EFFICACY OF USING PROBIOTICS WITH ANTAGONISTIC ACTIVITY AGAINST PATHOGENS OF WOUND INFECTIONS: AN INTEGRATIVE REVIEW OF LITERATURE

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Abstract:

The skin microbiota serves as a physical barrier to prevent invasion of pathogens. Skin damage can be a consequence of illness, surgery, burns. The most effective wound management strategy is to prevent infections, promote healing and prevent excess scarring. It is well established the probiotics can aid in skin healing by stimulating the production of immune cells. Probiotics also exhibit antagonistic effects against pathogens via competitive exclusion of pathogens. Our aim was to conduct a review of the recent literature on the efficacy of using probiotics against pathogens causing wound infections.

In this integrative review we searched through literature published in the international databases: PubMed, ScienceDirect, Web of Science and Scopus using the search terms: ’probiotic’ AND ‘wound infection’. A comprehensive review and critique of the selected research was carried out. According to the methodology 14 *in vitro* studies, 8 animal studies and 21 clinical studies were found. Two *in vitro* studies also included animal studies, therefore a final yield of 42 articles was included.

The most commonly used probiotics for all studies were typical strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus* and *Lactobacillus rhamnosus.* All *in vitro* studies showed successful inhibition of chosen skin or wound pathogens by the selected probiotics. Eight animal model studies on mice, rats and rabbits showed the possibility for using probiotics for counteracting wound infections. Most clinical studies showed a slight or significant lowering of surgical site infections, foot ulcer infection or burn infections for patients using probiotics. Several of these studies also indicated a significant wound healing effect for the probiotics groups.

This review indicates that exogenous and oral application of probiotics has shown reduction in wound infections and therefore the potential use of probiotics in this field remains worthy of further studies, perhaps focused more on typical skin inhabitants as probiotics with high potential.

Keywords: beneficial microbes, microbiota, antimicrobial action, contamination, disease-producing microorganisms

INTRODUCTION

According to the current definition, probiotics are live microorganisms that, when administered in adequate amounts, confer a health effect on the host. Both FAO and WHO, as well as The International Scientific Association for probiotics and Prebiotics (ISAPP), have developed and endorsed this definition of probiotics (1–3). The most common probiotics are lactic acid bacteria strains of the *Lactobacillus* species (e.g. *Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus delbrueckii* subsp. *bulgaricus*) and strains of the *Bifidobacterium* species (e.g. *Bifidobacterium infantis, Bifidobacterium animalis* subsp. *lactis, Bifidobacterium longum*). Also strains of other bacterial species (e.g. *Propionibacterium acidilactici, Lactococcus lactis, Leuconostoc mesenteroides, Bacillus subtilis, Enterococcus faecium, Streptococcus thermophilus* and *Escherichia coli*) and certain yeasts (e.g. *Saccharomyces boulardii*) are probiotics (4). The best studied microbiome-management niche in the body is the gut.

With increasing knowledge about the essential role of gut microbiome in the human health, the gut microbiota is now considered our important partner interacting with virtually all human cells (5). The discovery of the links, or the axes, for instance the "gut-brain" and "gut-brain-skin", has opened up a completely new dimension of research. Besides the studies of basic mechanisms, such as antimicrobial activity, competitive exclusion, immunomodulation and strengthening of the intestinal epithelial barrier function, studies are focused into mechanisms of microbiota effects on the central nervous system and endocrine system (6–8). Revolutionary discoveries about the importance of human microbiome for human health have also accelerated the development of the probiotic sector. Scientific evidence of probiotic benefits on human health is continuously expanding and there are enough data to justify testing of probiotics for treatment or prevention of several disorders from antibiotic and *Clostridium difficile*-associated diarrhoea, irritable bowel syndrome, inflammatory bowel disease, to anxiety, depression and wound healing (9–12).

The phrase "when administered", in the definition of probiotics, can refer to the application of probiotics into the gut as well as on other sites (skin and vagina). Beneficial effects of probiotics have also been demonstrated in topical and *per os* use of probiotics in dental medicine, for women (urogenital infections, vaginosis), among others applications. The use of probiotics is therefore widespread and one of the promising areas is prevention and treatment of skin diseases. This review will systematically summarize the most recent *in vitro*, animal and clinical studies on the antagonistic activity of probiotics against the pathogens of infected wounds.

SKIN MICROBIOTA

The skin is an important organ that represents the first line of defence against the external environment. Its main functions are to provide mechanical strength, regulate water and salt loss and protect the body from environmental damage, including that caused by microorganisms (13,14). Despite the tough physical characteristics of skin, particularly the desiccated, nutrient-poor, acidic conditions, skin is colonized by beneficial microorganisms and serves as a physical barrier to prevent the invasion of pathogens. When the barrier is disrupted or the balance between commensals and pathogens is disturbed, skin disease can appear. Using various state-of-the-art molecular and genetic/genomic methods, it was found out that the skin microbiota is dominated by bacteria from the phyla Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes; resident genera mainly include *Propionibacterium* spp., *Staphylococcus* spp., *Micrococcus* spp., *Corynebacterium* spp. and *Acinetobacter* spp., the main representatives of the fungi being species of the genus *Malassezia* (15–18).

The diversity of skin microbiota among individuals depends on the age, diet, gender, environmental and geographical factors. However, skin microbiota composition of healthy adults was found to be primarily dependent on the physiology of the skin site, with changes in the relative abundance of bacterial taxa. Sebaceous sites, for example, are dominated by lipophilic *Propionibacterium* species, whereas bacteria that thrive in humid environments, such as *Staphylococcus* and *Corynebacterium* spp., are preferentially abundant in moist areas, including the cubital fossa of the elbows and the underside of the feet. Overall, the skin harbours a heterogeneous community of microorganisms that each have distinct adaptations to survive on the skin (19).

SKIN DAMAGE AND WOUND INFECTIONS

Skin damage can be caused by a variety of different reasons such as trauma (including cuts, abrasions, chemical burns, fire burns, cold, heat, radiation, surgery), or as a consequence of underlying illnesses such as diabetes. The most effective wound management strategy is to prevent infections, promote healing, and prevent excess scarring (14). The wound classification system categorizes all surgeries into four groups: clean, clean/contaminated, contaminated, and dirty (20). Surgical site infections are currently one of the frequent type of nosocomial infections (21). Chronically-infected wounds, such as venous or arterial ulcers, diabetic foot ulcers, pressure sores, and non-healing surgical wounds delay wound healing, have a significant impact on the patients' quality of life, represent a significant cause of morbidity and mortality and result in enormous healthcare expenditures (14,22–24). Wound infections are most often caused by biofilm-forming bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus faecalis, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Peptostreptococcus* spp., etc., (25–32). Biofilms are adherent communities of microorganisms that secrete a biochemical and physical matrix for protection, support, and survival; this matrix is a semi-permeable barrier that limits diffusion of molecules that might otherwise gain access to planktonic microbes, such as quorum-sensing molecules and antibiotics. The ability to form biofilms is an important feature of microorganisms for the successful disposal of inflammatory and mature wound healing stages causing chronic wounds (14). Different microbes are present during the beginning of a wound infection at neutral pH and after the wound becomes chronic when the pH becomes more alkaline and anaerobes are more likely to be present; causative agents of infections also differ according to wound type (26,33).

ANTIBIOTICS: THE CONVENTIONAL TREATMENT FOR WOUND INFECTIONS

The traditional therapy for infected wounds include irrigation with saline, debridement of necrotic tissues, and use of appropriate medications to reduce the microbial load such as parenteral antibiotics and antiseptics with local or systemic action (26). However, an increasingly urgent problem is the resistance of microorganisms that commonly cause healthcare-associated infections to antimicrobial drugs (34).

Some experts claim, that topical use of antibiotics or other medication is very important for the treatment of infected wounds (especially burns and chronic wounds) because in such cases the active substances do not reach the site of infection in sufficient quantities. Namely, intravenous dosing of antibiotics is not as effective due to the reduction of microcirculation in the burned skin and the failure to eradicate biofilm infections. However, there are publications that state that topical use of antibiotics can lead to the development of resistance even more likely than systemic use of antibiotics (14,35).

PROBIOTICS AS ALTERNATIVES TO ANTIBIOTICS FOR WOUND INFECTIONS

Antimicrobial resistance poses a serious global threat of growing concern to human therefore, alternatives to the topical use of antibiotics on the skin are of great interest as well. While some alternatives include inhibitors of antimicrobial resistance (alginate, polyamines), other compounds with different mechanisms are currently being investigated: amino-benzimidazole, polyanionic substances, enzymes, potassium permanganate, antimicrobial peptides, metal ions (silver, bismuth, copper), halogen ions (chlorine, iodine), chitosan, phototherapy, various antibodies, as well as bacteriophages and beneficial microorganisms, such as probiotics (36–40).

In line with the concept of the Organisation for Economic Cooperation and Development (OECD) (41), it is stated that probiotics are one of the possible alternative therapies to the topical use of antibiotics due to the increasing occurrence and transmission of antibiotic resistant microorganisms. Since it seems that antimicrobial resistance is transmitted even more frequently by topical application of antibiotics, the use of alternatives is imperative. The OECD states that it is necessary to strengthen the scientific evidence of alternative therapies.

In the case of a disruption of the natural balance of skin microbiota, it is known that probiotics have a positive effect on the health of the host through the process of aiding in skin healing by stimulating the production of immune cells and/or competitive exclusion of pathogens that cause skin infections (32,42–44). Probiotics release bioactive molecules that inhibit pathogen growth and interfere with the pathogens' quorum sensing system, co-aggregate with pathogens, facilitate their removal from the skin via peristaltic elimination, and displace pathogens from the skin via high affinity binding to epithelial cell receptors (45). Some studies emphasize the use of cell-free probiotic metabolites, termed postbiotics, as safer than the use of live microbes (45), though this remains to be conclusively demonstrated. Other studies using cell, lysates have proven decrease in parameters associated with inflammation (46,47). Probiotics promote wound healing, while acting in the dermis, where they function as signalling receptors against pathogens and activate the production of beta-defensins, which enhance the immune capacity of the skin (48).

Several studies on the positive effects of probiotics on wound healing have been conducted *in vitro* or on animal models (42,49–53). There are also several clinical trials that prove efficacy of oral probiotics for various skin problems (22,54) and even for lowering the rate of surgical site infections (55–58). A recent meta-analysis (59), has also concluded that a reduction of surgical site infections following colorectal surgery was found for patients that were administered probiotics.

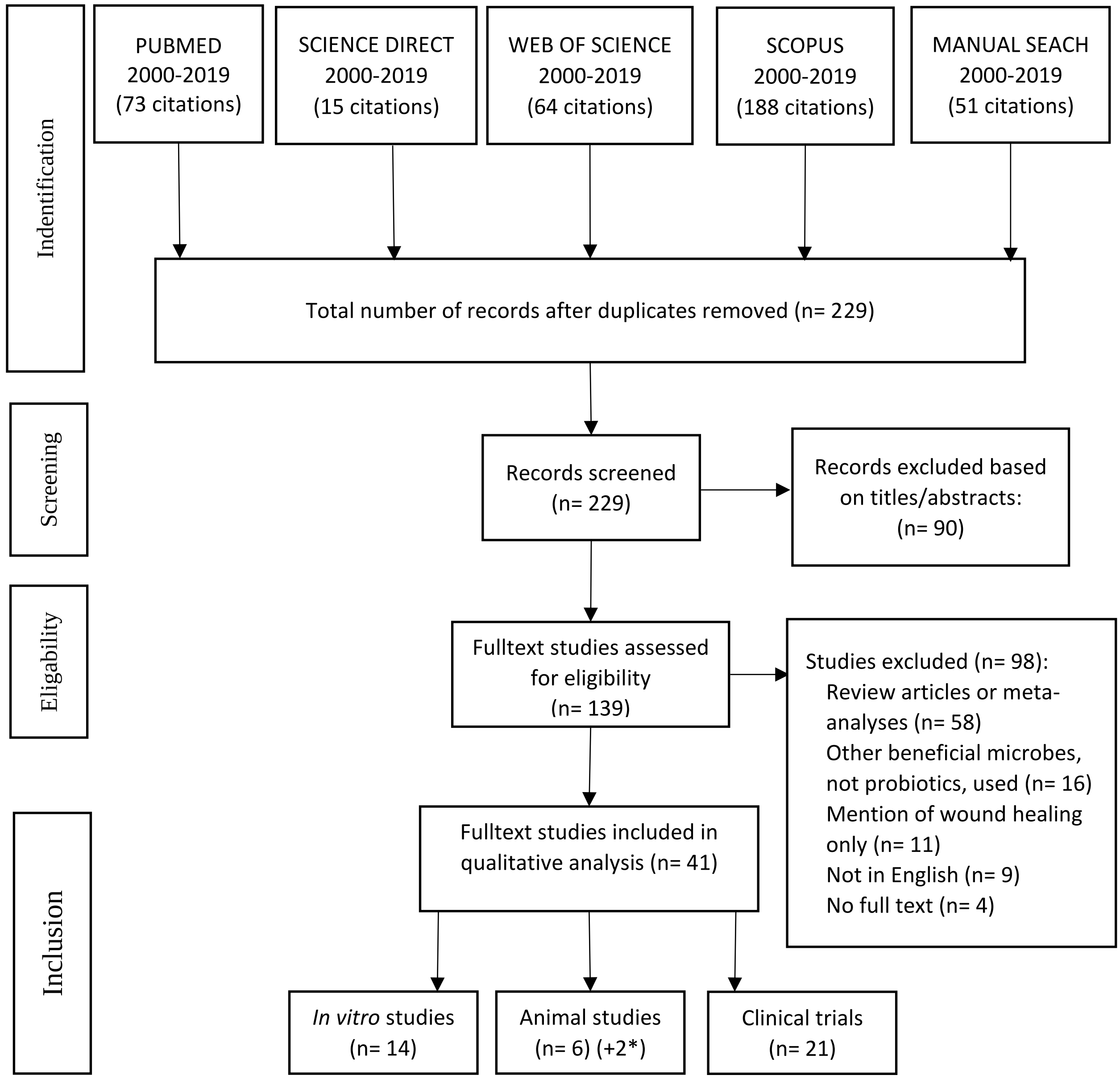
Some published studies also present the possibility of topical application of probiotics, probiotic supernatants or their metabolites for skin ulcers, burns and other wounds. Most of these studies were carried out on animal models where burns were induced on mice, rats, pigs and the wounds were then inoculated with selected pathogens (*P. aeruginosa, S. aureus*) and selected probiotics, and the reduction of the pathogen load was then observed (60,61).

The most important effect of probiotics is therefore their well-established antimicrobial effect against pathogens via the production of acids, bacteriocins or other antimicrobial molecules, and competitive exclusion. It follows that this is very important for wound healing since the presence of pathogens in wounds impedes the healing process of the skin (37,62). Exploring this antimicrobial effect of probiotics against wound pathogens was the main purpose of our review.

SEARCH STRATEGY AND REVIEW METHODOLOGY

The present review includes a screening of the most recent studies on the antagonistic activity of probiotics against the pathogens of infected wounds and makes a comparison of *in vitro,* animal and clinical studies as well as the mode of probiotic usage, namely topical or systemic. In order to obtain the most relevant selection of publications the international databases PubMed, ScienceDirect, Web of Science and Scopus were used to search for studies using various keyword combinations: 'probiotic'[MeSH] AND 'wound infection', 'probiotic' AND 'wound infection'[MeSH], 'probiotics' AND 'wound infections'. The PRISMA principles for data search were applied (http://www.prisma-statement.org/). Only English publications were included. Inclusion criteria were: available full text and use of oral or topical probiotics for treating wound infections, use of probiotics only; not live cultures associated with fermented foods, such as kefir, yogurt etc. Exclusion criteria: studies that only used probiotics for wound healing without mention of wound infections. Similar studies in articles' reference lists of reviews were also searched. A total of 391 articles were found (figure 1). After removing duplicates, a total of 230 articles were screened and 90 were excluded based on title and abstract. 140 fulltexts were assessed for eligibility and 42 were included in the final analysis. These articles were then sorted by experimental design (*in vitro,* animal and clinical studies) and entered in tables one to three in chronological and alphabetical order. The mode of probiotic use is noted in tables 2 and 3 as topical or systemic (=oral).

Figure 1: PRISMA flow diagram illustrating the process of literature screening, study selection and reasons for exclusion



* two studies reported an *in vitro* and animal study in the same publication

As noted in figure 1, the number of studies retrieved through database searching was very different for different databases despite the use of the same search parameters. This is probably due to the fact that each database contains different journals and publication sites. Several reviews were also found and their reference lists were screened with additional records noted in the manual search section.

IN VITRO STUDIES ON THE USE OF PROBIOTICS FOR WOUND INFECTIONS

To date there exists a large number of *in vitro* studies on the antimicrobial effects of probiotics against various pathogens (63). Table 1 includes only those *in-vitro* studies that include wound specific pathogens and the potential use of probiotics to prevent their growth and development. Fourteen *in vitro* studies were found that met the inclusion criteria.

Table 1. *In-vitro* studies on the antimicrobial effect of probiotics against wound pathogens.

Study	Pathogen species	Probiotic(s)	Method	Outcome	Potential use for humans
(61) #	*Pseudomonas aeruginosa*	*Lactobacillus plantarum* ATCC 10241	Co-culturing	Greatest inhibitory activity with whole culture, somewhat lower inhibition with acid filtrate	Local treatment of burn infections
(64)	*Escherichia coli, Staphylococcus aureus, P. aeruginosa,* MRSA, *Trichophyton mentagrophytes, Trichophyton rubrum*	*Lactobacillus fermentum* NCIMB 7230	Agar-well diffusion method	Nitric oxide-producing patch with probiotic, killed all common bacterial and fungal wound pathogens	Antimicrobial applications for infected wounds
(65)	*S. aureus, P. aeruginosa, Candida albicans*	*Lactobacillus reuteri* ATCC 55730, *Lactobacillus casei**, *L. plantarum**	Tri-phasic PLUS wound model	Different efficiency of probiotics against different pathogens	Potential benefit of wound colonization with single or mixed probiotics
(66)	*S. aureus, P. aeruginosa*	*L. fermentum**	Co-culturing and well diffusion assay	Both pathogens were successfully inhibited	Inhibition of common wound pathogens
(67)	*S. aureus*	*L. reuteri* ATCC 55730, *Lactobacillus rhamnosus* AC413	Cell culture	Inhibited adherence of pathogen to keratinocytes	Topical prophylaxis in preventing skin infection
(68)	*P. aeruginosa*	*L. plantarum* ATCC 10241 supernatant	Culturing pathogen with probiotic supernatant	Anti-pathogenic properties	Infected chronic wounds
(69) #	MRSA USA300	*Propionibacterium acnes* ATCC6919 extract	Agar spot with propionic acid	Effective inhibition of pathogen	Skin health
(70)	*S. aureus*	*Lactobacillus rhamnosus* GG lysate and spent culture supernatant	Normal human epidermal keratinocyte suspension	Inhibition of pathogen growth and reduction of pathogen adhesion	Damaged skin
(71)	*P. aeruginosa*	*L. rhamnosus* GG, *L. acidophilus**	well diffusion assay	Antimicrobial effect of probiotic bacteriocins against burn wound pathogen	Preventing hospital-acquired infections
(72)	*E. coli, P. aeruginosa, S. aureus, Propionibacterium acnes, Propionibacterium aeruginosa*	Supernatants of *Lactobacillus delbrueckii* DSMZ 20081, *Bifidobacterium animalis* CHR Hansen Bb 12, *L. acidophilus* La-5, L-10, L-26, *Bifidobacterium lactis* B-94, *Bifidobacterium longum* DSMZ 20088, *L. plantarum* 226v, *Lactobacillus brevis* D-24, *Lactobacillus salivarius* DSMZ 20555, *L. casei* DSMZ 20021, CHR Hansen 01, 431	Well diffusion assay; attachment assay	Prevent biofilm formation and exhibited antimicrobial activity against skin pathogens	Topical application for skin dysbiosis
(73)	*Enterobacter hormaechei, Klebsiella pneumoniae, Acinetobacter baumannii*	*L. reuteri* SD2112	Co-culturing	Differential gene response, pili formation, cell attachment	Polymicrobial wound infections
(74)	*P. aeruginosa, S. aureus*	*L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2	Probiotic encapsulation and co-culturing with pathogens	Encapsulated probiotics in combination with antibiotics results in complete eradication of pathogens	For topical co-administration with antibiotics
(75)	*P. aeruginosa,* MRSA	*L. plantarum* F-10 (a promising probiotic strain), cell-free extract	Agar well diffusion assay, biofilm formation, co-aggregation, quorum-sensing	Antimicrobial, anti-biofilm, anti-quorum sensing activity	Against skin infections
(76)	*P. aeruginosa*	*L. reuteri* DSM17938, *L. acidophilus* DSM, *Bacillus coagulans* DSM1, *L. plantarum*	Disc diffusion method	Some probiotics and antibiotics exhibited synergistic effects; other	Possible use of certain probiotics with certain antibiotics to create

		299v, DSM9843, *Bifidobacterium bifidum* DSM20456		combinations exhibited antagonistic effect	synergistic effects on wound healing.

#study also included animal model *Strain not specified

All fourteen studies in Table 1 showed efficient antagonistic effects of chosen probiotic strains against wound pathogens. Different variations of the agar-well diffusion assay were used in seven studies, the co-culturing method was used in five studies. The most commonly used probiotics were various strains of *L. plantarum* (six studies), *L. acidophilus* (four studies) and *L. reuteri* (four studies). Five studies included supernatants or extracts, whilst the other studies used live probiotic cultures. Nine studies included various monospecies probiotics, whilst five studies included multispecies probiotics. *S. aureus*, *P. aeruginosa*, *E. coli* and *A. baumannii* were the most commonly investigated pathogens. Two studies from Table 1 (61,69) also included animal model experiments and are additionally noted in Table 2.

Although two additional studies (77,78) showed that strains of *L. acidophilus* and *L. casei* exhibited efficient antagonistic effect against the wound pathogens using the well-diffusion method, they were not included in Table 1, since the lactobacilli were isolated from buffalo milk curd and yogurt and as such; according to the definition, have not been proven as probiotics. Significant antagonistic effects of lactic acid bacteria against wound pathogens (*P. aeruginosa, C. albicans, S. aureus* and *E. coli*) (79) and *Aerococcus viridians* against wounds infected with *S. aureus* and *Salmonella enterica* serovar Typhimurium (80), were also published in two studies 2000 and 1998 respectively; however the articles were not in English with no information on the methodology in the English abstract and were therefore also excluded.

ANIMAL STUDIES ON USE OF PROBIOTICS FOR WOUND INFECTIONS

All retrieved animal studies on the antimicrobial effects of probiotics against skin pathogens, deliberately added on burns or wounds on animals, can be found in Table 2. A total of eight animal studies met the inclusion criteria.

Table 2. Animal model studies on the antimicrobial effects of probiotics against wound pathogens.

Study	Animal	Wound type	Pathogen species	Probiotic(s)	Method	Outcome	Potential use for humans
(61) #	Mice	Burn wound	*Pseudomonas aeruginosa*	*Lactobacillus plantarum* ATCC 10241	Injection into burned area (10^5 cfu/mL injected into burned area on days 3,4,5,7and 9)	Inhibitory effect against pathogen and wound improvement	Local treatment of burn infections
(81)	Rats	Burn wound	*P. aeruginosa*	*L. plantarum*	Topical application on	Reduction of pathogen load	Intervention for

				ATCC 8014	burned area (single dose 10^8 cfu/mL)	in wound	prevention of multi-resistant pathogen infection in burns
(82)	Rabbits	Ischemic wound	*Staphylococcus aureus*	*Lactobacillus fermentum* 7230	Local application of patches designed with lyophilized probiotic microbeads (single dose of 10^6 cfu/mL)	Improvement of probiotic treated wounds through nitric oxide production	Chronic wounds
(69) #	Mice	Skin lesion	MRSA USA300	*Propionibacterium acnes ATCC 6919*	Local topical application of *Propionibacterium* (10^5 cfu/mL for 17 days)	Decrease in cfu of pathogen	Skin wound and skin health
(83)	Mice	Burn-sepsis wound	*P. aeruginosa*	*L. plantarum* ATCC 10241	Sub-eschar injection (10^9 cfu/mL daily for 5 days)	ower mortality rate and inhibition of pathogen in remote organs	Management of complicated burn injury
(84)	Rabbits	Burn-sepsis wound	*P. aeruginosa*	*L. plantarum* ATCC 10241	Local application (single dose of 3×10^8 cfu)	Curtailed severity and length of infection as well as reduced scarring	Counteracting burn wound infection and alleviate scarring
(85)	Rats	Full thickness wound	*S. aureus*	*L. plantarum* USM8613	Single local application of 10 % (v/v) protein rich fraction of cell-free supernatant with paraffin	Higher reduction of pathogen with probiotic and enhanced wound healing	Inhibition of wound pathogens
(86)	Rats	Third-degree scald burn	MRSA ATCC 43300	*L. plantarum* ATCC 10241	Local application (single dose of 1×10^6 cfu/mL)	Protective role when applied before pathogen	Promising role in prevention and treatment of wound infections

* article also contained *in vitro* study included in table 1, MRSA: methicillin-resistant *S. aureus*

All animal studies resulted in an efficient antagonistic effect of probiotics against wound pathogens, mainly *P. aeruginosa*, followed by *S. aureus*. Four studies used burn models and three studies used cut wound models. Three studies used mouse models, two used rats, and two used rabbit models. Local application of probiotics was used for 5 studies and only two studies included local injections of probiotics and no study utilized oral probiotic administration. The most frequently used probiotic was *L. plantarum* ATCC 10241.

Four studies, not included in Table 2 (87–89), used kefir and kefir extracts against various pathogens applying *in-vitro* methods and burn rat models with positive outcomes of effective antibacterial effects and wound healing. Although the kefir microbiota contains a diverse group of live beneficial microorganisms, it is not classified as a probiotic *per se* as it is not well-defined in terms of strain composition and stability (3), therefore these articles could not be added to Table 2. Another research by Al-Mathkhury and co-workers (90) not included in Table 2 showed that *L. plantarum, L. bulgaricus and L. acidophilus*, isolated from yogurt, vinegar and vagina, respectively, also exhibited antimicrobial properties when added to mice' wounds previously infected with *S. aureus* or *P. aeruginosa*. However, according to the panel of the ISAPP (3) live cultures, (traditionally associated with fermented foods) for which there is no evidence of a health benefit, are not probiotics, therefore this study could not be included as well. Another animal model publication (91) reported the effectiveness of a *Bacillus* strain against *Streptococcus pyogenes* infection of surgical wounds on rats, however only the abstract was in English and therefore also wasn't included in Table 2. The study (92) successfully used skin commensal *Staphylococcus epidermidis* on mice model with infected skin. Of note, some articles also recommend the use of bacteriophages for treatment of infectious wounds (93–95) which are also not part of the definition of probiotics.

CLINICAL STUDIES ON THE USE OF PROBIOTICS FOR WOUND INFECTIONS

In demonstrating the impact of probiotics on general health as well as in connection with the use for wound infections, the most important studies are randomized double-blinded clinical trials with a representative sample. We found a total of twenty-one clinical studies (twenty clinical trials and one case study) that met the inclusion criteria and are noted in table 3.

Table 3. Clinical studies on the antimicrobial effects of probiotics against wound pathogens.

Study	Study type	Wound type	Patients PR/CO	Pathogen	Probiotic /total cfu per day	Probiotics treatment	Wound infections (%) PR/CO	Outcome
(96)	Prospective, randomized	Abdominal surgery	64/65	*Staphylococcus aureus, Enterococcus faecalis,* coliforms, mixed anaerobes	*Lactobacillus plantarum* 299v ($5×10^7$ cfu)	Oral (7 to 12 days before surgery and 4 to 9 days after surgery)	NR	No statistically significant difference in protection against wound infections. No significant difference in the incidence of septic morbidity between the probiotic and control groups (p=0.74). Statistically insignificant increase of mortality in the probiotic group.
(97)	Prospective, randomized	Abdominal surgery	30/30	Not mentioned	*L. plantarum* 299***, ($2×10^9$ cfu) with fibres; heat killed bacteria as placebo	Oral (for 4 days after surgery)	0% / 3%	Lower incidence of surgical site infections, however not statistically significant
(98)	Randomized, controlled	Biliary cancer surgery	21/23	*S. aureus, E. faecalis, Enterococcus faecium, Enterobacter cloacae*	*Lactobacillus casei* Shirota, *Bifidobacterium breve* Yakult / ($2×10^8$ cfu)***	Oral (for 14 days after surgery)	NR	Statistically significant lower incidence of overall infections in the synbiotic group. Statistical significance for wound infections NR
(99)	Randomized, double-blind	Liver transplant surgery	33/33	*S. aureus*	*Pediococcus pentosaceus* LMG P-20608, *Leuconostoc mesenteroides* LMG P-20607, *Lactobacillus paracasei* subsp. *paracasei* LMG P-17806; *L. plantarum* LMG P-20606 (10^{10} cfu)***	Oral (starting on the day of surgery for two weeks)	0% / 3%	Lower incidence of wound infection for probiotics with prebiotics group, statistically significant lower overall post-operative bacterial infections in the same group
(55)	Randomized, controlled	Biliary cancer	41/40	Not mentioned	*L. casei* Shirota, *B. breve* Yakult /	Oral (14 days before and 1st day after	4.8% / 15%	Lower incidence of wound infection for

		surgery			(before surgery 5×10^{10} cfu)***; (after surgery 2×10^{8} cfu) ***	surgery for 14 days)		probiotics with prebiotics group, statistically significant lower overall post-operative infections for same group
(100)	Randomized, double-blind	Pancreaticoduodenectomy	40/40	Not mentioned specifically for wound infections	*P. pentosaceus* LMG P-20608, *L. mesenteroides* LMG P-20607, *L. paracasei* subsp. *paracasei* LMG P-17806*; L. plantarum* LMG P-20606 (10^{10} cfu)***	Oral (starting on the day after surgery for 8 days)	10% / 15%	Lower incidence of wound infection for probiotics with prebiotics group, statistically significant lower post-operative infections for same group
(22)	Prospective	Second and third degree burns	14/15	*S. aureus, Pseudomonas aeruginosa, S. epidermidis, E. cloacae, Klebsiella pneumoniae, E. faecalis*	*L. plantarum* ATCC 10241 (10^{5} cfu)	Daily topical application for 10 days	NA	Topical probiotic treatment of 2nd degree burn patients was as effective as silver sulphadiazine in control group in decreasing pathogen load.
(101)	prospective	Chronic infected leg ulcers	34/0	*S. aureus*, *P. aeruginosa, S. epidermidis, E. cloacae, K. pneumoniae, E. faecalis*	*L. plantarum* ATCC 10241 (10^{5} cfu)	Daily topical application, 10 days	NA	Statistically significant decrease of pathogen load after 10 days (P<0.001) compared to day 1 with topical probiotic treatment. However, non-probiotic group was not applied.
(102)	Randomized, double-blind, placebo-controlled	Colorectal cancer surgery	50/50	Not mentioned	*L. plantarum* CGMCC 1258, *L. acidophilus* LA-11, *Bifidobacterium longum* LB-88 / (2.6×10^{14} cfu)	Oral 16 days (6 days preoperatively and 10 days post-operatively)	6% / 10%	Low incision site infection rate, however not statistically significant
(103)	2-arm, randomized, controlled	Hepatic surgery	32/29	MRSA	*L. casei* Shirota, *B. breve* Yakult / (6×10^{8} cfu)***	Oral (14 days before operation and 11 days allowed food intake)	NR	No infectious complications after surgery in probiotic group (P<0.05)
(54)	Case study	Deep-dermal and full-thickness burn patient	1	*P. aeruginosa*	*L. casei* Shirota (6.5×10^{9} cfu)	Oral (for 2 weeks after infection which occurred 5 months after burn)	NR	Pathogen from wound changed from multi-drug resistant to multi-drug sensitive strain, thus implying effective intervention
(104)	Randomized, double-blind, placebo-controlled	Colorectal cancer surgery	30/30	Not mentioned	*B. longum**, *Lactobacillus acidophilus**, *Enterococcus faecalis** (3×10^{8} cfu)	Oral (3 to 5 days before surgery)	3.3% / 6.7%	Lower surgical site infection rate for probiotic group, however not statistically significant
(105)	Prospective, randomized	Liver transplant surgery	34/33	*Enterococci* spp, *Enterobacter* spp, *Escherichia coli*	*L. acidophilus* LA-14, *L. plantarum* LP-115, *Bifidobacterium lactis* BBL-04, *L. casei* LC-11, *Lactobacillus rhamnosus* LR-32, *Lactobacillus brevis* LBr-35 / (2.75×10^{10} cfu) ***	Oral (at least 7 days after oral fluid tolerance after operation)	NR	Incidence of postoperative infections was lower for probiotic with fibre group compared to fibre only.
(56)	Prospective, randomized, double-blinded, controlled	Colorectal cancer surgery	100/95**	*E. coli, S. aureus, P. aeruginosa, S. epidermidis, E. faecalis, Bacteroides fragilis, Serratia marcescens*	*Bifidobacterium bifidum** (3.3×10^{9} cfu)	Oral (7 days before and 5 to 10 days after operation)	18% / 17.9%	The antibiotic group only had statistically significant decreased surgical-site infections vs control group (P=0.014)
(106)	Clinical trial	Colorectal cancer surgery	75/81	Not mentioned	*E. faecalis* T110, *Clostridium butyricum* TO-A, *Bacillus mesentericus* TO-A (no information on concentration)	Oral (15 days prior surgery, restarted the same day the patient started drinking water after surgery	16% / 5%	Statistically significant lower surgical superficial incisional site infection (P=0.016)
(57)	Randomized, double-	Colorectal cancer	84/80	*Acinetobacter baumannii, P.*	*L. acidophilus* LA-5, *L. plantarum**, *B.*	Oral (1 day prior to operation and 14	20.0% / 7.1%	Decrease in surgical infections (P=0.02)

	blinded, placebo controlled	surgery		*aeruginosa*, MRSA	*lactis* BB-12, *Saccharomyces boulardii** / (5.5×10^{9} cfu)	days after surgery)		
(107)	Randomized, blinded	Burn injury	10/10	Not specified	*L. rhamnosus* GG (1.5×10^{10} cfu)	Oral (start within 10 days after burn and until 95% wound closure)	NA	Trend of less requirement for antifungal agents
(58)	Randomized, double-blinded, placebo controlled	Perampu llary neoplas ms surgery	23/23	Not specified	*L. acidophilus* 10, *L. rhamnosus* HS111, *L. casei* 10, *B. bifidum, S. boulardii** / (4×10^{9} cfu) ***	Oral (4 days before and 10 days after surgery)	NR	Statistically significant lower incidence of infection with synbiotics
(108)	Randomized, double-blinded, controlled	Burn	20/20	Not specified	*Lactobacillus fermentum** and *Lactobacillus delbrueckii** / (2.0×10^{9} cfu)	Oral - during hospital stay	35% / 60%	Trend towards decrease in infection incidence
(109)	Single-centre, randomized controlled	Colorect al resection	168/194	Not specified	*L. casei* Shirota, *B. breve* Yakult / (4.0×10^{10} cfu)***	Oral (7–11 days before surgery and reintroduced at 2–7 postoperative days)	17.3% / 22.7%	Trend towards lower surgical site infection rate for synbiotic group, however not statistically significant. Study was not blinded and no placebo product was used.
(110)	Randomized, double-blinded	Colorect al cancer surgery	30/30	Not specified	*B. longum**, *L. acidophilus**, *E. faecalis** / (3.0×10^{7} cfu)	Oral 12 days (5 before, 7 after surgery)	3.3% / 3.3%	No statistically significant differences in wound infection rates

PR/CO = probiotic vs control group; NR - not reported specifically for wound infection; NA - not applicable; *Strain not specified; **additional antibiotic group in study (99 patients), *** probiotic used together with prebiotic or fibre, MRSA: methicillin resistant *S. aureus*

Topical application of probiotics was used only in two studies on infected foot ulcers and burns (22,101). There were three additional studies of burn injuries with oral use of probiotics. All these studies resulted in a decreased pathogenic load.

The remaining sixteen studies listed in Table 3 used oral probiotic administration and were conducted on surgical patients with surgical site wounds and underlying disease or condition such as cancer, transplantation etc. Seven studies concerned colorectal cancer surgery, three studies were for liver surgery and two studies each for abdominal and biliary cancer surgery. Other surgeries included pancreaticoduodenectomy and perampullary neoplasms surgery (one each). The main reason for using probiotics in these clinical trials was to enhance wound healing and prevent systemic and surgical site infections after surgery. The studies were only included in Table 3 if there was a mention of recording surgical site infections for both the probiotics and control group. All of these studies noted a tendency to lower incidence of surgical site infections in the probiotics group, but only five noted a statistically significant difference. On the other hand, these same studies noted statistically significant lower incidence of systemic infections, bacteraemia, urinary tract infections, pneumonia, peritonitis and hence better healing, however not in all cases. Eight studies used synbiotics and eight studies used probiotics only. No statistically significant advantage for the synbiotic groups was found with regard to the lower wound infection rate.

The clinical study of patients undergoing pancreaticoduodenectomy (111) also showed that perioperative probiotics reduced postoperative infectious complications, however it was not included in Table 3 as only an abstract was available. Studies on the application of probiotics in the treatment of patients with non-healing purulent-inflammatory wounds (112), patients with colorectal surgery (113) were also found; however articles were not in English.

MOST COMMONLY USED PROBIOTICS FOR WOUND INFECTIONS

Table 4 includes the total set of probiotic species from tables [1-3] that have been used against common wound pathogens.

Table 4. Most commonly used probiotic species in studies against wound pathogens.

Probiotic species	**Study type**		
	In vitro	**Animal**	**Clinical study**
	references	**references**	**references**
Lactobacillus plantarum	(61)#,(65,68,72,75,76)	(61)#,(81,83–86)	(22,57,96,97,99–102,105)
Lactobacillus casei	(65,72,74)		(54,55,58,98,103,105,109)
Lactobacillus acidophilus	(71,72,74,76,78)		(57,58,104,105,110)
Lactobacillus rhamnosus	(70,71,74,114) (67)		(58,105,107)
Lactobacillus reuteri	(65,73,76,114), (67)		
Lactobacillus fermentum	(64,66)	(82)	(108)
Bifidobacterium breve			(55,98,103,109)
Bifidobacterium lactis	(72)		(57,105)
Bifidobacterium bifidum	(76)		(56,58)
Bifidobacterium longum	(72)		(104,110)
Enterococcus faecalis			(104,106,110)
Lactobacillus delbrueckii	(72)		(108)
Pediococcus pentosaceus			(99,100)
Leuconostoc mesenteroides			(99,100)
Propionibacterium acnes	(69) #	(69) #	
Saccharomyces boulardii			(57,58)
Lactobacillus brevis	(72)		(105)
Lactobacillus paracasei			(99,100)
Bifidobacterium animalis	(72)		
Lactobacillus salivarius	(72)		
Bacillus coagulans	(76)		
Bacillus mesentericus			(106)
Clostridium butyricum			(106)

study includes *in vitro* and animal model study

Regardless of the study type (*in vitro*, animal model or clinical study) by far the most commonly used probiotics were various strains of *L. plantarum*, followed by *L. casei, L. acidophilus, L. reuteri, L. fermentum* and *B. breve*. It is obvious that the genus *Lactobacillus* was the most commonly used. All other genera including *Bifidobacteria*, other lactic acid bacteria, such as *Enterococcus* spp., *Pediococcus* spp. and *Leuconostoc* spp. were only used in a few studies and mainly as a part of multispecies probiotics. There were also a limited amount of studies using bacteria from the *Bacillus* genera and the yeast *S. boulardii*. Only one study used a probiotic strain of the skin bacterium *Propionibacterium acnes*.

DISCUSSION AND CONCLUSIONS

Many centuries ago, even before mankind knew microbes existed and before the use of antiseptics and antibiotics, fermented milk was applied to wounds to improve healing and prevent infection (48). The use of bacteria to fight bacteria is therefore an old concept, especially with respect to the skin. According to Sprunt & Leidy (115) the first attempted replacement of one microorganism by another was done by Cantini in 1885 who claimed to replace *Mycobacterium tuberculosis* (then named *Bacillus tuberculosis*) in the lungs with another harmless organism. Metchnikoff, who is named the father of probiotics, also mentioned this principle in the early 1900s, as did Nissle, who, in 1916, used an *E. coli* strain for the treatment of various intestinal disorders (91,116). Today however, this represents a major shift in the paradigm of the current doctrine of wound treatment as well as the traditional teaching of 'germ theory' where the idea of using bacteria to fight bacteria is not intuitive (21,48). It has been 15 years since the publication of the review by Howard and co-authors on the possible use of probiotics in surgical wound infections, however not much has changed with regard to the traditional therapy of wound infections and more clinical evidence is still necessary for a paradigm shift in this area (117).

Several reviews on the use of probiotics for wounds in general or for specific conditions have been published (60,118–120), however, to the best of our knowledge, no systemic review specifically on the influence of probiotics against wound pathogens has been conducted. There are also several reviews on the general effect of probiotics on healing after surgery. The review by Besselink and coauthors (121) on the potential role of probiotics in the prevention of complications in surgical patients in general also concluded that probiotics show promising results in several clinical trials, although the review was not focussed on surgical site infections, but rather on bacterial translocation due to gut dysfunction at the mucosal barrier. The same conclusions were drawn in the review on the use of probiotics for patients undergoing abdominal surgery (122) and colorectal resection for cancer (123).

The most important studies that demonstrate the impact of probiotics on health in general are randomized double-blinded clinical trials with a representative sample and proper study design, but these trials represent the final phase of traditional product development trajectory, which can be conducted only after the successful completion of preceding robust preclinical studies. Reliance on *in vitro* data or animal models alone is not sufficient as these data may not directly correlate to clinical evidence and limited data presented in human studies (124). However, certain traits and characteristics of candidate probiotics for use in wound infections must be tested by *in-vitro* methods such as adhesion and inhibition of pathogen adhesion to human keratin as well as the production of antimicrobial substances (51,72).

All investigated *in vitro* studies on the antagonistic activity of chosen probiotics against common wound pathogens yielded the same general result, namely an effective inhibition of the growth of wound pathogens. This means that all these studies confirmed successful inhibition of pathogens by co-culturing or a version of the agar-well diffusion assay. However, this being only the first step does not yet take into account the influence of the host and system matrix, more specifically, the layers of the skin. The most commonly studied probiotic bacteria belonged to the genus *Lactobacillus*, and this taxon does not primarily belong to the skin microbiota (125). It should also be noted that probiotics are not expected to colonize the skin for extended periods of time, an often-misunderstood concept for successful probiotic action, rather, they are chosen due to their scientifically proven antagonistic effect against the conventional nosocomial and gastrointestinal pathogens, which are strikingly similar to the most common skin pathogens (126). An appropriate alternative for studying interactions between probiotics and pathogens, which is becoming more established, is the *in vitro* use of cell lines that mimic the original environment of the organism in the form of a biological matrix (127,128). For *in vitro* studies of the human skin function, the most popular cell line has been HaCaT, a spontaneously mutated keratinocyte cell line from immortalized adult skin (129). There is also some published literature on the use of models to simulate wound healing (114,130), but there is still no published literature on the use of probiotics with them. Another possibility is the use of the nematode's *Caenorhabditis elegans* epidermis as a model skin (131,132). There is even an international patent for microspheres from gelatin as a carrier for probiotic *Lactobacillus* spp. for treating skin wounds or lesions (133).

Our search yielded eight animal model studies using probiotics against wound pathogens, three on mice, and two on rats and rabbits. All studies confirmed an effective antagonistic effect of the probiotics, mainly various strains of *L. plantarum*, regardless of whether the wound was an infected burn or cut wound. Most studies used topical application of probiotics on the wounds with a successful reduction of the two most common skin pathogens *S. aureus* and *P. aeruginosa*. All studies concluded that the investigated probiotic could be applied to human wound infections. In terms of wound healing experiments, mice and rats are the most commonly used animal models. It must be stressed that these animals have a thinner epidermis and dermis compared to humans, thus bringing into question suitability of such an animal model. On the other hand, large animals such as pigs, which skin have been regarded as the closest surrogate to human skin with regard to similarities in structure and healing, have a disadvantage of extensive costs, handling, and lack of genetic manipulability (130,134).

The researched probiotics that have been reported to form robust biofilms *in vitro*, and shown to attach to various host biofilm sites include *L. casei, L. rhamnosus, L. plantarum, L. reuteri, L. acidophilus, B. bifidum*, and *B. breve* (135–140). Although probiotics form similar biofilm modalities as pathogens, research and evaluation of these biofilms has only occurred in recent years and not necessarily on the skin (43).

Only two clinical studies used topical application of *L. plantarum* ATCC 1024 on infected wounds, in one case, a burn wound and in the other case, chronic foot ulcers. In the clinical study on burns, it was found that the topical application of the *L. plantarum* ATCC 1024 on burns was as effective as topical application of silver ions (22). In the second clinical study on diabetic patients with chronic ulcers, topical application of *L. plantarum* ATCC 1024 on ulcers improved healing. Higher production of IL-8 and a reduction in the number of infected ulcers was also achieved (101).

Sixteen clinical studies in our review were conducted on patients with various abdominal surgeries (colorectal cancer surgery, liver transplantation, abdominal surgery, and others). The main reason for using probiotics in these clinical trials was to enhance wound healing and prevent systemic and other infections after surgery in general, one aspect being surgical site infections, although not the main focus. There were no studies that resulted in a higher incidence of surgical site infections as all resulted in either a lower but not statistically significant surgical site infection rate or, in five studies, a statistically significant difference.

However, this does not mean that all clinical studies on using probiotics before surgery result in benefit of intervention (141). The main pathogens found in surgical site wounds were *S. aureus, P. aeruginosa,* A. *baumannii, E. coli, E. cloacae, E. faecium or E. faecalis,* which coincides with the findings of other research (13). In the investigated clinical studies, the most commonly used probiotics were strains of *L. plantarum, L. casei* and *L. acidophilus*. These three species of the genus *Lactobacillus* have well known and well-studied strain-specific abilities. Selected strains of *L. acidophilus* and *L. casei* aid in effectively reducing *C. difficile* infections (142) and *H. pylori* infections. Selected strains of lactobacilli aid in epithelium restitution during wound repair and can inhibit colonisation of other species in the wound (143). It seems that lactobacilli successfully amplify the antimicrobial effect against pathogens in wounds, but may not specifically enhance the immune system of the host, which was in fact the main rationale behind studying probiotics in these clinical trials. Perhaps different combinations of strain specific probiotics (3) could be more successful in reducing wound infections through synergistic and complimentary mechanisms of action. It is well established that orally consumed probiotics aid in supporting the body's immune response and therefore systemic action of probiotics to promote wound healing is another important strategy. Some studies (97,144) have found that postoperative consumption of probiotics (mainly *L. plantarum* 299) *per os* improves immune response, reduces the number of postoperative infections, and reduces hospitalization time and the amount of prescribed antibiotics. All of these studies conclude that postoperative endpoints should continue to be thoroughly investigated. Two studies highlight the great potential of topical use of probiotics to protect the wound (15,17).

Eight of the sixteen clinical trials of our literature search included synbiotics for patients undergoing surgery, therefore one could argue that it is not possible to determine whether the positive influence can be attributed to the individual components, the probiotics or the prebiotics. Although it is well known that prebiotics are utilized by probiotics (145), when comparing these eight clinical trials and the other eight clinical trials on surgical patients that received only probiotics, differences or better results for the studies that utilized synbiotics compared to the studies that utilized probiotics only were not observed. As noted by (146) some studies lacked placebo control groups and were not double-blinded, thus limiting the ability to describe the efficacy of the administered probiotics. This was also confirmed in the review by Gurusamy and co-authors (147) on the methods for preventing wound complications after liver transplantation. The authors concluded that there were no statistically significant differences in the probiotics/synbiotics group in graft rejections, intensive unit stay, hospital stay and mortality; however, it was found that a statistically significant lower proportion of these patients in the probiotics group developed infective complications, thus confirming at least one positive affect after probiotic administration.

Although this review is directed at the antimicrobial role of probiotics in combating wound infections and has shown promising results as possible alternatives or adjuvant therapies, the problem is still more complex. In order to achieve optimal wound healing, it is necessary to address in parallel additional factors regarding the patient's general health or the wound's physical environment and the body's immune response (23,148). Despite the fact that it is known that wound healing is impaired by wound infection, the exact role of bacteria in delayed wound healing remains controversial due to discrepancy in clinical results (14,65,149). However, an impressive number of studies as noted in this review have shown that exogenous and oral application of probiotics has shown reduction in wound site infections and therefore the potential use of probiotics for wound infections remains worthy of some more intense future study (150), perhaps focussed more on typical skin inhabitants as probiotics with high potential.

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