

Probiotics as a Food Supplement: What are they and how do they Work?

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Introduction

Humans encounter numerous stress-inducing situations throughout life, which can contribute to the onset of various health conditions, including metabolic syndrome, obesity, diabetes, and even cancer (Fig. 1). Consequently, contemporary science is actively exploring alternative approaches to enhance individuals' quality of life and preempt the onset of these ailments. One such avenue presently under exploration involves the incorporation of probiotics.

requirement of either preventing or alleviating specific health issues in individuals. As a result, there is now a diverse range of probiotic microorganisms available on the market that have been employed for the prevention conditions such as obesity, diabetes, irritable bowel syndrome, colitis, Crohn's disease, and more (Fig. 2) (Hill et al., 2014).

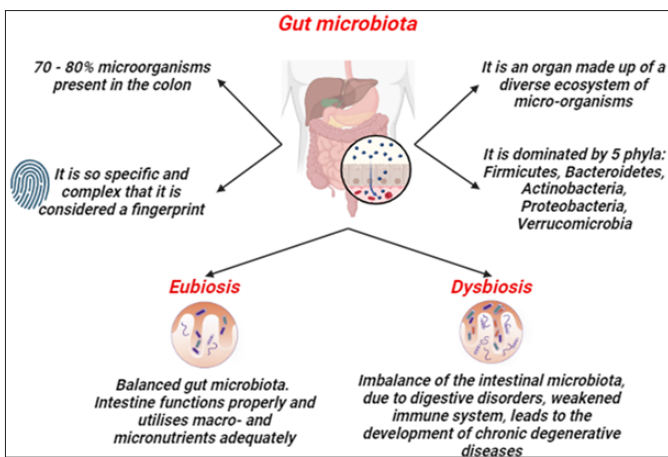


Figure 1: The significance of the gut microbiota. Created in BioRender.com

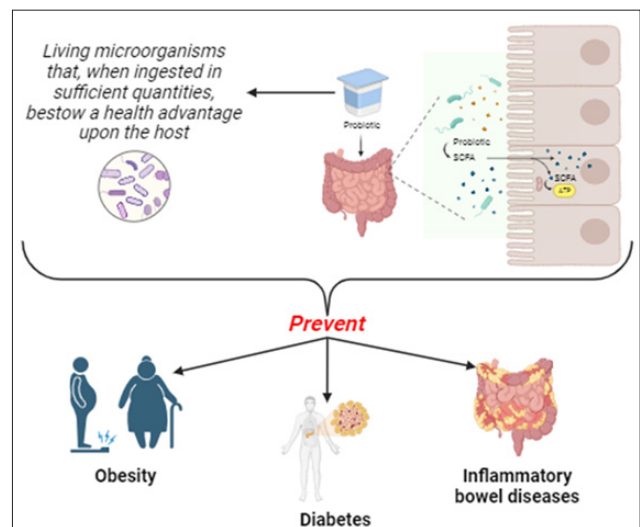


Figure 2: Benefits of probiotic consumption. Created in BioRender.com

Probiotics are living microorganisms that, when consumed in sufficient quantities, provide advantages to the host, ranging from safeguarding the integrity of the intestinal barrier to averting chronic degenerative diseases. These microorganisms have been isolated from diverse origins, including non-lactic fermented foods like infant feces and colostrum. The FAO and WHO have established criteria that a microorganism must meet to fulfill the requirements for potential probiotic status (Hill et al., 2014). Within the set criteria, it should meet the

Probiotics and Obesity

In recent times, there have been significant alterations in lifestyle habits, and at times, these changes have had a negative impact on individuals' well-being. Consequently, severe conditions like obesity have become more prevalent. Over the past decade, obesity has garnered global attention as its prevalence has noticeably surged, defying effective control measures, and is now recognized as a 21st-century pandemic.

Obesity is acknowledged as a significant health concern because of its rising incidence and its link to concurrent health conditions like type 2 diabetes, fatty liver, and cardiovascular disease that impact the wider population. This condition stems from an imbalance between the consumption of calories and the expenditure of energy, resulting in the accumulation of body fat and weight gain (Kobyliak et al., 2016; Lee et al., 2006). One of the factors involved in the development of obesity is the gut microbiota, as it exerts its influence on the metabolic and immune functions of the host. Obesity has been linked to an elevation in Firmicutes and a reduction in Bacteroidetes (Ley et al., 2006). Elevating the Firmicutes/Bacteroidetes ratio in obese mice has been shown to stimulate the expansion of adipocytes as an adaptive reaction to fat storage. Multiple studies have unveiled the connection between gut microbiota and obesity. Investigations involving the colonization of the intestines of germ-free animals with bacteria from the Firmicutes phylum have indicated an uptick in the expression of liver enzymes related to the de novo synthesis of fatty acids, including acetyl-CoA carboxylase and fatty acid synthase. Additionally, they noted elevations in the transcription factors ChREBP and SREBP-1, which play roles in the hepatic response to insulin and glucose, particularly in relation to lipogenesis (de Graaf et al., 2007).

Further research has demonstrated the involvement of the gut microbiota in regulating the balance of glucose and lipids, as well as various metabolic functions (Geurts et al., 2011; Ley et al., 2005).

The established advantages of manipulating the gut microbiota have sparked significant interest in the advancement of probiotics over the years, with the aim of enhancing or averting specific health conditions, including their potential as an option to combat obesity. Additional research has highlighted their positive impact on the immune system, as probiotics possess the capacity to influence the expression of pro-inflammatory cytokines like TNF- $\alpha$  and stimulate the production of anti-inflammatory cytokines such as IL-10 (Fig. 3) (Christensen et al., 2002).

In recent times, the gut microbiota has come to be recognized as an integral component contributing to an individual's physiological diversity and the regulation of gene expression across various pathways related to nutritional metabolism. The application of probiotics has been adopted to deliberately influence the gut microbiota, with the objective of assisting the host in averting metabolic and immunological disturbances linked to obesity (de La Serre et al., 2010). Hence, over the past few years, there has been a surge in research efforts directed toward identifying probiotic strains that possess advantageous qualities for averting obesity and diseases associated with it. Probiotics are living microorganisms that, when ingested in sufficient quantities, offer health benefits to the host. The majority of probiotic bacteria are members of the lactic acid bacteria (LAB) category, such as lactobacilli, which have a notable role in preserving the intestinal environment and bolstering the host's immune system (Saarela et al., 2002).

Numerous in vitro characteristics, including traits like adhesion, resilience in gastrointestinal environments, antimicrobial capabilities, and more, are typically assessed to determine the suitability of a chosen strain as a probiotic (FAO/WHO, 2002). Probiotic bacteria have been harnessed as a viable alternative in various therapeutic approaches for diverse conditions, underscoring their role in preventing metabolic and immune-related ailments linked to obesity (Castro-Rodríguez, Juárez-Pilares, et al., 2020; Castro-Rodríguez, Reyes-Castro, et al., 2020; Gauffin Cano et al., 2012).

Probiotics from the *Lactobacillus* and *Bifidobacterium* genera have attracted considerable attention because of their diverse range of advantageous functions, including addressing gastrointestinal issues, influencing the immune system, and alleviating lactose intolerance, among other benefits. Recent research has identified novel probiotic bacteria with health-enhancing properties from unconventional origins (Argyri et al., 2013; Castro-Rodríguez et al., 2015). One of these sources is the mead derived from *Agave salmiana*, a Mexican plant known as maguey pulquero that belongs to the *Agavaceae* family. This plant is utilized in the production of pulque, a traditional Mexican drink obtained through the fermentation of its sweet sap, which is known as aguamiel (Moreno-Vilet et al., 2014). The fermentation process involves a consortium of microorganisms, encompassing both yeasts and bacteria. *Zymomonas mobilis* is responsible for the production of alcohol in pulque, while the bacterium *Leuconostoc mesenteroides* is the key contributor to the production of the exopolysaccharide that lends viscosity to the beverage (Castro-Rodríguez et al., 2019; Escalante et al., 2004).

Consequently, probiotics have been introduced with the objective of adjusting the gut microbiota to assist the host in mitigating or managing metabolic and immunological disturbances linked to obesity. In recent times, there has been a growing emphasis on research endeavors aimed at identifying strains with health-enhancing attributes in the human context. Nevertheless, studies conducted with experimental animals remain significant, as they offer a higher degree of experimental control and offer valuable insights into the underlying mechanisms of this process.

### Probiotics and Diabetes

Diabetes is a complex metabolic condition influenced by a combination of genetic factors, environmental variables, and behavioral modification (Gomes et al., 2014). The condition is marked by persistent high blood sugar levels attributed to a combination of insulin resistance and inadequate insulin production resulting from dysfunction in pancreatic beta cells. Over the recent years, there has been a focus on investigating emerging risk factors like inflammatory markers, gut microbiota, and oxidative stress to comprehend the diverse mechanisms contributing to the onset of this condition (Gomes et al., 2014).

Diet plays a crucial role in altering the composition of the gut microbiota. An abundance of certain dietary elements can

induce metabolic shifts in the bacteria within the microbiota, including saturated and polyunsaturated fatty acids, while a deficiency of oligosaccharides and phytochemicals can have similar effects (Tao et al., 2020). These metabolic alterations in bacteria have a substantial impact on an individual's well-being. When there's a disruption in intestinal microbiota balance, it can lead to heightened intestinal permeability and an enhanced mucosal immune response, factors that could potentially play a role in the onset of diabetes (Samah et al., 2016). The rise in intestinal permeability arises from a reduction in the production of tight junction proteins, which, in turn, promotes the translocation of lipopolysaccharide (LPS), potentially resulting in metabolic endotoxemia and insulin resistance. The release of LPS triggers an inflammatory response by activating Toll-like receptors (TLRs), which serve as a crucial component of the innate immune system. It's worth noting that TLRs can also activate adaptive immunity when the release of LPS induces the secretion of inflammatory cytokines (Bagarolli et al., 2017).

Another mechanism through which the microbiota is linked to the progression of diabetes-related complications involves cellular oxidative stress, which results from elevated glucose levels. Oxidative stress represents an imbalance between free radicals and the body's antioxidant defenses, resulting in an escalation of reactive oxygen species (ROS) across various tissues and cells. As the release of ROS intensifies, the levels of superoxide dismutase (SOD), an enzyme responsible for breaking down ROS, decrease. The activity of this antioxidant enzyme diminishes as the duration of the disease increases (Pegah et al., 2021).

Diabetes also brings about alterations in the regulation of the hormone known as glucagon-like peptide-1 (GLP-1) (Pegah et al., 2021). This hormone holds great significance in the management of diabetes. GLP-1 is released by enteroendocrine L-cells located in the gastrointestinal tract (specifically, the ileum and colon) in response to digestion. It plays a crucial role in regulating post-meal glucose levels, which refers to the monitoring of sugar levels in the bloodstream after a meal (Müller et al., 2019). GLP-1 prevents the programmed cell death of beta cells ( $\beta$ -cells), consequently boosting insulin production. Moreover, it fosters the transformation of immature islet progenitor cells into mature beta cells (Johansen et al., 2005). GLP-1 additionally delays the emptying of the stomach, curbs appetite, and ultimately results in weight reduction. It has been documented to mitigate oxidative stress and inflammation while also demonstrating advantageous effects on cognitive functions like learning and memory.

The utilization of beneficial microorganisms, such as probiotics, serves as a preventive measure against the onset of diabetes. They achieve this by enhancing insulin sensitivity and fostering a healthier gut environment through the promotion of beneficial bacteria growth. Furthermore, probiotics contribute to the reduction of inflammatory markers and oxidative stress (Pegah et al., 2021). Prior research has documented positive outcomes associated with *Bifidobacteria* and *Lactobacillus*

strains in managing elevated blood sugar levels, oxidative stress, and inflammation. These bacterial strains exhibit the capacity to mitigate endotoxemia and encourage the release of short-chain fatty acids (with a primary emphasis on butyrate, acetate, and propionate). These particular strains are engaged in the secretion of gastrointestinal hormones, the preservation of gastrointestinal equilibrium, the regulation of epithelial cell growth and differentiation, as well as the synthesis of specific vitamins (Kocsis et al., 2020).

The mentioned factors collectively establish an ideal setting for the effective operation of the digestive system, thereby thwarting the onset of diabetes. In clinical investigations, the application of *L. acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12 notably decreased fasting blood glucose levels while elevating the performance of antioxidant enzymes (Rezazadeh et al., 2019). Experiments conducted on mice that were placed on a high-fat diet and developed type 2 diabetes demonstrated that *Lactobacillus casei* CCFM419 effectively reduced insulin resistance and high blood sugar levels (Li et al., 2017). In a separate investigation involving rats on a high fructose diet, the introduction of *Lactobacillus reuteri* GMNL-263 led to enhanced insulin sensitivity and a reduction in the development of hepatic steatosis (Hsieh et al., 2013). As previously discussed, probiotics have the potential to avert the onset of diabetes and consequently bestow advantageous impacts upon the host (Fig. 3).

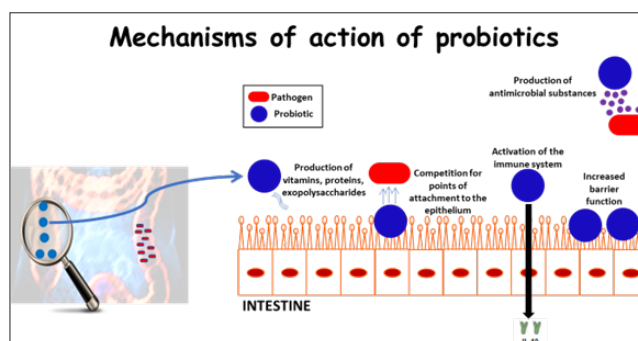


Figure 3: Effects of probiotic consumption.

### Probiotics and fetal programming

The overall well-being of expectant and breastfeeding women holds significant importance in a nation's progress. A mother's nutritional status has a bearing on her newborn's birth weight, which, in turn, can have lasting health consequences into adulthood. Insufficient nutrition during crucial developmental phases such as pregnancy and lactation has been linked to heightened oxidative stress, a factor implicated in the development of various diseases and developmental issues. Epidemiological studies have provided evidence that imbalanced maternal nutrition can influence the metabolism and microbiota composition in both the mother and her offspring. Consequently, the periods of pregnancy and lactation present opportune moments for adopting lifestyle changes that could mitigate adverse effects on both the mother and the child. One such change involves the incorporation of probiotics, microorganisms known for enhancing the protective functions of the digestive tract, thereby contributing to the amelioration



of metabolic and immunological irregularities associated with malnutrition.

The physiology and metabolic processes of fetuses and neonates are susceptible to modifications that occur during pivotal developmental stages like gestation and lactation, subsequently influencing the long-term health of the individual. This gives rise to the notion of “developmental programming,” which has evolved into the concept of the “Developmental Origins of Health and Disease (DoHaD).” It posits that deviations during development can trigger a lasting physiological adaptation in the fetus, ultimately culminating in adult-onset diseases (Zambrano et al., 2013). The foundation of the DoHaD concept lies in epidemiological research linking birth weight to the occurrence of cardiovascular and metabolic disorders (Aerts et al., 2003). Furthermore, in animal models, instances of malnutrition, obesity, excessive caloric intake, or exposure to hormonal agents like glucocorticoids during pregnancy increase the susceptibility of offspring to experiencing an array of physiological, metabolic, reproductive, and behavioral disorders (Reyes-Castro et al., 2012).

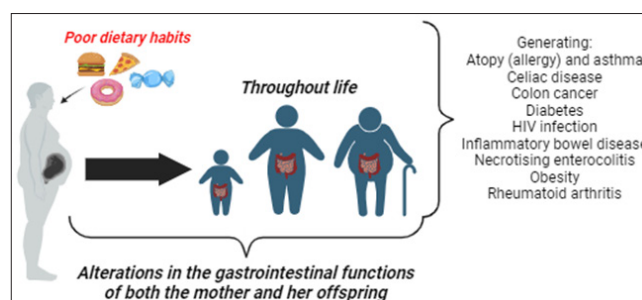
Inadequate nutrition during the initial phases of development, which encompass both gestation and lactation, correlates with heightened oxidative stress, a factor implicated in the onset of various ailments and developmental anomalies. The detrimental consequences of maternal malnutrition during pregnancy and lactation on the progeny encompass metabolic syndrome traits like insulin resistance, elevated blood sugar levels, augmented inflammatory responses, increased oxidative stress, alterations in gut microbiota, hypertension in adulthood, and reproductive issues, which can impact the fertility of male offspring (Barker et al., 1993; Fichorova et al., 2011).

The gut microbiota serves a pivotal function in preserving well-being over the course of one’s life. It begins to take shape gradually after birth and is subject to a multitude of influences, including the method of delivery, antibiotic usage, and the diet of the mother. In the initial days of life, infants undergo a rapid colonization by various bacteria, which are attributed to kickstarting the body’s defense mechanisms and fostering sound physical and immunological development (Sanz et al., 2009).

The colonization of the neonate’s gastrointestinal tract takes place through various means, including the placenta, amniotic fluid, the birth canal, and breastfeeding. These pathways play a pivotal role in establishing either a healthy or disrupted microbiota, which can subsequently give rise to various health conditions. A number of investigations have indicated that maternal immune cells and bacteria originating from the mother’s intestinal tract are capable of traversing the placenta and influencing immune responses in the developing fetus (Desai et al., 1995; Rautava et al., 2012). Moreover, research has revealed the distinctiveness of the microbiota in the mammary gland, which contains beneficial bacteria that reach the gland through an internal pathway and are subsequently passed on to the newborn during the onset of lactation. This

transmission establishes protective elements that will influence the offspring’s future well-being (Desai et al., 1995).

Numerous investigations have indicated that the dietary choices of mothers during lactation can lead to alterations in the gastrointestinal functions of both the mother and her offspring (Burdett et al., 1979; Craft, 1970; Gopalakrishna et al., 2020; Johnson et al., 2019; P. Liu et al., 2016). Consequently, the gastrointestinal system is recognized as a crucial element in the programming process (Fig. 4).



**Figure 4:** Effect of poor maternal programming on the development of the gastrointestinal system. Created in BioRender.com

While pregnancy represents a period when susceptibility to disease predisposition in postnatal life is heightened, it also offers a chance to introduce interventions aimed at enhancing the health of both the mother and, consequently, her offspring. Nowadays, women are increasingly attuned to the connection between nutrition and well-being, which has spurred the development of functional foods. These encompass a diverse range of substances used as ingredients in food or as nutritional supplements. Among the most prominently marketed are probiotics, which play a role in regulating early host-microbe interactions. Probiotic microorganisms have found application as an alternative in numerous therapeutic approaches for various conditions, most notably in the prevention of metabolic and immunological disorders resulting from malnutrition (Esposito et al., 2009; Gauffin Cano et al., 2012; Kaburagi et al., 2007; Million et al., 2017).

Throughout the duration of pregnancy, there is a shifting microbial diversity in the gut, and this alteration can have repercussions on the maturation and performance of the gastrointestinal system in both the mother and her offspring (Angelakis et al., 2012; Rautava et al., 2012). Research involving 91 pregnant women revealed that the makeup and arrangement of the gut microbiota undergo significant transformations throughout the course of pregnancy. These alterations persist from the early stages, extending through to the third trimester. The study’s findings suggested that the gut microbiota can influence metabolism in either a positive or negative manner, contingent on the dietary choices of the pregnant individuals (Koren et al., 2012). During pregnancy, daily probiotic intake may reduce the risk of pre-eclampsia (Brantsæter et al., 2011), maintaining serum insulin concentrations (Asemi et al., 2013) and reduce the frequency of gestational diabetes mellitus (Luoto et al., 2010). While

breastfeeding, probiotics play a role in initiating the formation of the newborn's microbiota, enhance the integrity of the intestinal barrier by decreasing permeability, and aid in the maturation of the infant's immune system (Donnet-Hughes et al., 2010; Matsuzaki et al., 2000). Probiotics have served as a supplementary therapy for reinstating a healthy microbiota in women with good health. In cases of vaginal infections, they also offer a more potent substitute for antibiotics and have proven effective in preventing subacute and subclinical mastitis (Fernández et al., 2014; M.-B. Liu et al., 2013).

## Conclusion

From the points mentioned earlier, we can draw the conclusion that our dietary choices have a significant impact on our health and can be the root cause of severe health issues. Consequently, the use of dietary supplements, including probiotics, has garnered substantial attention due to their numerous advantages. Nevertheless, it's crucial to gain a clear understanding of the mechanisms through which these microorganisms deliver their beneficial effects to the host.

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