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Probiotic Efficacy and Potential of *Streptococcus thermophilus* modulating human health: A synoptic review

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Abstract: *The use of probiotic bacterial cultures stimulates the growth of preferred microorganisms, crowds out potentially harmful bacteria, and reinforces the body's natural defence mechanisms. Streptococcus thermophilus has been exploited industrially for making cheese as well as yogurt. One of the most important properties of this bacterium which is being used is production of lactase, an enzyme that converts lactose (milk sugar) into a simple sugar, which helps people who are lactose intolerant to digest milk. So consumption of this microbe has facilitated to alleviate symptoms of lactose intolerance and other gastrointestinal problems. Due to this unique feature of the microbe, it has been added to several health supplements along with other bacteria with similar properties. Over and above, it also produces a variety of antagonistic factors that include metabolic end products, antibiotic-like substances and bactericidal proteins, termed bacteriocins which assist to prevent several types of infections from various pathogenic microbes. In addition, the bacterium is endowed with enormous important beneficial properties. The following review will discuss with some beneficial aspects of S. thermophilus.*

Key Words: *Streptococcus thermophilus, Probiotic, Lactose intolerance, Microflora, Dysbiosis, Bacteriocins*

I. Introduction

The term probiotic means “for life” and it denotes the bacteria beneficial for humans and animals. The original observation of the positive role played by some selected bacteria is attributed to Elie Metchnikoff, the Russian born Nobel Prize recipient working at the Pasteur Institute, who suggested that "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes"[1]. Fuller (1989) [2], pointing out towards the microbial nature of probiotics, redefined the term as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance". A more recent, but probably not the last definition is "live microorganisms, which when consumed in adequate amounts, confer a health effect on the host" [3]. Exploiting the probiotic bacteria has been proved beneficial as a potential preventive measure by providing a microbial stimulus to the host immune system by administering microorganisms that are characteristics of the healthy, human gut microflora. And as such research diversifies; one particular bacterial strain has attracted and is receiving special attention – *Streptococcus thermophilus* which comes to our diet through variety of fermented products. *S. thermophilus* is a Gram-positive bacterium belonging to the phylum Firmicutes, family Streptococcaceae and order Lactobacillales. It belongs to the clade of Lactic acid bacteria which include the species of genera *Carnobacterium, Enterococcus, Lactobacillus, Lactococcus, Leunostoc,* Oenococcus, Pediococcus, Tetragenococcus, Vagococcus and *Weissella* [4]. *S. thermophilus* is closely related to *Lactococcus lactis*, but it is even more closely related to other streptococcal species including several pathogens [5]. *S. thermophilus* is highly adapted to grow on lactose, the main carbon source in milk and rapidly converts it into lactate during growth. Lactose is transported into the cell by a lactose permease (LacS), which operates as a galactosideproton symport system or as a lactose-galactose antiporter. Lactose is efficiently transported into the cell and subsequently hydrolyzed by an intracellular b-galactosidase. The vast majority of *S. thermophilus* strains only metabolized the glucose moiety of lactose, while galactose is excreted into the medium. The milk is poor in free amino acids (AA) and short peptides, therefore for optimal growth; *S. thermophilus* requires either hydrolysis of caseins followed by the internalization and the degradation of the resulting peptides or de novo AA biosynthesis [6]. For many LAB including *S. thermophilus*, the hydrolysis of milk caseins (i.e. the AA supply) mostly depends on the activity of a cell-wall-anchored proteinase [7]. *S. thermophilus* and *L.* bulgaricus, lead to positive effects on the yogurt taste and aroma by symbiotic coexistence, described by the ecological term protocooperation (where two species interact with each other beneficially). Protocooperation is basis for creation of symbiotic relation between the two species (*S. thermophilus* and *L. bulgaricus*) and combined metabolism with positive effects on the fermented product. *Streptococcus* strain produces formic acid promoting

the growth of the *Lactobacillus* which, on its turn, provides flavour compounds (acetaldehyde) and the proteolytic activity to keep the *Streptococcus* strain growing in milk [8]. The genus *Streptococcus* includes Gram positive bacteria with similar metabolic properties but they live in different habitats and have many physiological differences. In the past two decades, several important *Streptococcus* species have been reclassified as members of recently named genera *Enterococcus* and *Lactococcus*. The only dairy *streptococcus* remained is *S. thermophilus*. Streptococci grouped as "oral", "pyogenic" and "other streptococci". "Oral" streptococci are also subdivided into four groups; *S. mutans, S. mitis, S. anginosus* and *S.thermophilus* groups [9]. Although *S. thermophilus* is a member of "*S. thermophilus* group" phylogenetically, it is the only bacterium in Streptococci with dairy origin. The Gram positive and cocci genera sharing the same habitat with *S. thermophilus* includes enterococci, lactococci, pediococci and leuconostocs. The pediococci is readily distinguished from other genera by the tetrad morphology in broth media. Some of the physiological differences which are helpful for the first grouping at the genus level are given in the table below:

Table: Classification of cocci lactic acid bacteria

Microrganism	Growth at 10°C	Growth at 45°C	Growth in 6.5% NaCl	Type Lactate formed	Gas from Glucose	Growth in broth at pH 9.6	Arginine Hydrolysis
Enterococcus	+	+	+	**ND**	-	+	+
Lactococcus	+	-	-	**L**	-	-	**V**
Streptococcus	-	+	-	**L**	-	-	**V**
Leuconostoc	+	+	-	**D**	+	**ND**	-

* ND indicates no data available, V indicates variable: some produce (+) results and some (-), L indicates levo-lactic acid and D indicates dextro-lactic acid

S. thermophilus is highly adapted to the dairy environment, and in the wild. It can only be isolated from dairy products. *S. waius* is a recently identified thermophilic Streptococcus isolated from stainless still pasteurization machinery of milk. It shares many phenotypic characteristics with *S. thermophilus* but can be distinguished by the fermentation of galactose, salicin, cellobiose, maltose, melibiose and D-raffinose [10].

Characteristics of *Streptococcus thermophilus* B4 isolated from Goat Milk (Sharma et al 2013) [10]

Gram Staining	Cell Morphology	Spore Formation	Catalase Activity	Fermentation Type	Glucose Fermentation	Nitrate Reduction
Positive	Cocci in chains	Negative	Negative	Homo	Positive	Negative

Sugar Fermentation *Streptococcus thermophilus* B4 isolated from Goat Milk (Sharma et al 2013) [10]

Sucrose	Lactose	Maltose	Dextrose	Ribose	Sorbitol	Mannose
Positive	Positive	Positive	Positive	Negative	Negative	Positive

II. History And Nomenclature

The name Streptococcus is derived from the Greek word which means "twisted berry" it is seen under the microscope as a chain that resemble a string of beads. Thermophilus is a Greek term which means heat, referring to an organism that is able to survive extreme cases of heat. Orla-Jensen (1919) [11] was the first to differentiate and describe *S. thermophilus* as a distinct streptococcal species. *S. thermophilus* is classified as a nonpathogenic, single Streptococcus species to possess a generally recognized as safe (GRAS) status [12]. It is also considered as "the second most important industrial dairy starter after *Lactococcus lactis*" [13]. Along with the use in manufacturing fermented food, streptococcus is reported to posses probiotic properties in adequate amount conferring a health benefit to the host [14, 15, 47].

Table1: Characteristics of *Lactobacillus bulgaricus* & *Streptococcus thermophilus* [16]

Characteristics of microbes	*Lactobacillus bulgaricus*	*Streptococcus thermophilus*
Growth on MRS agar at pH 6.3	Positive	Positive
Growth on MRS agar at pH 5.4	Positive	Negative
Incubation Temperature	30^{o}C	42^{o}C
Catalase activity	Negative	Negative
Gram reaction	Positive	Positive
Cell morphology	Rods	Cocci
Colony size	Small	Big
Colony shape	Circular, irregular	Circular,
Colony colour	Creamy grey	Irregular, Creamy white

III. *S. thermophilus* As Dairy Starter

A starter culture can be defined as a microbial preparation of large numbers of cells of at least one microorganism to be added to a raw material to produce a fermented food by accelerating and steering its fermentation process. *S thermophilus* is extensively used in starter cultures for dairy products like Swiss and Italian-type cheeses, Gouda cheese and yoghurt because of its metabolical traits such as production of lactic acid, flavouring compounds, exopolysaccharide production, fermentation of galactose, urease and proteolytic activity, [17]. A recent study conducted at National Dairy Research Institute, India shows that *S thermophilus* isolated from plant sources possess similar physiological and biochemical properties to those from dairy sources and can be considered for developing new starters [52].

IV. Antibacterial Activity Against Intestinal Microbes

S. thermophilus along with other probiotic bacteria possess inhibitory effects on some of intestinal pathogenic organisms and hence it is evident that it can be administered in order to prevent or ameliorate some diseases.

Table 2: Measurement of antimicrobial activity (zone of inhibition in mm) of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* against clinical isolates. (Adapted from [16])

Indicator organisms	Zone of inhibition(in mm)
Escherichia coli	4.0
Klebsiella sp.	4.2
Pseudomonas sp.	1.6
Proteus sp.	2.3
Salmonella sp.	0
Shigella sp.	1.8

V. Efficacy Against Antibiotic Associated Diarrhoea

In a study conducted to determine the efficiency of probiotic drink (containing *S. thermophilus* along with *Lactobacillus casei* ,and *L. bulgaricus*) for the prevention of diarrhoea associated with use of antibiotics and that caused by Clostridium difficale , it was found to reduce the incidence of AAD and also having the potential to decrease morbidity, healthcare costs and mortality if used routinely in patients of age greater than 50 [18].

VI. Efficacy Against Rotavirus Induced Diarrhoea In Infants

Rotavirus-induced diarrhea poses a worldwide medical problem in causing substantial morbidity and mortality among children in developing countries, and the development of preventive measures remains an important goal. In a double-blind, placebo-controlled trial, infants aged 5-24 months who were admitted to a chronic medical care hospital were randomised to receive a standard infant formula or the same formula supplemented with *Bifidobacterium bifidum* and *S. thermophilus*. It was found that the supplementation of infant formula with *B. bifidum* and *S thermophilus* can reduce the incidence of acute diarrhoea and rotavirus shedding in infants admitted to hospital [19].

VII. Role In Enteric Dialysis For Renal Failure

In a test conducted for the formulation of commensal and food grade bacteria that when ingested may become gut flora that catabolize nitrogenous toxins that accumulate in uremia flow into the gut by passive diffusion, an isolate *S. thermophilus* KB19 reduced urea concentration from 300mg/dL to 20mg/dL within 24 hours at pH 6.3 when inoculated in Artificial Intestinal Fluid at initial density of 10^9 cfu/ml. KB19 survived 3 hours in acidic pH 3.0 with only two logs loss in cfu and was able to pass through bile. In addition, this strain evinced no resistance to 8 commonly used antibiotics. These data indicate that *S. thermophilus* bacterial isolate can be used as a urea-targeted component in an enteric dialysis formulation [20].

VII. *S. thermophilus* for Skin Ailments

One of the most significant health benefits associated with the use of *S. thermophilus* bacteria in humans is the bacterium's ability to exert a positive effect upon the body's ceramide (a skin protective agent) levels. As shown in a recent study, which demonstrated the efficacy of the bacterium in vitro and in vivo? In vitro, it has shown a considerable positive impact on the ceramide levels measured in cultured human keratinocytes which have function in the formation of a barrier against environmental damage such as pathogens, heat, UV and water loss. Secondly in vivo, it has shown an equally beneficial effect on the level of

ceramides in stratum corneum, which forms a barrier to protect underlying tissue from infection, dehydration, exposure to chemicals and mechanical stress [21]. Additionally, *S. thermophilus* has been found to positively influence the levels of sphingolipids in human skin. A study which looked at about 11 patients who were treated with topical creams containing *S. thermophilus*, in all cases there were "significant improvements in levels of bacterial sphingomyelinase" [22].

VIII. Reduction In Colonization Of Nasal Pathogenic Bacteria

As obtained a study which looked upon the specific measurement of pathogenic bacteria in human nasal canals, the results showed that those patients who were given the supplemented yogurt experienced a markedly reduced level of nasal colonization of pathogenic bacteria – *Staphylococci aureus*, Streptococcus pneumonia and β haemolytic streptococci [23].

IX. *S. thermophilus* In Cholestrol Assimilation

Fifty four volunteers participated in a randomised cross over trial; the results of which revealed reductions of between 5-10 % in serum cholesterol levels after several weeks of moderate consumption of yoghurt fermented with *L. bulgaricus* and *S.thermophilus* [24].

X. *S. thermophilus* As Antioxidant

The damage caused to our cells and tissues by the free radicals has a critical role in progression of disease and process of ageing. Antioxidants act as first line of defence against the damage caused due to free radicals and thus are vital for optimal health maintenance .The antioxidant defence mechanism in the body is composed not just of endogenousantioxidants but also of exogenous antioxidants from several food sources (vitamins C and E,carotenoids, pholates, flavonoids, phytoestrogens and selenium). It has been recently demonstrated that the probiotic microorganisms can effectively trap reactiveforms of oxygen as such in the experiment conducted using rats which were deficient in vitamin E, has revealed that theintracellular extract from Lactobacillus sp. recovers this deficiency. The classical yoghurt bacteria *L. bulgaricus* and *S. thermophilus* inhibit peroxidation of lipids through scavenging the reactive oxygenradicals, such as hydroxyl radical, or hydrogen peroxide [25].

XI. Mucositis In Rats

A 2009 study in Adelaide, Australia has shown very positive results when *S. thermophilus* TH-4 was used to treat rats with mucositis (inflammation and ulceration of the mucous membranes) caused by chemotherapy drugs. Rats responded to the treatment by showing a normalization of healthy cell function in the affected areas and a significant reduction of distress to the tissue of the intestines [26]

XII. *S. thermophilus* In Folic Acid Production

While growing in milk, *S. thermophilus* is found to produce folic acid which is essential for numerous biological functions and becomes a vital component of yoghurt [27, 28].

XIII. *S. thermophilus* Against Bacterial Vaginosis

Bacterial vaginosis (BV) is the most common vaginal infection in reproductive aged women. This infection occurs when predominantly anaerobic bacteria such as *Gardnerella vaginalis*, as well as *Mycoplasma hominis*, *Prevotella* and *Peptostreptococcus* replace the dominant and normal *Lactobacillus* bacteria in the vagina. One hundred twenty healthy Chinese women with a history or recurring bacterial vaginosis (BV) were randomly assigned to a daily vaginal probiotic capsule as prophylaxis that contained 8 billion colony forming units of *Lactobacillus rhamnosus*, *L. acidophilus* and *S. thermophilus* or a daily vaginal placebo capsule. Women were to insert the capsule 7 days on, 7 days off and 7 days on. Probiotic prophylaxis resulted in lower recurrence rates for BV (15.8% [9/57 women] vs 45.0% [27/60 women]; P < .001) and *Gardnerella vaginalis* incidence through 2 months (3.5% [2/57 women] vs 18.3% [11/60 women]; P = .02). Between the 2- and 11-month follow-up periods, women who received probiotics reported a lower incidence of BV and G vaginalis. Aside from vaginal discharge and malodour, no adverse events were reported in either study group [43].

XIV. Bacteriocin Production By *S. thermophilus*

Bacteriocins are proteins produced by certain bacteria having a characteristic feature of inhibiting the growth of similar or closely related bacterial strains The incorporation of bacteriocins as a biopreservative ingredient into model food systems has been studied extensively and has been shown to be effective in the control of pathogenic and spoilage microorganisms [29]. Several strains of *S. thermophilus* have been found to produce bacteriocins which are being discussed in the following table:

Table 3: Summary of bacteriocins obtained from *S. thermophilus* and their antimicrobial activity

Strain	Bacteriocin	Inhibitory Action against	Reference
***S. thermophilus* ST134**	Thermophilin A	sensitive cells in the culture	[30, 31]
***S. thermophilus* 347**	Thermophilin 347	Listeria monocytogenes	[32]
***S. thermophilus* Sfi 13**	Thermophilin 13	*L. monocytogenes*	[33]
***S. thermophilus* 81**	Thermophilin 81	*Lactococcus lactis, S. typhimurium, E. coli*,	[34]
***S. thermophilus* ACA-DC 0040**	Thermophilin T	*Clostridium sporogenes*,C. tyrobutyricum	[35]
***S. thermophilus* ACA-DC0001**	Thermophilin ST-1	L.innocua,*Staphylococcus aureus , Enterococcus faecalis*	[36]
***S. thermophilus* 580**	Thermophilin 580	*C. tyrobutyricum*	[37]
***S. thermophilus* ST110**	Thermophilin 110	*Pediococcus acidilactic*	[38]
***S. thermophilus*SBT1277**	Thermophilin 1277	*C. butylicum, C. sprogenes, B. cereus*	[39]
***S. thermophilus* LMD-9**	Thermophilin 9	*L. monocytogenes*	[40]
***S. thermophilus* CHCC3534**		*S. typhimurium, S. aureus*	[41]
***S. thermophilus* B59671.**	Thermophilin 110	Pediococcus acidilactic	[42]

Table 4: Few Probiotic example activities of *Streptococcus thermophilus*

Probiotic Activity	Strain	Reference
Suppression of Ulcerative colitis	*S. thermophilus*ST28, *S.thermophilus* ATCC 19258	[48]
Lactose digestion	*S.thermophilus* MUH 341	[49]
Decrease in blood pressure	*S. thermophilus*TMC 1542	[50]
Reduction in Blood cholesterol	*S.thermophilus*	[51]
Anti-gastric activities	*S.thermophilus* CRL 1190	[46]
Against Chronic gastritis	*S.thermophilus* CRL 1190	[45]
Anti-tumor activity	*S.thermophilus*	[53]
Anti-listerial activity	*S.thermophilus*	[54]
Food Preservative	*S.thermophilus* CCHC 3534	[55]

XV. Stable Growth In Children

Food supplements containing *S thermophilus* have been found to maintain a stable growth rate in children. Children consuming S. thermophilus containing supplements had shown better growth during a 6-month period than children who did not receive the supplement [44].

XVI. Biotherapeutic

S. thermophilus is found to be potentially therapeutic against the associated chronic gastritis (ASA) [45] Gastritis is a common disorder in which discontinuity of the gastric mucosa is observed. It is caused by various factors like excess alcohol, infection, intensive consumption of anti-inflammatory drugs with Helicobacter pylori or may be stress. Also, ASA affects various mucosal defence lines such as bicarbonate secretion, mucus synthesis, and decrease of mucosal blood flow. The first therapeutic effect of the fermented milk with the polymer producing strain of *S. thermophilus* on chronic gastritis induced by ASA in mice. It was able to generate immune response in mice and increased the thickness of the gastric mucus gel layer. Studies suggest that recombinant lactic acid bacteria are the excellent candidates for the production of various bio therapeutic proteins and also their delivery to specific places of requirement within the gastrointestinal tract [46, 47]

XVII. Conclusion

It is evident from several studies that, *S. thermophilus* has the potential to be majorly beneficial to human health. Studies have already indicated many positive results stemming from *S. thermophilus*. As such research moves forward, other findings are attracting attention of scientists, such as the suggestion that food stuff containing such bacteria may have anti-carcinogenic cancer-fighting properties as well. For this reason, promoting a superior understanding of human health as it relates to the adequate balance of bacteria in the body is extremely important and warrants further research and investigation. Additionally, role of this bacterium is continuously expanding from use in health maintenance and supplementation in the event of dysbiosis

(microfloral imbalance) during antibiotic therapy, to a wide range of health applications including skin ailments. With the increase in knowledge and exploring other strains of importance, future trends envisage their increased inclusion in dietary supplements and food stuff that target to a diverse preventive measure in health maintenance needs. Furthermore, there is considerable desideratum to establish the dose which is more effective and strains required for optimal benefit either in a disease state, or as preventive Consequently, far more research is needed before complete implementation but still probiotics seem to be a reliable method of treatment.

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