Ageing Research Reviews 13 (2014) 65–74

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Matrix metalloproteinase enzymes and their naturally derived inhibitors: Novel targets in photocarcinoma therapy

Anshita Gupta, Chanchal Deep Kaur, Manmohan Jangdey, Swarnlata Saraf*

University Institute of Pharmacy, Raipur, Pt. Ravishankar Shukla University, Chhattisgarh 492010, India

ARTICLE INFO

Article history:
Received 1 July 2013
Received in revised form
15 November 2013
Accepted 2 December 2013
Available online 16 December 2013

Keywords:
Ultraviolet radiations
Non melanoma skin cancer
Extracellular matrix
Matrix metalloproteinase
Mitogen activated protein kinase

ABSTRACT

The continuous exposure of skin to ultraviolet radiations generates reactive oxygen species leading to photoaging in which degradation of dermal collagen and degeneration of elastic fibers occurs. Matrix metalloproteinase [MMP] enzymes are the proteolytic enzymes which have significant potentiality of cleaving extracellular matrix [ECM] against Ultraviolet [UV] radiation. The important MMPs are MMP1, MMP2 and MMP7 which promote skin cancer when irradiated by UV rays. In lieu of this, the investigation of MMPs and their inhibitors are constantly being studied for successive results. Recent researches have focused on some traditionally used bioactive moieties as natural matrix metalloproteinases inhibitors (MMPIs) and emphasized on the need of more extensive and specific studies on MMPIs, so that a good combination of natural or synthetic MMPIs with the conventional drugs can be evolved for cancer chemotherapy. In this review, we discuss the current view on the feasibility of MMPs as targets for therapeutic intervention in cancer. This review also summarizes the role of small molecular weight natural MMPIs and a clinical update of those natural MMPIs that are under clinical trial stage.

Contents

Abbreviations: MMP, matrix metalloproteinase; MMPIs, matrix metalloproteinase inhibitors; ECM, extracellular matrix; SC, stratum coreneum; UVB, ultraviolet radiations B; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; DNA, deoxyribonucleic acid; CPD, cyclobutane pyrimidine dimmers; NER, nucleotide excision repair; TCR, transcription-coupled repair; GGR, global genome repair; LE, lupus erythematosus; XP, xeroderma pigmentosum; TTD, trichothiodystrophy; ODC, ornithine decarboxylase; MAPKs, mitogen activated protein kinase; NOS, nitric oxide synthase; TRAP, telomeric repeat amplification protocol; CBD, collagen binding domain; ACD, allergic contact dermatosis; AD, atopic dermatosis; SRF, skin respiratory factors; TRF, tissue respiratory factors.

* Corresponding author. Tel.: +91-0771-2262832, Mob: +91 9425522945.
E-mail addresses: research_iop@rediffmail.com, anshita1912@gmail.com (A. Gupta), dr.chanchaldeep@gmail.com (C.D. Kaur), mmanusj@rediffmail.com (M. Jangdey), swarnlata_saraf@rediffmail.com (S. Saraf).

1568-1637/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.arr.2013.12.001

1. Introduction

Matrix metalloproteinase are the enzymes which have been vigorously studied for identifying their functions and role in the progress of cancer. They are the initiators of angiogenesis, metastasis, inflammation and other pathological consequences manifested in carcinoma. The idea of targeting MMPs as a therapeutic receptor in cancer treatment was laid down 30 years ago by Liotta et al. (Konstantinopoulos et al., 2008), by that time to now tremendous efforts have been made to target different MMPs for slowing the growth of cancer cells. Several clinical studies (Fisher et al., 2009) have demonstrated the promising aspects of MMPIs expression but very limited outcomes have been received. The utilization of Natural bioactives as a therapeutic drug targeting system toward MMPs in proliferation of photocarcinoma will be an innovative to support the traditional drug regimen for cancer (Mannello, 2006).

The human skin constitutes the most vital aspect in the defense mechanism against the exposure of ultraviolet radiation. It acts as an efficient barrier system to protect the underlying tissues from the external environment. But the intensity of incident solar radiation causes changes in the nature of skin. These changes can be fundamental, in order to protect the cells from the deleterious effect of ultraviolet radiations or it may be a pathological change rendering the provocation of biochemical alterations leading to the destruction of tissues (Soehnge et al., 1997). The alterations exhibited by the skin leads to inflammation, erythema, premature aging, fine lines and wrinkle formation, chapping and cracking and can develop into a severe pathological manifestation of atopic dermatoses, solar kerotosis, etc. (Gonzaga, 2009).

There are several mediators which through a predefined or an unknown mechanism can contribute in the controlling of the aging process. These mediators are either of herbal origin (Afaq, 2011; Saraf and Kaur, 2010) or the synthetic one. Depending upon the severity of photo-aging, the choice of adopting phytoconstituents as a remedy serves to be a safer option (Yaar and Gilchre, 2007). The characteristic of intrinsic aging is manifested by the atrophy of the dermis and epidermis and the flattening of dermal-epidermal junction. While the complications related to photo aging is dysplasia of epidermal cells, melanocytes heterogeneity and elastosis of the epidermis also termed as solar elastosis. The figure depicts the effect of ultraviolet radiations, generation of reactive oxygen species and cellular alterations causing photoaging and photocarcinogenesis (Fig. 1).

The herbal mediators chiefly the phytoconstituents are capable of treating the photoaging process at all levels which left untreated can lead to photocarcinogenesis (Afaq, 2011; Chanchal and Saraf, 2008):

- Gene longevity.
- Free radical scavenging.
- Reduction in cellular atrophy mediated by telomere shortening.

1.1. Impact of UV radiations

In skin cancer the normal restoring physiology of the epidermal and dermal cells against cell's excessive proliferation is completely paralyzed leading to the alteration in the normal cell signaling mechanism (Young, 2009). These changes are so specific that they give rise to new cellular characteristics like the production of new enzymes or complete alteration of enzymatic activities causing a dramatic mutational drift on the molecular cellular level. These shifts in biochemical pathways are very spontaneous in action and travel in traits to the upcoming progenies, leading to a complete mutation (Evans et al., 2004). On long term exposure to ultraviolet radiation, the protein encoding genes regulating cell division become mutated. These are the genes which participate and responsible for DNA repair, e.g. p53 genes (Evans et al., 2004). The hindrance of such genes from their normal biochemical functions leads to mutations in the cells. It has been estimated that approximately 35,000 genes in the human genome are associated with cancer and the number of genes associated with skin carcinoma is too less to be counted. Any change in their normal functioning can lead to a carcinoma. These malfunctioning genes can be broadly classified into three groups. The first is called proto-oncogenes which produce protein responsible for cell division or inhibiting normal cell death. Their mutated forms are termed as oncogenes (Thurstan et al., 2012). The second one, is known as tumor suppressor genes, which produces those genes which prevent cell division or cause cell death. The third group are DNA repair genes, which helps in preventing mutations that leads to skin cancer.

The UV radiations are well absorbed by the DNA and cell proteins and act as initiator as well as a promoter in the formation of mutagenic photoproducts inside DNA (Cooke et al., 2003). These photoproducts are formed between the adjacent thymine (T) and cytosine (C) base pairs and between the pyrimidine base pairs. These dimmers formed are known as cyclobutane dimmers and the pyrimidine (6-4) dimmers respectively (Rastogi et al., 2010). The 6-4 photoproducts are less mutagenic than CPD which is also termed as "hot spot mutation". In addition, they also interfere with the immune system of the body, cause immnosuppression and activate those genes which are directly responsible for causing mutation in DNA. The cells of the skin adopt DNA repair mechanisms to prevent mutation (Ouhtit and Ananthaswamy, 2001). It is an important step in decreasing the susceptibility of acquiring skin cancer. If the degree of DNA damage is not high, then the cell returns to normal state through the repair process but if the degree of damage is higher, then it cannot be repaired by DNA repair mechanism and undergoes apoptosis. Thus, the body prevents the proliferation of cells in the form of tumors. Role in Nucleotide excision repair (NER) in UV radiation associated damage repair process is highly significant (Teiti et al., 2011). There are two major pathways of NER called transcription-coupled repair (TCR) and global genome repair (GGR) which removes pyrimidine dimers in DNA, replacing the damaged site with a newly synthesized polynucleotide (Story et al., 1997). Here the noteworthy thing is that the TCR is more rapid in action than the GGR in removing damage from genes, regulated by p53 gene.

2. Matrix metalloproteinase enzyme system and novel inhibition strategy:

The degeneration of extracellular matrix (ECM) involves the activity of various protease enzymes. The prime focus moves toward the family of multidomain zinc and calcium dependent endopeptidase activity at neutral pH responsible for the damage caused to skin connective tissue (the dermis) (Quan et al., 2009). The typical family of MMPs can be divided into eight classes based on their structure. The common feature of all the MMPs is that they contain a N-terminal predomain followed by a prodomain which remains in close association with Zinc and calcium and catalytic domains. The catalytic domain consists of a zinc binding moiety having specific action. Other similar features found in all MMPs to be their collagen binding domain (CBD) which is involved in binding of collagen, elastin, fatty acid, etc. (Morrison et al., 2009; Langton et al., 2010).

The most important structural characteristics of MMPs are there trans-membrane domain which firmly anchors them to the cell surface. Each and every MMPs involves a process of regulation of activity exhibited by them. These fundamental processes are Secretion, Transcription, Pro-enzyme activation and activity

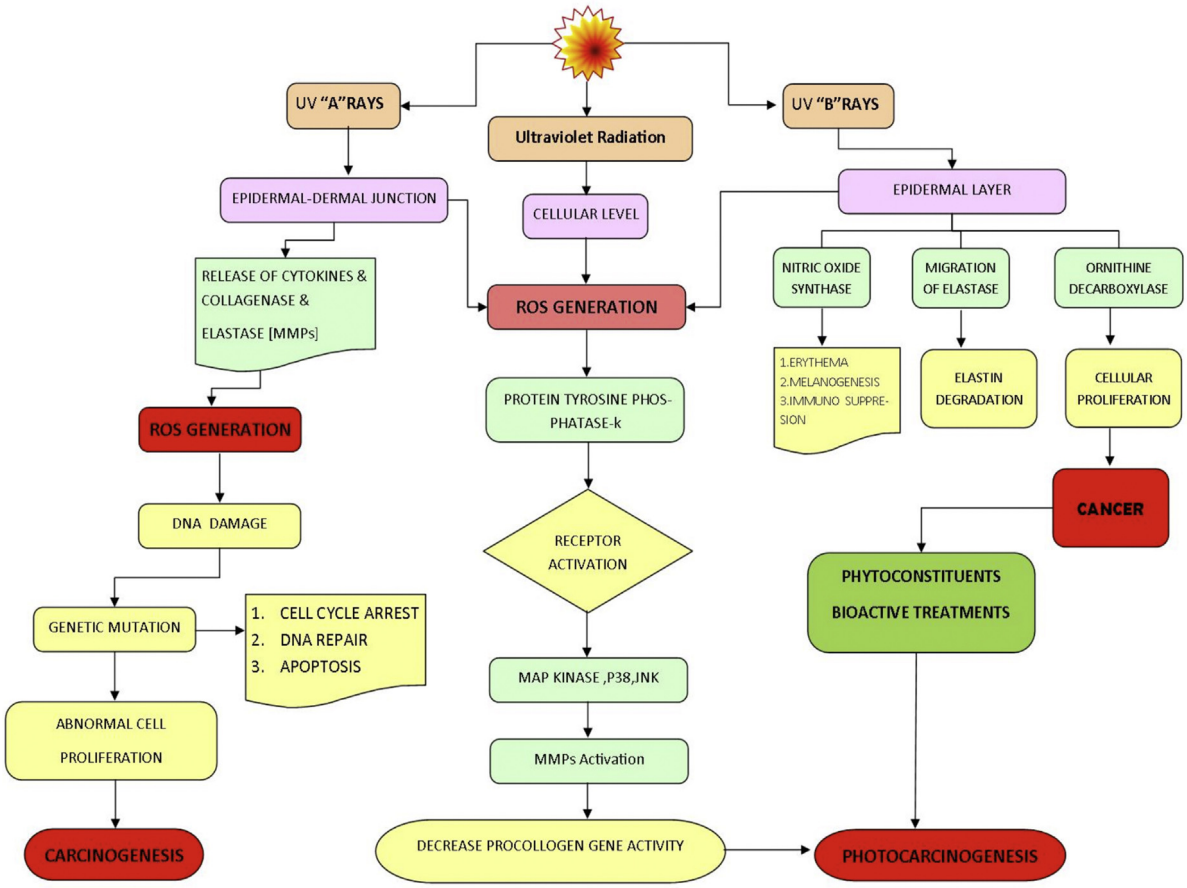

Fig. 1. Effect of ultraviolet radiations causing photoaging and photocarcinogenesis. [The diagram is a schematic representation of various events that occur during the progress of photocarcinoma. The ultraviolet radiations can be broadly divided into two categories depending upon the severity of their irradiation. UVA, being extremely carcinogenic in action penetrate deeper inside the epidermal tissues causing exafoliation of the dermal matrix. The degradation is brought upon by the activation of cytokines, collagenase and elastase enzymes. These enzymes further accelerates the generation of reactive oxygen species (ROS). The ROS generated leads to DNA damage. Meanwhile, the UVB, interacts with the epidermal layer of the skin causing activation of the DNA-altering enzymes which leads to pathological consequences like inflammation, elastin degradation, cellular proliferation, etc. At cellular level, the combined effect of UVA and UVB leads to the generation of reactive oxygen species which directly activates MMPs by following multiple cascade pathway which transcript the proinflammatory and proapoptotic genes. This whole consequences leads to inflammation and apoptosis and finally photocarcinogencity.]

exhibition (Armstrong and Kricker, 2001). But the most important fact regarding the role of MMPs is that they are involved in a number of pathological activities beyond the progress of cancer cell. Extracellular matrix degradation and the role of matrix metalloproteinases (MMPs) have been well established in recent years of oncological development.(Rees et al., 2008). Rise in the level of MMPs can be characterized as a biomarker in the evaluation of various types of cancer. Recent studies have proved their presence in different diseases like arthritis, lung cancer, cardiovascular disorders, etc. (Folgueras et al., 2004).

Collagenases also called as neutrophil collagenases namely MMP-8 (Fig. 2) extensively employed in cleaving fibrillar collagen whereas the gelatinase which are also known as MMP-2 and MMP-9 showed their remarkable presence in breast, colon lungs skin

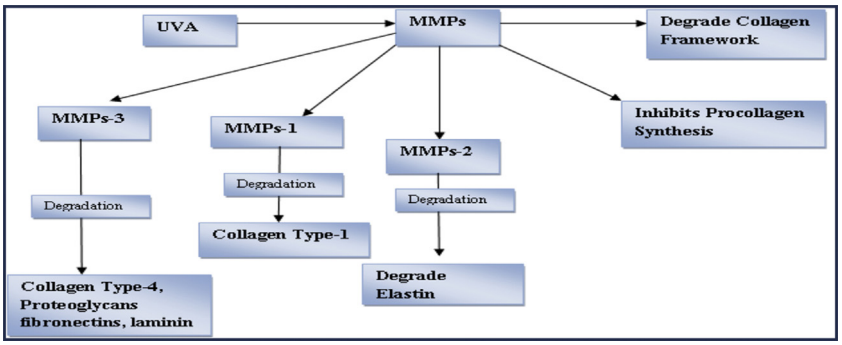

Fig. 2. The role of matrix metalloproteinase enzymes in degrading skin viscoelasticity. [The figure shows the degradation effects of MMPs on various extracellular matrix components. Ultraviolet radiation triggers the matrix metalloproteinase enzyme which further degrade the skin components in a very systematic manner, i.e. inhibiting the procollagen synthesis and disturbance of the collagen framework. MMP-3 degarde the proteoglycans fibronectin network, laminin and collagen type-4 while the MMPs-1causes deformation of collagen type-1. The elastins are degraded by MMPs-2.]

and ovary cancers (Fisher et al., 2009; Ala-aho and Kahari, 2005; Quan et al., 2009). They cleave collagen, elastin and other extracellular matrix components. They are proenzyme and need prior activation. These MMPs is profoundly involved in the growth of tumor cells, angiogenesis, metastasis, etc. The crucial involvement of gelatinase in angiogenesis has been strongly supported by in vivo and in vitro studies (Van and Libert, 2006; Bjorklund and Koivunen, 2005; Vihinen et al., 2005; Tu et al., 2008).

The stromelysins are the MMPs-3, MMP-10, and MMP-11. MMPs-3 and MMP-10 share the same structural configuration also degrades a large number of ECM components. The location of these MMPs is on the chromosome 11 while that of MMP-11, also known as Stromyelysins-3 resides inside Chromosome-22 and secreted as an active enzyme intracellularly (Armstrong and Kricker, 2001).

The Matrilysins are the group which consists of MMP-7 and MMP-26. They are responsible for degrading ECM component at various levels. Some other MMPs like MMP-14, MMP-15, MMP-16r and MMP-24 comes under the category of membrane activity (MT-MMP). Those MMPs which have not been grouped so far are MMP-12, MMP-20, MMP-27, MMP-19, MMP-23, MMP-27. MMP-12 also called as elastase is the crucial (Quan et al., 2011) player involved in macrophage migration. MMP-19 which is a basement membrane degrading enzyme is also involved in progress of skin cancer (Biljana et al., 2011; Verma and Hansch, 2007). Other MMPs, like MMP-20 found in tooth enamel. MMP-2 in various matured tissues, chief agents found in skin carcinoma. MMP-23 a different enzyme expresses itself in ovary, testes, etc. (Baker et al., 2002). The MMP-28 also called as epilysin found to have remarkable wound healing activity.

3. Expression of matrix metalloproteinases in different skin disorders

3.1. Leprosy

Leprosy is a chronic skin disease caused by Mycobacterium leprae causing excessive damage to the skin and peripheral nerves. Although the approach of estimating the destruction caused in leprosy to the presence of MMPs is ill understood. But the investigation carried out by Youssef et al. showed an increase in MMP-3 in type-2 leprosy (Youssef et al., 2009; Visse and Nagase, 2003). MMP-9 also showed a key marker role in pauncibacillary tuberculoid pole of leprosy stratum. This study is credited to be the first in its own, providing evidence about the involvement of MMP (MMP-3 and MMP-9) in different forms of leprosy. From the above findings it can be suggested that the MMP-3 and MMP-9 can be a better option for developing a targeted delivery system with desired inhibition criteria in various skin alignments.

3.2. Kaposi sarcoma

It is a syndrome which is directly associated with the human immunodeficiency. In a study a carried out over kaposi sarcoma patients treated with modified tetracycline CMT-3 showed a remarkable inhibition effect against MMP-2 but remained insignificant against MMP-9 (Coussens et al., 2002).

3.3. Allergic contact dermatosis

The allergic contact dermatitis is an immune response mediated by T-cells. Matrix metalloproteinase have gained significant attention in this case because they have demonstrated their presence in chronic phase of allergic contact dermatitis (ACD). In a study carried out by Mohammad Reza et al. on dermal wounds and fibroblast showed that the MMP-2 is over expressed in case of ACD and also suggested an interrelationship between IL-10 and MMP-2 (Youssef et al., 2009; Fingleton, 2007).

3.4. Atopic dermatosis

It is a type of inflammatory disorders having an impaired epidermal function. In a study carried by Katoh et al. reveals that the serum level of TIMPs and MMP-3 was found elevated in AD which proves its role as a marker in atopic dermatosis (AD). Since AD is manifested with the inflammation the increase in the TIMP-1 at the inflammation site has also been reported. This study also reports that the ratio of TIMP-1/MMP-3 was significantly varying in AD patient group and normal group.

In the case of AD it has been found that the excess production of TIMP over MMPs can cause degradation of the matrix component leading to dermal fibrosis (Fingleton, 2007; Khorramizadeh et al., 2004; Kuzminski et al., 2012). It suggests that TIMPs also have fibrolytic effect which reflects its auto-serene nature (Kuzminski et al., 2012; Amalinei et al., 2010). The conclusion that can be drawn from such studies is that a strict check on the activity profile of synthetic MMP inhibitors which IMP induces over production of TIMPs as an excessive and increased long term production of TIMPs can be led to other steroidal manifestation and degenerative eruptions.

3.5. Psoriasis

It is an acute type of skin inflammatory disorders characterized by hyperplasia of epidermis. There are several types of mediators which are involved in the progression of this disease. But the expression of MMP, induced by IL-18 has become highly significant. MMP-9 and MMP-2 are the enzymes induced by IL-18. From the study conducted by Lee and Lew, it can be concluded that MMPs have a remarkable role in the early progression of psoriasis (Kar et al., 2010; Fisher, 2006). They have reported the elevated levels of MMP-2 in psoriatic lesions by SP psoriasis patients. A detailed study of psoriasis with the point of MMP induced expressions can give new insight for the development of the new regimen for psoriasis.

In a study laid down by Koutroulis et al. in 2008 emphasized on the pathological involvement of MMPs in the development and progression of human CNS malignancies and the role of natural and synthetic MMP inhibitors in combating the diseases (Koutroulis et al., 2008).

Similarly, in a study carried out by Eva in 2010 showed that the inhibition of MMPs leads to the blockage of fibroblast mediated skin cancer and down regulate the expression of proangiogenic factors VEGF-A. Such studies potentiate the demand of natural or synthetic matrix metalloproteinase enzyme need as an adjuvant to chemotherapy (Eva and Woenne, 2010).

4. Design of drug for MMP inhibition

A wide number of MMP targeting strategies have been made but none of them can prove itself evident against the uncontrolled expression of MMP. Several synthetic MMPIs have been tested in (Kar et al., 2010; Roy et al., 2006) clinical trials-III phase in human like synthetic tetracycline derivatives were not up to the mark. Several other trails like Marimastat which was randomized double blind Phase-III showed modest improvement among survivals. This trial was done with the patients having gastro-esophageal adenocarcinoma (Lee and Lew, 2009; Weinberg, 2006). The best promising results were noticed in COL-3, done on 75 patients with AIDS and KS showing a response rate of 41%, toward hyper photosensitivity. All these strategies direct us toward the search of a new approach to cancer treatment.

A synthetic MMP inhibitors (MMPIs) consist of a chelating agent which get binds to the catalytic site of MMPs (Zn substrate) and

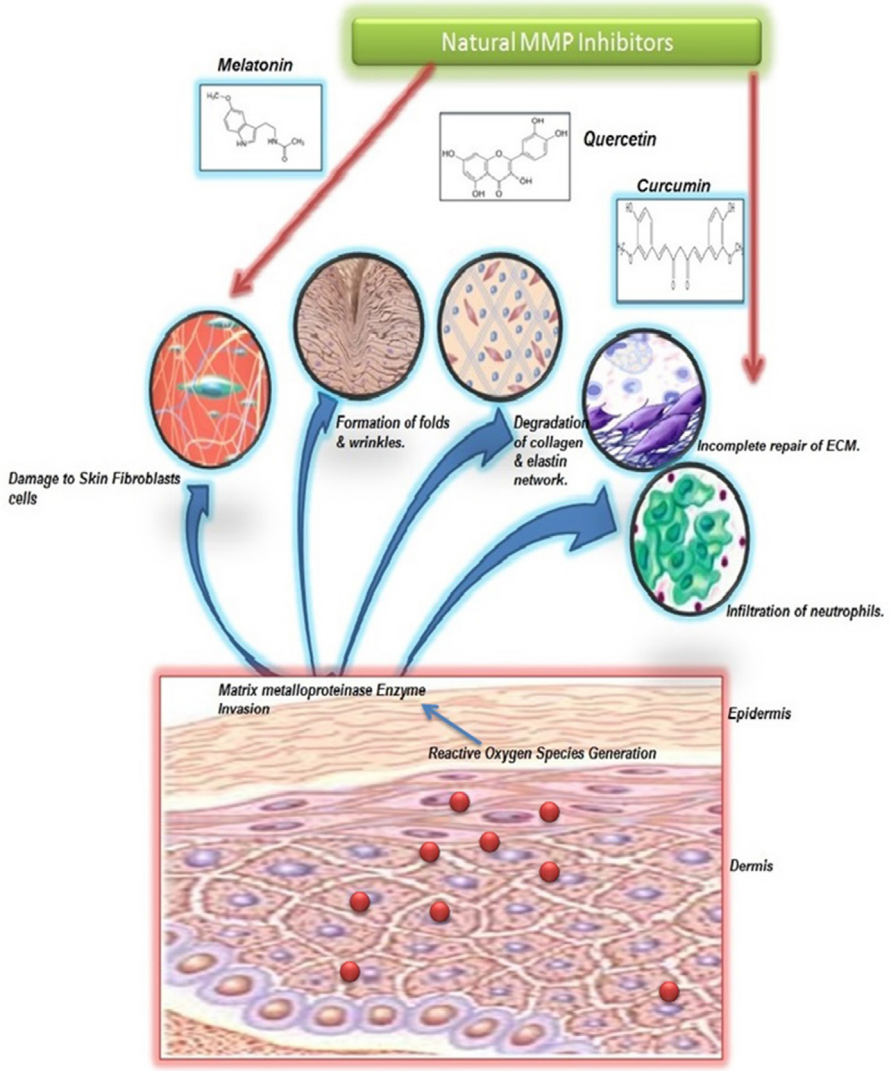

Fig. 3. Invasion of ECM components by MMPs and its counteraction by natural MMP inhibitors. [The above figure highlights the invasion of matrix metalloproteinase enzymes at different levels of extracellular matrix components (ECM). The damage caused to ECM components is a stepwise degradation triggered by MMPs which are activated by the generation of reactive oxygen species (ROS). The ROS are generated in the skin, when ultraviolet radiations are irradiated for a long time. Here, the role of natural MMP Inhibitors (for example, curcumin, melatonin, quercetin, aloin, etc.) are of immense interest because they can combat the damage caused by triggered MMPs and ROS at multiple levels synergistically.]

inhibits its activity. The MMP activation involves a series of cascade mediated by various proteases. For a perfect homeostasis the TIMPs and MMPs remain in harmonization and any disturbance in their balance causes rise of pathological consequences. For an intended inhibition of MMPs through a targeted delivery system (Yu et al., 1997) one of the following options can be opted as a methodology and optimize it further for promising benefits.

- Interaction of chelating agent with MMP catalytic site.
- Cleaving of enzyme with its substrate.
- Formation of a complex.

TIMPs are the proteins secreted in response to the overproduction of MMPs. Depending upon the activity spectrum exhibited by TIMPs, TIMP-1 is more potent than TIMP-2 and TIMP-3 against MMP-1, MMP-3 and MMP-9. Batimastat/BB-94, a broad spectrum hydroxamate formulated by British Biotech is the first MMPI entering the phase-I clinical trial. There are a number of MMPIs either in the laboratory phase or in the phase of clinical trial development but the market availability of these drugs is still out of the approach.

5. Natural bioactive as MMPs inhibitors

The herbal constituents' plays multidisciplinary role in combating the responses evoked as a result of photoreaction on exposure to solar radiations (Deep and Saraf, 2009). These are the agents which are indigenously antioxidant in nature also subsides the inflammatory responses, nourishes and smoothes the skin and rejuvenates it by supporting collagen synthesis (Wu et al., 2006). These phytoconstitutents which have remarkable matrix metalloproteinase inhibiting activity, (Fig. 3) collagenase or elastase limiting activity, safeguard the extracellular matrix from degradation on exposure to UV radiations (Kontogiorgis et al., 2005).

The role of skin respiratory factors [SRF] also called as tissue respiratory factors [TRF] are now very commonly employed because they have the ability to rejuvenate the skin through

stimulating cellular respiration by activating their metabolism rate. Warburg assay is employed to determine the SRF of any ingredients which measures its oxygen regulating ability into the living cell (Lia et al., 2009). There are a number of botanicals which can be employed to cure the fatigue caused inside the cell. This fatigue serves as a parameter, gets increased with aging of the cells and leads to oxidative stress (Bawarski et al., 2008).

In continuation to this the advancements in molecular biochemistry has also enabled us to estimate the exact amino acid sequence of matrix proteins like type-IV collagen and laminin which has led to the production of better alternatives, As in the case of peptides which are five to ten in amino acid sequence. The synthesis of collagen through a pro-collagen in skin can be a good option (Day and Robert, 2011; Varani et al., 2001) to treat all the elements of photocarcinogenecity as well as photoaging. The major target areas of UV photons are the skin chromophores like collagen, elastin, keratin, etc. They act as sensitizer toward irradiation of ultraviolet radiation causing the generation of H_2O_2 and other oxidative stress (Gonzaga, 2009). The degradation caused by H_2O_2 to the collagen is not reversible. The repetitive exposure of radiation causes execution of photodamage. The impact over the extracellular matrix and the enzyme MMP are the alarming sign of photo-damaging turning toward carcinoma (Morrison et al., 2009).

The MMP generated destroys the dermal collagen. The photosensitization can be inhibited by the use of sunscreens because photosensitization is caused when the unfiltered UVA/UVB radiations interact with the skin. Some botanicals also act as quenchers to inhibit the photo-damage or photo-hypersensitivity. The development of MMP driven targeted delivery systems (Korac and Khambholja, 2011) for cancerous cell can be of high therapeutic value. Their presence has given a new insight to develop such strategies which can enhance drug targeting. The knowledge of molecular aspects of bioactive phyto-constituents along with its mode of action can together lead to delivery system which will offer maximum topical photo-protection to the human skin (Panagiotis et al., 2008; Kontogiorgis et al., 2005).

Melatonin is a naturally occurring chronobiotic agent of indoleamine origin having therapeutic effect on circadian rhythm (Poeggeler et al., 1993; Konrad and Fischer, 2012). Melatonin is a potent antioxidant and also acts as activity enhancer in antioxidant enzyme system by gene transcripting of antioxidant enzymes like magnese superoxidase dismustase (Mn-SOD), copper zinc superoxide dismustase (Cu/Zn-SOD), etc. Therapeutically, melatonin is known to have potential antagonistic effects against skin irradiation by solar radiations. Melatonin is naturally secreted by the melanocytes present on the skin cells in response to solar radiation (Sanchez-Barcelo et al., 2010; Rees et al., 2008). This phenomenon is termed as tanning, but found to exert protective effects other than "Tanning" too. Certain clinical studies have shown that melatonin serves as a photoprotectant more effectively, if administered before UV exposure. It has also been found to decrease apoptosis by mono-aldehyde accumulation inside the cells (Tan et al., 1993). The effect of melatonin on skin cells viz. fibroblasts, keratinocytes, etc. showed a down regulation of expression of those genes that are prominent during the progression of photodamage and photocarcinoma (Swarnakar et al., 2011; Slominski and Wynn, 2008).

Further, the effect of melatonin as anatagonist to reactive oxygen species generation is also been documentated. Since, melatonin inhibits the progress of various intrinsic pathways (mitochondrial dependent apoptosis inducing pathways), it has significant activity in suppressing the generation of mitochondrial reactive oxygen species and has proved more potent than ascorbic acid and its analogs (Fischer et al., 2005; Mori et al., 2004). On irradiation of solar rays to the human skin, generation of melatonin occurs which causes activation of melatoninergic antioxidative system also termed as MAS which further leads to decrease in lipid peroxidation, protein oxidation and mitochondrial as well as DNA damage (León et al., 2005).

Melatonin has been found to play significant role in down-regulating the expression of MMPs. Matrix metalloproteinase enzymes are crucially involved in pathological and aging process. Melatonin which is a chemically a tryptophan derivative, proves multifunctional against several MMPs. The series of cellular event triggering the process of aging leads to generation of MMPs through activation of reactive oxygen species, causing the onset of various patho-physiological conditions. Melatonin having inbuilt antioxidant activity plays a key role in inhibiting inflammation, angiogenesis, endometriosis, fibrosis, etc. Clinical investigation on melatonin unravel the facts that it down regulates the activity of MMP-3 and MMP-9 in gastric ulceration and injury (Swarnakar et al., 2011). It also inhibits the expression of MMP-1, MMP-3 and MMP-10 as result of UV-induced photodamage. It has also been found to preserve keratinocytes cells against UV-erythema (Fischer et al., 2004).

Maximum clinical investigation has underlined that more scientific exploration of synthetic substrates for MMPs should be done (Kaur et al., 2007). The drawbacks that we are facing while using synthetic derivative can be overcomed by using natural substitutes to them. The best example to this approach is of Neovastat®,[1] an investigational drug extracted from shark cartilage squalamine showing inhibition of various MMPs because of the presence of TIMP like protein for possessing anti-MMPs activity (Panagiotis et al., 2008). The trial over Neovastat® is being carried out over patient's suffereing from non-small cell lungs cancer, multiple myeloma, reneal cell carcinoma, advanced refractory cancer, etc. Similarly, the genistein, chemically a isoflavanoid belonging to the family leguminosae showed remarkable anticancer effect in human breast cancer, stomach, bladder, lungs and blood cancer. It also inhibits MMP-2 and MMP-9 (Gonzalez et al., 2011; Skiles et al., 2004).

Some other compounds like Nobiletin, strongly inhibits MMP-2 and MMP-9 (Gonzalez et al., 2011; Skiles et al., 2004). Myricetin used in human colorectal carcinoma exhibit potent antitumour effect (Kim et al., 2007). Curcumin, the well known natural anticancer agent has demonstrated its anti-angiogenic activity in various in vivo and in vitro studies (Kaur and Saraf, 2011a,b). Some other compounds are resveratrol, xanthorrhizol, flavonoids, etc. have proved that natural bioactives can also be considered vital in accordance with the traditional chemotherapy to cancer (Kim et al., 2007; Kang et al., 2009; Pallela et al., 2010).

Anthocyanins are the frequently occurring flavonoid have remarkable role in cancer prevention. The extracts containing anthocyanins have been found to exert anti-invasive properties against MMPs in cancer cell lines. The anthocyanins down regulated the action of MMPS as well as urokinase plasminogen activator and upregulate the action of Tissue Inhibitors of matrix metalloproteinase enzymes (Li-Shu Wang and Stoner, 2008).

Recent studies on the *Aloe vera* extract have demonstrated that aloin is able to inhibit the clostridium histolyticum collagenase (ChC) reversibly and matrix metalloproteinase. The aloin has also shown remarkable structural similarity with inhibitory tetracyclines too (Barrantes and Guinea, 2003). Similarly, *Clitoria ternatea* also exhibit remarkable ECM protective activity and inhibition against hyaluronidase, elastase, and MMP-1 (Hidalgo and Eckhardt, 2001; Maity et al., 2012).

[1] AE-941; Aeterna Laboratories, Quebec City, Canada.

Honokiol, a newly found small molecule polyphenol isolated from *Magnolia obovata* has remarkable antiangiogenic, antiinflammatory, and antitumor properties demonstrated in preclinical studies, with minimum toxicity effects. Honokiol has certain chemical characteristics similar to the magnolol from the genus *Magnolia*, which possess significant action in skin carcinogensis. Moreover, honokiol has proven its therapeutic effects against reactive oxygen species generation. It is duly effective in immune related disorders, e.g. collagen induced arthritis, viral disorders, heart and liver cell peroxidative injury, etc. Thus, honokiol, can further be utilized as a natural analog in chemotherapy to various melanomas (Levi and Jack, 2009).

Recent studies on *Vernonia cinerea* extract showed inhibition of lung metastasis. It also down regulates the expression of MMP-2, MMP-9, lysyl oxidase, etc. (Pratheeshkumar and Kuttan, 2011). It also exhibit the invasion of B16F-10 melanoma cells across the collagen matrix. With the reference of a topical formulation containing herbal ingredients like *Capsicum annum, Juniperus communis melicotus alba*, etc. are found to have inhibitory effect over MMP-1, MMP-2, MMP-3, MMP-9 and human leukocytes elastase (Stephen et al., 2011).

Similarly, When the galls of *Terminalia chebula* Retz. Belonging to the family of Combretaceae was studied for anti-aging activity, showed extensive MMP-2 inhibition on fibroblasts (Manosroi et al., 2010). In an another study carried out to determine the cosmetic potentials of herbs the extract of the plants *Persicaria hydropiper* showed the highest elastase inhibition activity while *Typha orientalis, Pyrrosia hastata* and *Capsicum annum* showed down regulation of MMP expression (Clifford and Giovanni, 2010). Furthermore, *Terminalia catappa* and Raspberry extract was studied on UVB induced Photodamage in fibroblast cell lines. It also showed remarkable activity in lowering the concentration of MMP-2 and MMP-9 in lung cancer (Kim et al., 2006; Wen et al., 2010; Duncan et al., 2009).

Recent Studies on some Chinese herbs have also reported that the herbs *Paeonia suffruticosa*, *Scutellaria baicalensis*, *Saposhnikovia divaricata*, *Dioscorea opposita*, *Rubus chingii*, and *Salvia miltiorrhiza* have significant activity against MMP-9 (Lee et al., 2008). Experimental observation over coumarins isolated from *Fraxinus chinensis* showed remarkable decreases in the expression levels of MMP-1 mRNA and protein. In some studies carried out over *Calendula officinalis* showed down regulation of recombinant human matrix metalloproteinase (MMP) activity and decrease in the expression of tumor necrosis factor-α too (Saini et al., 2012). Procanthocyanidins which belongs to naturally occurring phenolic members group have significantly proven their anti-cancer activity in in vitro and in vivo studies (Nandakumar et al., 2008). They proved to have potent inhibition effect over MMP-2 & MMP-9 and thus can be utilized as an efficient targeting agent for various types of carcinoma.

In a study carried out by Katiyar et al. in 1997, the photoprotective effects of silymarin was investigated against UVB-induced skin cancer. In their study, they evaluated the effect of silymarin at different stages of progress of skin carcinoma. They applied the drug (silymarin) topically and observed the results in accordance with the percent of tumor incident, progression and multiplicity per UVB-exposure. They observed that the silymarin is significantly anticarcinogenic as well as anti-invasive in nature (Katiyar et al., 1997).

In an another study carried out by the same researcher, on proanthocyanidin revealed that it has significant potentials in curing the damage caused to the DNA through UVB exposure. It was found significant in repairing the cyclo-butane pyrimidine dimmer (CPD) formed in DNA (Vaid et al., 2010). It showed that the proanthocyanidin can prevent photocarcinoma by the involvement of interleukin-12 (IL-12). This also led the findings that proanthocyanidin can be utilized as novel therapeutic agents against XP.

Epigallocatechin-3-gallate (EGCG) is a potent polyphenolic compound from green tea having remarkable antioxidant properties. EGCG mainly acts on all transformational factors (AP-1, NF-κB, VGEF, ERK, AKT, STAT-3, etc.) participating in the progress of carcinoma. In UVB induced photocarcinoma the EGCG acts on AP-1 and NF-κB, and inhibits their further intiation.

Antheole a chief constituent of fennel, anise and camphor has significant anti-tumor activity. mIn a study carried out by Eun Jeong Choo et al., in 2011, demonstrated that antheole has the potential to inhibit the expression of MMP-2 and MMP-9 by suppressing the AKT, extracellular signal-regulated kinase (ERK), p38 and NF-κB (Choo, 2011).

In continuation with the above researches, *Evodia rutaecarpa* which is a very common plant of chinese origin and constitutes evodiamine and rutaecarpine as potent chemical constituents. This evodiamine possess significant anti-cancer activities proven both *in vitro* and *in vivo*. It inhibits the proliferation of cancer cell lines in culture. In certain studies, evodiamine has demonstrated apoptosis through various molecular pathways. Thus, alters cell cycle (Jiang and Changping, 2009).

Another natural bioactive agent, sulphoraphane, has been extensively studies for photoprotection effect against UVB radiation induced skin carcinoma. Sulphoraphane which is an isothiocyanate, commonly found in broccoli, has significant

Table 1
Active ingredients showing extensive MMP inhibition activity.

S. no.	Name of active ingredients	Mechanism of action	References
1.	Artemisinin	Inhibition of the activity of MMP-9.	Efferth (2007)
2.	Resveratrol	Inhibition of MMP-2 gelatinolytic activity.	Cao et al. (2005)
3.	Quercetin	Reduces the expression of matrix metalloproteinase (MMP)-2, MMP-9, defend activities of glutathione peroxides, reductase, and catalase dismutase, antioxidant.	Wang et al. (2012)
4.	Apigenin	Inhibition of the activity of MMP-9, reduced oxidative stress with enzymatic antioxidant.	Palmieri et al. (2012)
5.	Ascorbic acid	Prevents matrix metalloproteinases (MMPs) and increases collagen synthesis, and also activateprotein (AP)-1.	Cho et al. (2007)
6.	Carotenoids	Antioxidant in a lipid peroxidation. Inhibits MMPs.	Fuller et al. (2006)
7.	Silymarin	Decreases the secretion and cellular content of matrix metalloproteinase (MMP)-2/gelatinase.	Gaák et al. (2007)
8.	Coenzyme Q10 (ubiquinone)	Acts by down regulating MMPs. CoQ-10 also inhibits lipid peroxidation in plasma cell membranes.	Fuller et al. (2006)
9.	Flavonoid	Inhibition of collagenase activity inhibition of MMP-1.	Sim et al. (2007)
10.	Boswellia	Inhibition of the expression of activity of MMP-3, MMP-10, and MMP-12.	Roy et al. (2006)
11.	Eicosapentaenoic acid	Inhibition of the UV-induced MMP-1, MMP-9 and cyclooxygenase and increases collagen and elastic fibers.	Kim et al. (2006)

apoptopic and anti-proliferative activity. It causes cell cycle arrest and can be used as an adjuvant to chemoprevention (Choi et al., 2008).

In an another study by Pradhan et al. in 2010, quercetin (3,5,7,3′,4′-tetra-hydroxyflavone) and sulphoraphane combination was studied. In their study they found that the combination of both the bioactive components gave synergistic action in suppressing the melanoma, in comparison to the single bioactive administration. They reported that both the components was effective against proliferation in B16F10 cells. The study seems important in the field of photoprotection as it lead to the down regulation of MMP-9 which causes maximum damage to the extracellular matrix components (Pradhan et al., 2010).

Some of the bioactive agents specifically possessing matrix metalloproteinase enzyme inhibition activity are enlisted in Table 1.

6. Concluding remarks

Epidermis is that part of the skin which offers primarily to the defense of the body against ultraviolet radiation. Photo-carcinoma is emerging as a most common human cancer as a result of environmental factors and attaining significant attention due to the rapid growth of dermal cancer, fatal of mortality, inefficient drug delivery systems and associated dermatological consequences. The role of ultraviolet radiation in causing different types of skin cancer and their simultaneous relationship is still out of focus. Epidemiological and laboratory studies provide evidence that every year there is an average increase of 30% in skin cancer patients, worldwide. Direct exposure to solar radiation is the chief causative factor in causing NMSC. The development of photocarcinogenesis involves a planned failure of this defense system viz. inflammation, failure programmed cell death, failure in DNA repair, immune suppression, mutation, and carcinogenesis. Although we have developed various approaches to understand the mechanism underlying the UV radiation and initiation of photo carcinogenesis, still the rate of increase of skin carcinoma due to solar impact needs new strategies to develop a good photoprotective.

The extracellular matrix is the most important part of cellular regulation and signaling transduction. Any modulation in ECM is a sign of pathological onset. The damage caused to ECM by the MMPs is the alarming sign in photo carcinogenesis because it accelerates the aggressiveness of skin cancer by activating AP-1 and NF-B production. Thus, the development of the MMPI is highly anticipated. There have been various inhibition strategies laid down but none of them have been found 100% fulfilling the criteria. As the evaluation of MMPIs shows unexpected results in various phases of clinical trials, like, these drugs produce muco-skeletal toxicities in phase-I while no such characteristic features was identified in the previous preclinical evaluation. Although the phase-III results were mixed one, there is a hope that a perfect combination of MMPIs with the other chemo or therapeutic targets will soon be found to strengthen the anticancer drug regimen for future benefits.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

The authors acknowledge the University Grant Commission Major Research Project (F. No39-170/2010(SR)) & SAP [F. No.3-54/2011 (SAP-II)]New Delhi, India, for financial assistance. Two of the authors extend their gratitude towards the head of the cosmetic laboratory, University Institute of pharmacy, Pt, Ravishankar Shukla University, Raipur (C.G.) for providing facilities to carry out research work.

References

Afaq, F., 2011. Natural agents: cellular and molecular mechanisms of photoprotection. Arch. Biochem. Biophys. 508 (2), 144–151.
Ala-aho, R., Kahari, V., 2005. Collagenases in cancer. Biochimie 87, 273–286.
Amalinei, C., Carunt, I.D., Giusca, S.E., Balan, R.A., 2010. Matrix metalloproteinases involvement in pathologic conditions. Rom. J. Morphol. Embryol. 51 (2), 215–228.
Armstrong, B.K., Kricker, A., 2001. The epidemiology of UV induced skin cancer. J. Photochem. Photobiol. B 63, 8–18.
Baker, A.H., Edwards, D.R., Murphy, G., 2002. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. J. Cell Sci. 115, 3719–3727.
Barrantes, E., Guinea, M., 2003. Inhibition of collagenase and metalloproteinases by aloins and aloe gel. Life Sci. 72, 843–850.
Bawarski, W.E., Chidlowsky, E., Bharali, D.J., Mousa, S.A., 2008. Emerging nanopharmaceuticals. Nanomedicine 4 (4), 273–282.
Biljana, E., Boris, V., Cena, D., Veleska-Stefkovska, D., 2011. Matrix metalloproteinases (with accent to collagenases). JCAB 5 (7), 113–120.
Bjorklund, M., Koivunen, E., 2005. Gelatinase-mediated migration and invasion of cancer cells. Biochim. Biophys. Acta 1755, 37–69.
Cao, Y., Fu, Z.D., Wang, F., Liu, H.Y., Han, R., 2005. Anti-angiogenic activity of resveratrol. A natural compound from medicinal plants. J. Asian Nat. Prod. Res. 7 (3), 205–213.
Chanchal, D., Saraf, S., 2008. Novel approaches in herbal cosmetics. J. Cosmet. Dermatol. 7 (2), 89–95.
Cho, H.S., Lee, M.H., Lee, J.W., No, K.O., Park, S.K., Lee, H.S., Kang, S., Cho, W.G., Park, H.J., Oh, K.W., Hong, J.T., 2007. Anti-wrinkling effects of the mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil, and molecular mechanisms on hairless mouse skin caused by chronic ultraviolet B irradiation. Photodermatol. Photoimmunol. Photomed. 23 (5), 155–162.
Choi, W.Y., Choi, B.T., Lee, W.H., Choi, Y.H., 2008. Sulforaphane generates reactive oxygen species leading to mitochondrial perturbation for apoptosis in human leukemia U937 cells. Biomed. Pharmacother. 62, 637–644.
Choo, E.J., 2011. Anethole exerts antimetatstaic activity *via* inhibition of matrix metalloproteinase 2/9 and AKT/mitogen-activated kinase/nuclear factor kappa B signaling pathways. Biol. Pharmaceut. Bull. 34 (1), 41–46.
Clifford, J.L., Giovanni, J.D., 2010. The promise of natural products for blocking early events in skin carcinogenesis. Cancer Prev. Res. 3 (2), 132–135.
Cooke, M.S., Evans, M.D., Dizdaroglu, M., Lanes, J., 2003. Oxidative DNA damage: mechanisms, mutation and disease. FASEB J. 17, 1195–1214.
Coussens, L., Fingleton, B., Matrisian, L., 2002. Matrix metalloproteinase inhibitors and cancer: trials and tribulations. Science 295, 2387–2392.
Day, T.T., Robert, S., 2011. Potential photocarcinogenic effects of nanoparticle sunscreens. Austral. J. Dermatol. 52, 1–6.
Deep, C., Saraf, S., 2009. Herbal photoprotective formulations and their evaluation. Open Nat. Prod. J. 2, 57–62.
Duncan, F.J., Jason, R., Martin, Brian, C., Wulff, et al., 2009. Topical treatment with black raspberry extract reduces cutaneous UVB-induced carcinogenesis and inflammation. Cancer Prev. Res. 2, 665–672.
Efferth, T., 2007. Anticancer effect of artemisin (abstract). Plant Med. 734, 299–309.
Eva, C., Woenne, 2010. MMP inhibition blocks fibroblast-dependent skin cancer invasion, reduces vascularization and alters VEGF-A and PDGF-BB expression. Anticancer Res. 30, 703–712.
Evans, M.D., Dizdaroglu, M., Cooke, M.S., 2004. Oxidative DNA damage and disease: induction, repair and significance. Mutat. Res. 567, 1–61.
Fingleton, B., 2007. Matrix metalloproteinases as valid clinical targets. Curr. Pharm. Des. 13, 333–346.
Fischer, T.W., Scholz, G., Knöll, B., Hipler, U.C., Elsner, P., 2004. Melatonin suppresses reactive oxygen species induced by UV irradiation in leukocytes. Journal of Pineal Research 37 (2), 107–112.
Fischer, T.W., Zmijewski, M.A., Wortsman, J., Semak, I., Zbytek, B., Slominski, R.M., Tobin, D.J., 2005. On the role of melatonin in skin physiology and pathology. Endocrine 27 (2), 137–148.
Fisher, J.F., 2006. Shahriar Mobashery; recent advances in MMP inhibitor design. Cancer Metast. Rev. 25, 115.
Fisher, G.J., Quan, T., Purohit, T., Shao, Y., Cho, M.K., He, T., Varani, J., Kang, S., Voorhee, J.J., 2009. Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. Am. J. Pathol. 74 (1), 101–114.
Folgueras, A.R., Pendás, A.M., Sánchez, L.M., López-Otín, C., 2004. Matrix metalloproteinases in cancer: from new functions to improved inhibition strategies. Int. J. Dev. Biol. 48, 411–424.
Fuller, B., Smith, D., Howerton, A., Kern, D., 2006. Anti-inflammatory effects of Coq10 and colorless carotenoids. J. Cosmet. Dermatol. 5 (1), 30–38.
Gaák, R., Walterová, D., Ken, V., 2007. Silybin and silymarin – new and emerging applications in medicine. Curr. Med. Chem. 143, 15–338.
Gonzaga, E.R., 2009. Role of UV light in photodamage, skin aging, and skin cancer: importance of photoprotection. Am. J. Clin. Dermatol. 10, 19–24.
Gonzalez, S., Gilaberte, Y., Philips, N., Juarranz, A., 2011. Current trends in photoprotection – a new generation of oral photoprotectors. Open Dermatol. J. 5, 6–14.
Hidalgo, M., Eckhardt, S.G., 2001. Development of matrix metalloproteinase inhibitors in cancer therapy. J. Natl. Cancer Inst. 93, 178–193.
Jiang, J., Changping, H., 2009. Evodiamine: a novel anti-cancer alkaloid from *Evodia rutaecarpa*. Molecules 14, 1852–1859.

Kang, T.H., Park, H.M., Kim, Y.B., Kim, H., Kim, N., Do, J.H., Kang, C., Cho, Y., Kim, S.Y., 2009. Effects of red ginseng extract on UVB irradiation-induced skin agCho in hairless mice. J. Ethnopharmacol. 123, 446–451.

Kar, S., Subbaram, S., Carrico, P.M., Melendez, J.A., 2010. Redox-control of matrix metalloproteinase-1: a critical link between free radicals, matrix remodeling and degenerative disease. Resp. Physiol. Neurobiol. 174, 299–306.

Katiyar, S.K., Korman, N.J., Mukhtar, H., Agarwal, R., 1997. Protective effects of silymarin against photocarcinogenesis in a mouse skin model. J. Natl. Cancer Inst. 89 (8), 556–565.

Kaur, C.D., Saraf, S., 2011a. Photoprotective herbal extract loaded nanovesicular creams inhibiting ultraviolet radiations induced photoaging. Int. J. Drug Deliv. 3, 699–711.

Kaur, C.D., Saraf, S., 2011b. Topical vesicular formulations of *C. longa* extract on recuperating the ultraviolet radiations damaged skin. J. Cosmet. Dermatol. 10, 260–265.

Kaur, I.P., Kapila, M., Agrawal, R., 2007. Role of novel delivery systems in developing topical antioxidants as therapeutics to combat photoaging. Ageing Res. Rev. 6, 271–288.

Khorramizadeh, Moh.R., Falak, R., Pezeshki, Moh., Safavifar, F., Mansouri, P., Ghahary, A., Saadat, F., Varshokar, K., 2004. Dermal wound fibroblasts and matrix metaloproteinases (MMPS): their possible role in allergic contact dermatitis. Iran J. Allergy Asthma Immunol. 3, 7–11.

Kim, H.H., Cho, S., Lee, S., Kim, K.H., Cho, K.H., Eun, H.C., Chung, J.H., 2006. Photoprotective and anti-skin-aging effects of eicosapentaenoic acid in human skin in vivo. J. Lipid Res. 47 (5), 921–930.

Kim, Y.H., Kim, K.S., Han, C.S., Yang, H.C., Park, S.H., Ko, K.I., Lee, S.H., Kim, K.H., Lee, N.H., Kim, J.M., Son, K.H., 2007. Inhibitory effects of natural plants of Jeju Island on elastase and MMP-1 expression. J. Cosmet. Sci. 58 (1), 19–33.

Konrad, K., Fischer, T.W., 2012. Melatonin and human skin aging. Dermato-Endocrinology 4 (3), 245–252.

Konstantinopoulos, P.A., Karamouzis, M.V., Papatsoris, A.G., Papavassiliou, A.G., 2008. Matrix metalloproteinase inhibitors as anticancer agents. Int. J. Biochem. Cell Biol. 40, 1156–1168.

Kontogiorgis, C.A., Papaioannou, P., Hadjipavlou-Litina, D.J., 2005. Matrix metalloproteinase inhibitors, a review on pharmacophore mapping and (Q)SARs results. Curr. Med. Chem. 12 (3), 339–355.

Korac, R.R., Khambholja, K.M., 2011. Potential of herbs in skin protection from ultraviolet radiation. Pharmacog. Rev. 5 (10), 16.

Koutroulis, I., Zarros, A., Theocharis, S., 2008. The role of matrix metalloproteinases in the pathophysiology and progression of human nervous system malignancies: a chance for the development of targeted therapeutic approaches? Expert Opin. Ther. Targets 12 (12), 1577–1586.

Kuzminski, A., Przybyszewski, M., Graczyk, M., Bartuzi, Z., 2012. The role of extracellular matrix metalloproteinases and their inhibitors in allergic diseases. Postep. Derm. Alergol. 5, 384–389.

Langton, A.K., Sherratt, M.J., Griffiths, C.E.M., Watson, R.E.B., 2010. A new wrinkle on old skin, the role of elastic fibres in skin ageing. Int. J. Cosmet. Sci. 32 (5), 1–10.

Lee, S.E., Lew, W., 2009. The increased expression of matrix metalloproteinase-9 messenger rna in the non-lesional skin of patients with large plaque Psoriasis vulgaris. Ann. Dermatol. 21, 27–34.

Lee, M.H., Yang, Y.Y., Tsai, Y.H., Lee, Y.L., Huang, P.Y., Huang, I.J., Cheng, K.T., Leu, S.J., 2008. The effect of chinese herbal medicines on Tnf-A induced matrix metalloproteinase-1, -9 activities and interleukin-8 secretion. Bot. Stud. 49, 301–309.

León, J., Castroviejo, D.A., Escames, G., Tan, D.X., Reiter, J.R., 2005. Melatonin mitigates mitochondrial malfunction. Journal of Pineal Research 38 (1), 1–9.

Levi, E.F., Jack, L.A., 2009. Honokiol, a multifunctional antiangiogenic and antitumor agent. Antioxid. Redox Signal. 11 (5), 1139–1148.

Lia, N.G., Shib, Z.H., Tang, Y.P., Duan, J.A., 2009. Selective matrix metalloproteinase inhibitors for cancer. Curr. Med. Chem. 16 (29), 3805–3827.

Li-Shu Wang, Stoner, G.D., 2008. Anthocyanins and their role in cancer prevention. Cancer Lett. 269 (2), 281–290.

Maity, N., Nema, N.K., Sarkar, B.K., Mukherjee, P.K., 2012. Standardized *Clitoria ternatea* leaf extract as hyaluronidase, elastase and matrix-metalloproteinase-hyaluronidase ielastase. Pharmacology 44 (5), 584–587.

Mannello, F., 2006. Natural bio-drugs as matrix metalloproteinase inhibitors, new perspectives on the horizon. Recent Pat. Anticancer Drug Discov. 1, 91–103.

Manosroi, A., Jantrawut, P., Akihisa, T., Manosroi, W., Manosroi, J., 2010. *In vitro* anti-aging activities of *Terminalia chebula* gall extract [my paper]. Pharm. Biol. 48 (4), 469–481.

Mori, K., Shibanuma, M., Nose, K., 2004. Invasive potential induced under long-term oxidative stress in mammary epithelial cells. Cancer Res. 64, 7464–7472.

Morrison, C.J., Butler, G.S., Rodríguez, D., Christopher, M., 2009. Overall matrix metalloproteinase proteomics: substrates, targets, and therapy. Curr. Opin. Cell Biol. 21 (5), 645–653.

Nandakumar, V., Singh, T., Katiyar, S., 2008. Multi-targeted prevention and therapy of cancer by procanthocyanidins. Cancer Lett. 269 (2), 378–387.

Ouhtit, A., Ananthaswamy, H.N., 2001. A model for UV-induction of skin cancer. J. Biomed. Biotechnol. 1 (1), 5–6.

Pallela, R., Young, Y.N., Kim, S.K., 2010. Anti-photoaging and photoprotective compounds derived from marine organisms. Mar. Drugs 8, 1189–1202.

Palmieri, D., Perego, P., Palombo, D., 2012. Apigenin inhibits the TNFα-induced expression of eNOS and MMP-9 via modulating Akt signalling through oestrogen receptor engagement. Mol. Cell Biochem. 371 (1–2), 129–136.

Panagiotis, A., Konstantinopoulos, Michalis, V., Karamouzis, Athanasios, G., Papatsoris, Athanasios, G., Papavassiliou, 2008. Matrix metalloproteinase inhibitors as anticancer agents. Int. J. Biochem. Cell Biol. 40, 1156–1168.

Poeggeler, G., Reiter, R.J., Tan, D.X., et al., 1993. Melatonin: hydroxyl radical-mediated oxidative damage, and aging: a hypothesis. Journal of Pineal Research 4, 151–168.

Pradhan, S.J., Mishra, R., Kundu, P.A., 2010. Quercetin and sulforaphane in combination suppress the progression of melanoma through the down-regulation of matrix metalloproteinase-9. Experimental And Therapeutic Medicine 1, 915–920.

Pratheeshkumar, P., Kuttan, G., 2011. *Vernonia cinerea* Less. inhibits tumor cell invasion and pulmonary metastasis in C57BL/6 mice. Integr. Cancer Ther. 10 (2), 178–191.

Quan, T., Qin, Z., Xia, W., Shao, Y., Voorhees, J.J., Fisher, G.J., 2009. Matrix-degrading metalloproteinases in photoaging. J. Investig. Dermatol. Symp. Proc. 14 (1), 20–24.

Quan, T., Qin, Z., Robichaud, P., Voorhees, J.J., Fisher, G.J., 2011. CCN1 contributes to skin connective tissue aging by inducing age-associated secretory phenotype in human skin dermal fibroblasts. J. Cell Commun. Signal. 5 (3), 201–207.

Rastogi, R.P., Richa, A., Kumar, Tyagi, M.B., Sinha, R.P., 2010. Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. J. Nucleic Acids 2010 (2010), 1–32.

Rees, M.D., Kennett, E.C., Whitelock, J.M., Davies, M.J., 2008. Oxidative damage to extracellular matrix and its role in human pathologies. Free Radic. Biol. Med. 44, 1973–2001.

Roy, S., Khanna, S., Krishnaraju, A.V., Subbaraju, G.V., Yasmin, T., Bagchi, D., Sen, C.K., 2006. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to antiinflammatory Boswellia. Antioxid. Redox Signal. 8, 653–660.

Saini, P., Al-Shibani, N., Sun, J., Zhang, W., Song, F., Gregson, K.S., Windsor, L.J., 2012. Effects of *Calendula officinalis* on human gingival fibroblasts. Homeopathy 101 (2), 1092–1098.

Sanchez-Barcelo, E.J., Mediavilla, M.D., Tan, D.X., et al., 2010. Clinical uses of melatonin: evaluation of human trials. Curr. Med. Chem. 17, 2070–2095.

Saraf, S., Kaur, C.D., 2010. Phytoconstituents as photoprotective novel cosmetic formulations. Pharmacog. Rev. 4 (7), 1–11.

Sim, G.S., Lee, B.C., Cho, H.S., Lee, J.W., Kim, J.H., Lee, D.H., Kim, J.H., Pyo, H.B., Cheul Moon, D., Oh, K.W., Yun, Y.P., Hon, J.T., 2007. Structure activity relationship of antioxidative property of flavonoids and inhibitory effect on matrix metalloproteinase activity in UVA-irradiated human dermal fibroblast. Arch. Pharm. Res. 30 (3), 290–298.

Skiles, J.W., Gonnella, N.C., Jeng, A.Y., 2004. The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors. Curr. Med. Chem. 11, 2911–2977.

Slominski, A., Wynn, T.A., 2008. Cellular and molecular mechanisms of fibrosis. J. Pathol. 214, 199–210.

Soehnge, H., Ouhtit, A., Ananthaswamy, H.N., 1997. Mechanisms of induction of skin cancer by UV radiation. Front. Biosci. 2, D538–D551.

Stephen, B., Duret, P., Gendron, N., Guay, J., Lavallee, B., Page, B. Patent No. 20110311661; 22/12/2011 (WO/2006/053415).

Story, A., Robert, C., Sarasin, A., 1997. Deleterious effects of ultraviolet A radiation in human cells. Mutat. Res. 383, 1–8.

Swarnakar, S., Paul, S., Singh, L.P.K., Russel, R.J., 2011. Matrix metalloproteinases in health and disease: regulation by melatonin. J. Pineal Res. 50, 8–20.

Tan, D.X., Chen, L.D., Poeggeler, B., Manchester, L.C., Reiter, R.J., 1993. Melatonin: a potent, endogenous hydroxyl radical scavenger. Endocr. J. 1, 57–60.

Teiti, Y., Makita, K., Yamamoto, H., Menck, C.F.M., Schuch, A.P., 2011. Biological sensors for solar ultraviolet radiation. Sensors 11, 4277–4294.

Thurstan, S.A., Gibbs, N.K., Langton, A.K., Christopher, E.M., Griffiths, R., Watson, E.B., Michael, J.S., 2012. Chemical consequences of cutaneous photoageing. Chem. Cent. J. 6 (1), 341–347.

Tu, G., Xu, W., Huang, H., Li, S., 2008. Progress in the development of matrix metalloproteinase inhibitors. Curr. Med. Chem. 15 (14), 1388–1395.

Vaid, M., Sharma, S.D., Katiyar, S.K., 2010. Proanthocyanidins inhibit photocarcinogenesis through enhancement of DNA repair and xeroderma pigmentosum group A-dependent mechanism. Cancer Prev. Res. 3, 1621–1629.

Van, L.P., Libert, C., 2006. Matrix metalloproteinase-8: cleavage can be decisive. Cytokine Growth Factor Rev. 17 (4), 217–223.

Varani, J., Spearman, D., Perone, P., Fligiel, E.G.S., Datta, S.C., Wang, Z.Q., Shao, Y., Kang, S., Fisher, G.J., Voorhees, J.J., 2001. Inhibition of Type I procollagen synthesis of damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. Am. J. Pathol. 158 (3), 931–942.

Verma, R.P., Hansch, C., 2007. Matrix metalloproteinases (MMPs): chemical–biological functions and (Q) SARs. Bioorg. Med. Chem. 15, 2223–2268.

Vihinen, P., Ala-aho, R., Kähäri, V.M., 2005. Matrix metalloproteinases as therapeutic targets in cancer. Curr. Cancer Drug Targets 5 (3), 203–220.

Visse, R., Nagase, H., 2003. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ. Res. 92, 827–839.

Wang, L., Wang, B., Li, H., Lu, H., Qiu, F., Xiong, L., Xu, Y., Wang, G., Liu, X., Wu, H., Jing, H., 2012. Quercetin, a flavonoid with anti-inflammatory activity, suppresses the development of abdominal aortic aneurysms in mice. Eur. J. Pharmacol. 690 (1-3), 133–141.

Weinberg, J.M., 2006. Topical therapy for actinic keratoses: current and evolving therapies. RRCT 1 (53–60), 53.

Wen, K.C., Shih, I.C., Hu, J.C., Liao, S.T., Su, T.W., Chiang, H.M., 2010. Inhibitory effects of *Terminalia catappa* on UVB induced photodamage in fibroblast cell lines. Evidence Based Complement. Altern. Med. 2011 (2011), 201–209.
Wu, H.C., Chang, D.K., Huang, C.T., 2006. Targeted therapy for cancer. J. Cancer Mol. 2, 57–66.
Yaar, M., Gilchre, B.A., 2007. Photoageing: mechanism, prevention and therapy. Br. J. Dermatol. 1578, 74–887.
Young, C., 2009. Solar ultraviolet radiation and skin cancer. Occup. Med. 59, 82–88.
Youssef, S.S., Attia, E.A.S., Awad, N.M., Mohamed, G.F., 2009. Expression of matrix metalloproteinases (MMP-3 and MMP-9) in skin lesions of leprosy patients. J. Egypt Women Dermatol. Soc. 6, 80–87.
Yu, A.E., Hewitt, R.E., Connor, E.W., Stetler-Stevenson, W.G., 1997. Matrix metalloproteinases. Novel targets for directed cancer therapy. Drugs Aging 11 (3), 229–244.