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REVIEW ARTICLE

Phototoxicity of environmental radiations in human lens: revisiting the pathogenesis of UV-induced cataract

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Abstract

The magnitude of cataract pathology is indeed significant as it is the principal cause of blindness worldwide. Also, the prominence of this concept escalates with the current aging population. The burden of the disease is more tangible in developing countries than developed ones. Regarding this concern, there is a gap in classifying the pathogenesis of the ultraviolet (UV) radiation-induced cataracts and explaining the possible cellular and subcellular pathways. In this review, we aim to revisit the effect of UV radiation on cataracts categorizing the cellular pathways involved. This may help for better pharmaceutical treatment alternatives and their wide-reaching availability. Also, in the last section, we provide an overview of the protecting agents utilized as UV shields. Further studies are required to enlighten new treatment modalities for UV radiation-induced pathologies in human lens.

Keywords Ultraviolet radiation · Cataracts · Lens · Pathophysiology · Oxidative stress · Crystallin · Tryptophan · Phototoxicity · Cellular pathways · Protecting agents

Introduction

Cataracts are the leading cause of blindness in the world [1–3]. For the most people, the detrimental effects of solar ultraviolet (UV) radiation on the human eye are intangible as it has been more popular for skin complications [4]. Nevertheless, the UV radiation is a cumulative omnipresent hazard for every individual [5]. It was more than a hundred years ago when Widmark showed that UV radiation ruins the lens [6]. In contrast to UV's late discovery, human history has been acquainted with the phenomenon of cataracts. The earliest documented case of cataracts goes back to centuries ago, circa 2460 B.C. [7]. Then, it was during 600 B.C. when cataracts were further described in texts and surgical approaches were established [8]. A detailed history of cataracts can be found in a study by Rucker [9]. After centuries, scientific research shed light on the exact risk factors and the extent of their association with cataracts. In the literature, there has been a considerable focus on UVB, yet the probable effects of UVA are less investigated. In this review, we aim to gather the recent evidence behind the association of UV radiation and the cataracts, and cellular pathways responsible for this association. We categorized the probable pathways in six groups, namely (a) oxidative stress, (b) phototoxicity, (c) crystallin proteins, (d) tryptophan, and (e) apoptosis. Generally, oxidative stress is recognized as the fundamental mechanism igniting the apoptotic precursors, aging pathways, and enhancing protein aggregations [10]. On the other hand, crystallins and tryptophan-related pathways are identified as natural protective entities. The detailed exploration of these mechanisms may obviously

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Table 1 The classification of ultraviolet radiation to UVA, UVB, and UVC and their absorption within the eye [15, 16]

Name	Wavelength (nm)	Photon energy (eV, aJ)	Notes	Availability and exposure of sun UV	% of corneal UV absorption	% of aqueous UV absorption	% of lens UV absorption
Ultraviolet A	315–400	3.10–3.94, 0.497–0.631	Long-wave, black light, not absorbed by the ozone layer	15% absorbed by ozone layer	320 nm: 45% 340 nm: 37%	320 nm: 16% 340 nm: 14%	320 nm: 36% 340 nm: 48%
Ultraviolet B	280–315	3.94–4.43, 0.631–0.710	Medium-wave, mostly absorbed by the ozone layer	60–70% absorbed by ozone layer	300 nm: 92%	300 nm: 6%	300 nm: 2%
Ultraviolet C	100–280	4.43–12.4, 0.710–1.987	Short-wave, germicidal, completely absorbed by the ozone layer and atmosphere	Virtually 100% absorbed by ozone layer	100%	–	–

be supportive for further pharmaceutical, environmental, and public health research. Literature gaps and suggestions for future research are further discussed in the conclusion section.

The UV radiation

The UV radiation is a high-energy electromagnetic field with a broad range of wavelengths starting from 400 to 10 nm [11]. UVs with less than 200 nm wavelength have an ionizing effect when passing through the atmosphere; thus, they never reach the ground and are absorbed by atmospheric oxygen fluctuating in concentration in the ozone layer [12, 13]. There are different sorts of classification with regard to different UV properties from which the UVA, UVB, and UVC classifications are the most widely used ones in medical applications [14]. Table 1 shows wavelengths of these three types of UV radiation. With respect to this classification, it is not likely for UVC (wavelengths between 280 and 100 nm) to pass through the ozone layer [17]. Despite this fact, in a category of occupations such as arc welding and food sterilization, there is a large amount of UVC exposure and it is necessary for the workers to protect themselves sufficiently against UVC exposure. Nevertheless, UVA and UVB are primarily responsible for medical harms and pathologies [18] and are of the main focus in this study. Figure 1 demonstrates the percentage of the UV transmittance through the atmosphere [17]. Generally, UV transmittance depends on several environmental factors, namely clouds, aerosols, and surface reflectivity [19]. As shown in Fig. 1, a considerable amount of UVB attenuates through the atmosphere by the effect of the clouds. Yet, according to studies [20–22], UVB is the chief culprit for cataracts affliction. According to several studies [23–25], UVs of less than 240 nm (UVC) are completely absorbed by cornea. Also, it has been reported that UV radiation up to 295 nm of wavelength, including all UVC band, is fully absorbed by the cornea inducing acute photokeratitis and causing serious damage to the cornea [26]. In addition, Dixon et al. reported that as it is being completely absorbed, it does increase the risk of cataracts [27]. Furthermore, the human lens can absorb UVs of less than 370 nm (UVA and UVB). UVB is absorbed both by cornea and the lens, approximately 70% and 30% respectively.

The lens and cataracts

A cataract, the leading cause of blindness worldwide, is a condition in which the human lens becomes colored occluding the clear vision [28]. This process is mostly encouraged by accumulative sun exposure during aging and other risk factors including but not limited to smoking, diabetes, and alcohol [29, 30]. Cataracts may account for almost half of the

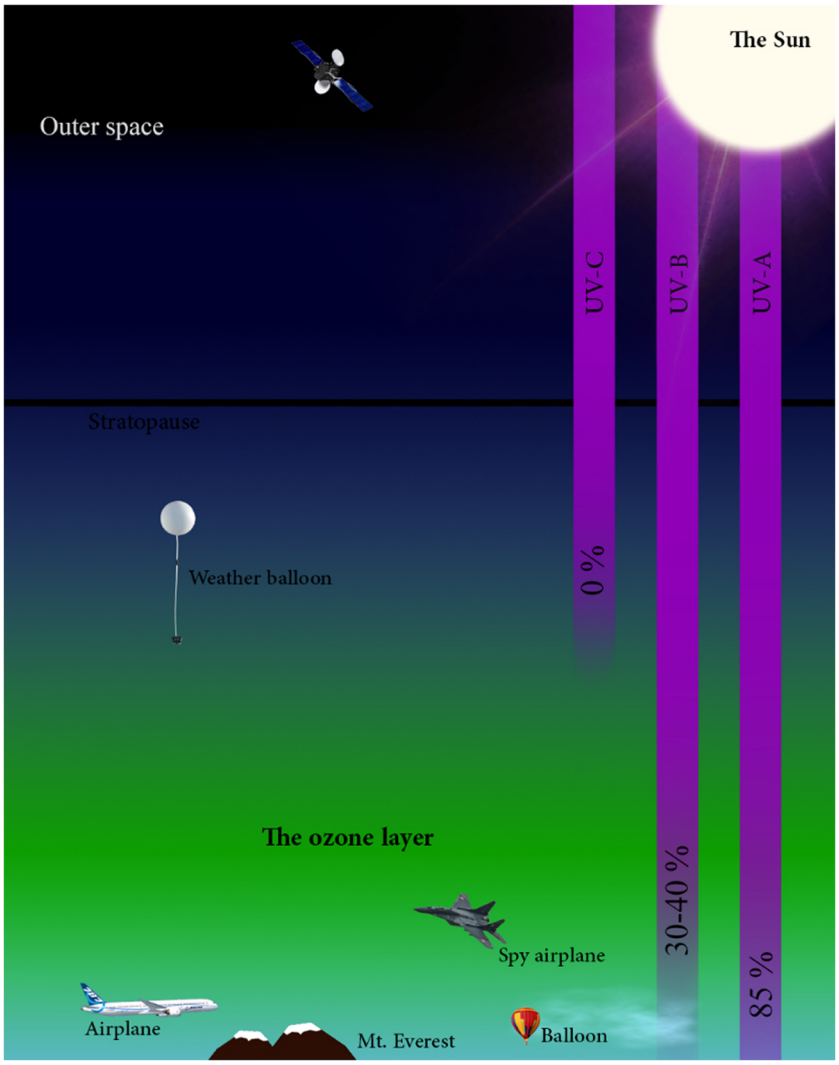

Fig. 1 UVC does not pass through the atmosphere, while almost all of UVA reaches the ground. The attenuation of UVB is mostly dependent on the meteorological conditions and cloud properties

blindness round the world, being the most appalling in African and developing countries, yet more benign in developed ones [3]. Still, its trend is expected to be rising even in developed countries including the USA as the population ages [31, 32]. But globally, those in low- or middle-income conditions are more affected. Cataracts have been thought to afflict more than half of the people at the age of 80 or higher [33]. In many countries, surgical services are inadequate, and cataracts remain the leading cause of blindness [32]. Since the present-day treatment of cataracts is still limited to surgery, high health expenditures have been allocated to confront this ailment [34]. In developing countries, the present burden is as yet later diagnosis, insufficient surgical facilities, or unaffordable costs of surgery, which results in visional sequels [35].

There are various proteins in human lens absorbing the UV radiation and protecting the eye from probable photo-induced damage [36]. These low molecular–weighted proteins are classified into tryptophan and non-tryptophan florescent compounds. Several studies have modeled the molecular effects and optical properties of these proteins [37–40]. This gradual and continuous filtering of UV radiation leads to clouding of the lens and blurred vision [41]. From a clinical point of view, there are mainly three types of non-congenital cataracts (i.e., nuclear, cortical, and posterior subcapsular) from which the nuclear type, the most common one, is more associated with aging [42]. Among these, there is abundant evidence showing that cortical cataracts are more associated with UV radiation and sun exposure [15]. This association might be in part due to the differential lens UV transmittance pattern of human lens. Pajer et al. have demonstrated that the anterior cortex of the lens is mainly responsible for low transmittance rate of UV and especially the substantial loss of transmittance of UVC [43].

Cataracts might be produced experimentally with UV lasers for research purposes. Ample research has been conducted to propose a new way of treatment, novel pharmaceutical approaches, and preventive techniques to fight the consequences following the cataracts [44–46]. However, practical progress has not been adequately made with respect to its

prevention. Presently, the UV-filtering (sun)glasses and lenses are the only ubiquitous and mostly known preventive practice [47]. Also, several external factors, including contact lenses, caffeine eye drops, zinc, vitamin E, and topical use of antioxidants, are proposed to protect the eye from UV-induced damage. Caffeine eye drops decrease the activation of caspase-3, so it has been reported to be a protective agent against cataracts [48]. Two other protective factors against UV exposure are zinc and vitamin E which both act through calcium-mediated mitochondrial apoptotic pathway to protect epithelial cells of the lens [49]. Kador et al. showed that topical antioxidant applications can protect the lens against UV-induced damage [50].

In aphakic eyes, the risk of retinal damage increases excessively [51]. Consequently, intraocular lenses (IOLs) absorbing UV radiation could protect the retina. A spectrographic check of UV transmittance by standard IOLs and UV absorbing IOLs has shown that the UV absorbing IOLs block all radiations below 400 nm [52, 53]. If diagnosed at earlier grades, symptoms may alleviate with filtering glasses and lenses blocking the UV radiation [54, 55]. In the last section, we will provide a review of the protecting agents and protective molecular pathways.

Crystallins are the prominent absorbers of UVB [56, 57]. It has been shown that the absorption of protein fractions increases by aging. Post-translational modifications enhanced by the aging process are a main cause of this phenomenon [58–60]. Alternatively, the modified crystallins and non-UV filter metabolites absorb the main portion of UVA [58, 61]. This is responsible for different protein aggregation pathways in UVA compared to UVB. Nevertheless, the beginning of both pathologies is roughly the same as seen in oxidative stress induced by phototoxicity [52]. Cellular mechanisms and pathogenesis of cataract are further discussed in detail in the next section of this study.

Pathogenesis: oxidative stress, phototoxicity, proteins denature, and apoptosis

Oxidative stress

Oxidative stress is known to be one of the central initiating elements which trigger cellular aging pathways and apoptotic cascades [10]. The imbalance between oxidative agents and antioxidants favors this phenomenon. The production of reactive oxygen species (ROS) and oxygen singlet after UV exposure is a known fact, yet the extent of this photodamage is of scientific value [62]. In young lens, glutathione and pyruvate are two natural protective mechanisms against oxidative stress induced by UV [63–65]. Further, the increased expression of numerous protective genes, including but not limited to superoxide dismutase, catalase, and glutathione peroxidase, supports a defense against intracellular oxidative stress [66–68]. However, according to a study by Bova et al., as the lens ages, the efficacy of this natural filter declines with a rate of 12% per decade [69]. Accumulated ROS gives rise to crystallin and tryptophan denatures which are explained later in this section. Also, an increased activity of xanthine oxidase has been shown to be associated with the increased oxidative stress in senile patients with cataracts [70]. Aside from these pathways, a mitochondrial induced oxidative stress suggests an increase in ROS driven out from UV-exposed respiratory chain leading to phospholipid hyperperoxidase which, in turn, enhances lipid peroxidation and cellular membrane damage in lens epithelial cells [71–73]. Also, Wu et al. showed that damaged gap junctions within the cell membrane induced by oxidative stress helps impair inter-cellular antioxidant communication [74]. Besides, It has been described that dysregulation of Na^+/K^+ ATPase activity caused by oxidative stress deteriorates osmoregulatory function in the cell [75]. In respect to genetic mechanisms responsible for oxidative stress in lens, the possible types of DNA damage and the effects of miRNAs are of considerable importance [76–78]. In this regard, Wu et al. proposed regulated miRNA target genes via binding to 3' UTR and the TATA box regions of oxidative stress genes as a cause of this occurrence [79]. A year later, Wang et al. demonstrated an association between miRNA dysregulations and H_2O_2 oxidative stress to explain pathogenesis of age-related cataract [80]. Also, Zhu et al. showed that leucine-rich repeat in G protein-couple receptor 4 decreases cellular tolerance to oxidative stress in mice lens augmenting cataract [81]. In addition, Nrf2-Keap1 has been known as a chief defense mechanism against oxidative stress [82]. Nrf2 is one of the nuclear transcriptional proteins which transcribe many antioxidant genes including glutathione-*S*-transferase, glutathione reductase, and thioredoxin reductase. Keap1 supports Nrf2 to maintain a reasonable level within the cell. Dysregulation in this system induces oxidative stress, which favors cataract [83]. Figure 2 summarizes the main pathways of oxidative stress relating it to other pathogeneses.

Phototoxicity

Vola et al. reported phototoxicity on lens and retina by UV radiation between 392 and 400 nm. During the first decade of life, radiations in this wavelength interval are not absorbed by the human cornea. Progressively, cumulative effect of near-UV on the lens follows fluorescent chromophore formations, reduced lens proteins synthesis, increased insoluble proteins, and lens pigmentation [53]. In 1982, a study by Lerman demonstrated photosensitized damage to the lens and retina with psoralen plus UV radiation (320–400 nm) (PUVA) in experimental animals and reported cataracts in patients undergoing PUVA therapy [84]. An et al. revealed that even though there were no significant differences in the retinal structures

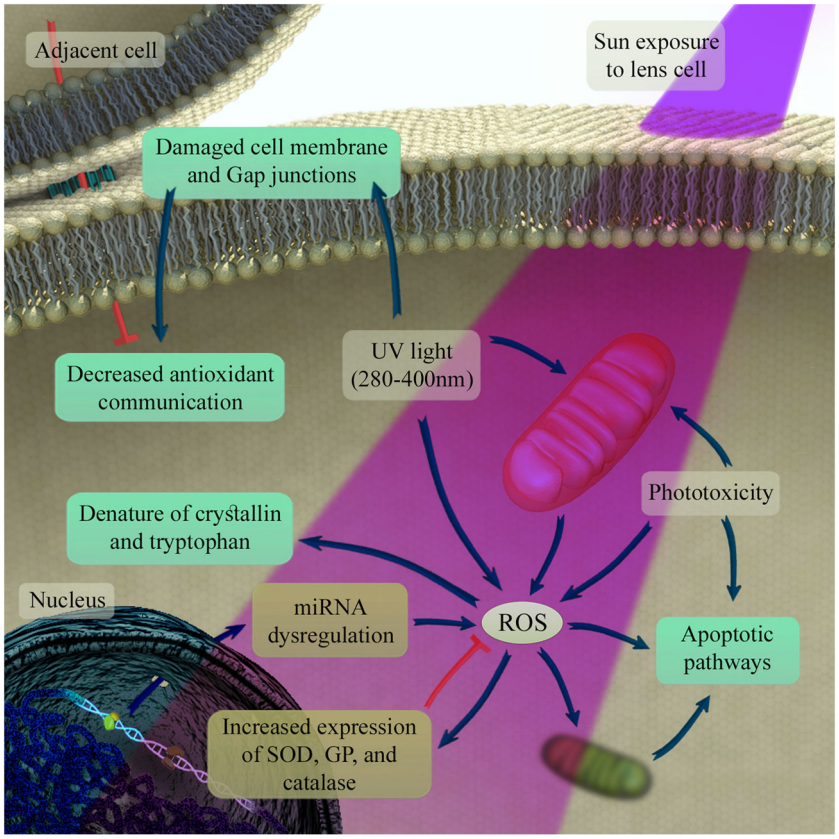

Fig. 2 Pathogenesis of cataracts. Various cellular pathways are shown in the figure. SOD superoxide dismutase, GP glutathione peroxidase, UV ultraviolet

comparing UVB-treated mice and the control group, the expression of apoptotic marker proteins, such as Bax, cytochrome c, and p21, decreased in the UVB-treated mice retinas [44, 85]. They argue that cone photoreceptors may be more susceptible to the low-energy UVB light than the other cell types in the retina; thus, low-energy UVB irradiation does not affect the retinal structure, yet it considerably alters cellular protein expression leading to apoptosis and decreased cell survival [85, 86]. Figure 3 shows the schematic view of pathogenesis in UV-induced cataract.

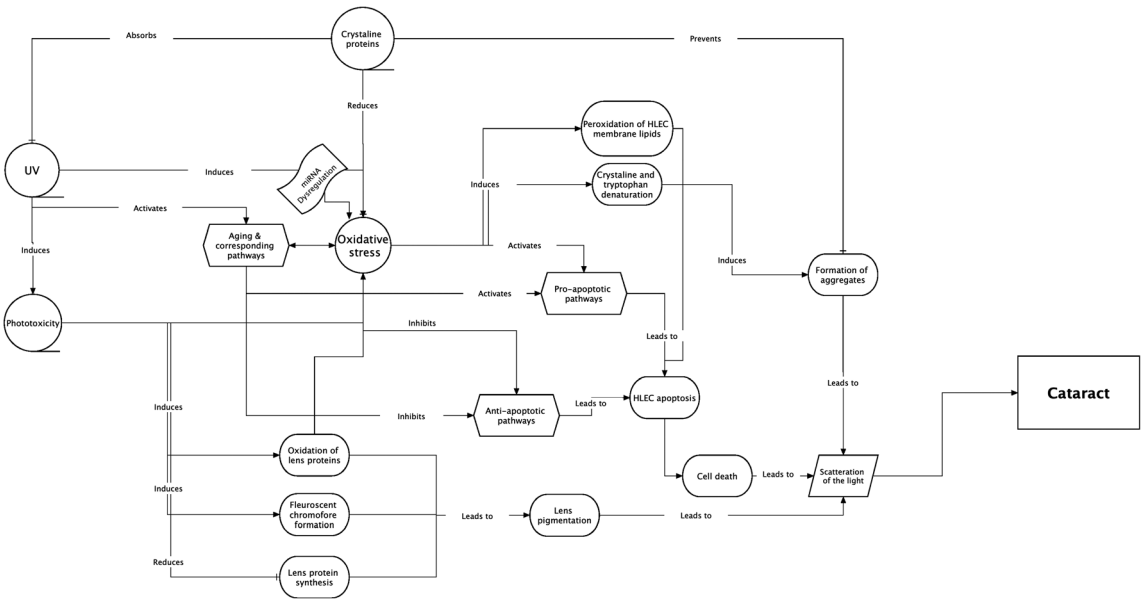

Fig. 3 A thorough schematic view of pathogenesis in UV-induced cataracts

Crystallin proteins

Through a series of transparent tissues, light is transmitted to reach the retina. Despite the fact that the vitreous is not much optically active, cornea and lens play a vital role in filtering the UV radiation. For a young eye, the cornea filters out all radiations with wavelengths less than 295 nm, yet the lens is responsible for absorbing both UVA and UVB [87]. The most abundant component of human lens is composed of a family of proteins called crystallins which cannot be repaired or fixed in case of any damage [88, 89]. α-Crystallins make up about 40% of eye lens proteins. Aside from its role in preventing the formation of aggregates which scatters the light, it plays an important role in sustaining the refractive index of the lens [89]. α-Crystallins are composed of αA and αB components [90]. Investigations on these subunits have shown that A subunit is more susceptible to UVA in contrast to B subunit; thus, the B subunit lingers in its function and keeps a protective role [90]. On the other hand, the B subunit is susceptible to high temperatures leaving the A subunit as the guardian of the lens in hot conditions [91].

In 2004, Fujii et al. investigated the effect of gamma and UVC radiation on the activity of crystallins. They showed that both radiations may affect these proteins. As stated in their research, it is noteworthy that the amount of gamma radiation needed for these effects is far more than the amount one may be exposed to in daily life. However, the situation is different for UVC. The observed effect is seen at lower levels of UVC with which people are actually exposed to on a daily basis [92]. In addition, it has been shown that mutation R116C can regulate α-crystallin capacity to resist stress-induced apoptosis [93]. Besides, it has been revealed that factors other than UV alone can impress the process of aggregation. For instance, hypericin, which is used mostly as an herbal treatment of depression, can make α-crystallins more susceptible to UV light and even incidental visible light [94].

The next key crystallins are the γD-crystallins in the nucleus of the lens. Photooxidation of γ-crystallins is thought to be the major cause in age-related and congenital cataracts which involves misfolding of the proteins and aggregates formations. Moran et al. suggested UVB irradiation as a cause of amorphous amyloid fibers aggregates which leads to cataracts [95]. To date, it has been proven that a wide variety of mutations in γ-crystallin gene make individuals susceptible to cataracts. In this regard, it has been reported that a mutant human γD-crystallin may cause congenital nuclear cataract in afflicted individuals [96]. There have been extensive bio-molecular investigations, mostly in vitro, in order to find out the mechanisms involved in the process of cataracts. In 2013, an in vitro investigation of Schafheimer et al. showed that tryptophan (Trp) clusters protect γ-crystallins by absorbing the energy of UVB light. They further hypothesized that aromatic subunits may absorb light energy protecting from free radicals production. In a further study, they have also found that tyrosine/cysteine clusters sensitize γD-crystallins to UV-induced aggregations [97, 98]. In a study on molecular dynamics simulations carried out in 2013, Xia et al. demonstrated that transformation of Trp to kynurenine (Kyn) under UV exposure affects the stability of γD-crystallins. Besides, they showed that Kyn draws extra water and other polar side chains owing to its additional amino and carbonyl groups on the damaged Trp side chains. Consequently, it breaks through the integrity of the adjacent dry center regions formed by two Greek key motifs in each domain. Large instabilities in the Tyr-Trp-Tyr sandwich-like hydrophobic clusters caused by the damaged Trp residues, in turn, break key hydrogen bonds bridging two b-strands in the Greek key motifs at the "tyrosine corner" [99]. Roskamp et al. investigated different pathways of γS-crystallin aggregations and suggested UVA exposure as the main cause of deamination and oxidation which subsequently leads to protein aggregations. They also proposed that there might be factors other than UV exposure involved in the process of crystallin aggregation. It was observed that wild-type γS-crystallins necessitate a low pH environment to form amyloid fibrils in body temperature [100].

In comparison, β-crystallins are identical to γ-crystallins in structure and play an important role in the maintenance of lens refractive index. Unlike γ-crystallins, β-crystallins have various forms of homomers and heteromers and become easily denaturized both thermally and chemically [101]. Domain substitution and N- and C-terminal extensions account for their oligomerization. This undergoes various modifications as the organism ages [102]. In 2012, Xu et al., in an in vitro investigation, showed that A2V mutations are linked with congenital cataracts by impairing tetramer formation and increasing βB2-crystallin aggregation [103].

Tryptophan proteins

The human eye protects itself against harmful effects of UV light through its UV filter compounds [104]. These proteins have extremely weak photosensitizing properties despite their high absorbance of UV light; thus, they can dissipate the energy from UV to heat and vibration efficiently [105]. The main compounds with such properties are derived from the amino acid Trp via the Kyn pathway. These compounds include Kyn, 3-hydroxykynurenine (3OHKyn) and 3-hydroxykynurenine-*O*-beta-D-glucoside (3OHKG) and reside in the central part of the human lens—i.e., its nucleus [105]. These compounds are abundant in human lens and have plentiful concentrations until the middle age, after which they decrease in concentration and become involved in chemical reactions, which renders them ineffective and rather harmful in the process of cataractogenesis. It has been shown that these molecules in their free forms can exert their protective effects against UV lights, but when bound to the proteins of the lens

(which consists of highest protein concentration in the body with 35% of its wet mass being proteins), they have harmful effects such as production of reactive oxygen species [40, 104]. The process of protein binding of Trp derivatives starts with spontaneous deamination of these compounds to form alpha1-beta unsaturated carbonyls [105]. These carbonyls in turn bind to various residues on lens proteins and glutathione (e.g., cysteine, lysine and histidine residues). Binding to these proteins, Trp derivatives become far better photosensitizers compared to their free counterparts and cause deleterious effects such as cross-linking of lens proteins, conformational changes in these proteins, and oxidative stress in the lens environment. These effects in turn cause alterations in the properties of lens proteins and make them less soluble and more prone to precipitation in the lens [105]. The oxidative stress caused by photosensitization of protein-bound Trp derivatives also increases oxidation of lens proteins and combined with decreased anti-oxidant effectiveness in the aging process, which makes the lens more prone to oxidative damage from UV [104, 106]. Other pathways can also cause oxidation of Trp derivatives, one of which is increasing concentrations of Cu(II) and Fe(III). These elements can decrease the amount of free Trp derivatives through UV-independent redox reactions [105].

The non-enzymatic degradation of Trp due to type I and II photosensitivity reactions is another pathway of oxidative Trp degradation. In these reactions, Trp degrades to compounds such as Trp and oxindolealanine. These reactions happen in the presence of UV light and substances such as riboflavin and advanced glycation end-products (AGEs) [104, 107]. This causes decreased levels of lens protective filters and contributes to cataractogenesis caused by UV in the aged population. AGEs play a key role in cataractogenesis of diabetic and old individuals [108, 109]. A study by Linetsky et al. has revealed the production of AGEs via the ascorbate photooxidation by protein-bound kynurenines induced by UVA [110]. It has also been shown that through aging and UV exposure, the concentration of riboflavin bound Trp increases, which can cause protein aggregation in the lens and contribute to cataractogenesis [111].

Apoptosis

Post-UV exposure apoptosis is a natural protective mechanism directed to remove damaged cells and prevent neoplastic changes; however, it may lead to several complications [112]. It is believed that human lens epithelial cell (HLEC) apoptosis is an initiating element in cataract development [113]. UVB-induced cataract initiates with damages to HLECs triggering apoptosis [71, 114]. In general, UVB-induced apoptosis is regulated by a number of molecular processes which target mitochondria initiating the cell death pathway. Besides, caspase activities may be initiated by the released cytochrome c (Cyt c) from mitochondria [115]. Herein, we discuss and review the studied molecular pathways.

Bax/Bcl-2

It has been well characterized that apoptosis is regulated by imbalance between bcl-2 and Bax as a pro-apoptotic factor [116]. Ji et al. proved that UVB-induced apoptosis in HLECs leads to lens opacification and cataract. According to the study, the apoptosis occurs by the promoted expression of pro-apoptotic Bax gene and an inhibited expression of anti-apoptotic Bcl-2 gene at both transcript and protein levels. Notably, the ratio of Bax/Bcl-2 displayed a high positive correlation with the proportion of apoptotic HLECs [71].

Caspase-3

It is believed that caspase-3 plays an important role in the execution of apoptosis [117, 118]. Also, the role of caspase-3 activity in HLECs has been noted in the formation of cataracts [118, 119]. After exposure to UV light, the activated caspase-3 is significantly increased in the cell which favors apoptosis [114, 119]. Kim and Koh exposed cultured HLEC lines to UV light and showed an increased expression of NOXA gene and caspase-3 without any increase in the expression of p53. This may suggest that UV-induced apoptosis is caused by a p53-independent pathway in human lens cells [114].

JNK cascade

Ultraviolet-B-induced c-Jun N-terminal kinase (JNK) activation preceded DNA fragmentation in lens [120]. Phosphorylation and activation of JNK are reported to occur prior to caspase-3 cleavage. Long et al. reported JNK activation as an early event in UVB-induced apoptosis which occurs within 30 min subsequent to UVB irradiation. Later, activation of caspase-3 occurs after 1 h and peaks 6 h after UV exposure [113].

MAPK cascade

Evidence suggests that MAPKs are critical in regulating lens apoptosis and cataractogenesis [113, 121]. The intracellular activation of MAPK cascade is a mechanism by which UV radiation mediates cellular responses. Bomser concluded that protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3-K) activities are not required for UVR-induced MAPK activation; thus, this is not a receptor-mediated event [121].

Table 2 Recently used UV protective agents are shown in the table

Agent	UV wavelength spectrum	Main molecular targets	Effect	Ref.
Ursodeoxycholic acid	Not specified	DDR-caspase 12	Reduced cataract formation via UV rays in diabetic mice	[135]
4-coumaric acid	Not specified	Undefined	Cataract formation was reduced by all group of UV light	[136]
Chaperon-like anticataract	UVB	Cellular stress–ROS pathways	A significant reduction was seen in the rate in which cataract was induced in rat models	[137]
Vitamins E and C	UVA	ROS pathway	Controversial results—may be useful in prevention in low duration contact	[138]
Caffeine	UVB	Cell membrane signaling	A positive effect was witnessed in reducing levels of glutathione, a surrogate of the negative action of UV light	[139, 140]
Pyruvate	UVB	ROS scavenger	Initial results support a role for pyruvate in reducing the magnitude of cataract involvement.	[141]
Carnosine	UVC	Inhibiting calpain proteolysis	Carnosine reduced the degeneration of lens proteins after UV exposure	[142]
Pirenoxine	UVC	Cellular stress pathway—UVC	Amelioration of selenite- and calcium-induced lens protein turbidity	[143]
L- and D-carnosine	Not specified	Alpha-crystallin amyloid fibril	Formation of deformed fibrils was reduced after exposure to carnosine.	[144]
Thioltransferase	UVB	Disulfide bonds	Causes a reduction in mixed disulfides and prevents them to be oxidized and less water soluble	[145]
Heat shock protein 27 (HSP27)	Not specified	Apoptosis pathway	Extends the cell viability responding to the apoptotic stimuli	[146]

CALML3

Overexpression of calmodulin-like 3 (CALML3) reverses the effects of UVB irradiation on apoptosis in human lens by decreasing the expression of caspase-3 and Bax and increasing the expression of Bcl-2. In fact, silencing CALML3 had similar effects on UVB irradiation and inhibited the activation of JNK1/2 and ERK1/2 pathways [120].

CRTAC1

Recently, novel mechanisms have been taken into consideration regarding the role of Cartilage acidic protein 1 (CRTAC1). Ji et al. studied the role of CRTAC1 gene in UVB-induced apoptosis in lens and revealed the inhibitory effect of CRTAC1 on oxidative stress and inflammatory response. This is accomplished by inactivating the calcium-signaling, p38, and JNK1/2 signal pathways. This, eventually, reduces UVB-induced apoptosis in HLECs, representing it as a novel target for cataract treatment [122].

Protecting agents

Along many degenerative diseases and abnormalities caused by DNA damage response (DDR) systems, various methods have been introduced in order to reduce the harmful effect of UV on the lens [123]. Various clinical in vitro and in vivo studies have been conducted examining the effect of various agents and their relative outcome. A noteworthy merit of these studies has been the use of diabetic models to evaluate the effect of protective agents [124]. Another merit of these studies is ROS and their corrosive effect on the lens. ROS are able to induce the DDR cascade leading to the activation and cross linking of DNA damage sensors, which in part activates transducers of DNA damage [125]. The two most efficient mediators discussed in these articles are ATM/CHK2 and ATR/CHK1 pathways [126]. These molecular structures activate downstream effector molecules such as p53 and are able to activate complementary systems of cellular stress, such as the VHL/HIF-alpha pathway. This pathway plays a critical role in the appearance of the dusky lens, typically evidenced in cataract. This pathway has also been the focus of various studies, including those exposing the lens to anti-VGEF agents [127]. The convergence of the DNA repair machinery and the angiogenesis cascade has led some researchers to use anti-ROS agents, as a therapy and prevention for UV-induced cataract. They argue that a single blow to the cellular genome and intracellular structures causes the avalanche of signaling which results in cataract [128]. Various agents have been used and the first results have remained rather controversial, as no definitive agent has been proposed, while the ones showing any

significant effect have limited availability in clinical contexts [129].

Other studies have suggested that initial molecules of the DDR machinery should be the main target of therapy and prevention. In a study by Zhao et al., it is reported that if the DNA repair machinery is sufficiently activated, or in some instances deactivated, it is possible to completely reverse the effects of ROS and aging, via directing cells to conservative genome repair pathways [130]. The MRN complex, RPA, and the 9-1-1 molecules have been of special interest in this regard [131, 132]. The in vitro and in vivo studies conducted had no follow-up clinical trials.

Most studies conducted on human subjects have used more invasive methods as protection strategies against cataract. Some scholars have proposed the use of intraocular lenses to reduce the harmful effects of the UV light. The trials pertaining to these methods have shown a significantly favorable clinical outcome, as rates of sever cataract have dropped and patients have gained functions such as sleep and dexterity [133]. Regardless of their benefits, these methods have not been without disadvantages, as no case selection has been proposed so far. In addition, the methods themselves are extremely invasive compared to the previously mentioned strategies which aim to reach optimal prevention using supplementary medication [134].

List of studies examining the effectiveness of some recently used agents in UV protection is mentioned in Table 2.

Conclusion

Due to the unquestionable significance of cataracts, in this review, we aimed to revisit the role of ultraviolet radiation in cataracts and to review the cellular pathways behind this ailment. Unlike age as a principal risk factor, ultraviolet radiation exposure can be modified and prevented. In the case of affliction, surgery has been the sole treatment alleviating the disease; however, in accordance with pathogenesis of cataract, more focus on its prevention and novel treatment modalities is expected in the future research. A cost-effective treatment strategy would be indeed indispensable, especially for developing countries as they face grave adversity of outnumbered blindness. The advent of pharmaceutical agents will help avoid considerable expenditure on surgical approaches. Also, new surgical methods and techniques might be clinically and economically facilitative. Further studies are required to enlighten a more detailed picture of signaling pathways in cataractogenesis. In addition, a preventive and curative approach on these pathways will offer original strategies fighting the onerous burden of disease. This review was written to bridge the gap for a detailed classification of ultraviolet effects on cataracts.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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