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Review

Therapeutic potency of probiotics in the treatment of gastrointestinal parasites

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ABSTRACT: Current World Health Organization estimates suggest that around 1.5 billion people worldwide and approximately a quarter of all people on earth, chiefly among the developing countries, are affected by intestinal parasites, despite the aggressive control and an alarming treatment over the years. Besides, the extensive use of the available chemotherapeutic agents, against the infection, has created widespread drug resistance problem. Probiotics, therapeutic non-pathogenic microorganisms have been recently identified as a novel alternative prophylactic and chemotherapeutic agents against several gastrointestinal parasites. They are mostly gram-positive bacteria, isolated from the human gut microflora or various dairy products such as curds, lassi and kulfi with characteristics non-pathogenic, resistant to low pH and acid. Their non-pathogenic symbiotic activities in the gut help in the restoration of gut bacteria microbiota by stimulating immune system, metabolism and anti-pathogenic effect, especially when administered in large quantity. In addition, several strains of probiotics have been identified to possess antiparasitic effects against some gastrointestinal parasites both in egg and larval stage of the parasites. This present review therefore elucidates the potential of probiotics in the treatment and management of gastrointestinal parasites. There is need for more clinical studies and especially molecular studies for better perception of the mechanism underlying the beneficial effects of probiotics on parasitic infections.

Key words: Chemotherapeutic, intestinal parasites, potency, probiotics, therapeutic.

INTRODUCTION

Probiotics are exogenous living microorganisms, which are beneficial to the host's health when administered in the digestive tract (Abadi, 2018). According to World Health Organization (2002), probiotics are live organisms which when administered in adequate amount confer a health benefit to the host. They are the organisms, isolated from the gut, that have the potential to improve human and animal health by their gut microflora modulating capacity. Their non-pathogenic symbiotic activities in the gut help in the restoration of gut microbiota by stimulating immune system, metabolism, and anti-pathogenic effect, especially when administered in large numbers (Mukhopadhyay and Ganguly, 2014). *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, some fungi and yeast are the most widely used as probiotic (Guarner et al., 2011; Hill et al., 2014; Abadi, 2018). Additionally, most probiotics are gram-positive bacteria, isolated from the human gut microflora or various dairy products such as curd, lassi (a savoury drink, sometimes flavored with cumin) and kulfi (a frozen dairy dessert from the Indian subcontinent) with characteristics non-pathogenic, resistant to low pH and acids, criteria that made them qualify to remain in the intestine (Gupta and Garg, 2009). Their medicinal efficacies have been more demonstrated in animal model than by direct clinical evidences and depend largely on the ingested dose. According to Marie-Agnes et al. (2011), the recommended dose is at least five billion colony forming units per day for at least 5 days. Such minimum dose takes

into consideration the survival capacity of the ingested probiotics in the gastrointestinal tract, where they are in competition with the resident bacteria (Oelschlaeger, 2010). Recently, Nathan (2018) reported that some communities were studied in Liberia and Indonesia and the research teams were able to discover that the gut microbes of the studied population were able to clear the infections without drugs. They also observed that the micro biome profile of those that were able to fight infection were distinctly different from those people who could not clear infection without treatment. Such and other similar findings over the years have proven probiotics to be effective chemotherapeutic agents especially in the treatment of gastrointestinal parasites (Vincent, 2003; Bratati and Nirmal, 2014).

Gastrointestinal parasitic protozoan and helminthes are still remaining a challenge posing a significant debilitating effect on public health, food safety, and agricultural industries worldwide (Torgerson and Macpherson, 2011). Their clinical manifestation varies but may include diarrhea, malnutrition, weight loss, anaemia and sometimes death (Opara et al., 2012). Among the gut dwelling extracellular protozoa, *Giardia intestinalis* and *Entamoaba histolitica* are the common causes of acute diarrhea while some species of *Crytosporidium*, intra-cellular parasites are the agent of diarrhea in infants. Prevalence of gastrointestinal nematode infection revealed that the number of infections remain static for 50 years since the late 1940s (Obiukwu et al., 2008). Complication arising from common nematode infection such as intestinal obstruction in ascariasis or dysentery and rectal prolepsis in tricouriasis are relatively rare but no specific effect or moderately infected population might impair childhood cognitive development and productivity. Heavy infestation with hooke worms may cause diarrhea and bleeding which are often associated with iron deficiency anemia. One possible effect of gastrointestinal parasite is their influence on the immune response to other infection such as HIV (Vincent, 2003).

In agriculture, the persistent presence of gastrointestinal parasite in life stock throughout the world is responsible for significant economic loss. Ineffective control of animal gastrointestinal (GI) parasite can cause numerous problems including stunted growth, edema, diarrhea and contamination of meat. Control measures against gastrointestinal (GI) parasites alone cost over £1 billion. Extensive use of chemotherapeutic agent to control gastrointestinal parasitic infections has created widespread drug resistance problem (Vincent, 2003).

Intuitively, the development of effective vaccine against common harmful GI parasite would reduce the disease burden in the individual host and limit the spread of infection. Despite many years of research there are few commercial vaccines against mucosal parasites and no recombinant vaccine. These have called for alarming search for new alternate therapeutic agents. Thus, the use of beneficial microorganisms, probiotics, is becoming interesting for its prophylactic or therapeutic application against several diseases including gastrointestinal parasites.

The use of probiotics to treat the gastrointestinal microbiome has been posited as a potential novel therapeutic agent (Luis et al., 2016). It is hypothesized that probiotics have the capacity to control the proliferation of intestinal microbes by initiating competition for occupation of a common ecological niche. This mechanism aims to prevent protozoan infections of the like of Giardiasis and eliminate its symptoms (Martin et al., 2014). One of the many functions of the varying types of probiotics, including bacteria and yeasts, is to regulate immunity by stimulating the immune system within the host such that probiotics can reduce the number of parasites and severity of associated symptoms. As such, early clinical indications support the use of probiotics as therapeutic adjuncts in the pharmaceutical treatment of parasite infections (Carlos et al., 2010).

MECHANISMS OF ACTION

Probiotics are effective for the decolonization of parasite from the gastrointestinal tract (G.I.T.), their potency against parasites in the gastrointestinal tract is believed to be achieved through three mechanisms of action (Travers et al., 2011).

Modulation of the intestinal environment

Probiotics with the ability to control the proliferation of neighboring microorganisms does so by antagonism for the habitation of a regular biotope (Gupta and Garg, 2009). An instance is seen in iron which is a limiting nutrient, it is essential for most microorganisms, and probiotics can compete for its availability. Lactobacillus can render iron out of stock for pathogenic microorganisms, either by binding ferric hydroxide on its surface (Elli et al., 2000) or by secreting siderophores that chelate and transport iron (Oelschlaeger, 2010). Probiotics are also able to influence the composition and equilibrium of the gut microflora (Wohlgemuth et al. 2010). Finally, probiotics can also control their biotic environment through regulation of intestinal motility and mucus secretion (Gupta and Garg, 2009).

Secretion of active molecules

Antibiotics, bacteriocin, free fatty acids and hydrogen peroxide are active molecules secreted by probiotics with the potency of controlling growth and survival of surrounding parasites. Bacteriocins are secreted peptides or proteins that generally kill closely related bacteria by

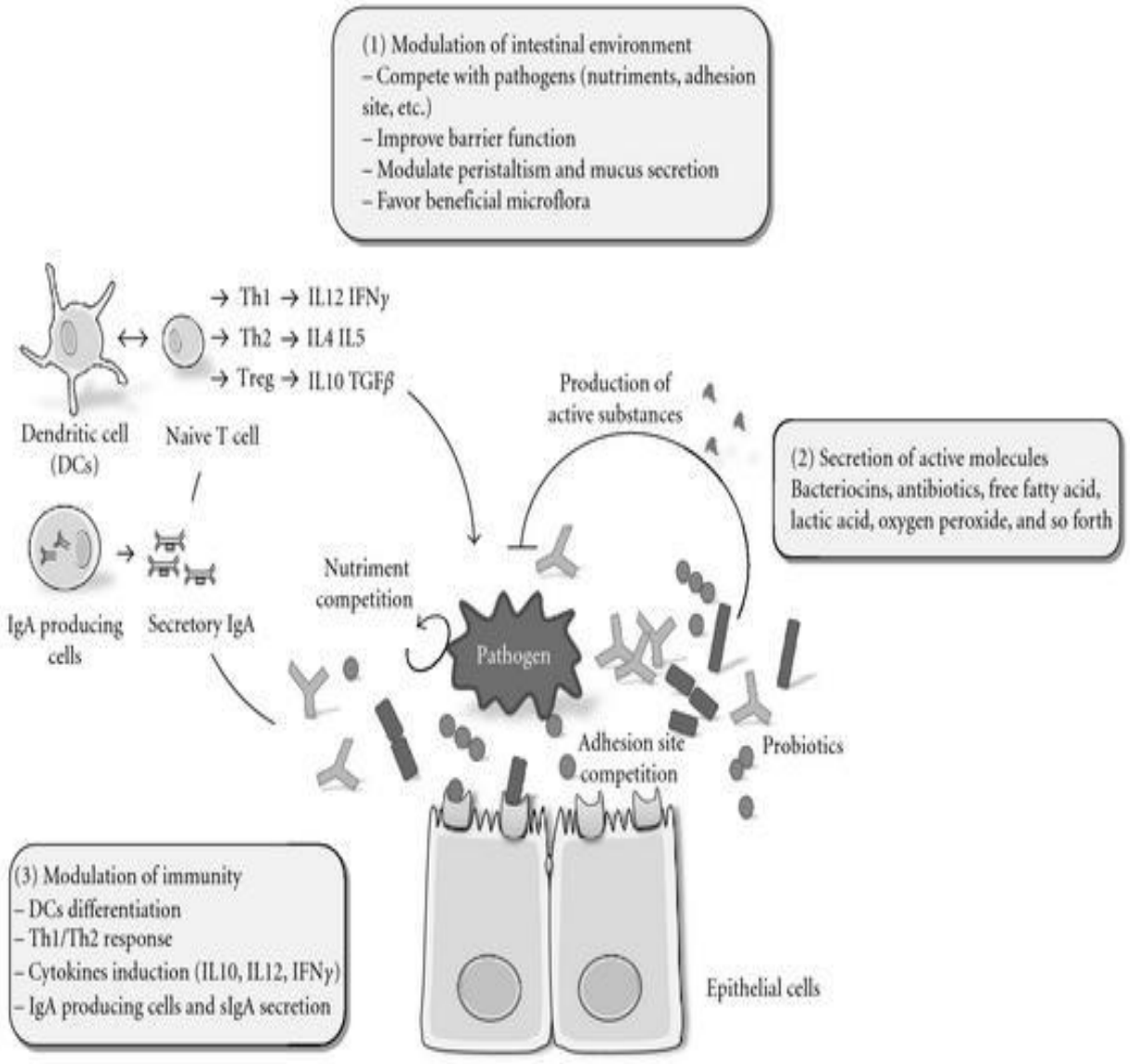

Figure 1. Schematic representation of the mechanisms of action of probiotics in controlling pathogens.
Source: (Marie-Agnes et al., 2011).

permeabilizing their membranes or by interfering with essential enzymes. *Lactobacillus reuteri* produces 3-hydroxy propion aldehyde, a broad-spectrum antibiotic, active against bacteria, yeast, fungi, protozoa, and viruses (Travers et al., 2011). By lowering the local intestinal pH with lactic acid, probiotics can also modify the growth of acid-sensitive organisms (Wohlgemuth et al. 2010).

Modulation of immunity

Probiotics modulate immunity by exciting the host immune response to a variety of pathogens. In the gut, probiotics interact with the epithelial cells, Peyer's patches M cells, and immune cells. These interactions result in a boost in the number of IgA producing cells accompanied by production of IgM and secretory IgA which are predominantly important in mucosal immunity, contributing to the barrier against pathogenic organisms (Marie-Agnes et al., 2011). Additionally, probiotics can also affect dendritic cells, whose function is the collection of antigens from gut and their presentation to nave T cells, giving rise to their differentiation to T-helper or T-regulatory lymphocytes. Probiotics have also been shown to modulate cytokine release (TNF-α IFN-γ, IL-10, IL-12) which play a central role in maintaining the delicate balance between necessary and excessive defence mechanisms (Travers et al., 2011). Pathogen killing or inhibition pictorial illustration of the mechanism by which probiotic control intestinal parasite is detailed in Figure 1.

SUCCESSES ON THE USE OF PROBIOTICS IN THE TREATMENT AND MANAGEMENT OF INTESTINAL PARASITES

Nematode or worm is responsible for trichinellosis, one of the most widespread and clinically important diseases in the world. Humans can be infected by eating infected food. Worms mature in the intestine of an intermediate host, such as pig, enter the blood and the lymphatic system and encyst in striated muscles (Marie-Agnes et al., 2011). The migration of larvae causes host tissue damages and inflammatory reactions with complications, which may lead to death. The efficiency of treatments based on mebendazole or albendazole is variable. Both viable and dead *L. casei* ATCC7469 were administrated orally to national institute of health (NIH) mice and induced a protective response with a significant reduction of both adult worms and larvae per gram of muscle (up to 70%). Treatment with culture supernatant of *L*. *casei* was less efficient but still showed a significant effect (32% reduction of adult worms) (Marie-Agnes et al., 2011).

Schistosoma mansoni, a blood-dwelling trematode worm, is the primary causative agent of bilharziosis. Human infection is initiated during water exposure to the free-swimming fork-tailed *cercariae*. After maturation in skin, larvae migrate through the skin, blood, lungs, and liver and finally reach the mesenteric venous plexus. Some of the eggs deposited by the female adults pass through the venule walls, cross the intestinal mucosa, and are evacuated with the fecal material. Eggs then infect their intermediate snail host, *Biomphalaria glabrata, Zymomonas mobilis*, a bacterium mainly known for its bioethanol-producing capabilities and originally isolated from alcoholic beverages, was reported to provide over 60% protection from the infection of *S*. *mansoni*, in mice, when orally administrated as a curative treatment (7 days after infection with *cercaria*) (Vasconcelos et al., 2004). The degree of protection was determined 60 days after infection, by the number of worms recovered from the murine liver by perfusion. As far as histopathology was concerned, lesions (granulomas) in the liver and the intestine were numerous and similar in the treated and no treated groups. Eggs were also abundant in the intestine, particularly in the jejunum-ileum part. On the contrary, the administration of Z*. mobilis* as a prophylactic way (7 days before infestation) did not significantly protect from infection, and worse, the combination of prophylactic and curative treatments exacerbated the symptoms (Dawson et al., 2005).

In addition, several strains of probiotics have been evaluated against Schistosomiasis. These including *Zymomonas mobilis*, probiotic labneh containing *Streptococcus salivarius* sub specie and different *Lactobacillus* species. Their anti-helminthic and immuno-modulatory effects on *S. mansoni* are summarized in Table 1.

Zowail et al. (2012) and Mohammed et al. (2016) reported that *Lactobacillus sporogenes* is among the most commonly studied probiotic strains that showed a significant anti schistosome effect in egg and larval stages of the parasite. This implies that it has remarkably reduced the worm burden as well as egg count.

Mc Clemens and others used a well-defined nematode i.e*. Trichurismuris* infection in mice model to investigate the effects of *Lactobacillus rhamnosus* (JB-1) treatment on host defence in nematode infections demonstrated that treatment with live JB-1 accelerates parasite expulsion and up regulates goblet cell hyperplasia in resistant (to infection) mice via the inter leukin (IL)-10 pathway (McClemens et al., 2013). Worm expulsion and goblet cell hyperplasia was noticed even in a susceptible strain (AKR) of mice, which was not observed in case of the resistant mice treated with γ-irradiated JB-1 or even in IL-10 knockout mice. Earlier study from this group has shown that IL-10 itself promotes goblet cell hyperplasia. Hence, the novel findings suggest the beneficial effect of the probiotic in innate defense during parasitic infections depicting new insights of its occurrence (Bratati and Nirmal, 2014).

In a similar example, acute amoebiasis caused by *Entamoeba histolytica*, the probiotic yeast named *Saccharomyces boulardii* (Ultra-levure) in combination with antibiotics has demonstrated a protective effect which significantly reduced the duration of disease symptoms as well as the presence of cysts in stools in succession (Mansour-Ghanaei et al., 2003). In addition, a summarized detail of different probiotics recently utilized against gastrointestinal parasites by different authors is presented in Table 2.

SAFETY OF PROBIOTICS

A number of species of *lactobacilli and bifidobacteria* are normal residents of, or transients through, the human digestive system and as such do not present toxicity (Pflughoeft and Versalovic, 2012). Conventional lactic acid bacteria, associated with food fermentation, are in general considered safe for oral consumption as ingredient of foods and supplements for the healthy population and at levels habitually used. Regulations for dietary supplements vary from country to countries. These regulations may be nonexistent in many countries, or much less strict than those that apply for drugs prescription and administration (Sirin and Aziz, 2017). At present, the Food and Drug Administration (FDA) in the United States has not been petitioned for any claims for probiotics that relate probiotics to a reduction in the risk of disease. Structure–function based on structure is a common claim used for probiotics, although these do not require approval by the FDA for use (Sirin and Aziz, 2017). Efficacy and side effects are likely to differ among strains, products, brands, or even within different lots of the same brand. Products purchased may not be identical with the form

Table 1. Anti-helminthic and immuno-modulatory effects of probiotics on *S. mansoni*

Probiotics strains	Dose/route	Mechanisms	Antiparasitic effect	References
Zymomonasmobilis	1 x 10^9 CFU/mL orally, at a dose of 0.3 mL/day	Provoke a secondary immune response	A 61% protection from the infection was observed in the treated group	De Fatima et al. (2004)
Probiotic labnch Containing Stresptococus Salivarius subsp. thermophiles, Lactobacillus Delbrueckii subsp. Bulgaricus and DVS-ABT2	Probiotic labnch and garlic and onions fed for 21 days before and 45 days after infection	Improving intestinal balance	50-66% reduction in worm burden; 70% and 56.44% egg count reduction in liver and intestine, respectively	Abdel-Salam et al. (2008)
Lactobacillus casei B-444; Lactobacillus plantarum B-531; Lactobacillus reuteriB-14141 and Lactobacillus acidophilus	1 x 10^6 CFU each mixed with feed	A significant stimulation for IgM response against SWAP before and after infection	Increased IgM; A decreased in the activity of AST, LDH and yGT	Ghanem et al. (2005)
Lactobacillus sporogenes	12.5 million spores/mice/week for 8 weeks daily	Decreased cytokine-induced chromosomal aberrations and DNA damage	Significant reduction in chromosomal aberrations	Zowail et al. (2012)
Lactobacillus sporogenes	12.5 million spores/mice/week for 8 weeks orally from the first day of infection	Reduced DNA damage; ameliorates the hepatic and intestinal damage	Reduced worm and egg count	Mohamed et al. (2016)

Table 2. Effect of probiotics on gut parasitic pathogen.

Parasitic Pathogen	Probiotics studied	Host	Treatment	Efficacy	References
Cryptosporidium parvum	Lactobacillus (L.) acidophilus NCFM/L, reuteri ATCC23272	Cell culture		25-50% reduction	Glass et al. (2004), Foster et al. (2003)
	L, acidophilus NCFM or L. reuteri 4000, 4020	Mouse	7-15 days before infection	50-75% reduction	Alak et al. (1999)
	L. reuteri 4000, 4020	Mouse	7.15days Before infection	75-100% reduction	Alak et al. (1997)
	L. reuteri 4000, 4020	Mouse	7.15days Before infection	50-75% reduction	Waters et al. (1999)
	L. casei Shirota and L. Rhamnosus GG	Human	After infection	Clinical case of resolution	Pickerd & Tuthill (2004)
	Pseudomonas (P.) Alcaligenes, Bacillus (B) brevis, Enterococcus (E.) faecium	Calf	Concomitant administration & infection	Insignificant effect	Harp et al., (1996)
	B. brevis, E. Faecium & P. alcaligenes	Cell culture		75-100% reduction	Deng et al. (2001)

Table 2. Contd.

	Bifidobacterium longum ATCC 15707 or B. breve ATCC 15698	Cell culture		75-100% reduction	
	Actimel/VSL ≠ 3	Neonatal rat	0-3 days before Infection	Insignificant effect	Guitard et al. (2006)
Giardia lamblia	E. faecium SF68	Mouse	3-7 days before Infection	75-100% reduction	Benyacoub et al. (2005), Shukla & Sidhu (2011)
	L. casei MTCC 1423	Mouse	Mouse 3-7 days before Infection	75-100% reduction	Shukla et al. (2008)
	L. Johnsonii LA1	Gerbil	3-7 days before Infection	50-75% reduction	Humen et al. (2005)
	L. Johnsonii LA1	Cell culture		75-100% reduction	Perez et al. (2001)
Giardia dwodenalis	Lactobacilli spp.	Human Dendritic cell Culture	Activated through released by Lactobacilli spp.	Enhanced Activation	Obendorf et al. (2013)
Ascarissuum	Bifidobacterium Lactis (pig isolate)	Pig	More than15 days	Undetermined	Solano et al. (2004)
Shistosomamansoni	Zymomonas (Z) Mobilis	Mouse	3-7 days before infection	50-75% reduction	De Fatima et al. (2004)
	L. acidophilus Lb33ac, L. salivariusLb 14c716c6	Cell culture		50-75% reduction	Tierney et al. (2004)
Eimeriatenella/ Acervulina	Mitogrow	Chicken	More than 15 days infection	25-50% reduction	Lee et al. (2007)
	Primalac	Chicken	More than 15 days Infection	50-75% reduction	Dalloul et al. (2003), Dalloul et al. (2005)
	Mitomax	Chicken	More than 15 days Infection	25-50% reduction	Lee et al. (2007)
Toxocaracanis	E. faecalis CECT 7121	Mouse	3-7 days before Infection	75-100% reduction	Basualdo et al. (2007)
Trichinella spiralis	L. casei ATCC7469	Mouse	3-7 days before Infection	25-50% reduction	Bautista et al. (2005), Garfias et al. (2008)

used in research (Szajewska et al., 2014). The question of the safety of probiotics has been raised with the more recent use of it been delivered in high numbers to severely ill patients. Use of probiotics in ill persons is restricted to the strains and indications with proven efficacy (Urbańska and Szajewska, 2014). Appropriate dosage of probiotics has proven to be safe in the treatment of GI parasites. On the stand point of prevalence of *Lactobacilli* in fermented food, as normal colonizers of the human body, and the low level of infection ascribed to them, the safety of these microbes has been reviewed and their pathogenic potential is deemed to be quite low (Muraro et al., 2014). From the stand point of FAO/WHO report in 2012, a multidisciplinary advance on previous researches is essential to examine the pathological, toxicological, genetic, gastroenterological, immunological, and microbiological safety aspects of novel probiotic strains (Morelli and Capurso, 2012).

On the stance of safety of probiotics, the following label is considered; genus and species identification, with nomenclature consistent with current scientifically recognized names, strain designation, viable count of each

strain at the end of shelf-life, recommended storage conditions, safety under the recommended dose, which should be on the basis of induction of the claimed physiological effect and finally an accurate description of the physiological effect.

CONCLUSION

Since the present management strategies of intestinal parasite is inadequate, the present review has proven that probiotics has therapeutic potency and may be better alternative in the treatment of gastrointestinal parasitic infections. Therapeutic approaches with probiotics help to decrease the risks of infestation by specific parasites or complement classical anti-parasite treatments. The intestinal parasites of the host can be modulated through the consumption or administration of probiotic microorganisms that establish an excellent means of remediation and deterrence against a variety of intestinal disorders and infections. Furthermore, investigations are thus needed using more define protocols, as well as extended clinical investigations. Given the lack and hazards of antibiotics, including reduction of micro biome diversity and antibiotic resistance, the use of probiotics instead of antibiotics is becoming increasingly acceptable. A better perception of molecular mechanisms underlying the beneficial effects of probiotic on the parasite infection is vital in validating the approach.

CONFLICTS OF INTEREST

The authors have declared no conflict of interest regarding the publication of this paper.

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