions

The first results derived from Human Microbiome Project [3], the Metagenomics of the Human Intestinal Tract (MetaHIT) [4], and the Asian Microbiome Project [5] indicate not only commonalities but also differences in the composition of gut microbiota of people of different ages, regions, and dietary habits. For instance, plant-based diets favored *Prevotella*, whereas animal- and dairy-based diets increased the relative abundance of *Bacteroides* and *Bifidobacterium* [6]. In addition, a study on the intestinal microbiota of adults from the Amazonas of Venezuela, rural Malawi, and US metropolitan areas illustrated that the major changes in the intestinal microbiota occur in the first 3 years of life [6]. This study also indicated a substantial average loss in microbial diversity of $\sim$25% in the US, possibly as a result of westernization and associated use of antibiotics. In addition, probiotic bacteria and those of the gut have different levels of persistence and can compete for receptor sites, necessitating 'reseeding' strategies when using a few well-defined probiotics for improving the stability and resilience of the human gut microbiota [7–9]. In this context, we wonder to what extent the interaction between a probiotic bacterium and the predominant species of the microbiota would consistently deliver the proclaimed health benefits. Furthermore, based on a study with children from rural areas in Burkina Faso, it was concluded that a diet high in fiber and carbohydrates selects for a highly-diverse gut microbiome that is protective against infection and inflammation, and extracts maximum energy from the low-calorie food [10]. This would support the use of a consortium of isolates from this intestinal microbiota for restoration of a healthy microbiome of children in this African setting, for example after antibiotic treatment. Alternatively, one could check the probiotic functionality of lactic acid bacteria isolated from indigenous fermented plant foods that were part of the children's diet, and then encourage the consumption of traditional foods [11]. Although both approaches will initially require significant resources, the subsequent delivery of the beneficial microbes via fermented foods will be less complex, as indicated below.

Specific nutritional and health requirements in different geographic regions

The impact of a claimed probiotic benefit will also depend on the health status and nutritional requirements of local populations, which vary according to lifestyle, diet, and genetic make-up. For instance, a probiotic benefit such as alleviation of lactose intolerance by virtue of the activity of the lactase enzyme is more relevant for lactose-intolerant Asian people compared to lactose-tolerant European people. In addition, the delivery of vitamins by, for example, particular lactobacilli or lactococci to the host – including

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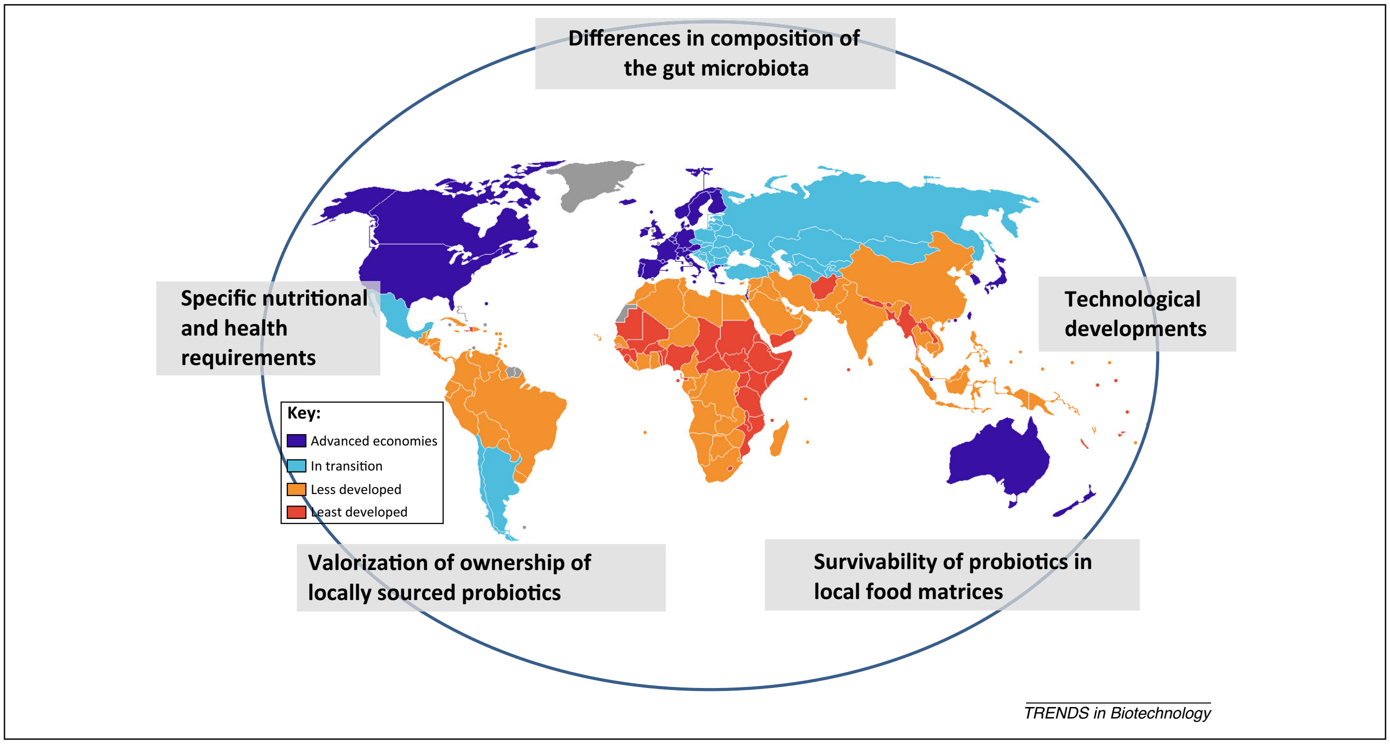

Figure 1. Five factors enhancing the development of, and access to, a new generation of locally sourced probiotics particularly benefiting subpopulations in the developing world. Source of map: International Monetary Fund 2009, in Wikimedia Commons, the free media repository.

folic acid (vitamin B11), riboflavin (vitamin B2), and cobalamin (vitamin B12) [12] – and breakdown of non-nutritive factors such as phytic acid, which inhibits the absorption of iron, are expected to be more relevant for people in developing countries or for the elderly. A more serious unmet medical need for which probiotics can be applied in developing countries is prevention of diarrhea or necrotizing enterocolitis, which occur most frequently in Africa and Asia, among children and preterm infants [13].

In addition, the risk of exposure via dietary intake to environmental toxins, such as heavy metals or aflatoxins, is a global health problem that is more pronounced in particular regions of developing countries. These compounds are highly toxic, causing human hepatic and extrahepatic cancers. Studies with lactic acid bacteria and yeasts as the most familiar probiotics have shown that toxin binding and detoxification takes place, and that the negative consequences of toxin contamination in foods and feed can be neutralized [14]. Another example refers to a bifidobacterium, recently isolated from the gut of a Kenyan infant, which had a high level of siderophores and the capacity to take up iron (P. Vazquez Gutierrez, PhD Thesis, ETH Zürich, 2015). The same researchers are now testing if such a strain could be used to counteract adverse effects observed in the gut microbiome, such as increased pathogen abundance [23].

Survivability in local food matrices

New or potential probiotic strains are often screened for their ability to remain viable over their shelf-life and survive passage through the GI tract, which includes exposure to low pH and bile salts. In this context, the importance of the diet has been reported as a factor to increase survival of probiotic lactobacilli in acidic environments [15]. Moreover, foods and beverages from Asia, Africa, or Southern America are often characterized by the presence of herbs and spices with antibacterial properties, such as *Capsicum annuum* (red pepper), *Allium sativum* (garlic), and tea [16,17]. Hence, it might be argued that potential beneficial microbes, when isolated from locally fermented foods, would be more resistant to particular spices and herbs, and have an advantage over other currently available probiotics in terms of stability, viability, and ultimately functionality after consumption.

Valorization of ownership of locally sourced probiotics

Today the access to affordable probiotics for resource-poor communities is limited, with the exception of locally produced generic probiotic strains [18]. There has been increasing insight into the mechanisms underlying probiotic functionalities, and the diversity, stability and resilience of the human gut microbiota are increasingly important. Therefore, the very diverse microbiome of people in developing countries offers them a unique source of beneficial microbes that may no longer be available in more-westernized populations [9]. Similarly, the prevalence of many traditional fermented food products in Southern America, Africa, and Asia offers a rich source of potential probiotic strains. For instance, *L. casei* LC2W has been isolated from a traditionally fermented dairy product from Inner Mongolia and is promoted as a probiotic strain that can produce antihypertensive exopolysaccharides (EPSs) [19]. Another example is the consumption of fermented millet-derived koko sour water containing live lactic acid bacteria, which was associated with greater reported well-being among children from Ghana [11].

The aforementioned rich sources of potential probiotics offer further opportunities for local entrepreneurs to develop locally adapted and affordable healthy food. Local organizations might also be in a better position to promote local solutions to nourishment, health maintenance, and restoration rather than relying on probiotic products from foreign companies, especially if these products are not part of the normal diet or are too expensive in a developing country. Similarly, the locally sourced probiotics could be used as complementary products to further stimulate emerging sectors such as the dairy sector in East African countries. Another opportunity is the use of probiotic lactic acid bacteria as starter cultures to reduce food waste that frequently occurs as a result of spoilage during uncontrolled food fermentations. All of the above developments could benefit from sustainable partnerships with specialized western companies, academic institutions, and/or nongovernmental organizations.

Technological developments

The further exploration of metagenomics and metatranscriptomics can stimulate the development of a new generation of probiotics, not only for developing countries but also for more-developed countries. These technologies will increase insight into the human microbiome and how the gut ecosystem contributes to human physiology; consequently, its modulation may help to maintain health and reduce disease risk. This knowledge will further contribute to setting a standard for selection of a next generation of probiotics consisting not only of lactic acid bacteria but also species such as Clostridia clusters IV, XIVa, and XVIII, *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Bacteroides uniformis* [20].

Up to now, the production and marketing of probiotics has been relatively expensive, mainly due to the need to confirm the functionality of probiotics in randomized clinical trials. For locally sourced probiotics efficacy and safety studies will remain essential. However, we expect a decrease in the relative costs of such studies. In terms of safety, when the strains are isolated from fermented foods with a safe history of use, this can cut costs. In terms of efficacy, costs can be saved by capitalizing on the growing insights into the mechanism of action of probiotics, metagenome analyses, and the development of validated biomarkers. Such biomarkers have been discovered for the production of vitamins, short-chain fatty acids, the presence of enzymatic activities such as phytase or lactase, antimicrobial properties towards locally existing undesired microorganisms, anti-inflammatory profile, H_2O_2 production, binding to mucus, and the ability to degrade particular carbohydrates from local diets [21].

From a technical point of view, we do not expect high barriers to entry because the production of health-promoting strains via fermented food is neither too complicated nor too expensive. The strains can be cultivated (i.e., be grown at limited cost) in locally fermented foods on broadly-available food raw materials such cereals, soybean, fruit, vegetables, milk, meat, or marine products [11].

Concluding remarks and future perspectives

Further insights into the microbiome composition of different people from different regions (characterized by having different diets and lifestyles), and a growing understanding of host–microbe interactions will synergize with local regional needs and entrepreneurship. We expect that this combination of factors will stimulate the development of specific locally sourced probiotics and increase access to healthy probiotic food, including traditionally fermented foods. We also expect that the prevalence of using current well-known probiotics will increase, especially when the mechanisms of probiotic functionality are likely to act independently from the composition of the gut microbiota for instance when using probiotics as vehicles for delivering active enzymes.

Furthermore, the five factors described in this paper could provide a justification for governments and health authorities to finance further research into the identification of new probiotics from local sources for local populations and install an appropriate infrastructure supporting economic development. Exposing the populations of developing countries to both the business- and health-promoting opportunities of locally sourced probiotic fermented food then offers a valuable, healthy, and affordable alternative to popular westernized fast food [22].

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