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Research Article

Mechanistic Perspectives on Cutaneous Toxicity Induced by the Multitargeted Kinase Inhibitor Sunitinib

Tuğçe Boran[1], Gül Küçükkahraman[2], Mahmoud Abudayyak[3]

[1]Department of Pharmaceutical Toxicology, Faculty of Pharmacy, İstanbul University-Cerrahpaşa, İstanbul, Türkiye
[2]Institute of Health Sciences, Istanbul University, İstanbul, Türkiye
[3]Department of Pharmaceutical Toxicology, Faculty of Pharmacy, İstanbul University, İstanbul, Türkiye

Abstract

Objectives: Multittargeted kinase inhibitor sunitinib is used for the treatment of some cancer types. It has been noted that sunitinib can cause cutaneous reactions and their mechanisms have not been known yet. The study aimed to investigate mechanistic bases of sunitinib-induced cutaneous reactions using HaCaT cell line.

Methods: Cytotoxicity of sunitinib was evaluated with MTT assay following 72 h exposure. Reactive oxygen species (ROS) generation and apoptotic/necrotic cell death were examined by flow cytometer, and mitochondrial membrane potential (MMP) was assessed by microplate reader with fluorescent dyes. Changes in malondialdehyde, reduced and oxidized glutathione levels were determined using ELISA kits. DNA damage was investigated with alkaline single gel electrophoresis (Comet) assay.

Results: Half maximal inhibitory concentration of sunitinib was determined as 3.10 µM after 72 h exposure. Our findings showed that sunitinib provokes ROS generation, glutathione and lipid oxidation especially at the highest concentration. MMP hyperpolarization was observed at high doses. Apoptosis was triggered at the highest dose, while necrosis and DNA damage were induced at all exposure groups upon sunitinib exposure.

Conclusion: Oxidative stress, cell death and DNA damage could be underlying causes of sunitinib-induced cutaneous reactions. Nevertheless, further studies are needed to confirm our findings.

Keywords: Sunitinib, Cutenous reactions, Oxidative stress, Cell death

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Sunitinib, multi-targeted small-molecule kinase inhibitor, exerts anticancer effect by inhibiting of some kinases including vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (c-Kit), and FMS-like tyrosine kinase-3 (FLT3).[1] It is approved by the US Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) following imatinib resistance, advanced renal cell carcinoma (RCC), and some pancreatic neuroendocrine tumors.[2]

Although sunitinib is therapeutically effective, some adverse effects which can be life-threatening have been reported such as hepatotoxicity and cardiotoxicity.[2] Studies reported that sunitinib treatment can be associated with cutaneous toxic effects[3] which include skin discoloration, stomatitis, xerosis, rash, alopecia, subungual splinter haemorrhage. In

Address for correspondence: Tugce Boran, PhD. Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University Cerrahpaşa, Istanbul, Türkiye
Phone: +90 (0212) 866 37 00 **E-mail:** tugce.boran@iuc.edu.tr

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addition to the most common and characteristic toxicity is the Hand-Foot Skin Reaction (HFSR)[4-7] and high-grade (Grade 3/4) mucocutaneous toxicities have been associated with sunitinib in non clear cell renal cell carcinoma patients.[8] HFSR is a particular cutaneous reaction that is restricted to the palms and soles.[4,5] Clinical signs of sunitinib – induced HFSR include erythema, numbness, tingling, dysesthesia, and the formation of hyperkeratotic lesions. These cutenaous adverse effects can negatively affect a patient's quality of life and treatment adherence, and frequently result in dose alteration or treatment discontinuation.[3]

The molecular pathways underlying sunitinib-associated cutaneous adverse effects have not yet been fully elucidated. Accordingly, this study aims to elucidate the underlying mechanisms of cutaneous toxicity induced by sunitinib in the human keratinocyte cell line (HaCaT) mainly focusing on oxidative stress, apoptotic/necrotic cell death and genotoxicity.

Methods

Cell culture: The immortalized human keratinocyte cells (HaCaT) were sustained in Dulbecco's Modified Eagle Medium (DMEM) enriched with 10% Fetal Bovine Serum (FBS) and 1% Amphotericin-Penicillin-Streptomycin solution. The culture medium was changed in every 2-3 days. The cells at 60-70% confluency, cells were harvested and subcultured.

Cytotoxicity assays: The cytotoxic potential of sunitinib on HaCat cells was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay. Since half-life of sunitinib was determined to be between 40 to 60 hours,[9] all experiments were performed after 72 h drug treatment. For cytotoxicity evaluation, HaCaT cells were seeded into 96-well plates at a density of 1 x 10^4 cells/well in 100 µL of complete culture medium. Following cell attachment, cells were exposed to different concentration of sunitinib (0.5-20 µM). After a 72 hour incubation period, MTT solution was added to each well, and the plates were incubated for an additional 3 hours at 37°C in the dark. Subsequently, cell culture medium was discarded, and the purple formazan crystals formed by viable cells were dissolved in 100 µL of dimethyl sulfoxide (DMSO). The optical density (OD) was measured at 590 nm using a microplate spectrophotometer (Agilent, USA). Cell viability was determined by considering 100% cell viability of untreated cells.

Intracellular reactive oxygen species (ROS) level determination: Intracellular ROS production was examined with fluorescent dye (2',7'-dichlorodihydrofluorescein diacetate -H_2D-CFH-DA) fluorescent dye (Invitrogen, USA). The cells in 6-well plates are incubated with sunitinib for 72 h. Following drug treatment, cells were collected with trypsinization, rinsed with PBS, and spinned at 1500 rpm for 10 min. The cell pellet was resuspended in PBS containing DCFH-DA and incubated for 30 minutes at 37°C, at dark. Then, cells were washed again with PBS to remove excess dye and redispersed in fresh PBS for analysis. Changes in fluorescent signal was measured using a flow cytometer (Agilent, USA). Data were assessed using NovoExpress software (Agilent, USA).

Measurement of Oxidative Stress Parameters using ELISA kit: To examine the oxidative stress induced by sunitinib on HaCaT cells, intracellular levels of reduced glutathione (GSH), oxidized glutathione (GSSG), and malondialdehyde (MDA) were measured using commercially available ELISA kits (BT LAB, China). All procedures were performed in accordance with the manufacturers' protocols. Protein concentration of each sample quantified using Bradford reagent (Biobasic, Canada). All results were normalized to the total protein content of the respective sample.

Apoptotic/necrotic cell death evaluation: The mode of sunitinib-induced cell death was quantified using Annexin V-FITC/PI Apoptosis Detection Kit (BioLegend, USA). Following sunitinib treatment, cells were harvested, washed, and stained with Annexin V-FITC and PI according to the manufacturer's protocol. Fluorescence signals were recorded by using a flow cytometry (Agilent, USA) and results were assessed with NovoExpress software (Agilent, USA).

Mitochondrial membrane potential investigation: Changes in the mitochondrial membrane potentia after sunitinib exposure were evaluated using JC-1 (5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide) dye in a commercial kit (Cayman Chemical, USA) following the manufacturer's instructions. HaCaT cells were seeded in black 96-well plates and incubated with sunitinib for 72 hours. Then, JC-1 staining solution was added to each well and incubated at 37°C. After incubation, cells were washed with assay buffer and fluoresecence signal was recorded at at 535/590 nm (Ex/Em) for JC-aggregate and 485/535 nm (Ex/Em) for JC-1 monomer using a fluorescence microplate reader (Agilent, USA) JC-agregate/monomer ratio was normalized to protein level of the samples.

Genotoxicity analysis: DNA damage induced by sunitinib was evaluated using the alkaline Single Cell Gel Electrophoresis (Comet) assay. Following drug treatment, cells were collected, washed, and suspended in 0.5% low melting point agarose (LMA). The suspension was spread over was normal melting agarose (NMA) pre-coated slides. The slides were immersed in a cold alkaline lysis solution and incubated overnight at 4°C in the dark. After lysis procedure, slides were electrophoresed and neutralized. Slides were imaged after staining with ethidium bromide using a fluorescence microscope (Olympus, Japan). Results were analyzed using Comet Assay IV (Perceptive Instruments, UK). Genotoxicity was quantified by measuring parameters DNA tail intensity.

Statistical Analysis

All assays were performed, at least, in triplicates. The results were expressed as the mean ± Standard deviation (SD). Statistical analysis was done with GraphPad Prism 10 software (GraphPad Prism software, USA). Statistical differences were calculated a one-way analysis of variance (ANOVA) by the post hoc Tukey test for normally distributed data and Kruskal-Wallis test followed by Dunn's test for non-normally distributed data. *p*-values <0.05 were considered statistically significant.

Results

Cytotoxic Effect of Sunitinib

Following 72 h sunitinib treatment, half maximal inhibitory concentration (IC_{50}) value was quantified to be 3.10 µM in HaCaT cells. Cell viability showed a concentration-dependent decrease (Fig. 1).

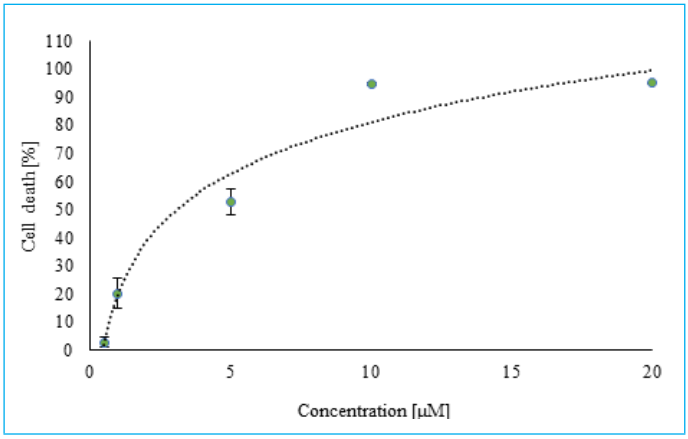

Figure 1. Cell death-concentration curve of sunitinib in HaCaT cells following 72 h exposure.

Oxidative Stress Evaluation

ROS production was induced in dose-dependent manner (Fig. 2). At the highest concentration group, ROS production demonstrated 3-fold increase compared to the control group after 72 h exposure and the increase was found statistically significant (p<0.0001).

Changes in Antioxidant vs Oxidative Stress Parameters

The levels of GSH, MDA and GSSG parameters dose-responsively elevated after 72 h sunitinib treatment (Fig. 3). The elevation in GSH (5.1-fold), GSSG (5.7-fold) and MDA

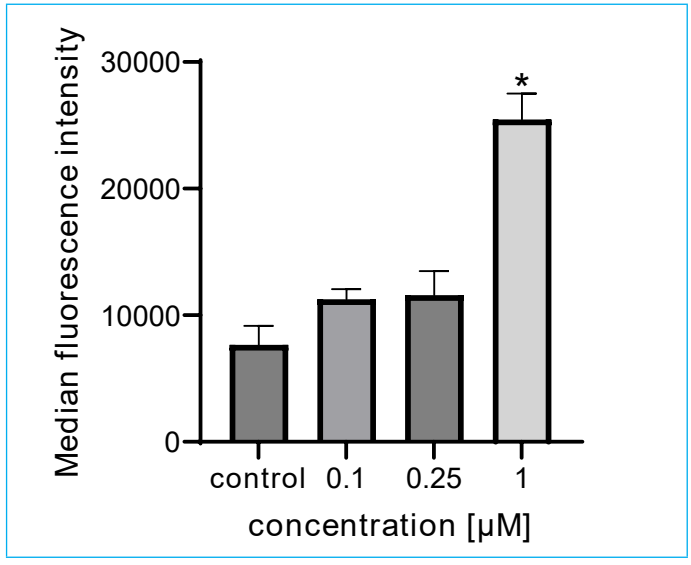

Figure 2. Changes in reactive oxygen species (ROS) production in HaCaT cells following 72 h exposure. *p<0.05

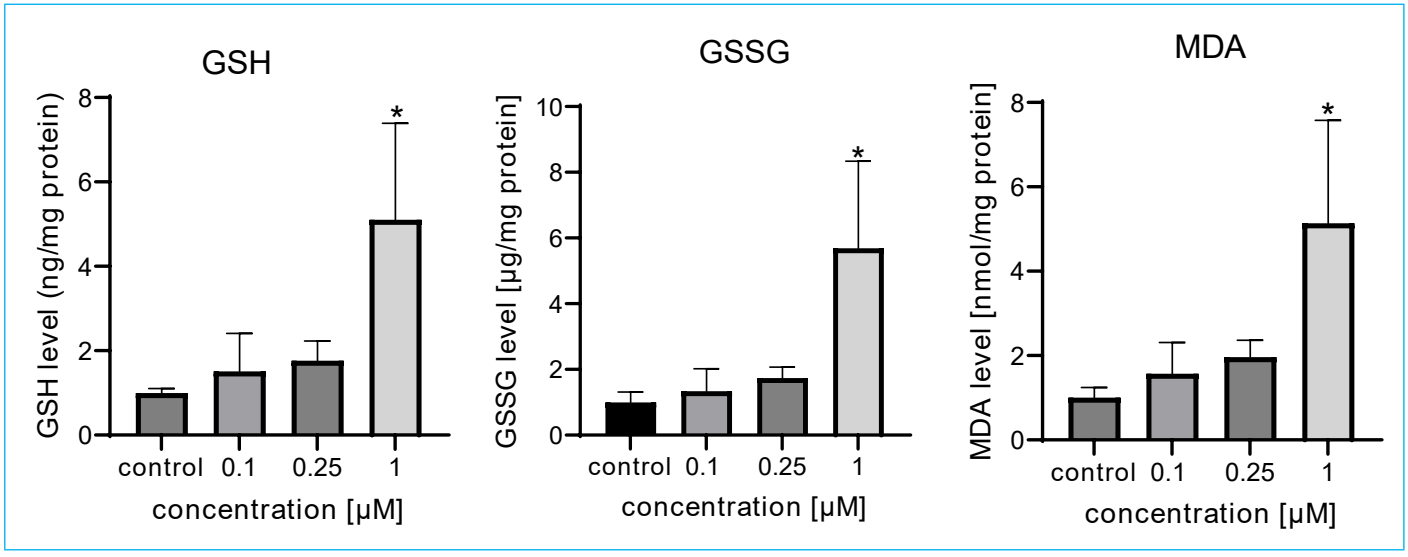

Figure 3. Changes in GSH, GSSG and MDA levels in HaCaT cells following 72 h sunitinib exposure. *p<0.05; GSH: Reduced glutathione; GSSG: Oxidized glutathione; MDA: Malondialdehyde.

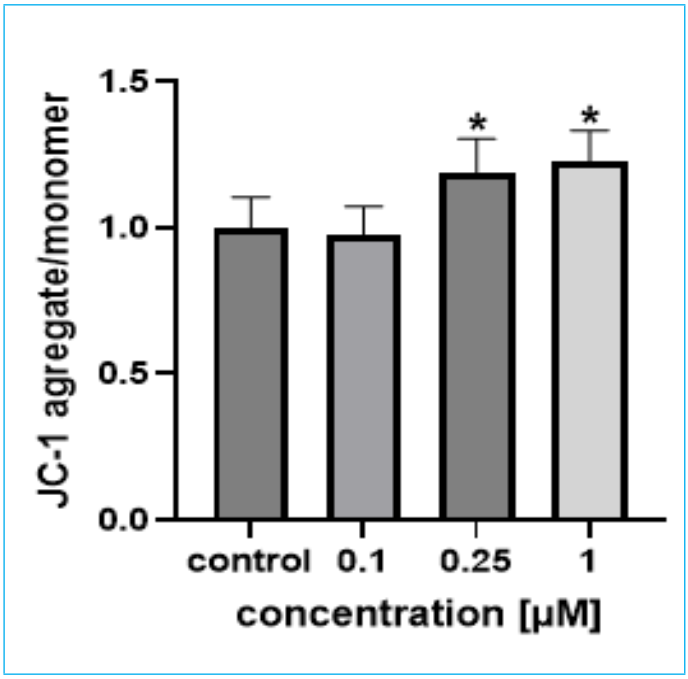

Figure 4. Changes in mitochondrial membrane potential in HaCaT cells following 72 h sunitinib exposure. *p<0.05

(5.1-fold) levels were statistical significance at the highest exposure group (1µM).

Changes in Mitochondrial Membrane Potential

As shown in Figure 4 it was observed that there was a significant increase in mitochondrial membrane potential at 0.25 µM and 1 µM concentrations following sunitinib exposure (>18%; p<0.05). However, the change in the lowest concentration was found insignificant (p>0.05).

Apoptotic and Necrotic Cell Death

Sunitinib significantly increased apoptotic cell death only at the highest exposure concentration and apoptotic cell ratio reached to 11.74% at 1 µM dose after 72 h treatment. Additionally, necrotic cell death ratio was notably induced (>2.8 fold) at all exposure doses after 72 h treatment (Fig. 5).

DNA Damage

Our study showed that DNA tail intensity which shows DNA damage was markedly elevated at all treatment groups following 72 h sunitinib exposure (>4.9 fold) (Fig. 6).

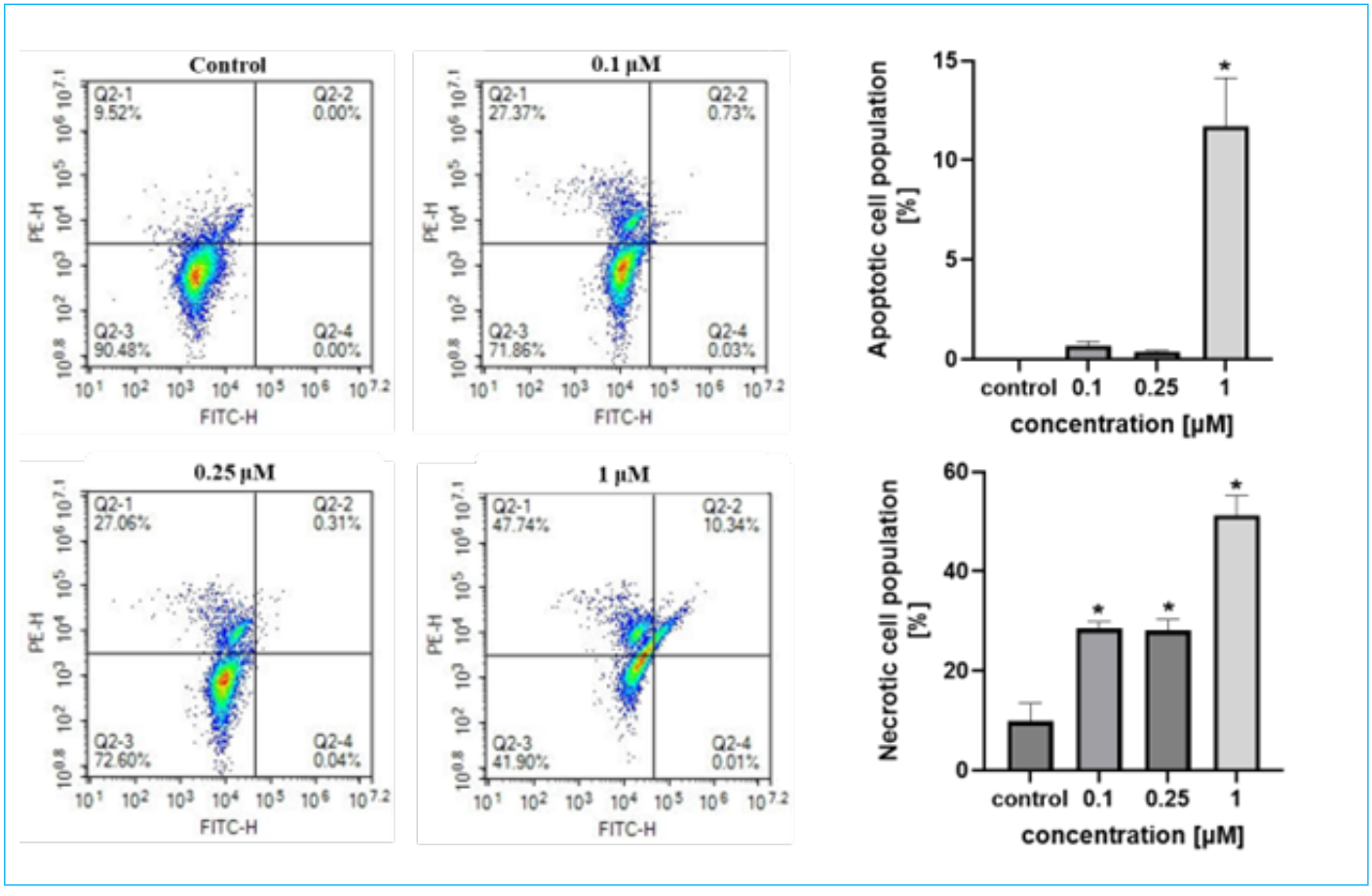

Figure 5. Changes in apoptotic and necrotic cell death population in HaCaT cells following 72 h sunitinib exposure. *p<0.05.

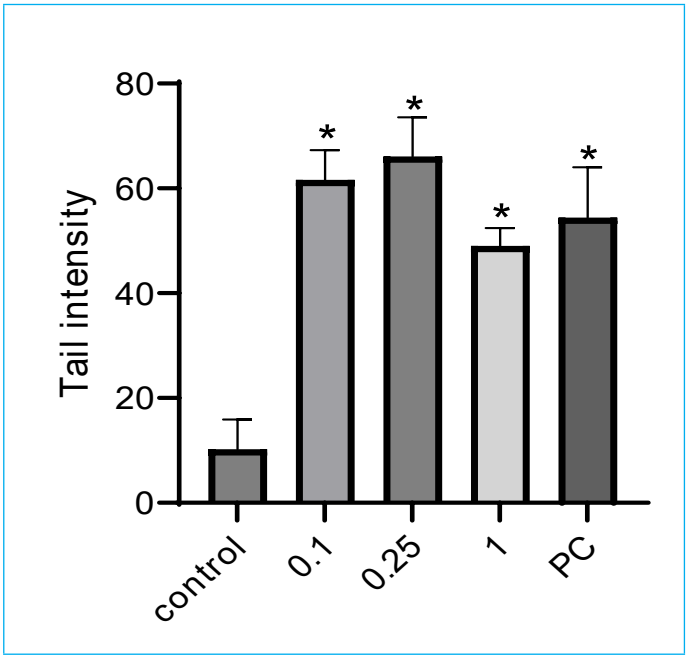

Figure 6. Changes in DNA damage in HaCaT cells following 72 h sunitinib exposure. *p<0.05; PC: Positive control (100 µM H_2O_2).

Discussion

Sunitinib is an effective multi-targeted tyrosine kinase inhibitor, but its clinical use can be limited by dermatologic adverse reactions, especially that these effects' cellular basics are still unclear. The present study was designed to elucidate the toxicity mechanisms of sunitinib-induced dermal toxicity on human keratinocytes (HaCaT) focusing on the roles of, oxidative stress, cell death, and genotoxicity.

The skin is an organ that is constantly being attacked by xenobiotics. Oxidative stress is one of the main mechanisms of skin pathologies and aging.[10, 11] In the study, sunitinib caused strong oxidative stress in HaCaT cells following 72 h exposure at the highest concentration. Additionally, it induced lipid peroxidation and glutathione oxidation. The cellular level of GSH has been shown to be a critical factor in the resistance of HaCaT cells to oxidative stress.[12, 13] For that reason, increase in GSH could be an adaptive defense mechanism against oxidative stress induced by sunitinib at the same concentration. Besides, some in vitro studies highlighted that enhancement in ROS production also play role in sunitinib-induced cardiotoxicity and hepatotoxicity.[14-16]

Mitochondrial membrane potential is critically important for ATP synthesis through oxidative phosphorylation.[17] Both depolarization and hyperpolarization of mitochondrial membrane potential can negatively affect ATP synthesis.[18,19] Previous data has highlighted that sunitinib dissipated mitochondrial membrane potential in cardiac and hepatic cells.[14-16] Conversely, an elevation in the mitochondrial membrane potential was detected at 0.25 and 1 µM doses after 72 h of exposure. Mitochondrial hyperpolarization can trigger excessive ROS production.[17,20] The increase in mitochondrial membrane potential may contribute to enhanced ROS production, lipid peroxidation and glutathione oxidation in HaCaT cells after sunitinib treatment. Taking together, the observed mitochondrial membrane alterations may underlie the oxidative stress pattern seen in this study, highlighting mitochondria as a key player in sunitinib-induced redox imbalance.

While the cell death is crucial for skin homeostasis, the apoptotic and necrotic cell death can be underlying mechanisms of skin diseases.[21] Previous studies show that the persistence mitochondrial membrane potential hyperpolarization sensitizes T cells to necrotic cell death in systemic lupus erythematosus patients.[22] A study highlighted that mitochondrial membrane potential hyperpolarization can induce cell death via apoptosis or necrosis rather than oxidative stress.[23] The relationship between cell death and hyperpolarized mitochondria could be associated with increase in calcium overload in mitochondria.[24,25] Hyperpolarization of mitochondrial membrane potential could be an early event of apoptotic cell death.[26] However, mitochondria may show heterogenicity; while some mitochondria, especially in the prolonged exposure, can be depolarized others could be hyperpolarized in apoptotic cell death.[27]

Sunitinib induced both apoptotic and necrotic cell death in different cell lines.[28-31] An *in vitro* study showed that sunitinib promoted keratinocyte apoptosis through STAT3 activity inhibition, which play important role in cutaneous homeostasis.[32] Kuang et al. [33] reported apoptotic cell death in HaCaT cells exposed to sunitinib (1.25 – 2.5 µM) with 10 ng/ mL EGF for 24 and 48 hours. Our findings suggest that sunitinib caused an increase in the necrotic cell population at all exposure concentrations, but apoptotic cell population significantly increased only at the highest exposure concentration. The differences in cell death pathways among the different exposure groups could be due to the variations in the severity of mitochondrial damages and thus in the energy stores in the cells. This, combined with the long exposure period (72 hours) in the study, may explain the different responses observed across the cellular subpopulations. Especially, the increase in the mitochondrial membrane potential appears to be the mechanism underlying the apoptotic and necrotic cell death following sunitinib treatment.

DNA damage was observed elicited at 0.1 µM, 0.25 µM and 1 µM doses upon 72 h sunitinib exposure in the study. Similarly, it was shown that sunitinib triggered DNA dam-

age following 24 h exposure at 2 µM concentration in renal carcinoma cells.[34] Another study also found that sunitinib caused an increase in DNA tail length at 10 µM concentration after 24 h exposure in different renal cancer cell lines.[35] It is known that oxidative stress triggers DNA damage.[36] Sunitinib-induced oxidative insult may promote oxidative DNA damage in HaCaT cells after 72 h exposure. Furthermore, DNA damage may provoke apoptotic and necrotic processes via activating different signaling pathways.[37, 38] Necrotic and apoptotic cell death seen after sunitinib treatment could result from DNA damage induced by sunitinib.

Conclusion

In conclusion, this study provides a novel insight into the mechanisms underlying the sunitinib- induced dermal toxicity in human keratinocytes. Our findings suggest that the exposure to sunitinib induces oxidative stress, disrupts mitochondrial membrane potential, lead to DNA damage, and causes apoptotic or necrotic cell death. The observed mitochondrial hyperpolarization appears to play a critical role in redox imbalance and cell death process. These results highlight that mitochondria as a target in sunitinib- related dermal toxicity and suggest cellular heterogenicity as factor influence the outcome of toxic responses. Further studies are needed to confirm the present findings and to explain the molecular mechanism and suggest protective strategies to overcome these adverse effects in the clinical settings.

Disclosures

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Author Contributions: Concept t – TB; Design TB, MA; Supervision – TB, MA; Materials – TB, MA; Fundings – TB; Data collection &/or processing – TB, GK, MA; Analysis and/or interpretation – TB, GK, MA; Literature search – TB, GK, MA; Writing – TB, GK, MA; Critical review – TB, GK, MA.

Conflicts of Interest: The authors declare that there are no conflicts of interest related to this study.

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