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Reactive Sulphur Species and Exposome: A Perspective on Potential Role in Alleviating UV-Induced Stress

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Authors' contributions

The work was derived from several discussion and brain-storming sessions among the authors. All authors read and approved the final manuscript.

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ABSTRACT

Exposome is a field of study that identifies and recognises the impact of environmental exposures on a person's health and development, starting from the prenatal period onward. Oxidative stress is commonly associated as one of the underlying mechanisms of ultraviolet radiation (UV)-induced damage in the skin, due to the overproduction of a reactive oxygen species (ROS) in the body. Evidently, overexposure to UV radiation will cause a disturbance in the ability to balance the ROS levels in the body, leading to damaging effects such as protein modifications, lipid peroxidation, and DNA mutations, which will progress into cell death. Reactive sulphur species (RSS) are molecules that have the capability to oxidise or reduce biomolecules under physiological conditions. In this review, the mechanism of UV-induced cellular damage will be discussed and later lead to the conclusion on how RSS plays an important role in combating oxidative stress induced by UV exposure.

Keywords: Exposome; ultraviolet radiation; reactive sulphur species; oxidative stress; skin.

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1. INTRODUCTION

The world is moving towards the personalised medicine era [1]. Huge amounts of effort and money were invested in sequencing and mapping the human genome for a better understanding of gene expression, protein function and metabolic processes which have been implicated in major chronic diseases. Genetic variability is commonly implicated in the biological detoxification system, which is known as metabolic polymorphism. Despite its low penetration, metabolic polymorphism is considered to be a commonly existing issue which can significantly contribute to the population disease burden [2]. Therefore, venturing into pharmacogenomic processes is thought to offer a high precision measure which can be employed in the management of diseases. In the context of "non-genetic diseases", a broad range of pathological conditions have been associated with exposure towards environmental electrophiles, yet much of the current fundamental understanding of such occurrences remains ill-defined [3]. The concept of exposome was first coined by Wild in 2005 as a "highly dynamic and variable entity that evolves during the lifetime of a person". Exposome refers to a variety of exposures, ranging from environmental and biological residues such as radiation, chemical or biological agents, and determinants, from conception to death [4-6]. Exposome is divided into three classifications; internal (such as ageing, the hormonal system and metabolic processes), specific external (for example chemical waste, radiation and lifestyle factors), and general external (for instance socio-economic status and physiological situations) [7-8]. Exposome is an intricate concept that requires a complex approach, as it involves a lifetime of exposure, from the prenatal period onwards. Hence, a continuous assessment of multiple time exposures over the course of a person's life are required to measure the exposome and scientifically understand its nature and possible outcomes [9]. The life sequence of exposome is often derived by exposure at certain time points, and the health impacts of certain exposures may be different [9]. In fact, co-exposures and the involvement of other elements can somewhat change the severity of a condition due to interactive or synergistic effects [10]. In 2016, it was estimated that approximately 80% of chronic diseases recorded worldwide have potentially originated as the negative effects of exposome [11]. The genome-related diseases, on the other hand, make up less than 20% [11]. Indeed, exposome necessitates important broad and transdisciplinary studies to discover the factors which lead to complex chronic diseases over time.

The skin is the largest organ in the human body and plays the most important role as the primary defence system against the harsh external environment and pathogens [12]. Sun radiation is comprised of UV radiation, infrared radiation, and visible light [13]. Exposure to these sun radiations is a naturally occurring process. In fact, exposure to UV radiation has been associated with several health benefits [14]. For example, sufficient amounts of UV exposure are good for vitamin D synthesis. Vitamin D supplies calcium to the body, which is very important in maintaining skeletal health [15]. However, overexposure to UV can cause many pathological skin conditions such as malignant melanoma and skin cancer, as reported in previous studies [16-17]. According to the US Environment Protection Agency (EPA), the UV index scale is divided into several categories; 0-2 (low), 3-5 (moderate), 6-7 (high), 8-10 (very high) and more than 11 (extreme). The UV index increases with increasing altitude and decreasing latitude. In Europe, the UV index is recorded at its highest during summer and can reach up to 12.1 in South Spain [18]. However, in tropical countries, the sun shines directly and high temperatures are experienced all year round. The average UV index recorded in these countries can be more than 7, which is close to the "very high" category [19]. Although UV exposure is high in some of these regions, the skin pigmentation of the inhabitants is often associated with the low incidence rate of melanoma as compared to the people of other regions [20]. Statistically, almost 5 million people in the United States undergo skin cancer treatments each year, which cost approximately USD 8.1 billion [21].

Indeed, the most general risk factor for skin cancer, that is modifiable, is UV exposure [22]. UV radiation is part of the exposome that contributes to the emergence of deleterious effects on human skin, including sunburn, cancer, immune suppression, and photoageing which leads to individual premature ageing [4]. UV photons are a part of the electromagnetic spectrum which falls between the gamma and visible light radiation wavelengths [23]. Ozone (O_3) plays a role as a selective filter that absorbs UVC and UVB, which make up the radiation of UVA (90- 95%) that reaches the earth [24]. Some

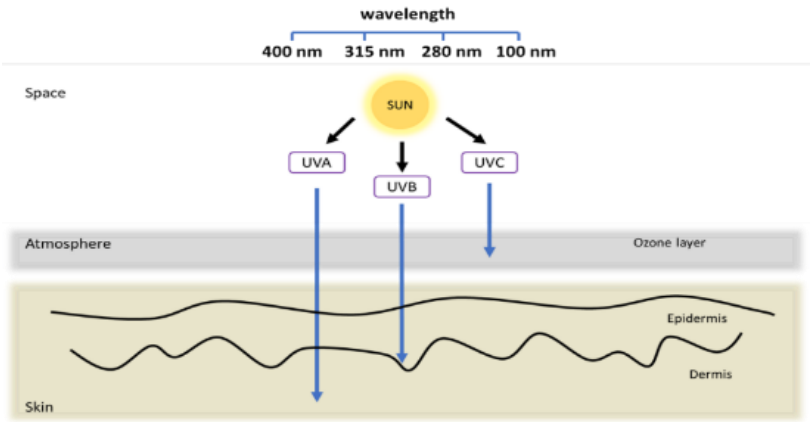

Fig. 1. The pathways of UV radiation through atmosphere into the skin

UVB (5-10%) can pass through the ozone layer and reach the earth [21]. UVC radiation, which has the highest energy and the shortest wavelength, induces mutagenic DNA lesions to form and substantially increases the risk of emerging cancer cells when the skin is exposed to it [23,25]. However, almost no UVC can penetrate the atmosphere of the earth, as its rays are completely hindered by the ozone layer, which makes the effect of its radiation less concerning [24,26]. As depicted in Fig. 1, UV radiation penetrates into the skin depending on the wavelength of each type [23]. UVA with a longer wavelength and the least energetic photons penetrates deeply into the dermis, while UVB with a shorter wavelength is almost entirely absorbed by the epidermis and has a relatively slight amount that reaches to the dermis [23]. Indeed, several antioxidant mechanisms have been identified that can help in providing protective mechanisms against UV irradiation [27-29]. Recently, reactive sulphur species (RSS), particularly the persulphides and polysulphides, were discovered in abundance endogenously [30]. These RSS compounds are highly nucleophilic and capable of neutralizing electrophilic insults such as those from ROS and heavy metals [31]. Nonetheless, the exact relationship between RSS activity in UV-induced pathogenesis has not yet been highlighted. In this review, the mechanisms of both UV damages and the anti-oxidative properties of RSS will be discussed further, in an attempt to tap into another possible mechanism that may be involved in alleviating UV-based pathogenesis.

2. MECHANISM OF UV-INDUCED CELLULAR DAMAGES

UV radiation possesses an important ionizing molecular property, and chemical reaction induction makes it distinguishable from visible rays. It acts as a powerful environmental mutagen by harming the components of cells, which can contribute to immunodeficiency-related diseases and causes fatal diseases such as cancer [24]. Immunosuppression, induced by UV, leads to skin cancer due to DNA damage and inhibited skin defence mechanisms via multiple pathways [26]. In cellular DNA, the most common UV-induced lesions are dimeric photoproducts which involve adjacent pyrimidine bases [32]. When the UV-induced DNA damage is too severe and is not able to be repaired, p53 which is a protein that has a significant role in apoptotic pathways is activated [33]. This will then lead to the induction of apoptosis to eliminate the damaged cells. UVB was identified as causing damage to epidermal proteins. Aromatic amino acids such as tryptophan (Trp), tyrosine (Tyr), and cysteine largely absorb UVB [34,35]. The absorption can lead to excited species. Several additional interactions involving excited Trp and Tyr are proposed, which could result in skin cell constituent disintegration and oxidative stress [34].

UV radiation is commonly known to cause injuries to DNA in situations which are oxygen-dependent and involving photosensitization. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) induced by UVA radiation will develop single strand breaks (SSBs) and base lesions such as 8-oxo-7,and 8-dihydroguanine (8-oxoGua)] [32]. UVA-excited photosensitizers can produce singlet oxygen, which can react further with proteins and results in protein modification [34]. Aggregation of modified proteins can cause harm to the cell and is associated with many diseases and the ageing process.

UVA and UVB are both capable of generating comparable singlet oxygen ($^1O_2$) and/or free radicals, either directly when interacting with components of the cell or when in the presence of photo-sensitizers [36]. At their ground state or lowest energy, these photoactive chemicals absorb incident radiation (UVA/UVB) within their absorption range. For instance, UVA light penetrates the skin and cellular chromophores such as bilirubin, urocanic acid, melanin, riboflavins, heme, pterins, and porphyrin, which all absorb the UVA light [37–39]. Then, the photons/energy absorbed by these photo-sensitizers gives rise to the singlet excited state, which is the excited state of chromophores [40]. An excited state molecule is created from the energy of the absorbed photon. This molecule is not stable under ambient conditions [36]. Energy is transferred from the excited species to the adjacent intracellular chemical moieties, especially molecular oxygen (O2); which when returning to the ground state converts into ROS (e.g. superoxide, singlet oxygen, hydroxyl radical or hydrogen peroxide) [36,39]. These ROS act on plasma membranes which are rich in lipids and begin a reaction known as lipid peroxidation [39].

ROS are chemical species that formed from incomplete oxygen reduction, namely superoxide anion (O^{2-}), hydroxyl radical ($HO^{\bullet}$), and hydrogen peroxide (H_2O_2) [41]. ROS contain unpaired valence electrons or unstable bonds [42]. ROS is commonly described as an electrophilic, that tends to attack other molecules in order to achieve stabilization, particularly the nucleophiles that are rich with electrons. ROS reactivity has been noted to be involved in various essential physiological processes. ROS plays a part in the different signalling cascades for instance, response to stimulation of the growth factor and regulation of inflammatory responses [42]. Besides, they are also responsible for regulating numerous biological processes such as immune functions, thyroid functions and cognitive functions. In contrast, ROS can also cause permanent functional modifications or even complete damage to cells as it reacts easily with carbohydrates, proteins, lipids, and nucleic acids at high concentrations [42]. Oxidative stress is a consequential pathological condition that occurs when the antioxidant components are no longer able to compensate for the amount of ROS (Fig. 2). Over-oxidation of the protein thiol group, which leads to the formation of sulfinic acid (RSO_2H) and sulfonic acid (RSO_3H) has been implicated with irreversible post-translational modification [43-48]. Such modification can render the enzymes or proteins to become dysfunctional. Moreover, nucleotides are prone to mutation by ROS (e.g., $HO^{\bullet}$, H_2O_2 and O^{2-}) which is generated by UV radiation [24]. Nucleotide base oxidation stimulates a mismatch of the base pair, resulting in mutagenesis [39-40]. For instance, one example of base mispairing prompted by ROS is the guanine to thymine transversion. This occur when the 8th position of guanine undergoes oxidation, forming 8-hydroxy-2′-deoxyguanine (8-OHdG) [40-41]. Instead of pairing with cytosine, 8-OHdG will tend to pair with an adenine, whereby the G/C pair will be mutated into an A/T pair [23].

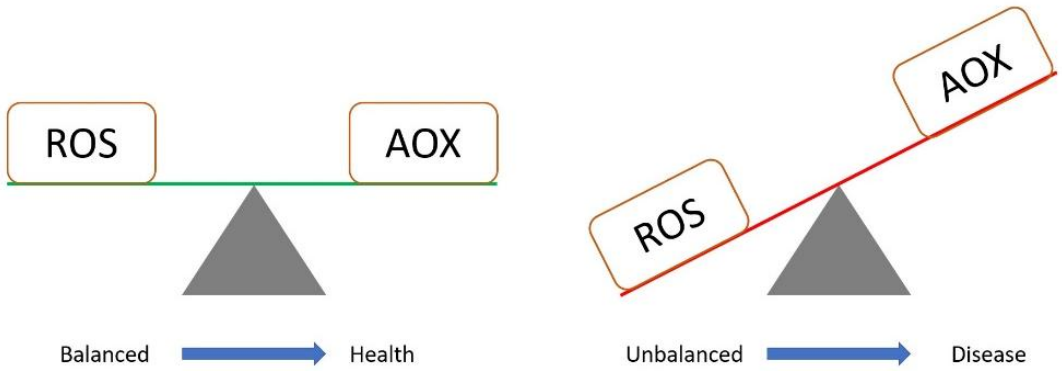

Fig. 2. (A) Equilibrium between antioxidant (AOX) defence and reactive oxygen species (ROS) production. (B) The imbalance between ROS and AOX, which is correlated with many pathologic conditions

3. REACTIVE SULPHUR SPECIES (RSS)

3.1 Overview of RSS

Endogenous reactive sulphur species (RSS) were recently discovered to exist in an appreciable amount in the body and play a vital role in cell signalling, metabolic regulation and redox homeostasis [49]. RSS can be described as a redox-active sulphur-containing molecule capable of reducing or oxidizing biomolecules under physiological conditions [50]. RSS are good reducing agents and nucleophiles in their most reduced state (S^{2-}) and these S^{2-} species may convert to the S^{1-} state by undergoing a one electron oxidation to generate thiyl radicals ($RS^{\bullet}$), or sulphydryl (HS), that combines to form hydrogen disulphide (HSSH), disulphides (RSSR), or related hydrosulphides/persulphides (RSSH) [49].

The RSS molecules are biologically present in different forms including hydropersulphide (RSSH), organic persulphides (RSSR) and inorganic persulphide (HSSH), and correspond with higher order polysulphides ($HSS_{(n)}SH$, $RSS_{(n)}SH$ and $RSS_{(n)}SR$) with n>1 and R ranges from low to high molecular compounds [51]. RSS are stronger acids, nucleophiles and reductants compared to the corresponding thiols. The only plausible explanation underlying this mechanism is the □-effect. According to the current understanding, the □-effect is described as the presence of unshared electron pairs, or in this case the sulfur atoms adjacent to the nucleophilic centre, causing the RSS to exert a higher nucleophilicity compared to the traditional thiol [52]. Consequently, the longer the sulphur chain which is present, the higher the nucleophilicity will become. Moreover, the pKa_1 value of a sulfur-containing compound is inversely proportional to the number of sulfur atoms [53].

The mitochondrial cysteinyl-tRNA (CARS2) was discovered to play a major role in producing endogenous low (such as cysteine persulphides, CysSSH, cysteine trisulphides, CysSSSH) and high molecular weight RSS (such as protein bound polysulphides, RS_nSH) [30]. Production of cysteine persulphide (CysSSH) is catalysed by CARS2 from CysSH and it can also be directly incorporated by the persulfidated amino acid into proteins [54]. Other enzymes such as cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), thioredoxin and sulfide:quinone reductase have been reported to produce low molecular weight RSS as well [55-58]. To date, RSS has been recognized to be critically involved in several important physiological functions including redox signaling and xenobiotic metabolism [59].

3.2 RSS and UV-induced Cellular Damage

RSS is highly nucleophilic and can readily scavenge ROS and various electrophiles [31]. For instance, RSS reacts with 8-nitroguanosine 3'-5'-cyclic monophosphate (8-nitro-cGMP). 8-nitro-cGMP is a secondary messenger of nitric oxide (NO) whose signalling mechanism is derived from the nitration of cGMP by NO [60]. The reaction of RSS with 8-NO-cGMP can result in the formation of 8-SH-cGMP, with nitrite anion being released [61]. In fact, several studies have indicated that RSS, including the glutathione and hydrogen sulphide-derivatives, contribute to the cellular detoxification system. RSS has been known to protect the cells against electrophiles such as heavy metals [31,62-63].

Our skin possesses a dynamic and powerful network of antioxidant molecules that detoxify reactive species to resist free radical modification of DNA and other macromolecules. GSH is undoubtedly one of the highly significant molecules with antioxidant properties in the skin cells. The sulfhydryl group of GSH performs a leading role in the detoxification and antioxidation of exogenous and endogenous compounds, including preserving the intracellular redox status [64]. As a reducing agent, GSH donates electrons to other reactive molecules which stabilizes the reactivity of free radicals. GSH is oxidized to GSSG during the process, but with the presence of glutathione reductase it can be reduced to its basal state through NADPH as an electron donor and can be recycled [64]. Hence, both forms (GSH and GSSG) of glutathione can be found in cells. Oxidative stress can be indicated when the reduction to the oxidized glutathione ratio becomes abnormal [23]. The action of glutathione against ROS is commonly known to be promoted by interactions with glutathione reductase and glutathione peroxidase [64]. Recent evidence indicates the existence of RSS in a form of free RSS or protein-bound RSS, that can readily react with oxidative stress to somewhat shift our understanding on available cellular protection mechanisms. RSS can provide better protection against the over-oxidation of protein. As aforementioned, the formation of RSO_2H and RSO_3H on cysteine moeities is an irreversible enzyme or protein modification that can lead to dysfunction. However,

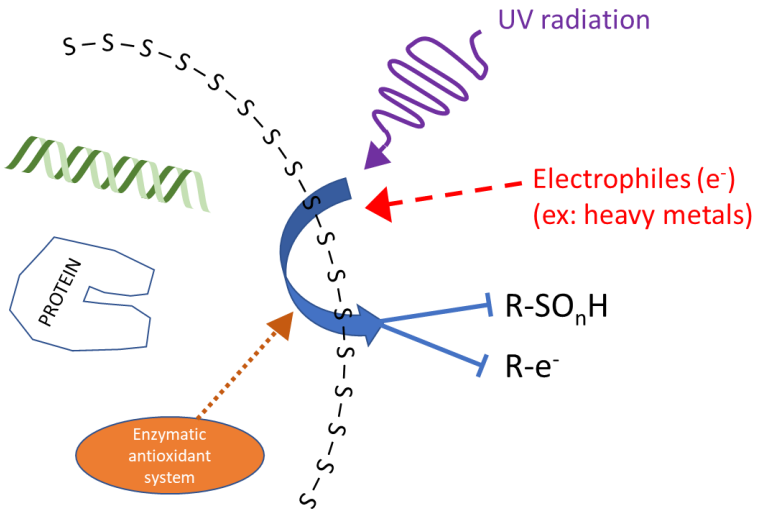

Fig. 3. Potential role of RSS in alleviating UV-induced cellular damage

polysulphurated cysteine residue, for example RS-S-SH, when exposed to over-oxidation, can form RS-S-SO_nH (n = 1-3), which can be reduced back to the original thiol somewhat [65].

The skin also possesses several other enzymatic and non-enzymatic antioxidant mechanisms. Catalase for example is an enzyme that has been attributed with the function of metabolizing H_2O_2 to H_2O, which mitigates the ROS-induced toxicity. Interestingly, Olson and his team further discovered that catalase has another function as a sulfide-sulfur oxido-reductase, making catalase as another key regulator of RSS [66]. The team further worked on another antioxidant enzyme, superoxide dismutase (SOD), and attempted to see whether the enzyme was possibly involved in RSS metabolism. Unlike catalase, SOD was found to unidirectionally oxidize H_2S and produce only small amounts of H_2S_2 [67]. The Kelch-like ECH-associated protein 1 (KEAP1)-NF-E2-related factor 2 (Nrf2) is a master regulator of antioxidants and detoxification enzymes [68]. KEAP1 is a repressor protein of Nrf2 and contains 5 cysteine residues in its intervening region that have been implicated with KEAP1-dependent Nrf2 ubiquitination [69]. Oxidative insult or covalent modification on these cysteine residues was identified as the cause of the dissociation of Nrf2 from KEAP1 [70]. The loss of Nrf2 has been associated with an increased risk of developing cutaneous squamous cell carcinoma in mice [71]. The KEAP1-NRF2 system however, was said to only prevent the harmful effects of UV irradiation caused by the UV-A that has a long wavelength, as compared to UV-B or UV-C. UV-A induces cellular damage through the ROS-dependent pathway which leads to KEAP1-Nrf2 orchestrating the activation of sequential antioxidant systems [72]. Interestingly, Nrf2 can work with CSE in a parallel manner in the repression of the electrophile-induced toxicity. Nrf2 detoxifies electrophiles via the formation of GSH adducts, while CSE mediates the sulfur adduct formation by RSS, suggesting that there is a canonical and non-canonical pathway of detoxification of environmental electrophiles conducted by Nrf2 and CSE respectively [73].

4. CONCLUSION

Several protective interventions, including the use of pharmaceutical products and dietary antioxidants, are commonly recommended in managing the risk of UV exposure. The application of both endogenous and topical photoprotection is sought to create a better prevention strategy in this scenario. In this review, the authors provided a brief perspective on the potential role of RSS in preventing and alleviating UV-induced damage (Fig. 3). The study of polysulfidomic is far from fully understood. There is much to understand on sulphur biology and how it potentially contributes to understanding pathogenesis which is related to UV-exposure. Despite a lot of research having been done on the crosstalk between ROS and RSS, the direct relationship between UV

irradiation with endogenous RSS will be an interesting subject to look further into. Indubitably, precise evaluation on the role of RSS in regulating ROS-dependent UV-induced dermal toxicity still requires more detailed studies.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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