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Role of Probiotics on Skin Health

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ABSTRACT

Like the internal digestive system, the largest organ of our body, the skin, maintains a healthy balance with the natural inhabitants of it. Skin act as a host for several microorganisms (about one million per square centimetre) including different types of bacteria, fungi, and viruses. This microbiome takes active role in the fighting with infection, providing protection against environmental damage, regulation of pH and in keeping the skin hydrated and healthy. Probiotics are live and healthy microorganisms that can be consumed directly to restore the pH levels and the balance in the guts. They act like good bacteria and are important to keep away the "bad" bacteria from multiplying in different organ of human body. They can also be applied on the skin to restore the skin's ecosystem, pH and immunity. Again, long term exposure to solar radiation may induce UV damaged skin cancer. The utilization of probiotic bacteria in skin cancer research may help in development of new skin cancer prevention and treatment options.

Keywords: *Lactic Acid bacteria; Probiotics; Bacteriocin; Skin Cancer*

INTRODUCTION

Skin, the widely spanned organ of the body is always exposed to external environment, so it is very much prone to attack by several groups of pathogenic micro-organisms. This is the basis of most of the dermatological disorders. According to the Global Burden of Disease (GBD), skin and subcutaneous diseases were substantial reason of non-fatal disease encumbrance globally in 2010 and 2013 and accountable for 42·9 million (95% UI 28·6–63·4) disability-adjusted life years (DALYs) and 4·86 billion (4·68–5·06) incidences globally in 2019. This number comprises of death and disability triggered by acne, alopecia, bacterial skin infections, decubitus ulcer, fungal skin diseases, pruritus, psoriasis, scabies, urticaria, viral skin diseases, and other skin diseases. Disability burden is calculated using DALYs, which is the sum of years lost following a disease or untimely deaths (YLLs) and years lived with disability (YLDs). For calculation of GBD, over 7,000 researchers beyond 156 countries, collected the data of early deaths and information of disability about over and above 350 diseases and injuries in nearly 200 countries on the basis of age and sex, from 1990 to the present. According to GBD, 2017, Asian countries also have a high incidence of skin problem that are often associated with itching (i.e., psoriasis, contact dermatitis, atopic dermatitis, and pruritus) (Urban *et al.*, 2021). Acne vulgaris, scabies, cutaneous leishmaniasis are also common in Asian countries. In India last few decades due to increased pollution, global warming, skin cancers are increasing at a faster pace. As a developing country with high population size the frequency of infectious skin disease is also very high in India. There were 4.07 million (95% uncertainty interval 2.65–6.19 million) years subsisted with disability as a result of skin and subcutaneous diseases in 1990, which amplified to 6.26 million (95% uncertainty interval 4.12-9.35 million) in 2017 (Kavita *et al.*, 2021). The incidence of skin infection is increasing day by day due to emergence of multidrug-resistant microbial strains and the growing numbers of immune-compromised patients owing to immunosuppressive therapy, malignancy, transplant interventions, or HIV/AIDS (Esposito *et al.,* 2016). Around 50% of these were fungal skin diseases and rest are bacterial, viral and parasitic (Johnson *et al.*, 2018). In a recent report a group of scientists had shown that several skin disorders are associated with coronavirus, SARS-CoV-2 infection (Akl *et al.*, 2021). Some are linked with the viral infection directly and some are happening due to an upsurge in PPE usage and hygiene actions (hand sanitizer gels, sprays, frequent hand washing with soaps etc.)

(Darlenski & Tsankov, 2020). Among the bacteria involved in skin infections, role of *Staphylococcus aureus* (including methicillin-resistant S. aureus/ MRSA strains), *Staphylococcus epidermidis, Cutibacterium acnes, Propionibacterium acnes* and beta-hemolytic Streptococci, Gram negative *Klebsiella* sp., *Pseudomonas* sp. are well studied. The common fungal diseases are fungal nail infection, *Candidiasis, Blastomycosis, Mucormycosis, Aspergillosis* etc. In recent study it has also been found that prolonged infection by *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter species* increased the propensity to cancer development, due to weakened immune system. During this 21st century with the advent of all modern techniques, equipment, scientific knowledge, treatment system, cancer remains one of the major causes of human death worldwide. Though incidence of malignancies in skin cancer is very less, worldwide increased cases of skin cancer has been observed during last few decades. In India people mostly suffer from squamous cell carcinoma (SCC). Malignant melanoma and Basal cell carcinoma (BCC), which is one type of Non-Melanomatous Skin Cancers (NMSC), are the other types of skin cancer found in India. Recent studies shows that due to ozone layer depletion higher exposure to Ultraviolet B radiation (UVB 290-320 nm), presence of arsenic in drinking water as well as in insecticides, pesticides, herbicides and poultry feeds, presence of other harmful pollutants like coal tar and various hydrocarbons are the important causing agent for increased cancer cases in India (Lal *et al.*, 2016). Conventional treatment system of cancer relies on either surgery or radiotherapy or chemotherapy or a combination therapy. Generally small molecule drugs like tyrosine kinase inhibitors and human or humanized proteins (e.g., monoclonal antibodies) are mostly used in chemotherapy (Nguyen & Nguyen, 2016). But long-term usage of these chemotherapeutic drugs makes the cancer cells resistant and due to non-specificity, the nearby healthy cells are affected heavily. Most of the cases antibiotics are prescribed along with the anticancer drugs to prevent infections. But due to emergence of antibiotic resistance microbial infections remain uncontrolled. So, an alternate approach is very much necessary for cancer cell specific and deal with the side effects of chemotherapeutic drugs.

LITERATURE REVIEW

Probiotics-the friendly microbes

Foods derived from microbial activity were common since the dawn of human civilization and fermented milks were possibly the first of its kind to have active micro-organisms. In 1908 Elie Metchnikoff, father of modern probiotics, observed a very interesting phenomenon showing regular intake of lactic acid bacteria in fermented dairy products, for instance yogurt, was related with enhanced health and longevity in Bulgarian peasant populations. Later few years there was an immense interest in search for the role of lactic acid bacteria as probiotics. Lilly and Stillwell originally coined the term 'probiotics' representing 'substances secreted by one organism which stimulate the growth of another' (Lilly & Stillwell, 1965). Later United Nations Food and Agriculture Organization and the World Health Organization (FAO/WHO, 2001) adopted an alternative definition of probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Upon ingestion the probiotic strain should show some beneficial effect on the host such as prevention of colonization of harmful micro-organisms in intestine, alleviation of lactose intolerance, relief of constipation, antitumor or anti-carcinogenic effect, improvement of growth rate and feed utilization of animals, improvement of balance of the intestinal micro-flora, maintaining a chronic and immunological balanced inflammatory response, maturation of immune system, anticholesterolemic effect etc. Scientific reports have already shown that use of probiotics is a sound choice in prevention and therapy of antibiotic associated diarrhoea, against traveller's diarrhoea, irritable bowel syndrome (IBS), IBD, lactose intolerance, peptic ulcers, allergy and autoimmune disorders etc. A variety of micro-organisms including lactic acid bacteria, *Bifidobacteria, Saccharomyces*, enteric, *Streptococci* and some other beneficial microorganisms have been targeted as potential probiotics with therapeutic application. A clinical study unveiled that prenatal administration of a probiotic strain of *Lactobacillus rhamnosus* GG (LGG) declines the development of atopic eczema in children (Foolad *et al.*, 2013; Kuitunen, 2013) following the anti-inflammatory properties of the above-mentioned bacterium.

Another study reported LGG intake by children with atopic dermatitis enhances the production of the anti-inflammatory cytokine IL-10 (Pessi *et al.*, 2013). Additionally, it has been seen that oral administration of *L. casei Shirota* strain to mice inhibited specific IgE production (Lim *et al.*, 2009). A double-blind, randomized, placebo-controlled trial by Abrahamsson *et al.*, (2007), have experienced that infants treated with *L. reuteri* ATCC 55730 strain had a reduced amount of IgE-associated eczema. It is known that, Lactic acid bacteria (LAB) are a cluster of associated bacteria that yield lactic acid as a result of carbohydrate fermentation. The genera *Lactobacillus, Leuconostoc, Pediococcus* and *Streptococcus* are vital members of this group. From ancient time they are present in different types of fermented foods like curd (*Lactobacillus* spp., *Lactococcus* spp.), yogurt (*Streptococcus* spp. and *Lactobacillus* spp.), cheeses (*Lactococcus* spp.), sauerkraut (*Leuconostoc* spp., *Lactococcus* spp.), sausage (*Pediococcus*) etc. They are Gram positive bacteria with GC content less than 50% in their DNA. Most LAB are non-spore forming rods or cocci as well as aero-tolerant anaerobes lacking cytochromes and porphyrins which makes them catalase and oxidase negative. This group of bacteria can be used for control of surface infecting pathogens as they produce several antimicrobial compounds like lactic acid, hydrogen peroxide, di-acetyl along with bacteriocins. Bacteriocins are synthesized in the ribosome small peptides and showed high antimicrobial activity to closely related species. They are non-toxic to eukaryotic cells and in addition bacteriocins also exert direct activity toward bacterial pathogens.

Bacterial therapy of cancer-a newer approach

The idea of using bacteria or the bacterial proteins in cancer therapy is one of the alternate approaches and it started after observing some practical incidences where bacterial infection helps in regression of tumor /cancer. At the end of 1890, American physician, Coley witnessed the liaison between bacterial infection and cancer regression and became pioneer in the field of immunotherapy by developing the first killed bacterial vaccine named as “Coley's toxin”. Bacteria release varieties of proteins, peptides, toxins, enzymes, immunotoxins etc. as their survival strategy. Antimicrobial peptides (AMPs) obtained from different groups of bacteria can be investigated for their anti-cancerous property and can be applied alone for both for treatment of skin infection as well as skin cancer (Coley, 1891 and 1893). They can also be combined with conventional chemo-therapeutic drugs (Felício *et al.*, 2019).

Characteristics like low toxicity, good solubility, high penetration to cells, high specificity, less interaction time with target cells which lower the chances of generation of resistance, membrane-permeabilizing ability make them attractive antimicrobial as well as anti-cancerous therapeutic agent (Woo *et al.*, 2022). Though most of the contemporary research on probiotics and cancer is restricted to gastrointestinal tumors, some recent evidences showed that the consumption of oral probiotics improve indirectly various skin disorders comprising atopic dermatitis, acne, and psoriasis. According to Weill *et al.* (2013), probiotics can directly regulate the cutaneous immune system and reinstate the homeostasis via the gut–skin axis. But a very less information is found about the effect of direct topical application of probiotics on skin cancer till date. Bacteriocin, one AMP mainly from probiotic bacteria, has both the antimicrobial as well as anticancer property. Bacteriocins are small peptides manufactured by ribosomes in several Gram-positive and Gram-negative bacteria. Most of them have GRAS status. Long time they have been used in food industry as natural preservatives. Due to their cationic and amphipathic nature, they are less toxic to mammalian cells, membrane dissolution ability, immuno-modulatory power and most importantly, their antimicrobial activities can be used directly topically to treat skin infections as well as in skin cancer. They can be formulated as ointments, combined with cosmetics, applied directly as anticancer agent or applied in conjunction with conventional cancer drugs. There are several evidences that show the topical application of bacteriocin decreases inflammation, colonization of infecting pathogen and even improve the acne, psoriasis.

From a work published by RocíoLópez-Cuellar *et al.* (2016), it is analyzed that though at the beginning of 21st century research on bacteriocin from Lactic acid bacteria was confined to food science, in the last decade about 37% of the published research was portrayed mostly on its biomedical applications.

During this time, the two main problems faced by the scientists worldwide are multi drug resistance and non-specificity of the applied drugs. In search of alternatives to complicacies like cancer, systemic infections, oral-care, vaginal infections, contraception and skincare, recent research is focused on therapeutic application of Anti-Microbial Proteins (AMPs). Huang *et al.* (2021) highlights the potential of bacteriocins as novel therapeutic treatments in microbe infection, cancer, and immune system in human body. Cesa-Luna *et al.* (2021) also reveal the advance usage of bacteriocin as biocontrol agent in medical and agricultural field. Along with these, they discussed about their mode of action and role of bacteriocins to modulate the signaling in host-associated microbial populations. Another report by Ovchinnikov *et al.* (2020) showed that two broad-spectrum bacteriocins, garvicin KS and micrococcin P1 act synergistically and with penicillin G, killed methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro*. They compared the effect of this formulation to Fucidin antibiotic cream, normally employed in skin infection treatments, and found its superiority in preventing resistance development. Kober *et al.* (2015) discussed the contribution of probiotics in acne and rosacea treatment, and protection against aging and photodamage.

Nguyen and Nguyen (2016) showed that Azurin a bacteriocin from Pseudomonas aeruginosa, can precisely penetrate human cancer cells and induce apoptosis. The study also mentioned about eight recognized bacteriocins from human gut pathogenic and commensal bacteria having functional properties quite like azurin and p28-azurin, with the help of bioinformatics approaches. Review article of Felgner *et al.* (2017) revealed the clinical trials performed during the last 150 years on bacteria mediated tumor therapy (BMTT). The dual activity of Antimicrobial proteins (AMPS) was also established. Rodrigues *et al.* (2019) reported that some infectious agents like *Streptococcus pneumoniae, Stomatococcus mucilaginous, Staphylococcus* spp., *E. coli*. *Klebsiella* spp., *Pseudomonas aeruginosa, Candida spp., Helicobacter pylori, Hepatitis* B and C, and Human Papilloma Viruses (HPV), related to the progress of cancer and bacterial proteins and peptides can be used as a treatment strategy against them. The preferable characteristics of proteins and peptides from bacterial sources that revealed activity against microbial infections and cancer, along with their efficacy *in vitro* and *in vivo* are also discussed.

The report of Benítez-Chao *et al*. (2021) gave emphasis on the necessity to increase in vivo testing of bacteriocins and advance the in vivo models that both evaluate the efficacy of bacteriocins as antimicrobial agents and introspect probable toxicity and side effects, which are crucial factors to define their achievement as prospective therapeutic agents in the fight against infections triggered by multidrug-resistant microorganism. In a recent report by Khalfallah *et al.* (2021), antimicrobials from two *Streptococcus salivarius* strains and one *Lactobacillus plantarum* were used to develop a plaster/bandage for the application to diseased skin. The anti-cancer activity of bacteriocin to other types of organs also reported. From the work of Al-Madboly *et al.* (2020), it is proved that enterocin (LNS18) from *Enterococcus* species can be used in treatment of liver cancer. Application of Nisin in head and neck squamous cell carcinoma (HNSCC) is well documented (Shin *et al.*, 2016). It has also shown activity in oral cancer.

Recently, Le Noci *et al.* (2018) revealed that probiotic aerosol therapy inhibits lung melanoma metastasis *Lactobacillus rhamnosus* GG strain. It can inhibit cancer progression and encourages apoptosis in mouse colon cancer HGC-27 and human colon cancer Caco-2, DLD- 1, and HT-29 cells as well (Orlando *et al.*, 2012). Application of prebiotics along with probiotics that is application of symbiotic (*Lactobacillus rhamnosus* + *Lactobacillus acidophilus* + inulin) had shown much more effectiveness in lowering the oxidative stress than the application of probiotics alone (Verma & Shukla, 2014). Sharma and Shukla (2016) also told that metabolites from probiotics can be applied independently or in conjunction with others in colon cancer or for other diseases. Sharaf *et al.* (2018) reported that application of probiotics (*Lactobacillus acidophilus* and *Lactobacillus rhamnosus* GG) in combination with celecoxib, a selective cox-2 inhibitor diminishes the incidence risk of colon cancer. Cancer patients receiving chemotherapy can be given probiotics as an adjunct therapy (Sankarapandian *et al.*, 2022).

Apoptosis-like morphological changes was observed after application of Enterocin 12a, a bacteriocin

from a vaginal isolate *Enterococcus faecium* 12a (Sharma *et al.*, 2021). The concept of gut-brain-skin axis and role of microbiomes in spreading cancer is also revealed (Misra & Raghuwanshi, 2022). In a similar study, bi-directional communication between gut and lung (termed as Gut–Lung axis) and role of probiotics in lung diseases is also established (Rai, 2021). The gut microbiota has a noteworthy effect on the skin good health as it is accompanying with various chronic inflammatory skin disorders, including acne, rosacea, atopic dermatitis, and psoriasis (Divyashri *et al.*, 2021). Probiotics may offer health benefits during vaginosis. This was reported by Hattiholi *et al.* (2021). From the report of Upadhaya *et al.* (2021), it can be seen that probiotics are useful in the prevention and cure of cancer through microbiota and AMPs, following the mechanisms like immune modulation, condensed bacterial translocation, enhanced gut barrier function, anti-inflammatory, anti-pathogenic activity, reduced tumour formation, reduced metastasis, and others.

CONCLUSION

This review attempts to mention about some recent observations that evidenced the potency of both oral and topical probiotics in preventing and treating skin diseases in addition to skin cancer. Due to antibiotic resistance and side effects of chemo and radiotherapy of cancer, combinational therapy can be encouraged as an alternative approach. Past few years' number of in vivo tests has increased in search of newer peptides or proteins with antimicrobial and antitumoral activity. Probiotics are source of varieties of such proteins and peptides. They can also be modified to decrease or eliminate their cytotoxicity and can be very target specific. Besides they can be applied directly with the conventional therapeutics which reduces the cost of the treatment.

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