REVIEW ARTICLE

Dermoprotective efficacy of ursolic acid an overview

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Abstract

Ursolic acid (UA) is a natural terpene compound, found in many plants, and has drawn attention for its potential benefits in skin protection. This review delves into its mechanisms of action. It highlights its antioxidant properties, which help combat oxidative stress in skin cells by neutralizing harmful reactive oxygen species. Ursolic acid also exhibits anti-inflammatory effects by targeting pathways involved in inflammation, such as nuclear factor-kappa B and Mitogen-activated protein kinase. In addition, it shows promise in preventing photoaging by inhibiting matrix metalloproteinases and promoting collagen synthesis, thus preserving skin elasticity and reducing wrinkles caused by ultraviolet radiation. Moreover, it aids in wound healing by stimulating keratinocyte proliferation, angiogenesis, and extracellular matrix remodeling. Recent studies suggest its antimicrobial properties, which could be beneficial in treating infectious skin diseases. Furthermore, it may regulate skin lipid metabolism, enhancing moisturization and skin barrier function. Overall, the diverse protective actions of ursolic acid make it a promising candidate for developing new treatments for various skin issues, from inflammation to wound healing and aging. Further research is needed to fully understand its mechanisms and clinical effectiveness in dermatology.

Key words: Angiogenesis, anti-inflammatory, antimicrobial efficacy, dermoprotective, keratinocyte proliferation, natural terpene compound, ursolic acid

INTRODUCTION

Ursolic acid (UA) is a natural terpene compound exhibiting many pharmaceutical properties. In this review, the current state of knowledge about the health-promoting properties of this widespread, biologically active compound, as well as information about its occurrence and biosynthesis are presented. Particular attention has been paid to the application of ursolic acid as an anti-cancer agent; it is worth noticing that clinical tests suggesting the possibility of practical use of UA have already been conducted. Among other pharmacological properties of UA one can mention the protective effects on lungs, kidneys, liver, and brain, anti-inflammatory properties, anabolic effects on skeletal muscles, and the ability to suppress bone density loss leading to osteoporosis. Ursolic acid also exhibits antimicrobial features against numerous strains of bacteria, HIV and HCV viruses, and Plasmodium protozoa causing malaria.[1]

In recent years, the widespread use of antibiotics globally has resulted in a rise in drug-resistant bacterial strains, posing a serious challenge to combat bacterial infections. Traditional Chinese medicine (TCM) has historically offered natural advantages in treating infectious diseases. Hence, there is a growing interest in further developing and utilizing TCM for managing clinical infections caused by drug-resistant bacteria. To investigate this, a literature search was conducted using various databases including PubMed, Web of Science, Google Scholar, and the China National Knowledge Infrastructure. The focus was on exploring the antimicrobial effects of herbal medicines, compounded, and monomeric compounds of herbal origin. Several mechanisms underlying the antibacterial properties of herbal medicine, such as altering membrane permeability, inhibiting protein and nucleic acid synthesis, and controlling bacterial enzyme activity. Moreover, the paper discussed how TCM could reverse bacterial drug resistance by eliminating resistant plasmids, inhibiting extended-spectrum β-lactamases, disrupting bacterial biofilm formation, and

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suppressing bacterial efflux pump activity. This review of recent literature on antimicrobial actions and resistance reversal mechanisms by ursolic acid serves as a valuable reference for clinical drug usage, bacterial infection prevention and control, and the development of novel drugs.[2]

A Simple Method to Obtain Ursolic Acid

A simple method has been developed to obtain ursolic acid (UA) by crystallization and recrystallization of the ethanol extract of *Clinopodium* revolutum. Its structure was confirmed by 1D (1H-, 13C-, DEPT 45, 90, and 135) and 2D (COSY, HMBC, and HSQC) nuclear magnetic resonance spectroscopy and Fourier transform infrared spectroscopy. The results provide a theoretical basis for considering the species *Clinopodium* revolutum with a source of UA.[3]

ANTIMICROBIAL MECHANISM OF URSOLIC ACID

A naturally occurring pentacyclic triterpenoid molecule, ursolic acid is present in many plants, such as apples, rosemary, oleander, and basil. Numerous studies have been conducted on its pharmacological characteristics, encompassing its antibacterial actions. Ursolic acid's antibacterial activity consists of multiple mechanisms:

Disruption of Cell Membrane Integrity

Bacterial cell membrane integrity can be compromised by ursolic acid. It has the ability to pierce the lipid bilayer of the cell membrane, causing intracellular contents to flow out and ultimately leading to cell death. The microbial cell's structural and functional integrity may be jeopardized by this disruption.[4-9]

Studies on the antimicrobial mechanisms of oleanolic acid (OA) and ursolic acid demonstrated that both of the pentacyclic triterpenoids can modulate resistance to two β-lactam antibiotics, ampicillin, and oxacillin, in four bacterial pathogens.[10]

Inhibit the Bacterial Protein Synthesis

Ursolic acid inhibits the synthesis of proteins in bacteria in several ways. It affects the translation, transcription, and RNA degradation processes in bacteria. Additionally, it has an impact on phosphotransferase system, glycolysis, and pentose phosphate pathway which are essential for bacterial energy and metabolism.[11]

A previous study indicated that both the transcriptional inhibitor and the various translational inhibitors all triggered an increased relative rate of synthesis of the components of the transcriptional and the translational machinery (RNA polymerase, elongation factors, ribosomal proteins, tRNA synthetases) in *Haemophilus influenzae*[12] and *Bacillus subtilis*.[13]

Inhibition of Bacterial Enzyme Activity

It has been demonstrated that ursolic acid inhibits the action of certain microbial enzymes necessary for cellular functions. For instance, bacterial DNA gyrase and topoisomerase, which are important in DNA replication and repair, may be inhibited by it. Ursolic acid interferes with these enzymes, disrupting essential cellular functions and ultimately resulting in microbial death.

Moreover, most of the metabolic enzymes involved in glycolysis displayed a decrease in their relative rate of synthesis on treatment with ursolic acid. The response to protein synthesis inhibition appears to concentrate the cell's biosynthetic activities on the protein folding and degrading system at the expense of metabolic functions.[14]

Interference with Biofilm Formation

Capped in an extracellular matrix (ECM) that the microorganisms themselves make, biofilms shield the cells from the effects of antibiotics. According to reports, some bacteria are unable to form biofilms, which increases their susceptibility to immune responses and antimicrobial drugs.[15]

Modulation of Oxidative Stress

Reactive oxygen species (ROS)-induced oxidative stress in microbial cells can be lessened by ursolic acid's antioxidant qualities. Ursolic acid can help eliminate oxidative damage to microbial cells by scavenging ROS and boosting the body's antioxidant defense mechanisms.[16]

Disruption of Quorum Sensing

Bacteria employ a communication technique called quorum sensing to control the expression of certain genes in response to the density of their cell population. It has been demonstrated that ursolic acid interferes with some bacteria's quorum sensing systems, impairing their capacity to coordinate the production of virulence factors and the creation of biofilms.[17]

Alteration of Cell Signaling Pathways

Numerous signaling pathways involved in the development and survival of microorganisms can be modulated by ursolic acid. It can cause microbial death and disturb vital cellular functions by interfering with these pathways. Overall, ursolic

acid's antibacterial mechanism is complex, combining direct and indirect effects to target various facets of microbial physiology and disease. It is a good contender for the creation of novel antimicrobial drugs due to its capacity to obstruct quorum sensing, enzymes, biofilm formation, oxidative stress, and signaling pathways.[18,19]

Increase Collagen Synthesis and Wound Healing

Preclinical and clinical studies to evaluate the potential of ursolic acid in promoting collagen synthesis, accelerating wound closure, and improving scar remodeling.

It has been found that ursolic acid-based topical formulations are very effective for wound healing applications. Ursolic acid exhibits wound healing properties by promoting fibroblast proliferation, angiogenesis, and re-epithelialization. Future research might focus on developing ursolic acid-based formulations for wound dressings or topical treatments to accelerate wound healing processes.[20]

Photoprotective Effects

It has been found that the bioactive compound ursolic acid possesses potent therapeutic properties including photoprotective effects against ultraviolet (UV)-induced skin damage, sunburn, photoaging, and photocarcinogenesis.

Exploration of the underlying mechanisms involved in the ability of ursolic acid to mitigate UV-induced oxidative stress, inflammation, and DNA damage.[21]

Skin Aging and Wrinkle Reduction

Ursolic acid has shown potential in reducing signs of skin aging such as wrinkles and fine lines. Future research may explore its mechanisms of action in promoting collagen synthesis and inhibiting matrix metalloproteinases, enzymes that degrade collagen in the skin.[22]

Skin Cancer Prevention

Some studies suggest that ursolic acid may have chemopreventive effects against skin cancer by inhibiting inflammation and oxidative stress, as well as modulating signaling pathways involved in carcinogenesis. Future investigations could delve deeper into its potential as a natural adjunctive therapy for skin cancer prevention.[23]

Anti-acne activity

Due to its anti-inflammatory and antimicrobial properties, ursolic acid holds promise as a therapeutic agent for acne vulgaris. Future clinical trials may assess its efficacy in topical formulations or combined therapies for acne management.[24]

Inhibition of Hyperpigmentation

Preliminary studies suggest that ursolic acid could inhibit melanin synthesis, making it a potential candidate for treating hyperpigmentation disorders such as melasma and post-inflammatory hyperpigmentation. Further investigations may explore its efficacy and safety in clinical settings.[25]

SKIN PROTECTIVE PROPERTIES OF URSOLIC ACID

Ursolic Acid as Potent Antibacterial Agents

Ursolic acid, a vital bioactive compound, was extracted from the aerial parts of *Sambucus australis* using ethanol. Two semi-synthetic derivatives were created by modifying C-3 to explore their antibacterial properties. The minimal inhibitory concentration (MIC) against 12 bacterial strains was determined using the microdilution method. The impact of these compounds on bacterial susceptibility to aminoglycoside antibiotics (neomycin, amikacin, kanamycin, and gentamicin) was also examined. The most notable synergy was observed with 3β-formyloxy-urs-12-en-28-oic acid in combination with kanamycin against *Escherichia coli*, reducing the MIC. The study concludes that ursolic acid and its derivatives possess significant antibacterial activity against various bacterial species and synergize with aminoglycoside antibiotics. This suggests the potential of *S. australis* as a natural source of free radical scavengers.[26]

Novel Ursolic Acid Derivatives as Effective Antimicrobial Agents

In response to the decline in food production and economic losses caused by plant bacterial diseases, there is a need for the development of new, effective, and environmentally friendly pesticides. Natural products offer a sustainable solution due to their low toxicity and eco-friendliness. In this study, three series of derivatives of ursolic acid were synthesized and evaluated for their antibacterial properties. Many of these compounds showed excellent antibacterial activity, with compounds A17 and A16 demonstrating the most promising results against *Xanthomonas oryzae* pv. *oryzae* and *Xanthomonas axonopodis* pv. *citri*, respectively. The mechanism of action revealed that compound A17 induced the accumulation of ROS in bacteria, leading to damage to the cell membrane integrity and subsequent bacterial death. In addition, the addition of low concentrations of hydrogen peroxide enhanced the effectiveness of compound A17 against *X. oryzae* pv. *oryzae*. These findings suggest that compound A17 induces apoptosis in the tested bacteria, offering a promising avenue for the development of antimicrobial agents targeting phytopathogenic bacteria. Overall, this study

highlights the potential of ursolic acid derivatives as effective pesticides for agricultural applications.[27]

Potential Synergistic Action of Ursolic Acid Against Skin Infecting Microorganisms

The skin is an important organ that acts as a physical barrier to the outer environment. It is rich in immune cells such as keratinocytes, Langerhans cells, mast cells, and T cells, which provide the first line of defense mechanisms against numerous pathogens by activating both the innate and adaptive response. Cutaneous immunological processes may be stimulated or suppressed by numerous plant extracts through their immunomodulatory properties. Several plants are rich in bioactive molecules; many of these exert antimicrobial, antiviral, and antifungal effects. The present study describes the impact of plant extracts on the modulation of skin immunity and their antimicrobial effects against selected skin invaders. Plant products remain valuable counterparts to modern pharmaceuticals and may be used to alleviate numerous skin disorders, including infected wounds, herpes, and tineas.[28]

Potent Anti-inflammatory Activity of Ursolic Acid

Ursolic acid (UA), a compound found in various plants such as apples, basil, and rosemary, is known for its antioxidant and anti-tumor properties, mainly attributed to its ability to suppress NF-kB activation. Given NF-kB's role in regulating inflammatory genes, it was hypothesized that UA might have significant anti-inflammatory effects. The study evaluated UA's impact on activated T cells, B cells, and macrophages, as well as its effects on various cellular signaling pathways. In animal studies, UA demonstrated efficacy in delaying acute graft-versus-host disease and reducing proinflammatory cytokine levels. Furthermore, UA showed promise as a therapeutic agent even when administered after mitogenic stimulation. Overall, this research sheds light on UA's detailed mechanism of action against inflammation and suggests its potential application in treating inflammatory disorders.[29]

Antibacterial and Anti-inflammatory Effects

The study aimed to evaluate the potential of *Syzygium jambos* L. leaf extract and its compounds against *Propionibacterium acnes*, a bacterium involved in acne vulgaris. Antibacterial and anti-inflammatory activities were assessed using various methods. Results revealed three known compounds, including squalene, an anacardic acid analog, and ursolic acid, isolated from the ethanol extract of *S. jambos* leaves for the 1st time. The extract and one compound, the anacardic acid analog, effectively inhibited *P. acnes* growth with noteworthy MIC. In addition, both the extract and certain compounds displayed significant antioxidant activity comparable to Vitamin C. Moreover, the extract and compounds such as ursolic acid and myricitrin demonstrated significant suppression of inflammatory cytokines interleukin (IL)-8 and tumor necrosis factor alpha (TNF-α). Transmission electron microscopy micrographs confirmed the lethal effects of selected samples against *P. acnes*. Overall, the study highlights the potential of *S. jambos* as an alternative anti-acne agent, suggesting further investigation in clinical studies.[30]

As Anti-Inflammatory and Anti-elastase Properties of Ursolic Acid

Cyperus sexangularis (CS), a plant from the *Cyperaceae* family, commonly found in swampy regions, is utilized for mat making and traditional skin treatments. Researchers investigated its phytochemical composition and various properties. Extracts were analyzed, yielding six compounds characterized by spectroscopy methods. These compounds exhibited antioxidant, anti-inflammatory, and anti-elastase effects. Notably, stigmasterol (1) showed significant antioxidant activity and moderate anti-inflammatory properties. However, its anti-elastase activity was lower compared to diclofenac. Other compounds showed comparable anti-elastase activity, albeit less effective than the standard, ursolic acid. This study identified three steroids, one fatty acid, and two fatty acid esters in CS for the 1st time, supporting its traditional use and suggesting potential applications in cosmeceutical formulations.[31]

Anti-inflammatory Potential of Ursolic Acid in *Mycobacterium tuberculosis*-Sensitized and Concanavalin A-Stimulated Cells

Ursolic acid (UA) is a natural compound (NC) found in various plants such as apples, basil, and berries, and known for its medicinal properties. A study explored UA's effects on inflammatory responses induced by *M. tuberculosis* in different cell types. It was found that UA significantly reduced the release of inflammatory cytokines and suppressed the expression of inflammatory mediators like COX-2 and iNOS. Moreover, UA showed potential as an adjunct therapy for tuberculosis treatment due to its anti-inflammatory properties, which could enhance the efficacy of existing antibiotic therapies. However, further research is needed to fully understand its role as an anti-inflammatory agent.[32]

Ursolic Acid Ameliorates DNCB-induced Atopic Dermatitis (AD)

Ursolic acid (UA), a NC found in plants, possesses various beneficial properties such as anti-inflammatory and antioxidant effects. However, its role in AD is unclear. This study aimed to assess the therapeutic potential of UA in AD mice and investigate its mechanisms. Methods involved inducing AD-like lesions in Balb/c mice using DNCB. Throughout the study, dermatitis scores, ear thickness, histopathological

changes, T helper cytokine levels, and oxidative stress markers were monitored. Immunohistochemistry staining was conducted to analyze the expression of nuclear factor-kappa B (NF-κB) and Nrf2. Furthermore, experiments on TNF-α/interferon gamma (IFN-γ)-stimulated HaCaT cells evaluated UA's effects on ROS levels, inflammatory mediators, and NF-κB/Nrf2 pathways. Results indicated that UA reduced dermatitis severity and ear thickness, inhibited skin proliferation, mast cell infiltration, and T-helper cytokine expression in AD mice. It also improved oxidative stress by regulating lipid peroxidation and antioxidant enzyme activity. *In vitro* experiments showed UA inhibited ROS accumulation and chemokine secretion in stimulated cells, possibly through modulation of the TLR4/NF-κB and Nrf2/HO-1 pathways. In conclusion, UA shows promise as a therapeutic agent for AD, warranting further investigation for its potential in AD treatment.[10]

Ursolic Acid Reduces Oxidative Stress Injury

In the study, researchers explored the potential of Ursolic acid (UA), a TCM known for its antioxidant properties, in alleviating inflammatory myocardial injury induced by experimental autoimmune myocarditis (EAM). They found that UA intervention in mice with EAM reduced inflammatory infiltration and myocardial fibrosis while improving cardiac function. Mechanistically, UA mitigated myocardial injury by suppressing oxidative stress, as evidenced by decreased levels of superoxide and normalization of pro- and antioxidant enzyme levels. Notably, UA intervention also increased the expression of antioxidant factors such as Nrf2 and HO-1. *In vitro* experiments showed that specific Nrf2 inhibitors reversed the antioxidant and antiapoptotic effects of UA, indicating that UA's beneficial effects in EAM were dependent on the Nrf2/HO-1 pathway. These findings suggest that UA could be a promising therapeutic approach for treating EAM-induced cardiac injury by enhancing Nrf2/HO-1 expression and reducing oxidative stress EAM.[16]

In Silico and *in Vivo* Wound Healing Studies of Ursolic Acid

A study conducted by Naika *et al*. focused on the wound-healing properties of Ursolic acid (UA) extracted from *Clematis gouriana* Roxb. a medicinal plant native to the Western Ghats. Through spectral analysis, UA was isolated from the methanolic extract (ME). *In silico* studies were conducted to evaluate its interaction with Glycogen synthase kinase 3-β (GSK3-β) protein, indicating UA's potential as an inhibitor of this protein. The study employed various wound healing models on Wistar strain rats, including excision, incision, and dead space wound models. Results showed significant wound healing activity, with UA-treated rats exhibiting increased skin-breaking strength and pronounced effects on granulation tissue weight, tensile strength, and hydroxyproline content in the dead space wound model. Moreover, animals treated with UA displayed enhanced collagenation and reduced macrophage accumulation at the injury site, indicating excellent wound healing potential. In summary, the study suggests that UA extracted from *C. gouriana* Roxb. has promising wound healing properties, potentially through its inhibition of GSK3-β protein function, as evidenced by both *in silico* and *in vivo* experiments.[33]

Skin Cancer Prevention

Our study aimed to investigate the potential cancer-preventive properties of various phytochemicals, including grape seed extract (GSE), resveratrol (RES), ursolic acid (URA), ellagic acid (ELA), lycopene, and N-acetyl-L-cysteine, using *in vitro* methods. We examined their ability to inhibit murine skin carcinogenesis and elucidate the mechanisms involved. Our assessments included measuring the ability of these phytochemicals to quench peroxyl, superoxide, and hydroxyl radicals. In addition, we conducted assays to evaluate their effects on ATP bioluminescence, Caspase-Glo 3/7, and P450-Glo (CYP1A1 and CYP1B1) to assess their antiproliferative, proapoptotic, and CYP-inhibiting properties, respectively. Furthermore, we investigated their impact on inflammatory hyperplasia using a murine skin carcinogenesis model induced by 7,12-dimethylbenz[a]anthracene over 4 weeks. In our *in vitro* assays, we utilized three murine keratinocyte cell lines: Non-tumorigenic (3PC), papilloma-derived (MT1/2), and squamous cell carcinoma-derived (Ca3/7) cell lines. Our findings revealed that GSE, ELA, and RES exhibited potent scavenging abilities against peroxyl and superoxide radicals. Notably, significant effects on caspase-3 and -7 activities were observed following GSE and URA treatments. Moreover, all tested compounds demonstrated protective effects against hydrogen peroxide-induced DNA damage. In a short-term complete carcinogenesis assay, we observed marked reductions in epidermal thickness with all selected compounds, except RES, which also reduced the percentage of mice with mutations in codon 61 of the Ha-ras oncogene.

In conclusion, the varied effects of the tested phytochemicals on critical events and processes for keratinocyte growth inhibition both *in vitro* and *in vivo* suggest that combinations of these compounds may be more effective in countering both tumor initiation and promotion/progression in the future.[34]

Ursolic Acid-based Hybrid Compounds as Antibacterial and Anticancer Agents

The molecular hybridization of two or more drugs into a single molecule is an effective drug design approach to reduce pill burden and improve patient treatment adherence. Ursolic acid-based hybrid compounds were synthesized and characterized followed by molecular docking studies. *In vitro* studies against various bacterial strains and human cancer cells (MDA-MB-231, HeLa, and MCF-7) were performed. Compounds 14–19, 21,

34, 31, and 30 demonstrated significant antibacterial activities with MIC values of 15.625 µg/mL. Compounds 29 and 34 were more cytotoxic than ursolic acid, with IC_{50} values of 46.99 and 48.18 µg/mL. Compounds 29 and 34 in the docking studies presented favorable binding interactions and better docking energy against the Epidermal Growth Factor Receptor than the parent compound, ursolic acid. The findings revealed that the ursolic acid scaffold is a promising precursor for the development of molecules with promising anticancer and antimicrobial activities. However, more studies are needed to fully understand their mode of action.[35]

OTHERS PHARMACOLOGICAL ROLES OF URSOLIC ACID

The Effect of Ursolic Acid on *Leishmania amazonensis*

Leishmaniasis is a significant global health issue affecting millions of people, with current treatments often causing severe side effects. This study examined the potential of ursolic acid (UA) and OA as new treatments for cutaneous leishmaniasis. In laboratory experiments, UA showed promising results against *L. amazonensis*, effectively killing the parasite with an EC_{50} of 6.4 µg/mL, similar to miltefosine, a standard treatment. However, OA had minimal impact on the parasite. UA-induced programmed cell death in the parasites, primarily through mitochondrial activity, without harming macrophages. In addition, UA effectively eliminated intracellular parasites and stimulated nitric oxide production. In tests on infected mice, UA treatment led to reduced lesion size and parasitic load compared to untreated mice, demonstrating its efficacy *in vivo*. These findings suggest that UA holds promise as a potential treatment for cutaneous leishmaniasis, given its ability to kill parasites and its effectiveness in animal models.[36]

Oral Delivery of Ursolic Acid-loaded Nanostructured Lipid Carrier (UA-NLC) Coated with Chitosan (CS) Oligosaccharides

Visceral leishmaniasis (VL) is a severe illness caused by *Leishmania donovani*, leading to dangerous levels of parasitic invasion in the liver, spleen, and bone marrow. Ursolic acid (UA), known for its anti-inflammatory, anti-bacterial, and anti-diabetic properties, has shown promise in treating various ailments. However, the need for a more effective and less side-effect-prone delivery system for UA is urgent. This study aimed to develop and assess the antileishmanial potential of UA loaded onto N-octyl-CS surface-decorated nanostructured lipid carrier system (UA-NLC) for macrophage delivery in VL treatment. UA-NLC was prepared and characterized for size, shape, drug loading capacity, and drug release. Results showed that UA-NLC had a nano-size range (103.7 ± 2.8 nm–143.0 ± 3.8 nm) with high drug loading capacity (12.05 ± 0.54%) and entrapment efficiency (88.63 ± 2.7%). *Ex vivo* evaluation demonstrated enhanced drug uptake by macrophages. UA-NLC exhibited significantly higher effectiveness against various cellular amastigotes compared to its free form. *In vivo,* studies revealed that orally administered UA-NLC suppressed parasite burden by 98.75%.[37]

New Prognostic Biomarkers and Drug Targets for Skin Cutaneous Melanoma (SKCM)

SKCM presents a significant challenge due to its aggressiveness and heterogeneous nature, necessitating personalized treatment approaches. To address this, researchers aimed to identify early diagnostic markers and treatment options. By analyzing expression data, a coexpression gene module for SKCM pathogenesis was constructed using weighted gene coexpression network analysis. Subsequently, a comprehensive bioinformatics analysis of selected hub genes was conducted. This led to the identification of 10 hub genes relevant to SKCM, validated through GWAS and DEG analysis. Survival analysis revealed eight hub genes significantly associated with poorer overall survival. Moreover, the hub genes were correlated with tumor purity and immune cell infiltration levels. Methylation analysis indicated differences between SKCM stages. Isomer expression analysis suggested therapeutic potential through alternative splicing. Mutations in all 10 hub genes were identified in skin tissue. In addition, drug prediction through CMap analysis highlighted four potential treatments: Cefamandole, ursolic acid, podophyllotoxin, and Gly-His-Lys. Immunohistochemical staining confirmed high expression of these hub genes in melanoma specimens compared to normal samples. These findings offer insights into SKCM pathogenesis and suggest GPR143 and SLC45A2 as potential immunotherapeutic targets and prognostic biomarkers. The study identifies four drugs with promising potential for SKCM treatment.[38]

Ursolic Acid Potentializes Conventional Therapy

Ursolic acid (UA), a versatile compound, exhibits various pharmacological benefits. In leishmaniasis, it effectively eliminates different parasite species, proving active in both cutaneous and visceral models. This study aimed to assess the therapeutic potential of combining conventional drugs, Amphotericin B (AmB) or glucantime (Glu), with UA in treating experimental forms of the disease. In hamsters infected with *Leishmania infantum*, treatment with AmB alone or in combination with UA was administered intraperitoneally. Similarly, *L. amazonensis*-infected BALB/c mice received Glu alone or combined with UA via intralesional routes. After 15 days of treatment, tissue parasitism and immune responses were evaluated. Results showed that hamsters treated with AmB combined with UA exhibited reduced hepatic and splenic parasitism compared to those receiving AmB alone. In cutaneous leishmaniasis, Glu

monotherapy demonstrated varying levels of effectiveness, with the highest dose showing significant activity. However, when Glu was combined with UA, a notably enhanced leishmanicidal effect was observed, correlating with improved lesions and increased IFN-γ production. Overall, the findings suggest that combining drugs for leishmaniasis treatment enhances efficacy and reduces associated toxicity compared to conventional monotherapy.[39]

Synergy between Ursolic and OAs from *Vitellaria paradoxa* Leaf Extract and β-Catteau Lactams Against Methicillin-resistant *Staphylococcus aureus* (MRSA)

Combining antibiotics with resistance-reversing agents is crucial in combating bacterial resistance. Through screening traditional medicinal plants, we discovered that a leaf dichloromethane extract from the shea butter tree (*V. paradoxa*) exhibited antimicrobial activity against MRSA, particularly when combined with β-lactams. Analysis using HPLC-MS revealed ursolic (UA) and OA as major constituents in the leaf extracts (21% and 6%, respectively). Both UA and OA demonstrated antimicrobial activity against MRSA strains, with UA displaying lower MICs (8–16 mg/L) compared to OA (32–128 mg/L). These acids synergized effectively with β-lactams, such as ampicillin and oxacillin, at subMIC concentrations. The reversal of MRSA phenotype was attributed to their ability to delocalize PBP2 from the septal division site, disrupting peptidoglycan synthesis, as observed through fluorescence microscopy. Furthermore, both compounds inhibited β-lactamase activity in living bacteria, but not in bacterial lysates, suggesting an indirect mechanism. In a murine model of subcutaneous MRSA infection, local administration of UA in combination with nafcillin reduced lesion size and inflammatory cytokine (IL-1β) production. These findings underscore the potential of triterpenic acids as resistance-reversing agents when combined with β-lactams against MRSA.[38]

β-Lactams against MRSA

Combining antibiotics with resistance-reversing agents is crucial in combating bacterial resistance. Through screening traditional medicinal plants, we discovered that a leaf dichloromethane extract from the shea butter tree (*V. paradoxa*) exhibited antimicrobial activity against MRSA, particularly when combined with β-lactams. Analysis using HPLC-MS revealed ursolic (UA) and OA as major constituents in the leaf extracts (21% and 6% respectively). Both UA and OA demonstrated antimicrobial activity against MRSA strains, with UA displaying lower MICs (8–16 mg/L) compared to OA (32–128 mg/L). These acids synergized effectively with β-lactams, such as ampicillin and oxacillin, at subMIC concentrations. The reversal of MRSA phenotype was attributed to their ability to delocalize PBP2 from the septal division site, disrupting peptidoglycan synthesis, as observed through fluorescence microscopy. Furthermore, both compounds inhibited β-lactamase activity in living bacteria, but not in bacterial lysates, suggesting an indirect mechanism. In a murine model of subcutaneous MRSA infection, local administration of UA in combination with nafcillin reduced lesion size and inflammatory cytokine (IL-1β) production. These findings underscore the potential of triterpenic acids as resistance-reversing agents when combined with β-lactams against MRSA.[39] The structure of ursolic acid is shown in Figure 1 and the summarized mechanism related to dermoprotective efficacy of ursolic acid is given in Table 1.

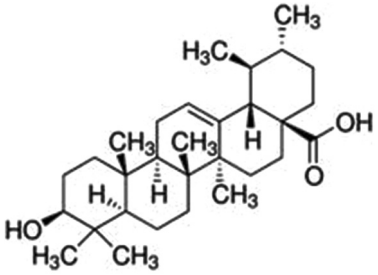

Figure 1: Structure of ursolic acid

Table 1: Mechanism of dermoprotective efficacy of ursolic acid

Dermoprotective efficacy of ursolic acid	
Antimicrobial activities	**Dermoprotective activities**
Disruption of cell membrane integrity	Increase collagen synthesis and wound healing
Inhibit the bacterial protein synthesis	Photoprotective effects
Inhibition of bacterial enzyme activity	Skin aging and wrinkle reduction
Interference with biofilm formation	Skin cancer prevention
Disruption of quorum sensing	Anti-acne activity
Alteration of cell signaling pathways	Inhibition of hyperpigmentation

Antileishmanial Activity of Isolated Triterpenoids from *Pourouma guianensis*

The ME from *P. guianensis* leaves contains various triterpenoids, some of which exhibit inhibitory effects against *L. amazonensis*. While fractions containing certain compounds such as apigenin, friedelin, and others show low inhibitory activity, those containing tormentic acid, 2alpha, 3beta-dihydroxyursan-12-en-28-oic acid, and others demonstrate potent inhibition of promastigote growth. Among the isolated compounds, only ursolic acid and OA effectively inhibit intracellular amastigotes, outperforming the control drug Glu. OA's activity targets the parasite directly but may also induce cytotoxic effects on macrophages at higher concentrations, affecting their phagocytic capacity. This suggests that compounds such

as ursolic and OAs could be promising candidates for new antileishmanial drugs, although modifications may be necessary to prevent non-selective cytotoxicity.[40]

Antiparasitic Compounds from *Cornus florida* L. with Activities Against *Plasmodium falciparum* and *Leishmania tarentolae*

The study aimed to identify antiplasmodial components from *C. florida* L. bark, a plant historically used for malaria treatment in North America. The bark was extracted with 95% ethanol and subjected to *in vitro* antiplasmodial-guided fractionation against *P. falciparum* (D10 strain). Eight compounds were isolated, including some novel ones like 3-epideoxyflindissol. While some compounds showed moderate antiplasmodial and antileishmanial activities, they do not fully support *C. florida*'s historical use as an antimalarial remedy. However, these findings suggest potential for *C. florida* constituents in treating *Leishmania*, despite not being traditionally used for it.[41]

Suppression of SARS-CoV-2 Spike Protein

The use of zebrafish as a model system for studying human viral diseases, including SARS-CoV-2, has been valuable. In this study, a humanized zebrafish model transplanted with human lung epithelial cells was used to evaluate the effects of Coronil, a tri-herbal medicine, in combating SARS-CoV-2 infection. At doses relevant to humans, Coronil showed promising results. It inhibited the SARS-CoV-2 spike protein, reduced mortality in humanized zebrafish, and alleviated symptoms such as fever. In addition, Coronil restored abnormal morphological and cellular changes and reduced inflammation in the swim bladder. Other positive effects included mitigating skin hemorrhage, renal cell degeneration, and necrosis. Analysis revealed several phytometabolites present in Coronil. In human lung epithelial cells, Coronil reduced cytokine secretions and transcriptional activity associated with inflammation. These findings suggest that Coronil possesses immunomodulatory properties and may have potential in combating SARS-CoV-2 infection.[42]

Protective Effects of NCs against Oxidative Stress in Ischemic Diseases

Ursolic acid: Biological functions and application in animal husbandry

The text discusses oxidative stress, an imbalance between ROS and antioxidants, which is implicated in various disorders like ischemic diseases and cancers. NCs with antioxidant properties have been recognized for their ability to alleviate oxidative stress. The review summarizes how NCs modulate oxidative stress by activating the Nrf2 signaling pathway. Specifically, it explores three NCs – ursolic acid, betulinic acid, and curcumin – and their cytoprotective effects in conditions such as myocardial ischemia, cerebral ischemia, skin cancer, and prostate cancer. In addition, it discusses formulation approaches, such as nano drug delivery systems, to enhance the therapeutic efficacy of NCs with poor water solubility.[43]

NOVEL TOPICAL FORMULATION OF URSOLIC ACID

Enhancing the topical delivery of ursolic acid could improve its bioavailability and efficacy in dermatological applications. Future research may explore novel delivery systems such as nanoparticles, liposomes, or microemulsions to optimize its skin penetration and retention.

Safety and Formulation Development

While ursolic acid is generally considered safe, more research is needed to evaluate its long-term safety profile, potential side effects, and optimal dosing regimens for dermatological use. In addition, the development of stable and cosmetically elegant formulations will be essential for its practical application in skincare products.

Bioactive Ursolic Acid-Loaded Electrospun CS-Polyvinyl Alcohol (PVA) Nanofiber Dressings

The urgent need for advanced dressing materials to treat chronic wounds like diabetic ulcers has led to the development of innovative CS-PVA-UA dressings. These dressings incorporate ursolic acid (UA) extracted from Chinese herbal plants into electrospun nanofibers made from CS and PVA. The resulting nanofiber mats closely resemble the structure of natural skin ECM, with good surface characteristics and sustained UA release. *In vitro,* tests revealed slight cytotoxicity at high UA concentrations but also demonstrated the dressings' ability to reduce inflammation and oxidative stress while promoting macrophage polarization and hemostasis. *In vivo* experiments on mice with diabetic wounds showed significant improvements in wound closure, revascularization, re-epithelization, collagen matrix deposition, hair follicle regeneration, and wound contraction rate. Overall, these findings suggest that CS-PVA-UA nanofiber dressings hold promise as effective treatments for challenging diabetic wounds due to their multifunctional properties, including anti-inflammatory, antioxidative, proangiogenic, and hemostatic effects.[44]

FUTURE PROSPECTIVE

Ursolic acid has demonstrated encouraging dermatoprotective efficacy in a number of studies, but more work has to be done before its full potential in dermatology applications is achieved. A naturally occurring triterpenoid molecule present in a wide variety of plants, ursolic acid has been shown to

have anti-inflammatory, antioxidant, and antibacterial actions. Topical delivery systems, safety and formulation development, acne treatment, wound healing, skin cancer prevention, skin aging and wrinkle reduction, and wound healing are some possible future directions for it in dermatology. All things considered, ursolic acid's dermatoprotective effectiveness offers promising prospects for further study and therapeutic application in a range of dermatological disorders. To clarify its methods of action, improve formulation techniques, and confirm its therapeutic promise through carefully thought-out clinical trials, more research is necessary.[39,44-46]

CONCLUSION

The molecular understanding of ursolic acid's dermoprotective effectiveness provides a strong basis for upcoming studies intended to maximize its therapeutic potential in dermatology. Its antioxidant, anti-inflammatory, and signaling modulatory qualities could be further explored, and clinical trials confirming its effectiveness could lead to the creation of innovative approaches to the treatment of skin conditions and preservation of skin health.

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