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Review Article

Plant Bioactives as Inhibitors of Matrix Metalloproteases and their Anti-skin Photoaging Potential

Madhuri Baghel[1,*], Hemant Badwaik[1], Sangeeta Patil[2], Azajuddin[3]

ABSTRACT
Because skin aging is so important in terms of looks, research into preventive and therapeutic treatments has proliferated. Ultraviolet (UV) radiation alters the extracellular matrix (ECM), stimulates matrix metalloproteinases (MMPs), while diminishes the elastin and collagen. MMPs are zinc-containing endo-peptidases that help to restore the ECM. The MMP families, based on substrate structure and specificity are: a) collagenases b) gelatinases c) stromelysins d) matrilysins and e) membrane type MMPs. Except for matrilysin, these enzymes contains haemopexin, propeptide and catalytic domains. Among the photoprotective strategies used to prevent and/or treat photoaging are topical sunscreens that work at the molecular level. We investigate photoaging mechanisms and plant bioactives. Skin photoaging is primarily caused by UV radiation from the sun, as it produces reactive oxygen species and disrupt DNA/cellular equilibrium, alter signal transduction pathways and inflammatory cascades, as well as immunosuppression and ECM restoration. Antiaging studies recently predicted the usage of natural chemicals from ancient civilizations. The sun protection factor and antioxidant properties of plants help prevent wrinkles and give the skin a youthful glow. Thus, the current study focuses on the development of anti-photoaging therapies that target specific MMPs connected to skin aging and wrinkle generation. We explored MMP suppressors or inhibitors found in plants.
Keywords: MMPs, Plant Bioactives, Photoaging, Anti skinaging, Reactive oxygen species.

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INTRODUCTION

Cosmetic use dates back to the Ancient Egyptians around 10,000 BCE and has continued throughout history; cosmetic use can be symptomatic of a civilization's practical considerations, like sunburn protection, beauty conventions and class or caste framework. The antiaging cosmeceutical market is projected to extend US$ 88.30 billion in 2026, with a CAGR (compound annual growth rate) of 7.10 percent between 2021 and 2026.[1] Asia, including India, Japan, China, and Korea, is currently the largest market. These Figures demonstrate how skin antiaging has exploded in popularity in recent years.

"Beauty from within" concept is gaining popularity that utilizes natural ingredients for manufacturing of cosmetics. Various factors are responsible for rapid growth of antiaging cosmetic market; these are regular exposure to sunlight, increased knowledge of beneficial effects of use of antiaging products, unhealthy lifestyle, rising geriatric population, improvement in technological advancements and most importantly willing to look younger and healthier skin.

Skin suffers from aging because it is the most ample organ of our body that is open to the elements of environment. There are 2 kinds of aging on the skin: chronological aging also known as intrinsic aging, which is produced as the time passages, and the extrinsic aging, premature aging, or also known as photoaging, which is caused by environmental attackers.

The solar spectrum is made up of electromagnetic rays of various wavelengths, extending from low energy, long wavelength IR (infrared) radiation and high energy, short wavelength UV (ultraviolet) radiation to visible light. The skin absorbs the majority of the solar spectrum.

UV exposure is the principal cause of extrinsic skin aging, accounting for 80-85 percent (approx) of facial aging. On exposure to UV light, photoaging occurs, which is a complicated process that results in skin changes throughout time. The extent of photoaging depends on skin type, extent of sun exposure, ethnicity, geographic location, and photoprotective practices. The epidermis thickens in photoaged skin while it becomes thinner in case of intrinsic skin aging.[2] The remarkable signs of photoaging include laxity, coarse or fine rhytides, decreased elasticity, sallow color, solar lentigines and telangiectasias.[3] The formation of neoplastic tumours is linked to cutaneous destruction triggered by persistent acquaintance to sun rays.

The concept of skin aging has been studied in numerous facets in Ayurveda, one of India's traditional systems of medicine. Natural skin care

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products are usually hypoallergenic and absorb quickly into the skin surface. Many plants, notably whole grains, vegetables, and fruits; contain antioxidants, like polyphenols, which scavenge free radicals and eliminate the metabolic by products. Natural resources are at the core of the entire spectrum of cosmetic practice as understood by the ancient civilizations and there has been a significant growth in recent years.[4] Because of their significant impact on skin aging and adverse reactions such as phototoxic or photoallergic reactions, allergic and irritant contact dermatitis, which are commonly associated with synthetic skincare products, herbal cosmetics are gaining popularity not just in Asia, but in many other parts of the world. MMPs are a crucial player in the development of age-related skin changes, and the goal of this article is to look into the many plant bioactives that have been found to have anti-aging properties when MMPs are inhibited or downregulated. A review of various plant bioactives is provided in the next part to emphasize the potential of plant bioactives as natural resources for skin aging protection.

REGULATION OF PHOTOAGING AND ROLE OF MATRIX METALLOPROTEINASES (MMPS)

MMPs are overexpressed in human skin after prolonged exposure to UV light. Elastin, collagen, proteoglycans, and fibronectin are ECM (extracellular matrix) proteins that are degraded due to MMPs and contribute to photoaging.[5-6] MMPs also contribute in photocarcinogenesis by modulating and/or influencing a variety of tumour progression pathways, including tumour formation, development, angiogenesis, and metastasis.[7] MMPs are a class of zinc dependent proteinases that create the connective tissue of the dermis, are responsible for the breakdown of ECM proteins.[8-9] Traditionally it was considered that MMPs are associated with degradation and remodeling of ECM but with the emergent of new substrate classes, now MMPs are considered as multifunctional proteases.[10]

According to NMR and X ray crystallographic analysis on 3D (three dimensional) structures of MMPs, The catalytic domains' polypeptide loops are largely superimposable, despite the fact that the core structures of MMP domains have little in common. The catalytic domain is made up of three structural and catalytic calcium ions, three α-helices, five stranded β-pleated sheets, two structural and catalytic zinc ions and connecting loops. The substrate binding region has a hydrophobic "S1 pocket", which contributes to MMP substrate specificity (Figure 1). The substrate binding pocket also comprises of "cysteine switch", where the cysteine's sulfhydryl group binds with the catalytic zinc ion. MMPs have numerous more active sites, termed as subsites (S) that interface with substrates and /or inhibitors in addition to the catalytic site. S_1, S_2, S_3,.....S_n are the names of the sub sites on the left side, and S_1',S_2',S_3',.....S_n' is found on the right side of the Zn^{2+} ion, as shown in Figure 1. P_1, P_2, P_3,…..P_n denotes the substrate functional groups that interact with these sub sites, and P_1',P_2',P_3',.....P_n' refers to the inhibitors' functional groups that engage with these sub sites. The sub sites, S_1 and S_3 are placed away from the catalytic center, while the sub site S_2 is situated near to the Zn^{2+} ion, and the sub site S_2 contains a variety of residues that provide substrate selectivity to specific MMPs. Due to variations in depth and size, the S_1 pocket allows specific inhibition of MMPs and has received a lot of interest in the development of MMPIs (matrix metalloproteinases inhibitors).[11] The domain structure of MMP groups is shown in Figure 2.

Currently, 28 members of the MMP family have been discovered in mammals. These play essential roles in variety of pathophysiological conditions for example photoaging, inflammation, wound healing, arthritis, angiogenesis, skeletal growth and remodeling, and cancer.[12-13] Presence of stimulus; ex: UV radiation, oxidative stress, and cytokines; activates keratinocytes and dermal fibroblasts to secret these MMPs.[14-15]

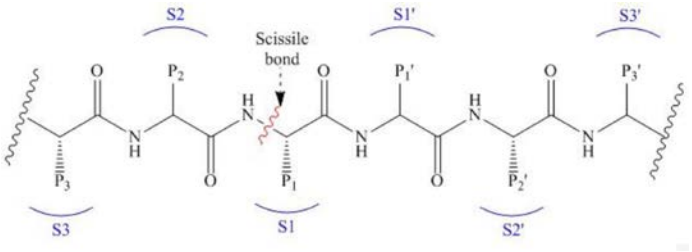

Figure 1: Amino acid residue nomenclature of peptide and binding sites. Pn to Pn' indicates residues of substrate, Sn to Sn' indicates the binding sites in the enzyme.

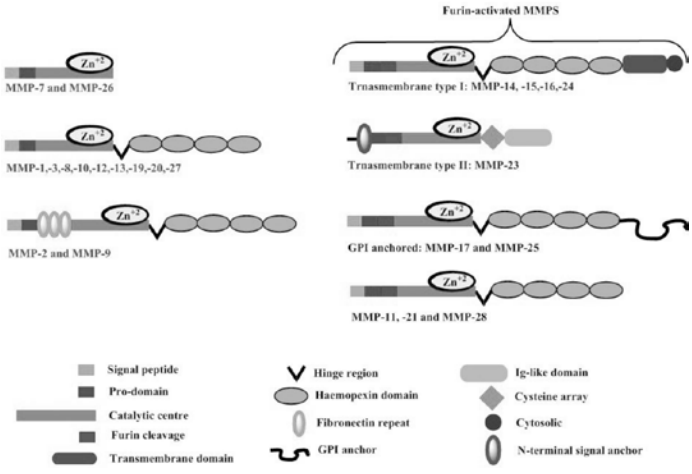

Figure 2: MMP Groups Domain Structure.
At least one catalytic domain, peptide and pro-domain, and are shared by all human MMPs.

As per the substrate specificity and their ability to secrete soluble proteins or bounding to cell surface, these are categorized into 5 different classes:

1. Collagenases [MMP'1; MMP'8 and MMP'13]: Collagenases are the first class of MMPs that have a hemopexin like domain. The capability of these enzymes to breakdown fibrillar collagen at a specific site is their defining property.[16]
2. Gelatinases [MMP'2 and MMP'9]: Gelatinase A and gelatinase B are referred as MMP'2 and MMP'9 respectively. They quickly decompose denatured collagens and gelatins, and they have the unique capacity to degrade all ECM components.
3. Stromelysins [MMP'3; MMP'10 and MMP'11]: Stromelysin-1 and stromelysin-2 are known as MMP'3 and MMP'10 respectively. The substrate specificity of these stromelysins is similar; however the former has a higher proteolytic efficacy than the latter. Because its sequencing and substrate selectivity differ greatly from those of MMP'3; MMP'11, also described as stromelysin 3, is sometimes clubbed in with other MMPs. Collagenases are similar, but they don't damage type I collagen fibrils.
4. Matrilysins [MMP'7 and MMP'26]: Matrilysin 1 and Matrilysin 2 are known as MMP'7 and MMP'26, sometimes known as endometase, belong to this category. MMP'26 degrades a range of ECM elements, whereas MMP'7 degrades other protein types. They have a hemopexin-like domain deficiency and can only digest type IV collagen.; type I collagen is not degraded.
5. Membrane type MMPs [MT-MMPs]: Because they all have a C-terminal trans membrane domain as well as a tiny cytoplasmic

Table 1: Different classes and function of MMPs.

MMP	MMP Family	Synonym	Role in photoaging	Ref
1	Collagenase	Interstitial collagenase and Collagenase Type I	Degrade type I and III Collagen	[17]
2	Gelatinase	Gelatinase A and 72 kDa collagenase type IV	Degrade type IV Collagen	[18]
3	Stromelysin	Stromelysin 1, Transin1 and Proteoglycanase	Degrade type I Collagen and Activate MMP'1, MMP'7, and MMP'9	[17]
7	Matrilysin	Matrilysin 1 and Pump 1	Degrade Elastin	[19]
8	Collagenase	Neutrophil collagenase	Restricted role	[20]
9	Gelatinase	GelatinaseB and 92 kDa collagenase type IV	Degrade type IV collagen	[21]
10	Stromelysin	Stromelysin 2 and Transin 2	Stimulate pro-MMPs	[17]
11	Stromelysin	Stromelysin-3	Stimulate pro-MMPs	[17]
12	Other type	Metalloelastase	Elastin degradaion	[22]
13	collagenase	Collagenase-3	Restricted role	[23]
14	Membrane type	MT 1 MMP	Restricted role	[24]
15	Membrane type	MT 2 MMP	Restricted role	[24]
16	Membrane type	MT 3 MMP	Restricted role	[24]
17	Membrane type	MT 4 MMP	Restricted role	[25]
19	Other type	RASI 1	Restricted role	[26]
20	Other type	Enamelysin	Restricted role	[27]
21	Other type	-	-	[28]
23	Other type	-	-	[29]
24	Membrane type	MT 5 MMP	Restricted role	[30]
25	Membrane type	MT 6 MMP	Restricted role	--
26	Matrilysin	Matrilysin 2 and Endometase	Restricted role	[31]
27	Other type	-	-	[32]
28	Other type	Epilysin	Restricted role	[33]

tail, MMP'25, MMP'24, MMP'17, MMP'16, MMP'15, and MMP'14 are categorized as MT-MMPs. First two MMPs are termed as glycosyl phosphatidylinositol i. e. GPI-anchored proteins, and the last two are type I transmembrane proteins. MT'1 to MT'6 MMPs is the names given to them. The enzymes MMP'16 and MMP'14 break down fibrillar type I collagen. Some MMPs, for example MMP'28 (Epilysin), MMP'23, MMP'20 (Enamelysin), MMP'19, and MMP'12 are not classified as such.[13] Different classes and function of MMPs are given in Table 1.

Photoaging is caused by UV radiation, which is a chief environmental element. The two wavelengths that produce UV induced skin damage are UV A (320 to 400 nm) and UV B (290 to 320 nm). UV A rays account for up to 95% of UV radiation that reaches the earth's atmosphere, while ozone levels have just a minor effect. Despite the fact that UV B reaches to the surface of earth in lower quantities than UV A; it has enough intensity to cause photoaging and may lead to skin cancer.[34-35] Both UV A and UV B radiation can cause oxidative damage in human skin, resulting in short and long-term genetic damage, increased AP1 (activator protein1) activity, and increased MMP synthesis.[36-37] Photoaging is caused by the aggregation and destruction of ECM components that provide structural and functional integrity to skin tissue. ECM proteins such as elastin and collagen, along with fibrous proteins in the ECM and connective tissue, deteriorate when exposed to the light on a regular basis. Type I collagen seems to be the most prevalent in the skin connective tissue, followed by type III collagen in modest amounts. Fibroblasts, which are found in the dermis, are in charge of producing collagen, which provides the skin its suppleness and strength.[38]

TIMP's (Tissue inhibitors of metalloproteinases) are natural inhibitors of MMPs that generally regulate collagen degradation. Activation of MMP is an essential contributor in the progression of age related skin modifications (Figure 3). Collagenase is a skin enzyme that breaks down fibrillar type I and type III collagens into specific fragments within the triple helix's centre. It is primarily produced by dermal fibroblasts and epidermal keratinocytes. Additionally, other MMPs, such as gelatinases, hydrolyze these components, impairing the function of the collagen-rich dermis.[39]

UV irradiation produces an increase in MMP'1 dermal fibroblast expression and synthesis, which is triggered by excessive production of ROS (reactive oxygen species) and it plays a vital role in photoaging. Excessive intracellular ROS viz hydrogen peroxide (H_2O_2); singlet oxygen ($^1O_2$), superoxide anion (O^2) and hydroxyl radicals (OH^-) are produced by UV irradiation. The MAPK (mitogen-activated-protein kinase) family of proline directed Serine/Threonine kinases includes ERKs (extracellular-signal-regulated kinases), p38, and JNK (cJun-NH_2terminal kinase).

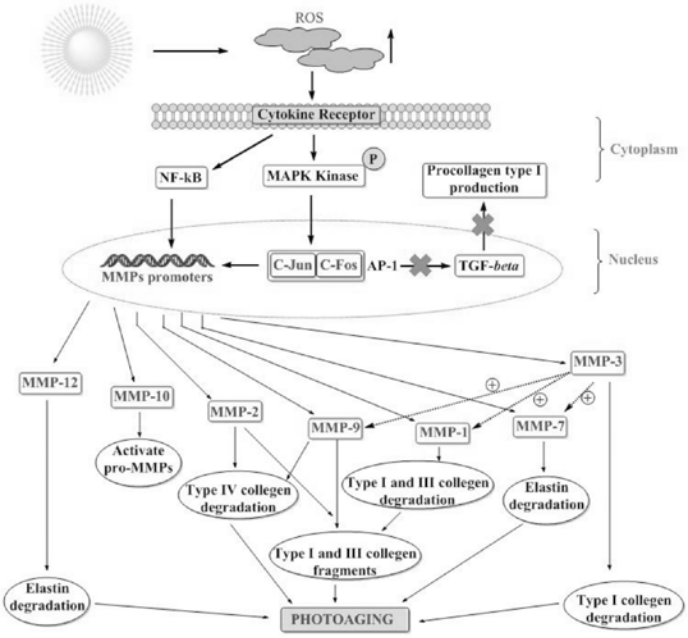

Figure 3: MMPs' involvement in photoaging.
ROS: Reactive Oxygen Species; MAPKS: Mitogen activated protein kinases; NF κB: Nuclear factor kappa B; TGF β: transforming growth factor beta; AP 1: Activator Protein 1.

For the formation of c-Fos, ERK is essential; while p38 and JNK stimulation are essential for the expression of c-Jun. When c-Jun and c-Fos join, the transcription factor AP-1 is generated, and it is important for the transcriptional control of MMP'9, MMP'3, and MMP'1 which leads in collagen breakdown. AP 1 also inhibits TGF (Transforming-growth-factor-beta) signaling, which is a critical controller of procollagen type I production, in human skin.

Procollagen production is reduced when the TGF β pathway is disrupted.[40-42] NF κB (Nuclear-factor-kappa-B) is another essential transcription factor which interacts to UV radiation in conjunction to AP 1. NF κB is a prevalent transcription factor that regulates the genetic synthesis of cytokines, cell adhesion molecules, chemokines and growth factors in both healthy and sick people. ROS induced regulation of MMP gene manifestation and transcriptional activation is mediated by NF κB. As a result, this component is critical in mediating UV irradiation responses. NF κB activation has been associated to the overexpression of MMPs such MMP'1 and MMP'3 in dermal fibroblasts.[43] As a result, both AP 1 and NF κB are engaged in the progression of photoaged skin.

AP 1 activation induced UV irradiation, boosts the MMP'9, MMP'3, and MMP'1 expression. MMP'3, also called stromelysin 1, is distinct from the collagenases in that it cannot breakdown collagen type I. Type X, IX, IV, and V collagens, fibrillin 1, gelatin, fibronectin, proteoglycans, and laminin are among the ECM proteins that it degrades. During ECM turnover, MMP'3s major function is to activate pro-MMPs such as matrilysins, gelatinase B, and collagenases. Partially activating pro-MMP'1 necessitates the synthesis of fully active MMP'3 and MMP'1, in particular. MMP'10, also referred as stromelysin 2, is a protein that aids in the activation of pro-MMPs by cleaving a variety of ECM proteins. When compared to MMP'3 activity, however, collagen type IV and V exhibit a negligible catalytic function.[13]

MMP'9, expression is heavily reliant on AP 1 activation. Human keratinocytes produces MMP'9 which can break down collagen type IV, a vital element of basement membrane of the skin The epidermal basement membrane is involved for epidermal dermal adherence, which is necessary for epidermal maintenance. Additionally, it plays a role in regulation of epidermal differentiation. MMP'2 and MMP'9 both have the potential to break collagen type IV. Other substrates degraded by both gelatinases include collagen types X, VII, and V, fibronectin, and elastin. After collagenases have degraded fibrillar collagen particles are necessary for their breakdown.[44] Collagenases are a type of MMP that causes breakdown of natural collagen without unraveling the substrate's triple helical structure. MMP'13, MMP'8 and MMP'1 belong to this category. Despite minor changes in substrate specificity, they have similar configurations and enzymatic activities. MMP'1, as previously stated, plays a vital part in the photoaging process. MMP'8 appears to play a minor impact in UV induced collagen degradation in the skin, although UV radiation was discovered to stimulate this enzyme. In cleaving collagen types I and type III, MMP'13 has five times lower effectiveness than MMP'1; nevertheless, it is five to ten times stronger in splitting type II collagen. As a result, MMP'13 and MMP'8 are likely to have a minor role in the total structural damage to collagen during photoaging.

The most powerful MMP against elastin is macrophage metalloelastase. In reaction to acute UV exposure, macrophages and fibroblasts release MMP'12. MMP'12 is responsible for formation of actinic or solar elastosis. The accumulation of dystrophic elastotic components in the skin's dermis is referred to as solar elastosis.[45] MMP'12 can degrade a range of ECM substrates along with type IV collagen fragments; laminin, fibronectin, chondroitin sulphates, fibrillin 1, vitronectin, entactin, and heparin, besides elastin. MMP'12 also activates pro-MMPs such as pro MMP'9, MMP'3, MMP'2, and MMP'1. MMP'7 can also degrade elastin, in addition to MMP'12. When exposed to UV radiation, MMP'7 may destroy a range ECM substrates, including cartilage proteoglycan aggregates, type IV collagen, entactin, laminin, and fibronectin.[46]

REGULATORS OF PHOTOAGING (MMP INHIBITORS)

Novel MMP inhibitors are proving to be potential targets in the fight against photoaging. Plant bioacives have aroused a lot of interest in preventing skin photodamage caused by UV radiation in recent years and are summarized in Table 2 and chemical structures of plant bioactives that inhibits or downregulates MMPs are illiustrated in Figure 4a and 4b.

Astaxanthin is an active component derived from the plant *Haematococcus pluvialis*. The antioxidant potential of Astaxanthin on MMP'1 expression and type I procollagen in rat's skin exposed to UV B radiation was evaluated by Sofiah *et al*.[47] Wistar rats were used in the study, which were treated with UV B radiation thrice a week for six weeks (dose-130mJ/cm^2). P_0, P_1 and P_2 were subjected to UV B radiation (P_0 without topical base cream treatment, P_1 with topical treatment of base cream, and P_2 using topical treatment of Astaxanthin cream created with cocoa oil vehicle). Creams were applied twice daily; at a dose of 0.3 g/cm^2 of irradiated skin, 20 min before and 4 hr after UV B exposure. Western blotting and semi-quantitative PCR techniques were used to study at the expression of type I procollagen and MMP'1. MMP'1 levels are significantly reduced in the P2 group compared to the P0 and P1 (p<0.05), indicating the involvement of Astaxanthin in reducing the overexpression of MMP'1 gene (by decreasing MMP'1 protein levels). Instead change in type I Procollagen mRNA expression was not observed against β-actin protein levels.

Oh and co-workers[48] have investigated the protective effects of DCEQA (3,5-Dicaffeoyl-epi-quinic acid) in HaCaT (human keratinocyte cell line) against UV B induced dys-regulation of MMPs. DCEQA is a plant bioactive isolated from the *Atriplex gmelinii* and characterized as per literature.[49] The effects of UV B exposure (15 mJ/cm2) on expression pattern, protein, and MMP'9, MMP'2, and MMP'1 release were studied in HaCaT cells with and without DCEQA administration. The stimulation of MAPKs, ERK p38 and JNK were also observed. Release of type Iα1 procollagen and MMP'9, MMP'2, and MMP'1 from UV B irradiated and non-irradiated HaCaT cells were evaluated by ELISA (enzyme-linked-immunosorbent assay). Significant reduction in overexpression of mRNA and MMP'9, MMP'2, and MMP'1 proteins while slight increase in type I procollagen production were observed when UVB irradiated HaCaTcells were treated with 10 μM of DCEQA. Flow cytometry was used to investigate into the triggering of MAPK levels. A decrease in dose dependent UV B induced activation of MAPKs level was observed that suggested the down regulation of collagen degradation by DCEQA.

The effect of genetic muzzling of Nrf_2 (nuclear-factor-erythroid-2 related factors) on UV A mediated MMP'1 up regulation by HaCaT cells through activation of MAPK/AP 1 signaling pathway was investigated by Chaiprasongsuk *et al*.[50] Bioactive component hispidulin (HD) and sulforaphane (SP) abundantly found in cruciferous vegetables were explored for its Anti photoaging potential. The BALB/c mice skin was subjected to repetitive UV A irradiation; the ability of HD and SP to trigger Nrf_2 in upregulating collagen and MMP'1 expressions along with MAPKs phosphorylation (JNK, p38 and ERK), c-Jun and c-Fos were accessed. They observed increase in MMP'1 activity and expression of mRNA due to reduction of Nrf_2. The researchers observed the increased mRNA expression along with increased activity of MMP'1 due to reduction of Nrf_2. The pretreated mouse skin with plant bioactive (HD and SP) showed protection against UV A mediated collagen reduction and MMP'1 stimulation that was associated with the diminished levels of c-Jun, c-Fos, and phosphorylated MAPKs over the mouse skin.

Table 2: Summary of antiaging plant bioactives and their action on MMP.

Sl. No	Plant bioactive	Mechanism	Reference
1	Astaxanthin	Reduction of MMP'1 expression; type I Procollagen mRNA expression not altered	[47]
2	3,5-Dicaffeoyl-epi-quinic acid (DCEQA)	Reduced in over expression of mRNA and MMP'9, 2, and 1 proteins; increased type I procollagen production	[48]
3	Sulforaphane and hispidulin	Decreased collagen reduction and MMP'1 stimulation	[50]
4	Fisetin	Reduced expression of MMP'9, MMP'3, and MMP'1; Reduced the COX 2 level.	[52]
5	Cordycepin	Reduction of MMP'3 and MMP'1 expressions; Activation of NF κB activity	[53]
6	Plantamajoside	Inhibition of up regulation of MMP'1 protein mediated through glycerAGEs; Reduces the expression of RAGE	[56]
7	Curcumin	Down regulation of MMP'3 and MMP'1; block NF kB and AP 1 activation	[60]
8	Timosaponin A-III	Improved TIMP-mRNA levels and reduction of MMP'1 level	[67]
9	Myricetin	Reduced MMP'9 expression	[12]
10	Berberine	Reduced MMP'9 expression	[80]
11	(−)-Epigallocatechin-3-gallate	Decreased MMP'9 and MMP'2 level	[118]
12	Mangiferin	Reduced MMP'9 level	[67]
13	Baicalein	Reduced MMP'1 expression	[85]
14	Youngiasides A and C	Reduced MMP'1 synthesis	[86]
15	Brazilin	Reduced MMP'3 and MMP'1 expression	[43]
16	Veratric acid	Reduced MMP'9, MMP'2, and MMP'1 expression	[119]
17	Ginsenoside Rg3	Inhibited MMP'2 activity	[89]
18	Triterpenoids	Reduced MMP'1 expression	[90]
19	Lutein	Suppression of MMP to TIMP ratio	[91]
20	Uracil, S-allyl cysteine, and Caffeic acid	Reduced expression of MMPs	[92]
21	Hesperidin	Reduced MMP'9 expression	[93]
22	Galangin	Decrease in MMPs level	[95]
23	Panduratin A	Inhibition of MMP'1	[96]
24	Asiatic acid and ursolic acid	Inhibition of MMP'2	[103]
25	Ferulic acid	Inhibition of MMP'9 and MMP'2 expression	[104]
26	Parthenolide	Block MMP'1 expression	[120]
27	Astragaloside IV	Reduced MMP'1 production	[112]
28	Ziyuglycoside I	Down regulating inflammatory cytokine IL 1, MMP'9, and MMP'2 mRNA expression	[113]
29	Chrysophanol, Physcion, Aloe-emodin, Emodin, Emodin-6-O-β-glucopyranoside, Emodin-8-O-β-glucopyranoside, Emodin-1-O-β-glucopyranoside, Nepodin-8-O-β–glucopyranoside and Chrysophanol-8-O-β-glucopyranoside	Inhibit MMP'13, MMP'8, and MMP'1	[115]
30	(±) Syringaresinol	Inhibited MMP'1 and AP 1.	[117]

3,7,3′,4′-tetrahydroxy flavone i. e. Fisetin is bioactive flavonol most abundantly found in vegetables and fruits like grapes, strawberries, apples, and onions.[51] On UV B mediated human skin fibroblasts, Chiang and colleagues[52] found that MMP'9, MMP'3, and MMP'1 expression was decreased. It also reduces the cyclooxygenase 2 (COX-2) levels. Further it decreased UV B mediated collagen degradation. With regard to MAPKs pathway, Fsetin reduces the expression of UV mediated p38, JNK, and ERK phosphorylation. They observed the increased level of p65; a major subunit of NF κB and decreased I κB (inhibitor κB) degradation. It inhibits NF kB translocation into the nucleus. It also subdued CREB protein (cAMP response-element-binding protein) the level of Ser133 phosphorylation in the PI3K (phosphoinositide 3 kinase) / PKB (protein-kinase B) or CREB pathway. Further Fisetin decreases the ROS generation, NO (nitric oxide) production and PGE 2 (prostaglandin E2) level intracellularly. These effects prove the anti-photoaging property of plant bioactive Fisetin that can be utilized for development of photo-protective agents.

The skin anti photoaging activity of 3'-deoxyadenosine i. e. Cordycepin was investigated by Lee *et al.*[53] A nucleoside derivative Cordycepin isolated from *Cordyceps sinensis* is a component of antiaging materials in

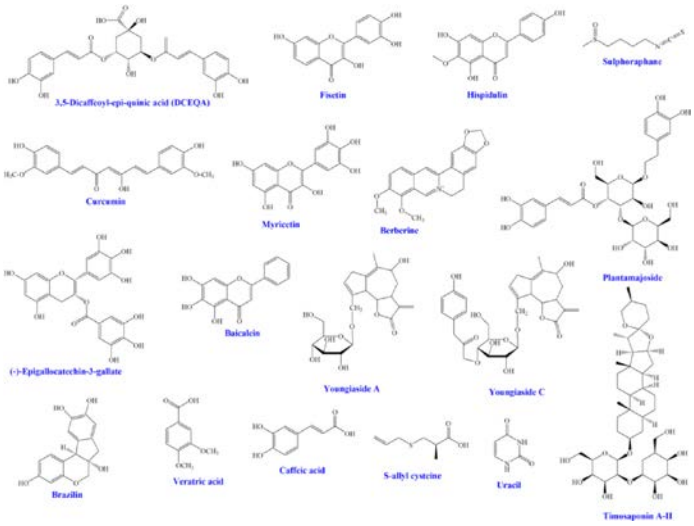

Figure 4a: Chemical structures of plant biactives.

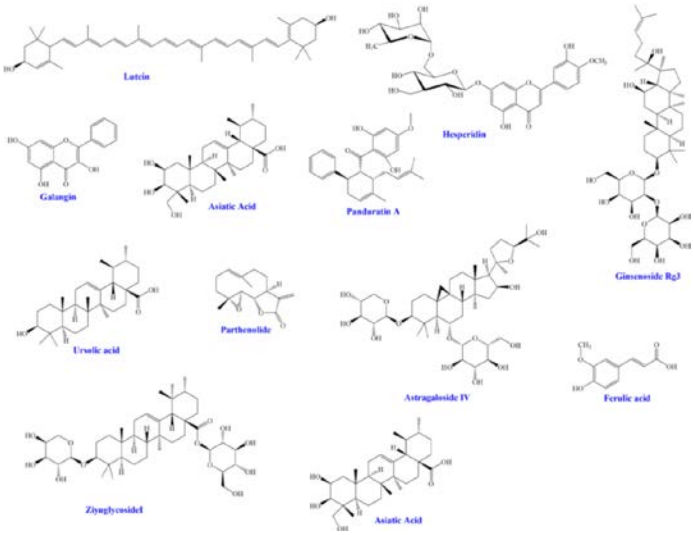

Figure 4b: Chemical structures of plant biactives.

Chinese herbal Medicine. A dose dependent reduction of UV B (25 mJ/cm^2) mediated MMP'3 and MMP'1 expressions were observed in HDF (human-dermal fibroblast; 2 ×10^6 cells) by western blot analysis and RTPCR. Stimulation of NF κB was investigated by NF κB binding; nuclear localization of p65 and p50 subunit; and degradation of Iκ Bα. HDF pretreated with Cordycepin showed decreased UV B mediated MMP expression and NF κB stimulation, which concludes the potentiality of cordycepin in prevention and management of skin photoaging.

Plantamajoside isolated from *Plantago asiatica*, proves to be anti-inflammatory[54] and antioxidant.[55] AGEs (advanced-glycation end products) are formed in sun exposed skin which further generates ROS and leads to MAPKs phosphorylation (including JNK, ERK, and p38), which stimulate NF κB (p65 and p50 subunits) and induces MMP'1 in skin fibroblasts. The protective effects of Plantamajoside on a HaCaT cells and HDF against trauma induced by glycerAGEs (glyceraldehyde induced advanced glycation end products) with UV B irradiation was assessed by Han and coworkers.[56] They observed that the formation of ROS in keratinocytes (glycerAGEs treated and UV B irradiated) was significantly more compared to AGE treated and UV B treated cells only. The increased ROS level was significantly decreased by Plantamajoside treatment and was equivalent to that of Quercetin treatment. RAGE (binding of AGEs to specific receptor) is upregulated and highly expressed in sunexposed skin. The researchers showed that Plantamajoside significantly reduces the expression of RAGE in HaCaT cells and HDF (in overexpressed and upregulated RAGE). Plantamajoside's effect on chronological and photoaging (including MMP'1 expression) was investigated further. Plantamajoside inhibited the upregulation of MMP'1 protein mediated through glycerAGEs with UV irradiation in HDF and HaCaT cells. The researchers concluded that the inhibitory action of Plantamajoside on JNK, p38, and ERK phosphorylation in the HDF cell line is responsible for this effect. Further NF κB signaling upregulated by UV B irradiation and AGE induced RAGE over expression was inhibited by Plantamajoside. These findings strongly suggest Plantamajoside, a promising therapeutic agent for prevention of skin photoaging.

A commonly used spice and polyphenol, Diferuloylmethane known as Curcumin is derived from Curcuma longa (turmeric). The anti-inflammatory,[57] antioxidant[58] and antiangiogenic[59] properties of curcumin are already proven. The MMP'3 and MMP'1 inhibitory potential of Curcumin in HDF cells were investigated by Hwang *et al*.[60] Levels of MMP'3 and MMP'1 were determined by ELISA and western-blot analysis on UV B (25 mJ/cm^2) mediated HDFs (2.0X10^6 cells). The Quantikine-ELISA Kit and Fluorokine-E Human Active MMP'1 Fluorescent-Assay Kit were used for estimation of MMP'3 and MMP'1 levels respectively. Curcumin significantly reduced the UV B mediated production and secretion of MMP'3 and MMP'1. The intracellular ROS concentration was investigated to study the effects of curcumin on UV B induced ROS production using DCF-DA (a fluorescent-probe dye, sensitive to oxidation), which was identified with a FACStar flow cytometer. The ROS level was significantly blocked by curcumin. Curcumin's effect on UV B induced NF kB and AP 1 signalling, as measured by EMSA employing nuclear extracts, was investigated to see if transcription factors were involved in reducing MMP expression. Curcumin inhibited the activation of AP 1 and NF kB in a considerable way. Further the effect of Curcumin on MAPK signaling was investigated, Curcumin significantly blocked p38 and JNK phosphorylation pathways.

Timosaponin A-III (TM A-III), abundantly found in *Anemarrhena asphodeloides* rhizomes has antidepressant, antipyretic, anticancer, and antidiabetic property.[61-65] Im *et al*[66] have evaluated the photo protective effect of TM A- III on UV B irradiated HaCaT cells. TM A- III was isolated by method described by Kim *et al*.[67] Cell viability assay was performed on nontumorigenic HaCaT cells (1×10^4) upon UV B exposure (20 mJ/cm^2) with and without TM A- III. Cells were nurtured in MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carbox-ymethoxyphenyl)-2-(4-sulfophenyl)-2H- tetrazolium)) for one hr to examine the cell viability; subsequently the formation of formazon due to reduction was measured. TM A- III treatment maintained the cell viability at 100.4% while in untreated cells, the cell viability diminished to 49.6%. MMP'1 level in UV B irradiated HaCaT cells with and without TM A -III was evaluated by ELISA. The treated cells showed decreased MMP'1 level. The mRNA levels were determined by qRTPCR using TaqMan assay that is specific for TNF α IL 8,, TIMP, and IL 1β. TM A- III treated cells showed improved TIMP-mRNA levels reduced due to UV B irradiation. Additionally, TM A- III treatment reversed the effect on inflammatory cytokines caused by UV B irradiation. This suggested anti-inflammatory activity aids the photoprotective effect of TM A- III. Clinical safety evaluation of TM A-III (0.25%) was carried out on 21 females, ages ranging from 43 and 55. The patch test was performed on, positive control (treated with sodium lauryl sulfate; 0.5%), negative control (treated with Squalane) and test group (treated with 0.25% TM A- III). To examine the skin reactions,

criteria specified by the guidelines of the Personal Care Product Council and, Frosch and Kligman method were followed. Participants showed no signs of dermatological toxicity. The subjects for the study were selected as per the guidelines and the wrinkles formation on skin was analyzed by Visioline® fabricated with SILFLO replica, at different time points. The parameters selected for analysis were- smoothness depth; maximum roughness; average roughness; and average roughness-arithmetic. TM A- III treatment significantly improved skin roughness as compared to control groups after four, eight and twelve weeks of treatment. Average roughness; smoothness depth were also expressively improved after twelve weeks of product use. Hence TM A- III provides photoprotection and reduces photoaging and wrinkle formation.

3,3',4',5,5',7-hexahydroxyflavone commonly known as Myricetin is a flavonoid mostly found in red wine, berries, onions and grapes.[68-74] It has antiinflammatory, antioxidant, anticancer and antitumor activity.[74-75,69-70] Jung and coworkers[12] studied the involvement of Raf in reduced MMP'9 expression and wrinkle formation by plant bioactive Myricetin. The photoaging study was performed on well-developed hairless mouse (SKH 1) to determine the influence of Myricetin on UV B irradiated (0.18 J/cm^2) wrinkle formation. The results showed that the wrinkle formation was considerably diminished by treatment with Myricetin. Further Western-blot analysis and gelatin zymography showed the decreased MMP'9 activity and reduced MMP'9 expression on UV B irradiated mouse dorsal skin. Also western-blot analysis investigated the inhibition of phosphorylation of p38, ERK, and MEK by Myricetin at a dose of 1 to 5 nmol in 200 ml acetone. But phosphorylation of Raf was not inhibited. The co-precipitation assay by Myricetin conjugated-Sepharose 4B beads investigated that Myricetin inhibited Raf kinase activity in a non ATP competitive manner.

An isoquinoline alkaloid, Berberine mainly found in Oregon grape (*Berberis aquifolium*), turmeric (*Berberis ristate*), barberry (*Berberis vulgaris*),[76] and goldenseal (*Hydrastis canadensis*) have shown to be antioxidant, cell cycle arrest, and anticancer activity.[77-79] Kim *et al.*[80] showed that Berberine decreased the UV mediated MMP'1 expression, and inhibited the lowering of type I pro-collagen expression in HDF. The increased level of MMP'1 (219.6±35.7% to that of control level) by UV irradiation (100 mJ/cm^2) was reduced to 131.3 71 8.9% of control level by treatment of Berberine (20 mM). Further the decreased type I procollagen expression (52.6, 75.7% to that of control level) was concealed to 107.7, 722.2% of control level.

The effect of epigallocatechin-3-gallate (ECG) on ECM metabolism was explored by the same group of researchers. ECG is obtained from green tea extracts that has powerful antioxidant, antiinflammatory, anti-cancer, and immune-modulatory property.[81-84] The researchers look into the effect of ECG on MMP and TIMP expression and compred it to the active component of retinoids, trans retinoic acid (tRA). 2% ECG was topically administered on UVA (20 J/cm^2) irradiated artificial skin. The gelatin zymography showed an average 31.7% and 35.3% reduced level of MMP'3 and MMP'1 expression respectively while tRA showed 24.9% and 35.2% decrease. Similarly ECG treatment showed decreased MMP'9 and MMP'2 level (43.9% and 51.7% respectively) while tRA reduced the MMP'9 and MMP'2 level by 12.5% and 10.4% respectively. After ECG treatment, there was a significant rise in TIMP 1 expression. ECG at 0.01 and 0.1 μM raised TIMP 1 expression to 152.1 and 210%, respectively as compared to the control group i. e. vehicle treated, 100%. TIMP 1 expression was raised by 12.5 and 19.8%, respectively, after treatment with tRA, 0.01 and 0.1 μM.

On UV B triggered tissue damage in hairless mice, the photoprotective efficiency of Mangiferin[67] isolated from A. asphodeloides was examined. Wrinkles appeared as a result of UV B exposure, as well as MMP'9 expression increased. The increased MMP'9 m mRNA levels (determined by RTPCR and Western blot analysis) on UV B induced (30 mJ/cm^2) Human keratinocyte (HEKa) cells, were inhibited by Mangiferin treatment, it significantly improved the MMP'9 mRNA levels. Oral administration of Mangiferin, on the other hand, inhibited these photoaging effects. Mangiferin inhibited UV B irradiated MMP'9 production in HEKa cells, which is controlled by the MEK/ERK pathway. Mangiferin also prevented UV B irradiated collagen fiber loss, wrinkle development and skin thickening in mice.

The *in vitro* activity of 5,6,7-trihydroxyflavone (Baicalein) isolated from Scutellaria baicalensis roots, against H_2O_2-induced damage was studied by Kim *et al.*[85] utilizing a model of human skin keratinocyte. Baicalein therapy considerably reduced H_2O_2 mediated elevation of MMP'1 mRNA and MMP'1 protein expression in cultured HaCaT keratinocytes. It also inhibited AP 1 transcriptional activity along with c-Jun and c-Fos production, two major elements of the AP 1 heterodimeric transcription factor. ERK and JNK, two proteins that are ahead of the AP 1 transcription factor, were likewise inhibited by Baicalein. According to the findings of this study, Baicalein reduces MMP'1 production generated by oxidative stress by inhibiting the ERK/JNK/AP 1 signalling pathway.

The effects of YGA (Youngiaside-A), YGC (Youngiaside-C), and YGD (*Youngia denticulatum*) extract[86] in UV B irradiated HDFs and HaCaT keratinocytes was studied. The molecular pathways involved in extrinsic aging were also studied. YGA, YGC, and YGD extract lowered MMP up-regulation and production in HDFs and HaCaT cells, while increasing collagen upregulation and production in HDFs, according to the findings. Furthermore, YGA, YGC, and YGD extract considerably boosted the expression of antioxidant enzyme in HaCaT cells; reducing UV B induced ROS generation as well as ROS induced AP 1 and MAPK signaling. Furthermore, YGA, YGC, and YGD extract inhibited p65, NF κB nuclear translocation and considerably inhibited proinflammatory mediators by reducing phosphorylation of IκBα and IKKα/β, blocking nuclear factor NF κB p65 nuclear translocation, and substantially suppressing proinflammatory mediators. Lastly, in AMPK inhibitor/ Nrf$_2$ (nuclear-factor erythroid-2 related factor-2); siRNA treated HaCaT cells; YGA, YGC, and YGDE increased UV induced AMPK phosphorylation, but YGA and YGC did not reduce MMP'1 synthesis.

The primary component of *Caesalpinia sappan L.*, 7,11b-dihydrobenz[b] indeno[1,2-d]pyran-3,6a,9,10 (6H)-tetrol (Brazilin), is a red pigment derived from plants that is used in histological staining. Researchers discovered that the Brazilin has a variety of biological effects that includes antihepatotoxicity, antiplatelet action, and Anti-inflammatory properties. Lee *et al.*[43] explored the influence of Brazilin on MMP'3 and 1 expression in UV B exposed human skin cells. Brazilin showed a beneficial effect in fibroblasts towards UV B-induced cell viability loss. Brazilin inhibited the production of reactive oxygen species (ROS) in fibroblasts exposed to UV B. Brazilin inhibited MMP'3 and 1 expression caused by UV B in a dose-dependent manner. In addition, Brazilin treatment completely blocked UV B induced NF κB activation. Brazilin inhibits UV B induced MMP'3 and 1 synthesis and release in human dermal fibroblasts through inhibiting NF κB activation, according to these studies.

The most common benzoic acid derivative found in medicinal mushrooms, fruits, and vegetables is phenolic 3,4-dimethoxybenzoic acid (Veratric acid, VA). VA contains antioxidant, anti-inflammatory, and photoprotective properties, according to studies. In HaCaT keratinocytes, VA reduced the development of cyclobutane pyrimidine dimers and prevented GSH (glutathione) depletion and death produced by UV B.[87] The photoprotective strategies of VA over UV irradiation in the rebuilt human epidermal model and HDFs were used to explore the anti-photoaging impact of VA. They employed Western-blot analysis, immunohistochemistry, hematoxylin, eosin staining and RTPCR. They

also looked into the clinical benefits of VA on human face wrinkle reduction. They observed that VA blocked MMP'9, MMP'2, and MMP'1 expression, enhanced type I procollagen, cell proliferation, filaggrin and TIMPs, against UV irradiation, but had negligible effect on elastic fiber expression. Furthermore, a research study indicated that applying a cream containing VA reduced the appearance of wrinkles on the face. These data show that VA lowers formation of wrinkles via modifying collagens; MMPs; and the integrity of the epidermal layer.

Ginsenosides[88] are primary bioactive components in ginseng that are responsible for a wide range of pharmacological effects. The photoaging protective properties of the two stereoisomers of Ginsenoside-Rg3; 20(S)-Rg3 and 20(R)-Rg3 on the skin were compared.[89] When the cultured human keratinocyte HaCaT cells were treated with the two stereoisomers prior to UV B irradiation (70 mJ/cm^2); fluorometric and confocal microscopic studies revealed that 20(S)-Rg3 suppressed UV B induced ROS levels intracellularly in a concentration dependent manner, while 20(R)-Rg3 did not reduce ROS level. In HDFs; 20(S)-Rg3 reduced UV B induced ROS levels but 20(R)-Rg3 did not. Under UV B irradiation, neither stereoisomer was able to modify the levels of nitric oxide in HaCaT cells, nor neither triggered cytotoxicity in cultured keratinocytes or fibroblasts. In HaCaT cells, 20(S)-Rg3 inhibited UV B induced MMP'2 activity. These findings suggest that 20(S)-Rg3 has both MMP'2 inhibitory and ROS scavenging properties, whereas 20(R)-Rg3 has none. These suggested that Ginsenoside-Rg3 has anti photoaging properties in the skin in a stereoselective manner.

Column chromatography was performed to isolate Oleanolic aldehyde acetate (A), Erythro-diol-3-acetate (B), Euphorginol (C), and Anhydrosophoradiol-3-acetate (D) from the shoots of Styrax japonica from the methylene chloride soluble fraction.[90] Compound A and D showed strong cytotoxicity against human dermal fibroblasts (IC_{50} values = 0.84 mM, 1.12 mM), while compound B, C showed no cytotoxicity against HDFs in the test doses of 0.01 to 1 mM; when compared to the UV irradiated control. In HDFs, the effects of B, C on the production of MMP'1 and type 1 procollagen were investigated by means of western-blot analysis. The activity of erythrodiol-3-acetate was equivalent to those of the positive control (EGCG), however euphorginol was inactive. In a dose dependent manner; erythrodiol-3-acetate enhances type 1 procollagen expression while suppressed MMP'1 expression at the protein level.

Lutein possesses photoprotective, antioxidant, anticarcinogenic, and antiinflammatory properties. The antiaging and anticarcinogenic effect of lutein was investigated via the regulation of the ECM remodeling. Philips and co-workers[91] investigated the effects of lutein on expression of MMPs, TIMPs in HDFs and melanoma cells. The regulation of membrane integrity, cell viability, and elastin expression in irradiated and non-irradiated UV A, and UV B fibroblasts were studied to determine Lutein's photoprotective potential. Lutein dramatically reduced MMP'1 transcription and protein levels in dermal fibroblasts while having little effect on TIMPs expression. In melanoma cells, it reduced MMP'1 production while boosting TIMP 2. Lutein suppressed elastin expression, increased cell viability, and membrane integrity in fibroblasts exposed to UV light, however more so in UV B exposed fibroblasts. In summary, the suppression of TIMP to MMP ratio in dermal fibroblasts and melanoma cells, as well as the prevention of elastin expression, membrane damage, and cell loss in UV radiation exposed fibroblasts, are the mechanisms of antiaging and anticarcinogenic potential of Lutein.

Kim and colleagues[92] studied whether the garlic compounds Uracil, S-allyl cysteine and Caffeic acid, alter the wrinkle formation caused by UV B radiation. It also has an impact on NF-B signalling and MMP expression. The findings revealed that these plant bioactives strongly prevented type I procollagen breakdown and expression of MMP *in vivo*, as well as helps in reducing oxidative stress and collagen fibre disorder. S-allyl cysteine and Caffeic acid were discovered to diminish inflammation and oxidative stress by regulating the activities of NF κB and AP 1. Uracil demonstrated an indirect antioxidant effect by lowering the production of iNOS (inducible nitric oxide synthase) and COX 2 as well as downregulating transcriptional factors. These data suggest that the antioxidant and anti-inflammatory properties of uracil, S-allyl cysteine, and caffeic acid are responsible for their anti-wrinkle effects. To summarise, uracil, S-allyl cysteine, and caffeic acid inhibited UV B induced wrinkle development by regulating MMPs via NF κB signalling.

The flavanone glycoside 3,5,7-trihydroxy-4-methoxyflavanone-7-(6-l-rhamnopyranosyl-d-glucopyranoside) [Hesperidin], abundantly found in citrus fruits, has been exerted to have immune regulating, antioxidant, and anti-inflammatory activities.[93] Hesperidin exerts an anti photoaging effect on UV B induced hairless mice by increasing MMP'9 synthesis via MAPK signalling pathways. UV B rays cause skin damage, including dryness and an increase in the TEWL (trans-epidermal water loss). Increased TEWL has an impact on enzymatic activity, making the skin appear dry and wrinkled. Because UV irradiation impairs the epidermal permeability barrier qualities of the skin, the TEWL is an important measure to examine the skin's photoprotective effects study. The use of hesperidin substantially reduced skin damage. This was linked to improved skin moisture as well as a decreasing TEWL.

Galangin is a natural favonol that has recently been identified to have antiviral, anti-infectious, antiatopic dermatitis, and antioxidative characteristics, that is tilized in skin care products.[94] Kim *et al*.[95] studied the preventive effect of galangin on UV B induced photoaging in HDFs (CCD986sk) using Western blot analysis and ELISA. NF κB and AP 1 are the primary transcription factors that upregulate MMPs in activated MAPK. Galangin inhibited phosphorylation of MAPK signaling pathway, resulting in a decrease in intracellular ROS, 4HNE, and MMPs, along with protection against oxidative destruction in skin fibroblasts triggered by UV B irradiation. Upregulation of type 1 procollagen and fibroblast growth factor 2 resulted as a result of this.

The effects of Panduratin A, a chalcone molecule derived from *Kaempferia pandurata* Roxb, on the expression of type 1 procollagen and MMP'1 in UV irradiated HDFs were studied by Jae Seok Shim *et al*.[96] UV (20 mJ/cm^2) was used to irradiate human fibroblasts, and Panduratin A was further administered to the fibroblast culture medium. Western-blot analysis and RT RCR were used to determine the levels of MMP'1 expression and type 1 procollagen. At the mRNA gene and protein levels, Panduratin A (concentrations: 0.001–0.1 mM) dramatically inhibited the expression of MMP'1 while inducing expression of type 1 procollagen. The effect of Panduratin A on UV induced stimulation of MAPKs signalling modules such as JNK, p38 kinase and ERK was also examined by the same group of researchers.[97] UV induced JNK, ERK, and p38 activation was strongly reduced by Panduratin A treatment (concentrations: 0.0 01 to 0.1 mM). Furthermore, Panduratin A inhibition of p38, JNK, and ERK resulted in lower c-Fos expression and c-Jun phosphorylation triggered by UV irradiation, which inhibited the activity of AP 1 DNA binding. Also Panduratin A exhibited better acivity than EGCG, a distinguished antiaging plant bioactive compound.

Centella asiatica contains Asiatic acid, a pentacyclic triterpene molecule that has traditionally been used as a tonic for skin ailments and leprosy.[98] Asiatic acid (AA) was reported to increase collagen formation and fibroblast proliferation, as well as promote ECM development, in a rat wound model.[99] Ursolic acid (UA), which is chemically similar to AA, is found in all parts of a variety of plants and has been linked to a number of biological consequences.[100] UA, in particular, has been shown to raise collagen synthesis in skin cells, as well as having anti-inflammatory, skin tumour prevention,[101] and anti-invasion[102] properties. Lee

and colleagues investigated the effects of triterpene compounds UA and AA on UV A modulated signalling pathways Employing HaCaT human keratinocytes as a basic biological system.[103] They found, UV A irradiation caused oxidative damage in the cells and elevated MMP'2 production. UV A induced lipid peroxidation and ROS generation were considerably reduced by UA and AA. The UV A triggered stimulation and production of MMP'2 was significantly reduced. When the cells were pretreated with UA and AA. UV A produced elevated expression of p53, which is a hallmark of UV mediated DNA damage or even death, was likewise considerably reduced by administration with UA and AA. In human skin cells, the combination of UA and AA appears to be an efficient inhibitor of UV A regulated signal transduction pathways.

The effects of Ferulic acid (FA), a common phenolic component existing in a number of dietary and medicinal plants, on UV B prompted MMP'9 and 2 activities in mouse skin were examined by Staniforth *et al*.[104] Immunohistochemical study revealed that inhibiting MMP'9 and 2 protein expressions reduced skin damage caused by continuous UV B irradiation. However, FA's *in situ* inhibitory effects did not interfere with MMP'9 and 2 transcription or translation, implying that its impact is conducted through the proteasome route. Histological investigations revealed that FA reduces UV B induced collagen breakdown, aberrant elastic fiber buildup, and epidermal hyperplasia, revealing the efficient and physiologic importance of FA effects in UV B exposed skin tissues.

A sesquiterpene lactone molecule, Parthenolide is present in the herbal plant Feverfew (Tanacetum parthenium) (*Tanacetum parthenium*), which has traditionally been used in Mexico to relieve inflammation. Parthenolide was found to impede the NF κB activation pathway on various levels, including reducing IκB kinase activity[105] and NF-κB DNA binding.[106] Tanaka and colleagues[107] explored the efficacy of Parthenolide in preventing the processes of UV B induced cutaneous changes in animal models and cultured cells. Parthenolide was discovered to efficiently block NF κB mediated gene expression as well as the generation of MMP'1 and bFGF (basic fibroblast-growth-factor) in cells that overexpresses p65, a key subunit of NF κB. Parthenolide was also discovered to decrease the UV B mediated proliferation of melanocytes and keratinocytes in the skin of mice.

3-O-D-xylopyranosyl-6-O-D-glucopyranosyl-cycloastragenol (Astragaloside IV, ASG-IV) is a saponin found in the traditional Chinese herbal medicine *Astragalus membranaceus Bge (Fisch)*; family-Leguminosae that has a variety of pharmacological actions[108] and is extensively used to treat cardiovascular disease. Previous research has found that ASG-IV has a variety of pharmacological effects, including antiinflammatory activities,[109] cardioprotective qualities,[110] and antioxidant activity.[111] The influence of ASG-IV on expression of MMP'1 in UV irradiated HDFs was studied by Yang *et al*.[112] They discovered that ASG-IV reduced UV prompted MMP'1 production at the mRNA, as well as at the protein levels. Furthermore, western blotting analysis demonstrated that ASG-IV reduced UV induced phosphorylation of p38 MAPKs, Jun-N-terminal kinase, and also extracellularly regulated protein kinase in a concentration dependent manner. Furthermore, ASG-IV therapy significantly reduced UV induced NF κB activity. These findings imply that ASG-IV inhibits UV prompted MMP'1 synthesis in HDFs, possibly through suppressing MAPK and NF κB activation.

On UV B induced hairless mice, the preventative benefits of a skin cream comprising Ziyuglycoside I, a plant bioactive obtained from *Sanguisorba officinalis*, were tested.[113] For 5 weeks, UV B irradiated hairless mice were topically treated with the skin cream once a day. The skin cream had no adverse effects on the mice's growth, resulting in normal food efficiency and body weight. The mRNA expression of interleukin (IL) 1, MMP'9, MMP'2, and MMP'2 protein on mice skin was likewise suppressed by the skin cream therapy. In addition, in UV B induced hairless mice, the skin cream pretreatment decreases degradation of collagen, formation of epidermal wrinkle, wrinkle thickness, and wrinkle depth. As a result, the skin cream was effective to reduce photoaging caused by UVB irradiation by down regulating inflammatory cytokine IL 1, MMP'9, and MMP'2, mRNA expression and suppressing MMP'2 protein expression.

Rumex species are abundant and widely grown all over the world. Rumex species contain mostly flavonoid anthranoids, naphthalenes, and tannin derivatives in their chemical makeup. Cassia, Rhamnus, and Aloe species contain considerable levels of anthranoids.[114] Sennosides and anthraquinones found in *Cassia sp.* include physcion, chrysophanol, rhein, emodin, and aloe-emodin. From the roots of Rumex crispus L. nine compounds were obtained: 1) chrysophanol (CH), 2) physcion (PH), 3) emodin (E), 4) aloe-emodin (AE), 5) emodin-8-O-β-glucopyranoside (E_8G), 6) emodin-6-O-β-glucopyranoside (E_6G), 7) chrysophanol-8-O-β-glucopyranoside (C_8G), 8) emodin-1-O-β-glucopyranoside (E_1G), and 9) nepodin-8-O-β–glucopyranoside (N_8G); and UV, IR, ESI-MS (electrospray ionisation mass spectrometry), 1D-NMR and 2D-NMR techniques were used to deduce the structures. These nine isolated compounds were subjected to molecular docking investigations employing MMP enzymes for screening and pre-evaluation before *in vitro* and *in vivo* experiments to save time and money and to examine antiaging properties. MMP'13, MMP'8, and MMP'1 enzymes were inhibited by binding energies less than 2 kcal/mol, according to the results of molecular docking experiments. MMP'13, MMP'8, and MMP'1, SPFs (sun protection factors) and enzyme inhibitory effects, of these substances were also explored. The aglycones with the greatest SPF values were E (SPF:30.6), while the glycosides with the highest SPF values were E6G (SPF:21.051) and E8G (SPF:18.526) compounds. It denotes the potential for protection against the sun's harmful rays. CH and PH an anthraquinone aglycones blocked MMP'13, MMP'8, and MMP'1 enzymes more than rhein, emodin, and aloe emodin aglycones, according to the findings. Other glycosides studied were shown to be less efficient on MMP'13 and MMP'1 enzymes rather than C8G. E1G, on the other hand, blocked MMP'8 enzyme more rather than C_8G.[115]

(±) Syringaresinol (SGR) is a plant bioactive belonging to the polyphenol's lignan family and it can be extracted from a variety of plant components, including the cortex of flax and Amelia seeds. SGR has been reported to have anti-inflammatory, antifungal and antibacterial activity. More recently, research outcomes relating to skin, like improvement in immunological disease, skin whitening, and antiaging property have been published.[116] *In vitro* studies of the ability of SR to counteract UV A induced alterations in HDFs and HaCaT keratinocytes were conducted by Oh *et al*.[117] The role of SR on UV A-induced changes was investigated using MMPs and their transcriptional upstream effectors, MAPKs, and pro-inflammatory mediators. Immunoblotting, ELISA, and RTPCR methods were used to evaluate expression levels. UV A irradiation increased MMP'1 synthesis while decreasing collagen formation. In UVA irradiated HDFs and HaCaT keratinocytes, SR treatment inhibited MMP'1 and increased collagen synthesis. In HaCaT keratinocytes, SGR suppressed UV prompted phosphorylation of JNK, p38, and ERK MAPKs, but it solely suppressed JNK phosphorylation in HDFs. SGR also subdued the synthesis of inflammatory cytokines such as IL 1, TNF α, IL 6, and COX 2 when exposed to UV light. It also inhibited the AP 1. As a strategy to limit UV A induced transcriptional activity leading to MMP'1 synthesis, SGR therapy reduced the levels of activated c-Fos and c-Jun in the nucleus. Finally, the current findings showed that SGR inhibited UV A mediated induction of MMP'1 in HDFs and HaCaT keratinocytes through decreasing MAPKs; AP 1 signalling.

FUTURE PROSPECTS AND CONCLUSION

UV irradiation from the sun has a significant impact on skin health. Chronic UV exposure causes photoaging, which causes premature skin aging. Cosmetology, as a branch of medicine, employs a variety of active chemicals to decelerate the aging progression of the skin. By modulating the age-related signaling pathways, plant bioactives have been shown to delay cellular senescence or *in vivo* aging. MMPs are employed as skin anti-aging components in cosmetology. Plant based medicines play a significant part in the health care system. Plant bioactives usage in cosmetics holds a lot of promise for new cosmetic discoveries. In fact, these are largely responsible for the beauty industry's current growth. Future study should hopefully lead to the discovery of new functionally active plant bioactives that work at the molecular level.

In cosmetology, natural inhibitors of MMPs are used in a variety of cosmetic formulations as chemicals that protect skin from harmful external factors and as potential antiaging agents. Wrinkles are a symptom of photoaging, and MMPs play a role in their production. MMP levels rise naturally with age and after exposure to irradiation; thus, one strategy for reducing photodamage to the skin is to regulate MMPs, as their actions lead formation of wrinkle. Free radical scavengers or antioxidants are being studied as a therapeutic alternative for lowering the harmful impacts of UV rays and preventing UV mediated photoaging due to their capability to reduce MMP synthesis, activation and expression.

Photoaging prevention and therapy necessitates a lot of clinical attention, which is currently the focus of cosmetology research. Natural-occurring chemicals, particularly plant bioactives, have attracted researchers' interest in recent decades because to their low toxicity, low cost, high biodegradability, and broad-spectrum bioactivities. In order for plant bioactive based anti-photoaging medications to proceed, protein targets or enzymes, signaling pathways, and intermediaries must all be identified because prevention and/or treatment for aging skin has become increasingly technologically invasive in recent years. Herbal remedies with plant bioactives, on the other hand, are still important, and combining them with the molecular methodologies will assist to maximise the results and sustain the intended anti photoaging advantages.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UV: Ultraviolet; **ECM:** Extracellular matrix; **MMPs:** Matrix metalloproteinases; **CAGR:** Compound annual growth rate; **IR:** Infrared; **MMPIs:** Matrix metalloproteinases inhibitors; **MT:** Membrane type; **AP1:** Activator protein1; **TIMP's:** Tissue inhibitors of metalloproteinases; **ROS:** Reactive oxygen species; **MAPK:** Mitogen-activated-protein kinase; **ERKs:** Extracellular-signal-regulated kinases; **JNK:** cJun-NH_2-terminal kinase; **TGF:** Transforming-growth-factor-beta; **NF κB:** Nuclear-factor-kappa-B; **DCEQA:** 3,5-Dicaffeoyl-epiquinic acid; **ELISA:** Enzyme-linked-immunosorbent assay; **Nrf_2:** Nuclear-factor-erythroid-2 related factors; **HD:** Hispidulin; **SP:** Sulforaphane; **COX-2:** Cyclooxygenase 2; **CREB protein:** cAMP response-element-binding protein; **PI3K:** Phosphoinositide 3 kinase; **PKB:** Protein-kinase B; **HDF:** Hhuman-dermal fibroblast; **AGEs:** Aadvanced-glycation end products; **TM A-III:** Timosaponin A- III; **ECG:** Epigallocatechin-3-gallate **YG:** Youngiaside; **TEWL:** Trans-epidermal water loss; **AA:** Asiatic acid; **FA:** Ferulic acid; **ASG-IV:** Astragaloside IV; **SGR:** Syringaresinol.

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