Review Article

Effects of blue-light irradiation during dental treatment☆

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Summary In dentistry, blue light is widely used for tooth bleaching and restoration procedures involving composite resin. In addition, many dentists use magnification loupes to enable them to provide more accurate dental treatment. Therefore, the use of light is indispensable in dental treatment. However, light can cause various toxicities, and thermal injuries caused by light irradiation are regarded as particularly important. In recent years, the eye damage and non-thermal injuries caused by blue light, the so-called ''blue light hazard'', have gained attention. Unfortunately, much of the research in this field has just begun, but our recent findings demonstrated that blue-light irradiation generates reactive oxygen species (ROS) and induces oxidative stress in oral tissue. However, they also showed that such oxidative stress is inhibited by antioxidants. There have not been any reports that suggested that the ROS-induced phototoxicity associated with blue-light irradiation causes direct clinical damage, but some disorders are caused by the accumulation of ROS. Therefore, it is presumed that it is necessary to suppress the accumulation of oxidative stressors in oral tissues during treatment. In the future, we have to promote discussion about the suppression of phototoxicity in dentistry, including concerning the use of antioxidants to protect against phototoxic damage.

Contents

1. Introduction

Recently, the esthetics of the smile and teeth, including tooth color, have become of great importance to patients, resulting in an increase in the frequency of requests for tooth bleaching. In-office vital tooth bleaching is one of the most popular bleaching methods and is based on the application of 25—40% hydrogen peroxide products to the external surfaces of the teeth. Moreover, various blue light-producing units for vital tooth bleaching, such as halogen curing lights, light-emitting diodes (LED), diode lasers, argon lasers, and plasma arc lamps, have been introduced in order to achieve better activation of hydrogen peroxide within a shorter time period, resulting in better esthetic outcomes. The bleaching mechanism underlying such treatment is considered to involve the penetration of hydrogen peroxide into teeth and the production of free radicals, which can oxidize organic stains [1,2]. In addition, since the 1980s blue light, which has similar biocidal effects to ultraviolet (UV) radiation, has been frequently applied to photo-activated resin compos-

ite systems to provide protection during tooth restoration procedures [3—5]. Furthermore, high-power LED irradiation has been used to shorten the treatment time relative to that of conventional dental therapy [6]. Therefore, blue light is indispensable for modern dental treatment.

While there has been lots of research into the damage to the eyes and skin caused by UV rays, there are few reports about the effects of blue light on the human body, particularly on oral tissue [7,8]. We have investigated the effects of blue light on biological tissues and cells. The reactions induced by blue light mainly involve reactive oxygen species (ROS), which are generated by pigment excitation and cause oxidative stress [9,10]. It has also been reported that the thermal reactions induced by light irradiation cause biological damage [11,12]. Since these effects are undesirable in biological systems, protective measures against them are required. This review summarizes the current understanding of the mechanisms underlying the effects of blue light on oral tissues and discusses possible protective measures against these phenomena.

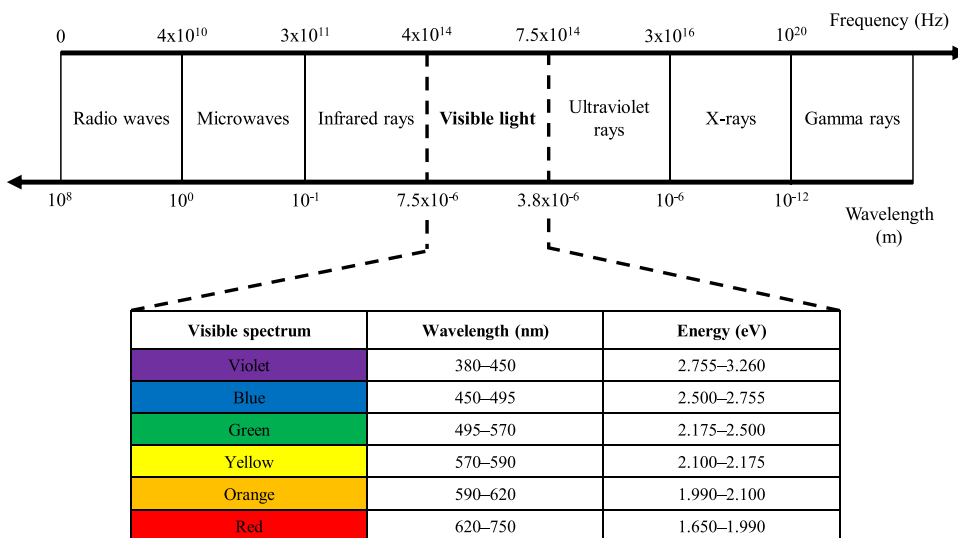| Visible spectrum	Wavelength (nm)	Energy (eV)
Violet	380–450	2.755–3.260
Blue	450–495	2.500–2.755
Green	495–570	2.175–2.500
Yellow	570–590	2.100–2.175
Orange	590–620	1.990–2.100
Red	620–750	1.650–1.990

Figure 1   The light spectrum is composed of electromagnetic waves of many different wavelengths.
Images are produced via the manipulation and presentation of different visible wavelengths of the electromagnetic spectrum. Visible light is the part of the spectrum with wavelengths ranging from 380 nm to 780 nm.
This figure was adapted from the diagram of Freedman et al. [14].

1.1. Characteristics of blue light

Light is radiation from within a certain portion of the electromagnetic spectrum. Visible light is usually defined as having wavelengths in the range of 400—700 nm; i.e., between those of infrared (with longer wavelengths) and UV (with shorter wavelengths) radiation [13]. Blue light has the shortest wavelengths of all types of visible light (380—495 nm). Accordingly, blue photons have greater energy than photons with longer wavelengths, and high-frequency blue light is sometimes referred to as high-energy visible light (Fig. 1) [14,15]. Generally, light at wavelengths in the neighborhood of 400 nm consists of the highest-energy photons that reach the retina; thus, there is concern about the effects of such high-energy light on the retina. The most well established effect of high-energy visible light on retinal health and vision is acute phototoxicity, which is seen in people who stare directly at an arc lamp or the sun [16]. Most UV radiation with a wavelength of <295 nm is absorbed by the cornea, whereas ultraviolet-B (280—315 nm, UV-B) and ultraviolet-A (315—400 nm, UV-A) are blocked by the lens. Some UV-B and UV-A can reach the retina; i.e., that in the spectral range from 300 to 340 nm. In this spectral range, the percentage of light transmitted through the eye peaks at about 8% at 320 nm [17]. The high susceptibility of the retina to damage by light with wavelengths of 320—325 nm could have serious consequences. In addition, it takes time to develop sufficient numbers of UV-absorbing chromophores, so in children's eyes some UV light centered around a wavelength of 320 nm is transmitted to the retina. Recent studies have shown that light at the border of UV-B and UV-A also reaches the retina in some adults, even in adults aged >60 years, whereas in other individuals the transmission of such light to the retina ceases by the age of 20 years [18]. Thus, children and some adults might be susceptible to light-induced retinal damage when exposed to UV-B/UV-A light. The extent to which blue and even green light is transmitted through the crystalline lens also exhibits great interindividual variability [19]. Therefore, it is important to block UV and blue light from entering the eyes in order to protect the retina [20,21]. As a result, UV and blue-blocking measures are commonly encountered in normal daily life, e.g., eyeglasses and even windows contain UV and blue-blocking materials. However, the fluorescent lamps and LED used for dental treatment emit high-intensity violet-to-blue light, which is associated with various types of tissue damage (referred to as the blue light hazard), but includes hardly any UV light [22]. Despite this, the effects of blue light on oral tissues have barely been examined.

1.2. Blue light hazard and the retina

Our current lifestyles, which involve the use of personal computers and other devices with electronic displays, as well as our increased longevity, have resulted in the exposure of human eyes to increased amounts of light stimulation. As phototoxicity contributes to the progression of retinitis pigmentosa [23,24] and age-related macular degeneration [25—27], which are major causes of blindness worldwide, the influence of light on the retina is a public health concern. It is well known that the first sign of senescence in the outer retinal layers is the appearance of residual bodies (lipofuscin) within the retinal pigment epithelium (RPE) [28]. Lipofuscin is a hallmark of ageing; i.e., it accumulates in post-mitotic cells, such as neurons, cardiac muscle cells, and RPE cells [29]. Lipofuscin is thus considered to be a biomarker of cellular ageing (autophagy) and cumulative oxidative damage [30]. The violet-to-blue light dependence of ROS generation by lipofuscin (ROS production is greater in granules exposed to blue light than in those exposed to light from other regions of the visible spectrum) might explain the so-called ''blue light hazard'' to the retina [31]. In particular, the accumulation of a fluorescent substance called *N*-retinyl-*N*-retinylidene ethanolamine (A2E), which is a major constituent of lipofuscin, in the RPE has recently attracted attention as an age-related change. A2E was the first of the compounds extracted from lipofuscin to be identified [32]. It is strongly oxidized by the high energy contained within blue light and so is considered to be able to produce large amounts of ROS, such as singlet oxygen ($^1O_2$), depending on the intensity of the light stimulus [33]. It was also suggested that A2E accumulation results in the pro-angiogenic conversion of RPE cell phenotypes [34]. In addition, laboratory studies have demonstrated that photochemical reactions in the oxygen-rich environment of the outer retina lead to the liberation of cytotoxic ROS [35]. Therefore, it is very important to develop methods that block blue light in order to reduce the associated ROS and A2E production and protect the eyes against blue light hazard.

The Japanese Ministry of Health, Labor, and Welfare drew up labor health management guidelines about the use of computer displays (visual display terminals) to prevent blue light hazard (Guidelines for Industrial Health Controls of VDT Operations of Japan International Center for Occupational Safety and Health in April 5, 2002). In addition, the Japan Ophthalmological Society established guidelines for preventing the side effects of light exposure in 2008 [36]. Therefore, a lot of research into the effects of blue light on the retina has been carried out, and the recognition of the side effects of blue light in general society has also improved. The effects of the blue light used in dental treatment on the eyes have been recognized for a long time, but little research into the effects of blue light on oral tissues has been done. In addition, many dental personnel use magnification loupes, and it was reported that the use of magnification loupes increases the amount of radiation received by the pupil [37]. Further studies are required to determine the ocular hazards of a focused stare when using a magnification loupe and the effects of the various types of curing lights used in dental offices. In addition, it is desirable to use an appropriate filter when using a loupe, as this makes it possible to safely prolong operation times [38]. Operating microscopes produce more highly magnified images than magnification loupes, so there is concern about their effects on the eyes [39]. However, there have not been any reports about damage to the eyes caused by the use of an operating microscope in dental treatment. This is probably because appropriate protection filters for preventing retinal damage are used during microscopy, which helps to protect the eyes.

Table 1 Increases in pulpal temperature (°C) associated with various light sources.

Light source	Light-curing unit	Exposure time (s)	Temperature increase (°C), (S.D.)
Halogen	HelioLux II	40	2.89 (0.30)
	Astralis 5	40	4.66 (0.47)
	QHL 75	40	5.59 (0.41)
	Optilux 500	40	7.33 (0.34)
	Elipar Highlight	40 (1-step mode)	6.94 (0.22)
	Hilux	40	6.35 (4.46)
	XL 3000	40	4.46 (0.24)
Plasma arc	ADT 1000 Plasma Arc Curing System	5	5.40 (0.31)
	ADT 1000 Plasma Arc Curing System	10	7.83 (0.86)
LED	Bluephase 16T	40	6.91 (0.26)
	Bluephase G2	40	5.81 (1.12)
	G-Light	40	7.03 (0.07)
	Elipar FreeLight II	40	3.47 (0.42)

This table was adapted from Eldeniz et al. [11], Leprince et al. [12], and Hannig and Bott [48].

2. Effects of blue-light irradiation on oral tissues

As mentioned earlier, active measures are taken to protect against the effects of blue light on the eyes. In addition, attention is also given to temperature rises caused by blue-light irradiation. Fortunately, apart from thermal injuries the use of blue light in dental care has not been found to have severe side effects. However, we have reported several negative effects of such light on oral tissues [9,10,40]. We will soon present research data regarding the effects of blue light itself, including its effects on oral tissues.

2.1. Study of the thermal changes induced by blue light irradiation

Electromagnetic radiation in the blue light range is absorbed by electrons in molecular orbitals, and this can lead to photochemical reactions or the internal conversion of light to heat. Internal conversion reactions have important consequences because the absorption of UV and visible light can result in energy transfer into vibrational states. Much of the energy that is absorbed from such sources is converted to heat [41]. Therefore, it is possible that the use of light irradiation units in dental treatment generates heat in the oral tissues. It is known that mucous membranes, such as those found on the lips, can be thermally damaged by the heat generated at the tips of irradiators [42]. Mucosal damage caused by direct thermal stimulation cannot be prevented by the use of a rubber dam. Therefore, in restorative dental procedures light tips should only be positioned over the restorative material. Photothermal damage occurs when light energy deposition due to thermal deactivation occurs faster than thermal diffusion, and so the temperature of the target tissue rises [43]. However, when a dental resin-curing light is used the dental pulp tissue is exposed to electron irradiation. As a result, the potentially damaging effects of temperature increases on dental pulp tissue during restorative treatment have become a matter of concern. An intrapulpal temperature exceeding 42.5 °C can result in

irreversible damage to dental pulp tissue [44,45]. In general, tissue that was exposed to blue light involving a power density of 200 mW/cm^2 was free from heat damage [46]. However, a standard curing light (a visible-light source) with an output power of >600 mW/cm^2 is typically used in clinical practice [47]. The reported tooth temperature increases induced by light irradiators are summarized in Table 1. It has been reported that irradiation with a halogen light, which were used as light sources in general resin irradiators in the past, raises the pulpal temperature by 2.89—6.94 °C. On the other hand, light sources containing a plasma arc designed for high-speed polymerization cause temperature rises of 5.40—7.83 °C [48]. It is generally considered that LED light sources produce smaller temperature rises, but in fact it has been reported that they result in temperature rises of 3.47—7.03 °C [12]. As described above, the intrapulpal temperature rises induced by various types of light source have been examined, and it was found that blue-light irradiation can cause serious damage to the pulp. Therefore, as a precaution dentists must recognize that during blue light-based procedures the irradiation time should not be any longer than necessary. Also, careful attention must be paid to the distance between the irradiation device and the target. Some clinicians believe that other methods, such as increasing the distance between the light tip and the target tooth, or reducing irradiance, can help to protect the pulp from thermal damage. However, because the reduction in radiant exitance values that occurs as the distance between the light tip and the target tooth increases might vary among light tips, such changes could compromise the polymerization of composite resin in the regions of the oral cavity that receive the least light, such as the cervical regions of class II cavity preparations [49,50].

2.2. Effects of blue-light irradiation on oral tissues

During resin curing and tooth bleaching, blue-light irradiation should be confined to the resin material and/or the target tooth itself. However, this is impossible with the current devices. In fact, the blue light not only irradiates
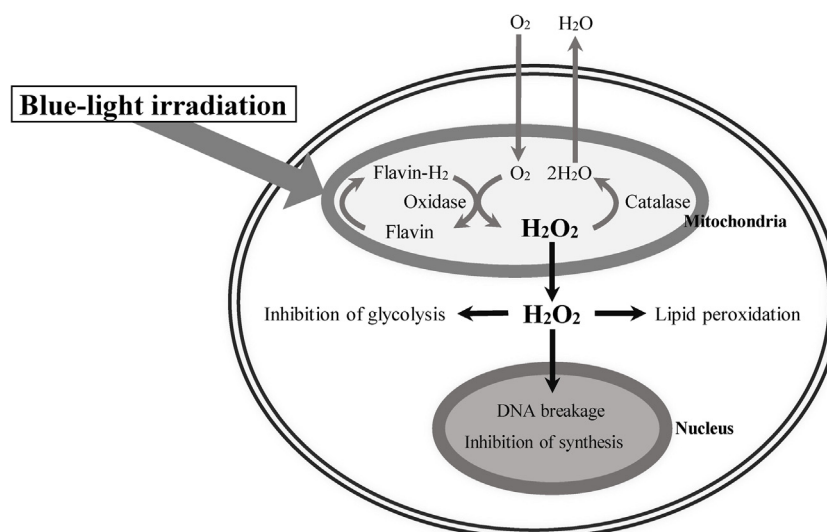
Figure 2   A model depicting the molecular events underlying light-induced hydrogen peroxide production and its detection in mammalian cells.
The process is initiated by the photoreduction of flavins and/or flavin-containing oxidases within mitochondria, resulting in hydrogen peroxide production. Hydrogen peroxide and its metabolites (hydroxyl radicals) can produce toxicities by causing genetic mutations, inhibiting glycolysis and DNA synthesis, and upregulating lipid peroxidation.
This figure was adapted from Hockberger et al. [53].

the target tooth, but also nearby tissue, including gingival tissue. Gingival tissue is commonly protected from the activated hydrogen peroxide produced during tooth bleaching by coating it with dental resin or petroleum jelly, such as Vaseline, but this method is not considered to be effective against blue-light irradiation [1,51,52].

Fibroblasts are among the most common gingival cells. The direct effects of blue-light irradiation on gingival fibroblasts have been examined previously. When dental resin irradiators were held at a distance at which no temperature rise was observed in the target tissue, irradiating light (250 mW/cm^2) from a blue halogen light or LED light source still caused a significant reduction in the proliferative activity of gingival fibroblasts. In addition, significant increases in intracellular ROS levels and intracellular mitochondrial disorders were observed [10].

Mitochondria contain flavin proteins, which might underlie the photoinduced hydrogen peroxide production caused by photoreduction [53,54]. It has also been reported that $^1O_2$ is generated by irradiating flavin with blue light [9]. Therefore, when tissue is irradiated with such light the pigment molecules within the target cells play a very important role in photodamage. All pigment molecules have an excitation wavelength, and ROS are always produced when oxygen is present inside and outside cells. In addition, there are other chromophores that absorb blue light in some cells. Short-wavelength blue light (around 400 nm) is absorbed by the Soret band in porphyrins, while longer wavelength blue light is absorbed by flavins and opsins [55,56]. Most of these chromophores can induce ROS production via different mechanisms. Moreover, blue light can also release nitric oxide (NO) from intracellular stores (hemoglobin and nitrosothiols) in mitochondria [57]. Damage to the mitochondrial electron transport chain has been suggested to be an important factor in the pathogeneses of a range of neurological disorders. Such increased/inappropriate NO

formation might contribute to energy depletion and neuronal cell death [58]. It is well documented that NO and its toxic metabolite, peroxynitrite, inhibit components of the mitochondrial respiratory chain, leading (if the associated damage is severe enough) to a lack of cellular energy [59]. Therefore, in some dental treatments care must be taken regarding the effects of the cellular environment on mitochondrial susceptibility to irradiation. Fig. 2 summarizes the current hypothesis regarding the relationship between blue-light irradiation and the generation of ROS in mammalian cells [53]. The effects of the blue light produced by LED light sources have been characterized in greater detail than those of the blue light produced by halogen light sources, and although it is believed to be safe to use LED in humans the results of this research have important clinical implications.

We must also pay attention to the existence of ROS. In *in vivo* studies, it has been reported that blue-light irradiation accelerates lipid peroxidation, which is an oxidative stress marker, by generating $^1O_2$, a ROS [9]. The concentration of lipid peroxidation products is the measure that is most frequently used to assess the role of free radicals in human disease [60]. It has been proposed that gingival recession might be induced by the inhibition of fibroblast proliferation and the degradation of collagen synthesis due to ROS [61—63]. ROS might also cause the tooth neck to become hypersensitive by exposing the root surfaces in association with gingival recession. Therefore, countermeasures against the ROS produced in response to blue light-based dental treatment might be very important (Fig. 3).

2.3. Effects of blue-light irradiation on blood vessels

In caries treatment using composite resin, appropriate blue-light irradiation of the target tooth is required. This is important for complete resin curing and the suppression of
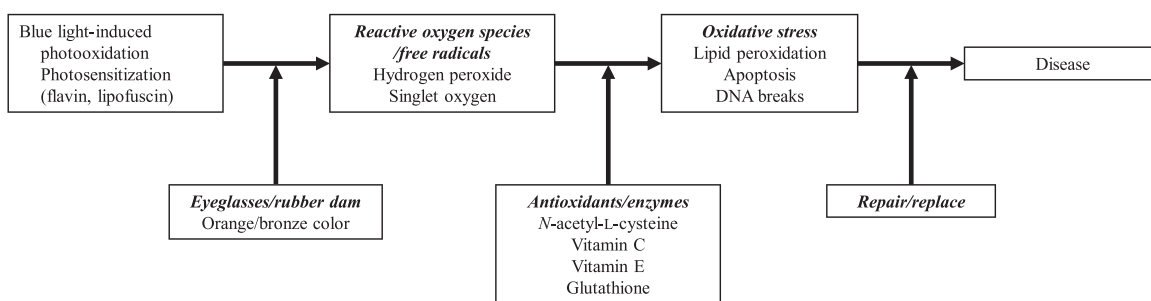
Figure 3 Schematic sequence of damaging reactions induced by blue light.
The sequence begins with either a photooxidation or photosensitization event and ends with damaging reactions that result in disease. Cells possess protective mechanisms for scavenging ROS and free radicals, including pathways involving antioxidants and enzymes, which minimize damage and the need for repair and replacement. Eyeglasses and rubber dams can reduce exposure to blue light, and hence, help to prevent light-dependent damage to ocular and oral tissues.

unnecessary light exposure. In Canada, dentists are recommended to improve their skills in blue light-based dental techniques using a patient simulator (MARC Patient Simulator [MARC PS], BlueLight Analytics, Halifax, Nova Scotia, Canada) [50]. However, even when irradiators are used properly the dental pulp is always irradiated with blue light. Therefore, the effects of such light on the microcirculation in the pulp should not be ignored. As described earlier, blue-light irradiation might generate ROS within pulp tissue. It has previously been suggested that the vascular system is affected first by the ROS generated by various pathological processes [64]. ROS can also cause oxidative stress via a variety of different mechanisms: lipid peroxidation; apoptosis; DNA damage; protein damage, including to gingival hyaluronic acid and proteoglycans; and pro-inflammatory cytokine release by monocytes and macrophages caused by the depletion of intracellular thiol compounds and the activation of nuclear factor κB [65—68]. We have studied the oxidative stress induced in isolated vascular smooth muscle by blue light [69]. Continuous blue-light irradiation of vascular smooth muscle enhances lipid peroxidation, which is indicative of oxidative stress caused by ROS. Blue-light irradiation of human aortic smooth muscle cells was found to significantly reduce cell proliferation in a time-dependent manner and upregulated the activity of caspase-3/7. In addition to such ROS-dependent changes, light irradiation-dependent vasoconstriction has also been reported to be induced by blue-light irradiation of vascular smooth muscle [40]. This suggests that the blue-light irradiation of teeth during bleaching and/or preservative restoration procedures might cause the numerous small blood vessels present within the dental pulp to constrict. Furthermore, prolonged and/or repetitive blue-light irradiation might cause temporary ischemia by inducing vasoconstriction in non-targeted dental pulp tissue. Ischemia is characterized by decreased levels of adenosine triphosphate in the local tissue, and this increases the concentration of hypoxanthine. ROS, such as superoxide and hydroxyl radicals, arise from reactions with hypoxanthine and the blood provided by reperfusion [70]. Therefore, the use of blue light in dental procedures not only induces vasoconstriction due to ROS generation caused by blue-light irradiation itself, but also promotes the generation of ROS during recovery from vasoconstriction. The ischemia-reperfusion damage and accompanying ROS-induced oxidative damage generated in this way cause biological dysfunction, and they also have the potential to accelerate the aging of the pulp. On the other hand, blue light can cause vasodilation due to the Furchgott effect. The role of NO in photorelaxation is disputed [71,72]. A number of investigators have proposed that NO dependence results from the photo-release of NO stores from nitrosothiols and that the endothelium and NO synthase are important for the replenishing of these stores (the stores that become depleted after each photo-stimulation episode) [73]. It has been suggested that blue light acts as a vasoconstrictor or vasodilator, depending on the experimental conditions, so further studies are required to assess the *in vivo* effects of blue light on blood vessels in oral tissues. The accumulation of oxidatively modified forms of proteins frequently occurs as part of age- and atherosclerosis-related changes, but it might be possible to fully heal injuries caused by short-term ROS exposure using antioxidants (both enzymatic and non-enzymatic factors) [74]. Therefore, it is considered that ROS production caused by a single irradiation event and/or brief blue light irradiation induces reversible cell damage.

The exposure of the oral tissues to blue light is increasing as direct bonding based on the concept of minimal intervention is being performed with increasing frequency around the world. For this reason, it is suggested that ROS might be frequently generated in dental treatment, and so the frequency and duration of irradiation should be kept to the utmost minimum in order to reduce oxidative stress.

3. Biological protection from blue light

The current measures employed to protect the eyes against blue light-induced damage are based on reducing the amount of blue light that passes into the eyes. Orange- and/or bronze-colored filters block blue light most effectively. Orange filters cut out more blue light than bronze filters [35]. Therefore, it is possible to greatly reduce the effects of blue light on the eyes by ensuring that it has to pass through filters, such as functional eyeglasses, that contain these colors. However, there are few methods for directly preventing blue-light irradiation of the gums and dental pulp during dental treatment. Some light irradiation methods used in dental treatment involve intermittent,

continuous, and pulsed irradiation. These methods are used because they create the optimal conditions for the target materials or reagents. Unfortunately, the total amount of light energy delivered does not change; therefore, it might not be possible to avoid blue light-induced tissue damage by changing the irradiation method. In the future, the most commonly used polymerization initiator (photoinitiator) might not require blue light, such as camphor quinone (which has an absorption peak at 470 nm) [75], and if a substance that is excited in the long wavelength region is found the use of blue light might no longer be necessary. Therefore, the development of such dental materials would help to prevent injuries caused by blue light.

Since it is presumed that most of the negative biological effects of blue light are due to ROS, various protective methods involving antioxidants have been reported. *N*-acetyl-L-cysteine (NAC) has been shown to scavenge oxidants directly and to increase intracellular glutathione levels, which is of paramount importance for protecting organelles from the oxidative stress associated with the ROS produced during coupled mitochondrial electron transport and oxidative phosphorylation [76–78]. Furthermore, NAC has been used clinically for the treatment of many diseases for decades [79]. In recent years, it was suggested that NAC might abrogate inflammation- or oxidative stress-induced hyperfunction in oral mucosal cells [80]. In particular, the blue-light irradiation of gingival fibroblasts increases intracellular oxidized glutathione levels by generating ROS [9]. The administration of NAC as a supplement increases the intracellular concentration of reduced NAC, which is an essential ROS scavenger. Thus, this might be a useful technique for protecting against blue light-induced damage. In addition, NAC also scavenges $^1O_2$ molecules [9]. Therefore, NAC not only increases the antioxidant activity of living organisms, but also acts as a direct ROS scavenger, so it is considered to be suitable for use during blue light-based dental treatment.

The lipid peroxidation of cell membranes is the most common negative biological effect of ROS. Vitamin E (α-tocopherol) and vitamin C (ascorbic acid) react rapidly with organic free radicals, and it is widely accepted that the antioxidant properties of these compounds are responsible in part for their biological activity [81]. Therefore, antioxidants, such as vitamin C and vitamin E, play an important role against lipid peroxidation, but unfortunately there are no reports about the use of these antioxidants to protect against blue light-induced damage to oral tissue. However, several studies about the use of antioxidant substances in periodontal treatment and their effects on salivary functions have been reported [82–85]. In the near future, it might be necessary not only to protect dental patients directly from blue light damage to the gums and oral mucosa, such as with rubber dams, but also to use antioxidants as an *in vivo* defense mechanism.

4. Conclusion

Dentists should be aware that the radiation absorbed by the endogenous and exogenous substances that accumulate in operators' eyes and skin (hands) as well as patients' oral mucosae can cause various phototoxic and photoallergic reactions. In recent years, the major type of light source used in dentistry has changed from conventional halogen light sources to LED light sources, but potential blue light-induced damaged should be considered carefully when selecting light sources for dental treatment. Currently, the most important recommendations regarding the use of blue light in dentistry are to read the manufacturers' instructions for curing devices and to use radiation-filtering protection goggles. In addition, we consider that it is also desirable to administer aggressive antioxidants before treatment with blue light. New devices and materials are frequently introduced into dental treatment, and they might subsequently be found to damage oral tissues. Blue light from various light sources can cause a range of physiological problems, including phototoxicity. Therefore, it is important to actively eliminate those that are most disadvantageous to patients, and dentists should aim to conduct highly safe dental treatment based on scientific evidence.

Conflicts of interest

The authors have no conflicts of interest relating to this study to declare.

Acknowledgement

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