Review Article

Ying and Yang of Urocanic Acid in Skin Pathogenesis: A Mini Review on Its Metabolism and Effects

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ABSTRACT

Urocanic acid (UCA) is a main chromophore responsible for absorbing ultraviolet (UV) radiation in the epidermis, particularly in the stratum corneum. It exists naturally as trans-UCA in the skin and undergoes photoisomerization to cis-UCA when exposed to UV radiation. It exerts diverse impacts on the health and diseases of the skin. This review aims to enhance our comprehension of the role of cis-UCA by examining its biological functions, therapeutic potential and pathological implications with a particular focus on its involvement in immune modulation, skin barrier function and oxidative stress response by highlighting existing knowledge gaps, novel experimental approaches, and future research. Previous research has extensively studied the immunomodulatory effects of cis-UCA and its role in maintaining skin barrier function. Additionally, its involvement in numerous pathological disorders such as skin cancer, skin allergies, and photoaging has also been extensively examined. Recent studies have revealed the potential therapeutic uses of cis-UCA, including its application in sun protection and skin disease therapy. Despite some notable progressions, the exact mechanisms and pathways by which cis-UCA produces its effects are not completely comprehended, thus requiring further investigation. This review also discusses the most recent research trends, emerging technologies, and prospects in the study of cis-UCA, intending to offer a thorough overview that highlights the significance of this molecule in the field of skin issues.

Keywords: urocanic acid, cis-urocanic acid, UV radiation, skin diseases

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1.0 Introduction

The skin barrier is important for shielding the body from infections, external threats and ultraviolet (UV) light. Urocanic acid (UCA), a naturally occurring metabolite in the epidermis, is one of the molecules involved in this protective mechanism. It helps with pH regulation, immunological modulation, and UV absorption. The enzyme histidase converts L-histidine into trans-UCA, the main isomer in the stratum corneum (1). Upon UV exposure, trans-UCA undergoes photoisomerization into cis-UCA, altering its biological activity (2). In addition to its function as a UV-absorbing molecule, cis-UCA has been associated with several skin diseases, such as inflammatory skin disorders, skin cancer, and photoaging (3). Although cis-UCA has long been classified as an immunosuppressive agent, new research indicates that it may also have a dual function in disease pathogenesis and skin protection, highlighting the "Yin and Yang" character of this molecule.

According to new research, it plays a role in immunological signalling pathways that lead to skin ageing and the advancement of the disease, including those involving oxidative stress, inflammatory cytokines, and matrix metalloproteinases (MMPs) (4). This mini-review examines the photobiology, metabolic pathways, and pathological implications of cis-UCA, focusing on its conflicting function in skin health and illness. This review intends to link molecular mechanisms with clinical implications by examining recent research, providing insights into potential therapeutic uses in the future.

Furthermore, analysis of the molecular composition of cis-UCA is necessary to fully understand its function in skin physiology. The cis-UCA chemical structure in Figure 1 with molecular formula $C_6H_6N_2O_2$, also known as imidazole-4-acrylic acid, is a histidine derivative characterised by an imidazole ring and a propenoic acid side chain. In the cis form, the double bond between the second and third carbon atoms is in the "cis" configuration, meaning that the hydrogen atoms attached to the carbons on the double bond are on the same side, creating a bent shape (1).

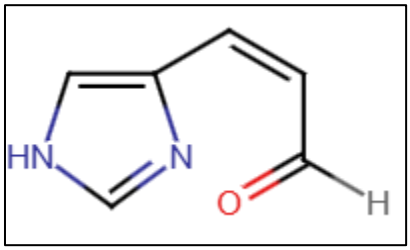

Figure 1: Chemical structure of cis-UCA (1)

UCA is found at uniquely high levels in the stratum corneum, the outermost layer of human skin, with concentrations that are relatively constant in a range of body sites. Level concentrations of UCA in human epidermal levels range from 4 to 34 nM/cm² and do not correlate with any parameter so far tested, including age, sex, pigmentation, skin phototype, and minimal erythema dose (1). UCA is a product of the amino acid histidine, formed by the enzyme histidase as a trans-isomer. This compound can be photoisomerised from trans-UCA form into cis-UCA form in a dose-independent manner (2). UCA is an endogenous molecule of skin, an essential component of hygroscopic and pH-regulating materials, and a photoprotective agent in our skin (3). This compound is a significant absorber of UV light in the skin and acts as a natural sunscreen. (4).

2.0 Metabolic pathway of cis-UCA

The outermost layer of skin naturally contains UCA, an important intermediary in histidine metabolism. The enzyme called histidase catalyzes the deamination process from L-histidine to produce trans-UCA as the main product (1). Histidine decarboxylase

catalyzes the conversion of histidine to histamine in another enzymatic route, whereas this activity takes place independently (2).

Upon UV radiation exposure, trans-UCA undergoes dose-dependent photoisomerization into cis-UCA (3). The immunomodulatory properties of UCA are impacted by the transition, which affects skin inflammation and immunological function. The primary metabolic fate of cis-UCA involves its conjugation with glutathione (GSH), catalyzed by glutathione-S-transferase (GST), leading to the formation of a cis-UCA-cysteine conjugate (CysSH). The hydrophilicity of these molecules is increased by these alterations, allowing excretion through sweat and urine (5). Upon UV radiation, the UCA, in a trans-UCA form, converts into cis-UCA in a dose-dependent manner (2). The metabolic pathway of cis-UCA is outlined in Figure 2.

Furthermore, the metabolism pathway of cis-UCA involves the conjugation of cis-UCA with glutathione (GSH) through the catalysis of glutathione-S-transferase (GST). This results in the further degradation of cis-UCA to form a cis-UCA-cysteine conjugate (CysSH), which makes the compound polar and readily excreted out of the body via sweat and urine (5) (Figure 3).

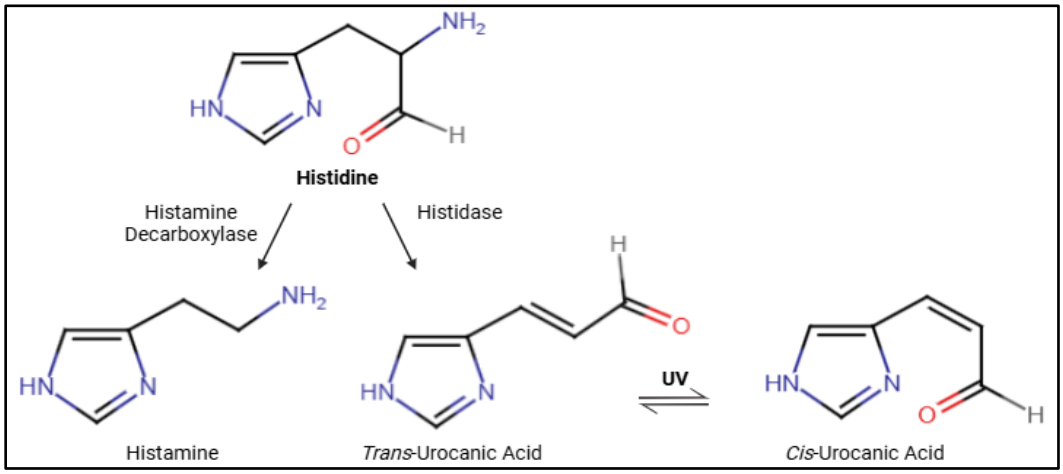

Figure 2: Metabolic pathway of UCA in the skin (1)

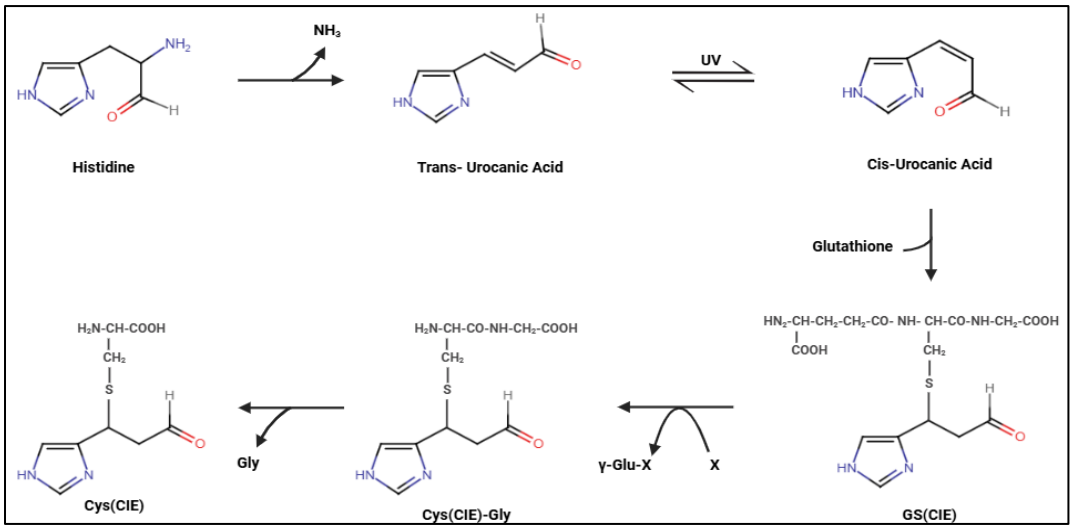

Figure 3: Metabolism pathway of cis-UCA (5)

3.0 Photobiology of cis-UCA

Trans-UCA undergoes photoisomerization upon exposure to UV light, resulting in the conversion to cis-UCA form. This photoisomerization is a reversible process, and the radiation dosage does not influence it. However, the urocanase enzyme, which is responsible for the degradation of UCA, is only present in the liver and brain (6). The lack of this enzyme in human skin results in cis-UCA accumulation following exposure to UV (7, 8). Cis-UCA is primarily eliminated through urine and sweat, with peak levels occurring 5 to 12 hours after exposure to UV radiation and persisting in the body for 8 to 12 days (9).

UCA plays a significant role as a potent UV-absorbing compound in the outermost epidermal layer of human skin (10). Consequently, it has been widely believed that its purpose is to serve as a UV filter to safeguard against DNA damage. Initially, trans-UCA was added to the sunscreen formulas. Nevertheless, daily exposure to UV irradiation with topically applied trans-UCA in mice increased the incidence of UV-induced tumours and the degree of malignancy (11), which might contribute to the immunomodulating effects of cis-UCA. Thus, cis-UCA has been linked to skin-related pathological processes, including immunosuppressive effects and changes in cellular antioxidant balance following exposure to UV radiation.

4.0 Pathological implications of cis-UCA on skin

4.1 Skin cancer

UV irradiation has been thought to be the main culprit of skin pathological conditions, especially skin cancer (12). Hence, the first UV sunscreen was developed in 1928 to prevent skin cancer. Nevertheless, despite the introduction of this revolutionary product, there was no substantial decrease in the incidence of skin cancer (13). It has been well established that pigmentation melanin is highly important in reducing the risk of developing skin cancer (14).

Since the mid-1980s, cis-UCA has traditionally been viewed as an immunosuppressive agent potentially hindering tumour control. Despite UCA being recognised as a UV photoreceptor years ago and its well-documented role in immune suppression, the specific mechanism of action is still unknown. Cis-UCA induces oxidative DNA damage, and the expression of genes related to apoptosis, cell growth arrest, and oxidative stress in cultured human keratinocytes (15). It inhibits tumour antigen presentation by Langerhans cells and reduces skin tumour incidence in UVB-irradiated mice treated with a cis-UCA-specific monoclonal antibody (16). Studies have shown higher cis-UCA levels in squamous cell carcinoma biopsies and increased cis-UCA production in patients with a history of skin cancer following UVB irradiation (17).

Cis-UCA has been discovered to inhibit immunological responses by impacting the activity of immune cells, such as dendritic cells, and triggering the production of IL-10 in T and B cells, contributing to immune suppression. In addition, cis-UCA binding to the 5-HT2A serotonin receptor decreases the immune response in mice. The immunosuppression was rescued by blocking the 5-HT2A serotonin receptor (18). This finding highlights the mechanism of immunosuppression caused by cis-UCA and its potential link to the development of skin cancer.

Additionally, cis-UCA can acidify the cytosol of tumour cells, initiating apoptotic pathways and cell death, as demonstrated in melanoma xenografts, bladder carcinoma cells, and urothelial carcinoma models (19,20) Cis-UCA also has immune modulation properties, and excessive immune system activation in

response to the cis-UCA isomerisation may influence interleukin production (IL-1β, IL-6) activating MMPs and contribute to inflammatory skin conditions and hypersensitivity reactions, accelerating skin damages (21).

4.2 Skin allergies (urticaria and atopic dermatitis)

The increased levels of cis-UCA following UV exposure may exacerbate atopic dermatitis (AD) symptoms in some individuals by affecting systemic immune response. Although cis-UCA has an immunosuppressive effect, it could also act as a pro-inflammatory factor under specific conditions. Filaggrin deficiency in AD shown can reduce trans-UCA levels; hence, altered cis-UCA activity where could disrupt the skin barrier (22).

UCA is one of the natural moisturising agents, along with lipids and proteins that contribute to sustaining the strength of the skin barrier through a complex relationship between them. The skin barrier is mostly composed of the stratum corneum, which is the outermost layer of the epidermis (23). The presence of this layer is vital in shielding the body from external factors such as environmental stresses, infections, and water loss (24). In AD, cis-UCA reduces skin inflammation by improving the skin barrier and reducing water loss, which helps alleviate symptoms.

However, in chronic spontaneous urticaria, patients exhibited higher concentrations of cis-UCA and an increased cis-UCA-to-trans-UCA ratio in the stratum corneum, potentially enhancing mast cell degranulation and promoting urticaria symptoms and worsening the condition by triggering allergic response. This was supported by evidence of cis-UCA-induced mast cell degranulation in the skin (25). Thus, while cis-UCA has therapeutic potential in AD, it may exacerbate urticaria due to its effects on immune cells (26).

4.3 Photoaging

Cis-UCA is involved in photoaging mainly because of its immunomodulatory properties and how it reacts to UV light (27). As an early sign of UV-induced damage, cis-UCA is generated when UCA undergoes photoisomerization. Although immune-suppressive properties are present in cis-UCA, its continuous formation due to repeated UV exposure may contribute to the chronic inflammatory responses observed in photoaging (28).

In addition, Kripke *et al.* (1992) (29) have demonstrated that UV radiation induces cis-UCA formation, which is responsible for suppressing immune functions in the epidermis. The expression of MMPs, particularly MMP-1, which specifically targets collagen, is increased, and cis-UCA indirectly amplifies the inflammatory response (30). Frequent exposure to UV radiation and ongoing MMP activity weaken the skin's collagen network, causing wrinkles and a decrease in skin elasticity, which ultimately results in photoaging (31).

It has been demonstrated that cis-UCA reduces cell viability. Research has shown that cis-UCA alone can enhance the generation of reactive oxygen species (ROS) in cells, resulting in oxidative stress and cell damage (32). In addition, Kaneko *et al.* (2011) (33) conducted a study utilising keratinocytes as a model for their research. They demonstrated that treating normal human epidermal keratinocytes with cis-UCA increased cell mortality. Cis-UCA generates ROS in a dose-dependent manner, but trans-UCA does not.

Exposure to UV radiation leads to increased ROS production, which triggers the activation of MMPs, particularly MMP-1, MMP-3, and MMP-9, leading to collagen degradation and skin ageing (28). Among

these, MMP-1 (collagenase-1) specifically breaks down type I and III collagen, reducing skin elasticity and accelerating wrinkle formation (31). In addition, oxidative stress markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) are significantly elevated following UV exposure, indicating increased DNA and lipid peroxidation damage, both of which contribute to photoaging (42). UV radiation also stimulates pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), further exacerbating chronic inflammation and degradation of the extracellular matrix (ECM) (28). These cumulative effects ultimately weaken the dermal structure, increasing the visibility of fine lines and sagging. The key biomarkers involved in UV-induced photoaging, and their functions are summarized in Table 1.

5.0 Therapeutics Potential of cis-UCA

5.1 Natural UV Filter

Cis-UCA is an endogenous molecule that absorbs UV light and acts as a sunscreen. According to Pelttonen *et al*. (2014) (3), its capacity to absorb and disperse UV rays increases the possibility of its use in topical photoprotective compositions. Cis-UCA-based sunscreen formulations have been studied and have demonstrated the ability to shield keratinocytes from oxidative stress and UV-induced immunosuppression. Verma *et al*. (2024) (4) stated that before cis-UCA is used in medical applications, its contradictory role in UV-related skin cancer risk must be taken into consideration.

On the other hand, Cis-UCA can effectively reduce acute and subacute skin inflammation, outperforming hydrocortisone and tacrolimus in mouse models by decreasing skin irritation, edema, and erythema without affecting neutrophil infiltration or epidermal thickness (37). Cis-UCA has been implicated in the pathogenesis of photosensitivity reactions (33). However, a recent study showed that

Table 1: Biomarkers Associated with Photoaging.

Biomarkers	Functions	Impacts on Photoaging	References
MMP-1 (Collagenase-1)	Breaks down type I and III collagen	Loss of skin elasticity, wrinkle formation	(28, 31)
MMP-3 (Stromelysin-1)	Degrades elastin and proteoglycans	Weakens the ECM, causing sagging skin	(28)
MMP-9 (Gelatinase B)	Degrades type IV and V collagen	Contributes to skin thinning and fragility	(28)
8-Hydroxy-2'-deoxyguanosine (8-OHdG)	Marker of DNA oxidation	Indicates UV-induced DNA damage and accelerated aging	(42)
Malondialdehyde (MDA)	Lipid peroxidation marker	Reflects oxidative stress-induced skin damage	(42)
IL-6, TNF-α	Pro-inflammatory cytokines	Promote chronic inflammation and ECM degradation	(28)

Abbreviations: matrix metalloproteinases, MMP; 8-hydroxy-2'-deoxyguanosine, 8-OHdG, malondialdehyde, MDA; interleukin-6, IL-6; tumor necrosis factor-alpha,TNF-α.

cis-UCA can be a photodynamic agent with potential anti-inflammatory and antiproliferative activity (38). In addition, two natural UCA derivatives, imidazole-4-carboxylic acid (ImCOOH) and imidazole-4-acetic acid (ImAc), were found to have an excellent safety profile after the preclinical test phase, including partial systemic exposure through skin penetration (39).

5.2 Cancer Therapy

Upon intravesical instillation of cis-UCA, this agent is protonated at the imidazolyl moiety in the mildly acidic extracellular tumour environment and penetrates the cancer cell. Once inside the cell and due to the slightly alkaline pH inside the tumour cell, cis-UCA is deprotonated, i.e., the imidazolyl proton is released into the cytosol, which raises the intracellular acidity. This acidification impairs many cellular processes, such as metabolic activity, and may lead to cell cycle arrest, induction of cellular apoptosis, and necrotic cell death. (40)

Moreover, new research has demonstrated that cis-UCA affects important intracellular signalling pathways, specifically the c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) mechanisms. A major component of the mitogen-activated protein kinase (MAPK) cascade, the ERK pathway plays a role in cell survival, differentiation, and proliferation (38). Although ERK activation normally stimulates cell development, sustained phosphorylation of ERK (p-ERK) in malignant cells can result in uncontrolled proliferation. Interestingly, studies indicate that cis-UCA suppresses ERK phosphorylation, leading to cell cycle arrest and inhibition of tumour growth (38).

The JNK pathway, on the other hand, is usually linked to cellular stress reactions, particularly apoptosis. It has been demonstrated that in tumour models, cis-UCA increases JNK activation, which upregulates pro-apoptotic proteins such as caspase-3 and Bax, hence promoting programmed cell death (40). This implies that cis-UCA might selectively target cancer cells while protecting healthy tissues by acting as an apoptotic inducer.

The exciting potential of cis-UCA as an anti-cancer therapy is highlighted by its simultaneous control of ERK (inhibition) and JNK (activation), especially when combined with targeted therapies that take advantage of the tumour weaknesses. However, more research is required to determine the ideal treatment parameters, such as dosage, formulation, and delivery methods, to optimize cis-UCA's anti-tumour effectiveness and minimize its off-target effects.

5.3. Skin Barrier Function

Cis-UCA is essential for protecting the function of the skin barrier. Reduced trans-UCA levels in filaggrin-deficient skin have been found to cause problems with skin hydration and pH balance, which can worsen diseases like chronic eczema and AD (35). In AD patients, impaired barrier integrity and skin hydration were noted due to reduced levels of natural moisture factor amino acids, including histidine and UCA (34). Treatment with a 5% cis-UCA cream reduced transepidermal water loss and erythema, and thus improved skin barrier function and suppressed inflammation in the human skin with mild and moderate AD (3). Filaggrin in the stratum corneum is the main source of UCA. An alternative approach involving L-histidine supplementation increased filaggrin production and improved skin barrier function, reducing AD severity by 40% in patients (35). The genetic mutations leading to reduced trans-UCA production might have evolved to allow better synthesis of pre-vitamin D with less UV radiation filtering in

lighter skin (35). Thus, cis-UCA-based treatments might help restore the metabolism of filaggrin, indicating a new therapy option for chronic dry skin problems.

5.4. Immune Modulation

Cis-UCA has been widely studied for its immunomodulatory properties, particularly in atopic dermatitis (AD), psoriasis, and other inflammatory skin diseases. Research has shown that topical cis-UCA reduces inflammatory cytokines including IL-1β and TNF-α**,** thereby mitigating skin inflammation (34) Modulating UCA isomer concentrations in diseased skin may offer therapeutic benefits for controlling inflammation and treating cutaneous disorders like AD. The use of topical cis-UCA resulted in the macroscopic features enhancement of AD-like skin lesions and reduction in the level of serum IgE in AD model mice, as reported by Rieko and Nakamura in 2016 (36).

Additionally, cis-UCA interacts with serotonin receptors, particularly 5-HT2A, which may contribute to immune regulation and skin homeostasis (18). These findings could potentially lead to novel treatment strategies for treating human AD using topical cis-UCA. Interestingly, a study by Abdul Hamid *et al.* (2022) (41) showed that the reactive sulphur species (RSS) could protect the keratinocyte cells from UV-A but not UV-B irradiation and further discovered that the cooperative interaction of RSS and cis-UCA potentially suppressed UV-B-induced inflammation and cellular damage. This can be significant in skin health, as UCA is primarily found in the skin and plays a role in regulating immune responses in the skin (41). Further investigations into the role of cis-UCA in inflammatory pathways may provide insights into new dermatological treatments.

6.0 Conclusion

The dual role of cis-UCA in both promoting skin cancer and potentially serving as a therapeutic target for other cancers points out its complex and multifaceted biological effects. Although the UV-induced immunosuppressive characteristics of cis-UCA enhance the development of skin cancer by enabling UV-damaged cells to avoid immune control, these same characteristics also present new possibilities for the compound's application in cancer therapy. According to recent studies, treating inflammatory skin disorders and other cancers may be possible by using its capacity to regulate immune responses. This contradiction draws attention to the need for a more thorough comprehension of the processes and mechanisms cis-UCA uses to function in skin biology and cancer. We can minimise the carcinogenic dangers of cis-UCA while better leveraging its therapeutic potential by exploring deeper into these processes. In order to efficiently target cis-UCA for therapies while reducing its pro-tumorigenic effects in skin cancer, future research will be crucial.

Authorship contribution statement

AY: Conceptualization, writing original draft **HAH**: Data evaluation, editing the manuscript. **NH**: Conceptualization, draft corrections, supervised. All authors discussed the draft and contributed to the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest in the current work.

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