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# PHOTO-PROTECTIVE EFFECT OF EPIDERMAL MUCOPROTEIN OF THE *SCARUS GHOBBAN* (FORSSKAL, 1775) AGAINST UV-INDUCED MODULATION OF TNF-α AND $P^{53}$ GENE

**Elayaperumal Natarajan*, Subramanian Sankarlal**

Centre of Advanced Study in Marine Biology, Faculty of Marine Sciences,

Annamalai University, Parangipettai, India.

ABSTRACT: Ninety percent of the reef fishes showing UV absorbance in their mucus and sunscreen compounds are produce in the external mucus of fish. In the present investigation, it was aimed to evaluate the photo protective effect of skin epidermal mucus (SEM) of parrot fish, *Scarus ghobban* against UV-B induced modulation of TNF-α and $p^{53}$ gene. SEM was collected and partially purified. Enzyme linked immunosorbant assay (ELISA) for cytokine estimation and RNA isolation, and RT-PCR of HaCaT cells was performed. The expression of TNF-α and $p^{53}$ gene was observed in UV-B irradiated HaCaT cells and significantly SEM treated HaCaT cells. The present study suggested that SEM was useful in dermatological formulations to support repair and regeneration of UV-B irradiated skin cells.

**KEYWORDS:** *Scarus ghobban*, Epidermal mucoprotein, UV-B absorbance, ELISA and TNF-α and $p^{53}$ gene.

**Corresponding Author: Dr. Natarajan Elayaperumal*** Ph.D.

Centre of Advanced Study in Marine Biology, Faculty of Marine Sciences, Annamalai University, Parangipettai, India. Email Address: menrajancas@gmail.com

## 1. INTRODUCTION

UV radiation plays a dual role in the development of skin cancer. On one hand, UV radiation induces genetic alterations in keratinocytes, leading to their neoplastic transformation. On the other hand, UV radiation depresses the immune responses in the skin, which can permit the growth of emerging tumors produced by the effects of UV induced DNA damage [1]. Immunological studies with skin cancer patients have indicated that the immune suppression

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induced by UV-B radiation is a major risk factor in skin cancer development [2]. The UV-B component of solar ultraviolet radiation has been shown to suppress the immune system and act as a tumor initiator, tumor promoter and co-carcinogen [3, 4, 5]. Keratinocytes are the major immunologically competent component of human skin, providing the initial barrier and response against environmental dangers such as UV-B irradiation. Cytokines/chemokines play pivotal roles in immunologic regulation in the human body and are involved in the induction of proliferation, differentiation, and cell death in many cell types, including keratinocytes [6,7,8]. UV-B irradiated human keratinocytes have been shown to secrete potent inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α. UV-B induce cytokine production in keratinocytes including interleukin (IL)-1, 1 IL-6, IL-8, IL-10, and tumor necrosis factor (TNF-α) [9,10,11]. UV-B exposure on the skin stimulates the inflammatory responses via upregulation of proinflammatory cytokines such as TNF-α , interleukin-1 (IL-1), IL-1, IL-6, and IL-8 [12]. TNF-α is a key proinflammatory cytokine in various skin diseases, [13]. Originally described as a cytotoxic factor for proliferating tumor cells; TNF-α has a wide range of pro-inflammatory and cytotoxic effects [14]. UVR-induced TNF-α production in keratinocytes has been implicated in UV-B induced inflammation and epidermal cell apoptosis, [15]. Cytokines such as IL-10, TNF-α, and IL-1α that can suppress the immune system and prevent T-cell mediated responses; these are known to be secreted by keratinocytes after UV damage [10]. An additional process of photodamage is apoptosis in cells that contain a high proportion of damaged DNA following UV irradiation [16]. The primary mediator responsible for removing UV-B induced DNA damage of keratinocytes in skin is believed to be p53 [17,18,19]. Importantly, the p53 gene is itself a frequent target of mutation in UV carcinogenesis of the skin [20], and the tumor suppressor protein p53 plays a critical role in the cellular response to DNA damage by functioning as a cell cycle checkpoint determinant [21]. The p53 tumor suppressor gene codes for a DNA binding protein and mutations or loss of p53 plays a key role in the process of carcinogenesis. It is the most frequently altered gene in human cancers (>50%). The human p53 gene is localized on the chromosome 17 (17p13) and contains 11 exons spanning 20 kilobases. The mouse p53 gene is localized on chromosome 11 and also contains 11 exons [22]. Recent work indicates that the p53 protein is a central element in fundamental cellular processes, including gene transcription, repair of DNA damage, control of the cell cycle, genomic stability, chromosomal segregation, senescence and apoptosis. DNA damage elicited by UV-B is thought to be an important trigger for p53 accumulation and transcriptional activation, leading to cell cycle arrest and allowing more time for DNA repair or elimination of damaged cells through apoptosis. Most nonmelanoma skin cancers have mutations in p53 [23]. The HaCaT cell line bears mutations in both alleles of the p53 gene; rendering a non functional, transcriptionally inactive protein with an increased half-life [24], and the mutations in p53 present in HaCaT cells are characteristic of the UV signature [25]. The p53 tumor suppressor gene appears to be one of the

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key UV-responsive genes, and mutations in this gene are thought to initiate the process of skin carcinogenesis [25]. The deregulation of p53 functions and slow repair of UV-induced photoproducts at particular codons may lead to the induction and accumulation of p53 mutations, particularly C-T or tandem CC-TT transitions thereby initiating the molecular process of carcinogenesis [26, 23]. Generally UV radiations initiate the carcinogenesis by consequence of genetic mutation and it modulates the immunosuppression reaction to enhance the tumour formation. So the present study was conducted to assess potential of SEM as photo protective agent against UV-B induced alteration in cytokine TNF-α and p53 gene expression.

## 2. MATERIALS AND METHODS

### 2.1. Sample Collection, Extraction and Purification

Live specimens of the fish *Scarus ghobban* were collected from Nagapattinam as by-catch. Mucus scrapping: Epithelial mucus was sampled by scraping a dull scalpel blade along the dorsal flank of live fishes, anterior to posterior. Mucus of the fish was collected from the dorsal region of the skin using blunt edged scalpel. Mucus was not collected from Ventral side of the fish to avoid urine and intestinal excreta [27]. The fish was placed on a flat non slippery surface with its head and eyes covered by palms to reduce the photophobic response (fear of light). Using a dull blade, mucus was gently scraped off the entire dorsal flank of fish as described by [28]. Mucus sample was taken from the anterior section by moving from the head towards the anus using a spatula and stored in the sterile Amber bottle and stored in ice, to avoid bacterial contamination and proteins degradation during the transportation Sample Preparation: 0.1002 g of sample was weighed and dissolved in 10 ml of methanol and diluted to 25 ml with methanol (Stored at -4$^{o}$ C). Preparation of Mobile Phase: Preparation of 0.2 % Acetic acid: 0.2 ml of Acetic acid mixed with 100 ml of distilled water, 75 ml of 0.2 % Acetic acid mixed with 25 ml of methanol and Filtered through and 0.45 μm nylon vacuum filter and sonicated. Sonication:Each sample was then mixed using a sonicator in an ice bath (Unisonics) for 20 min and left to leach for 24 h at room temperature. Centrifugation: The extracts were then centrifuged for 5 min at 18 000 × *g* and the supernatant was used for laboratory spectral UV analysis. Sample extraction: Samples were extracted in 1.5 ml of 100% methanol and homogenized. Partial purification of Parrot fish *Scarus ghobban* fish mucus: Partial purification of fish mucus was carried out by Silica gel chromatography.

### 2.2. Enzyme-Linked Immunosorbent Assay (ELISA) for cytokine estimation

ELISA is a method for the quantitative or qualitative detection of analytes (in our case the cytokine TNF-α). This technique is based on the specific binding between an antigen and its antibody, and is therefore highly specific.We use sandwich-ELISA Kits. The antibodies for the cytokine of interest were coated on each well of a 96-well polystyrene plate. When the serum or plasma was added, the cytokines will strongly interacted with their antibodies and formed very strong complexes. After washing steps to remove interfering molecules and unbound cytokines,

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we added secondary antibodies, which bound to the cytokines and which were conjugated with an enzyme. This enzyme therefore indirectly attached to the cytokines. Sometimes, the secondary antibodies were conjugated to a biotin molecule. Biotin has the feature to have a powerful interaction with streptavidin. The streptavidin carried the enzyme responsible for the conversion of the substrate (chromogen) was added in the last step, resulting in colour development. The intensity of the colour was directly related to the amount of cytokines bound to the antibodies, and was measured by the spectrophotometer. This allowed us to measure the concentration of the cytokine in the solution. The classical procedure of sandwich-ELISA was followed. The enzyme used was Horse radish peroxidase (HRP). It catalyzed the oxidation of a substrate by hydrogen peroxide, which led to a blue colour. The most common substrate is tetramethylbenzidine (TMB). To stop this enzymatic reaction, sulphuric acid was added since it denaturates HRP. The colour changed from blue to yellow, with a maximum absorption at 450 nm.

**2.3. RNA isolation and RT-PCR of HaCaT cells**

Total RNA was isolated from TRIZOL-(Sigma, India) according to the manufacturer's instructions. Briefly, the sample in TRIZOL was repeatedly pipetted to disrupt cells. The samples were incubated for 5 min at room temperature to permit complete dissociation of nucleoprotein complexes, 0.25 ml portions of chloroform were added, and the samples were centrifuged at 12,000 x g for 15 min at 4°C. Upper aqueous phase was mixed with five milligrams of RNase-free glycogen and 0.5 ml of isopropyl alcohol were introduced to precipitate nucleic acids for 15 min at room temperature, and the pellets were washed with 75% ethanol (in DEPC-treated water) (Invitrogen, U.S.A.). Pellets were resuspended in RNase free water, and DNase I (Invitrogen) treatment was performed according to the manufacturer's instructions. RT-PCR was performed in triplicate using Super Script ™ two Step RT-PCR with platinum® Taq kit according to the manufacturer's recommendations (Invitrogen, Carlsbad, CA, U.S.A.). For cDNA synthesis, Complementary DNA was synthesized from 1 µg total RNA from each sample in 20 µL of reaction buffer (contained 50 mM Tris-HCl, pH 8.3, 75 mM KCl and 3 mM $MgCl_2$) using SuperScript II reverse transcriptase enzyme (Genetech, RT-PCR mix- Germany) in a 20 µl volume reaction containing 10 mM dithiothreitol, 10 U RNase inhibitor (Promega, Madison, WI, USA), 1 mM dNTPs and 2.5 µM random hexamers. Each sample was incubated for 45 min at 45° C, followed by 10 min at 72° C in a Agilent amplicon system (AGILENT Biosystems), the prepared cDNA was stored in -20° C for further use. The cDNA (1 µl) was then amplified in 20 µl of reaction buffer for 40 cycles of denaturation (96°C for 30 s), annealing (56°C for 30 s), and extension (72°C for 30s) using primers. p53 mRNA: 5'- ACGTACTCTCCTCCCCTCAAT -3' (forward); 5' - AACTGCACAGGGCACGTCTT -3' (reverse).

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## 3. RESULTS AND DISCUSSION

### 3.1. UV-B-induced secretion of TNF-α in HaCaT cells

Using ELISA method was used for the determination of the concentration of TNF-α in the UV-B-induced and SEM pre-treated HaCaT Cells. The Normal HaCaT cells showed TNF-α in the (Table 1) (302.37 ± 15.08 pg /ml), whereas the level of TNF-α produced by the UV-B irradiated HaCaT cells was increased in high level (702.87± 27.22), UV-B irradiated HaCaT cells pre-treated with SEM (Figure. 1) showed significantly decrease in the production of TNF-α in dose dependent manner.

### 3.2. FME down-regulated UV-B induced p53 mRNA expression

To assess SEM had inhibitory effects on p53 gene expression, the mRNA levels were determined by RT-PCR. The Normal HaCaT cells showed the p53 gene expression in the means of experimental folds as shown in Figure. 2. The values are shown in Table 2. (0.95±0.07). After UV-B irradiation, the mRNA expression of p53 genes upregulated (3.42±0.04) and it was down-regulated by the pre-treated SEM in the UV-B irradiated HaCaT Cells in dose dependent manner 3 µg (2.16±0.09) and 10 µg (0.55±0.06) as shown in Table 2 respectively. SEM intervention significantly decreased higher mRNA levels induced by UV-B irradiation.

### 3.3. Enzyme-linked Immunosorbent assay (ELISA) for TNF-α Measurement

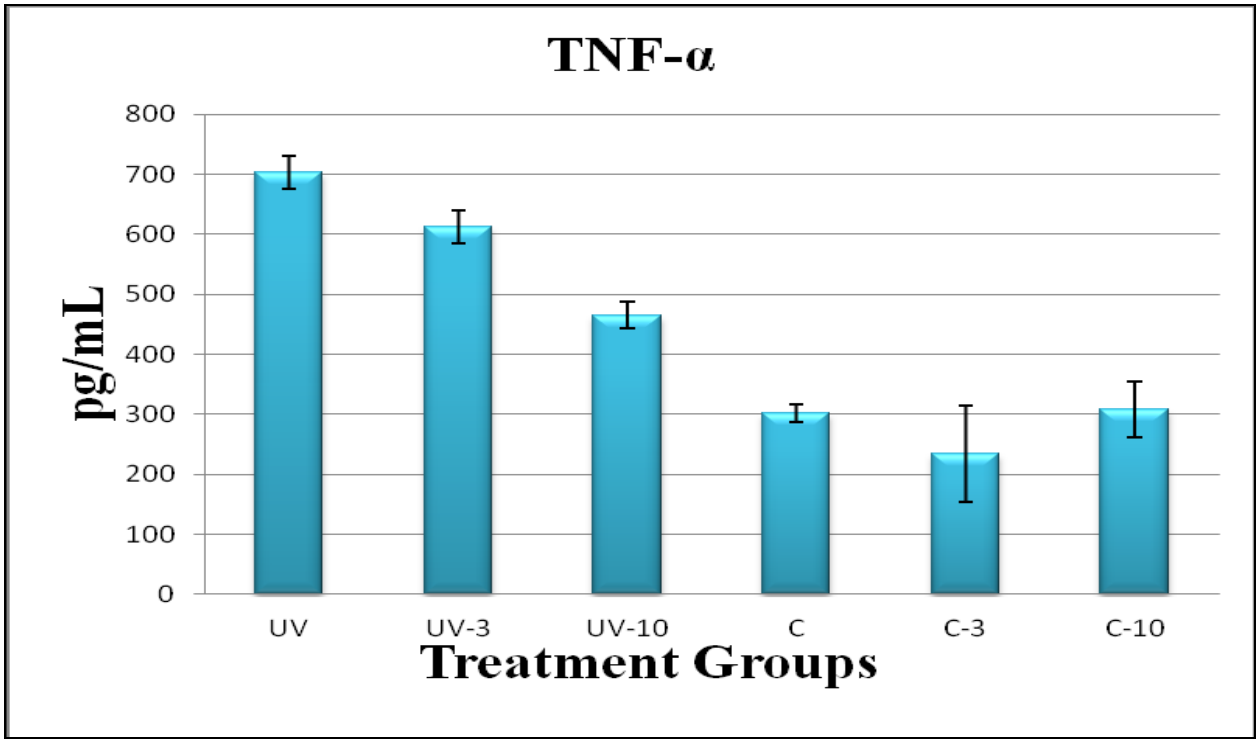


**Fig. 1. Effect of SEM on cytokine induced by UV-B radiation in HaCaT Cells**

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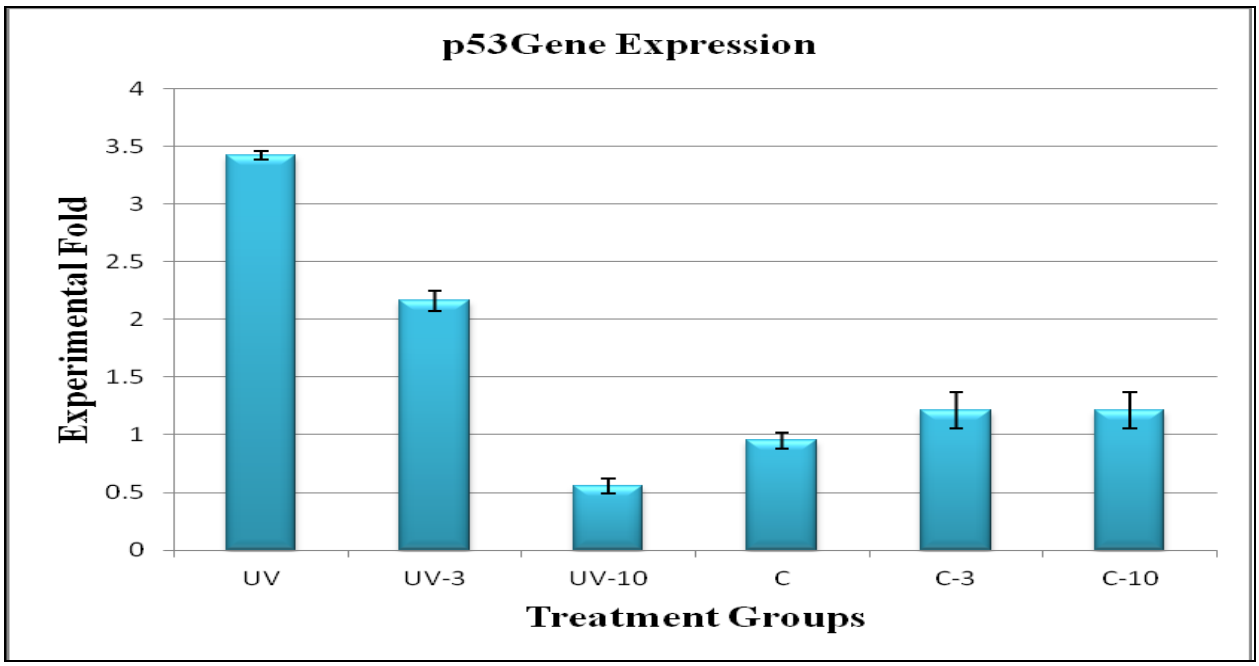
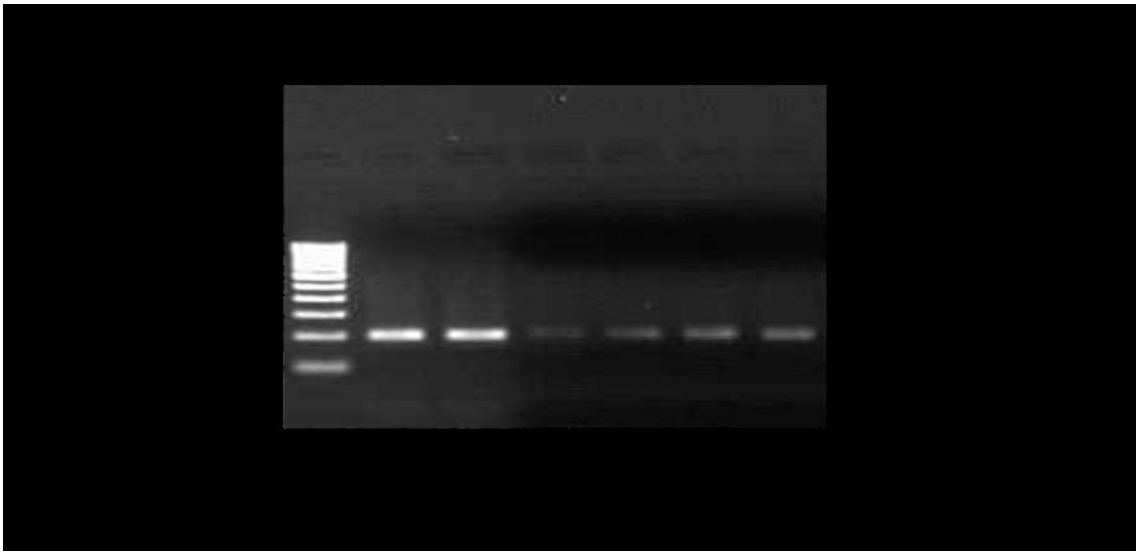



**Fig. 2. Effect of SEM on p53, induced by UV-B radiation in HaCaT Cells**



**M-Marker 1Kb DNA ladder, 1.HaCaT+UV-B,2. UV-B+3µg of SEM,3. . UV-B+10µg of SEM,4. Control-Normal HaCaT cells, 5. 3µg of SEM,6. 10µg of SEM**

**Fig. 3. Effect of** SEM **on p53 gene expression, induced by UV-B radiation in HaCaT Cells**

The Figure. 3 revealed that UV-B radiation up-regulated the p53 but pretreated SEM irradiated HaCaT Cells showed significant decrease in experimental folds. It clearly showed that SEM down-regulated the p53 gene expression.

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**TNF- A Production in Keratinocyte Cells**

**Table 1: Effect of SEM On Cytokine Induced By UV-B radiation in HaCaT**

| Treatment | TNF-α | | Average | S.D |
|---|---|---|---|---|
| **UV-B alone** | 683.62 | 722.11 | 702.87 | 27.22 |
| **UV-B With 3µg of SEM** | 592.34 | 631.99 | 612.17 | 28.04 |
| **UV-B With 10µg of SEM** | 449.69 | 480.28 | 464.99 | 21.63 |
| **Control** | 313.03 | 291.71 | 302.37 | 15.08 |
| **3µg of SEM** | 177.42 | 290.42 | 233.92 | 79.90 |
| **10µg of SEM** | 277.53 | 340.53 | 308.03 | 45.96 |

**3.4. Gene Expression**

**Table 2: Effect of SEM On P53, Induced By UV-B Radiation In HaCaT Cells**

| Treatment | $P^{53}$ | | Average | S.D |
|---|---|---|---|---|
| **UV-B alone** | 3.32 | 3.5 | 3.42 | 0.04 |
| **UV-B With 3µg of SEM** | 2.22 | 2.1 | 2.16 | 0.08 |
| **UV-B With 10µg of SEM** | 0.509 | 0.6 | 0.55 | 0.06 |
| **Control** | 1.0 | 0.9 | 0.95 | 0.07 |
| **3µg of SEM** | 1.32 | 1.1 | 1.21 | 0.15 |
| **10µg of SEM** | 1.32 | 1.1 | 1.21 | 0.15 |

**DISCUSSION**

Keratinocytes constitute 95% of the mass of human epidermal cells and play critical roles in skin physiology due to their autocrine and paracrine effects [29]. The constitutive productions of cytokines and other soluble factors are low in human keratinocytes, but various stimuli, including endotoxins and UV, can trigger the expression of proinflammatory cytokines [30]. Furthermore, exposure of the skin to UV-B radiation is known to enhance the levels of pro-inflammatory cytokines. As keratinocytes are considered to be major sources of cytokines, chemokines, growth factors, and many others, UV-B radiation can cause a series of changes in the cutaneous cytokine such as TNF- , IL-1 , IL-1 , IL-6, and IL-8 [12]. Human epidermal keratinocytes can produce TNF-α and the level of TNF-α has shown to increase after exposure to UV-B [30]). The effects of FME on inflammatory cytokine expression were examined in HaCaT cells, exposed to UV-B at 15m J/$Cm^2$ and incubated for 24 h were examined. In our study also, enhanced expression of TNF- was observed in UV-B irradiated HaCaT cells. Cells were exposed to UV-B at 15m J/$Cm^2$ in the presence of SEM at different concentrations was attenuated in the level of inflammatory cytokine. Our result was in accordance with the report of Yoshizumi *et al*. (2008) as mentioned above. In

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keratinocytes, apoptosis directly and initially trigger by UV-B can be via cytokines: upregulating expression of TNF-α and accumulation of the tumor suppressor gene p53 [18]. Over expression of p53 may lead to cell cycle arrest and apoptosis [31,,32,33,34]. UV radiation- induced DNA damages are considered to be an important event in the activation of apoptotic signaling. It has been already established that p53 is activated during UV light induced DNA damage [35]. In our study UV-B irradiated HaCaT cells showed over expression of p53 gene at 15mJ/$Cm^2$. UV-B induced expression of p53 mRNA level was repressed by SEM. These data showed that SEM might reduce UV-B induced apoptosis through blocking of the p53 expression. Ramachandran *et al.* (2012) recorded the same kind of result in his study on UV-B exposure in HDFa cells. He noted that UV-B exposure inhibited expressions of pro-apoptotic factors (p53 and Bax) and enhanced the expression of anti-apoptotic factor (Bcl-2), thus protecting HDFa from UV-B induced cell death. SEM from the parrot fish *Scarus ghobban* acted rightly and maintained the level of p53 and cytokine to protect the cells from UV-B radiation. Although the *in vitro* studies based evidences presented here suggested that SEM might be quite effective in preventing photocarcinogenesis.

## 4. CONCLUSION

In conclusion, SEM from the parrot fish *Scarus ghobban* had effective photo protective effect as proved in *invitro* study. The present study suggested that FME was useful as an active component in dermatological formulations to support repair and regeneration of UV-B irradiated skin. Development of broad-spectrum protective agents was found helpful to prepare more effective sunscreens with better protection.

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## CONFLICT OF INTEREST

Authors have no conflict of interest.

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