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Expression of Ifng and IL4 Genes in Protecting Against UVB-Induced Photoaging and Inflammation: A Comprehensive Review

Wega Nanda Marissa[1*], Oeij Anindita Adhika[2], Rita Tjokropranoto[3]
[1-3]Master's Program in Skin Aging and Aesthetics, Universitas Kristen Maranatha, Indonesia
Email: heyitiswega@gmail.com[1,3], anindita_adhika@yahoo.com[2]

**Corresponding Author: heyitiswega@gmail.com*

Abstract. To review the role of IFN-γ and IL4 gene expression in UVB-induced photoaging and inflammation, and to highlight the therapeutic potential of pineapple (Ananas comosus) peel extract especially in advanced topical formulations in modulating these cytokines to protect and repair skin. UVB radiation is a major extrinsic factor in skin aging, promoting excessive reactive oxygen species (ROS) generation, oxidative damage, and activation of redox-sensitive pathways such as NF-κB and AP-1. This leads to chronic low-grade inflammation ("inflammaging"), extracellular matrix degradation, wrinkle formation, and pigmentary disorders, including post-inflammatory hyperpigmentation. IFN-γ, encoded by IFN-γ, is a key pro-inflammatory cytokine that, when overexpressed, sustains tissue-damaging inflammation and contributes to melanogenesis via post-translational regulation of tyrosinase. In contrast, IL-4, encoded by IL4, is an immunoregulatory cytokine that suppresses pro-inflammatory mediators, promotes Th2-skewing, supports M2 macrophage polarization, and facilitates wound healing and extracellular matrix remodeling. An imbalance characterized by elevated IFN-γ and insufficient IL-4 is a critical feature of UVB-induced photoaging. Pineapple peel, rich in bromelain, phenolic compounds, and other antioxidants, has demonstrated significant antioxidant and immunomodulatory activities, including reduction of pro-inflammatory cytokines and enhancement of anti-inflammatory responses. Formulating pineapple peel extract into topical delivery system skin penetration, stability, and local bioavailability, thereby enhancing its ability to downregulate IFN-γ, upregulate IL4, and mitigate UVB-induced structural and functional skin damage.

Keywords: Ananas Comosus; Bromelain; Inflammaging; Photoaging; UVB.

1. INTRODUCTION

The skin as the largest organ of the human body and serves as a primary physical, chemical, and immunological barrier against environmental insults, including ultraviolet (UV) radiation and pollutants (Baumann & Saghari, 2009; Tortora & Derrickson, 2008; Gilaberte-Calzada et al., 2016). Clinically, skin aging is categorized into intrinsic (chronological) aging and extrinsic aging, the latter being mainly driven by chronic exposure to UV radiation, especially UVB, as well as pollution and lifestyle factors (Baumann & Saghari, 2009; Yusharyahya, 2021; Ansary et al., 2021; Adzhani et al., 2022; Tsatsou et al., 2012). With increasing age and cumulative UV exposure, the skin undergoes progressive structural and functional changes, including epidermal thinning, degradation of dermal collagen and elastin, impaired barrier integrity, wrinkle formation, and pigmentary alterations (Baumann & Saghari, 2009; Yusharyahya, 2021; Papaccio et al., 2022; Kaufman et al., 2018). Ultraviolet B (UVB) radiation is recognized as a key extrinsic factor contributing to the development of photoaging. Exposure to UVB leads to the excessive production of reactive oxygen species (ROS), which in turn induces oxidative damage to lipids, proteins, and DNA, and activates redox-sensitive signaling pathways (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022).

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These signaling pathways involve transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), which promote the upregulation of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021). The resulting condition of chronic low-grade inflammation, commonly termed "inflammaging", plays a significant role in extracellular matrix degradation, decreased skin elasticity, wrinkle formation, and the occurrence of post-inflammatory hyperpigmentation (PIH) (Baumann & Saghari, 2009; Yusharyahya, 2021; Tsatsou et al., 2012; Papaccio et al., 2022; Kaufman et al., 2018).

Cytokines serve a pivotal role in mediating the link between UV-induced oxidative stress and cutaneous damage. Interferon-gamma (IFN-γ) is a key pro-inflammatory cytokine that regulates cell-mediated immunity; however, its persistent elevation can sustain chronic inflammation and contribute to aging-related pathologies (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018). IFN γ signals through JAK/STAT pathways and promotes pro-inflammatory activity in endothelial and immune cells, contributing to photoaging (Ng et al., 2023; Castro et al., 2018). In the skin, IFN-γ has also been implicated in melanogenesis and PIH via post-translational regulation of tyrosinase, linking inflammatory processes to dyschromia (Kaufman et al., 2018; Mo et al., 2022). In contrast, interleukin-4 (IL-4) is an immunoregulatory cytokine associated with T helper 2 (Th2) responses, suppression of pro-inflammatory signaling, and promotion of tissue repair processes (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). IL 4 and interleukin-13 (IL 13) are critical regulators and effectors of wound healing and extracellular matrix remodeling, facilitating the resolution phase following tissue injury (Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). An imbalance characterized by heightened IFN γ activity and insufficient IL 4–mediated regulation may exacerbate tissue damage and impair regenerative processes in photoaged skin (Ansary et al., 2021; Papaccio et al., 2022; Oxenkrug, 2011; Ng et al., 2023; Shankar et al., 2022).

Natural products possessing both antioxidant and immunomodulatory properties have garnered increasing attention as adjunctive approaches for the prevention and management of photoaging (Papaccio et al., 2022; Erniati & Ezraneti, 2020; Fitriyani & Septiani, 2025; Widiyanto et al., 2023; Wahyono, 2013; Waslihati et al., 2019). Pineapple (Ananas comosus) contains a wide array of bioactive constituents, including vitamins, phenolic compounds, flavonoids, and the proteolytic enzyme complex bromelain (Ali et al., 2020; Hikal et al., 2021; Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021).

Pineapple peel, often discarded as agro-industrial waste, has demonstrated significant antioxidant activity (Fitriyani & Septiani, 2025; Hikal et al., 2021; Hatam et al., 2013) and immunomodulatory potential (Azizah et al., 2017; Amsia, 2020; Sornkayasita et al., 2024). Bromelain and pineapple-derived formulations exhibit anti-inflammatory and immunomodulatory effects in various experimental models and clinical contexts, and have been explored for their roles in wound healing and modulation of inflammatory pathways (Ali et al., 2020; Hikal et al., 2021; Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). In particular, extracts from pineapple peel and bromelain-based gels have shown promising effects on inflammation control and tissue repair in preclinical studies (Fitriyani & Septiani, 2025; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023).

The therapeutic efficacy of such bioactive compounds in topical formulations is largely determined by their capacity to penetrate the stratum corneum and reach viable epidermal and dermal targets (Van Ravenzwaay & Leibold, 2004; Takeuchi et al., 2011; Neupane et al., 2020). To address this limitation, advanced delivery systems have been developed to enhance cutaneous penetration, improve stability, and enable controlled release of active constituents (Fitriyani & Septiani, 2025; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Nunes et al., 2022; Servat-Medina et al., 2015). Biocompatible carrier systems are capable of encapsulating a wide range of bioactives, thereby increasing their bioavailability and prolonging their residence time within the skin (Nunes et al., 2022; Servat-Medina et al., 2015). Bromelain-containing and pineapple peel extract–based gels have been reported to be safe and effective in animal models, supporting their potential as topical therapeutic systems (Fitriyani & Septiani, 2025; Hikal et al., 2021; Fadhila et al., 2024; Thomas et al., 2023). Collectively, UVB-induced photoaging may be conceptualized as a consequence of sustained oxidative stress accompanied by dysregulation of cytokine networks, particularly involving IFN-γ and IL-4. Targeting this imbalance through antioxidant and immunomodulatory interventions derived from Ananas comosus, in conjunction with optimized topical delivery systems, represents a promising strategy for the prevention and attenuation of UVB-induced skin aging. This review aims to summarize the underlying mechanisms of UVB-induced cutaneous aging in relation to IFN-γ and IL-4 expression, and to highlight the therapeutic potential of pineapple peel extract as a natural immunomodulatory agent within advanced topical formulations.

Therefore, this review aims to (i) summarize evidence that UVB exposure increases IFN γ and decreases IL4 expression in photoaging, (ii) evaluate data supporting the ability of Ananas comosus peel extract to reduce IFN γ and enhance IL 4, and (iii) propose a mechanistic model in which pineapple peel counters UVB-induced cytokine imbalance and structural skin damage.

2. RESULT AND DISCUSSION

UVB-Induced Oxidative Stress and Inflammaging in Skin

Prolonged exposure to ultraviolet (UV) radiation, particularly UVB, constitutes a major environmental contributor to extrinsic skin aging, or photoaging (Baumann & Saghari, 2009; Yusharyahya, 2021; Adzhani et al., 2022; Tsatsou et al., 2012; Kulka, 2013; Tantari, 2003). UVB photons are absorbed mainly in the epidermis and upper dermis, where they induce direct DNA photolesions (e.g. cyclobutane pyrimidine dimers) and, more importantly in the context of aging, trigger excessive formation of reactive oxygen species (ROS) (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022). Keratinocytes, fibroblasts, and resident immune cells respond to this oxidative burden by activating redox-sensitive transcription factors such as NF κB and AP 1, which orchestrate broad inflammatory and catabolic programs (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021).

The generation of ROS promotes the activation of NF-κB, leading to the upregulation of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), chemokines, and adhesion molecules that facilitate the recruitment and activation of additional immune cells, thereby establishing a self-perpetuating inflammatory loop (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021). Concurrently, AP 1 activation drives increased expression of matrix metalloproteinases (MMP 1, MMP 3, and others), which degrade dermal collagen and elastin, resulting in loss of structural integrity, wrinkle formation, and impaired biomechanical properties of the skin (Baumann & Saghari, 2009; Yusharyahya, 2021; Adzhani et al., 2022; Papaccio et al., 2022; Wahyono, 2013; Waslihati et al., 2019). This sustained, low-grade inflammatory condition is commonly referred to as “inflammaging” and represents a key hallmark of photoaged skin (Yusharyahya, 2021; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021). UVB-induced inflammation exerts significant effects on epidermal homeostasis, melanocyte activity, and barrier integrity.

Dysregulation of keratinocyte proliferation and differentiation contributes to epidermal thinning and impaired stratum corneum function (Baumann & Saghari, 2009; Tortora & Derrickson, 2008; Gilaberte-Calzada et al., 2016; Yusharyahya, 2021).

Furthermore, elevated local levels of inflammatory mediators and ROS exert paracrine influences on melanocytes, leading to alterations in melanogenesis and pigment distribution, which clinically present as mottled hyperpigmentation and PIH (Adzhani et al., 2022; Papaccio et al., 2022; Kaufman et al., 2018; Mo et al., 2022).

Experimental animal models have been widely employed to elucidate the mechanisms underlying photoaging. UVB-induced photoaging models in rats and mice consistently demonstrate an initial phase of epidermal hyperplasia followed by atrophy, accompanied by increased dermal matrix metalloproteinase (MMP) expression, reduced collagen density, and elevated markers of oxidative stress (Tsatsou et al., 2012; Widiyanto et al., 2023; Wahyono, 2013; Waslihati et al., 2019; Damayanti et al., 2023; Mayangsari et al., 2024). In particular, Wistar rats exposed to controlled doses of UVB exhibit histopathological and biochemical alterations that closely resemble those observed in human photoaging, thereby supporting their validity for mechanistic and interventional investigations (Damayanti et al., 2023; Mayangsari et al., 2024; Rosidah et al., 2020; Wati et al., 2024). These models are especially valuable for examining cytokine dynamics, including the expression of IFN-γ and IL-4, as well as for evaluating the efficacy of novel topical therapies, such as plant-derived extracts and nanoformulation-based delivery systems.

Within this inflammatory context, IFN γ and IL 4 emerge as critical, functionally opposing mediators. IFN γ amplifies and sustains pro-inflammatory and tissue-damaging responses, whereas IL 4 contributes to immune regulation, resolution of inflammation, and tissue repair (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018; Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). The balance between these cytokines, rather than their absolute levels alone, appears to be a key determinant of whether UVB-induced injury progresses toward chronic damage (photoaging) or effective resolution and regeneration.

Pro-Inflammatory Role of IFN-γ (IFNG) in UVB-Induced Skin Damage

IFN γ is a type II interferon primarily produced by T helper 1 (Th1) cells, $CD8^+$ T lymphocytes, natural killer (NK) cells, and natural killer T (NKT) cells in response to antigenic and inflammatory stimuli (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018). IFN-γ exerts its biological effects through a heterodimeric receptor complex composed of IFN-γR1 and IFN-γR2, which activates associated Janus kinases (JAK1 and JAK2), leading to the phosphorylation and dimerization of STAT1 and its subsequent translocation into the nucleus to regulate IFN-γ–responsive gene expression (Ng et al., 2023; Castro et al., 2018).

The downstream transcriptional program includes the upregulation of antigen presentation machinery, chemokines, adhesion molecules, and additional cytokines, thereby reinforcing Th1-skewed immune responses and sustaining pro-inflammatory conditions (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018).

In the context of UVB-induced cutaneous injury, multiple converging mechanisms position IFN-γ as a key mediator of pathological inflammation and tissue damage. First, UVB-induced oxidative stress and keratinocyte injury promote the release of antigens and danger-associated molecular patterns (DAMPs), which in turn stimulate resident and infiltrating immune cells to produce IFN-γ (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021). Second, IFN γ itself enhances expression of MHC class II and co-stimulatory molecules on antigen-presenting cells, increasing T-cell activation and perpetuating the inflammatory loop (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018). Third, IFN γ synergizes with other cytokines (e.g. TNF α, IL 1β) to further activate NF κB and amplify local inflammatory responses (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Ng et al., 2023).

Chronic overexpression of IFN γ is not only associated with systemic aging and neuropsychiatric disorders but also with local tissue aging and structural deterioration (Oxenkrug, 2011). In the skin, sustained IFN γ signaling can:

1) Upregulate additional pro-inflammatory mediators and chemokines, promoting persistent leukocyte recruitment.
2) Increase ROS generation by immune and non-immune cells, reinforcing oxidative stress.
3) Induce catabolic enzymes that degrade extracellular matrix components, accelerating dermal atrophy and wrinkle formation (Ansary et al., 2021; Papaccio et al., 2022; Oxenkrug, 2011).

Notably, IFN-γ also exerts direct effects on melanocyte function and pigmentation. Emerging evidence indicates that IFN-γ can enhance melanogenesis through post-translational regulation of tyrosinase, the rate-limiting enzyme in melanin synthesis, by reducing its proteasomal degradation and thereby prolonging its enzymatic activity (Mo et al., 2022).

This mechanism establishes a link between chronic inflammation and the development of PIH, a common and cosmetically significant manifestation of photoaging, particularly in individuals with darker skin phototypes (Kaufman et al., 2018; Mo et al., 2022).

Moreover, IFN-γ–driven inflammation at the dermal–epidermal junction may interfere with melanocyte–keratinocyte crosstalk and disrupt melanosome transfer, leading to uneven pigment distribution (Adzhani et al., 2022; Kaufman et al., 2018; Mo et al., 2022).

These pigmentary changes, combined with structural Extracellular Matrix (ECM) damage, contribute to the heterogeneous clinical appearance of photoaged skin. Collectively, IFN-γ, encoded by IFNG, functions as a central pro-aging cytokine in UVB-exposed skin by linking oxidative stress to persistent inflammation, matrix degradation, and pigmentary dysregulation. Accordingly, targeting IFN-γ or its upstream regulatory pathways represents a promising therapeutic strategy for mitigating UVB-induced photoaging.

Protective and Reparative Role of IL-4 (IL4) and the IFN-γ/IL-4 Balance

IL 4 is a key Th2 cytokine produced by CD4+ Th2 cells, mast cells, eosinophils, and basophils. It signals via type I and type II IL 4 receptors, activating JAK–STAT6 and, to a lesser extent, other pathways such as IRS/PI3K and Mitogen-Activated Protein Kinases (MAPKs) (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). Through these signaling cascades, IL 4 orchestrates a broad shift toward anti-inflammatory and pro-repair immune responses. Several mechanisms underlie the protective role of IL 4 in the skin

Suppression of Pro-Inflammatory Cytokines

IL-4 suppresses the production of pro-inflammatory cytokines, including Tumor Necrosis Factor alpha (TNF-α), Interleukin-1 beta (IL-1β), and IL-6, as well as chemokines involved in the recruitment of Th1 and other pro-inflammatory immune cells (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). Through this inhibitory effect on upstream cytokine signaling, IL-4 can attenuate NF-κB activation and thereby limit both the magnitude and duration of UVB-induced inflammatory responses (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Ng et al., 2023; Shankar et al., 2022).

Modulation of Adaptive Immunity

By promoting Th2 differentiation and inhibiting Th1 polarization, IL 4 counterbalances IFN γ driven immunity (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022). In tissues, this Th1/Th2 balance is essential for resolving inflammation after an inciting insult.

In the photoaging context, insufficient IL 4 may allow unchecked IFN γ activity, whereas adequate IL 4 expression can dampen pro-inflammatory circuits and facilitate resolution.

Macrophage Polarization and Tissue Repair

IL 4 in conjunction with IL-13, serves as a key regulator of alternative (M2) macrophage activation (Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). M2 macrophages are characterized by the production of anti-inflammatory mediators, growth factors, and ECM components that collectively facilitate wound healing and tissue remodeling. In the context of cutaneous injury, IL-4/IL-13–mediated M2 polarization promotes collagen synthesis, angiogenesis, and re-epithelialization, thereby contributing to tissue repair following UV-induced damage (Wynn & Vannella, 2022; Shankar et al., 2022).

Regulation of Stromal and Epithelial Cell Function

IL 4 signaling can modulate fibroblast and keratinocyte behavior, including proliferation, differentiation, and production of ECM components and proteases (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). In balanced amounts, IL 4 supports matrix reconstitution and barrier restoration, potentially offsetting the catabolic effects of chronic NF κB/AP 1 activation in photoaging.

Emerging evidence indicates that IL-4 and IL-13 are not solely implicated in allergic responses but also function as key regulators and effectors of wound repair and fibrotic processes, exerting context-dependent beneficial or detrimental effects (Wynn & Vannella, 2022; Shankar et al., 2022). In UVB-exposed skin, where acute injury must be efficiently resolved without progressing to chronic fibrosis or tissue atrophy, a tightly regulated IL-4 response is essential. From a systems-level perspective, the balance between IFN-γ and IL-4 activity may represent an immunological "set point" that determines the cutaneous response to UVB exposure. A higher IFN-γ/IL-4 ratio is associated with sustained inflammation, ECM degradation, and pigmentary abnormalities, whereas a lower ratio—reflecting relatively enhanced IL-4 signaling—favors resolution of inflammation, ECM repair, and more complete restoration of tissue architecture (Ansary et al., 2021; Papaccio et al., 2022; Oxenkrug, 2011; Ng et al., 2023; Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). Consequently, strategies that simultaneously reduce IFN γ (or its downstream effects) and enhance IL 4–mediated pathways are particularly appealing for photoaging intervention.

Natural compounds capable of modulating this cytokine axis may provide a safer long-term approach than broad immunosuppressants, especially when delivered topically to target UV-exposed skin.

Immunomodulatory Potential of Pineapple Peel (Ananas comosus) and Bromelain

Pineapple (Ananas comosus) is a tropical fruit rich in nutrients and bioactive compounds, including vitamins (e.g. vitamin C), minerals, dietary fiber, phenolic compounds, flavonoids, and a complex mixture of cysteine proteases collectively known as bromelain (Ali et al., 2020; Hikal et al., 2021; Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021). Extensive reviews have documented its potent antioxidant capacity, anti-inflammatory properties, and a wide range of associated health benefits (Ali et al., 2020; Colletti et al., 2021; Chakraborty et al., 2021). Notably, pineapple peel, a major by-product of the fruit processing industry, contains substantial levels of phenolic compounds and demonstrates significant antioxidant activity, thereby representing an attractive and cost-effective source of functional bioactive ingredients (Fitriyani & Septiani, 2025; Hikal et al., 2021; Hatam et al., 2013).

Antioxidant Properties and ROS Scavenging

Pineapple peel extracts have been shown to possess strong free radical–scavenging activity in vitro, largely attributable to their content of phenolic compounds, flavonoids, and vitamin C (Fitriyani & Septiani, 2025; Ali et al., 2020; Hikal et al., 2021; Hatam et al., 2013). Through the neutralization of ROS, these extracts may interfere with the early stages of UVB-induced damage by reducing oxidative injury to lipids, proteins, and DNA, as well as attenuating the activation of redox-sensitive inflammatory pathways (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022). In the context of photoaging, such antioxidant properties may contribute to the preservation of collagen integrity, suppression of MMP induction, and reduction of the oxidative burden that drives inflammaging (Adzhani et al., 2022; Papaccio et al., 2022; Widiyanto et al., 2023; Wahyono, 2013; Waslihati et al., 2019).

Bromelain as an Anti-Inflammatory and Immunomodulatory Agent

Bromelain, derived from pineapple stem and fruit, has been extensively studied for its anti-inflammatory, antithrombotic, and immunomodulatory properties (Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021). It can modulate various components of the immune response, including cytokine production, cell adhesion, and leukocyte trafficking (Colletti et al., 2021; Chakraborty et al., 2021; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023).

Preclinical and clinical studies suggest that bromelain may:

a) Reduce levels of pro-inflammatory mediators such as TNF α, IL 1β, and IL 6.
b) Influence T-cell activation and differentiation.

c) Modulate NF κB and MAPK signaling pathways involved in inflammation (Colletti et al., 2021; Chakraborty et al., 2021; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023).

Bromelain-loaded nanocomposites have been shown to decrease inflammatory and cytotoxic effects in disease models, highlighting its therapeutic potential when delivered using advanced formulations (Mousavi Maleki et al., 2023). Moreover, modified kombucha beverages enriched with pineapple by-products exhibit immunomodulatory effects ex vivo, supporting the concept that pineapple-derived compounds can beneficially modulate immune function with aging (Sornkayasita et al., 2024)

Immunomodulatory Effects of Pineapple Peel Extract

Studies utilizing ethanolic extracts of pineapple peel have demonstrated notable immunomodulatory activity in animal models, including the modulation of leukocyte function and systemic immune responses (Fitriyani & Septiani, 2025; Azizah et al., 2017; Amsia, 2020; Wiyono & Yuliati, 2020; Fadhila et al., 2024). Additionally, ethanolic peel extracts and bromelain-containing gel formulations have been reported to exhibit favorable safety profiles in rodent hematological parameters and to effectively enhance wound healing, indicating good systemic and local tolerability (Fitriyani & Septiani, 2025; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). From a mechanistic standpoint, the combination of antioxidant phenolics and proteolytic enzymes in pineapple peel may act at multiple levels:

a) Upstream: Scavenging ROS, thereby reducing oxidative stress and NF κB/AP 1 activation.
b) Midstream: Inhibiting the production of pro-inflammatory cytokines (e.g. TNF α, IL 1, IL 6) and possibly IFN γ, while promoting anti-inflammatory cytokines such as IL 4 and IL 10 (Erniati & Ezraneti, 2020; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024).
c) Downstream: Supporting tissue repair through enhanced proteolytic removal of damaged matrix components and stimulation of wound-healing pathways (Fitriyani & Septiani, 2025; Colletti et al., 2021; Chakraborty et al., 2021; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023).

Although direct in vivo evidence regarding IFNG and IL4 gene expression in UVB-exposed skin treated with pineapple peel extract remains limited, findings from systemic inflammatory and wound-healing models suggest that these extracts can modulate the immune milieu toward a more regulatory and reparative phenotype (Erniati & Ezraneti, 2020; Fitriyani & Septiani, 2025; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). In the context of UVB-induced photoaging, this immunomodulatory shift may translate into reduced IFN-γ–driven inflammation alongside enhanced IL-4–mediated resolution and extracellular matrix restoration.

Topical Delivery of Pineapple Peel Extract and Integrated Mechanistic Model

A key determinant of the clinical efficacy of pineapple peel–derived bioactive compounds in the context of photoaging is their capacity to penetrate the stratum corneum and reach viable epidermal and dermal layers at therapeutically relevant concentrations (Van Ravenzwaay & Leibold, 2004; Takeuchi et al., 2011; Neupane et al., 2020). The "500 Da rule" suggests that compounds with molecular weight below ~500 Da and appropriate lipophilicity are more likely to permeate the skin; however, many phenolic compounds and enzyme complexes like bromelain may face significant barriers to penetration when applied as crude extracts (Van Ravenzwaay & Leibold, 2004; Takeuchi et al., 2011; Neupane et al., 2020).

Pineapple Peel–Based Gels and Safety in Animal Models

Several studies have developed topical gel formulations incorporating pineapple peel extracts or bromelain, including carbopol-based and lipophilic gel systems, and subsequently evaluated their efficacy in animal models (Fitriyani & Septiani, 2025; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). These formulations demonstrated:

a) Acceptable physicochemical stability and antioxidant activity in vitro (Fitriyani & Septiani, 2025; Fadhila et al., 2024).
b) Favorable hematologic safety profiles in rats after repeated topical application (Wiyono & Yuliati, 2020).
c) Enhanced burn wound healing and tissue regeneration in bromelain gel–treated animals compared to controls (Thomas et al., 2023).

Collectively, these findings support the feasibility of gel-based delivery systems as a safe and effective approach for the topical administration of pineapple-derived bioactive compounds.

Integrated Mechanistic Model

As illustrated in Figure 1, the proposed mechanisms of UVB, IFN-γ, IL-4, and pineapple peel topical extract in photoaging are integrated schematically. UVB exposure elevates ROS production, activates NF-κB/AP-1 signaling, and upregulates IFN-γ along with other pro-inflammatory mediators, resulting in ECM degradation, PIH, and structural skin aging (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Oxenkrug, 2011; Muzamil et al., 2021; Mo et al., 2022). In contrast, IL 4 supports the resolution of inflammation and ECM repair via Th2 skewing and M2 macrophage polarization (Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). Pineapple peel topical extract is proposed to exert effects at multiple levels by scavenging ROS, attenuating pro-inflammatory signaling (including IFN-γ), and enhancing IL-4–associated pathways, thereby restoring cytokine homeostasis and supporting tissue repair (Erniati & Ezraneti, 2020; Fitriyani & Septiani, 2025; Ali et al., 2020; Hikal et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023; Nunes et al., 2022; Servat-Medina et al., 2015). Overall, while UVB exposure tends to increase IFN-γ and reduce IL-4 levels, pineapple peel topical extract is suggested to decrease IFN-γ and enhance IL-4 expression, functionally counteracting the cytokine imbalance induced by UVB

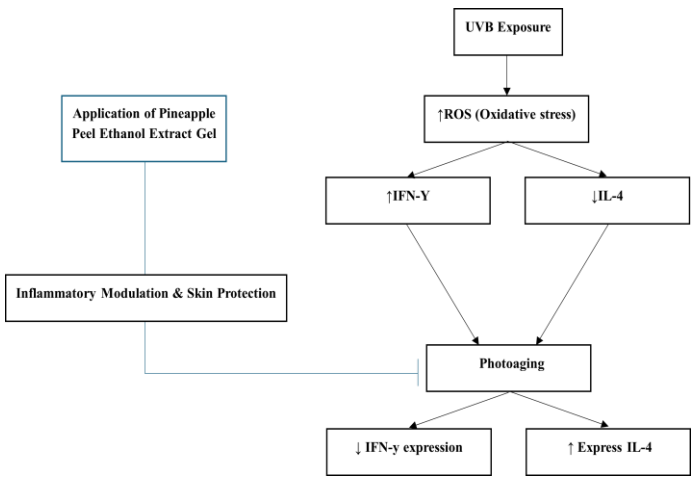

Figure 1. Proposed Mechanisms of UVB-Induced Photoaging and the Modulatory Effects of Pineapple Peel Topical Extract on IFN-γ and IL-4 Balance.

To further conceptualize the relative contributions of these factors, Table 1 contrasts the roles of IFN-γ, IL-4, and pineapple peel topical extract in UVB-exposed skin.

Table 1. Comparative roles of IFN-γ, IL-4, and pineapple topical extract in UVB-induced photoaging.

Factor / Intervention	Main source / formulation	Key mechanisms in UVB-exposed skin	Net impact on photoaging
IFN-γ (IFNG)	Th1, CD8+ T cells, NK, NKT	JAK/STAT1 activation; ↑pro-inflammatory cytokines; ↑ROS; promotes melanogenesis via tyrosinase	Sustains inflammaging; accelerates ECM degradation; contributes to PIH and structural aging
IL-4 (IL4)	Th2 cells, mast cells, eosinophils, basophils	JAK/STAT6 activation; Th2 skewing; M2 macrophage polarization; ↓TNF-α/IL-1β/IL-6; supports repair	Limits inflammation; promotes resolution and ECM remodeling; supports barrier restoration
Pineapple peel topical extract	Pineapple peel extract	Antioxidant ROS scavenging; ↓NF-κB/AP-1; ↓IFN-γ/TNF-α/IL-1/IL-6; ↑IL-4/IL-10; improved penetration and controlled release	Mitigates oxidative stress and inflammaging; rebalances IFN-γ/IL-4 axis; enhances tissue repair and may reduce PIH

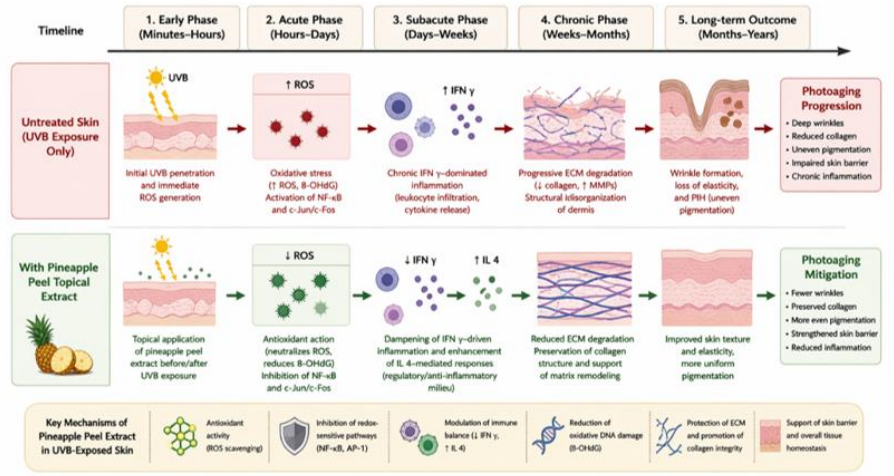

Figure 2. Conceptual timeline of UVB-induced skin changes and the potential modifying effects of pineapple peel topical extract.

In addition, Figure 2 illustrates a conceptual timeline of UVB-induced skin changes in the presence and absence of pineapple peel topical extract.
In the absence of intervention, repeated UVB exposure results in cumulative oxidative stress, persistent IFN-γ–dominated inflammation, progressive ECM degradation, and the subsequent development of wrinkles and PIH. In contrast, the application of pineapple peel topical extract may act at early stages by reducing ROS levels, attenuating IFN-γ–driven inflammatory cascades, and enhancing IL-4–mediated repair mechanisms. Over time, these combined effects may help preserve dermal structure, maintain more uniform pigmentation, and delay the clinical manifestations of photoaging.

Critical Appraisal, Limitations, and Future Directions

While the mechanistic link between UVB-induced oxidative stress, IFN-γ/IL-4 imbalance, and the proposed modulatory effects of pineapple peel topical extract is supported by existing evidence, several important limitations warrant consideration. Much of the current understanding of IFN-γ and IL-4 in cutaneous aging is extrapolated from general immunological and wound-healing studies, rather than from dedicated longitudinal investigations in human photoaging (Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Mo et al., 2022; Nappo et al., 2017; Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012; Castro et al., 2018). Although UVB-induced animal models reproduce key structural and inflammatory features of photoaged skin and have been instrumental in mechanistic studies, detailed temporal characterization of IFNG and IL4 gene expression across different exposure protocols and anatomical sites remains insufficient (Tsatsou et al., 2012; Damayanti et al., 2023; Mayangsari et al., 2024; Rosidah et al., 2020; Wati et al., 2024). Similarly, human data on IFN γ and IL 4 expression in chronically photoexposed vs. photoprotected skin, and their relationship to clinical severity of photoaging and PIH, are still relatively sparse.

Second, the immunomodulatory effects of pineapple-derived formulations, including bromelain and peel extracts, have predominantly been investigated in systemic inflammatory or infectious disease models rather than in the context of UVB-induced cutaneous injury (Fitriyani & Septiani, 2025; Ali et al., 2020; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Amsia, 2020; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). Although these studies provide valuable insights into the ability of pineapple constituents to regulate cytokine production and immune cell activity, their applicability to chronic, low-grade cutaneous inflammaging should be interpreted with caution. The skin represents a highly specialized microenvironment that differs substantially from systemic compartments with respect to cellular composition, barrier function, and continuous exposure to external environmental stressors.

Third, formulation-specific parameters critically influence the efficacy of topical therapies. The physicochemical characteristics of pineapple peel extracts such as polarity, stability, and molecular weight distribution, together with properties of the gel base, including carbopol concentration, pH, and rheological behavior, collectively govern skin penetration, release kinetics, and local tolerability (Takeuchi et al., 2011; Servat-Medina et al., 2015; Damayanti et al., 2023; Mayangsari et al., 2024; Rosidah et al., 2020).

However, many existing studies focus on isolated aspects, such as physicochemical stability or antioxidant activity, without integrating comprehensive evaluations of in vitro skin permeation, in vivo efficacy, and safety within a unified experimental framework.

Fourth, the dualistic view of IFN γ as purely "harmful" and IL 4 as purely "beneficial" is an oversimplification. IFN γ is essential for host defense and tumor immunosurveillance (Oxenkrug, 2011; Ng et al., 2023; Castro et al., 2018), while IL 4 and IL 13 can contribute to pathological fibrosis and atopic inflammation under certain conditions (Wynn & Vannella, 2022; Shankar et al., 2022; Gadani et al., 2012). The therapeutic goal in photoaging is not complete suppression of IFN γ or unrestrained enhancement of IL 4, but rather a controlled recalibration of their balance toward effective resolution of inflammation without compromising protective immunity or inducing undesirable fibrotic responses. Carefully designed dose–response and time-course studies are needed to define the "window" in which pineapple peel topical extract exerts beneficial immunomodulatory effects without tipping the balance toward adverse outcomes.

Fifth, considerable inter-individual variability must be taken into account, as differences in baseline skin characteristics, genetic predisposition, systemic health, cumulative UV exposure, and cosmetic practices can markedly influence responses to both UVB radiation and topical interventions. Notably, individuals with darker skin phototypes, who are more prone to PIH, may display distinct IFN-γ and IL-4 expression patterns compared with those of lighter phototypes (Baumann & Saghari, 2009; Yusharyahya, 2021; Kaufman et al., 2018). Personalized regimens, potentially guided by non-invasive biomarkers (e.g. tape-stripping cytokine profiling, high-resolution imaging of dermal ECM), may ultimately be required to optimize outcomes. Despite these limitations, the convergence of current evidence supports several key hypotheses that can guide future research.

IFN γ and IL 4 as Biomarkers and Therapeutic Targets in Photoaging

Longitudinal investigations in both animal models and human cohorts assessing IFN γ and IL 4 expression in response to controlled UVB exposure, with and without therapeutic interventions, would help clarify their utility as biomarkers of disease progression and treatment response (Tsatsou et al., 2012; Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Mo et al., 2022; Shankar et al., 2022; Gadani et al., 2012; Damayanti et al., 2023; Mayangsari et al., 2024; Castro et al., 2018).

Integrating these molecular analyses with clinical endpoints such as wrinkle depth, skin elasticity, and pigmentation, and with histological and biochemical parameters, including collagen density, MMP expression, and markers of oxidative damage, would enable a more comprehensive understanding of how modulation of these cytokines translates into structural and functional alterations in the skin.

Mechanistic Studies on Pineapple Peel Extract in UVB Models

Controlled experiments using standardized pineapple peel extracts (with defined phenolic and bromelain content) applied to UVB-irradiated rodent skin could quantify changes in IFNG and IL4 mRNA and protein levels, along with downstream mediators (TNF α, IL 1β, IL 6, IL 10, MMPs) (Fitriyani & Septiani, 2025; Ali et al., 2020; Hikal et al., 2021; Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Amsia, 2020; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Wiyono & Yuliati, 2020; Fadhila et al., 2024; Thomas et al., 2023). Such studies should include dose–response and time-course analyses, and compare whole extracts to isolated bromelain and phenolic fractions to determine whether synergistic effects exist.

Comparative Studies with Other Botanicals and Standard Treatments

Pineapple peel topical extract should be evaluated alongside other plant-based anti-photoaging agents (e.g. tomato extract, black garlic, butterfly pea flower) (Widiyanto et al., 2023; Wahyono, 2013; Waslihati et al., 2019) and established actives (e.g. retinoids, vitamin C, niacinamide) to position its relative efficacy and safety. Combination regimens may yield additive or synergistic benefits such as pairing pineapple peel topical extract with sunscreens or antioxidants to address both prevention (UV blocking) and repair (immunomodulation and ECM restoration) (Baumann & Saghari, 2009; Adzhani et al., 2022; Tsatsou et al., 2012; Widiyanto et al., 2023; Wahyono, 2013; Waslihati et al., 2019; Kulka, 2013; Tantari, 2003; Hapsah et al., 2014).

Translational and Clinical Research

Following preclinical validation, early-phase clinical trials in individuals with mild to moderate photoaging could be conducted to evaluate the tolerability, patient-reported outcomes, and preliminary efficacy of pineapple peel–based topical formulations, incorporating non-invasive imaging modalities and biomarker-based endpoints (Baumann & Saghari, 2009; Yusharyahya, 2021; Adzhani et al., 2022; Papaccio et al., 2022; Kaufman et al., 2018). Stratification according to skin phototype and baseline susceptibility to PIH would provide valuable insights into differential treatment responses.

In summary, UVB-induced photoaging arises from a complex interplay of oxidative stress, persistent inflammation, ECM degradation, and pigmentary dysregulation. IFN γ and IL 4 represent key, functionally opposing nodes in this network, and their imbalance is likely a crucial driver of chronic, tissue-damaging responses. Pineapple peel extract, rich in antioxidants and bromelain, exhibits promising immunomodulatory and reparative properties that may favorably influence the IFN γ/IL 4 axis. When delivered via advanced topical systems, these bioactives can potentially reach relevant skin layers at sufficient concentrations to meaningfully impact photoaging pathways. Well-designed mechanistic, preclinical, and clinical studies are now needed to substantiate this therapeutic concept and translate it into evidence-based interventions for the prevention and treatment of UVB-induced skin aging.

3. CONCLUSSION

UVB-induced photoaging is primarily driven by oxidative stress and persistent low-grade inflammation, accompanied by a characteristic shift in the cutaneous cytokine milieu toward a Th1-dominant profile. Evidence suggests that UVB exposure upregulates IFNG expression and enhances IFN-γ activity while concurrently attenuating IL-4–mediated regulatory and reparative responses, thereby facilitating ECM degradation, wrinkle formation, and PIH (Ansary et al., 2021; Adzhani et al., 2022; Papaccio et al., 2022; Kaufman et al., 2018; Oxenkrug, 2011; Muzamil et al., 2021; Ng et al., 2023; Castro et al., 2018; Mo et al., 2022; Shankar et al., 2022; Gadani et al., 2012; Rosidah et al., 2020).

Pineapple peel, an underutilized by-product of Ananas comosus, is a rich source of antioxidants and bromelain, and has demonstrated immunomodulatory, anti-tyrosinase, and anti-hyaluronidase activities relevant to skin aging (Fitriyani & Septiani, 2025; Ali et al., 2020; Hikal et al., 2021; Varilla et al., 2021; Colletti et al., 2021; Chakraborty et al., 2021; Azizah et al., 2017; Amsia, 2020; Sornkayasita et al., 2024; Mousavi Maleki et al., 2023; Dela Vrianty et al., 2019; Jusri et al., 2019). Through its capacity to scavenge ROS and modulate inflammatory signaling pathways, pineapple peel extract is proposed to reduce IFNG expression and IFN-γ–driven inflammation while enhancing IL-4–mediated resolution and tissue repair. Accordingly, topical formulations containing standardized pineapple peel extract may counteract the dual effects of UVB-induced IFN-γ upregulation and IL-4 suppression, thereby contributing to the preservation of extracellular matrix integrity, reduction of pigmentary alterations, and attenuation of photoaging progression.

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