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MINI-REVIEW

Radiation-resistant extremophiles and their potential in biotechnology and therapeutics

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Abstract Extremophiles are organisms able to thrive in extreme environmental conditions. Microorganisms with the ability to survive high doses of radiation are known as radioresistant or radiation-resistant extremophiles. Excessive or intense exposure to radiation (i.e., gamma rays, X-rays, and particularly UV radiation) can induce a variety of mutagenic and cytotoxic DNA lesions, which can lead to different forms of cancer. However, some populations of microorganisms thrive under different types of radiation due to defensive mechanisms provided by primary and secondary metabolic products, i.e., extremolytes and extremozymes. Extremolytes (including scytonemin, mycosporine-like amino acids, shinorine, porphyra-334, palythine, biopterin, and phlorotannin, among others) are able to absorb a wide spectrum of radiation while protecting the organism's DNA from being damaged. The possible commercial applications of extremolytes include anticancer drugs, antioxidants, cell-cycle-blocking agents, and sunscreens, among others. This article aims to review the strategies by which microorganisms thrive in extreme radiation environments and discuss their potential uses in biotechnology and the therapeutic industry. The major challenges that lie ahead are also discussed.

Keywords Radiation · Microorganisms · Extremophiles · Extremolytes · Extremozymes

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Introduction

Radiation is energy in the form of electromagnetic waves (i.e., gamma rays, X-rays, UV radiation, radio waves, etc.) that causes oxidative damage to vital biomolecules such as proteins, DNA, RNA, and enzymes. One of its most basic forms is the UV radiation (UVR) in sunlight, which has been known to cause changes to the molecular structure of DNA by forming dimers between the strands of DNA molecules. As a result, UVR has been linked to many harmful effects in humans including immune suppression, dermatitis, premature aging, and, in extreme cases, skin cancer (Agar et al. 2004). Radiation from various nuclear facilities (e.g., radionuclides) has also been linked to acute health effects in humans. Increased exposure can cause fatigue, weakness, fever, hair loss, dizziness, diarrhea, and, in extreme cases, leukemia and leucopenia. In addition, this type of radiation has been linked to poor fetal development, including smaller brain size, abnormal growth, and mental retardation (Ghirga 2010).

However, extremophiles—organisms including microbes, plants, and animals that are able to survive in extreme environmental conditions, such as hot springs, volcanic areas, extreme temperatures, high salt levels, high antibiotic concentrations, and radiation—have found ways to survive (Gabani et al. 2012b; Kumar et al. 2010; Mesbah and Wiegel 2008). The microorganisms that thrive under extreme radiation are referred to as radiation-resistant or radioresistant extremophiles. They have been found in wide environmental niches such as higher elevations (mountain ranges) and open fields where UVR levels are high. The continuous depletion of the ozone layer has greatly influenced the amount of UVR in Earth's biosphere. In addition, the extensive use of radioactive elements and compounds for energy, in medicine, research, and industry has produced radioactive wastes in the

environment (Pryakhin et al. 2012). Nuclear accidents such as the Fukushima Daiichi nuclear disaster in 2011 and the Chernobyl disaster in 1986 have also caused an increase in radionuclides and radioisotopes in the environment. Other forms of radiation encountered in the environment include gamma radiation and X-rays, which are known to be harmful to humans.

Despite the harmful effects of radiation on humans, different types of microorganisms have found their ways to survive under high levels of radiation (Fig. 1). The bacterium *Deinococcus radiodurans* is capable of withstanding the supra-lethal effects of ionizing radiation and UVR (>1,000 J/m^2) (Yuan et al. 2009a, b). Endolithic cyanobacteria are reported to be able to protect themselves from the harmful effects of UVR (Rastogi et al. 2010). Several microorganisms, such as *Rhodanobacter* sp. and *Desulfuromonas ferrireducens* have been observed to survive in the presence of high levels of radionuclides (Green et al. 2012). The ability of radioresistant organisms to survive high levels of radiation has been linked to their efficient DNA repair mechanisms and ability to produce protective primary and secondary metabolic products (Singh and Gabani 2011). The radiation-responsive metabolites, pigments, and enzymes they produce can be induced or activated by modern biotechnological techniques to produce useful drugs, especially anticancer drugs, as well as antibiotics and agricultural products of commercial significance (Kumar et al. 2010). However, the advantages of radiation resistant extremolytes and extremozymes in the field of therapeutic and biotechnology have not been implicated. This article aims to discuss the strategies by which microorganisms thrive in radiation-rich environments and their potential uses in biotechnology and the therapeutic industry. The major challenges that lie ahead are also discussed.

Types of radiation

Electromagnetic radiation of various types, including UVR and gamma rays (GR) continuously bombards the surface of the Earth. Most, if not all, UVR comes from the sun as a type of electromagnetic radiation with a wavelength of 10–400 nm and energies ranging from 3 to 124 eV. The continuous depletion of the ozone layer has increased the amount of UVR that reaches the surface of the earth. Because the skin is the largest organ of the human body, it faces a wide variety of harmful environmental factors, including UVR. UVR penetrates the layers of the epidermis, including keratinocytes, and leads to production of reactive oxygen species (ROS), which cause single and double DNA strand breaks, inflammation, immunosuppression, gene mutations, and ultimately carcinogenesis. Other types of DNA damage associated with UVR include cyclobutane pyrimidine dimmers and pyrimidine-pyrimidone(6-4) photoproducts leading to CC–TT or C–T transitions (Besaratinia et al. 2005) (Fig. 1). Among the mutations, the induction of cyclobutane pyrimidine dimers is well known to cause the alteration in the p53 gene, disrupting the normal cell cycle and shifting it towards carcinogenesis (Klein et al. 2010).

Similar to UVR, GR is also a form of ionizing radiation, and as a result, is biologically harmful to vital molecules such as DNA. Unlike UVR, which is mostly produced by the sun, GR is produced mainly by nuclear decay from high-energy-state atomic nuclei. Naturally occurring high-energy radioisotopes (i.e., potassium-40, uranium, and thorium) emit gamma radiation during their decay. GR is also generated as part of nuclear fission reactions, nuclear fusion reactions, lightning strikes, and cosmic rays (Fig. 1). The most common radioisotopes currently used in nuclear reactions are cobalt-60 (^{60}Co), plutonium-239 (^{239}Pu), uranium-238 (^{238}U), radon-222 (^{222}Rn), radium-226 (^{226}Ra), thallium-201 (^{201}Tl), iridium-192 (^{192}Ir), cesium-137 (^{137}Cs), and strontium-90 (^{90}Sr) (Kurnaz et al. 2007). Currently, the most common result of acute radiation exposure (i.e., gamma radiation and radioisotopes) is radiation sickness with nausea, vomiting, and headaches but increased exposure can lead to fatigue, weakness, hair loss, diarrhea, and low blood pressure (Ghirga 2010). Prolonged exposure to radioisotopes and radionuclides can lead to leukemia, leucopenia, and damage to the internal organs, mainly the kidneys (Ghirga 2010). Despite the harmful effects of radiation, many microorganisms have evolved molecular mechanisms to combat the deadly effects and survive in the presence of radioisotopes and radionuclides as discussed below.

Life under radiation

Outer space is one of the most harsh and hostile environments in existence, with high vacuum, temperature fluctuations, a full spectrum of extraterrestrial solar electromagnetic radiation, and cosmic ionizing radiation. Cryptoendolithic microbial communities and epilithic lichens have survived long term (1.5 years) on the outer surface of the International Space Station (Onofri et al. 2012). In another study, *Anabaena cylindrica*, *Nostoc commune*, and *Chroococcidiopsis* were exposed to extraterrestrial UV spectrum (>110 or 200 nm) for 548 days in low Earth orbit. It was found that cells of *A. cylindrica* and *Chroococcidiopsis* survived, but *N. commune* did not (Cockell et al. 2011). Table 1 lists several species of extremophiles isolated from various environments that have been shown to be resistant different types of radiation.

The genus *Deinococcus* is found to be radioresistant as vegetative cells to large doses of ionizing radiation isolated from deserts, oceans, lakes, and marine fish (Shashidhar and

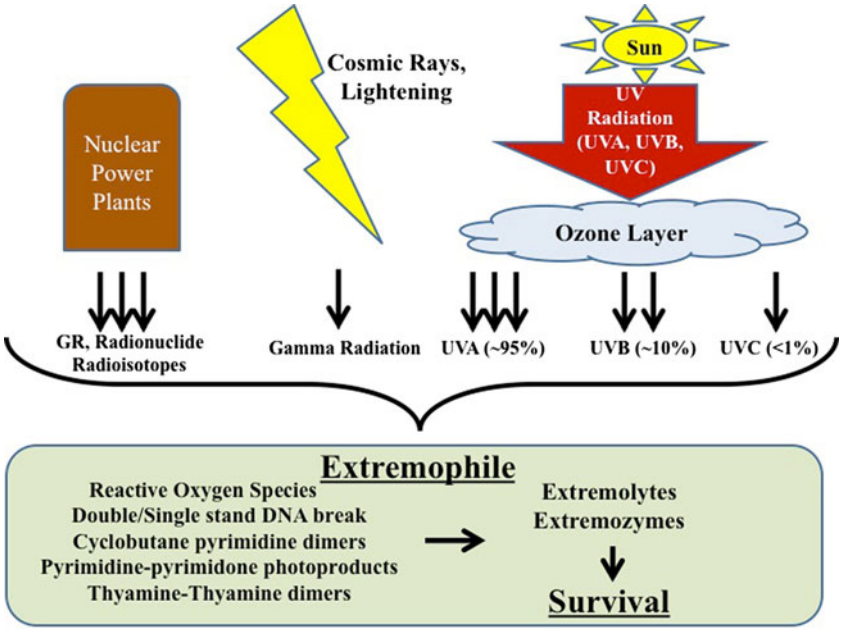

Fig. 1 Schematic of origin of different types of radiation and its effects on extremophiles

Bandekar 2009; Yuan et al. 2009a, b; Zhang et al. 2007c). It has been determined that specific proteins such as single-stranded DNA binding proteins and UVR-tolerant DNA repair enzymes present in *D. radiodurans* are extremely important for gamma radiation resistance. Surprisingly, a novel strain of *D. reticulitermitis* sp. nov. with a survival rate of 34 % at a dose of 100 J/m^2 UVR has also been isolated from a termite gut—not an environment regularly exposed to UVR (Chen et al. 2012). Table 2 summarizes several other species of *Deinococcus* found to be resistant to various forms of radiation.

Elevated resistance to gamma and UV radiation has been seen in *Hymenobacter xinjiangensis*, isolated from the desert of Xinjiang, China. This strain was also observed to be pink-pigmented, which may have played a role in the protection from UVR and gamma radiation (Zhang et al. 2007b). In *Rubrobacter radiotolerance,* the 24,000-Da monomer protein superoxide dismutase has been linked to the stability and survivability of this organism in the presence of GR (Terato et al. 2011). In a different study, it was reported that UVB radiation resulted in a 31.2, 14.4, and 6.3 % decrease in the use of amino acids, amines, and

Table 1 Radiation-resistant extremophiles isolated from different types of environments

Organism	Environment	Radiation	Reference
Cellulosimicrobium cellulans UVP1; *Bacillus pumilus* UVP4	Elevated land	UVR-type C	Gabani et al. (2012a)
B. pumilus SAFR-032	International Space Station	UVR	Vaishampayan et al. (2012)
Bacillus subtilis	Earth's megnetosphere	UVR	Nicholson et al. (2011)
B. subtilis HA101	Simulated Martian environment	UVR	Kerney and Schuerger (2011)
Hymenobacter xinjiangensis	Desert	UVR and gamma	Zhang et al. (2007a)
Rubrobacter radiotolerance	Unknown	Gamma	Terato et al. (2011)
Sphingomonas sp. RB2256	Unknown	UVR-type B	Joux et al. (1999)
Chroococcidiopsis sp.	Desert and hypersaline	X-ray	Billi et al. (2000)
Halobacterium salinarum	Unknown	X-ray	Robinson et al. (2011)
*Deinococcus radiodurans*R1	Canned meat	X-ray, UVR, and gamma	Shukla et al. (2007)
Bacillus megaterium	Lake	UVR	Zenoff et al. (2006)
Staphylococcus saprophyticus	Lake	UVR	Zenoff et al. (2006)
Acinetobacter sp. Ver3, Ver5, and Ver7	Lake	UVR-type B	Di Capua et al. (2011)
Streptomyces radiopugnans	Radiation–pollution	Gamma	Mao et al. (2007)

Table 2 Novel UVR and gamma radiation resistant strains of genus *Deinococcus* isolated from various environments

Organism	Source	Radiation	Radiation dosage	Reference
Deinococcus soli ZLM-202T	Arid soil, Xinjiang, China	UVR Gamma	>600 J/m^2 >10 kGy	Zhang et al. (2011)
Deinococcus humi MK03T	Soil, Seoul City, South Korea	UVR Gamma	Not tested >9 kGy	Srinivasan et al. (2012b)
Deinococcus daejeonensis MJ27T	Daejeon sewage, South Korea	UVR Gamma	Not tested >9 kGy	Srinivasan et al. (2012a)
Deinococcus depolymerans TDMA-24T	Fresh water, Misasa, Japan	UVR Gamma	>64 J/m^2 >16 kGy	Asker et al. (2011)
Deinococcus wulumuqiensis R12T	Radiation-polluted soil, China	UVR Gamma	>746 J/m^2 >10 kGy	Wang et al. (2010)
Deinococcus xibeiensis T13T	Radiation-polluted soil, China	UVR Gamma	>746 J/m^2 >10 kGy	Wang et al. (2010)
Deinococcus aerolatus 5516T-9	Air sample, Korea	UVR Gamma	Unspecified resistance Not tested	Yoo et al. (2010)
Deinococcus aerophilus 5516T-11	Air sample, Korea	UVR Gamma	Unspecified resistance Not tested	
Deinococcus aetherius ST0316T	Stratosphere, Japan	UVR Gamma	>1,000 J/m^2 >8 kGy	Yang et al. (2010)
Deinococcus aerius TR0125T	High atmosphere, Japan	UVR Gamma	Unspecified resistance >8 kGy	
Deinococcus aquiradiocola TDMA-uv53T	Freshwater, Misasa, Japan	UVR Gamma	Unspecified resistance >16 kGy	Asker et al. (2009)
Deinococcus aquatilis CUG 53370T	Water	UVR Gamma	Unspecified resistance Not tested	Kampfer et al. (2008)
Deinococcus aquaticus PB314T	Fresh water, South Korea	UVR Gamma	Not tested >6 kGy	Im et al. (2008)
Deinococcus caeni Ho-08T	Activated sludge, South Korea	UVR Gamma	Not tested >6 kGy	
Deinococcus radiomollis PO-04-20-132T	Mount Evans, CO, USA	UVR Gamma	>220 J/m^2 2.2 kGy	Callegan et al. (2008)
Deinococcus claudionis PO-04-19-125T	Mount Evans, CO, USA	UVR Gamma	>310 J/m^2 >3.6 kGy	
Deinococcus altitudinis ME-04-01-32T	Mount Evans, CO, USA	UVR Gamma	>550 J/m^2 >3.8 kGy	
Deinococcus alpinitundrae ME-04-04-52T	Mount Evans, CO, USA	UVR Gamma	>690 J/m^2 >4.0 kGy	
Deinococcus misasensis TDMA-25T	Radioactvie site, Misasa, Japan	UVR Gamma	Unspecified resistance >2.3 kGy	Asker et al. (2008)
Deinococcus roseus TDMA-uv51T	Radioactvie site, Misasa, Japan	UVR Gamma	Unspecified resistance >2.3 kGy	
Deinococcus peraridilitoris KR-200T	Coastal desert, Chile	UVR Gamma	Not tested >10 kGy	Rainey et al. (2007)
Deinococcus cellulosilyticus 5516J-15T	Air sample, Jeju Island, Korea	UVR Gamma	Unspecified resistance Not tested	Weon et al. (2007)
Deinococcus deserti VCD115T	Sahara Desert, Morocco	UVR Gamma	>500 J/m^2 >7.5 kGy	de Groot et al. (2005)

carboxylic acids and an increase in consumption of carbohydrates and phenolic compounds by 42.3 and 11.6 %, respectively, indicating a reduction in protein synthesis as a metabolic strategy to enhance survival (Santos et al. 2012).

An increase in trichloroacetic-acid-precipitable radioactivity has been reported in the culture supernatant of *Chroococcidiopsis* strains after X-ray irradiation, indicating an upregulation of excision processes involved in DNA

repair pathways (Billi et al. 2000). It was recently reported that exposure of *Halobacterium salinarum* to various types of ionizing radiation induced the expression of ROS-scavenging enzymes as well as non-enzymatic antioxidant processes (Robinson et al. 2011). It was hypothesized that the carotenoids might function to absorb the radiation, allowing the survival of the bacterial strains. Another Gram-positive bacterium, *Kineococcus radiodurans* sp. nov., isolated from a radioactive work area, showed resistance to 3.5 kGy of gamma radiation, carotenoids with absorption maxima at 444, 471, and 501 nm (Phillips et al. 2002).

Microbial molecular elements under radiation

The modulated molecular elements from radiation-resistant extremophiles may be useful for targeting radiation-prone disease types. It is of interest to understand the changes in the genomics, proteomics, and metabolic profiles (i.e., metabolomics) of radioresistant organisms grown under radiation to gain an understanding of how these organisms survive (Singh 2006; Singh et al. 2011). The induction of *uvrA* in *D. radiodurans* reveals UvrABC system protein A with functions including DNA repair and survival of the organism in UVR. Additional proteins with differential regulation identified include *recA, recD, recF, recG, recO, mutS, mutL, ruvB*, etc. (Singh and Gabani 2011). Our studies revealed that microorganisms, i.e., *Cellulosimicrobium cellulans* (UVP1) and *Bacillus pumilus* (UVP4), grown under radiation show differential expression of many yet to be identified proteins and metabolites (Gabani et al. 2012a). In the gamma-radiation-resistant *Bacillus* sp. HKG 112, two proteins, 38 kDa flagellin and 86.5 kDa S-layer protein, showed significant changes after radiation exposure (Gupta et al. 2011). Liedert et al. (2010) reported that in *D. geothermalis*, there were 34 abundant proteins that had no known function; these might relate to the extreme stress tolerance of the organism.

Several studies have focused on the potentially novel proteins in the nucleoids of radioresistant organisms. A comparative proteomics analysis of *D. radiodurans* and *Deinococcus deserti* revealed that the histone-like DNA-binding protein HU was the most abundant protein among the nucleoid-associated proteins (de Groot et al. 2005). *D. radiodurans* contains two *LexA* homologues, *LexA1* and *LexA2*, which are hypothesized to be transcriptional regulators associated with DNA damage response. It was found that in a *LexA2* disruptant strain, a *pprA* promoter was activated and a subsequent increase in the novel-radiation-inducible protein PprA noticed as reviewed in Singh and Gabani (2011). The presence of highly efficient DNA repair enzymes in *D. radiodurans* allows it to repair hundreds of double-stranded DNA breaks. Deletion of a novel polymerase, X family DNA polymerase, showed a decrease in the rate of repair of double-stranded DNA breaks and also an increase in sensitivity to GR (Leulliot et al. 2009). In addition, the increased expression levels of general stress protein DR1199 in *D. radiodurans* may be involved in the detoxification of the cell from ROS (Leulliot et al. 2009).

In addition to the identification of genes, proteins have been studied to determine their function in radiation resistance. In *Amphibacillus* sp. KSUCr3, a membrane-bound chromate reductase (for reduction of Cr(VI)) was found to be maximally active at 40 °C and a pH of 10.5 (Ibrahim et al. 2012). In *Chlamydomonas* sp. ICE-L isolated from Antarctic ice, the presence of UVB radiation increased the levels of Hsp70 protein approximately threefold (Liu et al. 2010). It was reported that in the presence of UVR, the expression of RadB and RadA in *Sulfolobus tokodaii* was increased. It was also reported that RadA and RadB preferred to bind to ssDNA and ssDNA-dependent ATPase (Sheng et al. 2008).

Dictyostelium discoideum, known as a DNA damage extremophile, is able to survive extremely high doses of radiation and DNA crosslinking agents due to the presence of the Fanconi anemia pathway (FA), translesion synthesis (TLS), and nucleotide excision repair. Zhang et al. (2009) revealed that disruption of Xpf nuclease in *D. discoideum* resulted in extreme hypersensitivity to crosslinks and radiation. It was also revealed that Xpf nuclease functioned with FA and TLS gene products (Zhang et al. 2009). Another study found that the protein Dclre1 was responsible for repair of double-strand breaks caused by radiation (Hsu et al. 2011). Muller-Taubenberger et al. (2011) reported that the presence of Dot1 contributed to UV radiation resistance in *D. discoidium*. Nath and Bharathi (2011) reviewed transcripts and the translational pattern of stress proteins in extremophiles.

Benefits of radiation-resistant extremophiles

The secondary metabolic reserves of extremophiles (i.e., extremolytes and extremozymes) are not involved in the direct survival, growth, development, and reproduction of the organism. However, the presence of these secondary metabolites does affect microbial survival when exposed to radiation. The unique features of extremolytes allow for far-reaching applications in biotechnology, ranging from bioremediation of nuclear waste products to the production of medically important drugs reviewed in Singh and Gabani (2011).

Therapeutic implications of radiation-resistant extremolytes

Progress has been made in searching for extremophiles that produce extremolytes with indications for anticancer drugs.

To date, several UVR-protective compounds have been isolated from UVR-resistant extremophiles, including Mycosporine-like amino acids (MAAs), scytonemin, ectoine, bacterioruberin, sphaerophorin, pannarin, and melanin. Table 3 summarizes different microbial metabolic products that have been isolated from UVR-resistant extremophiles and their therapeutic implications.

MAAs are characterized by a cyclohexenone or cyclohexenimine core conjugated with the nitrogen moiety of an amino acid, and are synthesized by the shikimic acid pathway via 3-dehydroquinic acid and 4-deoxygadusol, a known strong antioxidant (Shick and Dunlap 2002). MAAs have been isolated from red algae, sea stars, corals, dinoflagellates, and cyanobacteria with UVB irradiation (Shick and Dunlap 2002). A novel mycosporine isolated from the lichenized ascomycete *Collema cristatum* showed protection against UVR-induced membrane destruction, pyrimidine dimer formation, and erythema in cultured human keratinocytes (Russo et al. 2008). Due to the ability of MAAs to absorb UVR, they present as compounds that can be added to UV sunscreens. It has been found that the sunscreen ability of MAAs is greatly enhanced when they are applied extracellularly, indicating their role in photoabsorption (de la Coba et al. 2009); they can be used in the cosmetic industry to enhance the protective effects.

An alternate physiological role for MAAs is as antioxidants. Some forms of MAAs (Table 3) have been known to scavenge ROS produced by UVR exposure. In other species of extremophiles that produce MAAs, the biosynthesis can also be induced by osmotic shocks. A formulation of MAAs (Porphyra-334 and Shinorine) has been shown to maintain the antioxidant defense system of the skin in the presence of UVR-induced skin damage in mice (de la Coba et al. 2009). The authors (de la Coba et al. 2009) also showed that the formulation prevented stratum corenum, malphigian, dermal, and hypodermal thickening. Various other MAAs that have been shown to have antioxidant as well as photoprotective roles include palythine, asterina, palythinol, and palythene (Llewellyn and Airs 2010). Gao and Garcia-Pichel (2011) broadly reviewed the biosynthesis and the biochemistry of MAAs. While the MAAs are promising, their direct therapeutic implications as drug candidates have yet to be studied.

In addition to MAAs, scytonemin, a yellow to brown and lipid-soluble compound from cyanobacteria, has also shown promise as a sunscreen. Scytonemin is a symmetrical indole-alkaloid consisting of fused heterocyclic units, connected via a carbon–carbon bond (Fig. 2). This complex ring structure and its conjugated double bonds make the compound particularly stable and allow for the absorption of UVR. Spectrophotometric analysis has revealed that the sheath of scytonemin is effective in shielding the cells from incoming UVR but not visible light. Mechanisms to induce the production of scytonemin need to be identified in order to explore its biotechnology implications. Several studies have revealed that temperature and photo-oxidative stresses

Table 3 Therapeutic role of extremolytes isolated from UVR-resistant extremophiles

Compound class	Chemical	Organism(s)	Therapeutic role	References
Mycosporine-like amino acids (MAAs)	Palythine	*Gyrodinium galatheanum* and *Gyrodinium venificum*	Sunscreen and erythema	Llewellyn and Airs (2010)
	Asterina-330	*Palythoa tuberculosa* and *Palmaria palmate*	Antiproliferative agent	Yuan et al. (2009c)
	Palythinol	*Palythoa tuberculosa*	Antioxidant activity	
	Shinorine	*Mastocarpus stellatus*	Sunscreen, antioxidant activity	Aguilera et al. (2002)
	Porphyra-334	*Palmaria decipens, Porphyra tenera* and *Microcoleus* sp.	Antioxidant activity and sunscreen	Aguilera et al. (2002 and de la Coba et al. 2007)
	Palythene	*Pseudoterranova decipiens* and *Alexandrium tamarense*	Antiproliferative agent and antioxidant activity	Conde et al. (2003)
	Usujirene	*Synechocystis* sp.	Sunscreen	Conde et al. (2003 and Zhang et al. 2007a)
Scytonemin		*Nostoc punctiforme*	Sunscreen, protein kinase inhibitor, and antiproliferative agent	Soule et al. (2009)
Ectoine		*Heliamphora elongate*	Sunscreen and antioxidant activity	Buenger and Driller (2004)
Bacterioruberin		*Rubrobacter radiotolerans* and *Halobacterium salinarium*	DNA repair and sunscreen	Asgarani et al. (2000)
Sphaerophorin	Depside	*Lichens*	Sunscreen, antioxidant activity, and apoptotic activity	Russo et al. (2008)
Pannarin	Depsidone	*Lichens*	Sunscreen, antioxidant activity, and apoptotic activity	Russo et al. (2008)
Melanins		*Sporothrix schenckii* and *Cryptococcus neoformans*	Sunscreen, antioxidant activity and immune stimulatory activity	Romero-Martinez et al. (2000)

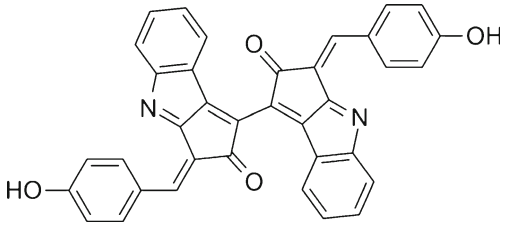

Fig. 2 Chemical structure of scytonemin

alone do not increase the levels of scytonemin in cyanobacteria (Dillon et al. 2002; Fleming and Castenholz 2008). However, a combination of UVA irradiation and the previously mentioned stresses is effectively able to increase levels of scytonemin (Dillon et al. 2002) (Fig. 3). Desiccation along with lack of fixed nitrogen and UVA irradiation has been reported to trigger the production of scytonemin in culture medium (Fleming and Castenholz 2008).

Soule et al. (2009) studied the biosynthesis of scytonemin, governed by a set of 18 gene clusters (NpR1276 to NpR1259), in *Nostoc punctiforme* ATCC 29133. In the proposed model, the genes downstream of the open reading frame (ORF) NpR1273 (*scyD*) encoded enzymes in the aromatic amino acid pathways. Furthermore, UVA radiation was able to induce *trp* and *typ* genes leading to the production of tryptophan and *p*-hydroxyphenyl pyruvate monomers likely to be involved in the biosynthesis of scytonemin (Soule et al. 2009).

Scytonemin has also been investigated as an ATP-competitive inhibitor of polo-like kinases (PLKs). Because PLKs control many oncogenes, become the target in cancer research for many years. Stevenson et al. (2002) showed that scytonemin was able to inhibit PLK1 in flash plate screening assays and showed the ability to treat hyperproliferative disorder (Fig. 3). In another study, scytonemin-mediated inhibition of PLK1 was able to induce apoptosis in osteosarcoma and other cancer cell types, suggesting that scytonemin may provide a novel pharmacophore for the development of protein kinase inhibitors as antiproliferative and anti-inflammatory drugs (Duan et al. 2010).

Several other compounds that have shown potential as therapeutics are ectoine, bacterioruberin, sphaerophorin, and pannarin. Buenger and Driller (2004) showed that UVA-irradiated human keratinocytes were protected from damage when ectoine was applied. Ectoine has also been shown to prevent damage induced by bacterial lipopolysaccharide by elevating levels of Hsp70 protein (Buommino et al. 2005). Bacterioruberin isolated from *Rubrobacter radiotolerans* may have a potential use in human therapeutics to repair damaged DNA strands caused by ionizing radiation and prevent skin cancer (Asgarani et al. 2000). Sphaerophorin and pannarin, isolated from lichens, have been evaluated for their ability to repair DNA damage induced by hydroxyl radicals, nitric oxide, and superoxide anion (Russo et al. 2008).

Ectoine has been widely studied for its ability to protect skin against water loss, desiccation, and UV damage (Buenger and Driller 2004). It was found that ectoine was able to protect skin from damage caused by sodium dodecyl sulfate and water loss as well as having a prophylaxic effect against dry skin. It has been proposed that this mechanism underlies the ability of Ectoin to block second messenger

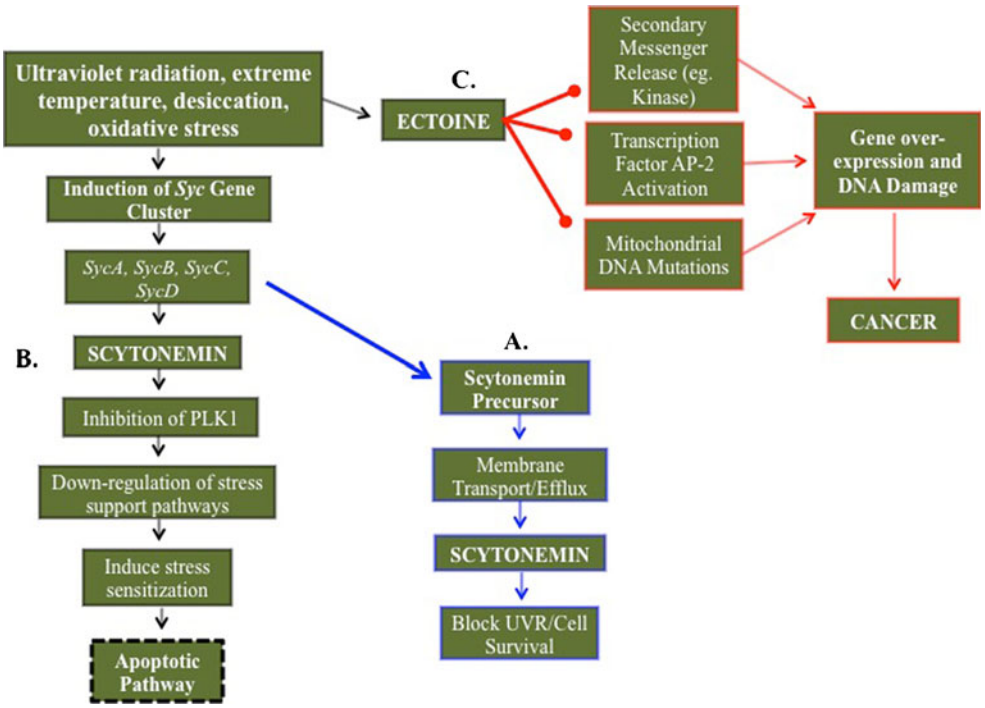

Fig. 3 Production of scytonemin with exposure of UVR. *A* Use of scytonemin as sunscreen product where scytonemin absorbs UVR resulting in cell survival. *B* Hypothetical pathway in which scytonemin inhibits PLK1 resulting in downregulation of stress support pathways and ultimately destruction of cancer cells via apoptosis. *C* Ectoine is a cell cycle blocker and acts by preventing the induction of secondary messengers, transcription factor AP-2 activation, and mitochondrial DNA mutations and ultimately leading to prevention of cancer induced by UV radiation or other extreme conditions

systems, transcription factor AP-2, intracellular adhesion molecule-1 expression, and prevent mitochondrial DNA mutations (Fig. 3c). In addition, the effect of ectoine is especially pronounced within the Langerhans cells, which present antigens crossing the skin barrier and induce T cell immune response. (Buenger and Driller 2004). In another study, it was found that ectoine played a cytoprotective role when cells were exposed to bacterial lipopolysaccharides (Buommino et al. 2005).

Biotechnological implications of radiation-resistant extremolytes

In addition to the therapeutic implications, recent studies have also implicated many biotechnological applications of radiation-resistant extremolytes. The use of radiation-resistant extremophiles in the bioenergy sector has not been extensively studied. The current challenge is to find an efficient and inexpensive process for the degradation of complex carbohydrates to produce bioethanol. Gabani et al. (2012a) reportedly isolated two novel strains of *C. cellulans* UVP1 and *B. pumilus* UVP4 that were able to survive in the presence of 1.03×10^{6} J/m^{2} and 1.71×10^{5} J/m^{2}UVC, respectively. Both *C. cellulans* and *B. pumilus* showed a tremendous ability to degrade cellulose under varying physical and chemical conditions (high temperature, high salt content, and acidic pH).

Radiation-resistant extremolytes have also been implicated for the bioremediation of nuclear waste. The enzyme c-type cytochrome in *Shewanella putrefaciens* and *Geobacter sulfurreducens* (Lloyd et al. 2003) has been found to reduce soluble uranium radioisotopes into insoluble species. In *Desulfovibrio desulfuricans*, it was observed that a Ni-Fe hydrogenase was able to reduce Tc (VIII) (Luca et al. 2001). Fujimoto and Morita (2006) isolated a novel strain of *Halomonas* sp. that was able to remove technetium from solution by making it insoluble. Kim et al. (2012) showed *Geobacter* sp. and *Rhodoferax ferrireducens* had the metabolic potential to reduce radioisotopes via enzymatic mechanisms similar to those discussed above.

Indirect enzymatic reduction of radionuclides has also been implicated as a way to bioremediate soil contaminated with nuclear waste. For this process, metal-reducing and sulfate-reducing microorganisms can be used to indirectly reduce soluble radionuclides. In this mechanism, the oxidation of organic compounds or hydrogen is coupled with the reduction of iron Fe(III) or sulfur S(IV) in the form of sulfate. This product can then be reduced further into multi-component insoluble species (van Hullebusch et al. 2005). For example, sulfate-reducing bacteria such as *Micobacterium flavescens* are capable of producing compounds such as organic acids, siderophores, and extracellular metabolites when grown in the presence of U, Th, Am, and Pu.

In addition to being reduced to their insoluble form, radionuclides can be adsorbed by radiation-resistant extremophiles. A brown marine algae *Cystoseira indica* showed effective adsorption of uranium radioisotope (Seyrig 2010). Other microorganisms showing effective adsorption of radionuclides include *Citrobacter freudii* and *Firmicutes* sp. Wu et al. (2006) developed a method to bioremediate high concentrations of uranium radioisotopes with the addition of ethanol.

Radioresistant organism *D. radiodurans* has been proven effective in bioremediation of heavy metals from acidic and neutral water (Misra et al. 2012). Misra et al. (2012) found that *D. radiodurans* was able to remove 70 % of 1 mM input uranium solution. In addition to heavy metals, *D. radiodurans* has been used for bioremediation of phthalate esters, which are widely used in cosmetics, perfumes, and plasticizers (Liao et al. 2010). This ability of *D. radiodurans* for bioremediation can be multiplied to include even more substrates with proper genetic engineering of the organism.

Many therapeutic and industrial applications of extremolytes and extremozymes have been patented; some from the past decade are summarized in Table 4. Verenium Corporation holds nine different patents for the development of thermostable enzymes via mutagenesis of thermophiles. This allows the corporation to manufacture enzymes that are stable and twice as efficient at high temperatures (>60 °C). Biotop AG uses a continuous fermentation method to produce Ectoin on a large scale for applications such as cosmetics and therapeutics. In a clinical trial conducted by Biotop AG, it was found that patients receiving eye drops and nasal sprays of ectoin, the symptoms of acute allergic rhinitis were significantly reduced.

Limitations and challenges in a 5-year view

The development of new-generation therapeutics, such as sunscreens and anti-cancer metabolites, with lack of allergenic potential in humans is promising (Siezen 2011). Because metabolites from extremophiles are naturally selected through evolution, they are considered to be environmentally friendly. The recent developments in "-omics"-based technologies (genomics, proteomics, and metabolomics) could assist in microbial biosynthesis of potential metabolites using genetically engineered microorganisms in bioreactors (Singh 2006; Singh et al. 2011). Several extremolytes and/ or manufacturing processes have been patented for use in pharmaceutical and cosmetic applications (Table 4). Many MAAs (i.e., Helioguard 365 and Helionori) from extremophiles are currently commercialized as sunscreen products for UVR protection due to their broad UVR absorption spectrum (de la Coba et al. 2007). In addition, scytonemin has potential to be the next "all in

Table 4 Major patents in last 10 years for extremophiles revealing potentials of extremolytes and extremozymes

Patent No.	Year	Authors	Patent description
EP2008/006959	2009	J. Krutmann, G. Lentzen, and T. Schwarz	Osmolytes for the treatment of allergic or viral respiratory diseases
WO/2008/086221	2008	CW. Podella, JW. Baldridge, and AH. Michalow	Enhanced oil recovery compositions comprising proteins and surfactants and methods of using the same
20110286946	2011	T. Oliphant and DA. Ashley	Sunscreen compositions containing hydrolyzed Jojoba esters for improved water resistance
20080279874	2008	F. Logonzo, G. Krishnamurthy, WW. Ding, XC. Tan, and JH. Patel	Compositions and methods for modulation of PLK1 Kinase activity
20100022512	2010	WA. Wisdom, AA. Colvin, and S. Koppenol	Compositions of CHK1 inhibitors and cyclodextrin
20070122464	2007	J. Krutmann	Use of osmolytes obtained from extremophilic bacteria for producing medicine for the external treament of neurodermatitis
20060246007	2006	J. Krutmann	Use of osmolytes obtained from extremophilic bacteria, the production of inhalable medicaments for the prophylaxis and treatment of pulmonary and cardiovascular diseases, and an inhalation device comprising an osmolyte as an active agent component
EP0363125	2010	M. Stoffel and P. Akpinar	Stimulation of pancreatic beta cell proliferation
20120070389	2012	GJ. Fisher, Y. Xu, and JJ. Voorhees	Methods for identifying treatments that treat and/or prevent UV irradiation inducing photoaging
20110262505	2011	G. Athwal	Seaweed-derived cosmetic compositions
WO/2012/112189	2012	C. Huang and JL. Ebersole	Novel method to generate commercially useful oils in algae
8269066	2012	DF. Loussaert, DO. Neill, CR. Simmons, and H. Wang	Nitrate reductase from red algae, compositions and methods of use thereof
20110038882	2011	B. Chiang, C. Chang, Y. Lin, K. Chu, H. Chou, and J. Jeng	Methods for treating allergic disease
EP1476562	2005	IC. Chew, SL. Lee, and HW. Talbot	Overexpression of extremozymes genes in pseudomonas and closely related bacteria
20070014734	2007	JP. O'donnel, W. Ownes, J. Duncan, and A. Shaw	Glucuronidated nevivolol metabolites
7763649	2010	SF. Lockwood, S. O'Malley, DG. Watumull, LM. Hix, H. Jackson, and G. Nadolski	Carotenoid ether analogs or derivatives for controlling connexin 43 expression
20050059659	2005	SF. Lockwood, S. O'Malley, DG. Watumull, LM. Hix, H. Jackson, and G. Nadolski	Carotenoid ether analogs or derivatives for controlling C-reactive protein levels
7723327	2010	SF. Lockwood, S. O'Malley, DG. Watumull, LM. Hix, H. Jackson, and G. Nadolski	Carotenoid ether analogs or derivatives for inhibition and amelioration of liver disease

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one" drug to prevent skin damage from UVR, cancer, and inflammation (de la Coba et al. 2009). However, because the biological activity of scytonemin is not well understood, further studies are required to understand its potential effects in humans. Lastly, melanin is widely used in the manufacturing of photo-protective sunscreens, but the production of melanin is becoming more and more expensive due to its complex molecular structure. Bacterial production of melanin promises an inexpensive way of obtaining melanin relatively easily (Liu and Simon 2003).

Current and future perspectives on extremophile metabolism, genetics, and physiology will likely yield new breakthroughs in biotechnological applications. In addition, future research in refinement of culture media, cell–cell communication, and high-throughput innovations can lead to novel insights into environments that were once thought to harbor no forms of life.

Despite current breakthroughs in the area of biotechnology, there are always limitations involved in producing effective extremolytes for human usage. One of the main limiting factors for the commercialization of extremozymes and extremolytes is the identification of the correct media to maximize production. The media need to have suitable nutrient, pH, and temperature levels (Copeland et al. 2012). Even slight variations in pH and temperature could greatly influence the metabolism of extremophiles. The amount of essential nutrients required also limits the product concentration; however, to overcome the nutrient limitation, fed-batch cultivation has been adapted widely and is currently used most often for cell culture processes (Copeland

et al. 2012). In addition, product recovery remains one of the most limiting factors for commercialization of extremozymes and extremolytes.

Conclusions

The ecology of various radioresistant microorganisms and their potential in biotechnology are imperative in today's modern technology. Studying the biology, genetics, and molecular mechanisms of extremophiles is essential in understanding the limits of life and may help us answer the question of whether life exists in extreme conditions on other planets. Here, we have described various radioresistant organisms and their habitats, which are unfriendly to most other forms of life. Knowledge of the evolution of extremophiles in extreme environments will increase our understanding of the evolutionary process and the genetic and molecular consequences of extreme environments. The biotechnological implications of radioresistant extremophiles are also of great importance. Radiation-resistant extremophiles provides limitless opportunities in human therapeutics, pharmaceuticals, biotechnology, and biodegradation of toxic and radioactive compounds. Because of the ability of extremophiles to survive in high radiation, the various metabolites and enzymes they produce can be manufactured and used for human therapeutics as well as bioremediation of radioactive compounds in nuclear waste fields. However, increased research efforts need to be made to fully investigate the potential of radiation-resistant extremophiles in therapeutic and biotechnological applications.

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