Journal of Nutrition & Food Sciences
ISSN: 2155-9600

Pervin et al., J Nutr Food Sci 2016, 6:6
DOI: 10.4172/2155-9600.1000560

Research Article OMICS International

Luteolin Suppresses Ultraviolet A- and B-induced Matrix Metalloproteinase 1- and 9 Expression in Human Dermal Fibroblast Cells

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Abstract

Ultraviolet (UV) irradiation induces significant changes to skin connective tissues as a result of the degradation of collagen, which is a major structural component of the extracellular matrix. This process may be mediated by matrix metalloproteinases (MMPs). In this study, we examined the protective effect of a polyphenolic flavone, luteolin, on the expression of two matrix metalloproteinases, MMP-1 and MMP-9, in UVA- and UVB-irradiated human dermal fibroblast cells. Luteolin is found in many medicinal plants as well as in a large number of vegetables, fruits and a variety of spices. It has a number of biological activities including anti-cancer, anti-oxidant, anti-inflammatory, anti-allergic and immunomodulatory activities. Human dermal fibroblast (HDF) cells were treated with luteolin at 1-10 μM, then irradiated with UVA at 10 J/cm^2 and UVB at 200 mJ/cm^2. Cells and culture supernatant were harvested 24 h after irradiation.

Our results show that luteolin at 1-10 μM dose-dependently suppressed the expression of MMP-1 and MMP-9 genes in UVA and UVB-exposed HDF cells, as measured by quantitative real-time reverse transcription–polymerase chain reaction (qRT-PCR). Luteolin was also found to reduce the production of MMP-1 protein in UVA and UVB-exposed HDF cells detected by enzyme-linked immunosorbent assay (ELISA) in a dose-dependent manner. The release of MMP-9 was also reduced by luteolin in UVB-irradiated HDF cells in a dose-dependent manner.

Our results indicate that luteolin can inhibit UV-induced MMP-1 and MMP-9 expression in HDF cells. Therefore, they may be potentially useful in the prevention and treatment of skin photoaging.

Keywords: Luteolin; Ultraviolet A; Ultraviolet B; Matrix metalloproteinase-1; Matrix metalloproteinase-9; Human dermal fibroblast cells

Introduction

Ultraviolet irradiation causes distinct changes to skin collagenous tissues as a result of the breakdown of collagen, a major component of the extracellular matrix. UVA (long length, 320-400 nm) and UVB (short length, 290-320 nm) tend to be associated with oxidative processes involved in photo aging. Exposure of the skin to UVA and UVB induces the intracellular generation of large quantities of reactive oxygen species (ROS). ROS-induced molecular damage produces a number of harmful effects on cellular function and homeostasis, while degradation of extracellular matrix (ECM) proteins, such as collagen, by ROS can cause major changes in skin connective tissue [1-5]. A cascade of gene expression is initiated following UV-irradiation, which results in the upregulation of MMPs such as MMP-1 (collagenase) and MMP-9 (gelatinase B). These alterations in the ECM, mediated by MMPs, are known to be a cause of skin wrinkling that characterizes premature skin aging and aged skin [1]. MMPs are zinc-dependent endopeptidases. To date, more than 20 members of the human MMP family have been described, but depending on their structure and substrate specificity, they are divided into subgroups: collagenases, stromelysins, stromelysins-like MMPs, gelatinases, membrane-types MMPs (MT-MMPs), and other MMPs [6]. MMPs are produced by many different types of cells including keratinocytes, fibroblasts, endothelial cells, monocytes, lymphocytes and macrophages [7]. MMP-1 and MMP-9 are capable of degrading collagen, which is the main structural protein (ECM) found in connective tissue in animals. Recently, it was suggested that excessive matrix degradation by UV-induced MMP-1 and MMP-9 secreted by keratinocytes and fibroblast cells contributes substantially to connective tissue damage that occurs during photo aging [8,9]. This evidence suggests that the expression of MMP-1 as well as MMP-9 plays a major role in the process of photoaging in fibroblast cells.

Luteolin, 3′,4′,5,7-tetrahydroxyflavone, is a flavone that is found in many medicinal plants, a large number of vegetables, fruits and a variety of spices (Figure 1). Dietary sources of luteolin are celery, green pepper, thyme, perilla, parsley, sage, carrots, and oregano [10]. Luteolin has many biological activities including anti-cancer, anti-oxidant, anti-inflammatory, anti-allergic and immunological activities [11-18]. Although luteolin has been tested in various bioactivity assays, only few studies have dealt with its modulation on gene expression and MMP protein production during the photo aging of human fibroblast cells. In the present study, we assessed the effect of luteolin on matrix metalloproteinase MMP-1 and MMP-9 activities in UVA- and UVB-irradiated human dermal fibroblast cells.

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Received August 31, 2016; **Accepted** October 17, 2016; **Published** October 27, 2016

Citation: Pervin M, Unno K, Nakamura Y, Imai S (2016) Luteolin Suppresses Ultraviolet A- and B-induced Matrix Metalloproteinase 1- and 9 Expression in Human Dermal Fibroblast Cells. J Nutr Food Sci 6: 560. doi: 10.4172/2155-9600.1000560

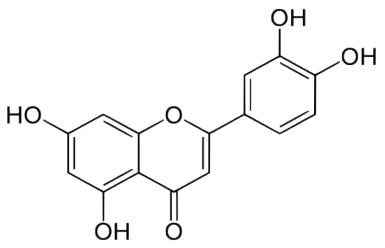

Figure 1: Chemical structure of luteolin.

Materials and Methods

Cell culture and UV irradiation

Normal human dermal fibroblast cells were purchased from (Lonza, Walkersville, MD, USA) and cultured in growth medium FGM™-2 BulletKit™ (Lonza) supplemented with 500 mL FBM® (fibroblast basal medium), 10 mL FBS (fetal bovine serum), 0.5 mL GA-1000 (gentamicin sulfate amphotericin-B), 0.5 mL insulin (recombinant human) and 0.5 mL rhFGF-B (r-human fibroblast growth factor-B) at 37°C in a humidified atmosphere containing 5% CO_2. HDF cells were maintained until 70-80% confluence then 1×10^5 cells /well/500 µL on a 24-well plate were pretreated with luteolin (Wako Pure Chemical Industries, Ltd. Osaka, Japan) at concentration ranging from 1 to 10 µM in 0.1% (v/v) dimethyl sulfoxide, DMSO (Wako Pure Chemical Industries, Ltd.) or DMSO alone (for control) in complete growth medium for 24 h. Medium was removed and cells were washed twice by phosphate-buffered saline, PBS (Takara Bio Inc., Shiga, Japan). Hank's balanced salt solution, HBSS (Sigma-Aldrich, Co., St. Louis, USA) was added and the cells were irradiated with UVA at (5, 10 J/cm^2) and UVB at (100, 200 mJ/cm^2) using a UV irradiator (NS-8F; Sanwa Medical, Saitama, Japan). The intensity of irradiation was monitored with the use of a UV intensity meter (model ATV-3W, product code: 3534032, Atto Corporation, Tokyo, Japan) and a photodetector for UVB (model CX-312, product code: 3534036, Atto Corporation,) and for UVA (model CX-365, product code: 3534037, Atto Corporation) with a UVB cutoff filter (Schott WG 345; UQG Ltd., Cambridge, England), positioned at the same distance from the UV source as the cells. During irradiation, control cells were treated identically, but without the exposure to UV light. After irradiation, HBSS was removed; fresh complete growth medium was added in the presence of the indicated concentration of luteolin and incubated for 24 h. Each concentration was tested in duplicate (n=2). In addition, we have determined the expression levels of MMP-1 and MMP-9 with the indicated doses of UV in a different time period (3 h, 6 h, and 24 h). We found that UVA (10 J/cm^2) and UVB (200 mJ/cm^2) for 24 h was the best for MMP-1 and 9 gene expression (data not shown). Therefore, UVA at (10 J/cm^2) and UVB at (200 mJ/cm^2) were used throughout the experiments.

Cell viability

To confirm the effect of UV on HDF cell viability, 1×10^5 cells/well/500 µl on a 24-well plate were exposed to UVA (10 J/cm^2) and UVB (200 mJ/cm^2) irradiation in the present of Hank's balanced salt solution, HBSS (Sigma-Aldrich). After exposure to UV, complete growth medium was replaced and cells were incubated for 24 h. Total cell viability was assessed by the alamarBlue® assay in which cells were treated with alamarBlue® (Bio-Rad Laboratories, Inc. Trek Diagnostic Systems, USA) for 3 h. Absorbance was measured at 570 nm and 600 nm with a microplate reader (SpectraMax® 190, Molecular Devices corporation, Sunnyvale, CA, USA) and results were analyzed by a software (Soft max Pro5.2, Molecular Devices corporation).

Enzyme-linked immunosorbent assay (ELISA)

To investigate the effect of luteolin on the release of MMP-1 and MMP-9 on UV-irradiated HDF cells, cell culture medium was measured by ELISA. Semi-confluent (70-80%) HDF cells were seeded into 24-well plates and pretreated with luteolin at 1, 2, 5 and 10 µM and incubated for 24 h. On the next day, the supernatant was removed, cells were washed with PBS, HBSS was added and then cells were irradiated with UV, fresh medium was replaced, test samples were added once more and incubated for 24 h. ELISA was performed with the culture medium supernatant according to the manufacturer's instructions (human total MMP-1, MMP-9, R&D Systems®, Minneapolis, MN, USA). Absorbance was measured at 450 nm by a SpectraMax® 190 microplate reader and the result was analyzed by Soft max Pro5.2 software.

Quantitative real-time reverse transcription–polymerase chain reaction (qRT-PCR)

Total RNA was extracted from cultured cells using an RNA extraction kit (NucleoSpin® RNA II Takara, MACHEREY-NAGEL GmbH & Co. KG., Düren, Germany) and quantified spectrophotometrically. Approximately 2 µg of RNA was used as a template for the synthesis of cDNA using the PrimeScript™ RT reagent kit, Perfect Real Time (Takara Bio Inc., Shiga, Japan) according to the manufacturer's protocol. To prevent possible contamination by genomic DNA, samples were treated with deoxyribonuclease (RT-grade; Wako Pure Chemical Industries, Ltd.) as recommended by the manufacturer. qRT-PCR was performed using the Thermal Cycler Dice Real Time (TaKaRa Bio., Tokyo, Japan) according to the manufacturer's instructions. Amplification conditions were as follows: 95°C for 30 s followed by 40 cycles consisting of 95°C-5 s, 60°C-60 s, 1 cycle: 60°C-30 s and 95°C-15 s. Primers were purchased from TaKaRa Bio., and are listed in Table 1.

Statistical analysis

All experiments were repeated at least three times. Data is presented as the mean ± standard error (SE). Statistical analysis was determined by the one-way analysis of variance (ANOVA). A P value of less than 0.05 was considered to be statistically significant.

Results

Effects of UVA and UVB on viability of HDF cells

To observe whether the doses of UV light applied induced toxicity, the viability of HDF cells was measured by the alamarBlue® assay. Human dermal fibroblast (1×10^5 cells/well/500 µL on a 24-well plate) were exposed to UVA (10 J/cm^2) and UVB (200 mJ/cm^2) irradiation and cells were incubated for 24 h. Total cell viability was assessed by the alamarBlue® assay in which cells were treated with alamarBlue® (Bio-Rad Laboratories, Inc. Trek Diagnostic Systems, USA) for 3 h. The cell viability was tended to be reduced but not significantly different between UV-exposed and control HDF cells (data not shown).

Luteolin suppresses UVA- and UVB-stimulated MMP-1 and 9-production in HDF cells

UV-irradiation damages human skin tissues and causes premature skin aging or photoaging by activating MMPs, which are responsible for the degradation of collagen, a major structural component of the extracellular matrix. To examine the effect of luteolin on the production of MMP-1 and MMP-9 in HDF cells, cells were exposed to UVA (10 J/cm^2) and UVB (200 mJ/cm^2) and MMP-1 and MMP-9 was measured in cell culture supernatants by ELISA. The results show that UVA and UVB induced the production of MMP-1 as well as MMP-9 in

HDF cells. The addition of luteolin reduced the production of MMP-1 in UV-irradiated cells in a dose-dependent manner (Figures 2 and 3). The release of MMP-9 was also reduced by luteolin (Figure 4) in UVB-irradiated HDF cells, but there was no change in UVA-irradiated cells (data not shown).

Luteolin suppresses UVA- and UVB-stimulated MMP-1 expression in HDF cells

To further ascertain whether luteolin regulates the expression of MMP-1 at the gene level, expression of the MMP-1 gene was examined in both UV-irradiated HDF cells. Cells were seeded into 24-well plates and pretreated with luteolin at 1-10 μM and incubated for 24 h. and cells were irradiated with UV, test samples were added once more and incubated for 24 h. Total RNA was extracted from cultured cells and MMP-1 expression was quantified by qRT-PCR. When HDF cells were exposed to UV, expression of the MMP-1 gene was up-regulated. The inclusion of luteolin in the culture medium decreased the expression of the MMP-1 gene against both UV-irradiated HDF cells in a dose-dependent manner.

Luteolin suppresses UVA- and UVB-induced MMP-9 expression in HDF cells

MMP-9 plays a prominent role in the breakdown of the extracellular matrix. In this process, collagen is cleaved by collagenase, and cleaved collagen is further degraded into gelatin and small peptides by gelatinase B, and induces breakdown of the ECM, which is a major factor responsible for wrinkle formation [19]. Total RNA was extracted from UV-irradiated HDF cells treated with luteolin and MMP-1 expression was quantified by qRT-PCR. Results demonstrated that UV-irradiation increased MMP-9 expression in HDF cells. The inclusion of luteolin in the culture medium decreased the expression of the MMP-9 gene against both UV-irradiated HDF cells in a dose-dependent manner.

Discussion

Luteolin is a polyphenolic flavone found in a large number of vegetables, fruits and spices (Figure 1) [1]. A number of studies have reported on the beneficial effects of luteolin [11,20-23] but only a few studies have focused on its anti-photoaging effects. Ultraviolet irradiation, both UVA and UVB, penetrates the atmosphere and plays an important role in premature skin aging, skin cancer and suppression of the immune system. Photodamaged skin induces certain MMPs that breakdown dermal matrix protein such as collagen and elastin of the extracellular matrix [3,4,24-25]. It was recently established that fibroblast cells secrete MMP-1 and MMP-9 against UV during photoaging [8,9]. Therefore, the suppression or inhibition of MMP-1 and MMP-9 overexpression induced by UVA and UVB could constitute a novel application to reduce photo aging.

Flavonoids, including epigallocatechin gallate (EGCG) [26], curcumin [27], and resveratrol [28] in the micro molar concentration range inhibit UV-exposed metalloproteinases activity *in vitro* and *in vivo*. However, a few studies have investigated the direct modulatory effects of luteolin on MMPs during photoaging [29-33]. Moreover, to date, a relationship between luteolin and MMP-9 against both UVA and UVB-irradiation has not been demonstrated, despite the importance of MMP-9 and collagen breakdown during photoaging using HDF cells [19]. To the best of our knowledge, this is the first report to show that luteolin suppresses both UVA and UVB-induced MMP-1 and MMP-9 in HDF cells in a dose-dependent manner.

Similar to our results, luteolin at 1-5 μM significantly inhibited UVA (15 J/cm^2)-induced MMP-1 mRNA expression in human keratinocyte HaCaT cells [29]. In another study, luteolin at 5-10 μM inhibited UVB (10 mJ/cm^2)-induced MMP-1 expression in a dose-dependent manner in human keratinocyte HaCaT cells [30]. Human dermal fibroblast cells exposed to UVA (6.3 J/cm^2) induced MMP-1 when luteolin was inoculated into the cell culture at 1-10 μM, reducing the expression of MMP-1 protein and mRNA [31]. Another study by Wölfle et al. showed that luteolin at 4 μg/mL inhibits MMP-1 expression against UVA-1 (20 J/cm^2)-induced human dermal fibroblast cells [32].

We showed the protective effect of luteolin at 1–10 μM (non-cytotoxic levels) [31] against both UVA (10 J/cm^2) and UVB (200 mJ/cm^2)-irradiated HDF cells. Our results demonstrate that luteolin suppresses both UVA and UVB-induced MMP-1 production at protein and gene expression levels (Figures 2-6). We also found that luteolin suppresses both UVA and UVB-induced MMP-9 gene expression

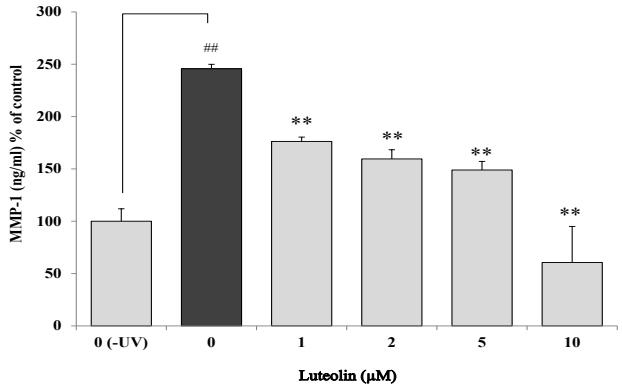

Figure 2: Effects of luteolin on MMP-1 protein release was quantified by enzyme-linked immunosorbent assay (ELISA). HDF cells were treated with different doses of luteolin for 24 h and then the cells were exposed to UVA (10 J/cm^2) irradiation. After exposure to UVA, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. ELISA was performed with the supernatant of the culture medium. Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

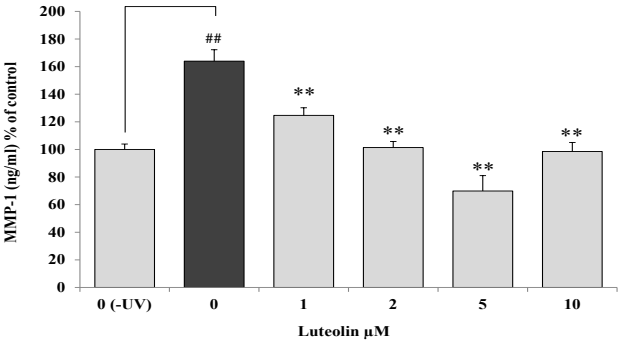

Figure 3: Effects of luteolin on MMP-1 protein release was quantified by enzyme-linked immunosorbent assay (ELISA). HDF cells were treated with different doses of luteolin for 24 h and then the cells were exposed to UVB (200 mJ/cm^2) irradiation. After exposure to UVB, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. ELISA was performed with the supernatant of the culture medium. Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

Gene name	Forward primer	Reverse primer	Sizes (bp)
Human MMP-1	5′-ATTCTACTGATATCGGGGCTTTGA-3′	5′-ATGTCCTTGGGGTATCCGTGTAG-3′	408
Human MMP-9	5′-CTGCCAGGACCGCTTCTACT -3′	5′-TGGTCCCAGTGGGGATTTAC-3′	153
Human ActB	5′-TGGCACCCAGCACAATGAA -3′	5′-CTAAGTCATAGTCCGCCTAGAAGCA-3′	185

Table 1: Primers used for Q-PCR.

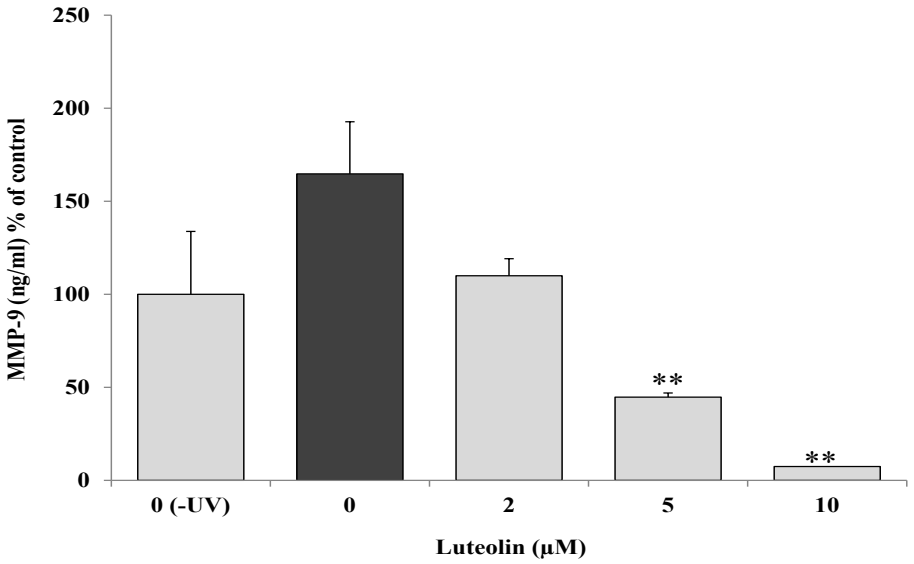

Figure 4: Effects of luteolin on MMP-9 protein release was quantified by enzyme-linked immunosorbent assay (ELISA). HDF cells were treated with different doses of luteolin for 24 h and then the cells were exposed to UVB (200 mJ/cm^2) irradiation. After exposure to UVB, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. ELISA was performed with the supernatant of the culture medium. Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

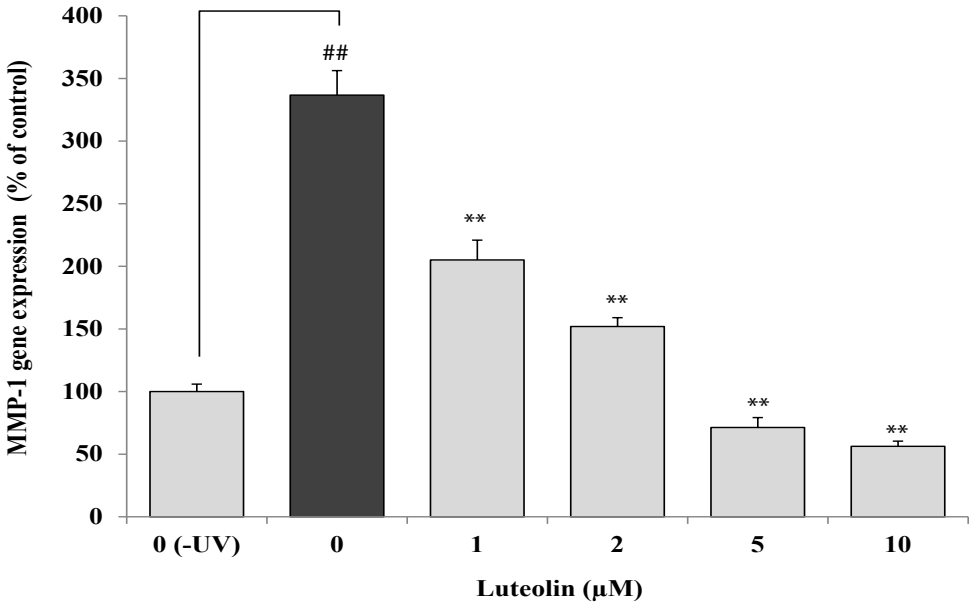

Figure 5: Effects of luteolin on MMP-1 gene expression in UVA-irradiated HDF cells. HDF cells were treated with different doses of luteolin for 24 h and then exposed to UVA (10 J/cm^2) irradiation. After exposure to UV, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. RNA was extracted from the cells, and MMP-1 gene expression was determined by qRT-PCR. Results were normalized using the level of Beta-actin (ActB). Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

(Figures 7 and 8) as well as protein production against UVB-induced HDF cells (Figure 4). However, the level of MMP-9 protein did not change in UVA-irradiated HDF cells. On the other hand, MMP-9 gene expression was much stronger than that of MMP-1. The variance observed in the data pertaining to gene expression and protein release of MMP-9 in HDF cells observed in our experiment might be due to biological differences in abundance between transcript and protein. Further studies are needed to resolve this discrepancy.

UV light irradiation induces signal transduction in skin photo aging. The activation of cell surface receptors, including cytokine receptors and growth factor receptors, by UV irradiation stimulates signal transduction pathways involving MAP kinase family members, including P13K and AKT, ERK, JNK and P38 which lead to activation of the activator protein-1 (AP-1) and nuclear factor kappa B (NF-kappaB) transcription factor family members. This activation results in an increase in the expression of several MMPs, including MMP-1, MMP-3 and MMP-9 [34,35].

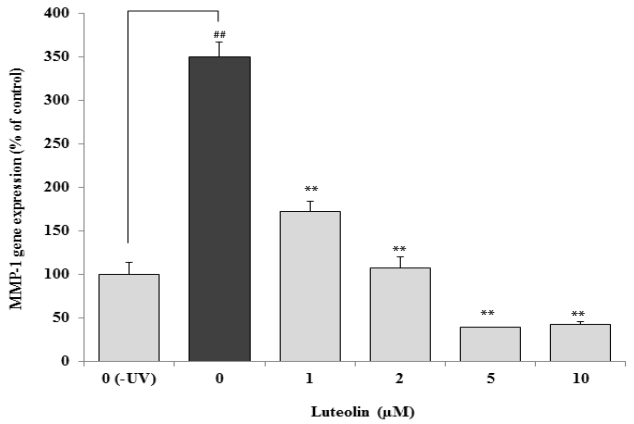

Figure 6: Effects of luteolin on MMP-1 gene expression in UVB-irradiated HDF cells. HDF cells were treated with different doses of luteolin for 24 h and then exposed to UVB (200 mJ/cm^2) irradiation. After exposure to UV, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. RNA was extracted from the cells, and MMP-1 gene expression was determined by qRT-PCR. Results were normalized using the level of Beta-actin (ActB). Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

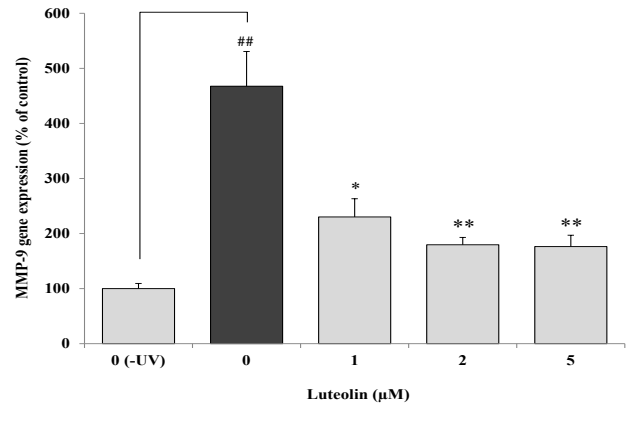

Figure 7: Effects of luteolin on MMP-9 gene expression in UV-irradiated HDF cells. HDF cells were treated with different doses of luteolin for 24 h and then exposed to UVA (10 J/cm^2) irradiation. After exposure to UV, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. RNA was extracted from the cells, and MMP-9 gene expression was determined by qRT-PCR. Results were normalized using the level of Beta-actin (ActB). Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

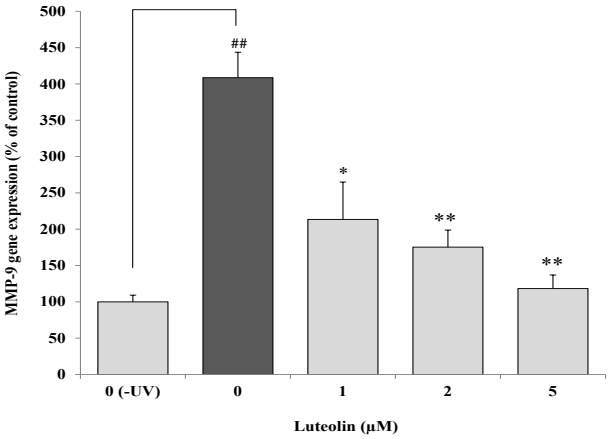

Figure 8: Effects of luteolin on MMP-9 gene expression in UV-irradiated HDF cells. HDF cells were treated with different doses of luteolin for 24 h and then exposed to UVB (200 mJ/cm^2) irradiation. After exposure to UV, fresh complete growth medium was added in the presence of the indicated concentrations of luteolin and incubated for 24 h. RNA was extracted from the cells, and MMP-9 gene expression was determined by qRT-PCR. Results were normalized using the level of Beta-actin (ActB). Data are expressed as a relative percentage value of the control. Results are mean ± SE. *P<0.05, **P<0.001 compared to UV-irradiated samples.

In conclusion, this study demonstrated that both UVA and UVB activate HDF cells and lead to the release of MMP-1 and MMP-9. Furthermore, luteolin at a micro molar concentration range inhibits the production of MMPs at the protein and gene levels. Luteolin may also suppress the development of skin photo aging.

Acknowledgment

We sincerely thank to Dr. T. Otah and Dr. Y. Katayanagi for technical assistance.

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Citation: Pervin M, Unno K, Nakamura Y, Imai S (2016) Luteolin Suppresses Ultraviolet A- and B-induced Matrix Metalloproteinase 1- and 9 Expression in Human Dermal Fibroblast Cells. J Nutr Food Sci 6: 560. doi: 10.4172/2155-9600.1000560