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Possible therapeutic role of short-chain fatty acids from skin commensal bacteria in UVB-induced skin carcinogenesis

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Abstract: Solar ultraviolet B (UVB) radiation is a major skin cancer-causing agent. Initiation, promotion, and progression are the diverse phases of UVB-induced carcinogenesis. Exposure to UVB causes abnormalities in a series of biochemical and molecular pathways: thymine dimer formation, DNA damage, oxidative stress, inflammatory responses, and altered cell signaling, eventually resulting in tumor formation. The increased skin cancer rates urge researchers to develop more efficient drugs, but synthetic chemotherapeutic drugs have more contrary effects and drug resistance issues, which have been reported recently. The current review focuses on the relationship between microbes and cancer. Human skin acts as a barrier against the external environment and serves as a protective shield for its inhabitant microbiota, collectively called skin microbes. The gut microbiome plays a vital role in cancer therapy. Production of short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate by intestinal microbes has anti-cancer properties against various cancer cell lines. Yet, the knowledge of SCFAs produced by skin microbes remains yet to be elucidated exhaustively. In this review, we strive to summarize the findings of studies performed to date regarding the anti-cancer properties of SCFA against various cancer cell lines and provide insight into future directions in the skin microbiome field.

Introduction

In the United States, about 40%–50% of all diagnosed cancers represent skin cancer (Bray *et al.*, 2013) and are extensively classified into (a) melanomas and (b) non-melanoma skin cancers (NMSCs) (Simões *et al.*, 2015). NMSCs include basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) (Apalla *et al.*, 2017). The aggressive form of skin cancer is melanoma which spreads to different areas of the body and accounts for around 70% of skin cancer-related deaths (Nikolaou and Stratigos, 2014; Stockert and Blázquez-Castro, 2022). BCCs have rare metastatic characteristics, whereas SCCs display a high metastatic rate (Didona *et al.*, 2018). Skin is generally susceptible to injury, as it is exposed to pathogens, solar ultraviolet radiation (UVR), and various chemicals that finally lead to the development of skin cancers (Ng *et al.*, 2018). Of all possible exposures, UVR from sunlight has been perceived as the primary causal agent of skin cancer (Solar and Ultraviolet Radiation, 2011). Both UVA and UVB are carcinogens. Especially, UVB directly causes DNA damage, prompting the development of massive damage between adjacent pyrimidine sites and the generation of reactive oxygen species (ROS) (Levav-Cohen *et al.*, 2014). Preventive measures should be taken to overcome the global increase in skin cancer rates (Domingues *et al.*, 2018). This review addresses the harmful side of UVB in skin cancer and the necessity of short-chain fatty acids (SCFAs) in managing them.

Harmful effects of ultraviolet B on the skin

The sun produces electromagnetic radiation that encompasses a broad range of wavelengths. Among them, only a few wavelengths are able to pass through the ozone layer and reach the earth surface; these include ultraviolet (UV) radiation, infrared (IR), and visible light (VL). Solar UV radiations occur in the wavelength range of around 200–400 nm; however, only UVA (400–315 nm) and UVB (315–280 nm) can reach the earthbound surface, while UVC (280–100 nm) is completely absorbed by the ozone layer (Svobodová *et al.*, 2003). Fig. 1 demonstrates how extreme exposure to UVB harms the capacity of basal keratinocytes for maintaining skin homeostasis and will prompt different skin diseases, which incorporate erythema, edema, sunburn,

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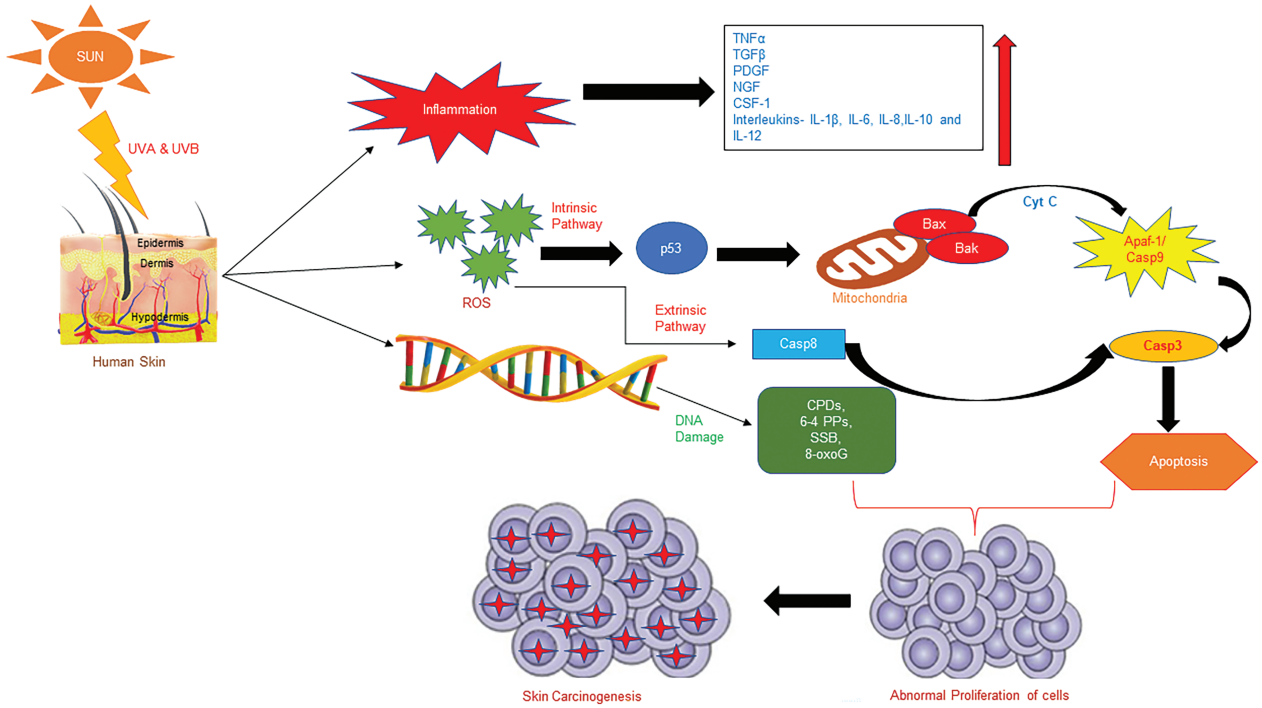

FIGURE 1. Effects of ultraviolet radiation on human skin. TNFα, tumor necrosis factor alpha; TGFβ, transforming growth factor beta; PDGF, platelet-derived growth factor; NGF, nerve growth factor; CSF-1, colony stimulating factor-1; Cyt C, cytochrome C; APAF-1, apoptotic protease activating factor-1; Casp9, caspase 9; Casp3, caspase 3; Casp8, caspase 8; SSB, single strand break; 8-oxoG, 8-hydroxy-2′-deoxyguanine.

keratinocyte hyperplasia, and causes DNA mutations, photo-aging, and skin cancer (Strozyk and Kulms, 2013).

DNA damage and skin cancer

UVB radiation instigated Different DNA damage classes, specifically cyclobutane pyrimidine dimers (CPDs), pyrimidine (6-4) photoproducts (6-4PPs), DNA strand breaks, and DNA cross-links (Brash, 1997). CPDs are the most cytotoxic lesions which are responsible for cell death, but 6-4PPs cause more prominent alterations in the structure of the DNA double helix (Kciuk *et al.*, 2020) and UVA does not induce 6-4PPs. However, longer UV wavelengths cause more DNA strand breaks (Sczepanski *et al.*, 2009). Upon exposure to UVA or UVB, 6-4PPs undergo photoisomerization to Dewar isomers (Kciuk *et al.*, 2020). Tandem pyrimidine residues form at the site of UV-induced DNA damage (Rochette *et al.*, 2003). After DNA damage, cells respond by promptly halting cell division to prevent further DNA damage, which allows the DNA repair mechanism to begin. If the DNA damage induced by UVB is not fixed, it brings about mutations in the genome, prompting skin carcinogenesis (Brash *et al.*, 1991). NER is essential in the repair of CPDs and 6-4 PPs (Sugasawa *et al.*, 1998). The p53 mutations, which include T→C transition or double base changes such as TT→CC transition, are frequently found in all types of skin malignancies, the so-called "UVB signature" (Wikonkal and Brash, 1999). UVA radiation causes indirect DNA damage by driving photons and energy transfer from cellular photosensitizers, such as porphyrins, bilirubin, and melanin, to oxygen molecules leading to the formation of singlet oxygen, which induces guanine moiety oxidation followed by structural rearrangement and formation of 8-oxo-7,8-dihydroguanine (8-oxo-G) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) (Klungland *et al.*, 1999).

The chief cause of both BCC and SCC is exposure to UVR. Almost all BCC occur on UVR-exposed body sites, and SCC originates from a malignant mutation of keratinocytes in the epidermis and skin adnexa and is capable of metastasis (Lo and Fisher, 2014). Early diagnosis of both BCC and SCC can be treated, but the metastatic potential of BCC and SCC is really lethal (Kumar *et al.*, 2015). Studies have proven that UV-induced DNA damage is the chief source of SCCs (Brash *et al.*, 1991). Tumor growth was controlled by Ras proteins which incorporate H-ras, K-ras, and N-ras (Bos, 1989). Any changes in Ras oncogene leads to NMSCs (Pierceall *et al.*, 1991). Hedgehog signaling, which is one of the very important pathways in embryonic development and furthermore identified to be associated with cancer promotion, was regulated by genomic phenylthiocarbamide protein (Wicking *et al.*, 1997).

Oxidative damage

Vulnerability to ultraviolet radiation is the fundamental source of skin carcinogenesis that disrupts cutaneous cells by reactive oxygen species (ROS) overproduction (Liu-Smith *et al.*, 2017). Direct exposure of the epidermis to UVR can lead to oxidative stress through NADPH oxidase activation or by prompting lipid peroxidation, which initiates ROS. Substantial increase in ROS by UVB irradiation triggers nuclear DNA damage via the development of cyclobutane pyrimidine dimers (CPDs), pyrimidine (6-4) photoproducts, and 8-hydroxy-2′-deoxyguanine (8-OHdG) (Gilbert *et al.*, 2012). 8-OHdG, a biomarker for oxidative DNA damage,

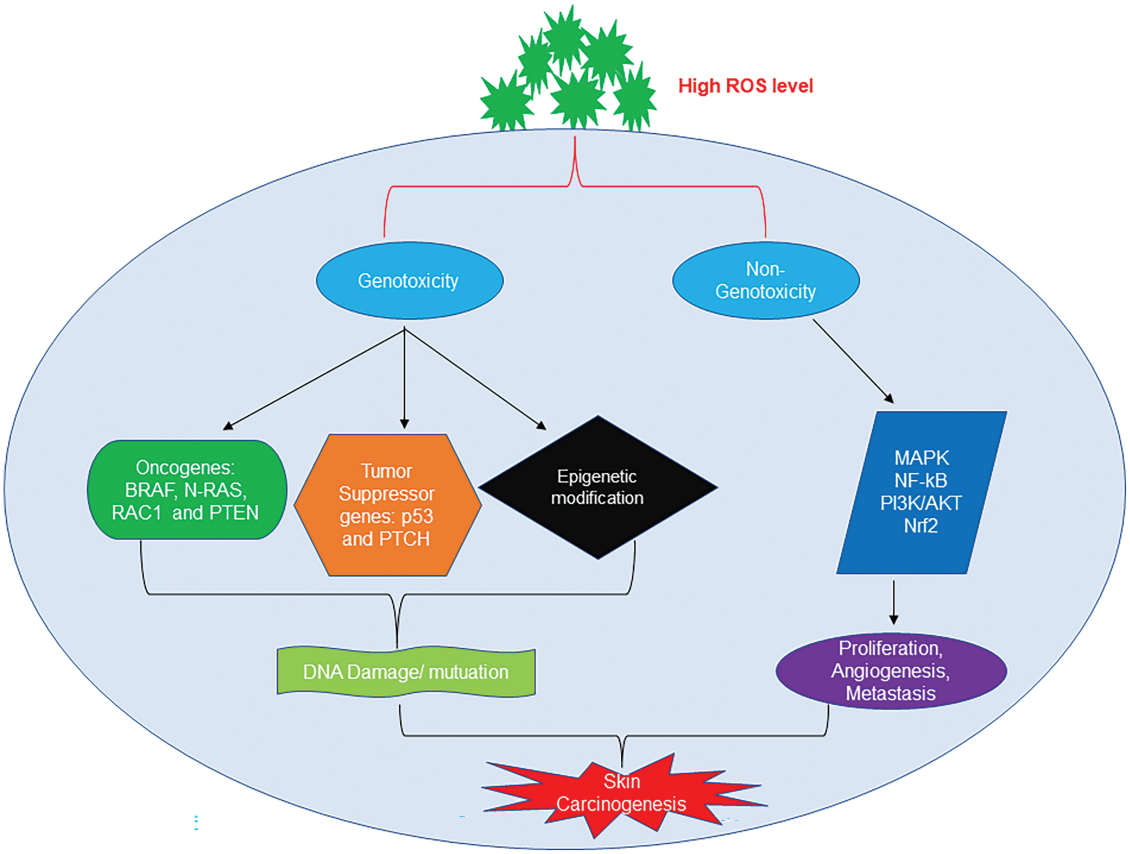

FIGURE 2. Reactive oxygen species (ROS)-mediated skin carcinogenesis. Increased ROS levels undergo genotoxicity and non-genotoxicity pathways and result in cancer.

binds with adenine rather than cytosine, suggesting that oxidative damage can be tumorigenic (Agar *et al.*, 2004). ROS-mediated carcinogenesis is of two types–genotoxic and non-genotoxic(Benedetti *et al.*, 2021). ROS-mediated genotoxicity causes protooncogene actuation (BRAF, N-Ras, Ras-related C3 botulinum toxin substrate 1, phosphatase and tensin homolog etc.), tumor suppressor gene deactivation (p53 and protein patched homolog 1), genomic instability, and epigenetic modification. These alterations may further lead to mutations (Farhood *et al.*, 2019; Xian *et al.*, 2019). Fig. 2 represents the non-genotoxicity-intervened carcinogenesis that circuitously affects DNA via activation of various pathways-oxidative-stress related pathways and antioxidant stress pathways (Farhood *et al.*, 2019; Xian *et al.*, 2019).

ROS induced by UVB is produced through various mechanisms. The very first mechanism is the induction of ROS by the enzyme catalase. Through the catalytic activity, the enzyme catalase degrades hydrogen peroxide into water and oxygen (de Jager *et al.*, 2017). The other antioxidant enzymes, such as glutathione and superoxide dismutase (SOD), are involved in scavenging ROS (Benedetti *et al.*, 2021; Kora *et al.*, 2023). Due to increased ROS production by UVB, these antioxidants fail to scavenge ROS, which altogether results in photocarcinogenesis (Xian *et al.*, 2019). ROS production leads to the activation of mitogen-activated protein kinases (MAPKs), such as extracellular-signal-regulated kinase (ERK) and c-Jun N-terminal kinases (JNK), further leading to the downstream activation of transcription factor AP-1. The regulation of genes involved in the cell cycle, proliferation, and apoptosis is controlled by activator protein 1 and nuclear factor κB (NF-kB) (Bickers and Athar, 2006).

Inflammation

Overexposure to UVR, particularly UVB, can cause inflammation of the skin. Inflammation is the self-defensive response of the body and is classified into-(i) acute inflammation-caused as a result of exposure to any causative agents, which starts rapidly and becomes severe within a few; (ii) chronic inflammation, which can last for a few weeks to several months. Studies have shown that there is a strong relationship between UVR-spurred inflammation and cancer in the skin. Cancer mostly forms at the site of chronic inflammation (Balkwill and Mantovani, 2001). Exposure to UVB primes the secretion of various cytokines and chemokines from different skin cells, i.e., keratinocytes and Langerhans cells secretes a number of cytokines, such as transforming growth factor beta (TGFβ), tumor necrosis factor-alpha (TNFα), growth factors such as platelet-derived growth factor (PDGF), nerve growth factor (NGF), colony stimulating factor-1 (CSF-1), etc., and interleukins such as IL-1β, IL-6, IL-8, IL-10, and IL-12. UVB irradiation induces keratinocytes to deliver these cytokines, and the liberation of this production has been depicted in several skin cancers (van Kempen *et al.*, 2003).

The activation of p38, MAPK, and Akt by UVB helps in the endurance of keratinocytes and opposes apoptosis that

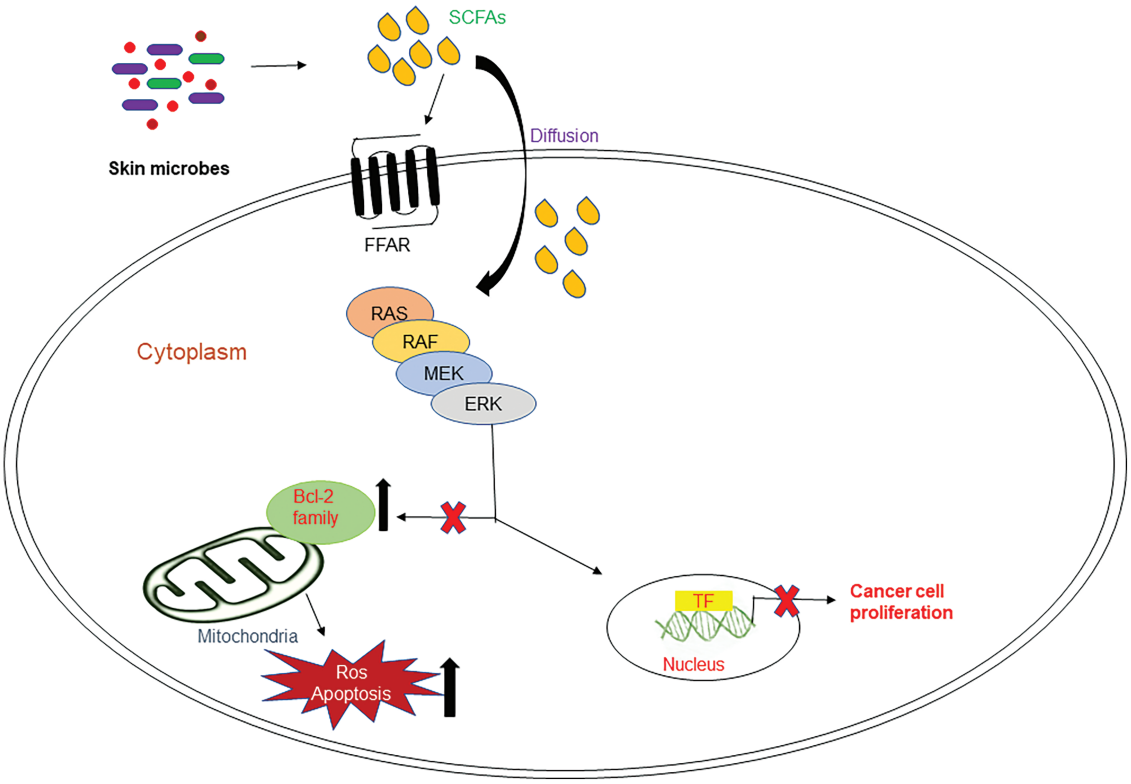

FIGURE 3. Production of small chain fatty acid. Intestinal microbes hydrolyze indigestible carbohydrates and produce short-chain fatty acids (SCFAs).

results in the accumulation of DNA damage, which may prompt malignant growth (Lee *et al.*, 2011). UVB instigates the PI3K pathway for cell survival and aggravation, accomplished as a downstream movement of epithelial growth factor receptor (Wan *et al.*, 2001). DNA damage by UVB is sufficient to intervene in NF-kB stimulation (Abeyama *et al.*, 2000). Besides, (Simon *et al.*, 1994) showed that UVB can directly actuate NF-kB from chromosomal DNA damage. Inhibitors of nuclear factor-kB kinase alpha (IKKα) and NF-kB assume a major function in maintaining skin homeostasis. Decrease in the outflow of IKKα promotes UVB-induced chronic inflammation and the process of carcinogenesis in mice models (van Kempen *et al.*, 2003). IKKα similarly has a role in the promotion of SCC (Van Waes *et al.*, 2007).

Apoptosis

Solar UVB is a potent genotoxic agent that leads to apoptosis, portrayed by membrane blebbing and nuclear fragmentation (Su *et al.*, 2015). Skin cells activate apoptosis to overcome the damage caused by UVB (Van Waes *et al.*, 2007). UVB irradiation, a strong inducer of apoptosis in cultured cells, triggers both intrinsic and extrinsic pathways (Su *et al.*, 2015). However, a few cells escape and may result in tumorigenesis. Henceforth, for the protection of normal cells from UVB, apoptosis aids as an essential process (Elmore, 2007; Zhang *et al.*, 2023).

(i) Intrinsic pathway: UVB-triggered cell death generally occurs through the intrinsic apoptotic pathway, which is initiated by p53. Transformed p53 often exists in non-melanoma skin cancers (Rodust *et al.*, 2009). In mitochondria, p53 increases the production of the pro-apoptotic protein, such as Bcl-2 associated X-protein (Bax), and diminishes the action of anti-apoptotic proteins, for example, B-cell lymphoma 2 (Bcl-2). The modification of the outer mitochondrial membrane structure by UVB gives rise to an imbalance in Bax/Bcl-2 ratio and delivers cytochrome c. Once delivered, cytochrome c and the apoptotic protease activating factor-1 form the apoptosome. This protein complex recruits and enacts caspase 9 and 3, bringing about apoptosis (Singh *et al.*, 2019).

(ii) Extrinsic pathway: The multimerization of CD95 (Fas/APO-1) by UVB brings out its attachment to the adapter protein Fas-associated protein with death domain, followed by the activation of caspase cascade from caspase 8 to caspase 3 (Bang *et al.*, 2003). After UVB irradiation, the TNF receptor is grouped and internalized in keratinocytes. TRAIL receptors, including TRAIL-R1 and TRAIL-R2, serve as lure receptors because of their competitive binding to cease apoptosis. UVB irradiation may change this equilibrium and may induce TRAIL-mediated apoptosis by the hindrance of binding with lure receptors (Qin *et al.*, 2004).

Epithelial-mesenchymal transition (EMT) and skin carcinogenesis

In the property of invasiveness, EMT plays a leading role in which the phenotypic changes combined with EMT contribute to tumor heterogeneity and therapeutic resistance (Shu *et al.*, 2013; Veloz *et al.*, 2021). EMT is facilitated by EMT-inducing transcription factors (EMT-TFs) and is connected with normal organ advancement, wound healing, and the intrusiveness of cancer cells (Sato *et al.*, 2016).

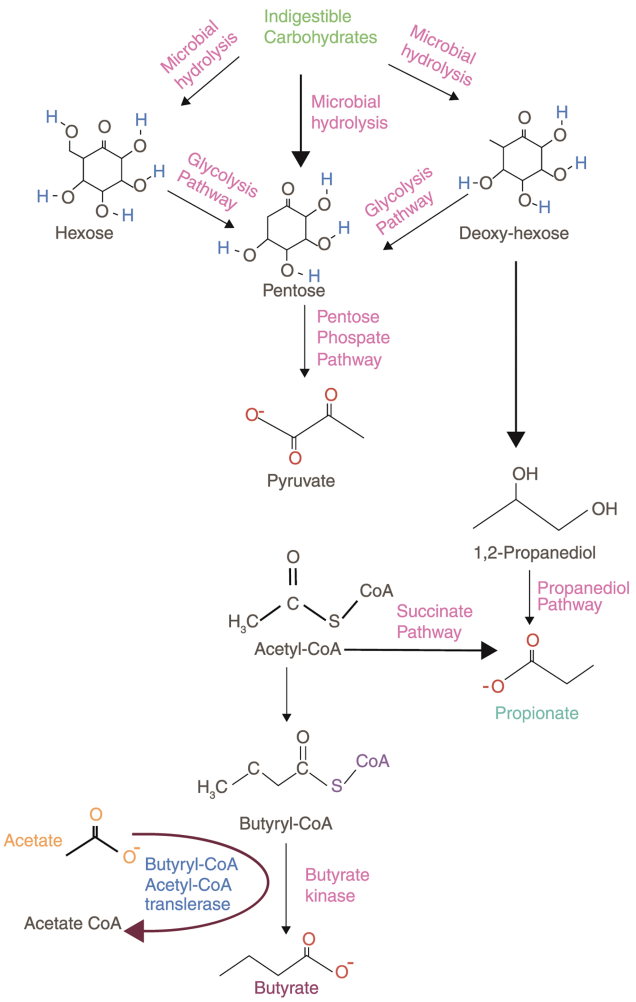

FIGURE 4. Short-chain fatty acids and their receptors. FFAR1: free fatty receptor 1; FFAR2: free fatty acid receptor 2; FFAR3: free fatty acid receptor 3; GPR40: G-protein coupled receptor 40; GPR41: G-protein coupled receptor 41; GPR43: G-protein coupled receptor 43; GPR109A: G-protein coupled receptor 109A; olfr78: olfactory receptor 78.

TGF-β is the key regulator persuader of EMT; also, the epidermal growth factor (EGF), fibroblast growth factor, hepatocyte growth factor, Wnt, and ECM components have been proven to prompt this action (Nieto and Cano, 2012). EMT-TFs can be classified into two groups, in which one group suppresses the expression of E-cadherin, Snail, Slug, ZEB1, ZEB2, E47, KLF8, and Brachyury directly correlate with the E-cadherin gene promoter to arrest gene expression. In contrast, the other group-Twist1, FOXC2, Goosecoid, E2-2, SIX1, and PRRX1 trigger the EMT without direct attachment to the E-cadherin gene promoter (De Craene and Berx, 2013; Yang *et al.*, 2021). N-cadherin, fibronectin, and vimentin are the mesenchyme-associated genes whose expression is initiated by EMT-TFs. EMT prompts the up-regulation of N-cadherin and simultaneous down-regulation of E-cadherin, termed as "Cadherin Switch Field" (Tyagi *et al.*, 2015). In various human cancers, overexpression of EMT-TFs has been identified in various human cancers (De Craene and Berx, 2013). UVB-irradiated HaCaT cells exhibit amplified aggressiveness with exaggerated migration and invasive potential, and mesenchymal phenotypes, which validate that UVB causes EMT and is related to skin carcinogenesis (Tyagi *et al.*, 2015).

Short-chain fatty acids in biological research

Fatty acids (FA) are essential components for energy metabolism, stability of cell membranes, and modulation in multiple biological processes. Based on the hydrocarbon chain length, FA is classified into short-, medium- and long-chain fatty acids (Fung *et al.*, 2011). The FA are mainly produced in the diet. SCFA can be easily absorbed, recycled, and metabolized in the body to make the body functional. Fig. 3 presents the pathway for SCFA production.

Even though the uptake of long-chain fatty acids (LCFA) and medium-chain fatty acids (MCFA) occur through similar mechanisms, there exist some differences. Both LCFA and MCFA are absorbed to some extent, and are the rate-limiting step for MCFA and LCFA is passaging across the brush-border membrane and unstirred water layer (UWL), respectively (Schönfeld and Wojtczak, 2016; Xu *et al.*, 2021). For cellular uptake, intracellular transport, and metabolism, LCFA needs free fatty acid-binding proteins. However, SCFAs require no or much fewer free fatty acid binding proteins for their intracellular transport and metabolism. Also, SCFAs are secreted endogenously, whereas MCFAs and LCFAs are exogenous (Schönfeld and Wojtczak, 2016).

Based on the efficiency and bioavailability of SCFA, it is broadly used in research. Acetate (C2), propionate (C3), and butyrate (C4) are most abundantly secreted SCFAs via the gut flora as an end product of anaerobic fermentation (Fig. 3) (Parada Venegas *et al.*, 2019). In the gut, Bacteroidetes and Firmicutes are the predominant bacterial phyla, whereas Actinobacteria, Proteobacteria, and Verrucomicrobia are the minor phyla. These microbes ferment most of the dietary substances and produce an array of metabolites, in which many are beneficial (Kobayashi *et al.*, 2018). SCFAs have been linked to beneficial effects on human health associated with their metabolic and signaling properties. Fig. 4 represents the regulatory functions of SCFAs produced by gut flora will depend on specific receptors expressed in different cell types, which are mainly free fatty acid receptors (Keshari *et al.*, 2019).

Each SCFAs bind to its specific free fatty acid receptors and mediates the cyclic adenosine monophosphate (cAMP) or extracellular-signal-regulated kinase 1/2 (ERK 1/2) signaling via G-protein dependent or independent pathways (Marinissen and Gutkind, 2001). The epithelial cells have free fatty acid receptors FFAR3 or GPR41, FFAR2 or GPR43, and GPR109A. Enteric neurons and intestinal leukocytes express GPR41 and GPR43, respectively, while intestine endocrine cells express both GPR41 and GPR43 (Sivaprakasam *et al.*, 2016). The list of SCFAs receptors and their functions are briefed in Table 1.

Evidence for the benefits of SCFAs

The comprehensive anti-tumor properties of acetate, propionate, and butyrate are mentioned in this review. Butyrate renders protection against carcinogenesis by delivering 70% energy to colonocytes and sustains intestinal barrier functions, reducing inflammation (Bedford and Gong, 2018). Butyrate is produced by specific gut bacteria

TABLE 1

Short chain fatty acids and the receptors. FFAR1: free fatty receptor 1; FFAR2: free fatty acid receptor 2; FFAR3: free fatty acid receptor 3; GPR40: G-protein coupled receptor 40; GPR41: G-protein coupled receptor 41; GPR43: G-protein coupled receptor 43; GPR109A: G-protein coupled receptor 109A; olfr78: olfactory receptor 78

S. No.	SCFAs	No. of carbon atoms	Systemic name	Simplified formula	Receptors	Expression of GPR receptors	Signaling of GPR receptors	Biological effects	References
1	Acetate	2	Ethanoic acid	(C2:0)	FFAR3 (GPR41); FFAR2 (GPR43); Olfr78	Pancreas, enteroendocrine cells, and enteric neurons	Gαi/o, β-gustducin	Dendritic cell maturation, inhibits gut motility and insulin secretion	Sivaprakasam *et al.* (2016), Brown *et al.* (2003), Le Poul *et al.* (2003), Trompette *et al.* (2014), Tang *et al.* (2015), Lu *et al.* (2020)
2	Propionate	3	Propanoic acid	(C3:0)	FFAR3 (GPR41); FFAR2 (GPR43); Olfr78	Adipocytes, enteroendocrine cells, innate immune cells, and gut epithelium	Gαi/o, Gαq, β-arrestin-2	Gut homeostasis, Treg proliferation, inhibits insulin secretion, tumor suppressor, neutrophil chemotaxis, GLP-1 secretion	Sivaprakasam *et al.* (2016), Brown *et al.* (2003), Le Poul *et al.* (2003), Maslowski *et al.* (2009), Tang *et al.* (2015)
3	Butyrate	4	Butanoic acid	(C4:0)	FFAR3 (GPR41); FFAR2 (GPR43); GPR109A	Adipocytes, innate immune cells, and intestinal epithelium	Gαi/o, β-arrestin-1	Gut homeostasis of colonic Treg cells, inhibits lipolysis, atherosclerosis, and inflammation in brain	Sivaprakasam *et al.* (2016), Lukasova *et al.* (2011), Coakley *et al.* (2014)

that come under the order Clostridiales, such as Lachnospiraceae (*Coprococcus, Eubacterium, Anaerostipes*, and *Roseburia*), Ruminococcaceae (*Faecalibacterium* and *Subdoligranulum*) and Erysipelotrichaceae (*Holdemanella*) (Louis *et al.*, 2014; Flint, 2016). Many investigations have shown that butyrate exhibits anti-cancer activity through various signaling pathways that control cell survival and apoptosis in multiple cancer cells (Candido *et al.*, 1978). Detailed information on the effects of butyrate on oncogenic signaling pathways is provided in an earlier publication (Chen *et al.*, 2019). *In vivo* investigations revealed that butyrate diminishes the rate of colon cancer (McIntyre *et al.*, 1993). Gonçalves *et al.* (2011) indicated that butyrate is a breast cancer-resistant protein (BCRP) substrate. Butyrate-induced apoptosis in a colon cancer cell line HCT116 (Fung *et al.*, 2011). The anti-cancer effect of butyrate was explored in a breast cancer cell line MCF-7 (Yonezawa *et al.*, 2007). The viability of U937 leukemia cells was decreased by butyrate to about 60% (Pulliam *et al.*, 2016). 12-0-tetradecanoylphorbol-13-acetate (TPA) induced skin tumors in mice were reduced by topical application of butyric acid (Gupta and Mehrotra, 1997). This provides us the evidence that butyrate has anti-cancer properties against multiple cancer cell types.

Acetate is one of the most important SCFAs and has been less explored than propionate and butyrate. Also, acetate is the net fermentation end product for most gut bacteria, while butyrate and propionate are produced by very specific species (Martin-Gallausiaux *et al.*, 2021). Acetate impedes proliferation and stimulates apoptosis in colon cancer cells, also acetate-induced apoptosis in CRC cells, further roots to mitochondrial alterations (Marques *et al.*, 2013). The primary end products of Propionibacteria were acetate and propionate, which destroys two human adenocarcinoma cell lines by apoptosis through co-cultures with the dairy species *Propionibacterium freudenreichii* and *Propionibacterium acidipropionici* (Jan *et al.*, 2002).

The anti-inflammatory properties of acetate and propionate were proved in human monocytes and *in vivo* colitis models (Cox *et al.*, 2009; Maslowski *et al.*, 2009). Propionate is considered the most powerful endogenic agonist for both G-protein coupled receptors, free fatty acid receptor 3 (FFA3) and FFA2 (Brown *et al.*, 2003; Le Poul *et al.*, 2003). Propionate is produced by Bacteroidetes and some Firmicutes, such as the Negativicutes (*Veillonella* and *Phascolarctobacterium*). Some other Firmicutes, belonging to Negativicutes (*Megasphaera*), Lachnospiraceae (*Coprococcus*), Ruminococcaceae, Proteobacteria, and Lachnospiraceae species (Martin-Gallausiaux *et al.*, 2021). *In vitro* studies have shown that propionate reduces BaF3 cell proliferation through a cAMP level-dependent pathway, and FFA2 activation changes BaF3 cell growth which shows that propionate decreases cancer cell proliferation in the liver. An ongoing investigation (Høgh *et al.*, 2020) revealed that the propionate causes metabolic changes bringing about the natural-killer group 2, member D (NKG2D) ligand surface expression, which renders as a potential immune activating anti-cancer therapy. Also, studies by Kim *et al.* (2019) have

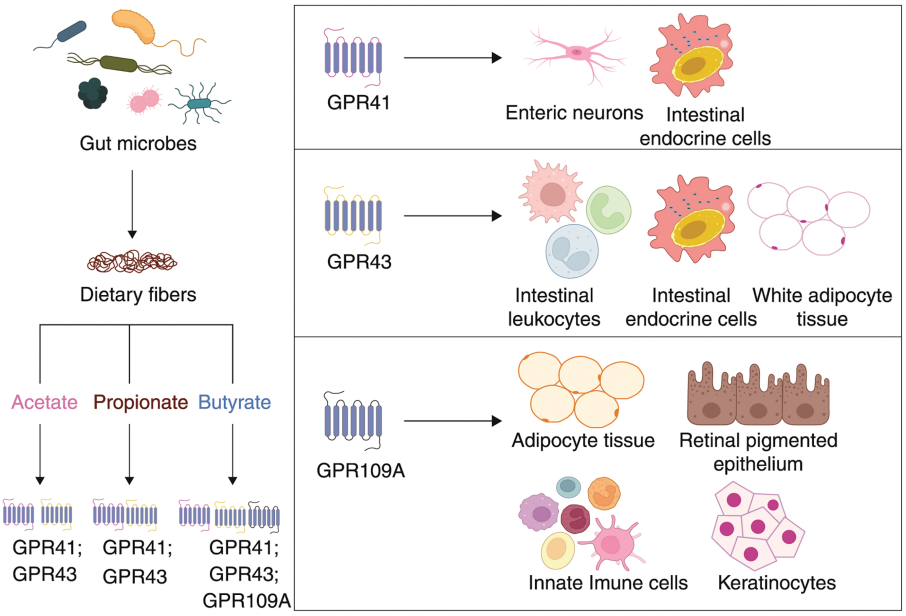

FIGURE 5. Possible mechanism of small chain fatty acids in cancer in the RAS-RAF-ERK kinase (MEK)-extracellular-signal-regulated kinase (ERK) signal transduction cascade. Skin commensal bacteria produce SCFAs that bind to specific FFARs and inhibit Bcl-2 family proteins, thereby increasing ROS and apoptosis, altogether inhibiting cancer cell proliferation.

demonstrated that propionate prompts cell apoptosis and cell cycle arrest in lung cancer.

The anti-cancer properties of these SCFAs against colorectal cancer cells has been listed in numerous publications (Gu *et al.*, 2012; Kobayashi *et al.*, 2018; Ohara and Suzutani, 2018; You *et al.*, 2018). In human colon cells and neutrophils, the anti-proliferative capacity of SCFAs has been related to the capacity of SCFA to hinder histone deacetylase function (Aoyama *et al.*, 2010). The most remarkable histone deacetylase inhibitor is butyrate, though propionate exhibited the intermediate profile and acetate didn't impact the deacetylase activity (Aoyama *et al.*, 2010). Studies by (Maslowski *et al.*, 2009; Pirozzi et al., 2018; Keshari *et al.*, 2019) have shown that butyric acid from skin commensal bacteria reduces inflammation by binding to its free fatty acid receptors. Fig. 5 shows the possible molecular mechanisms of small-chain fatty acids in cancer cell inhibition (He *et al.*, 2020).

Discussion

Being a very delicate organ, skin cells are very susceptible to UVR. The studies elaborated above clearly indicate the potential of UVB in prompting skin cancer. An increase in skin cancer rates triggers researchers to develop novel and efficient therapeutic strategies to treat skin cancer. The benefits of SCFAs in various cancer cell lines were listed out in this review. Although SCFAs produced by gut microbes play a vital role in reducing inflammation and carcinogenesis, the time required for them to travel the skin exceeds the optimal duration (Chen *et al.*, 2019). Thus, an effective methodology in which a considerable amount of SCFAs reaching the skin in enough time need to be discovered.

The skin is a resilient organ that provides diverse microbial habitats. The role of skin microbes on the skin remain understudied, and their microbiome are largely unknown. Along with SCFA, MCFA also have anti-inflammatory properties; however, the lower absorption capacity of MCFA remains a drawback. SCFAs are not just secreted by gut commensal bacteria, and even skin microbiome ferments glycerol in the skin and produces SCFAs (Sahuri-Arisoylu *et al.*, 2021). Glycerol metabolism in microorganisms has been investigated for >50 years. Therefore, the period of SCFAs drifting from gut to skin will be minimized if it is already produced by the skin commensals. MCFA and LCFA are not produced by the skin microbes, and it is only available through the diet. The knowledge of the underlying mechanisms of SCFAs from skin commensals is not yet clear. Hence, we propose that understanding the functions of SCFAs which are secreted by skin microbes, will be more supportive in studying their effects on skin cancer. Considering all the published reports, SCFAs are non-toxic to skin cells; the role of SCFAs from skin microbiome in skin cancer needs to be discovered with the actual aim of avoiding the intense effects of chronic UVB. Overall, a better understanding of skin commensals could lead the way to reduce skin cancer burden.

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Availability of Data and Materials: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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