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REVIEW ARTICLE

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Evidence of curcumin and curcumin analogue effects in skin diseases: A narrative review

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Curcumin, a natural polyphenolic and yellow pigment obtained from the spice turmeric, has strong antioxidative, anti-inflammatory, and antibacterial properties. Due to these properties, curcumin has been used as a remedy for the prevention and treatment of skin aging and disorders such as psoriasis, infection, acne, skin inflammation, and skin cancer. Curcumin has protective effects against skin damage caused by chronic ultraviolet B radiation. One of the challenges in maximizing the therapeutic potential of curcumin is its low bioavailability, limited aqueous solubility, and chemical instability. In this regard, the present review is focused on recent studies concerning the use of curcumin for the treatment of skin diseases, as well as offering new and efficient strategies to optimize its pharmacokinetic profile and increase its bioavailability.

KEYWORDS
curcumin, dermatology, inflammation, skin, topical use

Abbreviations: 5-LOX, 5-lipoxygenase; AAPK, autophosphorylation-activated protein kinase; AATF-1, arylamine *N*-acetyltransferases 1; AHR, aryl hydrocarbon receptor; AP-1, activating protein 1; AR, androgen receptor; Bcl-2, B-cell lymphoma protein 2; Ca^{2+} PK, Ca^{2+}-dependent protein kinase; CKCR4, chemokine (C-X-C motif) receptor 4; COX-2, cyclooxygenase 2; CREB-BP, CREB-binding protein; CTGF, connective tissue growth factor; DFF-40, DNA fragmentation factor 40 kDa subunit; DNA Pol, DNA polymerase; DR5, death receptor 5; EGF, epidermal growth factor; EGFR, EGF receptor; EGF-RK, EGF receptor kinase; ELAM-1, endothelial leukocyte adhesion molecule 1; EPCR, endothelial protein C receptor; ERE, electrophile response element; ERK, extracellular receptor kinase; ER-α, estrogen receptor-α; FAK, focal adhesion kinase; FGF, fibroblast growth factor; FPT, farnesyl protein transferase; FR, Fas receptor; GCL, glutamyl cysteine ligase; GST, gluthathione-*S*-transferase; H2R, histamine (2) receptor; HER-2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; HIF-1, hypoxia-inducible factor 1; HO, hemeoxygenase 1; HSP-70, heat-shock protein 70; IAP-1, inhibitory apoptosis protein 1; ICAM-1, intracellular adhesion molecule 1; IL-1, interleukin 1; IL-12, interleukin 12; IL-18, interleukin 18; IL-1R AK, IL-1 receptor-associated kinase; IL-2, interleukin 2; IL-5, interleukin 5; IL-6, interleukin 6; IL-8 R, interleukin 8 receptor; IL-8, interleukin 8; iNOS, inducible nitric oxide synthasel; IR, integrin receptor; JAK, janus kinase; JNK, c-jun N-terminal kinase; LDLR, low density lipoprotein-receptor; MaIP, macrophage inflammatory protein; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; MDRP, multidrug resistance protein; MIP, migration inhibition protein; MMP, matrix metalloproteinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NQO-1, NAD(P)H: quinoneoxidoreductase 1; Nrf, nuclear factor 2-related factor; ODC, ornithine decarboxylase; PAK, protamine kinase; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PhPD, phospholipase D; PKA, protein kinase A; PKB, protein kinase B; PKC, prorein kinase C; Pp60c-tk, pp60c-src tyrosine kinase; PPAR-γ, peroxisome preoliferator-activated receptor-γ; PTK, protein tyrosine kinase; Src-2, Src homology 2 domain-containing tyrosine phosphatase 2; STAT-1, signal transducers and activators of transcription 1; STAT-3, signal transducers and activators of transcription 3; STAT-4, signal transducers and activators of transcription 4; STAT-5, signal transducers and activators of transcription 5; TF, tissue factor; TGF-β1, transforming growth factor-β1; TMMP-3, tissue inhibitor of metalloproteinase 3; TNFα , tumor necrosis factor α ; uPA, urokinase-type plasminogen activator; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; WTG-1 , Wilms' tumor gene 1.

1 | INTRODUCTION

This review focuses on curcumin, the compound that imparts the yellow color to turmeric and that is used to flavor food. For centuries, turmeric has been used as a remedy for multiple conditions including dyspepsia, liver disorders, flatulence, jaundice, urinary tract diseases, colds, biliary disorders, rheumatism, sinusitis, chronic otorrhea, diabetic ulcers, cough, and various skin conditions (Hewlings & Kalman, 2017). Turmeric possesses more than 300 different components, including phenolic compounds and terpenoids (B. B. Aggarwal, Yuan, Li, & Gupta, 2013). Turmeric contains three naturally occurring curcuminoids: Curcumin or diferuloylmethane (75%), demethoxycurcumin (20%), and bisdemethoxycurcumin (5%; Akbik, Ghadiri, Chrzanowski, & Rohanizadeh, 2014). Chemically, curcumin is a lipophilic molecule (1,7-bis(4-hydroxy3-methoxyphenyl)-1,6-heptadiene-3,5-dione) and a natural polyphenol. Its chemical structure includes keto-enol tautomerism (depending on whether curcumin resides in an acidic or alkaline medium). The molecule rapidly permeates cell membranes and acts on multiple targets in various cellular pathways to elicit various therapeutic actions in a variety of diseases. Due to variable efficacy and the side effect profiles of many modern medications, it is an appropriate time to assess the therapeutic usefulness of ancient and traditional medications, including curcumin (Kocaadam & Sanlier, 2017). Curcumin's simple molecular structure, along with its varied therapeutic effects and its use in many disease conditions has attracted much attention (Cheppudira et al., 2013; Kunnumakkara et al., 2017). Curcumin can be used as an effective treatment in several diseases by targeting different molecular targets and with minimal toxicity to both humans and animals (Cheppudira et al., 2013; Kocaadam & Sanlier, 2017; Kunnumakkara et al., 2017).

Curcumin is well known to exert therapeutic effects against a variety of pathological conditions including cancer (Iranshahi et al., 2010; Momtazi et al., 2016; Teymouri, Pirro, Johnston, & Sahebkar, 2017), chemotherapy-induced adverse reactions (Mohajeri & Sahebkar, 2018; Rezaee, Momtazi, Monemi, & Sahebkar, 2017), metabolic syndrome (Panahi et al., 2015; Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014), osteoarthritis (Panahi, Rahimnia, et al., 2014; Sahebkar & Henrotin, 2016), dyslipidemias (Cicero et al., 2017; Ganjali et al., 2017; Sahebkar, 2014; Sahebkar et al., 2016; Simental-Mendia et al., 2017), diabetes (Hajavi et al., 2017; Panahi et al., 2017, 2018), nonalcoholic fatty liver disease (Rahmani et al., 2016), endothelial dysfunction (Karimian, Pirro, Johnston, Majeed, & Sahebkar, 2017), hyperuricemia (Panahi et al., 2016), respiratory diseases (Lelli, Sahebkar, Johnston, & Pedone, 2017; Panahi, Ghanei, Bashiri, Hajihashemi & Sahebkar, 2015; Panahi, Ghanei, Hajhashemi & Sahebkar, 2016), and autoimmune diseases (Abdollahi, Momtazi, Johnston, & Sahebkar, 2018; Momtazi-Borojeni et al., 2018). According to the literature, turmeric has been orally and topically used in the prevention and treatment of skin diseases, which include parasitic skin infections, infected wounds, premature aging, inflammation, and psoriasis (Vaughn, Branum, & Sivamani, 2016).

Skin is the largest organ of the human body and is responsible for covering, separating, and protecting the body from the external environment, receiving sensory stimuli, and regulating body temperature. Premature aging of the skin may be related to extrinsic factors and personal lifestyle choice such as smoking, solar radiation exposure, low air humidity, poor diet, and excess alcohol intake, as well as systemic diseases such as diabetes mellitus. According to the literature, curcumin possesses significant therapeutic effects for various skin conditions, including anti-inflammatory properties (B. B. Aggarwal et al., 2013), ultraviolet (UV) protection (H. Li et al., 2016), antioxidant effects (Xie et al., 2015), chemopreventive and chemotherapeutic activity (Jiang, Jiang, Li, & Zheng, 2015; Lelli, Pedone, & Sahebkar, 2017; Qiu et al., 2014; Toden et al., 2015), wound healing benefits (Akbik et al., 2014), and antimicrobial effects (Krausz et al., 2015). Due to its free-radical scavenging and anti-inflammatory properties, topical application of curcumin has allowed new therapeutic avenues for wound healing, protection against oxidative skin damage, skin cancer treatment (Qiu et al., 2014), control of pain resulting from dermal burns (J. Kim et al., 2016; Mehrabani et al., 2015), androgen-dependent skin disorders (Liao et al., 2001), and decreasing skin irritation and reducing the symptoms of autoimmune-related skin disorders such as psoriasis (Kang et al., 2016).

However, recent studies have highlighted curcumin's poor bioavailability, low aqueous solubility, chemical instability, rapid degradation, and rapid systemic elimination as major limitations for its use in clinical practice (Kharat, Du, Zhang, & McClements, 2017). This review aims to provide recent evidence for the usefulness of curcumin in dermatology, as well as to suggest strategies to increase its effectiveness and stability in vivo.

2 | ANTIOXIDANT

Exposure of human skin to solar radiation, chemical pollutants, and mechanical stress results in the generation of free radicals. Free radicals, like reactive oxygen species (ROS), are unstable chemical entities that are highly reactive, cause skin damage through inflammation, and may result in skin cancer. The resultant destruction of proteins, collagen, and elastic fibers is reflected in the signs of skin aging (Poljsak & Dahmane, 2012). Antioxidants are compounds that are protective by quenching free radical activity. The antioxidant system in the skin includes superoxide dismutases (SOD), catalases, and peroxidases (selenium-dependent glutathione peroxidases [GPx], for example). Aging and prolonged exposure to ROS-generating factors, which include poor nutrition, alcohol intake, UV radiation, stress, and environmental pollution, result in ROS accumulation, which in turn damages the skin (Lee et al., 2013).

While most of the antioxidants have either a phenolic functional group or a-diketone group, there are different functional groups including the B-diketo group, carbon–carbon double bonds, and phenyl rings containing varying amounts of hydroxyl and methoxy entities that make curcumin a unique and potent antioxidant. Curcumin's antioxidant activity is attributed to its diketone and phenol moieties (diferuloylmethane portion of the molecule), which are free radical quenchers (Lee et al., 2013). Masuda et al. (2001) proposed that the antioxidant

mechanism of curcumin includes an oxidative coupling reaction at the 3′ position of the curcumin structure with lipid and a subsequent intramolecular Diels–Alder reaction. Curcumin functions as a mediator in the regulation of genes related to the generation of proteins with antioxidant characteristics such as heme oxygenase-1, transcription and growth factors, and inflammatory cytokines (Kou et al., 2013; O'Toole et al., 2016). Curcumin also regulates antioxidant enzymes, scavenges hyperglycemia-induced ROS, and profoundly increases the intracellular antioxidant, reduced glutathione (GSH), which serves to decrease lipid peroxidation. Studies have also shown strong protective effects of curcumin against damage to the keratinocytes and fibroblasts in the skin induced by H_2O_2 (Phan, See, Lee, & Chan, 2001). Tetrahydrocurcuminoids obtained by hydrogenating cucuminoids (Prakash & Majeed, 2009) are one of the major colorless metabolites of curcumin, in the form of its glucuronide conjugate in bile. This conjugate compound has been shown to have enhanced antioxidant properties with superior free radical scavenging, free radical formation prevention, and increased lipid peroxidation inhibition compared to curcumin and vitamin E (Prakash & Majeed, 2009).

Therefore, the literature suggests that curcumin and its derivatives may be promising and effective antioxidants that can be used both orally and topically.

3 | ANTI-INFLAMMATORY AND WOUND HEALING

Acute and chronic inflammation are part of the body's defense mechanisms and involve immune cells, blood vessels, and molecular mediators in response to harmful stimuli such as pathogens or irritants. Pain, redness, immobility, swelling, and heat are the hallmark signs of skin inflammation. Cytokines and hormone-like polypeptide mediators like tumor necrosis factor α (TNF-α, a key proinflammatory cytokine) induce proinflammatory cytokines such as interleukins 1, 6, 8, 10, and 21 and result in the activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), c-Jun NH_2-terminal kinase, and mitogen-activated protein kinase (MAPK) in the skin. These factors play a major role in the pathogenesis of many inflammatory skin diseases and in the immunoregulatory responses. Most inflammatory skin disorders are associated with the overproduction of cytokines, dysregulation of cytokines, or alterations in cytokine receptors (Figure 1).

Curcumin's anti-inflammatory properties have been unequivocally established (R. Agrawal, Sandhu, Sharma, & Kaur, 2015; Koop, de Freitas, de Souza, Savi, & Silveira, 2015) in several different organs such liver and skin through modulation of autoimmune disease and prevention of injury to these organs–tissues (R. Agrawal et al., 2015). The primary mechanism by which curcumin modulates inflammation is by reducing the expression of the two main cytokines that are released by monocytes and macrophages (Figure 1; Akbik et al., 2014; Kang et al., 2016). These molecules are interleukin 1 (IL-1) and TNF-α, which have important roles in the regulation of the inflammatory response. Also, curcumin inhibits the activity of the proinflammatory transcriptional factor, NF-κB, which is responsible for the regulation of many genes involved during the initial onset of the inflammatory response. A variety of kinases (AKT, PI3K, and IKK) activate NF-κB (Jagetia & Rajanikant, 2015). Suppression of NFκB activation causes downregulation of cyclooxygenase-2 and inducible nitric oxide synthase, and prevents upregulation of vascular endothelial

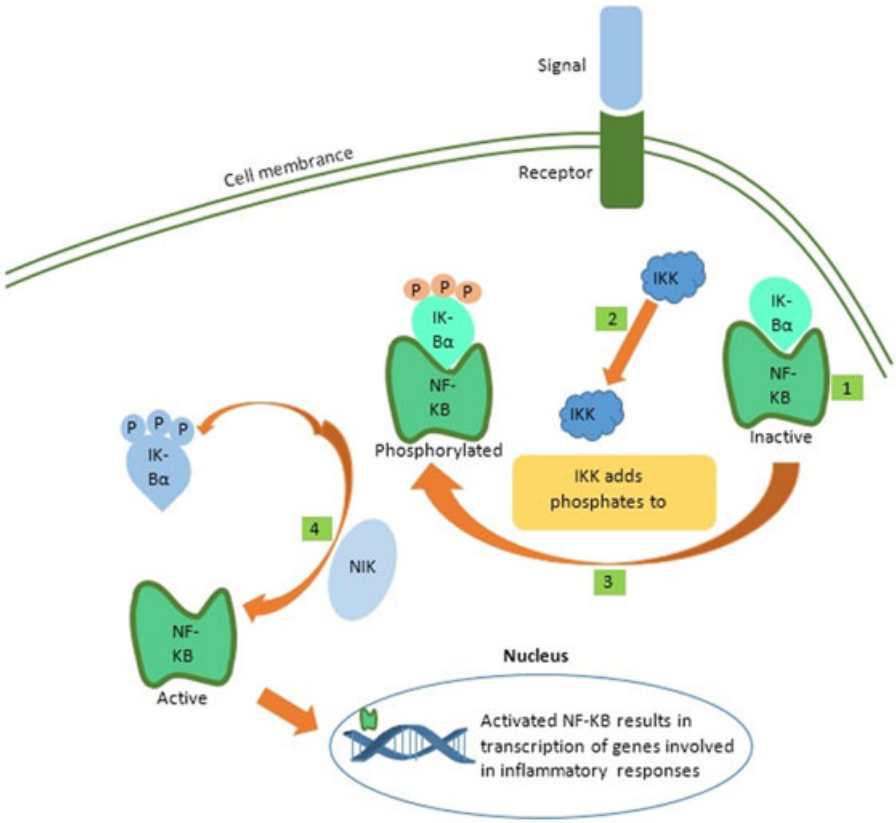

FIGURE 1 Activation of NF-κB plays a major role in the pathogenesis of many inflammatory skin diseases. NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells [Color figure can be viewed at wileyonlinelibrary.com]

growth factor (VEGF) messenger RNA and microvascular angiogenesis during inflammatory conditions. Curcumin's anti-inflammatory actions can be utilized to control inflammation of the skin resulting from different skin diseases. For example, Arunraj et al. (2014) studied the anti-inflammatory actions of curcumin and curcumin nanospheres (CNSs) to prevent denaturation of bovine serum albumin and compared it with diclofenac sodium (a nonsteroidal anti-inflammatory drug) both in vitro and ex vivo. The results of in vitro stability testing for heat-treated albumin at physiological pH showed that CNSs had a greater anti-inflammatory effect in comparison with curcumin and diclofenac across a dose range (25–1,000 μg/ml).

Skin is an essential protective organ for the body against the environment. Chronic injuries in skin cause the body to initiate a dynamic and multistep process of repair to regain tissue integrity. Four processes are involved during the wound healing process: hemostasis, inflammation, proliferation, and remodeling (Hussain, Thu, Ng, Khan, & Katas, 2017; Margolis et al., 2011). At the initiation of the injury, rapid aggregation of platelets via hemostasis causes clot formation. Migration of neutrophils and macrophages to the wound site and release of cytokines, thereby promoting fibroblast migration, results in inflammation at the wound site. Re-epithelialization, generation of new blood vessels (termed angiogenesis or neovascularization), and extracellular matrix protein deposition by fibroblasts (collagen fibers, granulation tissue, for example) occur to protect cell ingrowth. Collagen is used as the building block during this proliferation phase (Hussain et al., 2017; Margolis et al., 2011). The collagen remodeling and formation of scar tissue is the final phase of wound healing. Inflammation, part of the acute injury response, attracts neutrophils to the injured site resulting in the release of inflammatory mediators such as TNF-α and IL-1 (Arunraj et al., 2014). Neutrophils in the wound area are associated with high levels of destructive proteases and ROS molecules, which cause inflammation and result in tissue damage, as well as prolonging the inflammatory phase. The ROS molecules, bacterial infection, and protracted inflammation are the major reasons for delays in wound healing (Guo & Dipietro, 2010; Sorg, Tilkorn, Hager, Hauser, & Mirastschijski, 2017). Therefore, curcumin's potent antioxidant, anti-inflammatory, and anti-infectious actions can play a healing role in the process of wound resolution (Akbik et al., 2014; Mohanty & Sahoo, 2017). Topical application of curcumin has been shown to promote re-epithelialization in burn wound areas to increase the rate of wound healing (Kulac et al., 2013; Lopez-Jornet, Camacho-Alonso, Jimenez-Torres, Orduna-Domingo, & Gomez-Garcia, 2011). Clinical studies have indicated an increased rate of epidermal growth, increased thickness of the cuticular layer, and significant improvement in wound healing in curcumin-treated subjects when compared to untreated subjects (Kulac et al., 2013; J. Li, Chen, & Kirsner, 2007; Wen, Wu, Chen, Yang, & Fu, 2012).

Kulac et al. (2013) reported that topical treatment with curcumin at a concentration of 100 mg/kg body weight on burn wound healing in rats enhanced the healing process compared to the control group, with a decrease in inflammatory cells, and enhanced collagen deposition, angiogenesis, granulation tissue formation, and epithelialization. Castangia et al. (2014) used curcumin nanovesicles for wound healing in chronic cutaneous pathologies in both in vivo and in vitro studies. They showed that nanoentrapped curcumin prevented the formation of skin lesions and inhibited the biochemical processes that normally lead to epithelial damage. Based upon epidemiological evidence, they recommended the daily topical application of curcumin-loaded nanovesicles for patients at a higher risk of skin wound infection to afford better protection. Using liposomes and penetration enhancer-containing vesicles (PEVs) showed an additional benefit by enhancing skin penetration. Krausz et al. (2015) showed that topical use of curcumin-encapsulated nanoparticles in an in vivo murine wound model enhanced granulation tissue, re-epithelialization and decreased wound area after 14 days of treatment leading to improved wound healing. The results showed statistically significant acceleration of wound healing in mice treated with curcumin-encapsulated nanoparticles (curc-np) compared to untreated, silver sulfadiazine, coconut oil, control, control np, and curcumin (curc). Topical curcumin used in breastfeeding women suffering lactation-induced mastitis showed that curcumin effectively decreased mastitis-related pain, breast tenderness, and erythema. This reduction in inflammation occurred within 72 hr of administration without any side effects showing the efficacy of curcumin in this situation (Afshariani, Farhadi, Ghaffarpasand, & Roozbeh, 2014).

4 | PSORIASIS TREATMENT

Psoriasis is an epidermal hyperproliferative and autoimmune dermal chronic inflammatory disease caused by genetic and immunologic factors and normally affects the skin and joints (Lowes, Suarez-Farinas, & Krueger, 2014). Psoriasis shows triggering of intraregional T-lymphocytes that prime basal stem keratinocytes to proliferate excessively. Enhanced cell proliferation results in an excessive buildup of cells on the surface of the skin and rapidly forms scales and red patches that are itchy, inflamed, and sometimes painful. External triggers like stress, alcohol, injury, infection, and medications may initiate new psoriasis lesions. Psoriasis initiates from the premature maturation of keratinocytes induced by an inflammatory cascade in the dermis by dendritic cells, macrophages, and T cells. These immune cells move from the dermis to the epidermis and secrete inflammatory chemical signals (cytokines) such as IL 36-γ, interferon-γ (IFN-γ), TNF-α, IL-17, IL-6, IL-8, and IL-22, that stimulate keratinocytes to proliferate. Consequently, skin cells are replaced every 3–5 days rather than the usual 28–30 days, resulting in scales on the surface of skin.

Reports suggest that the anti-inflammatory effect of curcumin may allow it to act as an antipsoriasis agent (H. Liu, Danthi, & Enyeart, 2006; Sun et al., 2017). Some reports on the inhibitory activity of curcumin suggest that its action on the potassium channel subtype Kv1.3 in T cells plays a central role in psoriasis (Kang et al., 2016; H. Liu et al., 2006). Recently, Kang et al. (2016) showed that generation of T-cell inflammatory factors, such as IL-17, IL-22, IFN-γ, IL-2, IL-8, and TNF-α, decreased by 30–60% in mice with psoriasis-like diseases after 20 days of oral curcumin. Over 50% of T-cell proliferation was interrupted by application of a 100-μM curcumin preparation, and curcumin significantly decreased the signs of psoriasis and improved the condition of the

skin. Curcumin (10 μM) reduced the generation of inflammatory agents (IL-17, IL-22, IFN-γ, IL-2, IL-8, and TNF-α) in vitro in T cells by 30–60%. Sun et al. (2017) studied different formulations of curcumin (dose: 0.25 mg·day^{-1}·mouse^{-1}) and tacrolimus (dose: 0.1 mg·day^{-1}·mouse^{-1}) on the imiquimod (IMQ)-induced psoriasis-like mouse model both in vitro and in vivo, compared to a placebo vehicle as control. Their results showed that treatment using tacrolimus and 50 nm Cur-NPs gel reduced the white scale thickness and the pink hue in inflamed skin. Also, they demonstrated that encapsulation of curcumin into a poly(lactic-co-glycolic) acid (PLGA)-based nanoparticle-containing hydrogel facilitated penetration through the skin and into the circulation (Sun et al., 2017). In fact, this formulation had a superior performance when compared to curcumin hydrogel in this imiquimod (IMQ)-induced psoriasis-like mouse model, significantly improving the antipsoriasis activity of curcumin.

5 | RADIATION PROTECTION

Solar radiation induces both an acute and chronic reaction in animal and human skin. One of the most important agents causing ROS production in the body is UVB irradiation, which causes oxidative modification of cellular lipids, proteins, and nucleic acids and can lead to inflammation, gene mutation, and immunosuppression (Dupont, Gomez, & Bilodeau, 2013; Natarajan, Ganju, Ramkumar, Grover, & Gokhale, 2014). High levels of UV radiation kill most of the skin cells in the upper skin layer, and cells that are not killed are damaged. In its mildest form, sunburn leads to erythema on skin; however, severe sunburn may cause the skin to blister and peel, which is not only painful but also leaves the new skin unprotected and more prone to UV damage. Excessive UV radiation damages the skin's cellular DNA, producing genetic mutations that can lead to precancers like actinic keratoses, and to skin cancers including melanoma. UVB (290–320 nm) radiation is highly mutagenic and carcinogenic in animal experiments compared to UVA (320–400 nm) radiation.

Recently, several research groups have studied curcumin's protective effects against skin damage caused by chronic UVB irradiation (Khandelwal et al., 2016). They showed that curcumin exhibited photoprotective activity against acute UVB irradiation-induced photo damage. Topical application of curcumin before chronic UV irradiation delayed the appearance of dermal tumors, inflammation, and skin aging. H. Li et al. (2016) demonstrated that short-term topical application of emulsified curcumin (2 mg/ml curcumin was prepared in 0.5% carboxymethyl cellulose sodium [CMC-Na]) protected against acute UVB irradiation-induced inflammation and photoaging-associated damage in mouse skin without any adverse effects. They show that curcumin attenuated lactate dehydrogenase release induced by acute UVB irradiation in HaCaT cells. The photoprotective effect of curcumin can be attributed to its antioxidant properties and inhibition of UVB-induced oxidative damage by regulating the Nrf2 signaling pathway in mouse skin and HaCaT cells (Khandelwal et al., 2016; H. Li et al., 2016). Curcumin inhibited the generation of metalloproteases and NF-κB in human dermal fibroblasts, which play a key role in UVB exposure-induced skin damage.

Chopra et al. (2016) encapsulated curcumin with a biodegradable polymer, PLGA (150 nm size range), and termed this formulation–preparation PLGA-Cur-NPs. They studied the protective effect of curcumin in mouse fibroblasts (NIH-3T3) and human keratinocytes (HaCaT) against UV rays in vitro. They demonstrated sustained release of curcumin at a low level from the PLGA-Cur-NPs and suggested that this formulation could be an effective agent to protect skin from exposure to UV irradiation. The results of this study suggest that slow release of curcumin from PLGA-Cur-NPs could counteract the adverse effects of photodegradation on curcumin formulations upon exposure to UVA and UVB irradiation. UVB exposure can induce cyclobutane pyrimidine dimers, leading to DNA damage and skin cancer. According to various studies, considerable DNA damage occurred with free curcumin, whereas this was not the case with PLGA-Cur-NPs (Chopra et al., 2016).

6 | CANCER PREVENTION

Preclinical studies (Elad et al., 2013; H. Kim, Park, Tak, Bu, & Kim, 2014; Kuttan, Sudheeran, & Josph, 1987; Phillips et al., 2013, 2011) on curcumin have established its anticancer properties in breast, cervical, skin, and pancreatic cell lines. However, rapid systemic clearance, low aqueous solubility, poor physicochemical stability, and low cellular uptake have limited the applications of curcumin. Recently, use of nanotechnology for encapsulation of curcumin has improved its therapeutic index, delivery, and bioavailability (Mangalathillam et al., 2012). One of the most lethal skin cancers is melanoma, a result of carcinogenic transformation of melanocytes (the pigment-containing cells of the skin). The DNA damage caused by UV light exposure is central to the development of melanoma in people with low levels of skin pigment (Autier & Dore, 1998). Studies showed that cytokine expression can support the growth and metastasis of melanoma cells. Elias et al. reported that over 80% of human melanoma cell lines produce excessive levels of several cytokines and growth factors, such as transforming growth factor β (TGF-β), IL-8, IL-6, IL-1α, VEGF, platelet-derived growth factor-AA, and osteopontin (OPN), that are capable of stimulating tumor growth, invasion, and angiogenesis.

Jiang et al. (2015) studied the human melanoma cell lines A375, MV3, and M14 and the human normal lung fibroblast cell line MRC-5 in vitro, and showed that the viability of melanoma cells decreased with increasing concentrations of curcumin from 5 to 50 μm. They demonstrated that curcumin suppresses proliferation and induces double strand break, suppressing the activation of NF-κB (involved in tumor cell proliferation) and causing apoptosis in melanocytes. Curcumin also suppresses B-cell lymphoma protein 2 (Bcl-2) and myeloid cell leukemia-1 (Mcl-1) expression and upregulates the expression of Bax (a p53), which are primary drivers for apoptosis. Following curcumin treatment, the t-bax to Bcl-2 ratio increased, demonstrating that curcumin induced apoptosis. The regulation of Bax, Bcl-2, and Mcl-1 expressions indicates

that mitochondrial pathways play a key role in curcumin-induced apoptosis; thus, curcumin may provide antitumor efficacy and may offer hope to those with melanoma. Additionally, Huang et al. (1997) showed that topical application of very low doses (1–3,000 nM) of curcumin on mouse epidermis inhibited the mean values of the 12-*O*-tetradecanoyl-phorbol-13-acetate-induced epidermal oxidized DNA base 5-hydroxy-methyl-29-deoxyuridine and, hence, tumor promotion. Jose, Labala, Ninave, Gade, and Venuganti (2018) studied the synergistic effect of encapsulated curcumin in 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP)-based cationic liposomes, as well as complexed with signal transducers and activators of transcription 3 (STAT-3) small interfering RNA (siRNA); they demonstrated that in an animal model of melanoma skin cancer, liposomal encapsulation of curcumin and STAT-3 siRNA significantly inhibited tumor weight and volume progression when compared with either liposomal curcumin or STAT-3 siRNA alone. Consequently, these data suggest that curcumin may inhibit skin cancer and may provide adjuvant therapy without side effects in skin cancer treatment.

7 | ANTIAGING EFFECT

The in vivo study on male Wistar rats (Bala et al., 2006) showed that curcumin can significantly decrease the normal aging-related factors such as lipid peroxidation, lipofuscin concentration, and intraneuronal lipofuscin accumulation, and enhance the enzymes SOD, GPx, and Na(+), K(+) adenosine triphosphatase. Curcumin prevents premature aging of skin by quenching free radicals and reducing inflammation, and has antiproliferative properties through inhibition of NF-kB, TNF-α, and MAPK pathway inhibition, as well as suppression of TGF-β (Tsai et al., 2012). Curcumin also partially prevents UV damage that may decrease the development of skin tumors and be an effective factor for prevention of premature aging (Bala et al., 2006).

8 | ANTI-INFECTIVE PROPERTIES

Infectious diseases are a global issue and a wide range of synthetic–semisynthetic antibiotics have been developed for their treatment. The development of multidrug resistant bacteria is an evolving health problem and a major concern; hence, the need for new antibacterial agents. The major drawbacks of many of these new drugs are their expense, limited therapeutic window, mode of delivery, rapid bacterial resistance and their side effects. Minimal or limited side effects associated with natural products has led to an increasing research focus to further investigate their use in this scenario.

Curcumin's antimicrobial effects have been demonstrated in several studies (Krausz et al., 2015; Luer, Troller, Jetter, Spaniol, & Aebi, 2011). Krausz et al. (2015) studied the effect of curc-np as antimicrobial agents on wound healing. According to this study, curc-np exhibited a significant antimicrobial effect against methicillin-resistant *Staphylococcus aureus* strain (MRSA) and *Pseudomonas aeruginosa* (97.0% reduction of MRSA growth and 59.2% reduction of *P. aeruginosa* growth by colony-forming unit (CFU) quantification) from 8 hr onwards, in comparison to both untreated control and control np ($p \leq 0.0001$). They showed that curcumin decreases the bundling of FtsZ protofilaments (which are associated with binding ability to the cellular proteins FtsZ32 and sortase A). As a result, cytokinesis and cellular adhesion are interrupted, which also interferes with the formation of a biofilm. Curcumin's antibacterial mechanisms involve suppression of bacterial cell proliferation due to the inhibition of assembly dynamics of FtsZ (FtsZ polymerization) in the Z-ring, which subsequently leads to interruption of prokaryotic cell division. Also, Tortik, Steinbacher, Maisch, Spaeth, & Plaetzer (2016) showed that curcumin has high photo killing efficiency against microorganisms and a high photobleaching effect using a photodynamic inactivation technique. This technique combines a harmless visible light and a photosensitizer to kill pathogens through ROS generation. Natural photoactive compounds, like curcumin, are cost-effective and provide excellent biocompatibility for most conceivable applications. Consequently, the photosensitivity of human skin due to prolonged exposure is decreased. According to several studies, it is notable that the antibacterial effect of curcumin is greater against Gram-positive rather than Gram-negative species (due to less interaction with Gram-negative bacterial cell membranes; Afshariani et al., 2014; Bhawana, Basniwal, Buttar, Jain, & Jain N., 2011; Krausz et al., 2015; Luer et al., 2011; Tortik et al., 2016). To increase the antimicrobial effect of curcumin on Gram-negative species like *Escherichia coli*, Tortik et al. (2016) added calcium chloride to increase permeability of the Gram-negative bacterial cell membranes. Curcumin can also work synergistically with antibiotics (Bhawana et al., 2011; Mun et al., 2013), such as penicillin, ampicillin, oxacillin, and norfloxacin, against the MRSA. Curcumin's poor solubility in water can be improved by the preparation of polyvinylpyrrolidone-curcumin (Tortik et al., 2016), which is efficacious against liquid cultures of Gram-positive *S. aureus* as well as Gram-negative *E. coli* after in vitro permeabilization is enhanced with the inclusion of $CaCl_2$. Izui et al. (2016) studied the effect of curcumin against homotypic and heterotypic biofilm formation. Their results showed that curcumin prevented *Porphyromonas gingivalis* OMZ314 homotypic biofilm formation and that this effect was dose-dependent, inhibition surpassing 70% and 80% using 10 and 20 μg/ml of curcumin, respectively. The effect of curcumin in preventing the formation of heterotypic biofilm formation using *P. gingivalis* OMZ314 and *Streptococcus gordonii* G9B showed curcumin's inhibition of heterotypic biofilm formation was again dose-dependent, curcumin inhibiting biofilm formation by 55%, 80%, and 90% using 5, 10, and 20 μg/ml, respectively. Consequently, the anti-infective properties of curcumin make it a promising natural agent for wound healing, acne treatment and treatment of skin infections.

9 | ACNE TREATMENT

Acne vulgaris is a long-term and cutaneous pleomorphic skin disease of the pilosebaceous unit involving abnormalities in

TABLE 1 Studies of curcumin's effects in dermatological diseasesIn vivo

Condition–application	Formulation	Test model	Experimental design	Duration of exposure–treatment		References
Photodamage treatment	2 mg/ml curcumin in 0.5% CMC-Na (topical) 10 mM for the treatment of HaCaT cells	Hairless mice and HaCaT cells	In vivo, in vitro	1–4 days; 24 hr	Curcumin is an active agent for preventing and treating UV radiation-induced acute inflammation and photoaging due to antioxidant defenses and inhibition of oxidative damages via regulating Nrf2 signaling pathway	H. Li et al. (2016)
	10–30 μM curcumin	Human foreskin (human dermal fibroblasts)	In vitro	24 hr	Curcumin inhibit the UVB-induced expression of MMPs and blocks ROS production and the MAPK/NF-jB/AP-1 signalling pathway in human dermal fibroblasts (HDFs). Therefore, an effective therapeutic candidate for preventing and treating of skin photoageing	Phillips et al. (2013)
	10 μmol/L curcumin	Murine epidermal	In vitro	24 hr	Prevent UVB-induced both mTOR and FGFR2 signaling potentially leading to a new therapeutic candidate for advanced cancer with dual pathway dysregulation	Khandelwal et al. (2016)
Skin cancer treatment	25 μM curcumin	Melanoma cell culture	In vitro	24 hr	Curcumin-induced melanoma cell death by associated with mPTP opening	Qiu et al. (2014)
	15 mg/100 μl (topical and oral)	SKH-1 hairless mice	In vivo	-	Curcumin inhibits UV radiation–induced skin cancer and prolong time to tumor onset	Phillips et al. (2013)
	0.02% wt/wt (oral)	Mouse	In vivo	1–14 weeks	Curcumin present high anticarcinogenic activity in skin cancer through the inhibition of IGF-1 signaling	H. Kim et al. (2014)
	5 and 15 mg/day (oral)	SCID mice	In vivo	24 days	Curcumin inhibit skin squamous cell carcinoma growth and blocks tumor progression by inhibiting pS6 and mTOR pathway	Phillips et al. (2011)
	0.1–1.0 mg/ml CCNGs	Human melanoma cell, human dermal fibroblast, and porcine skin	In vitro	6–24 hr	Effective transdermal penetration of CCNGs could leading to specific advantage for the treatment of melanoma	Mangalathillam et al. (2012)
	Curcumin nanoniosome gel (3.15 ± 0.086 drug loading; topical)	Swiss albino mice	In vivo	7 weeks	Effective transdermal penetration of curcumin nanoniosome significantly inhibit proliferation of squamous cell carcinoma in DMBA-treated animals	R. Agrawal et al. (2015)

(Continues)

TABLE 1 (Continued)

Condition–application	Formulation	Test model	Experimental design	Duration of exposure–treatment		References
Antimicrobial	0.0003–0.0004 g/L curcumin loaded nanocubosomal hydrogel	*Escherichia coli*	In vitro	24 hr	Enhance bioavailability of curcumin able to increase curcumin antibacterial activity in topical drug delivery	Arunraj et al. (2014)
	50 or 100 μM curcuminbound to polyvinylpyrrolidone	*Staphylococcus aureus*, *E. coli*	Ex vivo (porcine skin model)	24 hr	Increase water solubility of curcumin and highly efficient against *S. aureus* an antibacterial against *E. coli*	Tortik et al. (2016)
	5–10 mg/ml curcumin-encapsulated nanoparticles	*Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* strain	In vitro	24 hr	Inhibit growth of Gram-positive and Gram-negative organisms	Krausz et al. (2015)
	100–400 μg/ml curcumin nanoparticles	*S. aureus*, *Bacillus subtilis*, *E. coli*, *P. aeruginosa*, *Penicillium chrysogenum*, *Aspergillus niger*	In vitro	24 hr	Higher aqueous solubility and more effective antimicrobial activity of curcumin nanoparticle compare to curcumin	Bhawana et al. (2011)
	7–250 μg/ml curcumin	*S. aureus*	In vitro	24 hr	Curcumin has synergistic effect in combination with antibiotics	Mun et al. (2013)
Wound healing	2 g/L curcumin in chloroform including dissolved polyvinylpyrrolidone and ethyl cellulose (topical)	Rat	In vivo	21 days	A combination of polyvinylpyrrolidone and ethyl cellulose significantly improve the permeation of curcumin transdermal patch leading to acceleration of wound healing and repair	Gadekar, Saurabh, Thakur, and Saurabh (2012)
	Curcumin cream (200 mg per pump; topical)	Breastfeeding women with lactational mastitis	Clinical	72 hr	Topical application of curcumin significantly decrease the signs of lactational mastitis such as pain, breast tension, and erythema	Afshariani et al. (2014)
	2% concentration curcumin ointment (topical)	Rat	In vivo	21 days	A decrease in size of the burn wounds and a reduction in inflammation after 14th day	Mehrabani et al. (2015)
	200 mg/cm^2 of curcumin (topical)	Mini-pig	In vivo	35 days	Reduce expression of cyclooxygenase-2 and NF-kB, and decrease the epithelial desquamation lead to stimulation of wound healing	J. Kim et al. (2016)
	10 mg/ml quercetin and curcumin-loaded phospholipid liposome nanovesicles (topical)	Newborn pig skin, mice	In vitro, in vivo	1 day, 4 days	Increase drug bioavailability and prevent the formation of skin lesion	Castangia et al. (2014)
	100 mg/kg body weight (topical)	Wistar-albino rats	In vivo	12 days	Rise in the hydroxyproline levels and expression of PCNA in skin tissuesbytopical application of curcumin leading much faster wound healing	Lopez-Jornet et al. (2011)

(Continues)

TABLE 1 (Continued)

Condition–application	Formulation	Test model	Experimental design	Duration of exposure–treatment		References
	Encapsulated curcumin loaded in polymeric micelles in thermo-sensitive hydrogel composite (topical)	Sprague–Dawley albino rat	In vivo	7 days	Very good wound healing activity present in both linear incision and full-thickness excision wound model in rats	Krausz et al. (2015)
	Curcumin-loaded hydrogel of xanthan and galactomannan (topical)	Rat	In vitro, in vivo	12 hr, 21 days	Curcumin loaded into xanthan–galactomannan hydrogels present good skin permeation and topical inflammation inhabitor	Koop et al. (2015)
Anti-inflammation	2 g/L of curcumin-loaded vesicular system (topical)	Female Laca mice and male Wistar rats	Ex vivo, in vitro	24 hr	Improve the skin permeability of curcumin and bioavailability leading to significant inflammatory inhabitation.	R. Agrawal et al. (2015)
	0.145% wt/wt nanocurcumin gel (topical)	Wistar rat	In vivo	12 days	High shelf life and effective anti-inflammatory	Al-Rohaimi (2015)
Psoriasis treatment	40 mg/kg curcumin (oral)	Mice	In vivo	20 days	Depress expression of cytokines and T-cell proliferation though Kv1.3 channelinhabitation lead to a great therapeuticeffect without obvious side effects.	Kang et al. (2016)
	Tablets containing 100 mg of standardized *Curcuma longa* extract with 12 mg of curcumin per tablet (oral)	Patient male and female	Clinical	75 days	Combination of the oral curcuma extract and UVA or visible light irradiation improve treatment rate of moderate-to-severe plaque psoriasis	Carrion-Gutierrez et al. (2015)
	10 μM of curcumin (oral)	Mouse	In vivo	20 days	Significantly inhibited secretion of inflammatory factors including interleukins, TNF-α in T cells and a great potential to treat psoriasis without toxicity to kidney	Kang et al. (2016)
	Encapsulation of curcumin in poly (lactic-co-glycolic acid) nanoparticles (topical)	Mice	In vivo	7 days	Significantly increase curcumin dispersion, sustained-release, accumulation, skin penetration and entrance the blood circulation, which improves antipsoriasis activity	Sun et al. (2017)

(Continues)

TABLE 1 (Continued)

Condition–application	Formulation	Test model	Experimental design	Duration of exposure–treatment		References
Acne treatment	0.43 μg/ml of Curcumin	Pig skin	In vitro	24 hr	Combined curcumin-lauric acid in the nanosized vehicles significantly inhibit the growth of *Propionibacterium acnes* and present a treatment of acne vulgaris	C. H. Liu and Huang (2013)
	100 mg/kg curcumin (oral)	Mouse	In vivo	20 days	Significant raise the glutathione concentration and activities of GPx and SOD enzymes in skin, whereas lipid peroxidation declined significantly meaning to antioxidant status of Curcumin	Jagetia and Rajanikant (2015)

Note. AP-1: activating protein 1; CCNG: curcumin-loaded chitin-nanogel; DMBA: 7,12-Dimethylbenz[a]anthracene; FGFR2: Fibroblast growth factor receptor 2; GPx: glutathione peroxidase; IGF-1: Insulin-like growth factor 1; MAPK: mitogen-activated protein kinase; mPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR: mammalian target of rapamycin; NF-kB: nuclear factor κ-light-chain-enhancer of activated B cells; PCNA: proliferating cell nuclear antigen; ROS: reactive oxygen species; SOD: superoxide dismutase; TNF-α: tumor necrosis factor α; UVB: ultraviolet B.

sebum production that occurs when hair follicles are clogged with dead skin cells and oil from the skin. Five important factors in the pathophysiology of acne generation are (a) excess sebum secretion from sebaceous glands, (b) bacterial infection *(Propionibacterium acnes*), (c) follicular epidermal hyperproliferation, (d) inflammation, and (e) genetics (Beylot et al., 2014; Williams, Dellavalle, & Garner, 2012). Different gene candidates have been proposed, including certain variations in *TNF-α*, *IL-1α*, and *CYP1A1* genes, among others. Acne can create either noninflammatory or inflammatory lesions, mostly affecting the face but also the back and chest. Although the use of antibiotics is a currently acceptable method to treat acne, the side effects of antibiotics and development of antibiotic resistance in *Staphylococcus epidermidis* demonstrates the need for nontraditional antimicrobial agents in the treatment of acne vulgaris.

Curcumin's anti-inflammatory and antimicrobial properties make it an ideal candidate for acne treatment. C. H. Liu & Huang (2012) developed a curcumin-loaded myristic acid microemulsion which was shown to be an excellent vehicle for delivering curcumin and inhibiting *S. epidermidis* (a bacteria involved in acne). Thus, curcumin is a promising therapeutic agent for the topical treatment of acne vulgaris. Also, in other studies by C. H. Liu & Huang (2013)), an emulsion of curcumin-loaded lauric acid lipid vehicles showed antibacterial activity against propionibacteria species (the primary agent involved in inflammatory acne). The effectiveness of this emulsion was considerably increased by the nanosized vehicle due to enhanced effective contact with the bacteria and increased cell membrane penetration.

10 | CURCUMIN ANALOGUES

In spite of these numerous advantages, the limitations to the use of curcumin, which include bioavailability challenges, low stability, low skin penetration, limited water solubility, and instability following exposure to light in the UV-visible range, has meant that this bioactive compound has found limited use as a pharmaceutical ingredient (Jafari, Sabahi, & Rahaie, 2016; Liang, Friedman, & Nacharaju, 2017). Notably, reports (Arunraj et al., 2014) have shown that curcumin's antioxidant and anti-inflammatory properties are not only decreased following light exposure but, in addition, it can induce oxidative stress, apoptosis–necrosis, cell injury, and cell death. In fact, the phototoxic and photosensitizing effects of crude curcumin are controversial. According to the literature (Mondal, Ghosh, & Moulik, 2016), the absorption spectra of curcumin falls in the UV-visible range, indicating its photodegradability. Additionally, poor bioavailability of curcumin (W. Liu et al., 2016; Prasad, Tyagi, & Aggarwal, 2014) makes it a class II drug in the biopharmaceutics classification system. In the last couple of decades, nanotechnology has been used to increase the stability of drugs, decrease side effects, and improve their delivery (Arunraj et al., 2014; Rachmawati, Budiputra, & Mauludin, 2015). Recently, to overcome some of the limitations of curcumin,

different curcumin encapsulated formulations on a nanosize and microsize scale, including liposomes–phospholipid (Manconi et al., 2017), nanogels (Mangalathillam et al., 2012), mono-oleine aqueous dispersion (Puglia et al., 2013), nanostructured lipid carriers (Chanburee & Tiyaboonchai, 2017), nanoemulsions (Kumar et al., 2016), polymeric micelles (M. Li et al., 2016) and polymeric nanoparticles (Yin, Zhang, Wu, Huang, & Chen, 2013), elastic vesicular systems (R. Agrawal et al., 2015), and lamellar and hexagonal mesophases (Fonseca-Santos, Dos Santos, Rodero, Gremiao, & Chorilli, 2016) have been investigated and have demonstrated improved aqueous solubility, bioavailability, and increased targeting potential. Additionally, continuous, low-level release of curcumin from encapsulated formulations should protect encapsulated compounds (including curcumin) from air-induced oxidation and may afford long-term activity and stability. As an example, Al-Rohaimi (2015) has shown that the permeation rate, drug release parameters, shelf-life, and anti-inflammatory activity of curcumin noticeably improved by using amorphous NanoCur as the source of curcumin, which was then incorporated into a nanoemulsion (o/w) using a water titration method and subsequently evaluated for topical drug delivery. Also, some research groups (Jeengar, Rompicharla, et al., 2016; Jeengar, Shrivastava, Mouli Veeravalli, Naidu, & Sistla, 2016) have introduced the use of emu oil as a carrier for topical curcumin application due to increased solubility and improved skin penetration, resulting in a synergistic anti-inflammatory effect. It should, however, be noted that the use of emu oil as an anti-inflammatory agent is controversial. On the other hand, ethanol, dimethyl sulfoxide, and propylene glycol were used as solvents for curcumin in aqueous formulations such as curcumin gels. Menthol has been proposed as a penetration enhancing agent in preparations of curcumin gels for topical application due to enhanced percutaneous flux and transdermal absorption of curcumin (Patel, Patel, & Patel, 2009). Also, some polymers, such as carbopol, hydroxypropyl methylcellulose, and sodium alginate have been introduced into formulations to serve as gelling agents and have shown enhanced bioavailability and dermal permeation of curcumin (Patel et al., 2009).

11 | CONCLUSION

Curcumin exhibits a variety of important properties and holds promise for the treatment of dermatological diseases as summarized in Table 1. Recently, clinical research and preclinical scientific studies have demonstrated curcumin's remarkable antioxidant, anti-inflammatory, and antibacterial activities, which can be effectively utilized to treat acne, psoriasis, dermal wounds, sun burn, premature aging, melanoma, and ROS agglomeration.

Finally, it would appear that the limitations of poor bioavailability and low stability of curcumin can be overcome using nanotechnology, including liposomes–phospholipid, nanogels, nanostructured lipid carriers, nanoemulsions, polymeric micelles, and various polymeric nanoparticulate methods, though further studies are needed to clarify the utility of curcumin.

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CONFLICT OF INTERESTS

Muhammed Majeed is the Founder and Chairman of Sabinsa Corporation and Sami Labs Limited. For remaining authors, there are no conflicts of interest.

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