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REVIEW ARTICLE

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The application prospects of honokiol in dermatology

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Abstract

Honokiol is one of the natural extracts of *Magnolia officinalis*. It is a small molecule, lipophilic compound with extensive biological effects. It has been used in the treatment of multisystem diseases, including digestive diseases, endocrine diseases, nervous system diseases, and various tumors. This paper reviews the biological effects of honokiol on the treatment of skin diseases in recent years, including antimicrobial, anti-oxidant, anti-inflammatory, anti-tumor, anti-fibrosis, anti-allergy, photo-protection, and immunomodulation. Most current researches are focused on the effects of anti-melanoma and photo-protection. Therefore, we summarized the specific mechanisms about these two effects. On the other side of treating skin diseases, the advantages of topical drugs cannot be replaced. As a small molecule fat-soluble compound, honokiol is suitable for external use. We reviewed the advantages and disadvantages of the topical mixed cream and various improved methods. These improvements include physical and chemical penetration enhancers, drug carriers, and chemical derivatives. In conclusion, honokiol has a wide range of effects, and its topical preparation provides a safe and effective way for treating skin diseases.

KEYWORDS
anti-melanoma, dermatology, honokiol, photo-protection, topical application

1 | INTRODUCTION

Magnolia trees mainly exist in the east and southeast Asia, and their barks have been used in Chinese and Japanese traditional medicines for many years. They are mainly used for the treatment of the gastrointestinal disorder, anxiety, stroke, and allergic disease.[1] Among the more than 250 ingredients extracted from the *genus Magnolia*, honokiol is the most famous active ingredients. Honokiol is a small molecular weight bioactive ingredient that can exist in all the parts of *Magnolia* plants. It is a phenylpropanoid compound and belongs to the neolignans, which have a para-allyl phenol and an ortho-allyl phenol joined together with the ortho-, para-C-C-coupling (Figure 1). Honokiol has been proved to have diverse biologic and pharmacologic activities, including anti-inflammation, anti-oxidant, anti-tumor, anti-lipid peroxidation, anti-angiogenesis, and neuroprotective role.[2] Because of its multifunctional activities, it had been found to play an important role in the treatment of skin diseases. However, its wide application was restricted by low water solubility, low bioavailability, and instability. Although it can be improved by some drug carriers, topical delivery acts as an efficient way to offer higher skin bioavailability and dermal targeting.[3] We reviewed the recent researches on honokiol relating to dermatology and external use way, to broader the therapeutic approach for skin diseases.

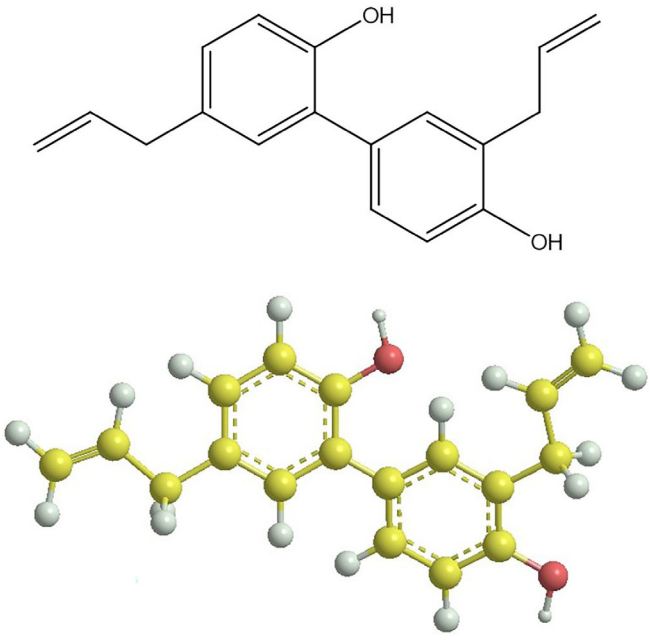

FIGURE 1 Chemical structure of honokiol and its three-dimensional display

through the Ras1-cAMP-Efg1 pathway.[7] Their further study found that honokiol acted as a pro-oxidant in *C. albicans* infections, and the ROS production is associated with mitochondrial dysfunction.[8] Honokiol could inhibit the biosynthesis of ergosterol, an essential component of the yeast cell membrane, and disrupt the H^+-ATPase activity, resulting in abnormal pH in the vacuole and cytosol of *C. albicans*.[9] Furthermore, honokiol combined with other drugs could increase anti-*C. albicans* effects. For example, vitamin C (VC) and E (VE) had been reported to have both anti-oxidant and pro-oxidant activities that is similar to honokiol, but VC significantly potentiated the antifungal activities of honokiol while VE reduced the effect of honokiol against *C. albicans*. Because VC is hydrophilic while VE is lipophilic, and lipids often become the prime target of oxygen radicals.[10] Honokiol combined with fluconazole (FLC) could provide a potential therapeutic method against FLC-resistant *C. albicans*.[11]

Recently, it had been reported that honokiol inhibited the common standard strains and clinical strains of dermatophytes by destroying the ergosterol biosynthesis. And it enhanced the terbinafine's activity against *Trichophyton rubrum*.[12] Honokiol could also be used against other bacteria or viruses associating with skin diseases, for example, *Propionibacterium acnes*[13] and Herpes Simplex Virus-1.[14]

2 | THE THERAPEUTIC APPLICATIONS IN DERMATOSIS

2.1 | The effects and mechanisms in skin infectious diseases

The first mention that honokiol has a strong anti-microbial effect was Clark at 1981. They exhibited that honokiol had significant activities against Gram-positive, acid-fast bacteria, and fungi.[4] In subsequent studies, researchers found that honokiol was effective against a variety of bacteria and fungi, but the *Staphylococcus aureus* and *Candida albicans* were studied most. *S. aureus* is the most common pathogeny of skin and soft tissue infections, about 30% of healthy people in the USA have its colonization.[5] Recent studies indicated that honokiol attenuated the inflammatory response induced by staphylococcal α-Hemolysin (Hla) by inhibiting NLRP3 inflammasome activation. This anti-Hla function was achieved by disrupting the assembled membrane channel.[6] Honokiol not only as a bactericidal be against *S. aureus*, but also be effectively against antibiotic-resistant strains such as methicillin-resistant *S. aureus* (MRSA) with low cytotoxic activity. Choi et al. found that in addition to antimicrobial activities against methicillin-sensitive *S. aureus* (MSSA) and MRSA, honokiol could modulate cellular response induced by *S. aureus* in mouse macrophages and inhibit bacteria entry into human lung epithelial cells.[5]

C. albicans can be the primary cause of skin disease or may arise secondary infections after atopic dermatitis, psoriasis, or diaper dermatitis. Honokiol showed significant inhibitory activities against *C. albicans* with the minimum inhibitory concentrations (MIC) of 30 μg/ml.[4] Sun et al. revealed that honokiol inhibited adhesion, a transition from yeast to hypha, and biofilm formation of *C. albicans*

2.2 | The effects and mechanisms in melanoma

Melanoma is an aggressive skin cancer, with high incidence, mortality, and potential to metastasize. However, the therapeutic options are limited. The honokiol has significant anti-neoplastic effects in various types of cancers such as breast cancers, lung cancers, ovarian cancers, bladder cancers, and gastric cancers.[2] Studies had shown that honokiol significantly inhibited melanoma cell's proliferation and viability, induced autophagy and apoptosis,[15] also inhibited the growth of melanoma cancer stem cells.[16] Besides in vitro studies, honokiol caused a significant reduction of tumor growth in melanoma xenogragts.[17] Moreover, honokiol could thwart the metastasis and migration of melanoma,[18,19] and be helpful to the drug resistance of melanoma. It also can be used as a supplement to enhance the effects of other anti-melanoma drugs.[20,21]

The mechanism of anti-melanoma was lined in the following. (a) Reactive oxygen signaling: honokiol was an effective scavenger of intracellular superoxide within melanoma cells.[22] Further research confirmed that honokiol inhibited the migration/extravasation and growth of melanoma cells by blocking the interaction of core proteins of the NADPH oxidase complex.[19] (b) PI3K-AKT–mTOR signaling pathway: honokiol significantly inhibited the AKT and mTOR phosphorylation in a dose and time-dependent manner, which were involved in the growth and drug resistance of melanomas.[23,24] (c) Notch signaling pathway: honokiol inhibited Notch signaling by inhibiting the essential members of the γ-secretase complex in melanoma cells.[24] Kaushik et al. further proved that honokiol affected the growth both of melanoma cells and melanoma stem cells by suppressing Notch-2 signaling.[15] (d) AMPK signaling pathway: honokiol could target melanoma stem cells and participate in melanocytes' autophagy

by activating the AMP-activated protein kinase (AMPK) signaling.[16] Then significantly decreased the number and size of melanospheres. (e) Mitochondrial dysfunction: administration of honokiol rapidly reduced mitochondrial respiration by inhibiting the electron transport chain (ETC) complexes I, II, and V, then induced cellular responses involving in cyclin-dependent kinases.[20] (f) Endoplasmic reticulum (ER) stress activation: honokiol could promote ER stress-dependent apoptosis and inhibit organ metastasis. This ER stress activation modulated the β-catenin/MITF axis and blocked epithelial-mesenchymal transition (EMT).[18] Glucose regulated protein 78 (GRP78) is a sensor of ER stress, honokiol interacted with it and the combination ability was stronger than that of Epigallocatechin gallate (EGCG).[25] (g) Hypoxia-related signaling pathway: hypoxia-inducible factor-1α (HIF-1α) acted importantly in the tumor's response to hypoxia. And honokiol could inhibit the growth and metastasis of melanoma by reducing the HIF-1α protein level.[26] (h) Through ubiquitination and inducing Keratin 18 (KRT 18) protein degradation. Because the KRT 18 acted as an oncogene and was highly expressed in melanoma tissues.

2.3 | The effects and mechanisms in the ultraviolet (UV) radiation-induced skin diseases

Solar ultraviolet radiation (UVR) causes skin damage via direct and indirect mechanisms. The indirect way is to dramatically increase the production of reactive oxygen species (ROS) which causes "oxidative damage" to cellular components like cell walls, lipid, membranes, mitochondria, and DNA. And eventually causes inflammatory responses, which are characterized by the development of erythema, edema, and hyperplasia, and causes premature aging and skin cancer.[27] Studies had demonstrated that honokiol prevents UVB-induced skin cancer in a dose-dependent manner, and through multiple mechanisms (Figure 2).

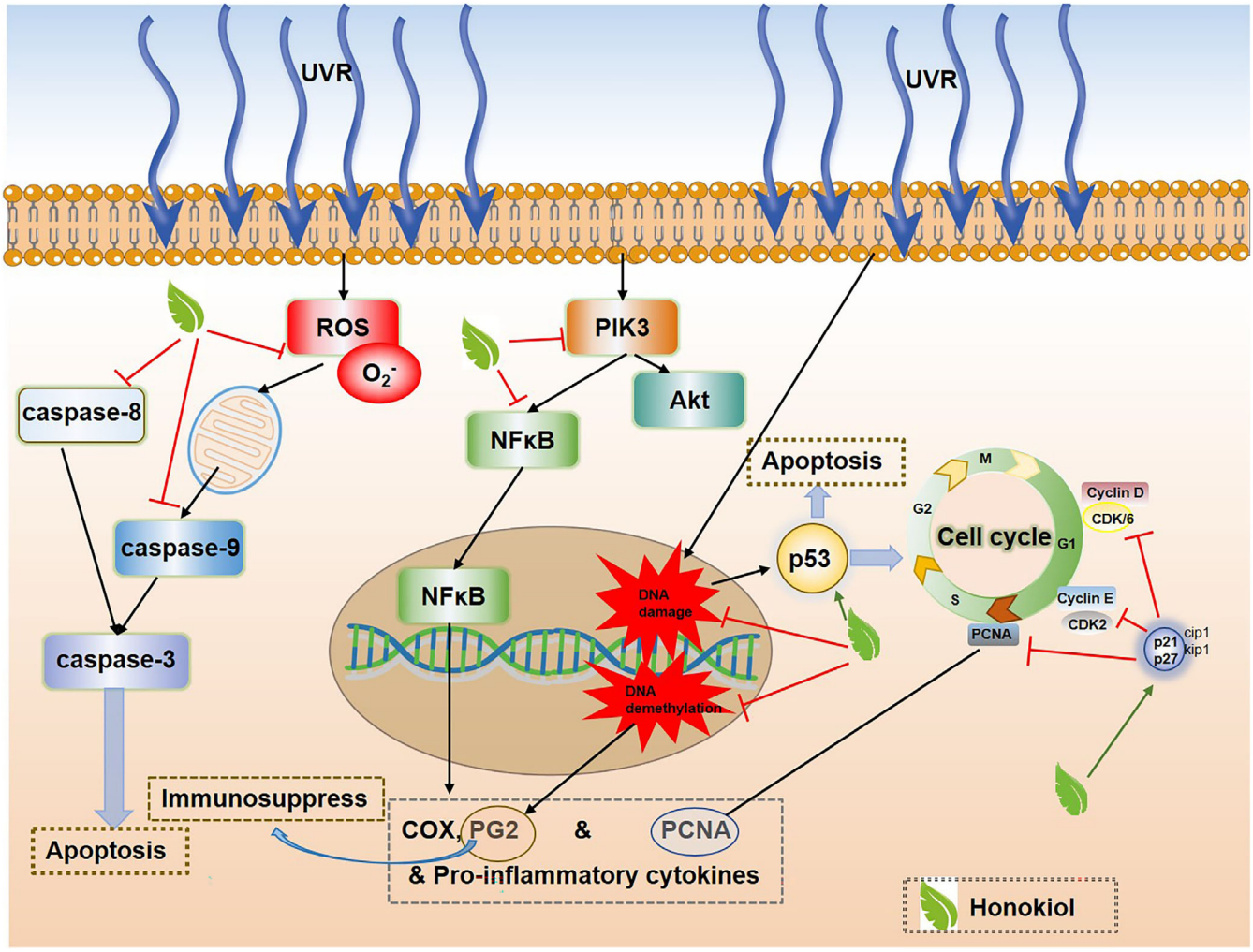

FIGURE 2 Improve the dermal and transdermal applications of honokiol through physical/chemical penetration promotion, drug carriers, and chemical derivatives. Penetration and absorption can be increased through penetration enhancers such as microneedles, oleic acid, and some natural products, as well as drug carrier F127. These methods both increase the dermal and transdermal, and are suitable for topical, transdermal, and systematic use. However, nanoparticle carrier and methylated honokiol only increase the drug concentration in the skin, which is conducive to the local/topical application for skin diseases

Honokiol is an effective scavenger of both superoxides and peroxyl radicals, and the ability to scavenge superoxide was 20-times higher than vitamin E in vitro.[22] Its elimination function of reactive oxygen species may be through inhibiting the activity of NF-κB, which plays a key role in the immune response of inflammation.[22] Further studies showed that honokiol inhibited UVB-induced inflammation reactions, including the inhibition of cyclooxygenase-2 (COX-2), prostaglandin (PGs), iNOS, and proinflammatory cytokines (TNFα, IL-1β, and IL-6).[28] And topical treatment with honokiol reduced the COX-2 expression in a dose-dependent manner.[29] The inhibition of the PI3K/p-Akt pathway by honokiol may regulate the activity of NF-κB, and in turn, regulate inflammatory factors and proliferation-related factors like proliferating cell nuclear antigen (PCNA).[28] In addition, honokiol inhibited skin tumors induced by the UVR through affecting the cell cycle. Honokiol induced cell cycle arrest at G0/G1 phase by upregulating Kip1/p27 and Cip1/p21 and reducing the protein levels of CDK2, CDK4, CDK6, cyclin D1, D2, and E in vitro and vivo.[28,30] After treatment by honokiol, the levels of PCNA were found decreased in UVB-exposed skin and skin tumors, which indicated tumor cell cycle arrest.[28] Honokiol could enhanced apoptosis in Human epidermoid carcinoma A431 cells.[30] The mechanism is possibly by activating proapoptotic proteins involving in caspase-3, caspase-8, caspase-9, and poly (ADP-ribose) polymerase (PARP) through both intrinsic and extrinsic pathways. And the topical application of honokiol could increase the expression of p53, then promoted apoptosis to antagonize tumors.[31] The UVR can directly induce DNA hypermethylation, which can increase the expression of PGs and result in immunosuppression. Honokiol inhibited the levels of ten-eleven translocation (TET) enzyme, which is responsible for DNA demethylation in UVB-exposed skin. The inhibition effect of UVB-induced immunosuppression was equivalent to imiquimod and 5-fluorouracil when be used topically in mice.[29]

2.4 | The effects and mechanisms in cutaneous immune diseases

The pathogenesis of cutaneous immune diseases is complex and difficult to treat. Most have no effective therapeutic drugs, but in some studies, honokiol had an effective therapeutic effect on skin immune diseases like psoriasis, vitiligo, lupus, and skin fibrosis. Wen et al. found that honokiol significantly decreased the percentage of Th1-expression $CD4^+$ T cells, but had no influence on the Th2-expression $CD4^+$ T cells. Honokiol could improve the phenotype of psoriasis in a dose-dependent manner and the histological features of psoriasis. Their studies suggested that honokiol exhibited the therapeutic effect of psoriasis through anti-inflammatory and anti-angiogenic. The key point is the inhibition of NF-κB and Vascular endothelial growth factor receptor-2 (VEGFR-2). Because the expressions of Th1 cytokines (TNF-α and IFN-γ), nuclear p65, and VEGFR-2 were down-regulated, as well as related phosphorylated proteins were suppressed when topical honokiol therapy in mice.[32] Yi et al. demonstrated a new mechanism of vitiligo: oxidative stress impaired the expression and activity of mitochondrial deacetylase sirtuin 3 (SIRT3) in vitiligo melanocytes. The deficiency of SIRT3 contributed to oxidative stress-induced melanocyte apoptosis via the SIRT3-OPA1 pathway. This indicated that the specific activation of SIRT3 could be a promising therapeutic method for vitiligo. Then they tested honokiol in vitro, and found that the expression of SIRT3 at both mRNA and protein levels were markedly increasing, and the acetylation of SOD2 was reduced. The mechanism of honokiol protects vitiligo melanocytes against oxidative stress was proved by activating the SIRT3-OPA1 axis.[33] Hexafluoro, a novel fluorinated synthetic honokiol analog, also affected SIRT3 and maybe a benefit for systemic sclerosis. Since it enhanced the expression of SIRT3 in normal lung and skin fibroblasts, blocked the intracellular TGF-β (transforming growth factor-β) signaling and fibrotic responses.[34] Similarly, honokiol also exhibited effective inhibition for tissue fibrosis in immune diseases of other systems. For example, it could significantly attenuate liver fibrosis by downregulating the TGF-β1/SMAD signaling pathway and autophagy.[35] These studies suggested that honokiol is a potential candidate for the treatment of tissues fibrosis, including the skin. In addition, honokiol could improve the renal function, albuminuria, and renal pathology on the accelerated, severe form of lupus nephritis mice after 3 or 5 weeks' intervention. And the therapeutic mechanism negatively regulated T cell function and inhabited NLRP3 inflammasome activation by enhancing SIRT1/autophagy axis.[36]

2.5 | The effects and mechanisms in other skin diseases

Honokiol could resist the IgE-antigen complex induced passive cutaneous anaphylaxis (PCA) reaction and compound 48/80-induced scratching behaviors in mice with the oral application. It exhibited inhibitory activity for the degranulation of RBL-2H3 cells induced by IgE–antigen complex with IC_{50} values of 55 μM, and inhibited the expressions of IL-4 and TNF-α. Therefore, it concluded that honokiol may improve IgE-induced allergic diseases, anaphylaxis, and atopic dermatitis.[37] Honokiol also had potent analgesic effects at the third degree burn induced by hot water method through the suppression of TRPV1 and P2Y nociceptors that inhibited the pro-inflammatory cytokines and oxidative stress.[38] Honokiol had an inhibitory effect on the hypertrophic scar both in vitro and in vivo. It could downregulate fibrosis-related molecules, inhibite hypertrophic scar-derived fibroblasts (HSFs) proliferation and migration, and activate myofibroblasts via Smad-dependent pathway.[39] Honokiol also protected skin from environmental damage, as well as had anti-aging and anti-wrinkle effects. Costa et al. demonstrated that honokiol protected skin cells against cigarette smoke-induced inflammation, collagenolysis, apoptosis, and senescence.[40] Bernard et al had shown that the honokiol had the inhibitory effect of 5-alpha-reductase type 1, and topical application to the faces of older men can reduce facial wrinkles. They considered that the reason for the improvement in skin aging parameters on men was that honokiol upregulated testosterone levels.[41] But they had not studied the specific mechanism and tested the link between testosterone pathway modulation and antiaging. So maybe some

TABLE 1 The therapeutic effects and mechanisms of honokiol in skin diseases

Disease	Study models	Dose/conc.	Results/mechanisms	References
Skin infections				
S. aureus	RAW 264.7, A549 cells; C57BL/6 mice	2–16 μg/ml (*in vitro*); 25–50 mg/kg	Inhibit the secretion of Hla and NLRP3 inflammasome	6
C. albicans	—	MIC:30 μg/ml	Inhibit adhesion, transition, and biofilm formation through Ras1-cAMP-Efg1 pathway; mitochondrial dysfunction; Inhibit the biosynthesis of ergosterol and H + -ATPase activity	4,7,8,9
Dermatophyte	—	MIC:8 μg/ml	Inhibit the biosynthesis of ergosterol	12
P. acne	THP-1 cells	MIC: 3–4 μg/ml; 5–15 μM	Anti-inflammation by inhibiting the NF-κB	13
HSV-1	Vero cells	IC_{50} = 10.51 μg/ml	Inhibit DNA replication	14
Melanoma	WM35, SKMEL2, MeWo, B16, B16/F10, CHL-1, A375 cells; nude mice, CB17 mice	0–100 μM (in vitro); 30–140 mg/kg oral or ip	Reactive oxygen signaling; PI3K-AKT–mTOR signaling pathway; Notch signaling pathway; AMPK signaling pathway; mitochondrial dysfunction; ER stress activation; Hypoxia-related signaling pathway; KRT 18 protein degradation	15,16,17,18,19,20
Skin cancer/SCC	A431 cells; SKH-1 mice, C3H/HeN mice	0–75 μM (in vitro); 30–60 μg/dose in 100/200 μl acetone, 0.5–1.0 mg/cm^2, or 1–3 mg/mice in cream topical application	Antioxidant, inhibit PI3K/p-Akt and NF-κB pathway, induce G0/G1 cell cycle arrest and promote apoptosis; inhibit immunosuppression	28,29,30,31
Psoriasis	HUVEC cells; K14-VEGF transgenic mice	2.6 μg/ml (in vitro); 0.1%, 0.5% and 1.0% cream 0.3 g/cm^2	Inhibit NF-κB and VEGFR-2	32
Vitiligo	PIG1 and PIG3V cells	5 μM	Against oxidative stress by activating SIRT3-OPA1 axis	33
SS	Skin fibroblasts; C57/BL6J mice	10 μM hexafluoro (in vitro); 70 mg/kg hexafluoro i.p.	Activate SIRT3, block the intracellular TGF-β signaling and fibrotic responses	34
SLE	Mouse macrophages, PBMCs; NZB/W F1 mice	1–10 μg/ml (in vitro); 30 mg/kg.d oral	Negatively regulate T cell function and inhibite NLRP3 inflammasome activation by enhancing the SIRT1/autophagy axis	36
Allergy/atopic dermatitis	RBL-2H3 cells; ICR and BALB/c mice	IC_{50} = 55 μM; 10 or 50 mg/kg id	Inhibit IgE-mediated skin allergy, antipruritic, and anti-inflammation	37
Alopecia	C57BL/6N mice	100–200 μl saline (20 mg honokiol in 5 ml) ip/mice	Accelerate to anagen stage via activating the Wnt/β-catenin pathway	42
Burn	BALB/c mice	10 mg/kg ip or 1 μg/paw honokiol in 20 μl saline for local treatment	Downregulate TRPV1 and P2Y receptors; anti-inflammation and antioxidant	38
Hypertrophic scar	HSFs; New Zealand white rabbits	0–8 μg/ml (in vitro); 100 μl honokiol in saline (8 μg/ml) injected	Inhibite HSFs proliferation, migration to myofibroblasts via Smad-dependent pathway	39
Anti-aging/wrinkle	Hacat and HEK293 cells; Caucasian healthy men	10–20 μM (in vitro); 1% honokiol cream	Reduce inflammation, collagenolysis, apoptosis, and senescence; Inhibit 5α reductase type 1 (IC_{50} = 75 μM)	40,41

Abbreviations: BMDMs, bone marrow-derived macrophages; ER, endoplasmic reticulum; Hla, α-Hemolysin; HSFs, hypertrophic scar-derived fibroblasts; HSV, herpes simplex virus; id, intradermal injection; ip, intraperitoneal injection; MIC, minimum inhibitory concentrations; Mtb, *Mycobacterium tuberculosis*; PBM, peripheral blood mononuclear; SCC, Squamous cell carcinoma; SIRT3, mitochondrial deacetylase sirtuin 3; SLE, Systemic lupus erythematosus; SS, Systemic sclerosis; TGF-β, tumor growth-factor-β; TRPV1, transient receptor potential cation channel subfamily V member 1; VEGF, vascular endothelial growth factor.

other effects like anti-oxidant or photo-protective effects make this wrinkle-resistant change possible. In another study, it was found that honokiol could activated the Wnt/β-catenin pathway, downregulated the transforming growth factor-β1 (TGF-β1), and finally promoted the hair growth in mice.[42] Combining with its inhibitory effect of 5α-reductase, we look forward to its therapeutic researches on androgenetic alopecia.

Table 1 shows the therapeutic potential of honokiol in dermatology, and elaborates the mechanism based on experimental evidences.

3 | THE TOPICAL PREPARATIONS AND SAFETY

Previous studies had shown that honokiol had rapid absorption, slow elimination, and low bioavailability. The absolute bioavailability of honokiol was only 5.3 ± 11.7% when orally administered.[43] Although using some drug carriers can improve the low water solubility and low bioavailability, the topical drug application was recognized as an effective therapy method for dermatologic diseases because of its higher skin bioavailability and lower adverse systemic effects. Moreover, as a small molecular weight compound (266.3 g/mol) with high lipophilicity (logP = 5.2), honokiol is very suitable for topical or transdermal delivery. It can be delivered through the skin passively and retains in the epidermis and dermis layers.[44]

Moreover, the safety of topical administration at a certain concentration has been confirmed in some studies. There was no cytotoxic effect at 5 μg ml^{-1}, but presented high cytotoxicity at above 25 μg ml^{-1} in HaCaT cells.[45] In animal studies, no erythema, edema, or any other apparent sign of toxicity in the skin was observed in 26 weeks' applications.[28] Bernard et al. verified that honokiol had no mutagenic and irritative effect under Ames and chorioallantois membrane of hen egg assays. Under the patch test study of 20 volunteers with normal skin, the 1% honokiol cream showed nonirritating after 30-min and 24-h readings, but at a 5% level, three volunteers were recorded skin irritation. Then applied this 1% honokiol cream to Caucasian healthy men's faces from 55 to 63 years old, and showed well-tolerated without safety concerns at a 56 day period.[41]

In these studies above, the external preparations used in vivo are usually formulated with hydrophilic cream[28,29,32,41] or acetone.[31] Some suggested that organic solvents may cause deleterious effects in some topical applications and formulation, and the hydrophilic cream was the better choice.[45] This cream consists of the base material of ointment or cosmetic, and the purified honokiol according to a certain ratio. But there was no study to test its stability, or whether this cream was the best pattern for honokiol topical administration. Compared with the abundant research on oral or intravenous administration of honokiol, the research on approaches to enhance skin penetration are few. The mechanisms and approaches include the chemical/physical enhancement methods, drug carriers, and

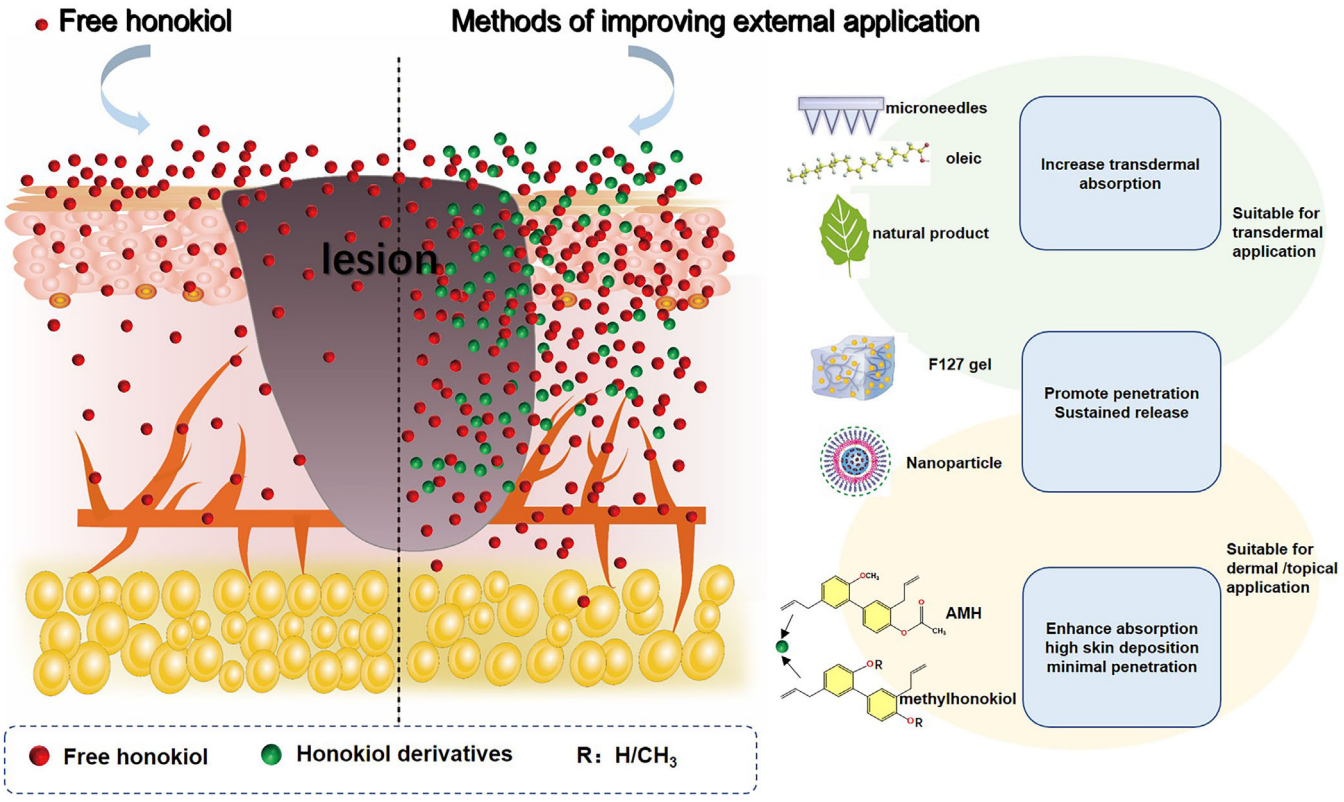

FIGURE 3 The photo-protective mechanism of honokiol. It can play a photoprotective role through antioxidant, anti-inflammatory, promoting apoptosis, affecting cell cycle and immunosuppression. These effects interact with each other and work together to improve UVR damage

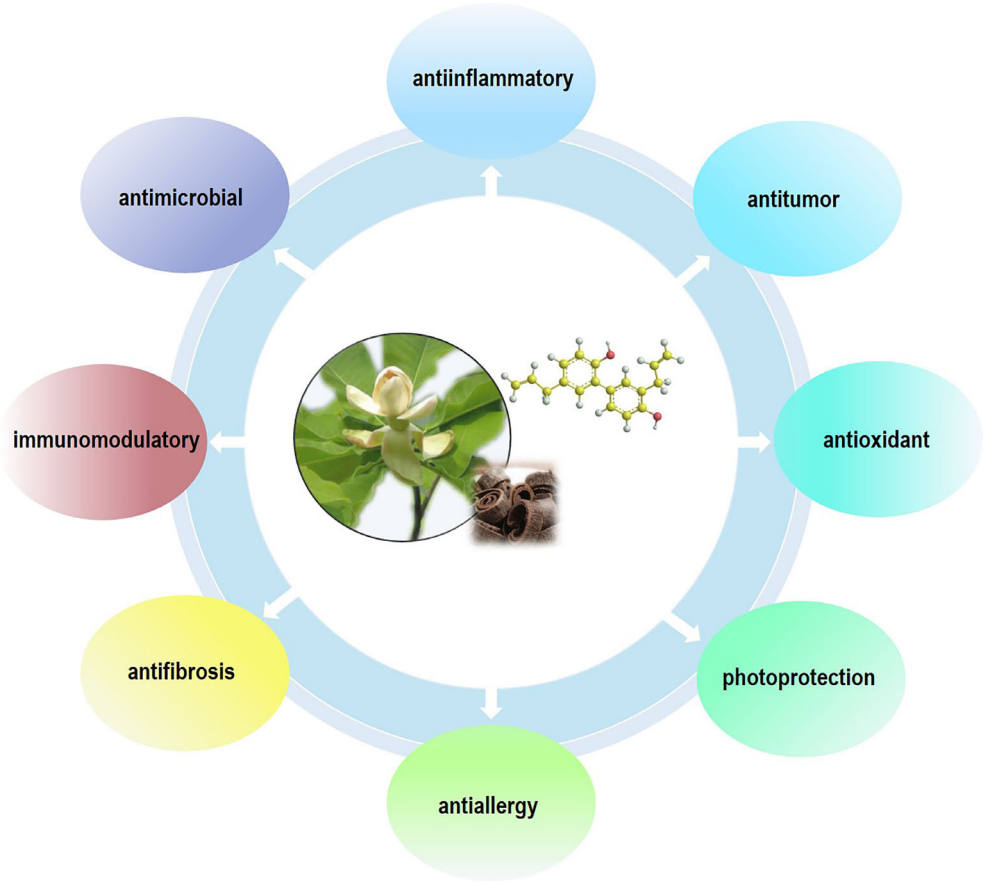

FIGURE 4 The effects of honokiol in the treatment of skin diseases in this review

derivatives (Figure 3). The easy way was the pierce of skin with microneedles, it could significantly increase the delivery of honokiol by threefold almost. Or using the chemical penetration enhancer, oleic acid, and propylene glycol, could increase the delivery by almost 27-fold.[44] Even natural products can promote each other. For example, the extracts of ligusticum chuanxiong can be used as penetrants to promote percutaneous absorption of honokiol.[46] The water solubility of honokiol was improved by encapsulation into F127 micelles, then they were mixed with Pluronic F127 aqueous matrix to form a kind of hydrogel. This formulation allowed honokiol could sustainably release and efficiently permeate through the skin. The preparation procedure was very simple, and the organic solvent is non-toxic.[47] The nanoscale transfersomes honokiol had been prepared for the topical treatment of melanoma. It could overcome the physiological barriers of the stratum corneum and the anomalous tumor microenvironment. And alleviated the immunosuppressive characteristics of melanoma cells via the downregulation of TGF-β signaling.[48] Methoxylated honokiol enhanced the inhibitory activities against inflammatory biomarkers such as COX-2, and could be a candidate for treating inflammatory skin disorders.[3] Moreover, the methoxylation of honokiol significantly enhanced skin absorption and exposition amounts, but the transdermal penetration across the skin decreased, indicated the feasibility of using methoxylated permeants for dermal but not transdermal. The relative absorption effect is dimethylhonokiol>4′-O-methylhonokiol>2-O-methylhonokiol>free honokiol.[3] Fang et al found that 2-O-acetyl-4′-O-methylhonokiol (AMH) led to a 10.5-fold improvement of skin absorption compared with honokiol. The high skin deposition and minimal penetration of AMH make it more conducive to topical administration.[49] In terms of security, the methoxylation of honokiol was relatively non-toxic toward keratinocytes in vitro. When the 30% ethanol of methoxylated honokiol was applied on nude mouse skin daily for 7 days, no erythema was observed. The dimethylhonokiol had no change of TEWL and pathological while free honokiol elicited a significant level of TEWL.[3] The same conclusion was found in AMH, long-term administration of honokiol prompted cutaneous inflammation while AMH did not.[49]

4 | CONCLUSION

Honokiol is a phenolic compound that is isolated from *Magnolia* plants *spp*. In previous studies, honokiol had no mutagenic and genotoxic potential in *vitro* and *vivo*, and different food safety authorities considered it safe.[50] It had demonstrated multiple pharmacological activities; parts of the effects are related to dermatologic disorders. We summarized the following effects according to previous studies: anti-bacterial, anti-inflammatory, anti-tumor, anti-oxidation, photoprotective effects, anti-allergy, anti-fibrosis, and immunomodulatory (Figure 4). And demonstrated it can be used in infectious skin diseases, malignant melanoma, some immune-related skin diseases, and UV radiation-

induced skin diseases, such as photoaging and UV-induced skin cancers. Despite researches on immune dermatosis and anti-aging had been under way in recent years, its many functions related to dermatology should be well worth exploring. And because it can play various pharmacological roles, some effects or mechanisms of these diseases need to be supplemented in this review.

Topical administration is an important therapeutic method in dermatology. As a small molecule lipophilic compound, honokiol is especially suitable for external use. Compared with the systemic administration of honokiol, there were little researches on external preparation. Of the only two studies on topical drugs carriers, one was to improve transdermal absorption. In this review, we concluded that 1% hydrophilic cream of honokiol is effective and safe. However, only one study had experimented on the human face. In the future, more experiments should be added to find the best and safest external preparative method. In short, honokiol is a safe and effective extract for dermatologic diseases, but compared with other phenolic extracts of herbs, the dermatosis-related research is still a rarity. It has the value to do further researches in dermatologic disorders. We expect that it can be more effectively applied in topical.

AUTHOR CONTRIBUTIONS

Yao Li: Methodology, Writing-Original Draft. **Chenglin Liang:** Visualization. **Xiyuan Zhou:** Conceptualization, Funding Acquisition, Writing-Review, and Editing.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not application to this article as no new data were created or analyzed in this study.

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