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Review Article

PROBIOTICS AND ITS HEALTH BENEFITS: A REVIEW

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ABSTRACT

Probiotics have become widely known as supplements for humans and animals and has positive effects on health. The key objective of this review is providing information about probiotic criteria of selection and medical applications of probiotics in the food industry. Lactic acid bacteria and bifidobacterium are widely used probiotic strains isolated from dairy and non-diary sources like cereal crops. The key step in selection and characterization of isolates is based on selection criteria for any probable probiotic microorganism, including acid and bile tolerance, adherence to mucus and epithelial cells of the intestine, and antimicrobial activity by producing antimicrobial substances. Further probiotic properties such as cytotoxic effect against oncogenes, cholesterol reduction, antioxidant activity is considered as a requirement for probiotic strain selection. Nowadays studies confirmed probiotics role in cancer and allergy treatment, fighting obesity and improving the immune system. As far as consumer's safety is concerned, there is a need to go through the appropriate quality and technological procedures before releasing the probiotics to the market.

Keywords: LAB, probiotics, safety, selection.

INTRODUCTION

The word 'probiotics' was coined by Lilly and Stillwell (1965) to describe growth factors produced by microorganisms. Probiotic is a Greek word, meaning 'pro-life', which is used to describe microorganisms and other useful substances with health benefits on humans and animals by altering the microflora in the intestine (Parker, 1974). The term 'substances' is ambiguous and even antibiotics would be included; therefore 'probiotic' is described as a viable microorganism feed that benefits the host by enhancing microbial balance in the intestine. This is a universally accepted definition, and it's a common understanding that probiotics are related to living microorganisms (Fuller, 1989). The current definition could be considered as 'a probiotic is either mono or mixed culture of live microorganisms that are important for humans and animals, which foster host's general health and well-being by enhancing the properties of the indigenous microflora. As per the newly-introduced description, 'probiotic' is limited to products containing live microorganisms, can have its effect in the mouth or gastrointestinal tract and improve the health status of the host (Havenaar and Huis, 1992). Most probiotic microorganisms belong to the LAB and Bifidobacteria. Lactobacillus species are the most commonly utilized group of microorganisms for their potential beneficiary properties as probiotic from within the group of LAB. Bacteria antagonistic activity is confirmed by inhibiting a broad spectrum of enteric and urinary pathogenic bacteria (Hooper and Macpherson, 2010).

Source of probiotics

Numerous microbial species inhabit our ecosystem, some are essential for the normal physiological function and few of them are pathogenic. Probiotic bacteria produce various compounds that are inhibitory to the growth of the enteric pathogen. Bacteriocin and reuterin are the well-studied substances produced by probiotic LAB which lowers the pH creating unfavorable conditions and thereby affecting the growth of the pathogen (Ahmed and Kanwal, 2004). Lactic acid bacteria are Gram-positive, rods or cocci with a G+C content of DNA usually below 50% and non-spore forming. They are strictly fermentative, aciduric or acidophilic, aero-tolerant or anaerobic and have wide range of nutritional requirements (e.g. carbohydrates, amino acids, peptides, fatty acid esters, salts, nucleic acid derivatives, and vitamins).

It has been estimated that the number of microorganisms inhabiting the GIT exceeds 10^{14}, majorly belong to the Bacteria domain. Recent information about studies of the Human Microbiome Project reported more than 2000 species originated from human, divided into twelve distinct phyla groups. Approximately 90% of all bacterial species belong to two divisions: Bacteroidetes and firmicutes (Zielińska *et al.*,2018). Most of the probiotic strains, are isolated from the human intestine (Ren *et al.*, 2014), and also from feces, such as *B. longum* and *L. acidophilus*, and rarely from the gastro intestinal tract of human such as *L. fermentum*, *L. gasseri*, *L.vaginalis*, *L. reuteri*, and *L. salivarius* (Ryan *et al.*, 2008). The common prerequisite of probiotics should endure gastrointestinal transit upon consumption

and always colonize the intestines for the advantage of the host (Sanders, 2011). It has been assumed that probiotics originating from the intestines of humans and animals have unique capacities for adhesion than probiotics found in food sources. Intestinal isolates generally have more adhesion capacity than isolates of the food source (Bunešová *et al.,* 2012). Many probiotic foods commercially available are focused on milk, but today's consumer preference lay more with plant-based dietary supplements with minimal cholesterol content. The aforementioned study is illustrated by previous studies in the American probiotic product market. Consumer need continues to rely on dietary supplements from botanical origin as compared to food fortification such as nutraceuticals. There is a wide range of popular non-dairy fermented beverages produced worldwide. Non-dairy probiotic drinks can be made from different raw materials, including fruits, vegetables, cereals and legumes (Wedajo, 2015). Cereal crops are the main source of protein, carbohydrates, nutrients and mineral. They also serves as source of indigestible carbohydrates, which help to induce the growth of lactobacilli and Bifidobacterium which exist in the colon. Cereals contain water-soluble fiber (such as β-glucan and arabinoxylan), oligosaccharides (such as galacto and fructo oligosaccharides) and starch (Shah, 2000).

Action mechanism of probiotics

Previous probiotic strain data suggest four ways of possible action: antimicrobial production, adhesion receptor competition, nutrient competition, and immune stimulation (Fuller *et al.,*1992). The main probiotic mode of action are listed in figure 1.

Production of antimicrobial substances

The ability of probiotic bacteria to prevent pathogen growth is due to the synthesis of antibacterial substances such as lactic acid, peroxide, bacteriocin and bacteriocin-like inhibitors.

Competition for adhesion receptors

Studies reveal intestinal pathogens need to adhere to the wall of the intestine and colonize the gut to cause disease. Probiotic strains are commonly selected due to their ability to attach to the epithelial wall and thus compete for attachment sites (Ljungh and Wadström, 2006).

Competition for nutrients

Gastrointestinal tract is serving as a source of nutrients by which many pathogenic and enteric bacteria compete for nutrient consumption, however, it was studied that bacteria require only one limiting nutrient to make this mechanism operation successfully (Ljungh and Wadström, 2006). Probiotics exclude various pathogenic enteric species in the competition for nutrients.

Stimulation of immunity

Human intestinal microflora plays a key role in the immune system. It has been found in recent years that probiotic lactobacilli can induce macrophage activity against several pathogenic bacterial species.

Requirements of probiotics

A successful probiotic product requires a proper description of the bacterial species. This is important because so many recent reports have shown that bacterial species recovered from probiotic products is not always correlate to the label on the product (Gueimonde and Salminen, 2006). Probiotic has to fulfill several key properties based on the purpose for which the probiotic is being

used and where this particular property has to be expressed. Besides, a range of other, basic characteristic requirements has to be met by the probiotic product.

Tolerance to gastrointestinal conditions

Probiotic bacteria viability along the GIT is considered as a requirement for ensuring their maximum functionality. Such bacteria have to pass two major biological challenges, the acidic and bile salt secreted in the duodenum after ingestion.The secretion of gastric acid and passage through the gut is the main defense mechanism that must be tackled by all ingested microorganisms, including probiotics (Gueimonde and Salminen, 2006). Probiotic microorganisms are mainly screened for their acid and bile resistance to ensure their viability during the passage through the gastrointestinal tract. The effect of acid and bile on the viability of probiotics has been investigated and LAB have different level of tolerance (Fuller *et al.*,1992). The lack of standard procedures for determining gastrointestinal resistance makes comparison difficult. Generally, tolerance to gastrointestinal conditions serves as a bench mark for probiotic selection. Different methodologies, such as stress adaptation mechanisms of probiotic bacteria, are being evaluated as possible technique to enhance their acid and bile resistance (Collado *et al.*,2005).

Adherence

Adherence to the intestinal mucosa is mostly essential factor in choosing probiotic strains. It may raise probiotic survival time in the gastrointestinal tract and frequent contact between bacteria and epithelial cells of intestine. Highly adhesive strains including *Bifidobacterium* and *L. rhamnosusis* are efficient in the prevention of acute infant diarrhea (Saavedra *et al.,* 1994). An essential criterion for evaluating probiotic bacteria is adherence to the host intestine, which would allow contact between bacteria and the host to provide health benefits. The tendency to anchor to intestinal mucosa is an essential requirement for occupancy of probiotic in the intestinal tract, avoiding their eventual expulsion by peristalsis and offering advantage in the GIT.

Aggregation

Aggregation is a process of temporary accumulation of cells that enables probiotic strains to precipitate spontaneously in the medium in which they are suspended. Autoaggregation involves clumping of bacteria belonging to the same strain, while co-aggregation results from cell-to-cell identification of two distinct bacterial strains. Auto-aggregation is associated with anchoring to intestinal epithelial cells, recognized as a requirement for colonization and enhancing gastrointestinal system stability (Janković *et al.,* 2012). Even though it's normal, the mechanism of auto-aggregation is widely debated in many cases. The autoaggregation phenotype may be triggered under certain conditions, such as pressure, oxygen scarcity or temperature change. Autoaggregation and co-aggregation potential is key screening criterion for probiotics selection (Reuben *et al.,* 2020). The development of autoaggregation can also play a role in defending the host immune system against enteric pathogenic bacteria (Trunk *et al.,* 2018).

Production of antimicrobial compounds

Probiotic strains like LAB produce organic acids, essential antimicrobial substances, because of their fermentative me-

tabolism. They produce commonly used antimicrobial compounds and have proved to be a safe option for food preservation. Probiotic LAB produces antimicrobial substances such as hydrogen-peroxide, diacetyl and bacteriocin. Bacteriocin play an antimicrobial role by suppressing the growth of pathogenic microorganisms. Bacteriocins may be considered as antibiotics, but they differ from antibiotics in a number of significant ways such as bacteriocins are ribosomally synthesized and their action of mechanism is not similar to antibiotics. They have a narrow bactericidal range and are thus usually only capable of killing bacteria closely related to the producing strain (Mills, 2004). H_2O_2 production and bacteriocins (antimicrobial peptides) has a significant role in the competitive exclusion of probiotic strains. H_2O_2 produced by some of the LAB strains prevents *Staphylococcus aureus* and Pseudomonas species effectively. In the upper part of the GIT (mouth) where oxygen is available, hydrogen peroxide is highly effective. H_2O_2 has a significant oxidizing effect on membrane lipids, sulfhydryl groups and bacterial cell in general (Dicks and Botes, 2010).

Antimicrobial activity

Probiotics have strategies to survive in competitive advantage with many other microorganisms in the complex GIT ecosystem. The anti-bacterial activity is due to competition for nutrients and space, but also by the production of aforementioned antimicrobials. The viability and the antimicrobial activity assigned to the production of substances such as organic acids, ethanol, H_2O_2, or bacteriocin-like protein materials. The overall pattern indicates several compounds and pathways that are taking part in the interrelationship between probiotics and pathogens.

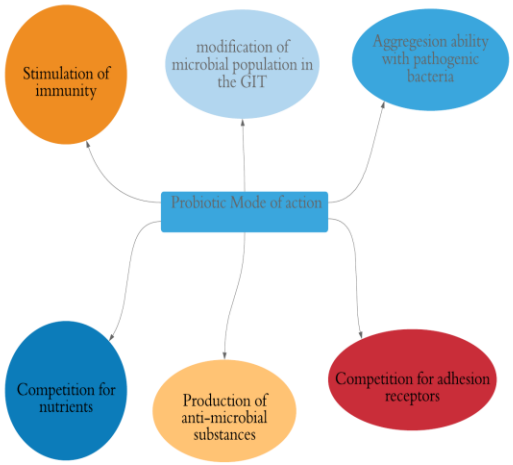

Fig. 1: Probiotics mode of action

Probiotics in medicine

There is increasing evidence that supports reports of beneficial impact attributed to probiotics, including improved bowel health, enhanced immune response, lowered serum cholesterol, and cancer prevention. Even if the availability of significant evidence to confirm probiotics application in treatment of antibody-associated diarrhea prevention, improvement of lactose tolerance, and acute diarrheal diseases, there is no substantial verification to prescribe medical conditions (Kechagia *et al.*, 2013). In double-blind, a placebo-controlled study for infants, acute diarrhea prevention has been reported. Probiotic bifidobacterium with *Streptococcus thermophiles* and *L. rhamnosus GG* were confirmed in preventing nosocomial diarrhea. *B. lactis, L. reuteri, and L. rhamnosus GG* were also studied as preventive therapy by lowering the frequency of acute diarrhea (Vanderhoof and

Young, 2004). Probiotics strain *L. rhamnosus* confirmed to have antibacterial activity against oral bacteria such as *S. mutans* and *P. gingivallis*. The inhibitory effect of *L. rhamnosus* is not yet elucidated, but it may be due to the production of bacteriocin (Angarita-Díaz *et al.,* 2020).

Probiotics has a significant role in extending food's shelf life due to the antimicrobial substances produced by LAB and bifidobacterium species. Nowadays, many food products like fermented milk products, yogurts, and buttermilk incorporate probiotic strains. Non-dairy food includes soy products, nutrition bars, cereals and a range of juices are suitable ways of delivering probiotics (Ewe *et al.,* 2010).

Lactose beta-galactosidase deficiency which is determined genetically that causes inability to hydrolyze lactose into its monomers: glucose and galactose. Individuals with lactose intolerance experience diarrhea, abdominal discomfort, and flatulence from dairy or milk products consumption. Probiotic strains *S. thermophilus* and *L. delbrueckii* are effective probiotic species with high galactosidase activity able to overcome lactose intolerance. Even though some individuals respond positively to a probiotic supplement, it should be prescribed by physicians as a treatment alternative (Vrese *et al.,* 2018). When lactose intolerant people consume probiotic products, the milk lactose would be assimilated and calcium absorption would also be facilitated. *Lactobacillus* in the probiotic's product produces lactase which is essential for the metabolism of lactose. It's possible to help our body hydrolyses lactose by consuming probiotic containing *L. acidophilus* and *L. casei*). Therefore, these bacteria can improve consumer's lactose tolerance for milk consumption (Tiwari *et al.,* 2012). Current evidence indicates that earlier time-life exposure to bacteria may possess a therapeutic role against allergy, and probiotics can provide a safe alternative microbial stimulus required for infants to build their immune system. A small number of strains in the treatment and prevention in infants have been tested for their efficiency against allergy. Recent studies reveal, *L. rhamnosus GG* to be efficient in preventing the occurrence of atopic eczema in high-risk infants *(*Kirjavainen *et al.,* 2001).

Immune system and probiotics

The microbes in gastrointestinal tract plays an essential role in keeping host's defense ability from pathogenic microorganisms and non-viable substances. Immunocompetent cells are reported to be activated in the gut and relocated to mucosal areas like urogenital tract and respiratory areas. Gut-associated lymph tissue (GALT) has also a significant role in fostering the immune system. Probiotic strains also favor the production of either suppressor or helper cells and stimulate lymphocyte differentiation (Havenaar and Huis, 1992). Probiotics have a major role in establishing and maintaining balance between necessary and excessive mechanisms of defense including innate and adaptive immune responses. In other study, *L. reuteri* RC-14 produce two active compounds, cyclic dipeptides cyclo (L-Tyr-L-Pro) and cyclo (L-Phe-L-Pro) cyclic which inhibit Staphylococcal quorum-sensing, which in turn lock the transcription of toxin-1 toxic shock syndrome in *S. aureus* MN8, which cuase toxic shock syndrome. The intestine has diversified lymphocytes

found under the mucous membrane of the intestine. The intestine must be able to efficiently protect the body due to its direct contact with external pathogens capable of triggering infections. It plays a vital role in human immunity. The natural bacterial flora of an individual has a contribution to the immune response through the intestinal epithelial cells and mucous membranes (Tiwari *et al.,* 2012). Recent studies reveal probiotic *L. plantarum* CBT LP3 had an anti-colitic effect *via* T helper cell modulation and goblet cell restoration in addition to suppression of inflammatory cytokines (Kim *et al.,* 2020).

Cancer and probiotics

According to the previous studies, cancer is a serious health threat for 8.2 million deaths and 14 million new cases reported in 2012. As per WHO report, over 70% of global deaths from cancer are from Asia, Africa, and the Americas. In recent years, organic sources with anti-carcinogenic effect such as probiotics, have obtained primary attention (Gayathri *et al.,* 2016). Probiotic bacteria was found to be an anti-cancer effect, hence recently become an important area of research. The underlying reason for their anti-cancer effects varied, including microbial suppression involved in early development of mutagens and carcinogens, an adjustment in the metabolism of carcinogens, and keeping DNA from oxide damage, as well as regulation of immune system (Motevaseli *et al.*, 2017). These have gained great interest from medical nutritionists, experts and manufacturers to work together to develop an effective drug with little or no side effects (Vafaeie, 2016). Studies showed probiotic strains, *L. fermentum* NCIMB-5221 and -8829, are incredibly excellent in destroying cancer cells from colon and rectum by producing ferulic acid. Even though *in-vitro* efficiency of probiotics in suppressing cancer is confirmed, further *in-vivo* studies need to demonstrated (George Kerry *et al.,* 2018). Recent studies both *in vitro* and *in vivo* reveals significant role of probiotics in preventing breast cancer by suppressing cell proliferation and apoptosis induction. In another study, probiotic strain *L. reuteri* found inhibiting the early stage of carcinogenesis in mice. *In vivo* study showed that intake of diary product fermented with *Lactobacillus helveticus* R389 enhance IL10 and decrease IL6 levels in mammary cell of mice which in turn inhibit breast tumor cells (Eslami-S *et al.,* 2020). Most recent research findings confirm probiotics potential to control gastrointestinal malignances (Shamekhi *et al.,* 2020).

Allergy and probiotics

Allergy is very common health problem worldwide which affects millions of people every year. Ongoing researches on probiotics reveal their role in protecting and managing allergic diseases. *In-vitro* studies reveal that probiotic *L. plantarum* L67 is an effective in preventing allergy-associated disorders due to interleukin-12 and interferon-γ production in their host (Song *et al.,* 2016). It is presumed that the colonizing microbes are important to orchestration of a strong immune response. Recent studies on countries with a high allergic prevalence condition has shown a difference in colonizing organisms compared to those from countries with low prevalence, with a reduction in lactobacilli, bifidobacteria and enterococci, on the contrary a rise in clostridia and *S. aureus.* It has also been proven that

distribution of species of colonizing LAB can be correlated with allergy (Harata *et al.*, 2018). IgE is active in mediating most allergic diseases. The secretion of IgE is initiated by Th_2 cells and their cytokines, such as IL-4 and IL-5, while IFN-γ secreted by Th_1 cells suppresses the response of Th_2 cells and can hinder the production IgE production. IgA is an important antibody in intestinal mucosal immunity and IgM and IgG are the major serum antibodies that prevent pathogenic microorganisms from emerging in the host. It's already stated that *B. breve* YIT4064 stimulated the humoral immune system and increased the development of IgG anti-rotavirus or IgG anti-influenza virus. Several studies confirm the role of probiotics in treating allergies (Hajavi *et al.*, 2019; Wang *et al.*, 2020).

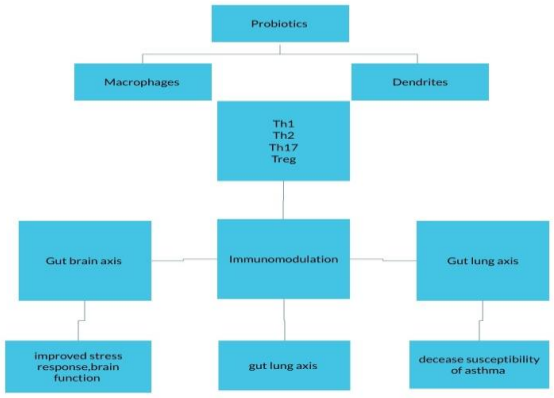

Fig. 2: Probiotic and allergy

Probiotics and central nervous system

GIT microbiota colonization effect on GIT is well studied in previous researches, as well as their effect on gastrointestinal diseases. Besides, several studies conducted in recent times to elucidate the effect of gut microbiota on the central nervous system (CNS). The impact of probiotic strains on the CNS was documented in trials from clinical perspective where it was evident that the role of intestinal microbiota influences the development of the human brain. Interactions between the microbiota and the brain are likely to begin in early development. Basically, fetus is considered as microbial free during its development in the uterus. Nevertheless, evidence indicates that bacteria may transmit from maternal to fetal through the amniotic fluid or umbilical cord blood. The connection between gastrointestinal and psychological symptoms is complex and not well revealed yet. Normal microflora has key role both in peripheral and central nervous system. Some probiotic strains of intestinal bacteria produce and secrete neurotransmitters, including biologically active substances such as GABA, serotonin, catecholamines and histamine (Tillisch, 2014). Seaweed containing medium cultured with *L. brevis* BJ20 found enriched with neuroactive amino acids (Oleskin and Shenderov, 2019). Gut microbiota play crucial role in the brain through the synthesis of neurotransmitters such as GABA, glutamate (Glu), serotonin (5-HT), DA, NE, histamine and acetylcholine (Ach). Even though gut derived neurotransmitters are functionally different from brain derived neuro transmitters, gut microbiota regulate the bioavailability of precursors of neurotransmitters. Probiotic genus like lactobacillus are confirmed to produce various types of neurotransmitters *in vitro* (Yong *et al.*, 2020).

Probiotics and obesity

An irregular or unhealthy accumulation of fat (obesity), which deteriorate health is associated with increased energy availa-

bility, greater control of ambient temperature, and sedentariness contributing to an imbalance in energy intake and expenditure (Kobyliak *et al.,* 2016). Probiotics can regulate host's physiological activity by altering the nature of microbes in the gastrointestinal tract. In most cases, thermogenic and lipolytic responses stimulate weight loss by activating the sympathetic nervous system. Probiotic strains of *L. casei, L. gasseri BNR 17, L. acidophilus* and *B. longum* exhibit inhibition of adipocyte tissue that are the main source of leptin and adiponectin (Karimi *et al.,* 2015). Probiotics stimulate adrenergic nervous system which in turn facilitate weight loss by thermogenic as well as lipolytic response. Certain probiotic species such as *L. reuteri* CRL1098 confirmed to lower cholesterol level in hypercholesterolemic conditions and downregulating triglycerides concentration. Current studies also reveal that *L. reuteri* CRL1098 play a role in reducing the proportion of high-density lipoprotein (HDL) to low density lipoprotein (LDL) without microflora translocation (Deepali *et al.,* 2019). Latest studies conducted on obese mice with high fat and high fructose diet (HFFD, predicts probiotic species of *L. rhamnosus LS*-8 and *L. crustorum* MN047 reduce inflammatory response by adjusting mRNA expression (Daniali *et al.,* 2020).

Safety of probiotic

It is important to make sure the probiotic strains are safe and healthy for human consumption before market release. Probiotic strains like Lactobacillus, Bifidobacterium and Streptococcus are confirmed safe and labeled as GRAS. However, some studies associate LAB with medical conditions such as bacteremia and endocarditis (Lara-Villoslada *et al.,* 2007). The European Food Safety Authority (EFSA) established the QPS (Qualified Presumption of Safety) standard as a guideline for the safety control of microorganisms used in food products. U.S.A has a GRAS standard to control microbial standardization of probiotic food products. For example, *L. rhamnosus LGG, L. reuteri DSM 17938* strains have been declared in North America as GRAS for their probiotic application (Jankovic *et al.,* 2010). The side effect from consuming probiotics is relatively low as compare to antibiotics. Since probiotic supplements only improve and adjust the natural flora that already exists in the human body. However, a 2008 research showed that people experiencing acute pancreatitis have higher death rates after taking a probiotic regimen. It's important to bear in mind that, probiotics may have also, side effects, like triggering allergic reactions and a side effect due to the interaction with other medicines (Tiwari *et al.,* 2012). The good opportunity for using probiotics as a dietary supplement is due to a low side effect since; they are already available naturally in the GIT. Side effects may be exhibited in people with impaired immune function, that's why it's important to counsel a medical doctor before ingesting any kind of probiotics product (Kwon *et al.,* 2005).

Recent advancements on probiotics

The demand of probiotics is growing globally. It become a very important part of everyday food products. It's global market is expected to reach $77.0 billion by the year 2025 (Ibrahim, 2019). A detailed understanding of gut microbiota is crucial in

for the development of future personalized health care strategies. New evidence is emerging in this regard to promote the beneficial use of selected probiotic strains in the treatment and prevention of numerous diseases. Probiotics have prophyylactic and therapeutic effect against inflammatory gastrointestinal diseases, celiac disease, metabolic syndrome, and diabetes (Kitazawa *et al.,* 2015). As an extension of the probiotic concept, the use of genetically engineered LAB to deliver compounds of health concern is presently gaining attention from the scholars in food science (Martín *et al.*, 2013).

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