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REVIEW

Advancements in Dermatological Applications of Curcumin: Clinical Efficacy and Mechanistic Insights in the Management of Skin Disorders

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Abstract: Curcumin, derived from *Curcuma longa* (turmeric), exhibits significant potential in dermatology, addressing conditions like atopic dermatitis, psoriasis, chronic wounds, skin cancer, and infections through its anti-inflammatory, antioxidant, anticancer, and antimicrobial properties. This review synthesizes evidence on curcumin's mechanisms, including modulation of immune responses and promotion of wound healing, showcasing its efficacy in reducing inflammation, cytokine levels, and enhancing skin barrier functions. Studies highlight curcumin's ability to selectively target tumor cells, suggesting a multifaceted approach to cancer therapy with minimal side effects. Despite promising therapeutic benefits, challenges remain in bioavailability, potency, and targeted delivery, underscoring the need for further research to optimize dosages, delivery methods, and assess long-term safety. The integration of curcumin into dermatological practice requires a balanced consideration of evidence-based efficacy and safety. Curcumin's comprehensive utility in dermatology, coupled with the necessity for advanced scientific exploration, emphasizes the importance of combining traditional knowledge with contemporary research to improve patient care in dermatology. This approach could significantly enhance outcomes for individuals with skin-related conditions, marking curcumin as a versatile and promising agent in the field.

Keywords: curcumin, atopic dermatitis, psoriasis, chronic wounds, skin cancer

Introduction

The skin, as the body's largest organ, serves a crucial role in providing protection, acting as a barrier, regulating body temperature, and enabling sensation. However, nearly 80% of the adult population has experienced skin disorders in their lives, with more than one-third of individuals facing a three or more simultaneous conditions.[1,2] It poses significant challenges to the quality of life for both adults and teenagers, as lesions in visible areas can lead to emotional distress, including sadness, low self-esteem, and social withdrawal, which may further predispose individuals to psychiatric disorders.[3,4]

Curcumin (CUR), constituting 2 to 8% of the compounds in *Curcuma longa* (turmeric) and recognized as a potent polyphenol, is celebrated for its therapeutic efficacy in traditional Chinese medicine (TCM).[5] It was first identified about two centuries ago by Vogel and Pelletier, who reported isolating a "yellow coloring-matter" from the rhizomes of *Curcuma longa* (turmeric).[6] Moreover, it is a diferuloyl methane molecule [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], consisting of two ferulic acid residues linked by a methylene bridge, and is one of the main curcuminoids alongside demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC), which are commercially available.[7] Furthermore, it exhibits a broad spectrum of beneficial effects, encompassing anti-inflammatory,[8] antioxidant,[9] anticancer,[10] and antimicrobial properties.[11] The diverse impacts of CUR stem from its ability to engage with various molecules and to modulate numerous molecular pathways along with their targets.[12] These characteristics have established CUR as a potent remedy for an array of dermatological conditions.[13] Despite CUR's extensive

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pharmacological benefits, its clinical use is limited by poor oral bioavailability and low stability; addressing these issues may involve structural modifications and innovative delivery systems to improve its properties and bioavailability.[14,15]

In recent years, many studies have validated that turmeric/CUR products and supplements, whether applied topically or taken orally, can offer therapeutic advantages for skin health.[16,17] This review aims to encapsulate the progress in CUR for treatment and management of skin disorders, offering insights that could guide both therapeutic practices and future clinical and foundational research in the realm of skin disorders.

Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing, and remitting skin condition marked by persistent itching and non-infectious inflammation.[18,19] The worldwide prevalence of atopic dermatitis is estimated to be up to 10% in adults and between 15% and 20% in children.[20,21] The mechanism behind AD involves genetic and environmental factors influencing skin barrier dysfunction, notably through mutations like filaggrin, leading to increased exposure to harmful substances, immune reactions, and dry skin due to transepidermal water loss.[21] It is also characterized by a shift towards Th2 immunity, weakening the skin's barrier and innate immunity, and promoting IgE-mediated allergies and eosinophil activation, with T1, Th17, and Th22 immunity also contributing in chronic stages, alongside IgE autoimmunity and skin dysbiosis dominated by S. aureus during flare-ups.[22,23]

CUR has been extensively validated as an effective agent in controlling skin inflammation through multiple signaling pathways. A study demonstrates that CUR can effectively mitigate AD and related asthmatic symptoms in mice induced with ovalbumin, by normalizing skin pathology, suppressing inflammatory cell infiltration and cytokine expression, and restoring redox and NF-κB signaling balances.[24] Another study assessed the immunomodulatory effects of different concentrations of CUR on acetone-induced atopic dermatitis in female Albino rats, finding that a 5% CUR treatment most effectively promoted skin healing, maintained normal epidermal thickness without inflammatory cell presence, and significantly reduced Interleukin (IL) 13 levels, suggesting its superiority in treating rat dermatitis with enhanced therapeutic outcomes and minimal complications.[25] Kong et al also illustrate CUR's capability in reducing allergic inflammation in Rat Basophil Leukemia (RBL)-2H3 and human pre-basophil (KU812) cell lines by hindering cell degranulation, decreasing histamine and beta-hexosaminidase releases, reducing intracellular reactive oxygen species (ROS) production, and diminishing expressions of high-affinity IgE receptor (FcεRI) and pro-inflammatory cytokines such as IL-4 and IL-13, as well as inhibiting protein kinase C delta (PKC-δ) translocation, effectively alleviating both Immunoglobulin E (IgE)-mediated and calcium ionophore A23187-stimulated allergic responses.[26] Nyoman et al also demonstrates that applying a 1% turmeric rhizome extract moisturizing nanoemulgel on BALB/c mice reduces atopic dermatitis (AD)-like skin lesions by lowering thymic stromal lymphopoietin (TSLP), IL-13, and IL-17 levels and improving dermatitis scores and histopathological features in a 2.4-dinitrochlorobenzene-induced model, though its effect on transepidermal water loss (TEWL) was not statistically significant.[27]

In clinical practice, Rawal et al concluded that Herbavate®, a topical polyherbal cream, significantly improved eczema symptoms with good local tolerance and minimal side effects, presenting it as an effective alternative management option for outpatient eczema treatment.[28] However, assessing the significance of the results is challenging due to the limited size of the control group, a significant dropout rate, and the potential influence of other ingredients in the cream. TOGNI et al suggested that Meriva®, a phytosome-based CUR delivery form, effectively reduces clinical signs of atopic dermatitis and lowers recurrence risk when used as an adjunct to standard management, demonstrating significant improvements in symptoms, skin health, and reduction in topical corticosteroid use.[29]

Psoriasis

Psoriasis, a chronic immune-mediated inflammatory skin condition, impacts around 2–3% of the global population across all ages, particularly within the 16–22 and 55–60 age brackets.[30,31] It is marked by red, painful, scaly plaques that can emerge on different areas of the body, leading to substantial physical and psychological distress, and in severe cases, may even culminate in suicidal ideation.[32,33] An expanding corpus of research suggests that psoriasis ought to be regarded as a systemic condition due to its association with a heightened risk of numerous comorbidities, including cardiovascular diseases, metabolic syndrome, diabetes mellitus, and obesity, among others.[34,35] The onset of psoriasis is marked by

complex genetic, immunological, and environmental interactions that activate plasmacytoid dendritic cells, triggering dysregulated immune responses, excessive keratinocyte proliferation, and the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-17, IL-22, IL-23, and IL-1β, which in turn stimulate further keratinocyte hyperproliferation and perpetuate chronic inflammation.[36,37]

CUR demonstrates significant efficacy and safety in treating psoriasis through various mechanisms, as evidenced by improved Psoriasis Area and Severity Index (PASI) scores, reduction in psoriatic dermatitis symptoms in mice, and decreased expression of inflammatory cytokines, suggesting that CUR, both as monotherapy and in combination with other treatments, is an effective strategy for managing psoriasis.[38] To be specific, Zhang et al, revealed that CUR effectively inhibits the NLRP3 inflammasome, reducing inflammation in a mouse model of psoriasis through topical application, with experiments showing significant reductions in NLRP3 expression and inflammation caused by IL-22 and IL-18, as well as a notable decrease in STAT3 phosphorylation.[39] Zhou et al demonstrated that progranulin (PGRN) plays a crucial role in the etiology of psoriasis and demonstrates that CUR, derived from turmeric, can mitigate the exacerbation of psoriasis-like skin lesions induced by PGRN deficiency in a mouse model, highlighting CUR's potential as a therapeutic agent by directly regulating keratinocyte proliferation and differentiation and reducing proinflammatory cytokine levels.[40] Cai et al also highlighted that CUR effectively mitigates psoriasis-like lesions in mice through oral administration, reducing PASI scores and inflammatory cytokines, enhancing IL-10 expression, and modulating gut microbiota, thereby suggesting CUR's potential as a promising treatment for psoriasis via regulating Th-17 related inflammatory factors and gut microbiome alterations.[41] They also concluded that CUR effectively reduces psoriasis-like lesions in mice, likely through inhibiting IL-6/STAT3 signaling pathways and decreasing the levels of TNF-α, IL-6, and the phosphorylation of STAT3 and its associated proteins, showcasing CUR's potential as a therapeutic agent for psoriasis.[42] Moreover, Skyvalidas et al also demonstrated that CUR significantly reduces the production of IFN-γ and IL-17 in peripheral blood mononuclear cells from patients with psoriasis and psoriatic arthritis, indicating its anti-inflammatory and immunosuppressive effects, potentially through the modulation of STAT3 activation, thereby reinforcing its use as a dietary immunosuppressant in managing psoriatic disease.[43] Furthermore, Mousa et al demonstrated that a combination therapy of CUR and ustekinumab significantly alleviates symptoms in imiquimod-induced psoriasis in a rat model more effectively than ustekinumab monotherapy by synergistically reducing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-17, IL-12 subunit p40, and IL-23, and enhancing levels of antioxidant biomarkers, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), indicating a promising, cost-effective approach for improving psoriasis treatment outcomes.[44]

Thus, the growing evidence supporting CUR's efficacy in psoriasis treatment reflects an encouraging trend towards blending traditional and modern therapeutic approaches. CUR's anti-inflammatory and immunomodulatory effects, particularly its influence on the IL-6/STAT3 pathway and the gut microbiome, highlight its potential as both an adjunct and an alternative to conventional psoriasis therapies. Despite promising results, the need for more comprehensive clinical trials remains to fully ascertain CUR's optimal usage, safety, and efficacy in psoriasis management. The integration of CUR into treatment regimens could offer a holistic solution to this complex disease, underscoring the importance of merging scientific research with traditional knowledge for improved patient outcomes.

Chronic Wounds

Wound healing issues represent a significant and growing clinical challenge, with recent reports indicating that approximately one billion people worldwide suffer from chronic and acute wounds.[45,46] Especially, the chronic wound, defined as one that does not follow a timely and orderly repair process to achieve sustained anatomical and functional integrity and may last from 4 weeks to over 3 months due to factors like trauma, infection, pressure, diabetes, vascular disease, or radiation, affects approximately 2% of hospitalized patients globally, with older adults at the highest risk due to impaired healing related to aging, leading to a 70% recurrence rate and a 34% chance of being accompanied by infection.[47,48] Impaired wound healing can be categorized into local and systemic factors. Local factors include inadequate oxygen supply due to disturbed blood circulation and wound infections.[49,50] Systemic factors encompass a range of issues such as smoking, obesity, malnutrition, impaired mobility, diabetes, and gender, with hormones playing a significant role; estrogens positively and testosterone negatively affecting wound healing.[51,52]

The primary mechanism in the wound healing process involves controlling inflammation, which is crucial for optimal skin regeneration.[53] CUR plays a significant role in modulating inflammation by inhibiting the production of TNF-α, NF-κB and IL-1, which are crucial in inflammatory response regulation.[54] This action underscores the link between oxidation and inflammation in wound healing, highlighting CUR's potential as a therapeutic agent in managing inflammation to optimize wound healing processes.[55] Furthermore, a combination of quercetin and curcuminoids, particularly at a 3:1 ratio, significantly enhances wound healing by demonstrating synergistic antimicrobial activity against S. aureus and P. aeruginosa, superior antioxidant capacity, and promoting fibroblast migration, highlighting its potential as an effective formulation for acute and chronic wound care.[56] In addition, CUR modulates wound healing in a biphasic dose-response manner, stimulating at low doses via the induction of stress response pathways, thereby suggesting its potential in addressing age-related delays in wound healing.[57] Fei et al demonstrated that CUR mitigates hypertrophic scarring by inhibiting fibroblast proliferation, migration, and α-SMA expression in a dose-dependent manner, primarily through suppression of the TGF-β1/Smad3 pathway and reduction of tissue inflammation, offering a scientific basis for its clinical application in scar treatment.[58] Wang et al also suggested that hypoxic preconditioning combined with CUR enhances the survival, cell cycle progression, and mitochondrial function of bone marrow mesenchymal stem cells (BMSCs), inhibits apoptosis, and promotes tissue repair, largely through the modulation of mitochondrial quality, oxidative phosphorylation, and the PGC-1α/SIRT3/HIF-1α signaling pathway, thereby accelerating cutaneous wound healing in a mice model and offering a promising approach for BMSCs-mediated tissue repair.[59]

In summary, CUR has been identified as a potent modulator of the wound healing process, with its multifaceted effects spanning the inflammatory, proliferative, and remodeling phases. Research indicates that by targeting these key phases, CUR effectively accelerates the wound healing timeline, showcasing its therapeutic potential in enhancing tissue repair.

Skin Cancer

Skin cancer stands as the fifth most prevalent cancer today and is anticipated to outpace heart disease as the leading cause of death, posing the greatest barrier to increased life expectancy in the future.[60] With around 9.6 million cancer-related deaths and 18.1 million new cases in 2018, projections suggest a steady uptick in melanoma incidences, estimated at 6% for males and 4% for females in 2023, with expectations of continued growth over the next two decades.[61,62]

The development of skin cancer, particularly prevalent among fair-skinned populations, is significantly influenced by excessive UV radiation exposure, accounting for nearly 90% of cases.[63] UV radiation not only plays a crucial role in vitamin D synthesis and immune regulation but also in DNA damage, leading to skin cancer through mechanisms like the mitogen-activated protein kinase (MAPK) signaling pathway and immune system suppression.[64,65] The complex interplay of UV exposure, immune suppression, genetic mutations, and viral oncogenesis underscores the multifaceted nature of skin cancer development.[66–69]

CUR exhibits remarkable anti-cancer properties by selectively targeting tumor cells while sparing normal ones.[70,71] It can activate apoptosis through the caspase activation pathway, involving caspase-8, 3, and 9, and disrupts cell survival by downregulating anti-apoptotic proteins.[72] It also interferes with cell proliferation by targeting cyclin D1 and c-myc and enhances the function of tumor suppressor proteins such as p53 and p21.[73] Furthermore, it regulates death signaling via upregulation of death receptors DR4 and DR5, disrupts mitochondrial function to induce cell death, and modulates kinase signaling pathways.[74,75] The ability of CUR to selectively affect tumor cells over normal cells is notably due to the differential expression and susceptibility of these cells to the pathways CUR influences, making it a promising, multifaceted approach to cancer therapy with minimal side effects.

Regarding the skin cancer, Parashar et al introduced Compound A, a synthetic analog of CUR, demonstrating for the first time its selective apoptotic induction in melanoma cells, enhanced anti-cancer activity with tamoxifen, and compatibility with taxol and cisplatin, offering a promising direction for developing selective and effective melanoma treatments with minimal toxicity to noncancerous cells.[76] Szlasa et al demonstrated the efficacy of CUR as an anticancer agent in photodynamic therapy (PDT) for treating melanotic (A375) and amelanotic (C32) melanoma cell lines, showing significant cytotoxic effects and increased apoptosis and necrosis upon light irradiation, along with caspase-3 overexpression and DNA cleavage, although it lacks selectivity towards melanoma cells.[77] Manica revealed that CUR significantly reduces viability, induces apoptosis, inhibits migration, and increases oxidative stress in the metastatic

cutaneous melanoma cell line SK-MEL-28, through elevated ROS levels and activation of the caspase pathway, highlighting its potential as an adjuvant therapy for CM.[78] Tremmel et al demonstrated that a topical combination of ursolic acid and CUR significantly inhibits skin tumor promotion in mice more effectively than either compound alone by blocking critical signaling pathways like EGFR, NF-κB, and Src, reducing proliferation markers and inflammatory gene expression, thereby showcasing a synergistic, detailed mechanism of action for cancer chemoprevention.[79]

In summary, despite the escalating epidemiological burden of skin cancer, characterized by a marked increase in incidence and mortality rates, the investigation into CUR's utility as a therapeutic agent within the dermatological oncology landscape, particularly regarding melanoma, is conspicuously nascent. Preliminary investigations have elucidated CUR's multifaceted anticancer mechanisms, encompassing the induction of apoptosis, disruption of cell proliferation cycles, and the modulation of critical cellular signaling pathways in melanoma cell lines. However, the scope of research dedicated to leveraging CUR's potential for innovative, synergistic treatment modalities that promise minimal adverse effects remains embryonic, underscoring a significant gap in the current academic discourse on skin tumor therapeutics.

Skin Infections

Skin and soft tissue infections (SSTIs), ranging from minor, superficial afflictions to severe, life-threatening conditions, are primarily incited by the ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), known for their formidable antibiotic resistance.[80] Particularly, Staphylococcus aureus and Pseudomonas aeruginosa, frequently isolated from chronic wounds, present escalating challenges due to their growing resistance to topical antibiotics.[81] The management of SSTIs hinges on the infection's severity, location, and the patient's underlying conditions, distinguishing between simple and complicated infections, as well as suppurative and nonsuppurative types.[82,83] While community-acquired infections are predominantly due to methicillin-resistant Staphylococcus aureus (MRSA) and beta-hemolytic streptococcus, the microbial landscape is broadening, partly due to factors like diabetes, immune dysfunction, and environmental exposure.[84–86] Diagnosis relies on clinical assessment, with laboratory tests supporting uncertain cases or deep infection evaluations. Initial antimicrobial treatment is empirical, tailored to cover staphylococci and streptococci for simple infections, or a broader spectrum for complicated cases necessitating hospitalization and possibly surgical intervention.[87]

The role of CUR in treating skin infections, particularly in controlling wound infections, has been widely validated and recognized for its effectiveness.[88] For example, Paolillo et al demonstrated that antimicrobial photodynamic therapy (aPDT) using CUR gel and blue LED light, combined with alcohol-based artificial skin, significantly enhanced bacterial reduction and wound contraction in infected skin wounds of Wistar rats inoculated with Staphylococcus aureus, with the combination therapy showing the highest bacterial viability reduction and comparable wound contraction rates, highlighting the efficacy of integrating aPDT and artificial skin in accelerating wound healing and microbial control.[89] Krausz et al demonstrated that CUR, when encapsulated in silane-hydrogel nanoparticles (curc-np), exhibits significant potential as a topical therapy for wound infections, showcasing effective action against methicillin-resistant Staphylococcus aureus (MRSA) both in vitro and within a murine model of burn wounds.[90]

Research indicates that CUR disrupts the membranes of both Gram-negative and Gram-positive bacteria, causing cell leakage in various species including E. coli, Enterococcus faecalis, Pseudomonas aeruginosa, and S. aureus, albeit at elevated concentrations.[91,92] It employs mechanisms akin to traditional antibiotics, including membrane disruption, induction of cell division interruption, efflux pump inhibition, and Reactive Oxygen Species (ROS), to exterminate microorganisms.[93] Notably, CUR obstructs bacterial efflux pumps, a critical resistance mechanism, in pathogens like Pseudomonas aeruginosa and S. aureus.[94] It also targets the α-hemolysin of S. aureus, preventing its self-assembly and subsequent hemolysis by binding and inhibiting conformational changes necessary for activity.[95,96] Furthermore, it suppresses genes involved in the carbohydrate metabolism and synthesis of Extracellular Polymeric Substances (EPS).[97,98] Additionally, CUR disrupts the bacterial cell division by interfering with FtsZ protein assembly, a strategy that has shown promise in targeting S. aureus.[99]

Furthermore, CUR has demonstrated antiviral activity against a variety of viruses. For example, studies have shown that low, non-toxic doses of CUR reduce the infectivity of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) both in vitro and in vivo, notably decreasing the expression of HSV-1 immediate early genes.[100] Similarly, CUR has been

found to reduce immediate early gene expression in human cytomegalovirus (HCMV) infections and exhibit varying effects on Epstein–Barr virus (EBV), inhibiting its reactivation in some studies while enhancing lytic reactivation in others.[101,102] Another study also concluded that various CUR derivatives exhibit excellent absorption, distribution, metabolism, excretion, and toxicity profiles. Based on these characteristics, the study recommends these derivatives as potential antiviral agents for treating Monkeypox and Smallpox virus infections.[103] In addition, CUR has shown significant anti-HPV effects in both laboratory and clinical settings.[104] It inhibits HPV-related oncogenes and restores tumor suppressor proteins like p53 and Rb.[105] Clinical trials, including a Phase II study, have demonstrated that CUR formulations can lead to approximately 80% clearance of HPV in affected patients.[106] Additionally, CUR enhances chemotherapy efficacy and increases radiation sensitivity in cancer cells, making it a promising candidate for HPV-related cancers.[107]

Conclusions

In conclusion, the examination of CUR's multifunctional role across various dermatological conditions—ranging from atopic dermatitis, psoriasis, chronic wounds, skin cancer, to skin infections—highlights its significant therapeutic potential. Through an impressive array of mechanisms, including modulation of immune responses, anti-inflammatory actions, antimicrobial activities, and promotion of wound healing, CUR emerges as a versatile agent capable of addressing a wide spectrum of skin disorders. Its efficacy in mitigating inflammation, reducing cytokine levels, enhancing skin barrier functions, and inhibiting tumor cell proliferation, alongside its role in disrupting microbial cell structures and resisting antibiotic-resistant strains, underscores the compound's comprehensive utility in dermatology. Despite these promising findings, this review also points to the necessity for further research to establish optimized dosages, delivery methods, and long-term safety profiles of CUR in clinical settings. As such, while CUR presents a promising adjunct or alternative to traditional therapies, its integration into mainstream dermatological practice necessitates a balanced consideration of evidence-based efficacy, safety, and the potential for novel therapeutic formulations.

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