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Article

Light Quality Modulates the Antioxidant Properties of "Microtom" Fruits: A Pilot Study Testing the Radioprotective Effect on Human Cells

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Abstract

The fruits of *Solanum lycopersicum* L. cultivar "Microtom" are a powerful source of antioxidants. We investigated whether two light-quality regimes, i.e., fluorescent white (FL) and red-blue (RB), influenced the antioxidant composition in such fruits, and assessed the potential radioprotective properties of their extracts on normal human cells exposed to clinical photons as used in cancer radiotherapy (RT). Increasing normal-tissue tolerance to radiation is critical for reducing the risk of RT-associated sequelae. Biochemical characterization showed that RB enhanced the content of antioxidant phytochemicals (i.e., polyphenols, flavonoids, total carotenoids, lycopene), while FL promoted ascorbic acid synthesis. Initially tested at 200 µg/mL, RB-derived extracts decreased radiation-induced DNA damage as measured by the cytokinesis-block micronucleus (CBMN) assay in epidermal HaCaT cells. Both RB and FL regimes were subsequently studied in MCF-10A breast cancer (BC) cells, a model of normal-tissue radioresponse in BC RT, using extracts at 100 and 200 µg/mL and also evaluating oxidative stress by a ROS detection assay. Both FL and RB afforded radioprotection. However, RB suppressed radiation-induced MN formation and oxidative stress to a greater extent compared to FL. Therefore, modulation of light-quality regimes represents an innovative approach for developing radionutraceuticals with potential benefits for RT patients.

Keywords: bioprospecting; functional foods; light quality; radiotherapy; radioprotection

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1. Introduction

Tomatoes (*Solanum lycopersicum* L.), an archetypal example of the Mediterranean diet where they are widely consumed as vegetables, play an essential role in human nutrition due to their well-recognized health benefits [1]. They are rich in vitamins, minerals, fibers, proteins, essential amino acids, monounsaturated fatty acids, carotenoids, and phytosterols [2–4]. Moreover, tomatoes are an excellent source of bioactive compounds with natural antioxidant properties, such as carotenoids (β-carotenoids and lycopene), ascorbic acid (vitamin C), and tocopherol (vitamin E), and are highly abundant in secondary metabolites, like phenolic compounds (quercetin, kaempferol, naringenin, and lutein, as well as caffeic, ferulic, and chlorogenic acids). These compounds are valuable in preventing human pathologies, such as cardiovascular disease (CVD) and neurodegenerative impairment, also exerting an anti-inflammatory action that may reduce cancer risk [5–7]. Therefore, the regular consumption of tomatoes may help alleviate symptoms or prevent the onset of several diseases, particularly those feeding on chronic inflammatory conditions [8]. At the cellular level, such beneficial health properties are likely due to a concentration-dependent protection that these molecules may afford to normal cells [9] by scavenging free radicals and neutralizing reactive oxygen species (ROS), suppressing apoptosis and metal chelation, aiding DNA damage repair, and modulating enzyme activities, cytokine expression, and signal transduction pathways [10–12].

Among tomato cultivars, "Microtom" presents peculiar traits: parthenocarpy [13,14], dwarf size allowing growth at high plant density in small indoor systems (up to 1357 plants m^{-2}), and a short life cycle (70–90 days from sowing to fruit ripening) [14]. Moreover, its intrinsic richness in bioactive compounds can be potentially enhanced through targeted light manipulation [15,16]. In fact, although Microtom already boasts high levels of antioxidants and other health-promoting phytochemicals, recent studies under controlled environments have demonstrated that the application of specific light-quality regimes, using light emitting diode (LED) technology, can significantly boost the synthesis and accumulation of these molecules. This makes Microtom an ideal candidate for producing nutrient-rich fruits and specialized extracts tailored for functional foods and nutraceuticals [10,11].

Recent studies have gone a step further, leveraging Microtom's unique characteristics to develop certain types of 'super-extracts'. For instance, research by Vitale et al. [15] and Hay Mele et al. [17] has shown that by optimizing light quality during cultivation, it is possible to obtain Microtom extracts with exceptionally high concentrations of antioxidants and phenolic compounds. These 'super-extracts' exhibit enhanced biological activity, making them highly attractive for several applications. Similarly, Paolillo et al. [18] have implemented comparable strategies in *Brassica* species, underscoring the versatility and scalability of this approach. Notably, the methodology is not limited to tomatoes or brassica: Costanzo et al. [19] have successfully translated these techniques to other crops such as mandarin, suggesting broad applicability across diverse plant systems.

The implications of these innovations are far-reaching. The production of highly enriched plant extracts opens avenues for research and development in multiple sectors. In addition to dietary supplementation, pharmaceuticals, and cosmetics, Microtom-enriched extracts may lend themselves to salutary applications in medicine, providing a natural radioprotection approach to mitigate cellular damage caused by ionizing radiation (IR) in patients undergoing cancer RT. RT has arguably proven to be a highly successful treatment modality, either alone or in combination with chemotherapy, surgery, immunotherapy, and other novel anti-cancer strategies [20–27]. However, RT very often entails irradiation of healthy tissues and organs at risk, especially in the case of deep-seated solid tumors. The radiosensitivity of these tissues is the factor that limits the maximum dose that can be

safely administered to achieve successful tumor control without increasing the occurrence of acute adverse reactions, such as skin erythema, or late complications, such as fibrosis or RT-induced secondary cancers [28]. Consequently, there is a strong need for radioprotectors to effectively counteract such deleterious effects. Plant-derived polyphenols have attracted attention due to their natural origin and expected lower intrinsic cytotoxicity [29]. To act as viable radiomitigators, these compounds must disrupt the molecular pathways responsible for the generation of highly reactive species following IR exposure. Via sustained levels of oxidative stress, these mechanisms can perpetuate the initial damage inflicted to DNA by radiation, leading to long-term genetic instability in the progeny of sublethally damaged normal cells/tissues [30]. ROS and reactive nitrogen species reinforce IR-induced geno- and cytotoxicity, thereby increasing the risk of sequelae [31]. By counteracting oxidative stress, it is possible to prevent structural and functional alterations of proteins and lipids, too [31]. Persistent oxidative stress, e.g., in the form of elevated ROS levels, may impair lipid metabolism, whose dysregulation is implicated in the alteration of the heterogeneous tumor microenvironment by promoting cancer cell proliferation and perturbing the crosstalk between the redox system and lipid metabolic reprogramming [32].

In the rapidly evolving field of nutraceuticals, natural compounds may therefore combine their ability of protecting normal tissue during curative cancer RT, while offering additional benefits when integrated into the diet of oncological patients or the general population to reduce the risk of cancer and CVD. Building on our previous studies, the aim of this work was to assess whether growing tomato plants (cv. Microtom) under different light-quality regimes could boost fruit antioxidant profiles, particularly polyphenols, and confer radioprotective effects against IR-induced damage in normal human cell lines, using clinically relevant assays that mimic radiotherapy conditions and their consequences for healthy tissues. To address this, plants were cultivated under two distinct light conditions: fluorescent light (FL) and red-blue light (RB). We characterized bioactive molecules with potential antioxidant capacity and quantified the polyphenol content of Microtom fruits, testing, in vitro, for the first time, the light-modulated polyphenolic tomato extracts on IR-exposed normal human cell lines. Pre-clinically relevant radiobiological assays were used to quantify the putative extract-induced reduction in DNA damage and oxidative stress levels following exposure to high-energy photons such as those employed in RT. Preliminary tests conducted on an immortalized human skin cell line showed a significant reduction in IR-induced micronuclei (MN) frequency when treated with extracts from RB-grown tomatoes at specific concentration. Encouraged by these results, we extended our analysis to both light conditions, testing two concentrations for each light regime on a breast epithelial cell line widely considered as a reliable in vitro model for normal-tissue radioresponse in BC [33,34]. These studies establish a novel approach based on the use of light-modulated plant nutraceuticals to mitigate RT side effects, offering a sustainable, non-toxic strategy to improve patient outcomes, adopting a concrete integration of plant ecophysiology and radiobiology, thereby opening new avenues for translational research.

2. Results

2.1. Total Phenolic Compounds

Data shown in Figure 1 clearly indicate that different light-quality regimes significantly influenced the total content of polyphenols, flavonoids, and anthocyanins in tomato fruits. In particular, the highest amounts of polyphenols (Figure 1A), including flavonoids (Figure 1B) and anthocyanins (Figure 1C), were found in RB tomato fruits compared to the FL fruits.

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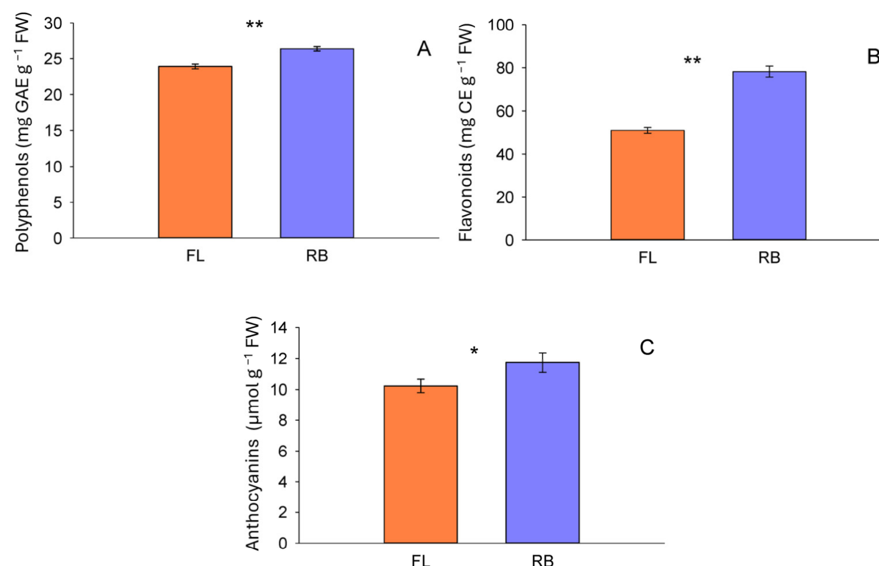

Figure 1. Total polyphenols (**A**), total flavonoids (**B**), total anthocyanins (**C**) in tomato fruits treated with different light regimes (FL and RB). GAE: gallic acid equivalents; CE: catechin equivalents; FW: fresh weight. Each bar represents the mean ± SE (n = 8). Asterisks indicate statistically significant differences (* $p < 0.05$, ** $p < 0.01$), according to T-test.

2.2. Total Carotenoids, Lycopene, and Ascorbic Acid

The change of light regime markedly influenced also the content of carotenoids, lycopene, and ascorbic acid in Microtom fruits: RB fruits exhibited a higher concentration of carotenoids (Figure 2A) and lycopene (Figure 2B) compared to FL. The opposite behavior was observed for the ascorbic acid, whose content appeared to be stimulated in FL fruits (Figure 2C).

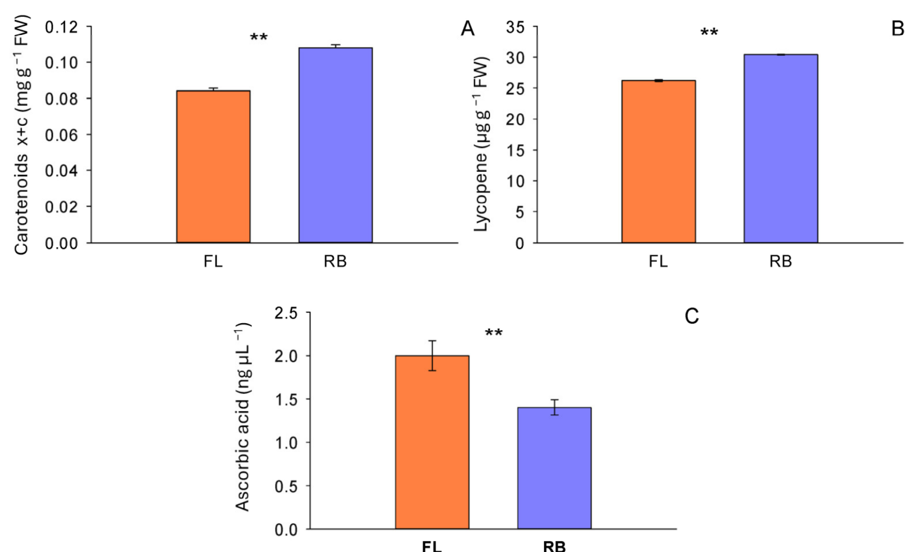

Figure 2. Total carotenoids (**A**), total lycopene content (**B**), and total ascorbic acid (**C**) in tomato fruits treated with different light regimes (FL and RB). Each bar represents the mean ± SE (n = 8). Asterisks indicate statistically significant differences (** $p < 0.01$), according to T-test.

2.3. Sample Antioxidant Activity

Total antioxidant capacity evaluated by the FRAP assay (Figure 3A) and the antioxidant activity assessed by the DPPH radical scavenging assay (Figure 3B) varied between FL and RB light regimes, confirming the significant effect of the light quality modulation on

fruit metabolites. Similarly to polyphenols, the highest values of antioxidant capacity were observed in tomatoes treated with RB light compared to FL.

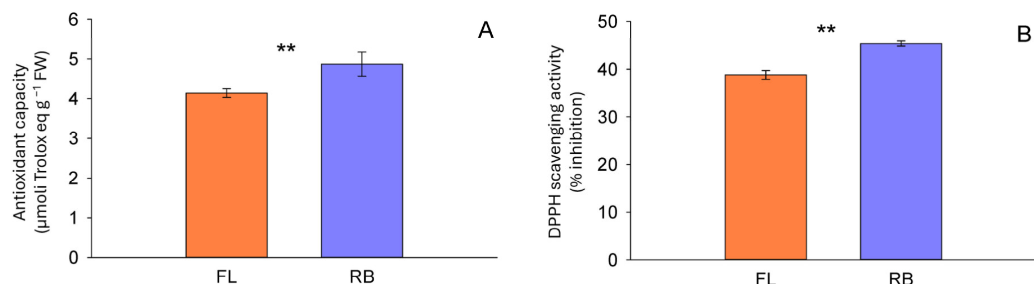

Figure 3. Total soluble antioxidant capacity (**A**) and DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging activity (**B**) in tomato fruits treated with different light regimes (FL and RB). Each bar represents the mean ± SE (n = 8). TE: Trolox equivalents; FW: fresh weight. Asterisks indicate statistically significant differences (** $p < 0.01$), according to T-test.

2.4. Radiation-Induced Genotoxicity

A preliminary series of experiments was carried out in the human keratinocyte HaCaT cell line with the aim to pre-screen a possible radioprotective action by the tomato extracts biochemically characterized as described above. To this end, the anti-genotoxic activity of the RB extract (200 μg/mL) was tested using the CBMN assay, as shown in Figure 4. Data clearly show that the extract did not increase the baseline MN frequency in unirradiated HaCaT cells (0 Gy), indicating that the RB extract does not cause genotoxicity per se. At all radiation doses, the presence of the RB-grown tomato extract significantly reduced MN frequency compared to cells irradiated without extract. At the lowest doses used, i.e., 2 and 0.5 Gy, RB-treated cells showed a marked reduction in MN frequency, between 30% and 25%, respectively. Although the protective effect appeared to diminish at the highest dose of 4 Gy, the extract-associated reduction in MN frequency remained statistically significant ($p < 0.05$).

Investigation into whether the radioprotective effect observed for the RB-derived extract at the 200 mg/mL concentration in the HaCaT cell line could also be detected at lower concentrations, and whether such radioprotection could be influenced by plant growth light regimes, was extended to the breast epithelial cell line MCF-10A, due to its pre-clinical relevance for healthy tissue radioprotection in BC patients. Modulation of cellular radioresponse by the two concentrations of the extracts derived from fruits grown under FL and RB light regimes is presented in Figure 5. Similarly to what had been found in HaCaT cells, the extract, irrespective of the light regimes, did not affect the baseline MN frequency in MCF-10A cells. Except for 100 mg/mL FL-derived extracts following exposure to 0.5 and 2 Gy of clinical photons (Figure 5A), both extract concentrations and light regimes demonstrated a significant radioprotective effect on cellular DNA compared to extract-untreated irradiated cells (Figure 5). Interestingly, the RB light regime resulted in concentration-dependent radioprotection, which exceeded the magnitude of the FL extract protection at each radiation dose. In detail, at the highest concentration (200 μg/mL) under RB light, the reduction in mean MN frequency ranged from 30 to 40% relative to untreated controls, consistently surpassing the effect observed at 100 mg/mL (Figure 5). For instance, after 0.5 Gy, a dose close to those affecting the healthy tissue in RT, 100 μg/mL of RB extract decreased MN frequency by 20% compared to the untreated sample, while at the same radiation dose, a concentration of 200 μg/mL achieved a reduction of 39% (Figure 5A vs. Figure 5B). Notably, at the highest tested radiation dose (4 Gy), the MCF-10A cells did not exhibit the decrease in radioprotection measured in the HaCaT cell line (Figure 4).

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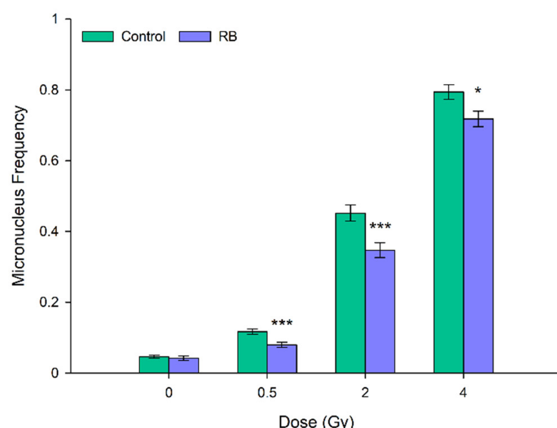

Figure 4. Dose-dependent radiation-induced MN frequency in the human keratinocyte HaCaT cell line treated with RB extract at 200 μg/mL. The results represent weighted mean values and relative SE from three independent experiments for each radiation dose, significance T-test levels being * $p < 0.05$, *** $p < 0.001$. At low and intermediate doses (0.5 and 2 Gy), RB extract showed the highest protection from radiation-induced genotoxicity ($p < 0.001$).

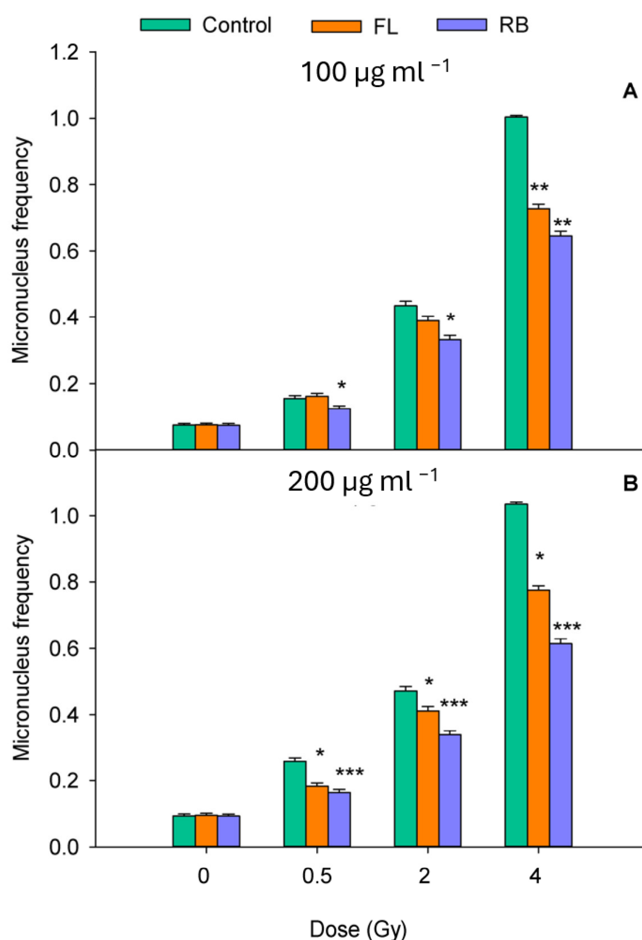

Figure 5. Dose-dependent MN frequency in the normal breast epithelial MCF-10 cell line, comparing cells untreated (controls) and cells treated with extracts obtained from tomatoes grown under FL and RB light regimes, and tested at two different concentrations, i.e., 100 μg/mL (**A**) and 200 μg/mL (**B**). Results represent weighted averages and relative SE of three independent experiments for each concentration and light regimen. MN frequency values were compared between extract-treated samples and their own non-irradiated controls. Asterisks indicate statistically significant differences (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Figure 6 portrays examples of scored MN in 0.5 Gy-irradiated binucleated (BN) MCF-10A cells treated with 200 µg/mL RB and FL extracts: note the presence of multiple MN in extract-untreated BN cells (Figure 6D) and the extract-mediated attenuation of damage in RB- and FL-treated ones, as shown Figures 6B and 6C, respectively.

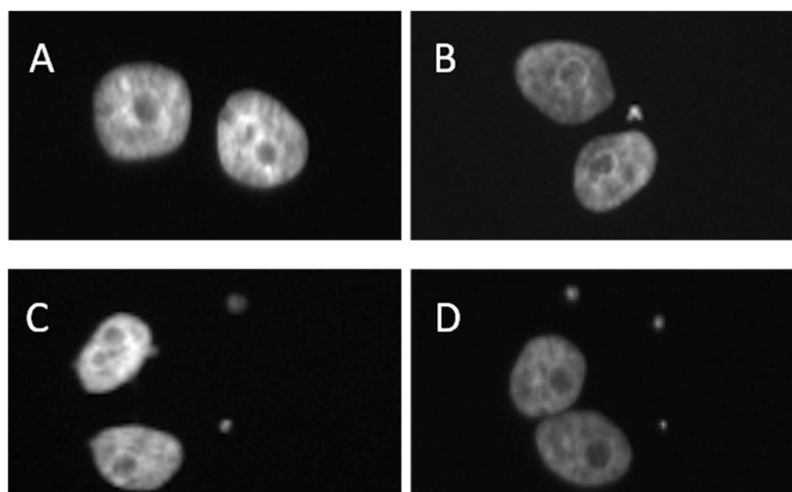

Figure 6. Micrographs (40× magnification) showing radiation-induced DNA damage in the form of MN in BN MCF-10A cells. (**A**) An example of a normal, undamaged BN cell (e.g., without MN); (**B**) Example of a BN cell with one MN; (**C**) and (**D**) show increasingly damaged DNA manifesting itself as two and three MN per BN cell, respectively.

2.5. Oxidative Stress Levels

The elevation of ROS-associated oxidative stress following exposure of MCF-10A cells to clinical photons was evaluated by the flow cytometry-based CellROX™ assay. Both FL and RB extracts were tested at a concentration of 200 µg/mL since this was found by the CBMN assay to provide the greatest reduction in radiation-induced DNA damage (Figure 5). As shown in Figure 7, radiation exposure led to a marked dose-dependent increase in the baseline level of intracellular oxidative stress in extract-untreated samples as measured 1 h post irradiation. More importantly, however, tomato extracts were able to significantly reduce such stress levels in both unirradiated controls and irradiated cells. This antioxidant effect was observed for both light regimes, although RB extract generally demonstrated greater efficacy, particularly at higher doses (i.e., at 2 and 4 Gy). Moreover, treatment with RB extract nearly restored ROS levels in cells exposed to 0.5 and 2 Gy to those measured in unirradiated controls (0 Gy). Specifically, the RB extract reduced ROS levels by approximately 43% at 0.5 Gy and 55% at 2 Gy compared to irradiated cells without treatment. The reduction in intracellular ROS levels observed after treatment with tomato extracts is likely due to the presence of polyphenols enriched by varying light regimes. Beyond their potential direct radical-scavenging activity, these phytochemicals are known to modulate redox-sensitive cellular pathways and endogenous antioxidant defense. Considering that ROS levels were measured 1 h post-irradiation, the protective effect likely reflects both immediate buffering of radiation-induced oxidative species and early regulation of intracellular redox homeostasis. The greater antioxidant capacity observed in RB extracts may therefore be associated with differences in light-induced modulation of their phytochemical composition.

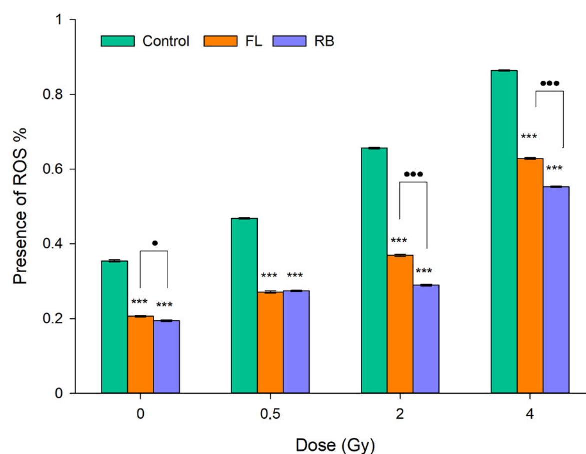

Figure 7. Oxidative stress expression in MCF-10A cells, either untreated (Control) or treated with extracts obtained from tomatoes grown under FL and RB light regimes at the concentration of 200 mg/mL of FL and RB extracts. Results represent weighted averages and relative SE of three independent experiments Here, "***" means a statistically significant difference ($p < 0.001$) between control and substance; "●●●" means a statistically significant difference ($p < 0.001$) between FL and RB, while "●" indicates a significance level of <0.05 as reported in previous figure legends.

3. Discussion

3.1. Effects of Light Quality on Antioxidant Properties of "Microtom" Fruits

This study demonstrates that different light-quality regimes can influence the concentration of bioactive molecules and the antioxidant capacity of *Solanum lycopersicum* L. cultivar "Microtom" tomato fruits, confirming that modulation of the light spectrum is a valuable tool for enhancing fruit nutritional and functional properties [35]. Notably, for the first time, we provide in vitro evidence that extracts from these tomatoes exhibit pronounced radioprotective activity in irradiated non-cancer cells. This may have important implications for the welfare of cancer patients undergoing RT. Mitigation of radiation-induced DNA damage and intracellular oxidative stress was proven by a significant reduction in the frequency of MN and by lowering of the ROS levels by 100 and 200 μg/mL of extracts from fruits grown under FL and RB light regimes.

The total antioxidant capacity of tomato fruits primarily arises from AsA, carotenoids, and polyphenols. FL light, for example, enhances AsA content in tomato fruits due to its broader spectrum, including far-red and UV wavelengths that can activate additional photoreceptors and signaling pathways involved in ascorbate biosynthesis. For instance, far-red light is significantly implicated in the regulation, synthesis, and accumulation of ascorbic acid in leaves and fruits, primarily acting through phytochrome-mediated signaling pathways [36,37]. As demonstrated by Hay Mele et al. [17], tomatoes grown under fluorescent or full-spectrum light exhibited significantly higher AsA levels than those cultivated under RB light, underscoring the importance of specific wavelength ranges in modulating antioxidant metabolism. While exposure to blue light is known to increase AsA content in detached tomato fruits compared to white, red, or green light [38–45], our study found that the enhanced antioxidant activity in fruits exposed to RB light was not due to increased AsA. Instead, it was attributed to elevated carotenoids and phenolic compounds [15,17,39]. This aligns with previous observations in the same cultivar, where an increase in total antioxidant capacity under RB regime was linked to a concomitant rise in polyphenols, including flavonoids, anthocyanins, and lycopene among carotenoids. The synthesis of these compounds is stimulated not only by red but particularly by blue wavelengths, which are mediated by cryptochrome perception [15,17,38,39,45–47], leading to increased antioxidant capacity and ROS scavenging potential. Interestingly, despite the

different chemical mechanisms of the DPPH and FRAP assays, both antioxidant capacity and radical scavenging activity increased under RB light. Structural features of ascorbic acid and carotenoids (e.g., lycopene) may affect direct electron or hydrogen donation, influencing the light-dependent results. Similarly, polyphenolic compounds, like flavonoids and anthocyanins, vary in scavenging efficacy based on hydroxyl group number/position, glycosylation, and proton/electron-donating ability. Therefore, the shift of phenolic profile under FL and RB light regimes likely drives the same FRAP-DPPH trend observed in our study [17,19].

Blue and UV-A light can also stimulate flavonoid and phenylpropanoid production by activating enzymes involved in the phenolic pathway, while red and far-red light promote compounds tied to ripening and oxidative stress responses. The enrichment of RB fruits in high-value nutraceuticals identifies this red-to-blue ratio as a favorable tool for the synthesis of these types of metabolites [48]. For instance, a recent study has demonstrated that tomatoes grown under RB light produce fruits richer in quercetin and derivates, like quercetin rutinoside, quercetin 3-O-Galactoside, and quercetin acetylhexoside [15,17]. These compounds are known for their free radical scavenging activity, modulation of pro-inflammatory cytokines, and inhibition of cancer cell proliferation. Blue light can also enhance the production of rutin, chlorogenic acid, and caffeic acid [17]. Notably, rutin and quercetin rutinoside have been associated with protective effects against cardiovascular diseases [17,49,50]. Additionally, RB tomato extracts enriched in chlorogenic acid and caffeoylquinic acid derivates, apigenin and apigenin-8-c-Glucoside, are recognized for their anticancer and anti-inflammatory properties [51–54]. Therefore, regular intake in the daily diet of such antioxidant compounds through fruits and vegetables can counteract ROS, promote human health [55,56], and exert antiproliferative and pro-oxidant effects on tumor cells [57], while providing anti-inflammatory activity in normal cells [58].

3.2. Radioprotective Effects of Light-Modulated Tomato Extracts on Human Cells

Despite the encouraging properties against oxidative stress-induced genotoxicity [18], scant data exist on the protective effects of tomato fruit-derived compounds on radiation-induced cytogenotoxicity in the therapeutic context of counteracting radiotoxicity of healthy tissues [59,60]. To our knowledge, this is the first report linking light-dependent metabolic modulation in tomatoes to radioprotective efficacy in normal human cells. The chosen radiobiological endpoints (MN induction and ROS levels) hold valuable pre-clinical relevance. The presence of MN in irradiated cells reflects chromosomal damage and mis-segregation that, if sublethal to the surviving proliferating cell, can be transmitted through cell division, compromising genomic stability and potentially inactivating the newly discovered cGAS-Sting pathway that stimulates systemic immune response [61–63]. Similarly, the perpetuation of oxidative stress is a known risk factor for RT-related secondary cancers [44,64].

The varying degrees of radioprotection observed in our study, directly influenced by the modulation of light regimes, indicate that extracts from plants grown under an RB light regime are more effective than those from plants grown under FL conditions in counteracting radiation-induced genotoxicity (Figures 4 and 5) and oxidative stress (Figure 7). The enhanced efficacy of RB-grown tomatoes appears to correlate with a marked increase in key antioxidant compounds, especially polyphenols. This enrichment is not merely a quantitative change; RB lighting triggers specific photoreceptors and transcriptional programs that enhance the biosynthesis of these molecules, effectively ‘priming’ the fruit to produce higher levels of defensive secondary metabolites, well known for their ability to scavenge radiation-induced ROS, stabilize cellular structures, and mitigate DNA damage in irradiated cells.

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In this context, natural compounds can reduce the adverse effects of RT and improve the tolerance to radiation of healthy cells [9]. Antioxidant compounds, as secondary metabolites, play a key role in plants, especially as a defense strategy in response to environmental stressors. Among these, light represents one of the most powerful environmental cues modulating plant metabolism. Different wavelengths can activate transcriptional pathways that lead to the synthesis and accumulation of antioxidant molecules [65,66].

In humans, through the ingestion of fruits and vegetables, these compounds act as antioxidants by counteracting ROS and promoting human welfare [67,68]. Therefore, the modulation of light during plant growth does not only influence agricultural traits but directly impacts the nutraceutical profile of the harvested fruits, ultimately determining their potential health-promoting properties. Food-isolatable nutraceuticals demonstrate antiproliferative and pro-oxidant effects on tumors [69,70], alongside antioxidant and anti-inflammatory activity in normal cells [71]. Indeed, the attractive double-edged potential of pure polyphenols or polyphenol-enriched extracts could be used to widen the therapeutic window in RT [72].

At least as regards the radioprotective capacity of tomato fruits, our preliminary experiments revealed that extracts obtained from tomatoes grown under RB light regimes at a concentration of 200 $\mu g\ mL^{-1}$ significantly reduced radiation-induced DNA damage in human HaCaT keratinocytes (Figure 4). This protective effect may be attributed to the several polyphenols composing the RB extract, particularly flavonoids [17], whose catechol-substituted B-ring and, to a lesser extent, 3-OH group confer strong hydroxyl radical scavenging activity [73]. Hesperidin, chlorogenic acid, quercetin, including quercetin-3-O-galactoside, rutin, and genistein collectively show antioxidant, anti-apoptotic, and radioprotective effects, limiting DNA damage, lipid peroxidation, and micronucleus formation and inhibiting cancer cell proliferation in mouse and human cells exposed to X or γ-radiation [74–85]. Although to a lesser extent, the FL extract also showed detectable radioprotective properties, plausibly due to compounds stimulated under this light-quality regime, such as naringin, resveratrol, and epicatechin, which mitigate oxidative DNA damage, inflammatory responses, chromosome aberrations, systemic organ stress, and infertility following ionizing radiation exposure [84–86].

This prompted us to focus our study on the MCF-10A cell line using the extracts from both growth light regimes. Not only did we confirm their DNA-protecting action against radiation-induced chromosomal damage, but we also found a pronounced ability to reduce radiation-elevated ROS levels. Since such results were obtained following exposure to photons as used in RT in the MCF-10A cell line, which is widely regarded as an in vitro model for normal-tissue reaction in BC patients in vivo [33,34], they hold pre-clinical importance. Hence, the extract-induced radioresistance supports the possible therapeutic use of such extracts as bioactive compounds capable of mitigating the adverse effects of radiation. The radiosensitivity of healthy tissues and organs is the main dose-limiting factor in curative RT because of late-occurring consequences such fibrosis and chronic inflammation. Indeed, this aspect is even more critical for BC, where mitigation of radiation-associated cardiotoxicity, often fueled by pro-inflammatory and pro-oxidant responses [87], has emerged as a priority for treatment of this malignancy [88].

It is important to note that even under baseline conditions, that is, when cell cultures were not exposed to radiation, the extracts protected cells by lowering physiologically oxidative stress levels. Moreover, the extent of protection granted by the extracts against radiation-induced effects depended on the specific light regime the plants from which they derived had been grown in. Thus, FL tomato extract reduced the percentage of intracellular ROS, albeit less efficiently than RB tomato extract. The difference between the extracts is significant for doses of 0, 2, and 4 Gy, while it is comparable at 0.5 Gy. Examining the

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data at 0 Gy in Figure 5A,B, we notice that the frequency of MN from tomato extracts is comparable to that of the control. While one might expect a similar trend for oxidative stress, this was not the case. This apparent discrepancy can be explained by the fact that the mechanisms underlying MN formation are not exclusively driven by oxidative damage. MN originating from acentric chromosomal fragments are typically linked to direct DNA double-strand break mis-repair, whereas those containing whole chromosomes result from mitotic mis-segregation. Therefore, oxidative stress is only one of several factors contributing to MN induction. Additionally, it ought to be considered that the probe used in the oxidative stress assay simultaneously assesses the presence of ROS in both the mitochondria and the nucleus. At a baseline level, nuclear ROS levels may remain unchanged, while mitochondrial ROS could be more responsive to the antioxidant activity of the extracts, as suggested by previous reports on compartmentalized ROS signaling [89]. This compartmentalization might thus account for the observed divergence between MN and ROS data at 0 Gy.

In conclusion, our results hold significant implications in BC RT scenarios because, by reducing late normal-tissue complications, particularly those linked with RT-induced CVD, through a toxicity-free nutraceutical approach, the therapeutic window for BC RT may be enlarged. Furthermore, such an approach may be interesting for the radioprotection of manned space exploration crews, who are exposed to a peculiar radiation field and physiological conditions [90–92], and share similarly serious long-term health hazards with RT patients, such as increased risk of radiation-induced CVD and cancer, which also require bioactive countermeasures [93,94].

These considerations collectively highlight the novelty of our results and justify further studies on the radiomodulatory properties of *Solanum lycopersicum* L. cultivar "Microtom" extracts from fruits grown under different light regimes. At the same time, it remains essential to determine to what extent the radioprotective effects observed in vitro can be translated and maintained under in vivo conditions, where digestion, metabolism, and bioavailability may influence the biological activity of tomato-derived polyphenols.

3.3. Limitations and In Vivo Relevance

Our findings were obtained under strictly controlled in vitro conditions, using a direct application of tomato extracts to human cell lines, bypassing complex in vivo physiological processes. However, it is known that in vivo, polyphenols and flavonoids undergo gastrointestinal digestion and gastric hydrolysis by pancreatic enzymes (trypsin, α-chymotrypsin, esterases) and bile salts, yielding metabolites like caffeic/ferulic/quinin acids from chlorogenic derivatives. They also form complexes with dietary proteins and fibers, leading to precipitation or reduced solubility, while exposure to oxygen and transition metals (Fe^{2+}, Cu^{2+}) in the gut lumen can induce auto-oxidation and polymerization, further depleting their free radical scavenging potential [95–98]. These metabolic conversions can alter polyphenols' redox properties and key physicochemical traits (lipophilicity, uptake, distribution, target affinity) essential for providing antioxidant and DNA damage responses. Since the compounds may differ from those originally present in the extracts tested in our cellular model, as a direct consequence, the magnitude of the antioxidant effect observed in vitro could not be the same in the human body. At the same time, it is noteworthy that in several clinical trials, metabolites derived from these compounds can retain biological activity [99]. For instance, curcumin reduces oral mucositis incidence and severity during radiotherapy [100], while polyphenol-rich supplements (pomegranate, green tea, broccoli, and turmeric) slowed prostate cancer progression [101]. Furthermore, in vivo effects are not exclusively related to direct radical scavenging, but also to the modulation of redox-sensitive signaling pathways [102]. In this regard, our work was designed as

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a proof-of-concept study aimed at evaluating whether specific light-quality treatments may enhance the intrinsic antioxidant and radioprotective potential of Microtom-derived phenolic extracts at the cellular level. We acknowledge that further studies are needed, including simulated gastrointestinal digestion models, bioavailability assessments, and ex vivo/in vivo validation, to better define the translational relevance of these findings. Regarding the ongoing debate on whether antioxidant supplements may be deleterious inasmuch as they could protect the cancer tissue as well, hence their administration to patients undergoing RT warrants caution, it must be noted that most tumors are hypoxic, and cancer cells do exhibit a lessened repair capacity [103]. Additionally, treatment plans are designed to deliver the highest radiation dose to the tumor volume.

4. Materials and Methods

4.1. Plant Growth Conditions and Experimental Design

Dry seeds of *Solanum lycopersicum* L. cultivar "Microtom", sourced from Holland Online Vof (Amsterdam, The Netherlands) and derived from the same batch, were sown in 1.2 L pots with a peat-based mix (86% peat, 9% sand, 3% quartz sand, 2% perlite). Pots were held in darkness until germination. At 15 days after sowing (DAS), seedlings were moved to a growth chamber and exposed to two different light-quality regimes (five pots per light treatment), namely FL regime (fluorescent tubes, Lumilux L36W/640 and L36W/830, Osram, München, Germany) and RB regime (60% red, R/40% blue, B, LED arrangements, LedMarket Ltd., Plovdiv, Bulgaria), specifically selected on the basis of previous studies on this cultivar that demonstrated the beneficial effects on photosynthesis and fruit quality [15,16]. The light spectral profiles (Figure 8) were measured using an SR-3000A spectroradiometer (10 nm resolution, Macam Photometrics Ltd., Livingston, Scotland, UK). The photosynthetic photon flux density (PPFD) in the growth chamber was fixed at 360 µmol photons m^{-2} s^{-1} (canopy level) under a 14 h photoperiod, 60–70% relative humidity and day/night air temperature of 25/20 °C ± 2 °C. Plants were watered weekly to field capacity with Hoagland's solution. Plant growth was monitored up to 120 DAS until fruit ripening. Harvested fruits were powdered in liquid nitrogen by a mortar and a pestle and stored at −80 °C (Ecology Laboratory, University of Naples Federico II) for biochemical assays and extract preparation for in vitro radiobiological tests on cell cultures.

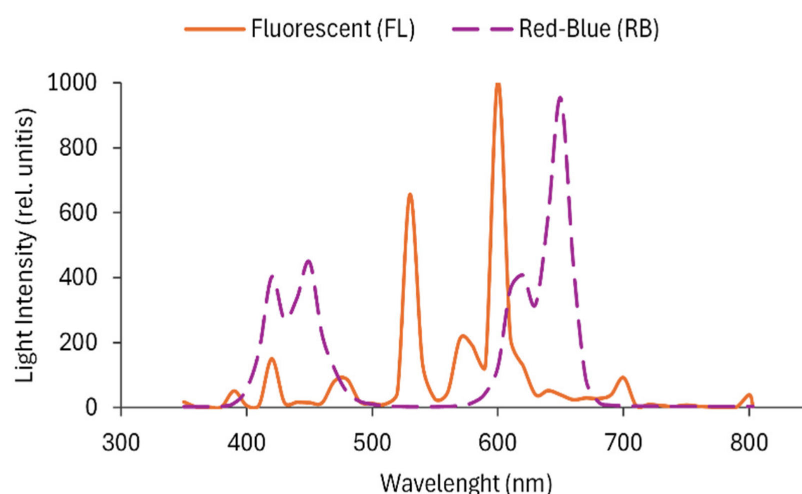

Figure 8. Light spectra used in the experiment. FL, white fluorescent tubes; RB, red-blue, LED. Photon flux density: 360 µmol photons m^{-2} s^{-1}. Irradiance range: 350–800 nm.

4.2. Determination of Total Polyphenol, Flavonoid, and Anthocyanin Content

Samples (0.200 g) were extracted in methanol, held for 1 h at 4 °C, and centrifuged at 11,000 rpm for 5 min.

To assess the total polyphenol content, extracts were mixed with 1:1 (*v:v*) 10% Folin–Ciocâlteu reagent and 700 mM Na_2CO_3 solution in the ratio 5:1 (*v:v*). Samples were kept for 2 h in the dark to read the absorbance at 765 nm (UV-VIS Cary 100, Agilent Technologies, Palo Alto, CA, USA). The polyphenol concentration was calculated using a gallic acid standard curve and expressed as milligrams of gallic acid equivalent per gram of fresh weight (mg GAE g^{-1} FW) [15].

Total flavonoid content was estimated by mixing the methanolic extracts with 5% $NaNO_2$, 10% $AlCl_3$, and 1 M NaOH solutions. The volume of the mixture was adjusted with distilled water, and the absorbance was read at 510 nm. Total flavonoid content was calculated with a standard catechin (CE) curve and expressed as milligrams of catechin equivalent per gram of fresh weight (mg CE g^{-1} FW) [104,105].

For anthocyanin concentration, samples (0.250 g) were extracted in the dark for 24 h with acidified methanol (1% HCl) at 4 °C. Once centrifuged, the absorbance of supernatants was read at 530 and 657 nm. The anthocyanin content was quantified by the following equation:

$$(\mu\text{moL g}^{-1}) = [\frac{(A_{530} - 0.33) \times A_{6570}}{31.6}] \times [\frac{\text{volume (mL)}}{\text{weight (g)}}] \quad (1)$$

where the extinction coefficient is 31.6 M^{-1} cm^{-1} [106,107]. All reagents used in these assays were purchased from Sigma-Aldrich (St. Louis, MO, USA).

4.3. Determination of Total Carotenoid, Lycopene, and Ascorbic Acid Content

To determine the total carotenoid content, samples (0.100 g) were extracted with cold 100% acetone (Carlo Erba Reagents, Milan, Italy) and centrifuged (Labofuge GL, Heraeus Sepatech, Hanau, Germany) at 5000 rpm for 5 min. The absorbance was measured with a spectrophotometer (Cary 100 UV-VIS, Agilent Technologies, Santa Clara, CA, USA) at 470, 645, and 662 nm wavelengths, and carotenoid concentration was expressed as milligrams per gram of fresh weight (mg g^{-1} FW) [108].

To quantify the lycopene concentration [109,110], samples (0.500 g) were treated with hexane: ethanol: 0.05% BHT in acetone (*v:v:v*, 2:1:1), preliminarily preparing the solution of butylated hydroxytoluene (BHT) in acetone at the final concentration of 0.05% (*w:v*). The mixture was stirred for ~15 min at room temperature. After shaking, deionized water was added to each sample, and the shaking step was repeated for 15 min. The sample was then left at room temperature for 5 min to allow phase separation.

The lycopene concentration was calculated using the sample absorbance read at 503 nm, the extinction coefficient of lycopene in hexane (17.2×10^4 M^{-1} cm^{-1}), and the lycopene molecular weight (536.9 g mol^{-1}) and expressed as milligrams per gram of fresh weight (mg g^{-1} FW). For this assay, the ethanol and BHT were purchased from (Sigma-Aldrich, St. Louis, MO, USA), while the hexane was obtained from VWR Chemicals (Avantor, Milan, Italy).

The AsA concentration was determined using the AsA Assay Kit (MAK074, Sigma-Aldrich, St. Louis, MO, USA). Samples (10 mg) were homogenized in 4 volumes of cold AsA buffer and then centrifuged at 13,000 rpm for 10 min at 4 °C. Samples were then mixed with the kit reagents for starting the colorimetric coupled enzyme reaction. The absorbance of the colored product, proportional to the amount of AsA, was read at 570 nm, and the AsA concentration was calculated using a standard curve and expressed in nanograms per microliter.

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4.4. Antioxidant Capacity (FRAP Assay) and Free Radical Scavenging Activity (DPPH Assay)

The antioxidant capacity was assessed through the Ferric Reducing Antioxidant Power (FRAP) assay [111,112]. Samples (0.250 g) were treated by means of the extraction solution (methanol: water, 60:40, *v:v*) for 1 h and centrifuged for 15 min at 14,000 rpm at 4 °C. The extracts were mixed with the FRAP reagents and incubated in the dark for 1 h. The absorbance was read at 593 nm. and the antioxidant capacity was determined using a Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) standard curve and quantified as micromoles Trolox equivalents per gram of fresh weight (μmol TE g^{-1} FW).

The free radical scavenging activity of tomato fruit extracts was evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay [111,113]. The methanolic extract was added to a 6×10^{-5} M DPPH methanolic solution (1:28, *v:v*). The mixture was stirred and incubated at 37 °C for 20 min. The absorbance of the sample was read at 515 nm and converted to DPPH radical inhibition percentage using the following equation:

$$Inhibithion(\%) = \frac{Ab_{blank} - Ab_{sample}}{Ab_{blank}} \times 100 \quad (2)$$

where Ab_{blank} is the absorbance of the blank, and Ab_{sample} is the absorbance of the sample. Trolox was used as the positive control. All reagents used in both assays were purchased from Sigma-Aldrich (St. Louis, MO, USA).

4.5. Cell Cultures

Two cell lines were used in this work. They were grown and serially sub-cultivated according to conventional cell culture techniques. The spontaneously immortalized HaCaT cell line, derived from adult human epidermal cells and retaining the capacity to proliferate and differentiate in a manner similar to basal keratinocytes in vivo, was purchased from the Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna (IZS-LER), Brescia, Italy. HaCaT cells were grown in DMEM (Dulbecco's Modified Eagle Medium), supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, 1% L-glutamine, and 1% sodium pyruvate (Gibco, ThermoFisher Scientific, Paisley, UK). Non-tumorigenic breast epithelial MCF-10A cells were kindly donated to the Radiation Biophysics Laboratory, University of Naples Federico II, by Dr P. Chaudhary, Queen's University Belfast, UK. As described in detail by Debnath et al. [114], two DMEM/F12-based culture media (Gibco, ThermoFisher Scientific, Waltham, MA, USA) are required for maintenance of these cells: one formulation is intended for optimal growth and is enriched with 5% horse serum, endothelial growth factor (20 ng/mL), hydrocortisone (0.5 μg/mL), insulin (10 μg/mL), and cholera toxin (100 ng/mL), all from Sigma-Aldrich, Merck, Darmstadt, Germany; the other, devoid of all supplements but rich in horse serum (20%), is used for routine passaging, i.e., for trypsin quenching and dilutions for cell counting prior to plating. Both cell lines were grown in standard tissue T75 culture flasks placed at 37 °C in a humidified atmosphere with 5% CO_2.

4.6. Extract Treatment of Cell Cultures

To evaluate the putative radioprotective properties of tomato fruits grown under FL and RB light regimes, we started from the HPLC-based component analysis of the plant phenolic extracts, as carried out in our previous work [17]. Then, the phenolic extracts were preliminarily dried at a temperature of 50 °C for 30 min in a Rotavapor RII (BÜCHI Labortechnik AG ®, Flawil, Switzerland). The dry material was weighed and solubilized in methanol to reach the concentration of 1000 mg/mL (stock solution). The phenolic extracts were then tested at two final concentrations, 100 and 200 mg/mL, by adding them to the medium of exponentially growing cells in either slide flasks (Nunclon, ThermoFisher

Scientific, USA, 9 cm^{-2} growth surface) for DNA damage evaluation by the CBMN assay or in the T25 tissue culture flasks for the ROS assay. Cultures were thus incubated for 24 h and then exposed to radiation in the presence of the extracts. Immediately after irradiation, cells were rinsed thoroughly with phosphate-buffered saline (PBS) solution and subjected to the assay procedure. Cultures irradiated in the absence of the extracts served as controls.

4.7. Cell Exposure to Clinical Photons

Irradiations of cell cultures prepared as described above were performed at Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples, Italy, with a Synergy Agility LINAC (Elekta, Stockholm, Sweden). Such an accelerator is conceived to deliver RT doses for treatments of oncological patients; therefore, routine quality control checks are performed to make sure the dose delivered adheres to the prescribed one as computed by a Treatment Planning System (TPS). Three-dimensional conformal radiation therapy (3D-CRT) treatment plans were designed specifically for these experiments by means of a dedicated software application (Monaco v5.11.03 TPS, Elekta, Sweden). Flasks were imaged by a computed tomography (CT) scan in the exact position they were treated.

By means of the CT image-based TPS, the volume to be treated was thus contoured, and the calculation of the prescribed radiation dose to be administered was performed. To achieve a homogeneous dose distribution within the irradiated field, the geometric setup consisted of two opposing fields at 0° and 180°. Specifically, two 6 MeV squared photon beams covering a surface of 20 × 20 cm^2 were used to deliver doses of 0.5, 2, and 4 Gy to the cells. To ensure adequate build-up during dose delivery by the LINAC rotating gantry, flasks were placed between layers of solid-water slabs of appropriate thickness, namely 2.8 cm for the upper slab and 5 cm for the lower slab. The associated dose uncertainty was estimated to be less than 3%, in line with standard tolerances routinely adopted in RT.

4.8. Measurement of Radiation-Induced DNA Damage

The well-established CBMN genotoxicity assay [115] was performed to evaluate the putative radioprotective effect exerted on DNA by the tomato extracts from plants grown under FL and RB light-quality regimes. In the CBMN assay, DNA damage manifests itself in the form of round portions of DNA, called MN, originated from lagging chromosomes or acentric chromosome fragments at anaphase [116,117] that fail to be incorporated into either of the two daughter nuclei. Based on this, because MN can be associated with the daughter nuclei before cytokinesis ends the telophase stage, they must be scored in BN cells. The amount of IR-induced damage is quantified by the presence of those MN that meet well-defined morphological criteria as described by Fenech et al. [115]. The actin-destroying agent Cytochalasin B (CytB), which inhibits cleavage of the cytoplasmic furrow during cytokinesis, was used for arresting cells at the BN stage. Measurement of the MN frequency in BN HaCaT and MCF-10A cells allowed the evaluation of eventual mitigation of radiation-induced genotoxicity following treatment with the tomato extracts.

Micronucleus Frequency Measurement

After photon irradiation (0, 0.5, 2, and 4 Gy), cells were treated for 24 h with 2.0 μg/mL of CytB. These were the optimal treatment duration and CytB concentration, as determined by preliminary tests, to yield the highest proportion of BN cells compatibly with the lowest CytB-induced baseline genotoxicity. Subsequently, the CytB-containing medium was removed, and cells were rinsed in PBS and fixed for 20 min at −20 °C with freshly prepared 4:1 Carnoy's solution (methanol:acetic acid) that had been pre-cooled at −20 °C for 30 min. After removal of the fixative solution, slides were air-dried for 24 h and then stained with 14 μL of ProLong Gold DAPI in antifade (ThermoFisher Scientific, USA). Control samples were subjected to the same procedure. The analysis was

then manually performed with an Axioplan 2 epi-fluorescence imaging microscope (Carl Zeiss AG, Oberkochen, Germany), using a 40× magnification objective. MN frequency was determined in BN cells according to the formula:

$$f = \frac{MN_1 + (2 \times MN_2) + (3 \times MN_3) + (4 \times MN_4)}{BN} \quad (3)$$

where MN_n is the number of BN cells with n MN, and BN is the total number of BN cells scored. Between 500 and 1500 BN cells were scored for each sample, depending on the radiation dose, for statistical robustness.

4.9. Determination of Radiation-Induced Oxidative Stress

The level of oxidative stress was determined in MCF-10A breast epithelial cells to evaluate the antioxidant action exerted by the tomato extracts from plants grown under FL and RB light-quality regimes. Cells were irradiated with the same doses employed for the CBMN assay, i.e., 0, 0.5, 2, and 4 Gy. Oxidative stress was measured by means of a flow cytometer-based assay (Invitrogen Attune NxT Flow, ThermoFisher Scientific, USA) using a commercially available kit composed of the fluorogenic CellROX™ Green Reagent for measurement of cellular oxidative stress in live cells, and the SYTOX™ AADvanced™ Dead Cell Stain Kit (both from ThermoFisher Scientific) to discriminate live cells against the dead cell population. Upon oxidation by ROS and subsequent binding to DNA, the cell-permeant CellROX dye, weakly fluorescent while in a reduced state, emits bright green, fluorescent light, with absorption/emission maxima of 485/520 nm.

ROS Level Measurement

Cells were treated 1 h after irradiation. Firstly, they were harvested by trypsinization and centrifuged (200× g for 5 min). The pellet was resuspended in medium using Eppendorf tubes to a concentration of about 2×10^5 cells/mL. The staining procedure by the CellROX green (250 mM) was carried out for 30 min in the incubator at 37 °C, using 0.5 mL of cell suspension containing a final number of 1×10^5 cells in accordance with the manufacturer's guidelines; afterwards, the Sytox AADvanced stain (1 μL per 1 mL of cell suspension) was added for 5 min at room temperature. Flow cytometry analysis followed immediately. "Blank" samples, i.e., without fluorescent probes, were used to set the mean cellular autofluorescence level so as to avoid overestimating the presence of intracellular ROS and, hence, to position the quadrants to discriminate between alive non-stressed cells, alive stressed cells, false double positives, and dead cells. Cells not treated with the tomato extracts were used as controls and underwent the same experimental procedure.

4.10. Statistical Analysis

Statistical analysis and data representation were performed using Sigma Plot 12.0 (Jandel Scientific, San Rafael, CA, USA). Concerning biochemical investigations, statistically significant differences between FL and RB samples were checked by T-test, based on a significance level of $p < 0.05$. All data were expressed as means ± SE (n = 8). As regards the radioprotective effect of tomato extracts, within each radiation dose (0, 0.5, 2, and 4 Gy) and for each extract concentration (100 and 200 mg/mL), FL and RB extract-treated cell lines were compared to controls by a T-test based on a significance level of $p < 0.05$. The normal distribution of data was verified by Shapiro–Wilk test. Error on the frequency f of MN and on that of ROS-positive cells was assumed to follow a binomial distribution per each individual experiment according to Equation (4):

$$Error = \sqrt{\frac{f \times |1 - f|}{n}} \quad (4)$$

For both CBMN and ROS assays, results were then plotted as the weighted means (Equation (5)) with relative SE (Equation (6)) from at least three separate experiments per each cell line, extract concentration, light-quality regime, and radiation dose, the individual weights w_i being the inverse of the squared SE:

$$Weighted\ mean = \frac{\sum_{i=1}^{3} w_i f_i}{\sum_{i=1}^{3} w_i} \quad (5)$$

$$Weight\ error = \sqrt{\frac{1}{\sum_{i=1}^{3} w_i}} \quad (6)$$

5. Conclusions

For the first time, this study evaluated in vitro whether phenolic extracts of "Microtom" fruits, grown under FL and RB light regimes, may provide radioprotection on normal human cell lines. Our findings suggest that light spectrum quality can profoundly shape the biochemical profile of tomato fruits. The tomato extracts, administered at 100 and 200 µg/mL, effectively mitigated normal-tissue radiotoxicity in normal breast cells exposed to therapeutic photon beams. Notably, the RB extract, at a concentration of 200 µg/mL, provided the greatest degree of radioprotection. This is in keeping with our findings that tomatoes grown under RB lighting were richer in polyphenols, flavonoids, carotenoids, and lycopene, thereby resulting in higher antioxidant capacity compared to those grown under FL light. These findings underpin the potential of targeted light regimes as powerful tools to produce healthier nutrient-enriched food and their possible usefulness for breast cancer patients undergoing radiotherapy. Overall, our results may represent a starting point for further research aimed at (i) elucidating the molecular pathways through which RB light enhances the synthesis of radioprotective polyphenols in tomato fruits; (ii) determining whether similar light-induced biochemical profiles can be achieved in other edible plant species; and (iii) developing standardized tomato-derived extracts or formulations to mitigate radiotherapy (RT)-induced normal tissue toxicity.

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Abbreviations

The following abbreviations are used in this manuscript:

RB	Red-Blue
FL	Fluorescent White
RT	Radiotherapy
CBMN	Cytokinesis-Block Micronucleus
BC	Breast Cancer

CVD	Cardiovascular Disease
ROS	Reactive Oxygen Species
LED	Light Emitting Diode
IR	Ionizing Radiation
MN	Micronuclei
BN	Binucleated
AsA	Ascorbic Acid
DAS	Days After Showing
CE	Catechin
HPLC	High-Performance Liquid Chromatography
BHT	Butylated Hydroxytoluene
FRAP	Ferric Reducing Antioxidant Power
DPPH	1,1-diphenyl-2-picrylhydrazyl
TPS	Treatment Planning System
CT	Computed Tomography

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