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REVIEW

Regulatory Mechanisms of Natural Active Ingredients and Compounds on Keratinocytes and Fibroblasts in Mitigating Skin Photoaging

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Background: The mechanism underlying skin photoaging remains elusive because of the intricate cellular and molecular changes that contribute to this phenomenon, which have yet to be elucidated. In photoaging, the roles of keratinocytes and fibroblasts are vital for maintaining skin structure and elasticity. But these cells can get photo-induced damage during photoaging, causing skin morphological changes. Recently, the function of natural active ingredients in treating and preventing photoaging has drawn more attention, with researches often focusing on keratinocytes and fibroblasts.

Methods: We searched for studies published from 2007 to January 2024 in the Web of Science, PubMed, and ScienceDirect databases through the following keywords: natural plant, natural plant products or phytochemicals, traditional Chinese Medicine or Chinese herbal, plant extracts, solar skin aging, skin photoaging, and skin wrinkling. This review conducted the accordance of Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Results: In total, 87 researches were included in this review (Figure 1). In keratinocytes, natural compounds may primarily regulate signal pathways such as the NF-κB, MAPK, PI3K/AKT, and Nrf2/ARE pathways, reducing inflammation and cellular damage, thus slowing skin photoaging. Additionally, in fibroblasts, natural active ingredients primarily promote the TGF-β pathway, inhibit MMPs activity, and enhance collagen synthesis while potentially modulating the mTOR pathway, thereby protecting the dermal collagen network and reducing wrinkle formation. Several trials showed that natural compounds that regulate keratinocytes and fibroblasts responses have significant and safe therapeutic effects.

Conclusion: The demand for natural product-based ingredients in sunscreen formulations is rising. Natural compounds show promising anti-photoaging effects by targeting cellular pathways in keratinocytes and fibroblasts, providing potential therapeutic strategies. However, comprehensive clinical studies are needed to verify their efficacy and safety in mitigating photoaging, which should use advanced pharmacological methods to uncover the complex anti-photoaging mechanisms of natural compounds.

Keywords: photoaging, natural ingredients, natural compounds, keratinocytes, fibroblasts

Introduction

Skin photoaging is marked by the emergence of skin alterations, such as wrinkles, laxity, roughness, pigmentation changes, and skin tumors resulting from exposure to ultraviolet radiation (UVR).[1] The surplus of UV energy may result in the premature aging of the skin, intensifying the modifications brought about by physiological chronologic aging.[2] UVR can be categorized into three distinct kinds based on the wavelength: UVC, UVB, and UVA. In the ozone layer, UVC is totally taken in, leaving UVA and UVB as the main factors accountable for the onset of photoaging.[3]

UVA, accounting for 90–95% of the total UVR, has an extraordinary ability to penetrate the dermis of the skin.[4] It infiltrates the dermis, reaching cellular constituents within subcutaneous tissue regions, including fibroblasts, endothelial cells and Langerhans cells, boosting the activation of Matrix Metalloproteinases (MMPs). Consequently, this cascade

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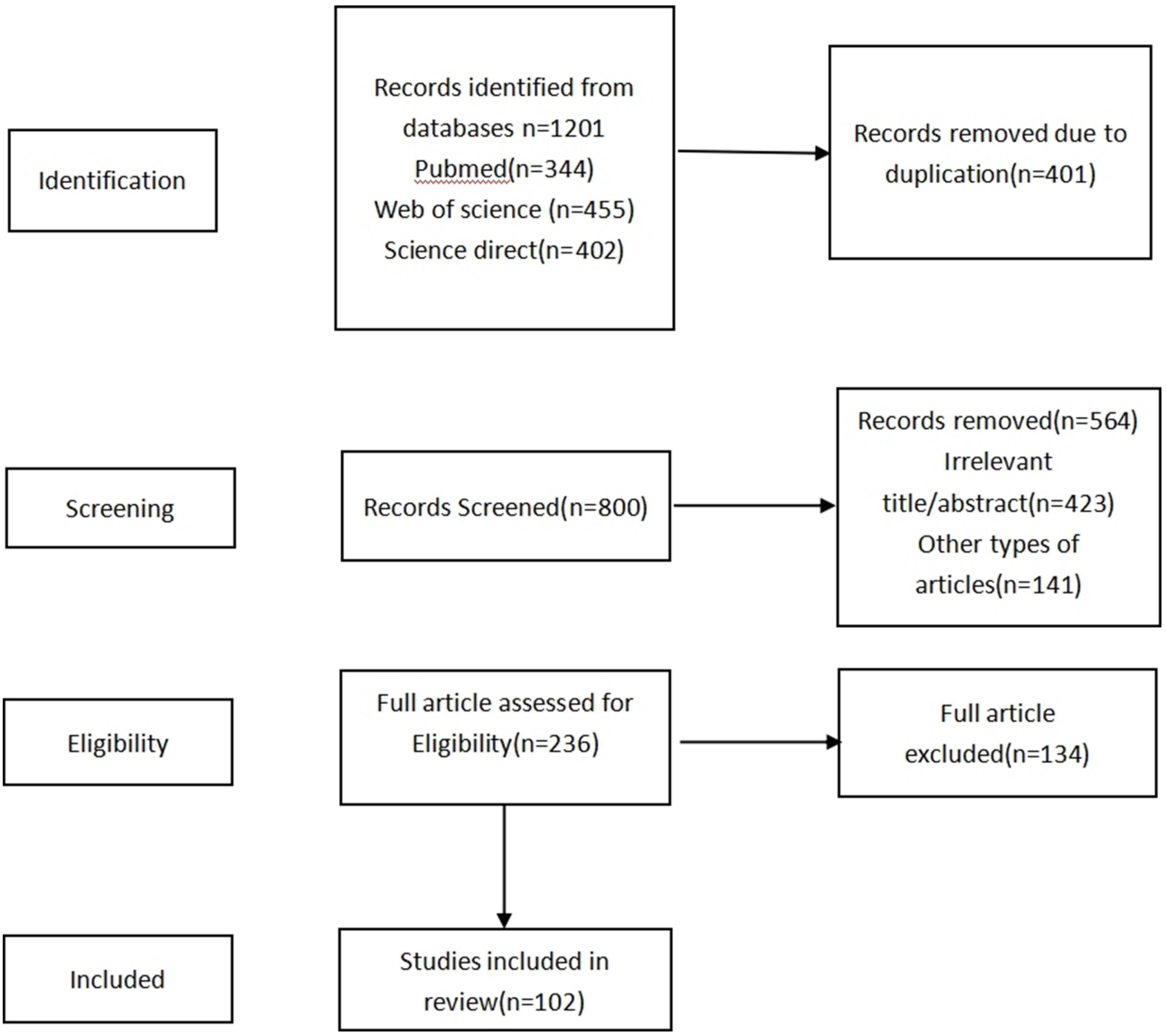

Figure 1 The PRISMA flowchart of the selection procedures for the included studies.

triggers the degradation of collagen and elastic fibers, causing disorder in the skin structure.[5] That type of damage poses a significant challenge in terms of restoration, exerting prolonged effects on dermal tissue and ultimately manifesting as overt signs of photoaging, such as skin laxity, sagging and excessive proliferation of wrinkles.[6] UVB contributes to photoaging by directly harming the DNA, causing mutations and cellular dysfunction. This causes the emerging of ROS, oxidative stress, inflammation and degradation of collagen and elastin fibers. This process accelerates skin photoaging, resulting in uneven pigmentation, loss of elasticity, and wrinkles. UVB also activates pathways that result in the increased expression of MMPs, enzymes that break down the structural proteins of the skin, further exacerbating signs of aging.[7] Meanwhile, Pourang et al found that human skin is affected not only by ultraviolet radiation but also by the wavelength of visible light emitted by sunlight, electronic devices and light-emitting diodes. The visible light wavelength is related to the photoaging process. Different visible wavelengths of light may have both beneficial and deleterious effects on photoaging through interactions with specific photoreceptors, ROS production, and other photo-mediated responses.[6]

The molecular mechanism mainly involves DNA destruction, oxidative stress, inflammatory response, changes in collagen structure, and cell apoptosis The major signaling pathways of skin photoaging are mainly divided into mitogen-

activated protein kinase (MAPK) signaling pathway, nuclear factor kappa-B(NF- κ B) signaling pathway, nuclear factor erythroid 2-related factor 2 (Nrf 2) / antioxidant-response element (ARE) signaling pathway, and transforming growth factor-β (TGF-β) signaling pathways, which are crisscrossing and associated with each other.

Recently, there has been increasing attention to the natural compounds in photoaging therapy and the identification of revealing their underlying mechanisms in photoaging. The natural sources of polyphenols include *tea, cocoa, grape/wine, soy, pomegranate, and Polypodium leucotomos*. The non-phenolic phytochemicals include *carotenoids, caffeine and sulphoraphance*. Plant-derived natural compounds could be potential sources for the development of effective medications for photoaging as their formulations and therapeutic principles are defined by multi-ply gene targets, ingredients and signaling pathways.

This review compile the regulatory mechanisms of natural compounds derived from plants in the photoaging responses of fibroblasts and keratinocytes.

Data Acquisition Method

This review was prepared according to the PRISMA guidelines. We included papers assessing the effect of plant natural compounds on the response of fibroblasts and keratinocytes to photoaging. The exclusion criteria were as follows: (a) papers of natural compounds from non-natural products and non-herbal materials; (b) grey literature, commentaries, editorials, and review articles; and (c) duplicate studies and irrelevant articles.

Results

Finally, a total of 87 studies were included in this review, as indicated in the flowchart (Table 1). The data were summarized and sorted according to regulatory mechanisms and compounds. Plant compounds include phenolics, alcohols, terpenoids, and phenolic acids, which offer diverse bioactivities such as antioxidant and anti-inflammatory activities. Different plant compounds have been found to participate in the occurrence and development of photoaging in keratinocytes and fibroblasts through various cell factors and signaling pathways.

Keratinocytes Response in Photoaging

Keratinocytes make up 95% of the mass of human epidermis cells and have crucial functions in skin physiology.[8] Different stimuli like UV can promote the expression of pro-inflammatory cytokines in keratinocytes. In contrast to genetically induced skin aging, skin photoaging reduces the activity of keratinocytes in the epidermis, slows the refresh rate and weakens epidermal function, leading to skin dryness and peeling.[9] Keratinocytes are the main skin cells responsible for cytokines.[10] Thus, they may activate the p38/JNK pathway after UVB irradiation. After UVB irradiated, keratinocytes may create some pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α.[11] UVB-induced inflammation starts with the interaction of different components of the IL-1 complex.[12] Severe ultraviolet irradiation causes in the excretory of one additional pro-inflammatory cytokine, and after about 12 h UVB irradiation its serum level reaches its peak.[13] A total of 29 articles published on keratinocytes. Polyphenols and flavonoids accelerate the regeneration and repair of keratinocytes by restraining the production of inflammatory cytokines and facilitating the synthesis of growth factors when acting on keratinocytes. Many natural compounds regulate pathways, such as MAPK, Nrf2/ARE, NF-κB and PI3K/AKT pathways.

Fibroblasts Response in Photoaging

Human dermal fibroblasts (HDFs) are the mainly cells which are responsible for the synthesis of white fibers that maintain flexible ability in the dermis.[14] In the dermis, HDFs are the main cell type which regulate ECM, collagen production, and wound healing.[15] HDFs play a key role in preventing skin photoaging and maintaining the structure and normal function of the skin, so they are essential for skin repair and regeneration.[16] Apart from their role in UVB-induced inflammation, cytokines can produce distinguished types of MMPs by stimulating fibroblasts. After UVB irradiation, IL-6 expression may lead to elevated MMP 1 and MMP 9 expression, resulting in a decrease in EMC.[17] In the skin dermis, if fibroblasts is reduced, collagen and elastin's synthesis will slow and breakdown will accelerate.[18] The key differences in histology between UVR-induced aging and naturally aged skin are excessive accumulation of

Table 1 Effects of Natural Active Ingredients and Compounds on Keratinocytes and Fibroblasts for Skin Photoaging

Plant Name	Active ingredient	Class	Solvent	In vivo	In vitro	Effects on Keratinocytes and Fibroblasts Response	Regulatory Mechanism	Ref
Mixture of marigold and rosemary	Lutein and carnosic acid	Polyphenols	Hexane and ethanol	Swiss Albino mice	HaCaT	IL-1, IL-6, IL-10, IL-12, TNF-α, COX-2,8-OHG, ROS, MMP↓ SOD, CAT, GPx↑	NF-κB ↓	[65]
Leaves of Coffea arabica	Caffeic acid	Polyphenols	Methanol		HFFs	ERK, JNK, p38↓	MAPK↓	[66]
Michelia alba	M. alba leaves extract	Polyphenols	Ascorbic acid		HFFs	MMP-1,MMP-3,MMP-9,p-JNK, p-ERK, c-Fos, c-Jun, AP-1↓ hyaluronic acid↑	MAPK↓	[67]
Blueberries	Resveratrol	Polyphenols	Methanol	ICR mice	HaCaT	caspase-3, caspase-9, MMP-1, MMP-9, MMP-3, ROS, L-6, TNF-α, P-JNK, P-ERK1/2, P-P38, MAPK↓ GSSH, SOD, GPX-4, HO-1, Nrf2↑	Nrf2↑ MAPK↓	[68]
Quercus acuta	Ellagic acid	Polyphenols	Ethanol		HaCaT	ROS, MDA, caspase-3, Keap-1↓ Bcl-2/Bax, HO-1, SOD, Nrf2↑	Keap1–Nrf2 ↑	[69]
Adult aloe shoot extract	Aloe polysaccharides	Polyphenols	Ethanol		NHDFs	ROS, MMP-1, IL-6↓ TGF-β1↑	TGF-β1↑	[70]
Green tea	Gallic acid	Polyphenols	Formaldehyde	Hairless mice	NHDFs	ROS, IL-6, MMP-1, AP-1, c-Jun, c-Fos↓ type I procollagen, TGF-β1↑	TGF-β1↑	[71]
Red Rice	Red rice extract	Polyphenols	Ethanol		HDFs	MMP-1,2, IL-6, IL-8,p38, JNK,NF-kB, AP-1 ↓	MAPK,NF-kB↓	[49]
Phyllanthus emblica Linn	PE extract	Polyphenols	Ethanol		HaCaT	ERK/TGF-β/Smad, MAPK/AP-1↓	TGF-β, MAPK/AP-1↓	[72]
Oryza sativa L	Cyanidin-3-O-glycoside chloride	Polyphenols	Ethanol		HaCaT HDFs	MMP-1,3, ERK, JNK, p38 ↓	MAPK↓	[73]
Eucalyptus globulus	Gallic acid	Polyphenols	Ethanol		HDFs	TGF-β1, Smad2/3↑ IL-6, MMP-1, MMP-3,c-Jun (p-c-Jun), c-Fos (p-c-Fos), Smad7↓	TGF-β1↑	[74]
Ribes nigrum L	Anthocyanin	Polyphenols and anthocyanins	Ethanol		NHDFs	MMP-1, IL-6, ERK, JNK, p38, p-c-fos, p-c-jun, NF-κB↓ HO-1, Nrf2,TGF-β, p-Smad2/3↑	MAPK/AP-1, NF-kB↓ Nrf2/HO-1 ↑	[75]
Acer tataricum subsp. ginnala	Ginnalin A	Polyphenols	Distilled water		HDFs	MMP1, ERK, c-Fos, c-Jun, NF-κB, IκB, IL-1β, IL-6, Smad7, JNK, p38, AP-1↓ Type I Procollagen, TGFβ, RII, Smad3↑	MAPK/AP-1, NF-κB↓ TGF-β/Smad↑	[51]

Malus baccata (L). Borkh leave	Benzofuran	Polyphenols	Methanol		HaCaT	MMPs, COX-2, IL-1β, IL-6, HYAs, p53↓ TGM1, FLG, HASs, Sirt1, Col1A1↑	MAPK, NF-κB↓	[52]
P angularis L seeds	Gallic acid	Polyphenols	Ethyl alcohol		HaCaT	MMP-1, MMP-3, Smad7, p-ERK, p-JNK, p-p38, p-c-fos, p-c-jun, TGF-β1, DLD, Nfr2, HO-1, NQO-1↓	MAPK/AP-1 ↓	[76]
Artemisia scoparia	Reynosin and santamarine	Polyphenols	Methanol		HDFs	MMP-1, MMP-3, MMP-9, p38,JNK, p-c-Fos, p-c-Jun, Type I Procollagen, Smad7↓ p-Smad2/3, Smad4, TGF-β, Nrf2, SOD-1, HO-1 ↑	MAPK/AP-1,TNFα↓ Nf-kB,TGF-β/Smad↑	[77]
Galla chinensis	Gallic acid and methyl gallate	Phenolic acids	Methanol		NHDFs	ROS, MMP-1, IL-6↓ procollagen type I, TGF-β1↑	TGF-β1↑	[78]
Foeniculum vulgare Mill	Chlorogenic acid, ferulic acid	Phenolic acids	Methanol	Hairless mice	HDFs	MMP-1, ERK (p-ERK), p38, p-p38 ↓ procollagen type I, elastin, TGF-β1, Nrf2↑	MAPK ↓ Nrf2↑	[79]
Thymus vulgaris	Rosmarinic acid	Phenolic acids	Methanol	Albino hairless mice (HR-1)	HDFs	MMP-1, IL-6, ERK (p-ERK), p38 (p-p38), pJNK (p-JNK), c-fos (p-c-fos), c-jun (p-c-jun) ↓ procollagen type I, TGF-β1, Nrf2, HO-1, NQO-1↑	Nrf2-ARE, TGF-β1↑ MAPK/AP-1↓	[80]
Helianthus annuus L	Chlorogenic acid and caffeic acid	Phenolic acids	Ethanol		NHDFs	ROS, COX – 2, iNOS, TNF – α, IL - 6, VEGF, MMP-1, MMP-3, c-fos, p-c-jun, p-ERK, p-JNK, p-p38↓ type I procollagen, TGF-β1, HO-1, NQO-1 ↑	Nrf2↑ MAPK/AP-1, NFAT↓	[81]
A. himalaicum	Neochlorogenic acid	Phenolic acids	Ethanol		HaCaT Hs68 HDFs	MMP-1, procollagen type I, c-Fos, c-Jun, ERK, c-Jun JNK, p38, caspase-14↓	MAPK↓	[82]
Carica papaya leaf	Caffeic acid	Phenolic acids	Ethanol		NHDFs	MMP-1, MMP-3, IL-6, JNK, p38, ERK, c-Jun, c-Fos, ROS↓ TGF-β1, Type I procollagen↑	MAPKs/AP-1↓	[83]
Coumestrol	Coumestan	Phenolic acids	Ethanol		HDFs	MMP-1, MEK/ERK, Akt/p70S6K, ERK, Akt↓	Ras/MEK/ERK, Akt/ p70S6K↓	[84]
	Caffeic acid and sinapic acid	Phenolic acids			Hs68 HDFs	MMP-1, ROS, ERK1/2, p38, JNK, NF-κB↓	MAPKs/NF-κB↓	[85]
Rosa gallica	Gallic acid and methyl gallate	Phenolic acids	Ethanol	SKH−1 hairless mice	HDFs	c−Fos, ERK1/2, MEK1/2, c−Raf↓	MAPK↓	[86]
	Kaempferide	Flavonoid		C57BL/6 mice	NIH-3T3 cells	MMP-1, MMP-3, IL-6, IL-8, MCP-3, ROS ERK, p38, JNK, AKT↓	MAPK↓	[30]

(*Continued*)

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Table 1 (Continued).

Plant Name	Active ingredient	Class	Solvent	In vivo	In vitro	Effects on Keratinocytes and Fibroblasts Response	Regulatory Mechanism	Ref
	Vicenin-2	Flavonoid			HDFs	ROS, ERK-1, JNK, p38, AP-1, MMP-2, MMP-9, MMP-12 ↓ SOD, CAT, GPx, GSH↑	MAPK↓	[26]
	Luteolin	Flavonoid			HaCaT	ROS, IL-20, AP-1, c-Jun, c-Fos, MMP-1↓	MAPKs↓	[87]
	Myricetin 3-O-β-d-Galactopyranoside	Flavonoid			HaCaT HDFs	MMP-1, MMP-9, COX-2, iNOS, TNF-α, IL-1β, IL6, p38, ERK, JNK, AP-1↓ Type Iα1 Procollagen, TGFβ- Smad 4, Smad 2/3, ERK↑	MAPK↓ TGF-β ↑	[88]
Prunella vulgaris L	Rosmarinic acid	Flavonoid	Ethanol		NHDFs	ROS, TNF-α, IL-6, p-JNK, p-ERK, AP-1, NF-κB, p65↓ procollagen type I, TGF-β1, p Smad2/3↑	TGF-β1/Smad↑ MAPKs, NF-κB↓	[53]
Potentilla glabra	Quercetin, kaempferol, and naringenin	Flavonoid	Ethanol		HaCaT	SOD-1,Bcl-2↑ Bax, COX-2, IL-1β, IL-6, c-Jun, c-Fos, p-TAK1, p-MKK3/6, p-p38, p-MEK1/2, p-ERK1/2, p-c-Jun, p-c-Fos↓	p38/ERK/AP-1↓	[89]
	7,8-Dihydroxyflavone	Flavonoid			Hs68 HDFs	ROS, ERK, p38, JNK, MMP1, TNF-α↓	MAPKs/Akt↓	[90]
Vitex negundo	Purified Vitexin Compound 1	Flavonoid		FVB mice	HDFs	SA-β-gal, p16, MMP-1↓	MAPK↓	[91]
	Eriodictyol	Flavonoid			HaCaT	MMP-1, TIMP-1, COL-1, JNK, ERK, p38↓	MAPKs↓	[92]
	Naringenin	Flavonoid		SKH-1 hairless mice	HaCaT HDFs	MMP-1,p90RSK, FRA1, ERK2, MMP-13↓	ERK2↓	[93]
H. cordata	Quercitrin	Flavonoid	Ethanol		HDFs	ROS, IL-6, IL-8, MMP-1, c-Jun, ERK, JNK↓	MAPK ↓	[94]
Safflower	Acacetin	Flavonoid	Ethanol		HaCaT HDFs	MMP-1, JNK1/2, c-jun↓	MAPK↓	[27]
Selaginellaceae	Amentoflavone	Flavonoid	Ethanol		HaCaT	MMP-1, MMP-2, MMP-3, MMP-9, JNK, p38, ROS, NF-κB, p65↓ Procollagen↑	MAPK↓	[95]
Nelumbo nucifera	Lotusine	Flavonoid	Ethanol		HaCaT	MMP-1, AP-1, NF-κB, MEK1/2-ERK1/2-p90RSK, MKK3/6-p38, JNK1/2, and Akt-p70S6K↓	MAPK↓	[64]

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Kaempferia pandurata Roxb.	4-Hydroxypanduratin A	Flavonoid	Ethanol		HDFs	MMP-1, ERK, JNK, p38, c-Jun, c-Fos↓	MAPK↓	[96]
Prunus yeonesis Blossom	Rutin	Flavonoid	Ethanol		NHDFs	ROS, MMP-1, MMP-3, p-ERK, p-JNK, p-p38, p-c-fos, p-c-jun, Smad7↓ Type I procollagen, TGF-βI, p-Smad2/3, NQO1, HO-1, Nrf2↑	MAPK/AP-1 ↓ TGF-βI/Smad, Nrf2/ ARE↑	[97]
Alpinia officinarum Rhizome	Kaempferide	Flavonoid	Ethanol	Hairless mice	NIH-3T3 cells	MMP-1, COL1A1, IL-6, IL-8, MCP-3, AKT, ERK↓	MAPK↓	[98]
Humulus japonicus	Glycosyl flavones	Flavonoid	MeOH		Hs68 HDFs	JNK, ERK, p38, c-Fos, c-Jun↓	MAPK, AP-1↓	[99]
Chenopodium formosanum	Rutin	Flavonoid	Ethanol		Hs68 HDFs	MMP-1, MMP-3, MMP-9, p-c-Jun, c-Fos, TGF-β, Smad3, ROS ↓	Nrf2/HO-1 ↑	[100]
Watermelon	Citrulluside H and citrulluside T	Flavonoid	Ethanol		HDFs	MMP- 1, MMP- 3, ERK1/2, p38 MAPK, JNK, ROS↓	MAPK/AP- 1, NF-κB↓	[101]
	quercetin	Flavonoid			HDFs	MMP-1, p-ERK, p-JNK, c-Jun, c-Fos↓ p-Smad 2/3, Smad 4↑	TGFβ/Smad↑ MAPK↓	[102]
Glycyrrhiza uralensis Fisher	Licoricidin	Isoflavonoid	Ethanol		HDFs	ROS, MMP-1, ERK, JNK, p38, c-Jun, c-Fos↓	MAPK↓	[103]
Euphrasia officinalis	Caffeic acid	Flavonoid	Ethanol		NHDFs	MMP-1, MMP-3, IL-6, AP-1, JNK(p-JNK, ERK (p-ERK) p38(p-p38)↓ TGF-β1↑	MAPK, AP-1 ↓	[104]
Neem Leaves	Rutin	Flavonoid	Ethanol	Hairless mice	NHDFs	ROS, c-Fos, p-c-Fos,MMP-1,IL-6↓ TGF-β1↑	TGF-β1↑	[105]
Pueraria montana var. lobata root		Isoflavones	Ethanol		HDFs	ROS↓ Nrf2, HO-1, NQO-1↑	Nrf2↑	[107]
Ginkgo biloba	Laricitrin 3-Rutinoside	Flavonoid	Ethanol		HDFs	TNF-α, ROS, MMP-1, ERK, JNK, IL-6, IL-8↓	MAPK↓	[108]
Cryptotanshinone (CTS)	Anthraquinone	Terpenoid	Ethanol		HaCaT HDFs	SA-β-gal,IL-6, IL-8, MMP-3, MMP-1, ROS, CPD, γ-H2AX, caspase-3, caspase-9↓ HO-1, NQO1, Nrf2, p-AMPK, SIRT1, PGC-1α↑	AMPK/SIRT1/PGC-1α, Nrf2 ↑	[60]
Obovatol	Biphenol	Terpenoid	Ethanol		HDFs	Smad-3, TGF-β↑ ERK, p38, MMP-3 ↓	TGF-β↑ MAPK↓	[109]
Zingiber zerumbet Smith	Zerumbone	Terpenoid			HaCaT	ROS, Bax, Keap-1↓ Bcl-2, Nrf2, HO-1, γ-GCLC, GSH↑	Nrf2/Keap-1↑	[110]

(*Continued*)

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Table 1 (Continued).

Plant Name	Active ingredient	Class	Solvent	In vivo	In vitro	Effects on Keratinocytes and Fibroblasts Response	Regulatory Mechanism	Ref
Coffee silverskin	Atractyligenin	Terpenoid	Ethanol		NHDFs	ROS, MMP-1, MMP2, MMP-3,p38, ERK, JNK, c-Jun, c-Fos↓	MAPK, AP-1↓	[111]
Brown Pine Leaf	Trans-Communic Acid	Diterpenoid	Ethanol		HaCaT	MMP-1, AP-1, PI3K↓	PI3K/Akt↓	[112]
Siegesbeckia glabrescens	Kirenol	Terpenoid		Albino hairless mice	Hs68 HDFs	MMP-3, MMP-13, c-Jun, c-Fos, ERK, JNK, p38, NF-κB, IL-6, IL-8↓;catalase↑	MAPK/NFκB↓	[113]
Dehydroabietic acid	Diterpene resin acid	Terpenoid			HDFs	MMP-1, JNK, c-Fos, c-Jun, AP-1, p38, p-ERK↓	MAPK↓	[28]
Ginseng seeds	Ginseng seed embryo (GSE) and ginseng seed coat (GSC)	Terpenoid	Ethanol		Hs68 HDFs	MMP-1, MMP-3, ERK, JNKp38, c-jun, c-fos, AP-1, Smad 7 ↓ Smad 2/3, TGF-β ↑	MAPK ↓ TGF-β/Smad↑	[41]
Pterocarpus santalinus L	Taxifolin, quercetin, and naringenin	Flavonoid	Ethanol		NHDFs	ROS, MMP-1,MMP-3,MMP-9, IL-6, p-c-fos, p-c-jun, AP-1, p-ERK, p-JNK, p-38, Smad7↓	MAPK/AP-1↓ TGF-β/Smad ↑	[114]
	Syringaresinol	Lignan			HaCaT HDFs	MMP-1, MMP-9, Procollagen Iα1, TNF-α, COX-2, iNOS, IL-6, p38, p-ERK, p-JNK, TNF-α, IL-1β, c-Fos, c-Jun↓	MAPK/AP-1↓	[115]
Sesamum indicum Linn.	Sesamin (SSM)	Lignan			HaCaT	MMP-1, MMP-9, MDA, ASK-1, JNK, p38↓ GSH, SOD ↑	ASK-1-JNK/p38 MAPK↓	[116]
Myristica fragrans	Macelignan	Lignan	Ethanol		Hs68 HDFs	MMP-1, ERK, JNK, p38, ROS, c-Jun, Smad7↓ Type I Procollagen Secretion, Smad3↑	TGF-β/Smad↑ MAPK↓	[117]
Saururus chinensis	Sauchinone	Lignan	Ethanol		HaCaT	MMP-1, ROS, HO-1, GSH, peRK, pJNK, pp38 ↓	MAPK↓	[118]
Anemarrhena asphodeloides	Mangiferin	Lignan			HaCaT	MMP-9, MEK/ERK ↓	MAPK↓	[119]
Ginseng seeds	Ginsenosides	Saponins	Ethanol		HDFs	MMP-1, MMP-13, ERK, p38 MAPK, JNK, NF-kB, c-Jun, c-Fos↓	MAPK/AP-1, NF-kB ↓	[32]
Licorice root	Glycyrrhizic acid	Saponins	Ethanol		HFFs	Pro-collagen 1, ROS, caspase 3, NF-kB, cytochrome C↓	NF-kB↓	[120]
Geniposide	Iridoid glucoside	Saponins			HDFs	ROS, proMMP-2↓ GSH, SOD, Nrf2↑	Nrf2 ↑	[121]

Gardenia jasminoides J. Ellis	Geniposide	Saponins	Ethanol		HaCaT	ROS, MMP-1, IL-1β, IL-6, TNF-a, c-Fos, c-Jun, NF-κB, IjBa, ERK1/2, p38MAPK, JNK1/2 ↓ type I procollagen↑	MAPKs, NF-κB/AP-1↓	[122]
Notoginseng Stem-leaf	Ginsenosides	Saponins	Ethanol		NHDFs	ROS, MMP-1, MMP-3, IL-6, p-c-fos, p-c-jun, ERK, JNK, p38, Smad7↓ procollagen type I, TGF-β1, p Smad2/3↑	MAPK/AP-1 ↓ Nrf2, TGF-β/Smad↑	[123]
Asiaticoside	Centella asiatica	Alkaloids	Ethanol		HaCaT	TGF-β1, Smad2, Smad3, ROS↓ SOD↑	TGF-β1/Smad↑	[42]
Andrographolide sodium bisulfate (ASB)	Labdane diterpenoid	Alkaloids	Ethanol		HaCaT	ROS, IL-1β, IL-6, TNF-α, p65, IκBα, ↓ GCLC, NQO1, Nrf2, keap1↑	NF-κB↓ Nrf2↑	[124]
Zingiber zerumbet Smith root	Zerumbone	Sesquiterpene			HDFs	MMP-1, ROS, c-Fos, c-Jun↓ Collagen III, Nrf2↑	Nrf2/ARE↑	[125]
Black Soybean Seed Coats	Anthocyanins	Anthocyanins	Ethanol	Hairless mice	HaCaT	ROS, caspase-3↓ Bcl-2↑	NF-κB, PI3K /Akt↓	[126]
Bog blueberry	Anthocyanins	Flavonoids	Ethanol		HDFs	ROS, MMP-1, MMP-8, MMP-13, JNK, p38, NF-κB↓ procollagen↑	NF-KB, MAPK↓	[127]
Ishige okamurae	Diphlorethohydroxycarmalol (DPHC)	Phlortannin	Ethanol		HDFs	TNF-α, IL-6, IL-1β, p-p38, 274 - p-ERK, p-JNK, p-c-Jun, p-c-Fos↓	NF-κB↓	[128]
Sargassum horneri	(-)-Loliolide	Sesquiterpenoid lactone	Ethanol		HDFs	IL-1β,IL- 6, IL-8,IL- 33, TNF-α, MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-13↓	NF-κB, MAPK↓	[129]
Hizikia fusiforme	Fucoidan	Polysaccharide	Ethanol		HDFs	MMP-1, MMP-8, MMP-13, PGE2, TNF-α, IL-6, IL-1β, ROS, IκBα, (p-c-Jun, p-c-Fos), (p-ERK, p-JNK, p-p38, p50, p65)↓	NF-κB, MAPK↓	[130]
Chrysanthemum	Handelin	Phenylpropanoid	Ethanol		HaCaT	AMPK, p70S6K↓	AMPK-mTOR↓	[131]
Salvia plebeia R. Br	Homoplantagin	Phenylpropanoid	Ethanol	Kunming mice	HaCaT	ROS, MDA, IL-6, MMP-1, SA-β-G, alM, p-ERK, p-JNK, p-38, Smad7↓ procollagen type I, TGF-β, p-Smad2/3↑	MAPK↓ TGF-β/Smad2/3↑	[132]
Hydrangea serrata	Hydrangenol	Terpenoid	Ethanol	HR-1 hairless mice	Hs68 HDFs	MMP-1, MMP-3 HYAL-1, HYAL-2, COX-2, IL-6, IL-8, IL-1β, ROS, AP-1, STAT-1, p38, ERK↓	MAPK / AP-1↓	[133]

(*Continued*)

Table 1 (Continued).

Plant Name	Active ingredient	Class	Solvent	In vivo	In vitro	Effects on Keratinocytes and Fibroblasts Response	Regulatory Mechanism	Ref
Disporum sessile D.Don		Liliaceae			HaCaT NHDFs	Type-I procollagen MMP-1, ERK 1/2, JNK, p38, NF-kB, p-IKKα, p-IκBα↓	MAPKs, NF-kB/p65 ↓	[134]
Orobanche cernuaLoefling	Acteoside	PHONYLE THANOID glycoside	Ethanol		NHDFs	p-c-fos, p-c-jun, c-jun, c-fos, p-Smad7, TGF-β 1, p-ERK, p-JNK, p-p38, ERK, JNK, p38, ROS, MMP-1, IL-6↓ Nrf2, HO-1, NQO-1, Smad2/3↑	MAPK/AP-1↓ TGF-β/Smad↑	[135]
Propolis	Caffeic acid, quercetin, apigenin	Phenlics, lavoid, flavonoid	ETHANOL		Hs68 HDFs	MMP-1, PI3K, PDK1, Akt ↓	PI3K-PDK1-Akt↓	[136]
Dendrobium officinale	Bibenzyl derivatives	Aromatic compounds	Ethanol		HDFs	ROS, MMP-1↓ SIRT-3↑	MAPK↓, TGF-β1↑	[40]
Perilla seed meal	Tocopherols, policosanols, and phytosterols	Unsaponifiable matter	Ethanol		HDFs	MMP1, MMP3, Collagen ROS, AP-1, p-JNK、p-ERK, p-p38Smad7↓ TGF-β, Smad2/3 ↑	MAPKs↓ TGF-β↑	[29]

Abbreviations: ↑, Activation ↓:Inhibition.

elastic fibers in photoaged skin, abnormal fractures in the dermal tissue of photoaged skin, and structural confounding of collagen fibers.[19] A total of 58 articles conducted relevant research on fibroblasts. Polyphenols, flavonoids, terpenoids, and saponins regulate levels of collagen-related factors, inflammatory cytokines, growth factors, and oxidative stress-related factors. In fibroblasts, natural active ingredients primarily promote the TGF-β pathway, inhibit MMPs activity, and enhance collagen synthesis while potentially modulating the mTOR pathway, thereby protecting the dermal collagen network and reducing wrinkle formation.

Key Signaling Pathways That Regulate Cellular Responses

MAPK Signaling Pathways

MAPKs are among the highly conserved signal transduction pathways and have been extensively utilized throughout evolution in numerous physiological processes. ROS activates the MAPK family, encompassing ERK, JNK, and P38 kinase.[20] MMPs is a family of zinc-dependent enzymes which is the cause of the ECM degradation. Activation of MAPK enables overexpression of the transcription factor AP-1, which leads to MMP growth. MMP-1 initiates the degradation of Type I collagen which is a major collagenase, and further hydrolyzed by other MMPs.[21] The skin's stability and tensile strength depend on the action of collagen In addition, UVB-induced ROS accelerated MMPs expression through the activation of MAPK pathway.[22]

MAPK are a class of serine/threonine protein kinases that play a crucial role in cellular signal transduction. Studies have shown that several components of the MAPK signaling pathway play significant roles in skin aging, including extracellular signal-regulated kinase (ERK) and MAPK p38. The activation of these pathways can lead to the degradation of the extracellular matrix (ECM) and the downregulation of new collagen. The loss of collagenous proteins is frequently regarded the primary factor contributing to wrinkle formation during photoaging.[17] Subsequently, the activated MAPK proteins enter the nucleus, where they sensitize multiple transcription factors, such as AP-1, c-Myc, COX-2, and NF-κB ultimately induce photodamage.[23]

Many plant-derived compounds inhibit the MAPK pathways through diverse molecular targets, that reduce inflammation after photoaging. Some studies found that UVR stimulates the pro-inflammatory cytokines and epidermal growth factors, and this in turn increased MMPs levels. Imokawa found that the L-6, which elicited upregulation of MMP-1, is a powerful stimulator of photoaging.[24] Studies have found that many cellular and molecular pathologies of UVB-irradiated cells could be impeded by *luteolin*, which is a flavonoid that targets the MAPK signaling pathway.[25] For example, Vicenin-2 known as a flavonoid is extracted from several medicinal plants and prevents UVB radiation-induced MAPKs, thereby preventing photoaging in HDFs.[26] Experiments on keratinocytes have found that *Carthami Flos* can prevent UVB-irradiation by inhabiting oxidative stress and inhibit on the markers of photoaging.[27] Natural compounds, like ihydroisocoumarins, stilbenes and secoiridoids have been isolated from hydrangenol, a dihydroisocoumarin derived from *Hydrangea macrophylla Ser*, and have shown significant promise in suppressing UVB-induced inflammatory mediators, including IL-6, COX-2, and IL-1β.[28] Unsaponifiable matter markedly reduced ROS production and minify MMP3 induced by UVB and MMP1 expression by restraining MAPKs pathway.[29] Oxidative stress induced by the accumulation of ROS can lead to lipid, protein, nucleic acid and organelle damage, thus leading to the occurrence of cellular senescence, which is one of the core mechanisms mediating skin aging. Kaempferide is a flavonoid found in *Kaempferia galanga L*t. It can treat photoaging by activating UVB-induced phosphorylation of MAPKs and AKT.[30] Resveratrol can take action on cellular signaling pathway mechanisms related to UV-induced skin photodamage, including MAPK, NF-κB.[31] *Panax L*., a herb medicine, treat and prevent photoaging by interposing the MAPK and NF-κB signaling pathway.[32]

TGF-β1/Smad Signaling Pathways

Wrinkling is one of the most visible signs in photoaging, this phenomenon results from the decrease of collagen and the increase in its breakdown. TGF-β regulates the breakdown of Collagen, which is synthesized from procollagen secreted by HDFs.[33] During skin photoaging, collagen fibers are broken down by MMPs.[34] After exposure to UV radiation, Type I procollagen levels reduced. The activation of TGF-β is in charge of collagen synthesis.[35] The mechanism responsible for dermal collagen synthesis is based on the communication between TGF-β and TGF-β cell surface receptor complexes (TβR I–III).[36] In the dermis, TGF-β

can promote the proliferation and differentiation of fibroblasts, increase the synthesis and secretion of collagen fibers, and also inhibit the degradation of collagen fibers. Therefore, the TGF-β/Smads signaling pathway plays an important regulatory role in the synthesis and metabolism of dermal collagen fibers.[37]

Gao found that UVB can downregulate TGF-β, but this trend was reversed by *Rubus mesogaeus*.[38] Similarly, treatment with unsaponifiable matter from *Perilla frutescens (L). Britt*. upregulate TGF-β and Smad2/3. In contrast, Smad7 was upregulated after UVB.[29] *Coriandrum sativum L*. (CS) is a Chinese herb that belongs to the Apiaceae family. Linolenic acid is the primary component of CS ethanol extract. CS ethanol extract decreases the degradation of collagen and elastin fibers by boosting TGF-β1 pathway and restraining the expression of MMP-1.[39] The extract of Dendrobium officinale zymosised by Lactobacillus plantarum GT-17F strengthens the protection against photoaging. Moreover, *D. officinale polysaccharides* (DOPs) are capable of regulating the transforming TGF-β1 pathway to intervene in UVB-damaged fibroblasts, decrease the content of ROS and MMP-1, and safeguard photoaged fibroblasts.[40] *Panax ginseng C. A. Mey*. seeds counteract photoaging by inhabiting the levels of Smad 7 and improving the levels of Smad 2/3 and TGF-β.[41]

Herbal compounds such as daidzein, apigenin, mustard side, and astragalus side have been shown to prevent collagen reduction and upregulate collagen synthesis in UVR induced senescence by restoring the TGF- β/Smad pathway. Asiaticoside delays aging and attenuates ROS generation in UV-exposure cells by regulating the TGF-β1/Smad signaling pathway.[42–44]

NF-κB signaling pathways

NF- κ B is a family of transcription factors whose consortium proteins can be divided into the following "Rel" proteins, including RelA, c-Bel, RelB, NF- κ B1 and NF- κ B2.[45] The most significant role of these transcription factors lies in regulating inflammation, immune responses, cell proliferation, and differentiation caused by UVB.[45] Members of the NF- κ B family remain dormant by binding to the inhibitory protein I κ B in the cytoplasm. The inhibitory effect of I κ B is eliminated by the phosphorylation of kinase proteins, the kinase protein, the I κ B kinase, leading to ubiquitination of I κ B and degradation of the proteasome.[46] A variety of factors lead to the sensitization of NF-κB in the cellular cytoplasm; among them, ROS produced by UVB is the most significant, indicating that ROS have a crucial member in activating IKK. The activated members of NF-κB enter the nucleus and commence transcription by binding to their corresponding DNA regulatory sequences. The NF-κB pathway can be set off by a number of stimulations, with inflammatory cytokines such as TNF-α and IL-1β included, and these trigger the classical pathway.[47]

This pathway plays a vital role in photoaging by mediating phlogistic response, cell damage and apoptosis, thereby impairing the immune response. Many natural active ingredients can inhibit NF-κB activation and reduce oxidative stress and inflammation, protecting the skin photoaging damage. Polyphenolic compounds, such as lutein, carnosic acid, *Ribes nigrum L, Acer tataricum subsp. ginnala*, combat photoaging by affecting the NF-kB signaling pathway.[48–52] Similarly, some flavonoid compounds (*Prunella vulgaris L*) can restrain this pathway, thereby achieving an anti-photoaging effect.[53]

Nrf2/ARE Signaling Pathways

Oxidative stress is regarded as a crucial biological consequence of UVR irradiation on skin cells, which promotes collagen degradation.[54] Pro-oxidants and antioxidants keep a balance in a healthy body. However, when the levels of ROS increase, this balance is disrupted, resulting in oxidative stress. To cope with this stress, the body possesses an antioxidant defense system.[55] The major defense systems utilized is the Nrf2/ARE signaling pathway. When skin cells are stimulated by ROS, Nrf2 promptly migrates to the nucleus and binds to ARE, facilitating the transcription of antioxidant enzymes like HO-1, NQO-1, and NAD(P)H.[56] Thus, compounds that activate the Nrf2/ARE pathway might prevent oxidative damage in the skin.

Nrf2 can trigger the expression of antioxidant enzymes and genes that facilitate homeostasis and regulate processes related to the pathology of numerous diseases. Endogenous Nrf2 has the capacity to safeguard the skin from UV irradiation.[57] Nrf2 can also alleviate the symptoms of skin photoaging (such as wrinkle and the loss of skin flexibility).[58]

Grape stems possess several phytochemicals, the most affluent of which are stilbenes (trans-resveratrol and ε-viniferin), they can prevent cells from photoaging by Nrf2 pathway.[59] Cryptotanshinone is a component mainly obtained from *Fabaceae* plants. When UVR radiation of cells before radiation exposure, it can improve the photoaging damage of UVR radiation to epidermal keratinocytes and dermal fibroblasts, and effectively delay cell aging. *Cryptotanshinone* achieves its anti-aging effect by lowering the level of ROS in cells, alleviating DNA damage, activating the Nrf2 signaling pathway, reducing mitochondrial dysfunction and suppressing apoptosis.[60]

PI3K-AKT Signaling Pathways

The PI3K/AKT pathway is a well-defined and significant one that is activated in response to DNA damage. ATM, ATR, and DNA-PKcs are members of the PI3k-like kinase family that are activated upon DNA damage and induce the production of γ H2AX.[61] Photoaging is the premature aging of the skin caused by long-term ultraviolet radiation, manifested as wrinkles, skin laxity, pigmentation, etc. The signaling pathway involved in PI3K is closely related to processes such as cell survival, proliferation, metabolism, and cytoskeleton reorganization. After the skin is exposed to ultraviolet radiation, the PI3K signaling pathway may be activated, thereby triggering a series of reactions.[62] For example, it may affect the antioxidant defense mechanism of cells, regulate the inflammatory response, or affect the balance of synthesis and degradation of the extracellular matrix, thereby influencing the process of photoaging.[63]

Lotusine suppresses the expression of UVR-induced MMP-1 in HaCaT. Furthermore, lotusine hindered UVR-induced MMP-1 transcription by restraining AP-1 and NF-κB translation. Hence, lotusine could be as a latent new anti-wrinkle material in cosmetic formula to prevent skin photoaging. Brown Pine Leaf Extract and its component Trans-Communic Acid can inhibit the expression of MMP-1 by targeting PI3K pathway.[64]

Summary of the Regulatory Mechanisms of Natural Plant Compounds

Fibroblast and keratinocyte-mediated protective processes are critical in reducing skin damage. Many natural compounds act on fibroblasts and keratinocytes to alleviate inflammation after UVR by inhibiting signaling pathways and molecular targets including NF-κB, MAPKs, PI3K/AKT, IL-6, IL-8, and pro-oxidant enzymes. But some plant compounds rise the activation of Nrf2/HO-1 and TGF-β (Figure 2). Most of natural compounds regulate multiple targeting mechanisms that adjust fibroblast and keratinocyte response (Table 1).

Discussion

The cells involved in photoaging include epidermal cells (particularly keratinocytes involved in forming the stratum corneum), fibroblasts in the dermis, basal cells, and skin immune cells such as dendritic and macrophages cells. In photoaging research, studies on keratinocytes and dermal fibroblasts are the most extensive and in-depth. These cells undergo pathological changes upon exposure to UVR radiation, leading to skin photoaging. Current research reveals intricate pathways contributing to photoaging, including the NF-kB signaling pathway associated with UV-induced inflammation, MAPK pathways (ERK, JNK, p38) influencing cell fate, the PI3K/Akt signaling pathway affecting cellular functions, the TGF-β pathway affecting proliferation and immune responses, the Wnt/β-catenin signaling pathway implicated in skin homeostasis, the p53 pathway responding to UVR-induced DNA damage, and the potential involvement of the AMPK pathway in energy regulation. Their interactions and responses to light exposure play pivotal roles in understanding the mechanisms underlying skin photoaging through these pathways. These interconnected pathways offer a comprehensive understanding of the complex mechanisms involved in photoaging.

Natural plants, which act on keratinocytes and fibroblasts, are involved in nearly all the discovered pathways of photoaging. They inhibit or activate these pathways to achieve anti-photoaging effects through anti-inflammatory and antioxidant actions. However, most research is limited to cellular and animal models, lacking clinical studies, and the investigation of mechanisms is relatively monolithic, with unclear relationships between different signaling pathways and actions. In the future, novel pharmacological research methods and models, such as proteomics, genomics, and three-dimensional skin reconstruction models, could be fully utilized to further elucidate the mechanisms by which natural plants affect keratinocytes and fibroblasts in skin photoaging.

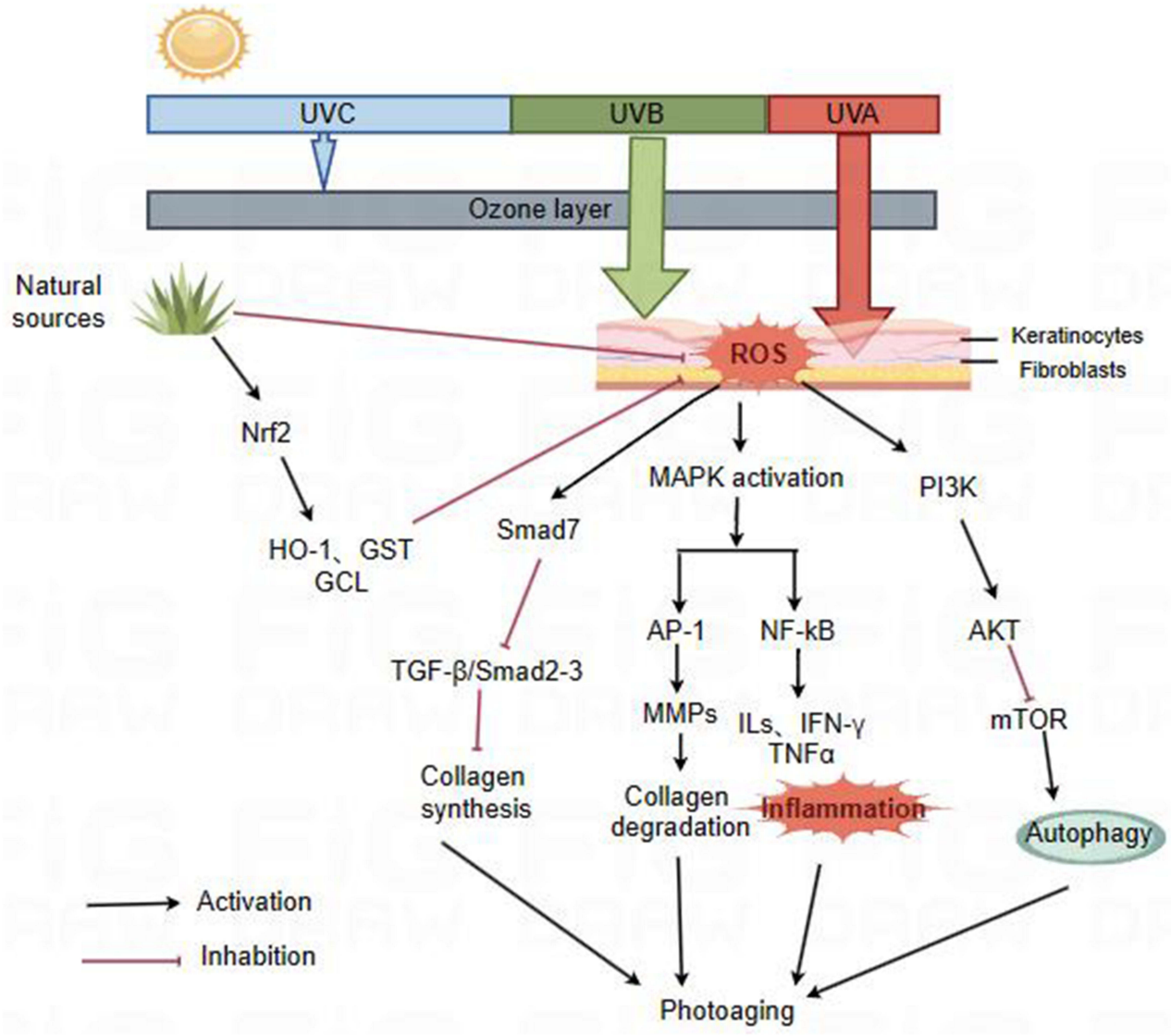

Figure 2 Summary of the regulatory mechanisms of plant-derived natural compounds.

Conclusion

The skin is an important organ aesthetically, so the damage of skin photoaging is a major problem that cannot be ignored. It is for this reason that researchers are more focused on understanding the mechanisms involved in photoaging of the skin, to seek its applicability in aesthetics and the clinic. According to the literature, numerous natural compounds regulate cellular responses by targeting diverse receptors, molecules, and proteins to restrain neuroinflammation and facilitate neurological renew. The topical utilization of plant-based natural product components is advocated in the pharmaceutical and cosmetic sectors as natural constituent sunscreens cream, anti-cancer substances, and anti-photoaging molecules rather than the synthetic ones accessible because of their extremely low or no side impacts and easy availability. This review thoroughly summarizes the regulatory mechanisms of natural active ingredients and compounds on keratinocytes and fibroblasts in mitigating skin photoaging. So it's necessary for the future clinical research to obtain information about their dosage, security, and efficacy, and to pick the best ingredient lead for human beings.

Abbreviations

AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; COX, cyclooxygenase; HIF-1α, hypoxia inducible factor-1; HO-1, hemeoxygenase-1; IL-, interleukin-; JNK, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; Nrf2, nuclear factor erythroid 2-related factor 2; NOX, NADPH oxidase; PI3K, phosphatidylinositol 3- kinase; ROS, reactive oxygen species; SIRT1, silent information regulator 1; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor-β; TLR, Toll-like receptors; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; ECM, extracellular matrix; MMPs, matrix metalloproteinases; UVR, Ultraviolet radiation; Smad, drosophila mothers against decapentaplegic; HaCatT, Human Keratinocytes (HaCaT) Cell; HDFs, Human dermal fibroblasts; HFFs, Human Foreskin Fibroblasts; NHDFs, Normal Human Dermal Fibroblasts; NIH-3T3, Mouse Embryonic Fibroblast; PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-Analysis; ARE, antioxidant-response element; AP-1, activator protein 1; IKK, IκB kinase; iNOS, inducible nitric oxide synthase.

Data Sharing Statement

All data are fully available without restriction.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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