

## Protective roles of bromelain and flavonoids derived from pineapple peel against UV-induced skin cell damage: A systematic review

### Peran protektif bromelain dan flavonoid dalam kulit nanas terhadap kerusakan sel kulit akibat paparan sinar UV: Sebuah tinjauan sistematis.

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#### Abstract

Exposure to ultraviolet (UV) radiation is a significant cause of skin cell damage through DNA damage, oxidative stress, and the activation of inflammatory pathways. Skin protection generally relies on sunscreens, but increasing interest in natural agents has driven the exploration of bioactive compounds derived from agricultural waste such as pineapple (*Ananas comosus*) peel. Pineapple peel contains flavonoids and bromelain with antioxidant, anti-inflammatory, and photoprotective potential. This systematic review aims to assess the scientific evidence regarding the protective role of these compounds against UV-induced skin damage. A literature search was conducted using PubMed, ScienceDirect, ProQuest, and Google Scholar in accordance with PRISMA guidelines. The inclusion criteria were *in vitro*, *in vivo*, and formulation studies evaluating the effects of pineapple peel extracts on skin damage parameters, including oxidative stress, cytokine modulation, antioxidant enzymes, and sun protection factor (SPF). Eight studies met the criteria. The results showed that formulations containing pineapple peel extract, such as creams, gels, lotions, or biocomposites demonstrated SPF ranging from low to ultra levels of protection. Flavonoids play a role in scavenging free radicals, reducing reactive oxygen species (ROS), and modulating anti-inflammatory effects. Bromelain supports the viability of UV-exposed fibroblasts and enhances the effectiveness of synthetic sunscreens such as octyl methoxycinnamate. Pineapple peel shows strong potential as a source of natural active ingredients for photoprotection through the activity of flavonoids and bromelain. However, further research with standardized designs and clinical trials is needed before it can be applied in sustainable cosmetic and therapeutic formulations.

**Keywords:** Bromelain, flavonoid, pineapple peel, protective, UV radiation.

#### Abstrak

Paparan radiasi ultraviolet (UV) merupakan penyebab utama kerusakan sel kulit melalui mekanisme kerusakan DNA, stres oksidatif, dan aktivasi jalur inflamasi. Perlindungan kulit umumnya menggunakan tabir surya, namun meningkatnya minat terhadap agen alami mendorong eksplorasi senyawa bioaktif dari limbah pertanian, seperti kulit nanas (*Ananas comosus*). Limbah ini mengandung flavonoid dan bromelain yang memiliki potensi antioksidan, antiinflamasi, dan fotoprotektif. Tinjauan sistematis ini bertujuan untuk menilai bukti ilmiah mengenai peran protektif senyawa tersebut terhadap kerusakan kulit akibat UV. Pencarian literatur dilakukan melalui PubMed, ScienceDirect, ProQuest, dan Google Scholar sesuai pedoman PRISMA. Kriteria inklusi meliputi penelitian *in vitro*, *in vivo*, dan formulasi yang mengevaluasi efek kulit nanas terhadap parameter kerusakan kulit, termasuk stres oksidatif, modulasi sitokin, enzim antioksidan, dan nilai faktor perlindungan matahari (SPF). Delapan studi memenuhi kriteria. Hasil menunjukkan bahwa formulasi yang mengandung ekstrak kulit nanas, seperti krim, gel, losion, atau biokomposit meningkatkan nilai SPF dari proteksi rendah hingga ultra. Flavonoid berperan dalam penetralan radikal bebas, pengurangan spesies oksigen reaktif (ROS), dan modulasi efek antiinflamasi. Bromelain mendukung viabilitas sel fibroblas yang terpapar UV dan meningkatkan efektivitas tabir surya sintetis seperti *octyl methoxycinnamate*. Kulit nanas memiliki potensi tinggi sebagai sumber bahan aktif alami untuk fotoproteksi melalui efek flavonoid dan bromelain. Namun, penelitian lebih lanjut dengan desain yang terstandarisasi dan uji klinis diperlukan sebelum dapat diterapkan dalam formulasi kosmetik dan terapeutik berkelanjutan.

**Kata Kunci:** Bromelain, flavonoid, kulit nanas, protektif, radiasi UV.



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## Introduction

Ultraviolet (UV) radiation is a part of the electromagnetic spectrum invisible to the eye, which is divided into three main ranges, i.e., UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). The ozone layer successfully filters most UVC radiation, but UVA and UVB still penetrate the atmosphere and reach the Earth's surface, where they can cause severe damage to the skin. Continuous UV exposure has been proven to be one of the most important environmental risk factors in the development of skin cancer, both non-melanoma carcinoma and melanoma, with incidence rates continuing to increase in recent decades. In addition, excessive exposure also accelerates photoaging, which is characterized by skin thickening, wrinkling, collagen loss, and dilation of small blood vessels [1,2].

Skin damage from UV exposure involves complex biological mechanisms, including direct DNA damage, excessive production of reactive oxygen species (ROS), and activation of inflammatory signalling pathways [3,4]. Characteristic DNA lesions such as cyclobutene pyrimidine dimers (CPDs) and 6–4 photoproducts play an essential role in the genetic mutations underlying skin carcinogenesis [2], while ROS accumulation leads to oxidative stress and impairment of endogenous antioxidant defenses [3,4]. Activation of signalling pathways such as MAPK and NF- $\kappa$ B triggers the secretion of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ , which exacerbating tissue damage [5,6].

Protection against the harmful effects of UV radiation has traditionally relied on chemical and physical sunscreens. However, growing interest in the use of natural bioactive compounds is driving research into new candidates with antioxidant and anti-inflammatory properties, with the ability to reduce ROS, suppress inflammation, and support DNA repair. A natural-based approach not only offers health benefits but also opens up economic opportunities through the utilization of value-added agricultural waste [7].

Pineapple (*Ananas comosus*) peel, which can account for 25–60% of the total fruit weight, is one of the largest waste products from the pineapple processing industry and often causes environmental problems and high disposal costs. Interestingly, various studies have reported that this waste is rich in valuable bioactive compounds, including bromelain and flavonoids, which have significant pharmacological activities [8,9]. Bromelain, a proteolytic enzymes complex present in the pineapple peel, exhibits anti-inflammatory, immunomodulatory, and antioxidant activities, and has been shown in in vitro studies to suppress UV-induced cell death and modulate pro-inflammatory cytokine pathways. Meanwhile, flavonoids and other phenolic compounds, along with vitamin C, act through free radical scavenging mechanisms, activating antioxidant defense pathways such as Nrf2/ARE, and exerting anti-inflammatory and anti-melanogenesis effects. Evidence from recent reviews also emphasizes the role of flavonoids as prime candidates for mitigating UV-induced skin cell damage. Therefore, the combination of bromelain and flavonoids is considered highly potent for application in skin photoprotective formulations [4,8,10].

Although several preliminary studies support the photoprotective potential of pineapple peel, existing evidence remains fragmented and limited to in vitro and preclinical studies with varying extraction methods, dosages, and outcome measures. To date, no systematic review has comprehensively synthesized these findings across different study designs, nor has any study comparatively analysed the relative contributions of bromelain and flavonoids in mediating photoprotective effects. This situation suggests the need for a systematic review that synthesizes the evidence from existing research, combines findings from various studies, and assesses the methodological quality of existing studies. This study aimed to systematically review the scientific evidence regarding the protective role of bromelain and flavonoids derived from pineapple peel against UV radiation-induced skin cell damage.

## Methods

### Search Strategy

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted across multiple electronic databases, including PubMed, ScienceDirect, ProQuest, and Google Scholar. The search strategy was designed to identify studies investigating the protective roles of bromelain and flavonoids derived from pineapple peel against ultraviolet (UV)-induced skin cell damage. Boolean operators were applied using the following keywords: "bromelain," "flavonoids," "pineapple peel," "UV-induced damage," "oxidative stress," "photoprotection," and "skin cells."

### Data Extraction

The inclusion criteria for this systematic review were designed to encompass studies that investigated the protective effects of bromelain and flavonoids derived from pineapple peel against ultraviolet (UV)-induced skin cell damage. Eligible studies included preclinical research (in vitro or in vivo), formulation studies, clinical trials, and observational studies that employed a comparative or experimental design. Only studies reporting at least one of the following outcomes were included: reduction in UV-induced oxidative stress markers (e.g., ROS, MDA), modulation of pro-inflammatory cytokines (e.g., IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), attenuation of matrix metalloproteinase (MMP) activity, improvement of antioxidant defense systems (e.g., SOD, catalase, glutathione), or enhancement of skin barrier integrity and photoprotection (e.g., SPF). Studies were excluded if they were not directly related to UV-induced skin damage, if they reported only pharmacokinetic or chemical characterization data without biological outcomes, or if they were case reports, review articles, conference abstracts, editorials, or unpublished manuscripts. Additionally, studies lacking cellular, molecular, or clinical outcomes or those without a relevant comparator group were excluded to ensure the robustness of the findings. A manual search was conducted without the application of snowballing techniques. All identified studies were subsequently screened and evaluated in accordance with the predefined inclusion and exclusion criteria. No restrictions were applied regarding the year of publication to ensure comprehensive coverage of relevant evidence. However, the search was limited to articles published in English and Bahasa.

Data extraction was carried out independently by two reviewers. The extracted data included authors and year of publication, study location, study design, and total sample size. Population characteristics were documented according to the specific experimental model, including details of cell lines, animal species, or human participants. Information regarding the intervention was extracted, including dosage, formulation, and whether the active compound studied was bromelain or flavonoids derived from pineapple peel. The comparator group, follow-up duration, and outcome measures were also noted. Primary outcomes focused on indicators of UV-induced skin cell damage, such as oxidative stress parameters, cytokine modulation, inhibition of matrix metalloproteinases, enhancement of antioxidant activity, and photoprotection markers. Secondary outcomes included effects on skin barrier integrity, cell viability, histopathological changes, and safety profiles. Main findings of each study were summarized, alongside reported limitations, to highlight methodological constraints and potential sources of bias. Any discrepancies in data extraction were resolved through consensus with a third reviewer.

### Risk of Bias Assessment

We use TOXRTTool to assess the risk of bias. This tool is a questionnaire used to assess the reliability and potential risk of bias in toxicological studies, applicable to both in vivo and in vitro research. This tool enhances the Risk of Bias (RoB) procedure for systematic reviews by evaluating the methodological quality of studies based on the criteria established by Klimisch et al. (1997) [11]. This tool essentially comprises a list of evaluation criteria. The criteria are subdivided in five groups: 1) test substance identification, 2) test system characterization, 3) study design description, 4) study results documentation, and 5) plausibility of study design and data. The Reliability Categorization tool, a key component of TOXRTTool, classifies studies into four reliability categories: Category 1 (reliable without restrictions), which includes studies with high scores (in vivo 18-21, in vitro 15-18) and are considered fully reliable for inclusion; Category 2 (reliable with restrictions), which includes studies with moderate scores (in vivo 13-17, in vitro 11-14), deemed valid but requiring further relevance review; Category 3 (not reliable), which includes studies with significant flaws (in vivo <13, in vitro <11), generally unsuitable as key studies but may still serve in weight-of-evidence

approaches; and Category 4 (not assignable), which applies to studies with insufficient documentation, typically excluded as key studies but may provide supportive evidence. This systematic categorization ensures that only studies with adequate reliability are used for drawing conclusions, mitigating bias, and improving the overall validity of the review's findings. The assessment was carried out independently by two reviewers, and any discrepancies were resolved through discussion or consultation with a third reviewer to ensure reliability and objectivity.

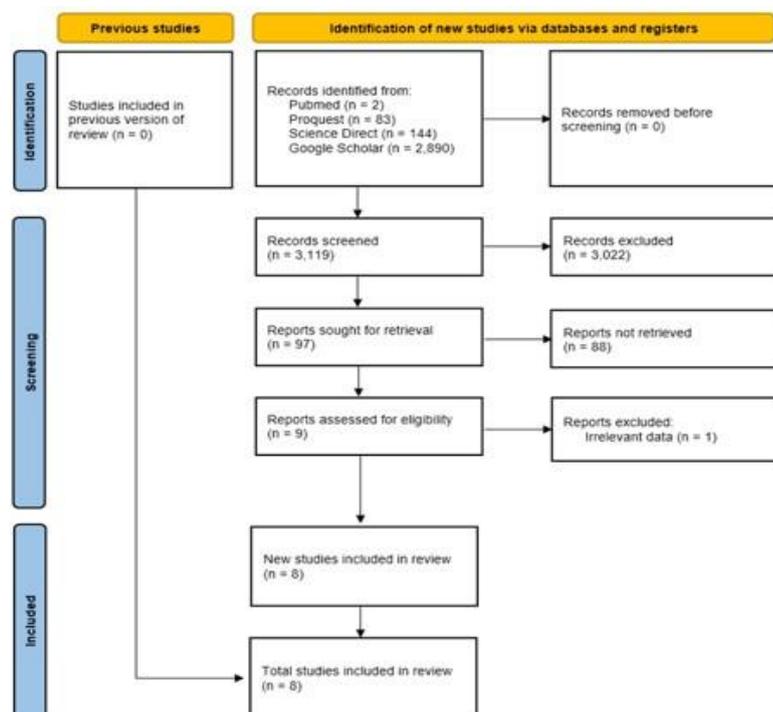
### Data Synthesis and Analysis

Data from the included studies were synthesized using a narrative approach. The outcomes of interest were summarized and presented qualitatively, with descriptive statistics provided where available. For preclinical and clinical findings, data were compiled and compared across studies to highlight similarities and differences in results. The synthesis focused on the reported protective effects of bromelain and pineapple peel-derived flavonoids against UV-induced skin cell damage, including reductions in oxidative stress markers, modulation of pro-inflammatory cytokines, inhibition of MMP activity, enhancement of antioxidant defense systems, and improvements in skin barrier integrity. Studies were categorized according to experimental models (in vitro, in vivo, or clinical) and type of compound investigated (bromelain, flavonoids, or combination). Data synthesis was performed independently by two reviewers and subsequently reviewed by a third reviewer to ensure accuracy and comprehensiveness.

## Results

### Data Searching

Initial search from database in this study identified 3,119 records. After screening, 3,022 records were excluded due to irrelevance or failure to meet the inclusion criteria. A total of 97 reports were sought for retrieval, of which 88 could not be retrieved, leaving 9 reports available for full-text eligibility assessment. Following detailed evaluation, 1 report was excluded due to irrelevant data, resulting in 8 studies that fulfilled the eligibility criteria and were subsequently included in this systematic review (**Figure 1**).



**Figure 1.** PRISMA flow diagram

### The Characteristics of Included Studies

We included 8 studies, comprising both in vitro and experimental designs, conducted primarily in Indonesia, with additional contributions from Thailand and Hawaii. Most investigations focused on the

evaluation of pineapple peel extracts or their formulations in relation to ultraviolet (UV)-induced skin protection. Several studies concentrated on sunscreen potential by assessing the sun protection factor (SPF) of creams or lotions formulated with pineapple peel extract. Damogalad (2013) employed an in vitro design to evaluate SPF of pineapple peel extracts at 200 ppm derived from different growing regions in Indonesia, reporting the combined effects of bromelain and flavonoids. Similarly, Harmonyzha (2023) tested a combination cream derived from pineapple and papaya peel extracts, with flavonoids identified as the primary active compounds, though no comparator group was provided. Karlina (2021) further examined pineapple peel extract cream formulations at varying concentrations (2%, 4%, and 8%), with base cream serving as a control, to determine their photoprotective efficacy. Lubis (2023) expanded the scope by investigating pineapple weevil waste (*Ananas comosus*) formulated into gel and lotion preparations containing 2% ethanol extract. This study emphasized both bromelain and polyphenols as active agents, with blank formulations used as comparators. Marissa (2025) provided one of the few in vivo models, utilizing nine albino rabbits (*Oryctolagus cuniculus*) to test bromelain cream alone and in combination with octyl methoxycinnamate (OMC). This study assessed SPF, dermal irritation, and ocular safety, with follow-up periods ranging from one hour to fourteen days.

Beyond formulation-based research, mechanistic studies were also identified. Mori (2023), using Detroit 551 fibroblast cells, demonstrated the cellular effects of bromelain powder (30 µg/mL) under UVB exposure, with untreated UVB-exposed cells serving as the comparator over 72 hours. Mutiah (2019) developed five different pineapple peel extract cream formulations (0%–20%), highlighting the roles of flavonoids and tannins in SPF determination and stability testing. In contrast, Wongkom (2016) from Thailand evaluated biocomposite preparations incorporating pineapple peel-derived carboxymethylcellulose and carboxymethyl chitosan, testing their SPF potential and comparing commercial versus pineapple-derived CMC. Overall, the evidence base illustrates diverse experimental approaches ranging from formulation-focused in vitro assays to limited in vivo animal studies, with bromelain and flavonoids consistently identified as key bioactive compounds responsible for UV-protective and antioxidant effects (Table 1).

The majority of studies employed in vitro or experimental designs, primarily focusing on formulation development and SPF evaluation rather than clinical efficacy. Only one study utilized an in vivo animal model (rabbits), and one study involved human skin fibroblast cells, underscoring the limited availability of translational or clinical data. Sample sizes were frequently not reported, reflecting the formulation-oriented nature of most studies, although specific experimental models included 551 fibroblast cells and 9 rabbits. The primary bioactive constituents investigated were bromelain, flavonoids, and other polyphenolic compounds, with some studies also incorporating tannins or biocomposite matrices to enhance formulation performance.

Comparator groups were heterogeneous and included base creams, blank formulations without active ingredients, untreated UV-exposed cells, different extract concentrations, and variations in raw material sources (e.g., pineapple from different geographic locations). Follow-up duration was generally not reported in most studies, reflecting their in vitro or formulation-based nature; however, one in vivo study assessed short-term SPF (24 hours) and dermal irritation over a period of up to 14 days. Overall, the findings highlight substantial heterogeneity in study design, intervention composition, comparator selection, and outcome measurement, with a strong emphasis on early-stage laboratory evidence and limited progression toward standardized clinical evaluation.

### The Outcomes of Included Studies

Across the included studies, the primary outcomes focused mainly on the photoprotective efficacy of pineapple peel-derived compounds, particularly as measured by sun protection factor (SPF), antioxidant activity, and cellular protective mechanisms. In vitro studies consistently demonstrated the potential of pineapple peel extract to enhance SPF. Damogalad (2013) reported ultra-protection SPF levels from pineapple peel extracts sourced from different regions of Indonesia, with bromelain and flavonoids identified as active contributors. Harmonyzha (2023) observed an SPF of 11.35 in a combined pineapple–papaya peel cream, accompanied by acceptable physical qualities, although the study did not isolate pineapple peel extract specifically. Similarly, Karlina (2021) showed that increasing concentrations of pineapple peel extract cream (2%, 4%, and 8%) were associated with higher SPF, suggesting a concentration-dependent effect. Lubis (2023) expanded the scope by testing pineapple weevil extracts formulated into gel and lotion preparations, which demonstrated SPF of 30.15 and 42.23, respectively, both falling within the ultra-protection category. Beyond SPF assessment, antioxidant and photoprotective activities were evaluated in vivo by Marissa (2025), who demonstrated that bromelain, especially in combination with octyl methoxycinnamate (OMC), enhanced both

antioxidant function and SPF without causing dermal or ocular irritation. These findings highlight the dual potential of bromelain-based formulations as both photoprotective and antioxidant agents, although the study was limited by its small rabbit sample size and lack of human data.

At the cellular level, Mori (2023) reported that bromelain protected Detroit 551 fibroblasts from UVB-induced cell death and unexpectedly increased TNF- $\alpha$  mRNA expression, contrary to the original hypothesis. Mutiah (2019) focused on microemulsion formulations of pineapple peel extract, finding stable physicochemical properties and consistent SPF performance across varying extract concentrations. In contrast, Wongkom (2016) demonstrated modest SPF potential (2.47) in pineapple peel-derived biocomposites, though the results suggested supplementary roles in UV protection rather than standalone efficacy. Collectively, these findings indicate that pineapple peel-derived bromelain and flavonoids contribute to both photoprotection and antioxidant defense, with outcomes ranging from enhanced SPF in formulations to direct cellular protection against UV-induced damage (**Table 2**).

The photoprotective mechanisms of bromelain and flavonoids derived from pineapple peel are primarily mediated through a combination of UV absorption, antioxidant, and anti-inflammatory activities. Flavonoids and phenolic compounds act as natural UV filters by absorbing ultraviolet radiation while simultaneously scavenging reactive oxygen species (ROS), thereby reducing oxidative stress induced by UV exposure. Bromelain contributes by modulating inflammatory responses and promoting cellular repair pathways, enhancing skin resilience against UV-induced damage. Additionally, synergistic interactions between bioactive compounds and conventional UV filters (e.g., OMC) further improve photoprotective efficacy. Formulation factors, such as microemulsions or biocomposites, also influence the effectiveness of these compounds by enhancing their stability, dispersion, and UV-filtering capacity, although their contribution may vary depending on the delivery system rather than concentration alone.

Several studies included in this review did not exclusively utilize pineapple peel as the primary source of bioactive compounds, which may limit the specificity and comparability of the findings. The study by Harmonyzha (2023) employed a combination of pineapple and papaya peel extracts; therefore, the specific contribution of pineapple peel to the observed photoprotective effects could not be clearly isolated. Similarly, Lubis (2023) utilized pineapple weevil ethanol extract, which originates from the inner core (a residual part of the pineapple flesh) rather than the peel, potentially resulting in a different phytochemical profile and limiting direct comparability with peel-based studies. The study by Marissa (2025) investigated bromelain derived from pineapple stems in an isolated form, which, although relevant as a pineapple-derived compound, does not fully represent the complex matrix of bioactive constituents present in pineapple peel. Furthermore, Mori (2023) used extracts from multiple parts of the pineapple (crown, flesh, skin, and stem), making it difficult to attribute the observed biological effects specifically to pineapple peel-derived compounds.

### Risk of Bias

Risk of bias was assessed by TOXRTTool with scores ranging from 12 to 18. Studies by Damogalad (2013), Lubis (2023), Mutiah (2019), and Harmonyzha (2023) scored 12 or 13, indicating that they are reliable with restrictions, suggesting that while these studies provide valuable data, they may have limitations such as incomplete controls or missing statistical details. On the other hand, Marissa (2025), Mori (2023), and Wongkom (2016) scored 15 to 18, indicating they are reliable without restrictions, meaning their methodologies are robust and do not present significant limitations that would affect the validity of their results. Overall, the studies show a high level of reliability, though some may require further validation or refinement in certain areas (**Table 3**).

**Table 3.** Risk of bias

Author, Year	Score	Interpretation
Damogalad, 2013	13	Reliable with restrictions
Harmonyzha, 2023	12	Reliable with restrictions
Karlina, 2021	12	Reliable with restrictions
Lubis, 2023	13	Reliable with restrictions
Marissa, 2025	18	Reliable without restrictions
Mori, 2023	15	Reliable without restrictions
Mutiah, 2019	13	Reliable with restrictions
Wongkom, 2016	15	Reliable without restrictions

**Table 1.** Study characteristics

Author, Year	Study Design	Intervention	Comparator	References
Damogalad, 2013	In vitro	Pineapple peel extract	Different pineapple growing sites	[12]
Harmonyza, 2023	Experimental Study	A combination of pineapple and papaya peel extract cream	N.R.	[13]
Karlina, 2021	Experimental Study	Pineapple peel extract cream	Base Cream	[14]
Lubis, 2023	Experimental Study	Pineapple weevil ethanol extract formulated into gel and lotion preparations	Blank formulations	[15]
Marissa, 2025	Experimental study	Bromelain cream only and in combination with OMC	Cream base and OMC	[4]
Mori, 2023	In vitro	Bromelain powder	UVB exposure without bromelain treatment	[10]
Mutiah, 2019	In vitro	Pineapple peel extract cream	N.R.	[16]
Wongkom, 2016	In vitro	Preparation of biocomposites using carboxymethyl chitosan and pineapple peel carboxymethylcellulose.	Commercial CMC vs. pineapple peel CMC	[11]

CMC = Carboxymethyl Cellulose; N.R. = Not Reported; OMC = Octyl Methoxycinnamate; UVB = Ultraviolet B.

**Table 2.** Outcomes of included studies

Author, Year	Main Findings	Mechanisms	Limitations
Damogalad, 2013	The level for Pemalang honey pineapple extract is 286.24 ( $\mu\text{g/ml}$ ); Subang honey pineapple extract is 198.00 ( $\mu\text{g/ml}$ ); Purbalingga honey pineapple extract is 351.10 ( $\mu\text{g/ml}$ ); and all three pineapple extracts belong to the SPF Ultra Protection category.	High SPF is attributed to flavonoids and phenolics that absorb UV radiation and scavenge ROS.	The study lacks clinical tests and has limited test parameters.
Harmonyza, 2023	The combination cream preparation has a pH of 4.58, a spread power of 9.02 cm <sup>2</sup> , and an SPF of 11.35.	Photoprotection arises from synergistic antioxidant and UV-absorbing effects of combined bioactive compounds.	The study does not explicitly use pineapple peel extract, lacks clinical tests, limited test parameters.
Karlina, 2021	Pineapple skin extract cream 2% has shown a minimal SPF, and increasing the concentration to 4% and 8% demonstrates higher SPF	Increased SPF reflects a dose-dependent enhancement of UV absorption and antioxidant activity.	The study lacks clinical tests and has limited test parameters
Lubis, 2023	Pineapple weevil extract gel has an SPF of 30.15 (ultra protection), and the lotion has an SPF of 42.23	Bromelain and antioxidants contribute to UV filtering and anti-inflammatory protection against skin damage.	This study was a lab-based testing with a minimum parameter
Marissa, 2025	Bromelain and OMC together demonstrated the most excellent SPF in terms of photoprotection, as determined by SPF, showing increased photoprotective efficacy.	Bromelain enhances anti-inflammatory repair while OMC provides UVB absorption, resulting in synergistic photoprotection.	The study was preclinical nature, using a small number of rabbits, the absence of human testing, and limited formulation dose-response evaluation.
Mori, 2023	Bromelain raised the amount of TNF- $\alpha$ mRNA expression and shielded skin cells from UV-dependent cell death.	Bromelain may promote cell survival by modulating stress-response pathways despite increased TNF- $\alpha$ expression.	The study's hypothesis on reducing TNF- $\alpha$ expression was not supported by the results.

Mutiah, 2019	The study's findings demonstrated that the pineapple peel extract microemulsion produced outcomes that satisfied the requirements and that changes in the extract's content had no effect on the microemulsion preparation's SPF.	SPF stability is likely influenced more by formulation characteristics than by extract concentration alone.	The study was limited to in vitro SPF testing only, did not include in vivo or human skin testing.
Wongkom, 2016	The biocomposites prepared from pineapple peel CMC showed UV protection potential with an SPF of 2.47	UV protection is mediated by combined light scattering and limited UV absorption from biocomposite materials.	The study did not include in vivo trials, and the SPF is relatively low compared to typical sunscreen products

CMC = Carboxymethyl Cellulose; OMC = Octyl Methoxycinnamate; SPF = Sun Protection Factor; TNF- $\alpha$  = Tumor Necrosis Factor Alpha; UV = ultraviolet.

## Discussion

This systematic review synthesizes evidence from eight studies investigating the photoprotective potential of pineapple (*Ananas comosus*)-derived compounds, particularly bromelain and flavonoids, against UV-induced skin damage. The findings reveal that these compounds exert photoprotective effects through antioxidant activity and UV absorption, but the evidence is characterized by substantial methodological heterogeneity that complicates direct comparisons and definitive conclusions.

One of the most striking observations from this review is the wide range of SPF reported across studies, from “low” to “ultra-protection” [12,17]. This variability is not merely a reflection of differing extract potencies but rather stems from fundamental methodological differences that must be critically examined to interpret the findings accurately.

The extraction technique significantly influences the phytochemical profile and, consequently, the photoprotective efficacy. Damogalad et al. (2013) employed maceration with 96% ethanol for 5 days, yielding an extract with minimal SPF when formulated into creams at 2-8% concentrations [12]. In contrast, Lubis et al. (2023) also used 96% ethanol maceration but extracted from pineapple *weevil* rather than peel, achieving ultra-protection SPF [17]. This dramatic difference suggests that the source material (peel vs. weevil) may contain distinct phytochemical profiles, with the weevil potentially possessing higher concentrations of bioactive compounds. Notably, the study by Mutiah et al. (2019) demonstrated that even with ultrasonic-assisted extraction, which generally enhances yield, the resulting microemulsions containing up to 20% pineapple peel extract achieved only minimal SPF, reinforcing that source material may be more critical than extraction efficiency [16].

The formulation vehicle appears to play a crucial role in determining final SPF. Lubis et al. (2023) directly compared gel and lotion formulations containing the same pineapple weevil extract concentration (2%) and found that lotions achieved a substantially higher SPF compared to gels [15]. This difference may be attributed to the lotion's oil-in-water emulsion system, which can enhance the dispersion and stability of active compounds, leading to more uniform UV absorption. In contrast, Wongkom et al. (2016) developed a biocomposite system using pineapple peel carboxymethylcellulose with a crosslinker (ferulic acid) and achieved only modest SPF, even with the inclusion of synthetic UV filters (TiO<sub>2</sub> and PBSA). This finding suggests that while the biocomposite matrix successfully incorporated the active ingredients, the overall UV protection remained limited, potentially due to suboptimal release characteristics or insufficient concentration of UV-absorbing compounds [11].

Karlina et al. (2021) provided the clearest evidence of concentration-dependent activity within a single formulation type, demonstrating that increasing pineapple peel extract concentrations from 2% to 8% in cream formulations resulted in progressively higher SPF [14]. Similarly, Mutiah et al. (2019) observed a positive correlation between extract concentration and SPF in microemulsion preparations [16]. However, the magnitude of increase remained modest, suggesting that crude peel extract alone may have inherent limitations in achieving high SPF, regardless of concentration. This stands in contrast to the findings of Lubis et al. (2023), where weevil extract at comparable concentrations (2%) produced ultra-protection SPF, further supporting the hypothesis that the weevil contains a superior phytochemical profile for UV protection [31].

The most compelling evidence for achieving high SPF comes from studies combining pineapple-derived compounds with conventional UV filters. Marissa et al. (2025) demonstrated that a cream containing 3% bromelain combined with 5% octyl methoxycinnamate (OMC) achieved a high SPF *in vitro* and *in vivo*, representing a substantial improvement over formulations containing either bromelain alone or OMC alone. This synergistic effect suggests that bromelain not only contributes its own UV-absorbing properties but also enhances the performance of synthetic filters, possibly through improved formulation stability or complementary antioxidant activity [4]. The study by Harmonyzha et al. (2023), which combined pineapple peel with papaya peel extracts, achieved a moderate SPF, further illustrating that combinations of natural extracts can yield moderate protection. However, the inability to isolate the specific contribution of pineapple peel in this combination limits the conclusions that can be drawn about its independent efficacy [13].

The study by Mori et al. (2023) yielded an unexpected but potentially significant finding: bromelain treatment (30 µg/mL) of UVB-exposed Detroit 551 fibroblasts increased TNF-α mRNA expression while simultaneously protecting cells from UV-induced death. This finding challenges the simplistic assumption that photoprotection must correlate with reduced inflammation and requires a more nuanced interpretation of TNF-α's role in UV-exposed skin [10].

TNF- $\alpha$  is traditionally recognized as a pro-inflammatory cytokine; however, a substantial body of literature demonstrates that its effects are context-dependent. In the setting of acute UV exposure, TNF- $\alpha$  can exert paradoxical protective functions through its interaction with TNF receptor 2 (TNFR2). Activation of TNFR2 triggers downstream signaling cascades, particularly the nuclear factor kappa-B (NF- $\kappa$ B) pathway, which promotes cell survival by upregulating anti-apoptotic genes and suppressing the activation of caspases [18]. In the context of skin biology, Candel et al. (2014) further established that TNF- $\alpha$  signaling through TNFR2 protects against oxidative stress-induced inflammation, maintaining skin homeostasis [19].

Therefore, the increased TNF- $\alpha$  expression observed by Mori et al. (2023) following bromelain treatment may represent an adaptive stress response that enhances cellular resilience against UV-induced damage [10]. Rather than simply reducing inflammation, bromelain may prime skin cells by upregulating survival pathways, enabling them to better withstand UV exposure. This interpretation aligns with the observed increase in cell viability despite elevated TNF- $\alpha$  levels. However, it is important to note that the study by Marissa et al. (2025) did not observe TNF- $\alpha$  modulation in their *in vivo* rabbit model, where bromelain cream was applied topically. This discrepancy may reflect differences between acute exposure in isolated fibroblasts versus the more complex tissue environment of intact skin, where multiple cell types and regulatory mechanisms modulate inflammatory responses [4].

The contrasting hypotheses proposed by Mori et al. (2023), that bromelain either induces a protective TNF- $\alpha$ -mediated survival response or, alternatively, acts as a foreign substance that inadvertently triggers inflammation, highlight the need for further mechanistic studies [10]. Future research should employ selective receptor antagonists (e.g., TNFR2 blockers) or gene silencing approaches to directly test whether the observed TNF- $\alpha$  upregulation is causal to bromelain's protective effects. Additionally, time-course studies examining the kinetics of TNF- $\alpha$  expression relative to cell death would help clarify whether TNF- $\alpha$  elevation precedes or follows the initiation of survival pathways.

Beyond SPF, several studies evaluated the physicochemical properties of their formulations, providing important insights into product development considerations. Karlina et al. (2021) reported that creams containing pineapple peel extract met basic requirements for homogeneity, pH, and adhesion, with the pH values falling within the physiologically compatible range for topical application [14]. Lubis et al. (2023) similarly confirmed that both gel and lotion formulations maintained appropriate pH, spreadability, and adhesion properties [15]. These findings suggest that pineapple-derived extracts can be successfully incorporated into stable topical formulations without compromising basic quality parameters [15].

Marissa et al. (2025) conducted the most comprehensive stability evaluation, including freeze-thaw cycling tests over six cycles. Their results showed that while physical appearance and viscosity remained stable, pH values exhibited significant changes over time, indicating potential sensitivity to temperature fluctuations. This finding underscores the importance of formulation optimization, particularly for products containing enzymes like bromelain, which may be susceptible to degradation under stress conditions. Importantly, this study also included dermal and ocular irritation tests on rabbits, demonstrating that bromelain-based creams (3%) did not induce erythema, edema, or corneal irritation, providing preliminary safety data that is absent from the other included studies [4].

The strengths of this body of evidence include the consistent identification of flavonoids and bromelain as key bioactive compounds responsible for photoprotective activity, the demonstration of concentration-dependent effects across multiple studies, and the promising evidence of synergistic effects between natural extracts and synthetic UV filters. However, several critical limitations must be acknowledged.

First, the methodological heterogeneity identified across studies, including differences in source material (peel vs. weevil vs. stem), extraction methods (maceration vs. ultrasonic-assisted), solvents (various ethanol concentrations), and formulation types (creams, gels, lotions, microemulsions, biocomposites) precludes meta-analysis and limits the ability to draw definitive conclusions about the optimal approach for maximizing photoprotective efficacy. Second, the geographic concentration of research (predominantly Indonesia) and the use of specific pineapple cultivars raise questions about generalizability to other regions and varieties. Third, the lack of standardized outcome measures beyond SPF, particularly regarding anti-inflammatory mechanisms, DNA repair, and long-term safety, represents a significant gap. The study by Harmonyzha et al. (2023) is particularly limited in this regard, as the combination of pineapple and papaya extracts makes it impossible to attribute effects specifically to pineapple peel [13]. Fourth, with the exception of Marissa et al. (2025), none of the included studies conducted *in vivo* testing or safety assessments, leaving significant gaps in the translational evidence base [4]. Finally, the absence of clinical trials on human skin means that the efficacy and safety of these formulations in real-world settings remain unproven.

## Conclusions and Future Directions

This review suggests the photoprotective potential of pineapple peel extract, which may be attributed to bioactive compounds such as flavonoids and bromelain that provide antioxidant and UV-filtering effects. However, the current evidence remains preliminary, as it is largely derived from in vitro studies with considerable methodological heterogeneity in extraction and formulation approaches. These limitations along with a lack of clinical trials and long-term safety assessments, indicate that future research should focus on standardized extraction protocols and comparative evaluation of flavonoid- and bromelain- rich fraction. In addition, studies using advanced models, such as 3D reconstructed skin (skin equivalent), followed by rigorous clinical trials, are required to validate and translate these promising findings into practical applications.

## Conflict of Interest

The authors declare that there are no conflicts of interest related to this work. No financial or personal relationships exist that could have influenced the objectivity of the study, the interpretation of the results, or the preparation of the manuscript.

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