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Evaluation of skin cancer prevention properties of probiotics

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Abstract

Bacteria play a crucial role in human health and disease pathogenesis. In recent years, the therapeutic potential of probiotics has gained increasing attention, with studies suggesting their application in treating various diseases, including cancer. We evaluated clinical data supporting the use of oral and topical probiotics for skin malignancies by conducting a literature search in PubMed and Google Scholar. Although limited, clinical trials investigating probiotics in cancer prevention and treatment have shown promising results, particularly in controlling tumor progression and enhancing therapeutic outcomes. Emerging research suggests that probiotics may contribute to skin cancer prevention by modulating the gut and skin microbiomes, enhancing immune responses, exerting antioxidant and anti-inflammatory effects, and inducing apoptosis. Given their antiproliferative and pro-apoptotic effects on carcinoma cells, probiotic-based therapies may serve as potential cancer-preventive agents and adjunctive treatments during conventional therapies. Key findings from our review highlight the ability of probiotics to influence cancer progression through immune regulation, apoptosis induction, and modulation of inflammatory pathways. However, further well-designed clinical trials are needed to validate these findings and establish probiotics as a viable therapeutic approach in oncology.

Keywords Skin cancer, Probiotics, Prevention

Introduction

Non-pathogenic microorganisms that have beneficial properties for human health are known as probiotics [1]. The most important probiotic microorganisms include lactic acid bacteria such as Lactobacillus, Pediococcus, and Bifidobacterium species. Immunomodulatory properties, anti-pathogenic activity, and anti-obesity effects are among the well-known functions of probiotics [2]. Probiotic by-products can also have a therapeutic effect similar to that of live microorganisms in their absence [3]. Also, other probiotic products, such as postbiotics, can inhibit pathogenic factors such as bacterial tyrosines, organic acids, diacetyl, and acetaldehydes [4, 5].

Oral probiotics are safe and effective in a variety of conditions. Today, they are used in the management of a wide range of symptoms and diseases, including diarrhea

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and inflammatory bowel disease in the gastrointestinal tract, and the treatment of atopic dermatitis, acne, psoriasis, bacterial vaginosis, and genital candidiasis in the dermatological and infectious fields. They are also used to reduce serum cholesterol levels [6, 7].

The ability of probiotics to modulate cancer signals has brought them into particular focus [8]. The ability of probiotics in cancer treatment management includes the ability to induce apoptosis, induce autophagy, reduce and inhibit mutagenic activity, reduce the expression of oncogenes, inhibit kinase enzymes, reactivate tumor suppressors, and prevent metastasis [9, 10]. Metabiotics play a key role in the anticancer properties of probiotics. Structural components of probiotic microorganisms, their metabolites, and signaling molecules with a specific chemical structure are called metabiotics. Their properties include optimizing specific physiological functions of the host, as well as regulatory, metabolic, and behavioral responses related to host activity [11].

Probiotics inhibit tumor growth and disease progression by inducing apoptosis, and this ability to induce apoptosis could be a promising target in cancer therapy [12]. Apoptosis can be defined as self-initiated programmed cell suicide, leading to DNA fragmentation, cytoplasmic shrinkage, membrane changes, and ultimately cell death. This process occurs without lysis or damage to neighboring cells [13]. The main function of apoptosis is to inhibit tumor growth. The mitochondrial/intrinsic pathway, the death receptor/extrinsic pathway, and the perforin/granzyme pathway, which are three interconnected pathways, play a major role in apoptosis. Tumor necrosis factor (TNF), inhibitors of apoptosis proteins, caspases, B-cell lymphoma (Bcl)-2, and the p53 gene are the five main groups of genes involved in apoptosis. A study has shown that the induction of apoptosis in cancer cells by probiotics occurs by modulating Bax/Bcl-2 and caspases [10].

The ability of colicin, a bacteriocin isolated from Escherichia coli, to create micropores on the plasma membrane can lead to the destruction of cancer cells [14]. The induction of apoptosis and cell cycle arrest in the G1 phase is due to the formation of these pores. In addition, nisin and doxorubicin are two compounds that, when applied simultaneously, can reduce tumor volume by about 66.82% compared to the untreated control group [15]. C-jun N-terminal kinase (JNK)-mediated apoptosis is a characteristic of probiotic-derived tumor suppressor ferrochrome molecules. In addition, Lactobacillus plantarum (LPCLA) produces conjugated linoleic acid, a functional lipid that induces apoptosis in breast cancer cells through inhibition of the NFκB pathway [16]. By upregulating the expression of Bax, IFN-γ and TNF-α and downregulating the expression of Bcl2, the two probiotics Lactobacillus acidophilus and Bifidobacterium bifidum were able to show greater cytotoxic effects against breast and colon cancer cell lines. L. acidophilus is another probiotic that increases mRNA expression of survivin and decreases the mRNA expression of SMAC induction apoptosis [10]. Studies have shown that in the HT29 43 colon cancer cell line, hBD-2 gene expression is significantly increased by the probiotic Lactobacillus casei [17]. In the study by Jo et al., nisin was shown to induce apoptosis and reduce proliferation in HNSCC cells through the activation of several steps. These steps include increasing intracellular calcium, inducing cell cycle arrest, and activating cation transporter homolog 1 (Chac1) [18].

Materials and methods

A review of the keywords of scientific journal articles on probiotics and cancer, especially skin cancers and tumors, showed that important topics in the field of probiotics use include: the role of probiotics in the treatment of neoplasms, induction of apoptosis by cell membrane perforation, increase or decrease in the activation or inhibition of genes related to the activation of apoptosis pathways in human and animal studies. We tried to summarize and summarize the studies related to the title to provide useful information to the readers. In writing this review, the scientific databases PubMed, Scopus, Google Scholar, and Web of Science were used.

Skin cancer

Skin cancers are divided into two categories: non-melanoma skin cancers (NMSCs) and melanoma skin cancers. NMSCs such as basal cell carcinoma (BCC)and SCC are more common and have a keratinocyte origin, and on the other hand, there are melanocytic cancers that have a melanocytic origin and have the worst prognosis among skin cancers [19].

Melanoma accounts for about 1% of all skin cancers, and about 160,000 people are diagnosed with this cancer each year [20], mostly in Northern Europe and Australia [19]. The prevalence of melanoma has been increasing in the past few years [21]. Melanoma development is driven by multiple factors, including sun exposure and BRAFV600 mutations, which activate the MAPK/ERK signaling pathway. The advent of BRAF and MEK inhibitors has significantly transformed the treatment paradigm for melanoma, offering targeted therapeutic options that improve patient outcomes [22]. Melanoma treatment in the early stages includes surgery and lymphadenectomy [23], but in metastatic cases, treatments such as radiotherapy and drug treatments are needed [24]. Drug therapies available for the treatment of melanoma include: BRAF inhibitors (such as vemurafenib, dabrafenib, and encorafenib), mitogen-activated protein kinase kinase (MEK) inhibitors (such as trametinib and

cobimetinib) [25, 26], a monoclonal antibody against Cytotoxic T-Lymphocyte Antigen (CTLA- 4) (such as ipilimumab) and monoclonal antibody targeting programmed cell death protein 1 (PD-1) (such as nivolumab and pembrolizumab) [27–30]. A review of emerging therapeutic targets such as ERK5, CD73, ALDH1A1, PLA1A, and DMKN suggests potential enhancements in treatment precision and overcoming resistance. Additionally, innovations like mRNA vaccines and CRISPR-Cas9 are transforming personalized oncology by providing effective strategies for addressing genetic mutations and enhancing immune responses. Nevertheless, challenges such as patient response variability, toxicity issues, and the limited effectiveness of RAF inhibitors in non-BRAF-mutated melanomas underscore the necessity for alternative therapies. Future research should prioritize optimizing treatment combinations, refining patient selection, and identifying predictive biomarkers to enhance therapeutic success. Advancing these strategies is vital for improving patient survival and revolutionizing melanoma treatment [22].

Keratinocyte carcinomas, known as non-melanoma skin cancers, are the most common malignancies in the world, including BCC (the most common skin malignancy) and SCC which together account for 95% of NMSCs [31, 32]. BCC, is a slow-growing skin tumor that originates from basal cells in the epidermis, in the histological examination of this tumor, nests of basaloid cells are found in the epidermis, which, depending on the type of BCC, can spread to the dermis. This tumor metastasizes in less than 0.01% of cases, but if not treated in time, it can cause physical deformities [33–35]. SCC accounts for about 20% of skin cancers and originates from keratinocytes and adnexal structures or their precursors [36, 37]. In the histology of this tumor, atypical and apoptotic keratinocytes, cells, hyperchromasia, nuclear polymorphism, and loss of polarity can be seen [38]. These changes can cross the basement membrane and spread to the dermis, creating invasive types [39]. Exposure to ultraviolet radiation, especially UVB [40], exposure to ionizing radiation, immunodeficiency [41, 42], chronic inflammation [43], and family history [25, 44] are risk factors for keratinocyte cancers. Surgical excision [45], topical 5-FU [46], and topical imiquimod for superficial BCCs [47] are common treatments for keratinocyte tumors.

In some studies, the relationship between skin cancer and microbiota imbalance has been discussed [48], for example, it has been observed that the abundance of Staphylococcus aureus in cells with SCC is higher than in healthy cells [49–51] and the abundance of Malassezia in cells with SCC less than normal cells. And since these fungi can inhibit the formation of Staph aureus biofilms, they can act as an anti-staph agent in people with SCC [52]. On the other hand, Staph epidermidis has been observed to have anti-proliferative properties against cancers such as SCC and melanoma [53, 54]. In some studies, the association between stage three and four melanoma and Corynebacterium spp has been seen [55]. According to some studies, Fusobacterium's role in the development of melanoma has also been mentioned. This bacterium is also associated with pancreatic, oral, and colon cancer. Many studies are being conducted on the efficacy and safety of melanoma treatment with a combination of probiotics and immunotherapy [56].

A recent study utilized publicly available genome-wide association study (GWAS) summary data to conduct three two-sample Mendelian randomization (MR) analyses, investigating potential causal relationships between the gut microbiome and BCC, melanoma skin cancer, and ease of skin tanning. MR analysis revealed differential effects of various gut microbiota groups on these traits. Sensitivity analyses supported these findings, showing no evidence of instrument heterogeneity or horizontal pleiotropy. Using GWAS data from individuals of European ancestry, the researchers identified seven independent single nucleotide polymorphisms (SNPs) associated with the gut microbiome and BCC, four SNPs with melanoma skin cancer, and fourteen SNPs with ease of skin tanning, all reaching genome-wide significance. In total, 25 gut microbial traits, encompassing 148 SNPs, demonstrated causal associations with these skin-related conditions. These results suggest a potential role of the gut microbiome in the development and progression of BCC, melanoma skin cancer, and tanning response, warranting further investigation [57]. A study investigating the heritable components of the skin microbiome analyzed samples from 45 individuals, including monozygotic and dizygotic twins and their mothers (aged 26–55 years). The findings showed that skin microbial diversity was significantly influenced by age and skin pigmentation. Heritability analysis revealed that both genetic factors and shared environmental influences shaped the skin microbiome. Notably, the abundance of Corynebacterium jeikeium was strongly associated with SNPs in the FLG gene, which is critical for epidermal barrier function. Although genome-wide analyses identified QTL regions linked to innate immune activation, these regions did not overlap with those found in our investigation, likely due to differences in SNP selection strategies. While our study focused on genes known to affect skin structure and function, recent research highlights the importance of exploring SNPs within flanking regions and distant regulatory elements, such as enhancers and promoters. Future studies examining these long-range interactions are expected to provide deeper insights into the genetic regulation of the skin microbiome [58]. Jeremian et al. utilized a large UK Biobank cohort—including

cases of BCC, cutaneous squamous cell carcinoma, melanoma in situ, invasive melanoma, and healthy controls — to explore how genetic and environmental factors jointly influence skin cancer risk. By analyzing 8,798 SNPs across 190 DNA repair genes and 11 demographic and behavioral risk factors, they found that darker skin and hair colors significantly reduced cancer risk. Eleven SNPs were significantly associated with BCC, three of which also correlated with invasive melanoma. Gene–environment interaction analysis identified 201 significant SNP–environment interactions involving 90 genes (FDR $q < 0.05$). Notably, FANCA gene variants (rs9926296, rs3743860, and rs2376883) demonstrated consistent interactions with clinical factors across BCC and M-inv groups. This study uncovered novel genetic risk factors for keratinocyte carcinomas and melanoma, emphasized the prognostic relevance of FANCA alleles in individuals with sunlamp use and childhood sunburn history, and highlighted the value of integrating genetic and clinical data for improved disease risk stratification [59].

Probiotic

Characteristics of probiotics

Most of the studies conducted on the role of probiotics in dermatology are related to atopic dermatitis. Changes in gut microbiota have been shown to increase the risk of developing atopic dermatitis [60]. The benefits of treatment with probiotics have been reported in other chronic skin diseases such as psoriasis [61], rosacea [62], oral lichen planus [63], and seborrheic dermatitis [64]. In some studies, the therapeutic effects of probiotics in reducing photoaging by reducing oxidative stress, reducing extracellular matrix remodeling, and reducing the incidence of inflammatory processes have been mentioned [65]. Other uses of probiotics in medicine include regulating the immune system and the digestive system [66] including reducing the severity of diseases such as irritable bowel syndrome, Crohn's disease, ulcerative colitis, and antibiotic-associated diarrhea [67]. The surface of the skin and mucous membrane of mammalian species are colonized with various types of microorganisms (100–100 trillion microbial cells) such as bacteria, fungi, viruses, protozoa, etc. known as microbiota [68]. The activity and composition of these microorganisms can affect the health of the body [69]. Different articles consider the beginning of this colonization immediately after birth [70], this colonization changes in different stages, for example, during breastfeeding, about 10^9 bacterial cells per liter of healthy microbiota are transferred from mother to child [71], and with increasing age and under the influence of race, geographic region, social and economic status, type of nutrition, exercise, taking drugs such as antibiotics, suffering from some inflammatory diseases, diabetes, and stress, changes occur [72]. Microbiota affect metabolism, the immune system, and homeostasis and can have a double-edged effect in aggravating or reducing physiological or pathological processes such as cancer [73].

According to the definition of the International Scientific Association of Probiotics and Prebiotics, probiotics are live microorganisms that, if consumed in sufficient amounts, can have beneficial effects on the health of the host [74]. Probiotics are classified and identified based on specific strains, genera and species, and subspecies [75]. The mechanism of action of different species and strains of probiotics is diverse and can include competitive elimination of pathogenic species, inactivation of carcinogenic substances, and production of short-chain or branched fatty acids that affect other peripheral tissues in addition to the intestine. In particular, increased tissue sensitivity to insulin, cell adhesion, and mucin production, effects on the immune system, including increased differentiation into T-regulators and increased anti-inflammatory cytokines (such as interleukin-10), and growth factors. Such as transforming growth factor) and its effects on the endocrine and nervous systems.

Most probiotic compounds on the market include lactobacilli and other lactic acid-producing bacteria such as lactococci, streptococci, and bifidobacteria. Other strains include propionibacterium, bacillus, and Escherichia and yeasts from the saccharomyces group [76].

Complications from the use of common probiotic species such as lactobacilli, bifidobacterium, lactococci, and some yeasts are uncommon in healthy individuals and are recognized as "generally recognized as safe" (GRAS), while other types of probiotics exist. (such as streptococci, enterococci, bacilli, and other spore-forming bacteria) that are not classified as GRAS [77]. In some texts, severe complications such as bacteremia and fungemia in premature infants and immunocompromised patients have been reported [77–79].

Safety FDA approval

According to the Food and Drug Administration (FDA), a drug is a compound intended for the diagnosis, treatment, or prevention of disease. Therefore, for the use of probiotics, regulatory requirements differ depending on whether they are used as a drug or a dietary supplement [80]. A probiotic that is to be used as a drug should undergo regulatory processes similar to other new drugs. Before a drug can be used clinically, it must be approved by the FDA. The process of distributing probiotics in the pharmaceutical market must be carried out after the necessary safety tests of these products [81].

Compounds that are considered dietary supplements are placed under the umbrella of "foods" by the FDA's Center for Food Safety and Applied Nutrition, including probiotics [82]. In 1994, the Dietary Supplement Health

and Education Act (DSHEA) defined a dietary supplement as an edible product that contains a "food" that is taken to supplement the diet. These compounds must contain more than 1 of the following nutrients: a vitamin; a mineral; a plant or other herb (excluding tobacco); and an amino acid [83].

The human skin microbiome

Millions of bacteria, fungi, and viruses live on our skin, making up the skin microbiota. The skin microbiome plays a fundamental role in protecting against invading pathogens, training the immune system, and breaking down natural products, similar to the function of microorganisms in our gut [84]. Skin physiology, including moist, dry, and oily skin, determined the composition of the microbial communities. Staphylococcus and Corynebacterium species were abundant in the elbow and foot folds, which are relatively moist, and Propionibacterium species were abundant in oily areas of the skin fungal community composition was similar across body sites and was not associated with physiology. A more diverse mix of Malassezia species, Aspergillus species, and Cryptococcus were dominant in the lower limb sites of the feet, and Malassezia fungi dominated in the midsection and arm. This abundance was in contrast to the bacterial communities found throughout the body [85, 86]. The skin microbiota has adapted to survive in cool, acidic, and dry environments. These microorganisms use resources found in sweat, sebum, and the stratum corneum as a source of nutrition [87]. After puberty, the skin supports the proliferation of lipophilic species Propionibacterium spp, Corynebacterium spp [88], and fungal Malassezia spp [89, 90]. In contrast, the skin before puberty and during childhood has a higher abundance of Firmicutes (streptococcus spp.), Bacteroidetes, and Proteobacteria (betaproteobacteria and gammaproteobacteria) [88]. A range of microorganisms, particularly eukaryotic viruses and Merkel cell polyomavirus, have been implicated in skin diseases. Some of these, such as polyomavirus, may be an oncogene in some aggressive skin cancers [91].

The potential role of probiotics in skin cancer prevention Emerging research indicates that probiotics may help prevent skin cancer by modulating the skin and gut microbiomes, boosting immune responses, providing antioxidant and anti-inflammatory benefits, and apoptosis induction (Fig. 1) [92].

Gut-skin axis and immune modulation The gut microbiome plays a crucial role in shaping the host immune system by defending against external pathogens and priming immunoprotective responses. The gut is recognized as a key immune organ, with the gut-associated lymphoid tissue (GALT) serving as its most intricate immune compartment. Within the GALT, Peyer's patches function as organized lymphoid structures and primary sites for initiating mucosal immune responses. Research has shown that dendritic cells within Peyer's patches produce IL-10 and drive T-helper cell differentiation. Cytokines and activated immune cells from these patches can enter circulation and influence the skin's immune status, potentially enhancing defense mechanisms and reinforcing gut-skin communication. Studies also suggest that probiotics exert immunomodulatory effects through GALT components, with Peyer's patches playing a particularly significant role [93, 94]. Levkovich et al. reported that feeding mice yogurt containing the probiotic Lactobacillus reuteri induced a notable "glow of health" phenotype. This was marked by anagen-phase follicular shifts, enhanced folliculogenesis, and increased sebocytogenesis, resulting in thicker, shinier fur. The probiotic exerted these effects by modulating the immune system, promoting the production of the anti-inflammatory cytokine IL-10, which stimulated peripheral regulatory T (Treg) cells. Additionally, it triggered the release of hypothalamic hormones that enhanced epithelial integrity and immune tolerance [95–97]. Nenciarini et al. investigated the immune-modulating interactions between Saccharomyces cerevisiae and Lactobacillus species. Using strains derived from kefir, probiotics, and stool samples of a Crohn's disease patient, they found that co-culturing these microbes stimulated immune cell activation while promoting a tolerant immune response. Their findings highlight the potential of leveraging microbial interactions to regulate immune function [98, 99].

Anti-inflammatory and antioxidant mechanisms Oral and topical probiotics, by modulating the skin microbiome and gut-skin microbial interactions, hold promise for preventing and managing skin photoaging. They achieve this by reducing oxidative stress and inhibiting the inflammatory cascade. Oxidative stress plays a key role in activating the NF-κB pathway by stimulating the cytoplasmic inhibitor of NF-κB (I-κB) kinase, leading to I-κB phosphorylation and degradation. This process facilitates the release of NF-κB, allowing its translocation to the nucleus, where it promotes the expression of inflammatory cytokines and prostaglandins. Additionally, NF-κB activation is linked to UV-induced oxidative modifications of cell membrane components [100]. A study demonstrated that probiotic-fermented Portulaca oleracea L. effectively alleviated DNFB-induced atopic dermatitis by modulating the NF-κB signaling pathway. The treatment led to a downregulation of key inflammatory cytokines associated with atopic dermatitis, including TNF-α, interleukin-4, and interferon-γ while also increasing filaggrin expression. Additionally, it inhibited the expression of IKKα, NF-κB, and TNF-α genes, as well as the proteins p-NF-κB, p-IKKα,

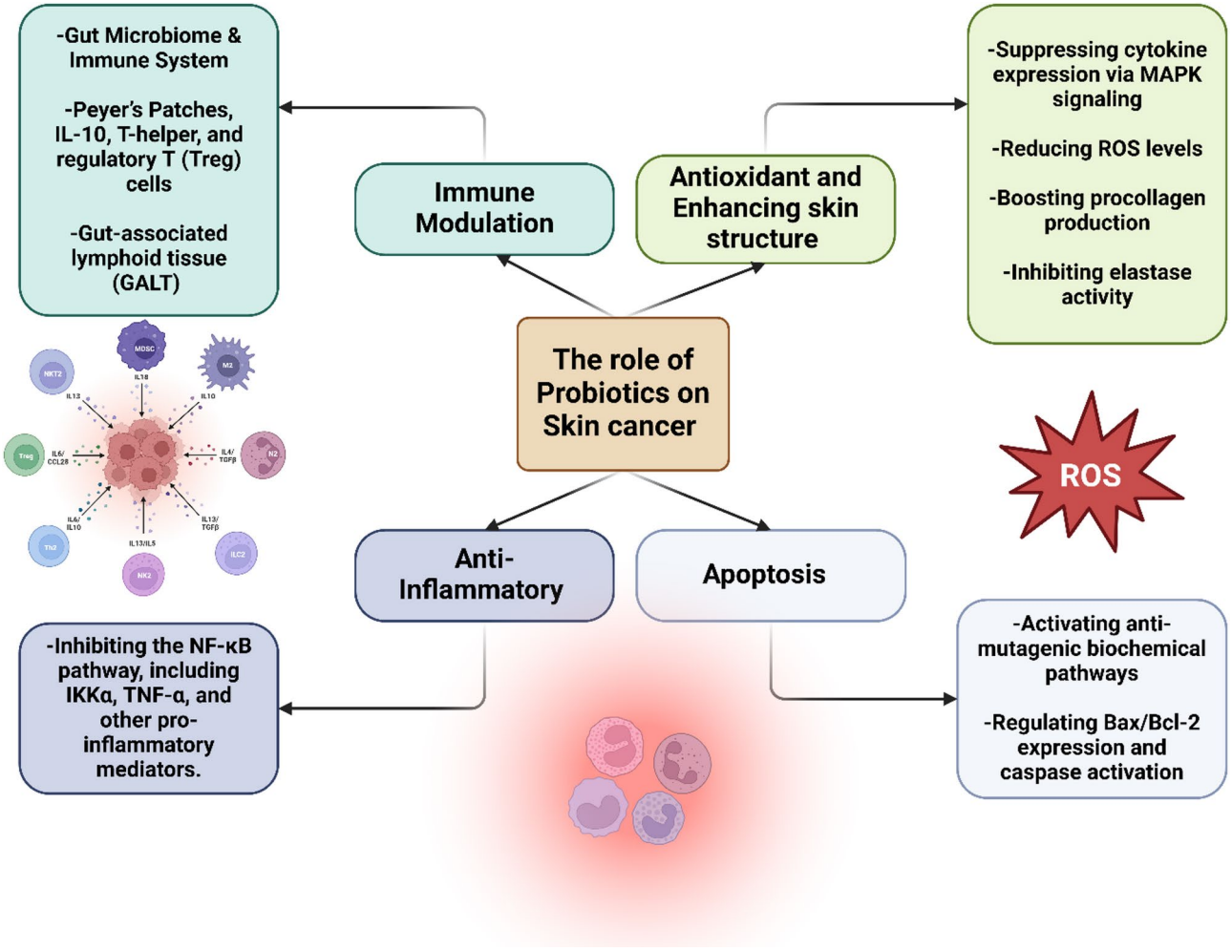

Fig. 1 Probiotics play a crucial role in skin cancer prevention through various mechanisms. They modulate the immune system by enhancing gut microbiome interactions, involving Peyer's patches, IL-10, T-helper cells, regulatory T (Treg) cells, and gut-associated lymphoid tissue (GALT). Their antioxidant properties help suppress cytokine expression via MAPK signaling, reduce ROS levels, boost procollagen production, and inhibit elastase activity, contributing to skin structure maintenance. Additionally, probiotics exert anti-inflammatory effects by inhibiting the NF-κB pathway and key pro-inflammatory mediators such as IKKα and TNF-α. Furthermore, they promote apoptosis by activating anti-mutagenic biochemical pathways and regulating Bax/Bcl-2 expression and caspase activation

TNF-α, and p-IκBα, which are involved in the NF-κB signaling pathway [101]. Chen et al. demonstrated that topical application of Limosilactobacillus fermentum XJC60 helped stabilize mitochondrial function, reduce reactive oxygen species (ROS) production in UVB-damaged skin cells, and promote overall skin health [102]. Furthermore, the research has highlighted oxidation resistance as the primary mechanism through which Lacticaseibacillus rhamnosus and Lacticaseibacillus casei strain Shirota mitigate skin photoaging [103]. Lim et al. found that topical Lactobacillus acidophilus has strong antioxidant properties, significantly reducing elevated ROS levels in HaCaT cells after UVB irradiation, and mitigating skin photoaging caused by oxidative damage [104]. Another study suggested that oral administration of Bifidobacterium breve (Yakult) could prevent ROS production and reduce UV-induced skin barrier damage and oxidative stress in animal models [105]. Kang et al. demonstrated that a plant extract fermented with Lactobacillus buchneri applied topically alleviated ROS effects in a UVB-induced photoaging model in vitro. This was achieved by increasing type I procollagen synthesis, inhibiting elastase activity, and boosting the expression of UVB-induced MMPs in HaCaT keratinocytes and dermal fibroblasts [106]. Kim et al. discovered that dietary supplements containing Bifidobacterium longum and galacto-oligosaccharides helped protect the skin from UVB-induced photoaging. This protective effect was attributed to their anti-inflammatory and antioxidant properties. The supplementation also elevated serum levels of short-chain fatty acids (SCFAs), particularly acetate, which has been shown to enhance and activate skin-resident Tregs through histone acetyla-

tion [107, 108]. Kupper et al. showed that oral administration of Bifidobacterium breve B-3 in UV-irradiated mice significantly decreased UV-induced production of IL-1β in the skin [109]. Research indicates that Lactobacillus acidophilus IDCC3302 can inhibit pro-inflammatory cytokine production via the MAPK signaling pathway, helping to reduce UVB-induced skin inflammation [110]. Research suggests that probiotics exert anti-inflammatory effects through Toll-like receptors (TLRs) in various pathological conditions [111–113]. Plantinga et al. found that the Bifidobacterium breve strain induced lower levels of the proinflammatory cytokine interferon-gamma (IFN-γ) compared to Lactobacillus rhamnosus and Lactobacillus casei. Both B. breve and lactobacilli activated cytokine production via Toll-like receptor 9 (TLR9), but the reduced inflammatory response of B. breve was attributed to the inhibitory effects of TLR2 [114].

Apoptosis induction

Many studies indicate that lactic acid-producing bacteria (LAB) can hinder the onset or advancement of cancer. Lactic acid influences tumor development through several mechanisms, such as encouraging apoptosis, inducing cell cycle arrest, and exhibiting anti-oxidative, anti-angiogenic, and anti-inflammatory properties [115–117]. The research indicates that probiotic bacteria play a beneficial role in reducing mutagenic factors. In particular, Bifidobacterium lactis (B. lactis) probiotics have been found to significantly lessen the mutagenic effects of AFB1 in many studies [117–132].

A study led by Monica Kwakwa and her colleagues demonstrated that postbiotic supplements can stimulate anti-mutagenic biochemical pathways, boost immune responses, inhibit the proliferation of cancer cells, and trigger both apoptosis and necrosis. In this regard, restoring the intestinal microbiota in cancer patients may help stabilize and improve the function of the intestinal barrier. Additionally, it supports other vital biological pathways that specifically target tumor cells [123]. Furthermore, one review study that was performed in 2022 in Italy showed that probiotics have significant health benefits besides their disadvantages and potential risks [127]. Another study in China pointed out that lactic acid bacteria exopolysaccharides (LAB EPS) have anti-proliferative effects on plenty of tumor cells from the intestine, liver, and breast [117]. An In vivo study performed in Brazil in 2018 revealed that ultra-high temperature milk has significant potential for growth prevention and control of the neoplastic cells of the intestine [133].

Most research has focused on the role of probiotics in gastrointestinal cancers, including intestinal, colon, and rectal cancers. These studies consistently demonstrate the positive effects of probiotics in inhibiting the proliferation of cancer cells [115, 118, 119, 123, 131, 133–137]. In a 2022 study conducted by Garbacz, it was discovered that lactic acid bacteria (LAB)—a group of gram-positive microorganisms naturally found in fermented food products and utilized as probiotics—can exert a moderating effect. The anticancer effects of LAB appear to be multifaceted, and some of their underlying mechanisms remain not fully understood. Considering LAB's role in inhibiting intestinal carcinogenesis, consuming these bacteria through food increases the population of beneficial intestinal microflora, which helps prevent the growth of cancer cells and reduces the activity of pathogenic microorganisms involved in the synthesis of tumor promoters and procarcinogens. The anticancer activity of LAB has been confirmed both in vitro and in animal models against various types of cancer cells through several mechanisms, including anti-proliferative activity, induction of apoptosis, and cell cycle arrest, as well as through anti-mutagenic effects. Additionally, LAB exhibits anti-angiogenic and anti-inflammatory properties that contribute to the inhibition of tumor growth [115].

Another study showed that three Lactobacillus strains have antioxidant and DNA-protective properties and they do not lose these activities in an artificial intestinal medium [122]. An additional study in Iran in 2017 reviewed the kefir effect on inducing apoptosis and anti-proliferative power in cancerous cells [137].

In the studies conducted by Mehdi Pakizeh et al. and Monika Kvakova et al., the effects of the probiotic Bifidobacterium lactis on human samples were examined. Both studies highlighted the anti-mutagenic and anti-inflammatory properties of this probiotic [123, 126]. A variety of studies have examined the effects of probiotics in an in vitro setting [53, 118, 120–122, 124, 129–132, 138–142]. One of those research that was done in India in 2020 showed multiple effects of probiotic yeasts in the sense that they can be used as potential therapeutic agents for the prevention and treatment of various kinds of diseases such as colon cancer, type 2 diabetes, and gastrointestinal infections [127].

In addition to these, some research has been carried out in vivo [133, 134, 137, 143], and several others have offered thorough reviews of the current literature [116, 117, 127, 128, 135, 136, 144]. Across all these investigations, a common conclusion is evident: probiotics possess a notable capacity to inhibit the growth of cancer cells. Also, Studies have shown that oral LTA can significantly diminish the growth of existing skin tumors after UV exposure, emphasizing its therapeutic potential alongside its known preventive advantages. These findings imply that oral LTA may serve as a viable immunotherapeutic approach for conditions impacting the skin's immune system [142, 145]. Additionally, the oral administration of Lactobacillus johnsonii (La1) may support skin immune function and homeostasis following

UV radiation exposure; however, it did not demonstrate significant effects in the absence of UV exposure [146]. Furthermore, the injection of 6-HAP has been shown to effectively inhibit the growth of B16F10 melanoma without causing systemic toxicity in animal models. The identification of 6-HAP-producing strains within the metagenomes of healthy individuals suggests that certain microbiomes may play a protective role against skin cancer, highlighting a novel function for beneficial skin bacteria [53]. (Table 1)

Anti-mutagenic properties of probiotics

It has been proven that certain types of intestinal microbes, especially lactic acid bacteria, have anti-inflammatory and anti-cancer effects [147, 148]. The occurrence of cancer is a multi-step process that begins with mutations in proto-oncogenes and tumor suppressor genes. Mutations may be either by activation of oncogenes or inactivation of tumor suppressor genes, or sometimes both of them [149]. Cooking food with high fat and protein such as meat at high temperatures and sometimes the methods of storing and preparing food leads to the release of strong mutagenic agents [149–151]. Sometimes genotoxic compounds are also produced by gut microbial flora, which contribute to an increased risk of cancer. On the contrary, some intestinal bacteria reduce the formation of mutagens [152].

The type of food consumed is directly related to the type of intestinal microbial flora. Therefore, a balanced diet helps to create a beneficial microbial flora for the host and inappropriate food with high protein and fat and low fiber increases harmful intestinal microorganisms [152]. Colonic anaerobic bacteria are involved in the conversion of primary bile acids to secondary bile acids, which are carcinogens in animal models [153, 154]. It has been shown that Oral administration of probiotic bacteria in humans leads to a reduction in the amount of urinary mutagens which is caused by reducing their absorption from the intestine due to absorption or decomposition by probiotics [155].

Antitumoral mechanism of probiotics may be due to: (a) inhibition of carcinogens and/or procarcinogens (b) inhibition of bacterial flora that convert procarcinogens to carcinogens (c) activation of the immune system; (d) reduction of intestinal pH of the intestine to reduce microbial activity; and (e) increase of intestinal motility and transit time [156, 157]. The use of a high-fiber diet and probiotics have been shown to improve the therapeutic response of melanoma patients treated with anti-programmed cell death 1 (anti–PD–1) chemotherapeutic drugs [158]. Cutaneous squamous cell carcinoma and actinic keratosis have been associated with a decrease in skin commensals and an increase in certain strains of S. aureus [159]. A decrease in skin commensals has been associated with BCC [160]. Commensal skin bacteria like S. epidermidis might protect against non-melanoma skin cancer by the production of 6-N-hydroxyaminopurine (6-HAP), a chemical compound with anti-proliferative activity against neoplastic cells [53, 161].

Melanoma has been associated with increased levels of Fusobacterium and Trueperella genera [162]. Topical probiotics may alter the tumor microenvironment by altering immune responses, which may lead to therapeutic effects [163]. Disturbances in the skin microbiome have been mentioned in the pathogenesis of some skin neoplasms. The relationship between Staphylococcus aureus infection and the severity of cutaneous T-cell lymphoma has raised the potential role of a staphylococcal superantigen in the carcinogenesis of this skin tumor [164–166]. (Table 1)

Cancer prevention

Certain strains of S. epidermidis protect against the development of UVB-induced cutaneous papillomas by inhibiting the proliferation of tumor cells [53]. C. acnes and S. epidermidis can protect the skin from UV-induced DNA damage [167]. The use of probiotics can reduce the risk of skin cancer and even during the treatment of skin neoplasms, can improve the response to treatment [166]. Treatments with topical probiotics are suggested to reduce the risk of skin cancer by the possible mechanism of reducing chronic inflammation and increasing immune surveillance [167]. Topical probiotics may play a role in the treatment of skin tumors by changing immune responses and as a result, changing the tumor microenvironment [163]. Oral consumption of lipoteichoic acid from lactobacilli reduces skin damage caused by ultraviolet rays and thus reduces skin cancer [142].

Recently, it has been shown that strains of S. epidermidis by producing a nucleobase molecule, selectively prevent tumor proliferation and topical application of these strains reduced the incidence of UV-induced skin tumors in mice [53]. (Table 1)

Probiotics in combination therapy Given their antiproliferative and pro-apoptotic effects on various carcinoma cells, probiotic-based therapies may offer the potential for cancer prevention and serve as adjunctive treatments during cancer therapies. Immunotherapy agents offer a promising treatment for patients with metastatic melanoma, and researchers are increasingly focused on identifying factors that could predict a positive response. Recent studies have highlighted potential links between the gut microbiome and immunotherapy outcomes, suggesting that variations in the microbiome may impact both treatment efficacy and the occurrence of side effects [168]. Evidence indicates that the response of patients to immunotherapy is linked to the composition of their gut

Table 1 A summary of preclinical and clinical studies of probiotics properties in skin cancers

Probiotic(s)	Type of study	Possible effect and Mechanism	References
Staphylococcus aureus	Preclinical	S. aureus increases SCC cell proliferation via hBD-2 expression	Madhusudhan, 2020 [49]
Staphylococcus aureus	Preclinical	S. aureus secreted compounds increased oncogenesis in SCC and AK through DNA repair pathways downregulation, oxidative stress activation	Krueger, 2022 [50]
Malassezia globosa	Preclinical	expression of MgSAP1 produced from M. globosa inhibits biofilm formation of S. aureus	Li, 2018 [52]
Staphylococcus Epidermidis	Preclinical	6-N-hydroxyaminopurine produced from S. epidermidis intravenous injection suppressed the growth of B16F10 melanoma in mice	Nakatsuji, 2018 [53]
Staphylococcus Epidermidis, propionibacterium Acne	Preclinical	S. epidermidis promote melanocyte survival via TRAF1, CASP14, CASP5 and TP73 upregulation. P. acnes inhibit survival through apoptosis induction after UVB radiation	Wang, 2018 [54]
Bifidobacterium longum, Lactobacillus helveticus, Lactococcus lactis, Streptococcus thermophiles, Lactobacillus rhamnosus	Preclinical	Treatment with the probiotic mixture significantly reduced chronic skin inflammation via downregulation of pro-inflammatory and upregulation of anti-inflammatory cytokines	Holowacz, 2018 [60]
Enterococcus durans strain K11, Lactiplantibacillus plantarum strain St3	Preclinical	Hyaluronic acid produced from E. durans and L. plantarum highly protects human keratinocytes against UVB radiation	Shaheen, 2023 [65]
Lactobacillus paracasei	Preclinical	AGR 4 produced from L. paracasei decreased the proliferation in human melanoma cells A375	Plessas, 2020 [67]
Polyomavirus	Preclinical	Polyomavirus increases the proliferation in Merkel cell carcinoma	Feng, 2008 [91]
Lactobacillus rhamnosus GG	Preclinical	Oral Administration of lipoteichoic acids to UV radiated mice delayed the process of skin cancer appearance	Weill, 2013 [142]
Lactobacillus rhamnosus GG	Preclinical	lipoteichoic acid from L. rhamnosus plays a preventive and therapeutic role in mouse cutaneous squamous cell carcinoma via modulation of dendritic cells	Friedrich, 2019 [145]
Lactobacillus johnsonii	Preclinical	L. johnsonii administration to mouse alleviated the risk of UV radiation immune suppression through IL-10 decrease and Langerhans cell density modification	Guéniche, 2006 [146]
Trueperella pyogenes, Fusobacterium necrophorum	Preclinical	Ther high quantity of Truperella and Fusobacterium were seen in melanoma pig models	Mrázek, 2019 [162]
Bifidobacterium	Preclinical	Oral-administration of Bifidobacterium alone to mouse advanced melanoma control and combination with with PD-L1 almost stopped melanoma outgrowth	Sivan, 2015 [169]
Staphylococcus aureus	Clinical	A Strong association between presence of s. aureus and SCC has been reported	Kullander, 2009 [51]
Corynebacterium spp.	Clinical	Corynebacterium can increase melanoma proliferation through IL-6 induction	Mizuhashi, 2020 [55]
Bifidobacteria infantis 35,624	Clinical	B. infantis oral administration can reduce the systemic inflammatory biomarkers in patients with ulcerative colitis, chronic fatigue syndrome, and psoriasis	Groeger, 2013 [61]
Lactobacillus crispatus P17631, Lacticaseibacillus paracasei I1688	Clinical	EUTOPLAC as a mixture of these probiotics can reduce symptoms of Seborrheic dermatitis through reducation of Malassezia genus	Truglio, 2024 [64]
Staphylococcus aureus	Clinical	Abundance of S. aureus were seen in SCC and AK patients lesions more than non-lesional skins	Wood, 2018 [159]
methicillin-sensitive staphylococcus aureus colonization	Clinical	The percent of s. aureus colonization were higher in cutaneous T-cell lymphoma comparing to healthy control group	Nguyen, 2008 [164]
Staphylococcus aureus	Clinical	s. aureus with superantigens enterotoxins were commonly found in cutaneous T-cell lymphoma patients	Jackow, 1997 [165]
Ruminococcaceae family	Clinical	Abundance in Ruminococcaceae family was observed in responder patients' fecal samples to Anti-PD-1 immunotherapy	Gopalakrishnan, 2018 [170]
Bacteroides caccae, Faecalibacterium prausnitzii, Bacteroides thetaiotamicron, and Holdemania filiformis, Dorea formicogenerans	Clinical	In melanoma patients responers to IN, the gut microbiome was enriched for Faecalibacterium prausnitzii, Bacteroides thetaiotamicron, and Holdemania filiformis. In *P* responders, the microbiome was enriched for Dorea formicogenerans.	Frankel, 2017 [171]

microbiota. Sivan et al. investigated melanoma growth in mice with different commensal microbiota and found variations in spontaneous antitumor immunity, which were nullified when the mice were cohoused or underwent fecal transfer. Their findings demonstrated that oral administration of Bifidobacterium alone resulted in tumor control comparable to anti-PD-1 therapy. Moreover, combining Bifidobacterium with anti-PD-1 therapy produced a synergistic antitumor effect [169]. Studies in human cohorts have shown that responders (Rs) and non-responders (NRs) to immunotherapy exhibit distinct differences in their gut microbiomes. Specifically, for anti-PD-1 therapy, fecal samples from Rs demonstrated greater microbial diversity and a higher abundance of certain bacteria, including Clostridiales, Faecalibacterium, and Ruminococcaceae compared to NRs [170]. A clinical study investigating the combination of anti-CTLA-4 and anti-PD-1 therapies found that fecal samples from responders were enriched with specific gut microbes, including Bacteroides thetaiotamicron, Faecalibacterium prausnitzii, and Holdemania filiformis [171]. Also, many researchers have investigated the relationship between gut microbiota and chemotherapy, particularly in the context of treatment-related toxicity. One notable and often debilitating side effect of chemotherapy and radiotherapy is mucositis, a condition characterized by inflammation and damage to the intestinal epithelial cells, leading to mucosal barrier injury [172, 173]. A meta-analysis of 12 randomized controlled trials involving 1,013 patients found that orally administered probiotics may help reduce the incidence of chemotherapy-induced diarrhea and oral mucositis [174].

Limitations in probiotic research and future prospective While probiotics demonstrate promising benefits, their effects can vary due to strain specificity, dosage, and individual factors such as gut microbiota composition. Selecting an appropriate probiotic is challenging due to the often-overlooked factors of strain-specificity and disease-specificity. Strong evidence supports that probiotic efficacy varies based on both strain and disease type. A meta-analysis including randomized controlled trials of identifiable probiotic strains (either single or mixed) assessed their effectiveness across different diseases. The findings highlight that efficacy should be evaluated within strain-specific sub-groups, yet this approach is not consistently applied in clinical research [175]. The effectiveness of probiotic therapy is significantly influenced by the composition of the gut microbiota. The resident microbial community determines how probiotics colonize, interact, and exert their beneficial effects. Probiotics impact gut microbes both directly and indirectly. Direct mechanisms include producing inhibitory compounds (e.g., short-chain fatty acids and bacteriocins) and providing substrates that support microbial growth (e.g., vitamins, sugars from undigested carbohydrates, and exopolysaccharides). Indirectly, probiotics enhance gut health by stimulating mucin production reducing inflammation, and strengthening the gut barrier which fosters a microbiota balance associated with improved gut physiology [176, 177]. Due to these reasons, several studies have examined the effects of probiotics on skin cancer, with some finding no significant preventive benefits. In melanoma treatment, research suggests that over-the-counter probiotic supplements may negatively impact the response to cancer immunotherapy. One study reported that melanoma patients using probiotics had a 70% lower likelihood of responding to anti-PD-1 checkpoint inhibitors [178]. Fecal microbiota transplantation (FMT) involves transferring fecal matter from a donor to a recipient for therapeutic purposes. While fecal samples primarily contain commensal gut bacteria, they may also include viruses and fungi, although maintaining sample consistency can be difficult. FMT is most commonly used to treat recurrent Clostridium difficile infections, with response rates varying based on the method of administration. Colonoscopy or enema delivery generally yields the highest success rates, followed by nasogastric tube or oral capsule administration. Additionally, FMT has been explored as a therapeutic option for bone marrow transplant (BMT) patients who undergo pre-procedure antibiotic treatment. A trial in BMT patients demonstrated that autologous FMT can help restore the gut microbiome after transplantation [179, 180].

Conclusion

With the advancement of technology and science in the field of application of probiotics in medical fields, they can be considered as a tool for cancer diagnosis and treatment. In this review, we investigated probiotics and their therapeutic effect on different skin cancers. Various factors such as abnormal activation or reduction of immune system activity, production of metabolites and toxins, disruption of the barrier, and ultraviolet radiation may be associated with precancerous changes in the skin. However, few studies have investigated the role of probiotics in cancer treatment. Therefore, more studies are needed to clarify the role of probiotics in skin cancer. With the expansion of animal studies in investigating the anticarcinogenic effect of probiotics, it can be considered probable that soon this strategy will be used as comprehensive drug delivery carriers for the treatment of non-invasive cancer in humans. Studying the role of probiotics in various cancers, including skin, is currently ongoing. If research continues systematically in the field of probiotics, we are confident that the complex host-microbe interaction and its role in skin cancer will be better understood in the future. Early detection,

preventive measures, and complementary treatment of skin cancer can be one of the potential features of a wide range of probiotics.

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