Perspectives on the microorganism of extreme environments and their applications

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ABSTRACT

Extremophiles are organisms that can survive and thrive in conditions termed as “extreme” by human beings. Conventional methods cannot be applied under extreme conditions like temperature and pH fluctuations, high salinity, etc. for a variety of reasons. Extremophiles can function and are adapted to thrive in these environments and are sustainable, cheaper, and efficient, therefore, they serve as better alternatives to the traditional methods. They adapt to these environments with biochemical and physiological changes and produce products like extremolytes, extremozymes, biosurfactants, etc., which are found to be useful in a wide range of industries like sustainable agriculture, food, cosmetics, and pharmaceuticals. These products also play a crucial role in bioremediation, production of biofuels, biorefinery, and astrobiology. This review paper comprehensively lists out the current applications of extremophiles and their products in various industries and explores the prospects of the same. They help us understand the underlying basis of biological mechanisms exploring the boundaries of life and thus help us understand the origin and evolution of life on Earth. This helps us in the research for extraterrestrial life and space exploration. The structure and biochemical properties of extremophiles along with any possible long-term effects of their applications need to be investigated further.

Introduction

Extremophiles have developed certain adaptations to survive in inhospitable or extreme environmental conditions eg: “water cages” in halophiles, reduced pore sizes in acidophiles, etc. (Coker, 2019). Extremophiles that can survive in more than one type of extreme environment are called polyextremophiles (Gupta et al., 2014). Extremolytes are small organic molecules, either synthesized or taken up by extremophilic bacteria, that accumulate inside the cells. They protect molecules and cell structures of extremophiles by forming and stabilizing protective water layers (Becker and Wittmann, 2020). Extremozymes, enzymes isolated from extremophiles, are highly stable at extreme temperature and pH and are resistant to denaturing agents, detergents, organic solvents, chaotropic agents (Gupta et al., 2014). They work as biocatalysts in the food, detergent, pulp, and paper industries. Some extremozymes such as cellulases, proteases, lipases, esterases, catalases, keratinases, peroxidases, etc. have a wide variety of applications in several industries (Drioli and Giorno, 2018). Biosurfactants, amphiphilic surface-active biomolecules produced by extremophiles, have applications in pharmaceutical, medicine, food, and agricultural industries since they are less toxic, more biodegradable, more selective and specific than chemical surfactants and they reduce surface and interfacial tension (Shekhar et al., 2015; Saha and Rao, 2017; Markande et al., 2021; Rath and Srivastava, 2021; Md, 2012). Extremophiles produce carotenoids, natural hydrophobic pigments capable of producing colors like bright yellow, red, etc., which act as precursors for vitamin A, as growth regulators, and as antioxidants as they help minimize the damage caused by oxidation and high sun exposure on cells and therefore, can be used in pharmaceutical, cosmetics, food and textiles industries (Rodrigo-Banos et al., 2015). Looking at the current global energy trends, utilization of extremophiles to produce biofuels is an extremely efficient and sustainable way to...
produce bioenergy (Zhu et al., 2020). Extremophiles help in bioremediation, which is the clean-up of contaminated and polluted environments, through processes that include transformation, immobilization or degradation of contaminants or pollutants into nontoxic substances by biodegradation, biosorption, bioemulsification, bioreduction etc. (Donati et al., 2019; Marques, 2018; Jeong and Choi, 2020). In Astrobiology, extremophiles play a significant role in providing information on the origin and evolution of life on Earth as they throw light to their survival mechanisms. Extremophiles from the Planetary Field Analogue Sites (PFA sites) provide beneficial information on boundaries of life and habitatibilty beyond our planet and can be used as model organisms for studying the survival of life in outer space, LEO (Low Earth Orbit) and in the International Space Station (ISS) (Thombre et al., 2020).

Protein adaptations in extremophiles

To survive in harsh environmental conditions, extremophiles require special survival mechanisms, including genetic changes which are followed by further change in protein sequence and structure (Basak et al., 2020). Table 1 shows some of the protein adaptations developed by extremophiles to survive in various habitats (their different habitats are shown in Fig. 1).

Thermophiles: Extreme temperatures cause irreversible folding of the proteins which in turn exposes the hydrophobic cores resulting in aggregation (Basak et al., 2020). Therefore, oligomerization and large hydrophobic core, increased number of disulfide bonds, surface charges, and salt bridging are found in thermophilic and hyperthermophilic proteins to stabilize them (Hunter, 2018; Basak et al., 2020).

Psychrophiles: Psychrophiles have the adaptations to survive their cold habitats based on their Cold Shock Proteins (CSPs) and Cold Acclimation Proteins (CAPs). CSPs are expressed under mild conditions while CAPs are overexpressed after extreme cold shocks, up to 4 °C. The protein structures are modified as they replace alanine with glutamic acid, lysine by arginine, and valine is replaced by alanine (Basak et al., 2020; Kumar et al., 2018). Conformational flexibility of enzymes due to reduced rigidity of protein core and reduced interactions between interdomains gives them added stability and specificity at low temperatures (Hunter et al., 2018).

Halophiles: Halophiles have evolved various adaptations to thrive in extremely saline environments as salt acts as a key element in altering the solubility, stability, and conformation of the protein (Mokashe et al., 2018). Osmotic pressure within the cell is maintained by preventing the entry of inorganic salt as well as by synthesizing organic osmolytes (Raval et al., 2018). In regions of extremely high salt concentrations (>0.1 M), salt and water form an ionic lattice, and this in turn reduces the availability of water to internal proteins (Basak et al., 2020). Thus due to dehydration, the interaction between hydrophobic amino acids increases and they form aggregates. Halophilic proteins are unique and have relatively greater salt bridge when compared to those proteins found in normal conditions e.g., P45 protein (protect denaturation, resist deactivation of malate dehydrogenase), transcription binding protein (TBP), and TATA-box-binding protein (enhanced DNA interaction) (Kumar et al., 2018). Other adaptations include increased acidic residues, decreased hydrophobic residues, salt-dependent folding, halophilic peptide insertions, etc. (Hunter et al., 2018).

Acidophiles: In acidic conditions, the charges of polar charged residues and proteins are changed due to protonation, thus decreasing the permeability of the cell membrane and maintaining the proton gradient across it. Cytoplasm buffering is observed in acidophiles which maintain a neutral intracellular pH. Acidophiles decrease their membrane permeability by decreasing their membrane pore size (Basak et al., 2020). For example, an exceptionally large external loop is observed in Thiobacillus ferrooxidans which reduces the pore size and ion selectivity (Kumar et al., 2018). Negative surface charge is increased in acidophiles (Hunter et al., 2018).

Alkaliphiles: Alkaliphiles have an enzyme named phosphoserine aminotransferase (vitamin B6-dependent) which can form a homodimer (Kumar et al., 2018). They are structurally similar to their mesophilic counterparts, but they differ in having increased hydrogen bonds, increased hydrophobic interactions at the dimer interface, and negatively charged amino acid residues and these variations enhance their stability and activity in extremely alkaline conditions (Kumar et al., 2018; Basak et al., 2020).

Piezophiles: Piezophilic proteins show the presence of hydrophobic cores, smaller amino acids, and multimodulation of protein by hydrogen bonding between protein subunits (Basak et al., 2020). They also have fewer proline and glycine residues which break and destabilize helixes and reduce compressibility by decreasing conformational space, therefore, reducing protein flexibility (Hunter et al., 2018). Thermococcus barophilus accumulates small organic osmolyte mannosylglycerate that minimizes the hydration layer around the protein at ambient pressure (Brininger et al., 2018). Bacteria living in deep-sea hydrothermal vents have a pressure-sensing operon system that regulates their growth according to temperature and pressure (Basak et al., 2020; Kumar et al., 2018).

Radiophiles: Ultraviolet radiation in sunlight forms dimers between the strands and therefore alters the molecular structure of DNA (Roy, 2017). Extremophiles can repair the radiation-damaged DNA efficiently and therefore, can survive in zones of high ultraviolet (UV) and ionizing radiation (IR). Fanconianemia pathway (FA), translesion synthesis (TLS), and nucleotide excision repair (XPF), observed in Dictyostelium discoideum, help it survive high radiations and cross-linking agents (Kumar et al., 2018). Another extremophile, Deinococcus radiodurans, has a unique condensed genomic structure which helps it reduce the nucleic acid damage caused by reactive oxygen species (ROS) formed by ionizing radiation. Due to the tightly linked and ring-like nuclei, D. radiodurans protects its DNA from damage and repairs it efficiently (Jin et al., 2019b).

Industrial applications of extremophiles

Agricultural industry

Extremophiles play an extremely crucial role in maintaining plant growth and crop productivity in regions with adverse conditions like low temperature, high salinity, drought conditions, etc. as biofertilizers, bioinoculants, and biocontrol agents (Yadav and Saxena, 2018).

Biofertilizers and bioinoculants

These microorganisms act as biofertilizers and bio-inoculants since they help in nutrient cycling, nutrient fixation, mineralization, and solubilization and can be used as substitutes to conventional agricultural technologies. They also have resistance-inducing characters and can be applied as biocontrol agents. (Yadav and Saxena, 2018; Tiwari et al., 2019). Their genetic diversity can be exploited in the agro-industrial sector, therefore, replacing chemical-based products and promoting cost-effective, eco-friendly, and sustainable agriculture (Yadav, 2021; Chakraborty and Akhtar, 2021). Soil salinity (a high concentration of soluble sodium salts in soil) causes soil degradation and inhibits the growth of plants and is a major obstacle in the agricultural industry (Otlęwska et al., 2020). Fig. 2 shows the different applications of extremophiles. Plant Growth Promoting Bacteria (PGPB) can be epiphytic, endophytic, and rhizospheric and promote plant growth by producing phytohormones (indole acetic acids or IAA, gibberellic acids or GA, cytokinin), biological nitrogen fixation, solubilizing and binding nutrients (phosphorus, potassium, zinc) and show 1-aminocyclopropane-1-carboxylate (ACC) deaminase activity (Yadav et al., 2018).

Extremophiles like Enterobacter and Gluconacetobacter help in nitrogen fixation. Methylobacterium, Microbacterium, and Ochrobactrum produce phytohormones. Halophilic extremophiles under salinity stress promote seedling germination, roots and shoot length, biomass, yield and increase the chlorophyll content. Haloarcula argentinensis and
### Extremophiles - Types, adaptations and their sources.

| References | Examples | Source | Adaptations | Growth conditions | Extremophiles |
|------------|----------|--------|-------------|-----------------|---------------|
| (Singh et al., 2019; Coker, 2019; Gupta et al., 2014; López-Ortega et al., 2021) | Pyrobaculum, Pyrococcus, Thermotoga marine, and Aquifex pyrophilus | Hot springs and deep-sea, Submarine hydrothermal vents. Yellowstone National Park, USA. | Protein thermostability by increased bond networks decreased the length of surface loops and higher core hydrophobicity. Ether-based lipids and fused lipid bi-layer in archaea resistant to hydrolysis. | Optimum: Extreme thermophiles (60-80 °C), Hyper-thermophiles (>80 °C). Extreme: 110 - 121 °C | Thermophiles (Temperature) |
| (Singh et al., 2019; Coker, 2019; Gupta et al., 2014; López-Ortega et al., 2021) | Synechococcus lividus, Psychodesmomonas | Polar regions and glaciers, subterranean, upper atmosphere, Antarctica coastal, Island. | Near neutral cytoplasm. -very charged cell wall. The secondary cell wall is made acidic by teichuronic acid or polyglutamic acid. Membrane pore size is reduced. The net potential across the membrane is positive. Impermeable cell membrane , therefore, H+ active transport. | Optimum: Low temperature (<15 °C) Extreme: -17 to -20 °C | Alkaliphiles (pH) |
| (Singh et al., 2019; Gupta et al., 2014; López-Ortega et al., 2021) | Arthrobacler, Natronobacterium, Psychrobacter, Vibrio | Soda lakes, Lake Abijanta, Ethiopia. | Regulate fluidity of membranes by increasing the no. of unsaturated fatty acids. Synthesizing temperature-related chaperones, anti-freeze proteins as cryoprotectants to transport. | Optimum: At pH levels of ≥ 9 Extreme: pH-11 | Acidophiles (pH) |
| (Singh et al., 2019; Gupta et al., 2014; López-Ortega et al., 2021) | Thiobacillus ferroxidans | Volcanic springs, acid mine drainage. Soliflactic hydrothermal Hokkaido, Japan. | Incorporate polyunsaturated and monounsaturated fatty acids or phosphatidylglycerol and phosphatidylylcholine in their membrane. Alterations in the number of certain archaeols. | Optimum: At pH levels of ≤ 3 Extreme: pH = 0.06 to 1.0 | Piezophiles/ Barophiles (Pressure) |
| (Singh et al., 2019) | Halobacterium salinarum, Dunaliella salina | Near neutral cytoplasm. -very charged cell wall. | Regulate fluidity of membranes by increasing the no. of unsaturated fatty acids. Synthesizing temperature-related chaperones, anti-freeze proteins as cryoprotectants to transport. | Optimum: High pressure Extreme: 1100 bar | Radiophiles (Radiation) |
| (Singh et al., 2019; Coker, 2019; Gupta et al., 2014; López-Ortega et al., 2021) | Campylobacter jejuni and Helicobacter pylori | Natural brines hypersaline lakes. For example Hamelin Pool, Shark Bay, Australia. | Volcanic areas, hydrothermal vents, and industrially polluted sites. Exclusion by a permeability barrier. Active efllux pumps. Reduction in the sensitivity of cellular targets towards metal ions. Salt-in organisms: Evolved a proteome (acidic proteins + acidic residues), typically found on the surface of most of their proteins - “Water cage” (acidic residues coordinate with water molecules around proteins). Salt-out organisms: Actively accumulate ions and organic osmolytes. | Optimum: At pH levels of ≤ 3 Extreme: pH = 0.06 to 1.0 | Leptolyngbya, Helicobacter recurvirostre, Anaerobaena, Chroococcidiopsis |
| (Singh et al., 2019) | Radiation resistant: high Mn: Fe ratio. | Volcanic areas, hydrothermal vents, and industrially polluted sites. Exclusion by a permeability barrier. Active efllux pumps. Reduction in the sensitivity of cellular targets towards metal ions. Salt-in organisms: Evolved a proteome (acidic proteins + acidic residues). Salt-out organisms: Actively accumulate ions and organic osmolytes. | Volcanic areas, hydrothermal vents, and industrially polluted sites. Exclusion by a permeability barrier. Active efllux pumps. Reduction in the sensitivity of cellular targets towards metal ions. Salt-in organisms: Evolved a proteome (acidic proteins + acidic residues). Salt-out organisms: Actively accumulate ions and organic osmolytes. | Optimum: High pressure Extreme: 1100 bar | Aspergillus, Saccharomyces, Enterobacter aerogenes, Micrococcus |
| (Singh et al., 2019) | Chroococcidiopsis | Volcanic areas, hydrothermal vents, and industrially polluted sites. Exclusion by a permeability barrier. Active efllux pumps. Reduction in the sensitivity of cellular targets towards metal ions. Salt-in organisms: Evolved a proteome (acidic proteins + acidic residues). Salt-out organisms: Actively accumulate ions and organic osmolytes. | Volcanic areas, hydrothermal vents, and industrially polluted sites. Exclusion by a permeability barrier. Active efllux pumps. Reduction in the sensitivity of cellular targets towards metal ions. Salt-in organisms: Evolved a proteome (acidic proteins + acidic residues). Salt-out organisms: Actively accumulate ions and organic osmolytes. | Optimum: High pressure Extreme: 1100 bar | Leptolyngbya, Helicobacter recurvirostre, Anaerobaena, Chroococcidiopsis |

### References
- Singh et al., 2019
- Coker, 2019
- Gupta et al., 2014
- López-Ortega et al., 2021
- Gupta et al., 2014
- Wierzchos et al., 2015
- Mergelov et al., 2018
- Singh et al., 2019
- Coker, 2019
- Lopez-Ortega et al., 2021
- Singh et al., 2019
- Coker, 2019
- Lopez-Ortega et al., 2021
- Lopez-Ortega et al., 2021
- Lopez-Ortega et al., 2021
Haloferax alexandrinus show phosphorus solubilization and increase phosphorus in hypersaline soils (Yadav and Saxena, 2018). They also show ACC deaminase activity (lowers ethylene, a plant growth-inhibiting hormone) which reduces saline stress (Verma et al., 2017). Psychrophilic extremophiles are used as bio-inoculants since they solubilize nutrients, fix nitrogen, produce phytohormones and siderophores thus promoting plant growth under low temperature and resistance against pathogens (Yadav et al., 2017). As shown in Table 2, Arthrobacter and Bacillus produce cold-active enzymes and anti-freezing compounds (Verma et al., 2017). Desert plants microbes thrive under extreme temperature fluctuations, high radiations, water scarcity, and soil salinity. Bacterial phyla like Actinobacteria, Bacteroidetes, and Cyanobacteria combat drought conditions by increasing the expression of dormancy and osmoregulatory genes and decreasing catabolism (Alsharif et al., 2020). Acidophilic extremophiles like Azotobacter, Bacillus, Flavobacterium, Pseudomonas show plant growth promoting attributes and are used as bio-inoculants and biocontrol agents in acidic soil. Drought-tolerant and phosphorus-solubilizing extremophiles are suitable bio-inoculants and utilizing them for agriculture in desert landscapes might help in achieving global food security for the overgrowing human population (Verma et al., 2017).

Biocontrol agents
Extremophiles survive stressful conditions through an expression of certain specific genes which are studied to provide a broad scope of industrial and biotechnological applications. One research outcome is the utilization of such microorganisms for biological disease control (Mehetre et al., 2021). Rhizobacteria defend plants against pathogens by producing ammonia, hydrogen cyanide, siderophores (Iron-chelating compounds), chitinases, and several secondary metabolites (Pandey et al., 2021). These biocontrol agents remain active in a wide range of extremities and limit pathogens and several nematodes by interfering with their reproductive cycle and competing for nutrients. Some examples are Bacillus, Clavibacter, Microbacterium, and Pseudomonas, which act as inhibitors to plant pathogens (Verma et al., 2017).

Biosurfactants used in the agriculture industry
Biosurfactants are utilized in enhancing the bioremediation of soils and used as a replacement for chemical surfactants in the production of pesticides. They also show antimicrobial activity and stimulate plant defense. Rhamnolipids can be used against the Phytophthora zoospores (Rath and Srivastava, 2021). They reduce water infiltration in arid soils by increasing hydrophilization, therefore providing a means to expand sustainable agriculture in desert regions (Shekhar et al., 2015; Markande et al., 2021).

Food industry
Extremophilic microorganisms produce a broad range of bioactive compounds, secondary metabolites, and value-added products such as flavors, food ingredients, and vitamins, therefore, making them widely applicable in the food and food processing industries (García-López and Cid, 2016). These compounds enhance the potential, add a positive health benefit to the food products and mitigate certain long-term diseases (Raddadi et al., 2015). Carotenoids, due to their properties, are used in the food industry as additives, color intensifiers, antioxidants, etc. (Saini and Keum, 2019). They provide several health advantages to consumers along with enhanced nutrition content and oxidation stability in meat content and poultry products (Nabi et al., 2020). Other health-promoting factors are their enrichment in provitamin A, anti-aging properties, immune system enhancement, and protection against cancer (breast, cervical, prostate), and other physiological disorders (Meléndez-Martínez, 2019). These visually appealing colorants with probiotic health benefits can be used...
in sauces, baby foods, processed cheese, milk products, breakfast cereals, and fruit and energy drinks. *Bradyrhizobium* sp. and *Haloferax alexandrinus* contain canthaxanthin, which is used as colorants in food and beverages and pigmentation of salmon flesh (López et al., 2021). Microbial food-grade pigments are obtained from Riboflavin in *Ashbya Gossypii* and carotene in *Blakeslea trispora* (García-López and Cid, 2016). Microalgal biomass is also utilized to extract carotenoids which serve as dietary supplements. Astaxanthin, obtained from microalgae *H. pluvialis* and extremophiles from the red snow in Antarctica, is used as a dietary and feed supplement (Torregrosa-Crespo et al., 2018).

**Biosurfactants used in the food industry**

Biosurfactants influence the emulsification of partially broken fat tissues (emulsification of edible oil by liposans), affecting the characteristics of flour and therefore can be used in bakery and meat products (Rath and Srivastava, 2021). Biosurfactants like lecithin and its derivatives, fatty acid esters containing glycerol, sorbitol, or ethylene glycol, and ethoxylated derivatives of monoglycerides are good emulsifiers and hence can be used as additives in the food industry (Shekhar et al., 2015). Fouling is caused by heavy deposits of thermo-resistant microbes and is a major problem as it affects the quality of the milk products and decreases their nutritional value. A biosurfactant produced by *Streptococcus thermophilus* controls fouling in heat exchanger plates in the food industry (Shekhar et al., 2015). Another species of the same genus, *Geobacillus* sp. 12AMOR1, produces a highly specific thermostable monoacylglycerol lipase (GMGL) which acts on monoacylglycerol substrate (Tang et al., 2019; Li et al., 2020; Jin et al., 2019a). Another class of extremozymes named agarases helps in the hydrolysis of agar and consequently, in the recovery of DNA from agar gel and in the production of neoagar-o-oligosaccharides (Jin et al., 2019a). β-agarase AgaP4383, produced by a deep-sea bacterium called *Flammeovirga pacifica* WPAGA1, helps in the degradation of agar and thereby produces neoagar-o-oligosaccharides (NAOS) like NA4 (neoagarotetraose) and NA6 (neoagarohexaose) as shown in Table 2 (Jin et al., 2019a; Qu et al., 2020; Park et al., 2020). These NAOS exhibit

**Pharmaceutical, medical industry, and therapeutic agents**

**Biotechnological applications of extremophiles and extremozymes**

Extremozymes and poly extremozymes have utmost importance in different industries such as nutraceutical, pharmaceutical, and food industries (Dumorné et al., 2017). Intramolecular interactions in these enzymes make them structurally rigid and hence, prevent unfolding at high temperatures. Due to their stability at relatively higher temperatures because of their adaptations, they can enhance solvent miscibility and rate of the reaction while still exhibiting high activity (Jin et al., 2019a). Their ability to be thermostable and pH-stable makes them an excellent fit for many processes like organic biosynthesis, grease, and others (Dumorné et al., 2017).

For instance, they produce proteases such as thermolysin (obtained from *Bacillus thermoproteolyticus*) which is used in the synthesis of dipeptides, and prolidase (obtained from *Pyrococcus furiosus*) which helps in the cleavage of dipeptides (Jin et al., 2019a; Alsoufi and Aziz, 2019). In addition to this, several other proteases like DNA-processing enzymes and pretaq protease also help in the clean up of DNA before PCR amplification (Bruins et al., 2001). Several studies have reported that the extremophilic bacterium *Geobacillus* sp. EPT9 produces a highly thermostable recombinant lipase that retains 44% residual activity at temperatures as high as 80 °C (Zhu et al., 2015). Another species of the same genus, *Geobacillus* sp. 12AMOR1, produces a highly specific thermostable monoacylglycerol lipase (GMGL) which acts on monoacylglycerol substrate (Tang et al., 2019; Li et al., 2020; Jin et al., 2019a). Another class of extremozymes named agarases helps in the hydrolysis of agar and consequently, in the recovery of DNA from agar gel and in the production of neoagar-o-oligosaccharides (Jin et al., 2019a). β-agarase AgaP4383, produced by a deep-sea bacterium called *Flammeovirga pacifica* WPAGA1, helps in the degradation of agar and thereby produces neoagar-o-oligosaccharides (NAOS) like NA4 (neoagarotetraose) and NA6 (neoagarohexaose) as shown in Table 2 (Jin et al., 2019a; Qu et al., 2020; Park et al., 2020). These NAOS exhibit
hepatoprotective and cholesterol-lowering activities, increase antitumor immunity as well as enhance inhibition effects against-glucosidase, tyrosinase, and melanin biosynthesis (Qu et al., 2020). β-agarase Aga4436 from Flammovirga sp. OC4 is also highly active and highly stable at high temperatures and pH. Thus, they are quite beneficial and have several biotechnological and pharmaceutical applications (Jin et al., 2019a; Park et al., 2020).

Halophiles are one of the richest resources for the pharmaceutical industry. The halophilic fungi, from deep-sea, are extremely important because they produce secondary metabolites under extremely saline conditions.
conditions. Some esterase genes have been reported to be extremely active in harsh saline conditions (Yadav and Saxena, 2018). Several extremozymes, with halophilic and thermophilic features, such as proteases, mercuric reductases, DNA polymerase (obtained from Archaeon SCGC-AAA261G05), etc. have also been found (Jin et al., 2019a).

Extremozymes from psychrophilic and psychrotrophic microorganisms have become extremely useful for different processes in the pharmaceutical and medical industry, in molecular biology, among others. Processes like cryosurgery and cryopreservation utilize antifreezing compounds derived from these extremozymes (Yadav et al., 2019). In molecular biology, certain biological processes call for cold-adapted and heat-labile enzymes since they can function at lower temperatures and be inactivated at temperatures relatively lower than usually required (Bruno et al., 2019; Mangiapalli et al., 2020). Because of these relatively lower temperatures required for inactivation, the need for additional chemical extraction steps is eliminated as the relatively lower temperatures would prevent the melting of dsDNA (Jin et al., 2019a). Esteras are extremely useful as catalysts in the pharmaceutical industry as they are cold-active and highly stable, e.g. esterase Est11 from Psychrobacter pacificensis is cold-adapted, halotolerant and is resistant to organic solvent and EstO from Pseudalteromonas arctica increases the solubility of anti-inflammatory drugs (naproxen, ibuprofen, etc.) by hydrolyzing them (shown in Table 2) (Jin et al., 2019a; De Luca and Mandrich, 2020).

Extremozymes have a wide variety of applications, especially in the pharmaceutical industry. Extremozymes produce water-soluble, colorless, low molecular weight compounds, MAAs, which perform photosynthetic functions and act as biological antioxidants. Their absorption gradient is between 268 and 362 nm and they have high molecular weight. Chemical extraction steps is eliminated as the relatively lower temperatures required for inactivation, the need for additional chemical extraction steps is eliminated as the relatively lower temperatures would prevent the melting of dsDNA (Jin et al., 2019a).

Medical applications of extremozymes and their products

Halocins and Diketopiperazines: Extremozymes, being producers of antibiotics, antifungals, and antitumor molecules are known to generate antimicrobial peptides (found in Halobacteriaceae and Sulfolobus species) and diketopiperazines. Antimicrobial peptides such as halocins (that usually have specific ranges of activity) are effective at killing archaeal cells but don’t harm microorganisms pathogenic to humans (Coker, 2016). Diketopiperazines (obtained from halophiles like Haloterrigena hispanica and Natrionomonas occultas) function as antimicrobials, antifungals, antivirals, and antitumors as well as affect blood clotting in humans (Kaur et al., 2019). They can potentially be used as an alternative treatment for drug-resistant Pseudomonas aeruginosa infections since they activate and inhibit the quorum-sensing pathways (Coker, 2016). PHAs (Polyhydroxyalkanoates): Extremozymes also produce PHAs which can be used as carbon storage for microbial cells and produce bioplastic which is a better alternative to plastics made from petroleum since they are biodegradable, and biocompatible (Coker, 2016; Koller, 2017). PHAs are extremely useful as biopolymers as they lack cytotoxicity and can be used in implants, drug delivery systems, etc. (Goswami et al., 2020).

Recombinant vesicles: Halobacterium sp. NRC-1, Halobacterium salinarum, Haloferax terraei and Haloquadratum walsbyi produce recombinant gas-filled vesicles. These vesicles have relatively low toxicity, can elicit a strong immune response, and can be used as an adjuvant (Hill et al., 2020; Coker, 2016). The gas vesicles and polar lipids have shown promising results in experiments on mice and hence, they can be used as an alternative vaccine delivery system (Coker, 2016).

DNA polymerases: DNA polymerases have been obtained from thermophiles to be utilized in the field of medicine and biotechnology e.g., Taq from Thermus aquaticus, Pfu from Pyrococcus furiosus, and Vent from Thermococcus litoralis. PCR, which uses Taq polymerase from the thermophile Thermus aquaticus, is the most important example (Coker, 2016; Irwin, 2020; Arora and Panosyan, 2019).

Lipases: Hyperthermophilic bacterium Aeropyrum pernix K1 produces an extremozyme nucleoside phosphorylase which can be used in anti-viral therapies as they help in the synthesis of nucleoside analogs. Hence, thermozymes have a wide variety of clinical applications due to their high-temperature enzyme activation & lower viscosity to substrates utilized (Coker, 2016; Singh et al., 2019).

Therapeutic applications of extremozymes and their products

Pyochelin, an antifungal and iron-binding compound, derived from Pseudomonas sp. acts against Candida and Aspergillus sp. A halophile, Dried Dunaliella has chelating and cryoprotectant properties as it has antifreeze proteins (Tripathi et al., 2018; Salwan and Sharma, 2020). They also produce β-carotene which can be used as a colorant in pharmaceutical industries and as a supplement in food products (Tripathi et al., 2018; Salwan and Sharma, 2020; Lafarga et al., 2021). Two benzoxazine glycosides (arcticoside and C-1027 chromophore-V) obtained from a marine Streptomycetes strain showed inhibitory activity against Candida albicans isocitrate lyase along with breast and colorectal carcinoma cells (Sayed et al., 2020).

Extremozymes are useful in therapeutics because of their anti-proliferative and anti-inflammatory activities and their ability to act as chemo-preventive agents. Several metabolites like biosurfactants, bio-polymers, and peptides are produced by extremozymes and are extremely useful as therapeutic agents and in the pharmaceutical industry (Salwan and Sharma, 2020).

Carotenoids, mainly β-carotene and astaxanthin, play a crucial role in the color of the retinal macula (yellow) and this color helps offer protection from the sun (by acting as a sunblock) to some parts of the retina so, carotenoids help in maintaining healthy vision in humans (Inoue et al., 2017). Many bacterial pigments can act as carcinogenesis preventing agents due to antioxidative and anti-free radical activities. Ex., prodigiosin, caroten, and xanthophylls. Carotenoids also contribute to the production of antibiotics. Ex., Nonomuraea sp. produces an antibiotic called glycopeptide (García-López and Cid, 2016).

Biosurfactants used in pharmaceutical and medical industry and therapeutic agents

Biosurfactants have several applications in the pharmaceutical industry. They show antimicrobial, antiviral, antitumor, and sometimes even antitumor activities (Markande et al., 2021). A biosurfactant produced by Bacillus circulans shows antimicrobial activity against MDR and other pathogenic and semi-pathogenic microbial strains (Gontia-Mishra et al., 2017). Biosurfactants can be used in anti-aging creams and gels (purified lactone sophorolipolipid stimulates the production of new collagen fibers), recovery of intracellular products (help in the lysis of cells after fermentation), etc. (Shekhar et al., 2015). Biosurfactants combat adhesion and colonization of pathogenic microbes with their antiadhesive and antiadhesive abilities e.g. surgical implants treated with biosurfactants obtained from Lactobacillus fermentum, a thermo-acidophilic lactic acid bacteria were found to inhibit the infection of Staphylococcus aureus, PVC plates and vinylurethral catheters treated with surfactin showed reduced biofilm formation of E. coli (Ephrem et al., 2019; Markande et al., 2021; Shekhar et al., 2015). They can potentially be used in gene transfection (specifically liposome-based biosurfactants) and can act as alternatives for gene delivery mechanisms and immunological adjuvants because of their low toxicity and pyrogenicity (Shekhar et al., 2015).
Cosmetic industry

Mycosporines and mycosporine-like amino acids used in cosmetic industry

The UV exposure can cause sunburn and premature aging on short term exposure and even skin cancer on long term exposure (Singh et al., 2021). MAAs are more efficient than currently existing synthetic sunscreens with synthetic organic filters (oxybenzone, avobenzone, aminobenzoic acid, etc.) or inorganic filters (titanium dioxide, zinc oxide, etc.), or both (Besegatto et al., 2018). They can protect the skin against aging (with their antioxidative activity, etc.), microbes and absorb UV radiation while also having a less negative impact on marine life (bioaccumulation and hormonal changes in fishes, production of hydrogen peroxide, and bleaching of corals), inducing little to no side effects in humans (allergic reactions, phototoxicity, endocrine disorders) and being more eco-friendly (Geraisdes and Pinto, 2021; Singh et al., 2021; Corinaldesi et al., 2017).

MAAs, are produced by lichens, fungi, and cyanobacteria when exposed to UV radiation, are extremely stable at high pH and temperatures, and are primarily used as a natural bioactive ingredient in cosmetic products (Corinaldesi et al., 2017). While they offer proper protection from UVA radiation, they offer relatively less protection against UVB radiation (Geraisdes and Pinto, 2021; Singh et al., 2021). Some studies show that they provide minimal protection against UV A and UV B because of the addition of substances with antioxidant properties is essential in the production of sunscreens as the synthetic UV filters in them absorb the photons rather than reflecting them the synthetic UV filters in sunscreens absorb the photons rather than reflecting them (Corinaldesi et al., 2017; Mendes-Silva et al., 2020). The synthesis of carotenoid pigments and other metabolites (lycopene, astaxanthin, etc.), are examples of the biochemical adaptations of extremophiles that help them survive and thrive in extreme conditions as well as make them preferable alternatives to conventional products. Carotenoids have anti-UV properties and act as natural antioxidants that help in reducing the production of free radicals and, by extension, reduce the skin’s photodamage (Mendes-Silva et al., 2020). Some halophiles like D. salina are excellent sources of β-carotene (Lafarga et al., 2021).

Biosurfactants used in cosmetic industry

Properties of biosurfactants like foaming, emulsification, water binding, etc., make them suitable alternatives to other surface-active substances (Rath and Srivastava, 2021). The yield of monoglyceride, a popular surfactant, from glycerol tallow can be maximized by using psychrophile Pseudomonas fluorescens lipase treatment (Kaur et al., 2019; Shekhar et al., 2015; Corinaldesi et al., 2017). Arthrobacter, Pseudomonas, Halomonas, Bacillus, etc. are some marine organisms that can be used for the production of biosurfactants and bioemulsifiers (Corinaldesi et al., 2017).

Textile industry

Extremozymes used in textile industry

Extremozymes are environment-friendly and can work on a wide range of substrates (Madhu and Chakraborty, 2017). Fabric or yarn undergoes various stresses (like bending and tension) which degrades the threads of the fabric and makes it less appealing so extremozymes are employed in the finishing process which improves the quality of the fabric. They work well under mild conditions, are biodegradable, and increase the speed of the reaction by decreasing the activation energy via substrate specificity (Hari, 2020; Vashisth and Sharma, 2018). Table 2 shows the Extremozymes used in Textile Industry.

To protect the damage caused by weaving the fibers are treated with starch and/or its derivatives in a process called sizing. Since this protective layer could interfere in further processes, it needs to be eliminated in a process called desizing (Besegatto et al., 2018). Desizing is done by a single enzyme-like α-amylase or using multiple enzymes like amyrase, lipase, and proteases to increase the lubricity of the yarn in cases of denim and cotton fabrics. These enzymes are produced by extremophiles like Thermus thermophilus HB8, Euplotes foci, Alkalibacillus sp. NM-Da2, and Geomyces sp. (Vashisth and Sharma, 2018). The hydrolysis of starch can be done at high temperatures with a class of enzymes called thermostable amylolytic enzymes which will result in a higher reaction rate and will reduce the risk of contamination (Jin et al., 2019a).

A deep-sea bacterium Martiella mediterranea produces cold-active and alkaliphil-stable β-glucosidase (Jin et al., 2019a). Cold-active amylases (glucosidas, Optisize®R COOL and Optisize NEXT) isolated from psychrophiles can be used in the desizing of woven fabric at low temperatures (Jin et al., 2019a). Stains and color preservatives can be removed from the fabric with cellulase Puradax HA obtained from Bacillus sp. and Pseudomonas stutzeri (Raddadi et al., 2015; Aparna et al., 2021).

Bioscouring is the removal of non-cellulosic impurities (pectin and waxes) from fabric surfaces (Dash and Sahoo, 2021). The conventional scouring process was tedious, degraded the quality as it required vast resources, and caused environmental pollution (Mladenovic et al., 2016). Enzyme scouring enhances the washing ability and the fabric’s absorbance nature and is also environment friendly. Pectinase, xylanase, protease, lipase, and their combinations can remove large amounts of impurities (Arputharaj et al., 2016). Alkaliphil-thermophilic thermozymes are employed in enzyme bioscouring due to their ability to tolerate alkaline pH and high temperatures (Kakkar and Wadhwa, 2021). Bacillus sp. and Pseudomonas sp. produce alkaline pectinases, which can be used for cotton bioscouring to protect cellulose and fiber damage (Kavuthodi and Sebastian, 2018; Babu, 2019). Studies show that the thermostable pectinase from Candida is active under a wide range of pH and temperature, and produces a higher quality of cotton (increased absorbency, lower weight loss, and dyeability towards reactive dyes for coloration) (Aggarwal et al., 2020; Sani and Krishnaraj, 2017). Several extremophilic sources of impurities removing extremozymes have been identified e.g., pectinase from Tetracladium sp. and xylanase from Flammeovirga pacifica strain WPAGA1 (Kakkar and Wadhwa, 2021).

Bleaching leads to the production of pure white cotton fibers by removing the natural pigments present and in bio-bleaching, the glucose oxidase enzyme oxidizes the glucose molecule into gluconic acid and hydrogen peroxide in an oxygen-rich medium (Maiti et al., 2018; Madhu and Chakraborty, 2017). Similarly, catalase and laccase enzymes are employed for bleach cleanup, which converts the leftover hydrogen peroxide into hydrogen and oxygen in an eco-friendly way (Arputharaj et al., 2016). Catalase and laccase have been isolated from the extremophile Geobacillus thermo philus pakistaniensis. By encoding the CAT gene which is responsible for the catalytic activity for cold-adapted psychrophiles, engineered and recombinant extremozymes of catalase have been produced. This enzyme shows activity in a wide range of temperatures (Kakkar and Wadhwa, 2021). Microbial laccases are being increasingly employed in the textile industry as artificial dyes show carcinogenic properties and are hazardous to health. Laccase (LacT) from Brevibacillus agri is a better alternative to the usage of indigo dye in denim bleaching. Laccase is also obtained from bacterial species Streptomyces psammoticus and Stenotrophomonas maltophilia which serve as good decolourising agents (Panwar et al., 2020; Ashraf et al., 2020). Further research in this field has led to the identification of a serine protease from Bacillus sp. which can show efficient serine-degrading, silk-degumming, and color-bleaching properties (Kakkar and Wadhwa, 2021). The cellulase enzymes help in biopolishing (removing fuzz and pilling) and biostoning (denim finishing) of fabrics and make them more appealing (Behera et al., 2017; Choudhury, 2017). Prodi-giosin from Vibrio sp. can be used as a bio-dye for coloring wool, acrylics, and silk, and Violacein dye from Chromobacterium violaceum are perfect examples of bio-dyes (García-López and Cid, 2016).
Bioremediation and biodegradation

Bioremediation is the need of the hour and is extremely important as it helps in the cleanup of contaminated and polluted environments. Microorganisms, particularly extremophiles, can decompose heavy metals and organic pollutants, detoxify contaminated soil, waste water, radioactive waste, and help in degrading plastic (which is a major pollutant) (Canak et al., 2019). Many industrial processes result in the contamination of the environment by heavy metals and radioactive pollutants which can be very harmful to humans and the ecosystem (Krzmarzick et al., 2018). Extremophiles can transform, immobilize or degrade these pollutants into nontoxic substances by biodegradation, biosorption, bioconversion, bioaugmentation, etc. (Donati et al., 2019; Marques, 2018). Extremeenzymes produced by these microbes act as biocatalysts by catalyzing and helping insolubilization and precipitation of pollutants by catalyzing redox reactions and minimizing the production of secondary pollutants (Jeong and Choi, 2020; Marques, 2018; Ahmed et al., 2018; Atanasova et al., 2021).

Treatment of pollutants by thermophiles

Bioremediation of heavy metals (Mn, U, Te, Co, Mo, Au, and Hg) can be done by using thermophiles due to their ability to tolerate high temperatures and reduce metals, e.g., the high biosorption capacity of Geobacillus thermanaeruccicus and Anaerococcus amylolyticus helps them to bind with heavy metals (like Cr, V, Co, etc.) and account for their removal from polluted environments (Mir et al., 2021; Jeong and Choi, 2020). They transform pollutants into nontoxic substances (Mehta et al., 2016). Thermophiles like Bacillus sp. have applications in many industries, e.g., aliphatic and aromatic hydrocarbons and synthetic dyes can be removed by thermophiles (Voros et al., 2019; Orellana et al., 2018). Petroleum industries and oil spills can result in contamination of soil and groundwater as they release harmful substances such as poly-cyclic aromatic hydrocarbons and long-chain alkanes (C10 to C32) which can be decontaminated by certain strains of extremophiles, namely Bacillus, Thermus, and Geobacillus (Sun et al., 2015; Jeong and Choi, 2020). A Geobacillus SH-1 strain helps in degrading saturated alkanes ranging from C12 to C33 and naphthalene. Long alkyl (C32 and C40) hydrocarbons can also be transformed into nontoxic substances through bioaugmentation by thermophiles such as Geobacillus thermostarophilarumIR2, Geobacillus stearothermophilus IR4, and Bacillus licheniformis (Jeong and Choi, 2020). The Thermus scotoductus, Thermoterrabacterium ferrireducens, Pyrobaculum landicum and, Thermoanaerobacter sp. were found to be helpful in the treatment of radioactive waste as they can reduce certain radioactive compounds like enzymatic uranium and technetium (Tapadar et al., 2021). Several hypertherophilic species like Pyrococcus sp. help in the reduction of uranium (Krzmarzick et al., 2018).

Treatment of pollutants by acidophiles

Acidophiles are supposed to be the best candidate for the detoxification (through bioleaching and bio-oxidation) of heavy metal pollutants like Cd, Cu, etc. which are extremely detrimental to plant and animal health (Orellana et al., 2018; Gumulya et al., 2018; Canak et al., 2019). Bioleaching on a large scale can be performed using Acidithiobacillus strains, particularly Acidithiobacillus ferrooxidans. Eg, At. ferrooxidans and Acidithiobacillus ferrivorans can be used for copper precipitation under acidic conditions (Gumulya et al., 2018). The enzymes by acidophiles have several adaptations because of which they can function efficiently and thrive under extremely acidic conditions. Acidocella aromatica FFB1 and Acidiphilum symbioticum H8 can efficiently reduce vanadium ions and perform biosorption of Cd cations in highly acidic conditions, respectively (Jeong and Choi, 2020). Lactic acid bacteria produce extremely stable and active biomolecules called S-layer proteins that seem to be promising for decontamination of toxic heavy metals (Cd, Pb) under low pH (Kililova et al., 2017). Lactobacillus plantarum YW11 produces S-layer proteins that have a high Pb adsorption capacity. Two strains of Lactobacillus kefiti (CIDCA 8348 and JCM 5818) were able to adsorb Cd\(^{2+}\), Zn\(^{2+}\), Pb\(^{2+}\), and Ni\(^{2+}\) ions when their S-layer proteins interact with each other (Jeong and Choi, 2020). A recent study of bioaugmentation reported that more than 90% Cu\(^{2+}\), Cd\(^{2+}\), Hg\(^{2+}\), and Zn\(^{2+}\) ions were extracted from a microbial consortium, and surprisingly the main species involved in this consortium were Acidithiobacillus thiooxidans, At. ferrooxidans, Acidiphilum cryptum, and Leptospiroplum ferrooxidans (Jeong and Choi, 2020).

Optimal growth of Ferroplasma spp. are adapted to extremely low pH conditions like acid mine drainage (AMD) and hence they can oxidize metals with maximum efficiency. Among other acidophiles like Thiomonas arsenitoxydans, Acidithiobacillus caldus, and Acidithiobacillus ferrooxidans, with high heavy metal tolerance, Acidithiobacillus ferrooxidans is mainly used in the process of bioleaching of minerals (Tapadar et al., 2021). E-waste generated by electronic gadgets also accounts for the generation of a huge amount of toxic heavy metals (Cu, Pb, Zn, Ni, etc.). Decontamination of such industrial effluents is carried out more efficiently by a mixed culture of acidophiles (A. ferrooxidans and A. thiioxidans) when compared with their pure culture alone (Kucmanová et al., 2021). Another potential strategy for bioremediation is low-pH iron oxidation. For example, autotrophic acidophilic and neutrophilic bacteria are capable of catalyzing the reduction of gaseous, toxic H\(_2\)S in effluents to nontoxic zero-valent sulfur (ZVS) under low redox conditions (Tapadar et al., 2021). Apart from this, thermoacidophiles act as potential biodegraders of pollutants from industrial wastewater, as their activity is not compromised at either high temperatures or low pH. Eg, Sulfolobus solfataricus can degrade phenol at 80 °C and pH 3.2 (Tapadar et al., 2021; Krzmarzick et al., 2018).

Treatment of pollutants by psychrophiles

Psychrophiles are extremely stable and active at low temperatures and can utilize organic pollutants, especially hydrocarbon mixtures and halogen compounds, and make them nontoxic (Orellana et al., 2018). Psychrophilic bacteria, Pseudoalteromonas sp. P29 and Oleispira antarctica RB-8T, have adaptations that help them survive and thrive at low temperatures, are extremely efficient at degrading crude oil, jet fuel, etc. (Jeong and Choi, 2020). Arthrobacter psychrolithophilus can help in the clarification of wastewater as it can degrade organic compounds (mainly synthetic xenobiotic compounds) (Tapadar et al., 2021). Arthrobacter sp., Rhodotorula sp., etc. use the enzymes catechol 1,2 dioxidegenase (C1, 2D), catechol 2,3 dioxygenase (C2, 3D) for degrading aromatic hydrocarbons (Chaudhary and Kim, 2019). In case of oil spills, psychrophiles Oceanospirillales, Colwellia and Cycloclasticos can consume alkanes, ethane, BTX, and many other pollutants (Canak et al., 2019). Some psychrophiles, namely Flavobacteria (Tenasibaculum and Polaribacter), Rhodobacteraceae, etc., can degrade dissolved organic matter and organics.

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with high molecular weights in marine water (Tapadar et al., 2021). Psychrophiles belonging to genera *Shewanella*, *Moritella*, and *Psychrobacter* play a major role in plastic degradation. An important adaptation of psychrophiles to survive in cold marine conditions is their growth inside biofilms which are formed as a result of attachment to surfaces (Urbanak et al., 2018). The formation of biofilms on plastic debris can result in the possible breakdown of the debris because of the promotion of metabolic reactions in the microbial assemblages. Some species of psychrophiles can be extremely useful in biodegradation, namely *Pseudomonas* sp. and *Lysinibacillus* sp. because they provide better adhesion to plastic surfaces because of the increased production of extracellular matrices (Atanasova et al., 2021).

**Treatment of pollutants by basophils/alkaliphiles**

The toxic cyanide waste produced by the gold mining and jewelry industry (cyanide, cyanate, and various metal-cyanide complexes) act as the sole source of nitrogen for *Pseudomonas pseudoalcaligenes*, so these species play a key role in eliminating cyanide pollutants from wastewater. Aliphatic nitriles are removed by highly salt-tolerant and obligate alkaliphile *Natronocella acetinitrilica* as they exclusively use aliphatic nitrile for obtaining carbon and energy. Removal of acetonitrile is carried out by alkaliphilic bacteria, namely, *Pseudomonas putida*, and *Rhodococcus* spp. through nitrile hydratase/amidase enzymatic pathway, an acetonitrile serves as a source of carbon, nitrogen, and energy, as shown in Table 2 (Tapadar et al., 2021). Effluents from various industries including wood, textile, paper mill, and breweries contain Tributyltin (TBT), phenol, and hydrocarbons, and alkaliphiles can remove these toxic pollutants. *Stenorophomonas chelatiphaga* helps in reducing the concentration of TBT whereas *Arthrobacter* sp., an obligate alkaliphile helps in the degradation of phenol. Synthetic dyes from textile industries cause depletion of dissolved oxygen. Alkalophilic bacteria (*Bacteroides* spp., *Eubacterium* spp., *Clostridium* spp., *Proteus vulgaris*, *Streptococcus faecalis*, *Bacillus* spp., and *Sphingomonas*) and their consortia help in the degradation of azo dyes from textile effluents (Tapadar et al., 2021). Plastic degradation by microbes, especially alkaliphiles and acidophiles is an area that has received the least attention although pH variations are a key environmental factor that affects both solubilities as well as softening of plastics. The life of plastic materials used in bleaching processes is shortened considerably by low pH conditions (Atanasova et al., 2021). The limited information regarding these extremophiles suggests that alkaliphiles that are responsible for the degradation of plastic are predominantly obligate species that belong to the *Bacillaceae* family. Studies have also reported that alkaliphilic bacteria found in hypersaline conditions (pH 11) can degrade low-density polyethylene (LDPE) (Torre et al., 2018; Atanasova et al., 2021; Cada et al., 2019).

**Treatment of pollutants by halophiles**

Halophilic bacteria produce extracellular polymeric substances (EPS) which help in their adhesion to other surfaces and the formation of biofilms (Marques, 2018). EPS increases the efficiency in the treatment of organic toxic pollutants by solubilizing aromatic hydrocarbons and also boosts the rate of phenanthrene degradation. Eg, the degradation of hydrocarbons at the Deepwater Horizon spill site was done by EPS producing *Halomonas strain* TG39. Halophiles such as *Bacillus licheniformis*, *Vibrio Parahaemolyticus*, etc. secrete exopolysaccharides which are found to be beneficial in the emulsification of hydrocarbons (Jeong and Choi, 2020; Gontia-Mishra et al., 2017). Organic pollutants in hypersaline environments like biphenyl, phenanthrene, anthracene, and naphthalene can be transformed into useful sources of carbon by *Marinobacter sedimentalis*, *Marinobacter fabrimaris*, and *Marinobacter nanhai* D15–8 W. Degradation of paraffin and other hydrocarbons along with the utilization of crude oil as the sole carbon source can be done by *Halobacillus* sp. EG1H1P4QL (Jeong and Choi, 2020). *Nesterenkonia* sp can produce butanol, ethanol, and acetone, some strains of halophiles can produce OPAA (organophosphorus acid anhydrases) which in turn can denature organo-phosphorus chemicals and derivatives because of their hydrolytic properties, etc. Organophosphorus substances can be detoxified by cloning OPAA compounds (Tapadar et al., 2021). Though there have only been some reports on using halophiles for the removal of toxic heavy metals, the results appears quite promising, and more research can be done on the same. Several studies have shown that the high adsorption capacity of halophilic bacteria *Vibrio harveyi* enhances the accumulation of cadmium cations. Additionally, chelation of heavy metal pollutants (Cd, Cu, Co) from mixed-salt solutions was reported to be done by another halophile *Enterobacter cloacae* (Jeong and Choi, 2020).

Several species of *Halofex* help in the degradation of oil, alkanes (C9-C40), benzene, biphenyl, anthracene, naphthalene, and/or phenanthrene (Krzmarzick et al., 2018). Azo dyes deteriorate the quality of water and are major pollutants of textile wastewater (Selvaraj et al., 2021). Halophilic microorganisms can function efficiently under high salinity conditions and can decolorize azo dyes. Eg: *Halomonas* sp. can decolorize reactive black 5, remazol brilliant violet 5R, and *Marinobacter* strain plays an important role in MYG biodegradation (Tian et al., 2021). Polyhydroxyalkanoates (PHAs) and polyhydroxybutyrate (PHB) serve as sources of energy and act as carbon reserves. Halophiles produce PHAs like *Halococcus* *walsbyi*, *Halorhabdus* *tiamatea*, *Halomonas campsisialis*, *Halopiger aswanensis*, *Halobacterium halotolerans*, and *Natrinema altunense*, though the best producer of PHAs is *Halofex mediterranei* (Gontia-Mishra et al., 2017). The biopolymer can be isolated from Halophilic strain 226S *Halomonas boliviensis* in its stationary phase and, also by culturing in fed-batch culture with glucose, sucrose, etc. (Atanasova et al., 2021; Koller, 2017). *Cyanobacteria* species have been recorded on plastic debris which indicates that it not only plays an important role in the formation of biofilms but also in degrading plastic. Non-biodegradable plastic polymers like polyethylene and polystyrene can be degraded by the formation of biofilms but also in degrading plastic. Non-biodegradable plastic polymers like polyethylene and polystyrene can be degraded by the formation of biofilms but also in degrading plastic. 

**Treatment of pollutants by radiophiles**

Treatment of radionuclides in soils or aqueous mediums is being done by surface-modified nanomaterials that can selectively adsorb some toxic heavy metals (Sadegh et al., 2017). For the desalination of radioactive iodine anions, modified gold (Au) nanomaterials are extremely effective as adsorbents (Mustag et al., 2017). The treatment of radioactive waste with extremophiles is done through the processes of biomineralization, biotransformation, and biosorption (Shukla et al., 2017). In the biominneralization of radionuclides from a contaminated area, there is the mineralization of the target element of the radionuclide inside the bacterial cell. Reduction of U(VI), Pu(IV), Am(V), and Th(IV) (alpha nuclides) to make them harmless can be done by some strains of radiophiles, namely *Shewanella* and *Geobacter* strains. Uranium (U) can be removed from aqueous media by the use of cete-stimulating *Geobacter* species and the removal can be made even more efficient by adding certain electrons donors (glucose, acetate, etc.) (Jeong and Choi, 2020). *D. radiodurans* can be used for the treatment of radionuclide-contaminated environments onsite and the removal of radioactive pollutants because they can survive and thrive under extremely high levels of ionizing radiation, making them extremely radio-resistant. Precipitation of radioactive cobalt (60Co) and oxidized uranium pollutants can be done by a bacterial Ni/Co transporter or a non-specific acid phosphatase from *Salmonella enterica serovar Typhi* from *Salmonella enterica serovar Typhi* strain, respectively (Irwin, 2020). In recent years, using extremophiles and nanotechnology together has shown very promising results. Eg The removal of radioactive iodine (125I) by *D. radiodurans* with biogenic Au nanoparticles is not just an extremely stable but also efficient method (Jeong and Choi, 2020; Irwin, 2020).
Bioenergy, biofuels, and biorefinery

The current global energy trends and non-renewable resources demand urgent development of an alternative, sustainable, efficient, and financially viable energy source to power the world (Ray, 2019). Hence, biofuels are one of the most promising alternative sources of green parametric bioenergy (Ahorus et al., 2018). Using organic substrates like sugars, starch, and oil crops, lignocellulosic biomass, and agricultural and animal wastes, leads to the production of biofuels like bioethanol, biodiesel, biobutanol, and biogas are produced. The energy extracted from solid, liquid, and/or gaseous organic substrates like bioethanol, biodiesel, biomethane, etc., is referred to as bioenergy (Zhu et al., 2020). The fuels derived from biomass like starch and oil crops as well as the biodegradable constituent of industrial and municipal wastes are termed biofuels (Barnard et al., 2010).

Biofuels can be obtained from crops containing sugar, starch, and vegetable oils (first generation), corn stover, jatropha and bagasse (second generation), and algae (third-generation) biofuels e.g., bioethanol, biodiesel, and biobutanol (Callegari et al., 2020; Chakraborty et al., 2020; Coker, 2016). Growing crops for the production of these biofuels requires land, fertilizers, refinery processes, and energy inputs which leads to the emission of carbon dioxide, water shortage, deforestation; thus making the procedure less eco-friendly than predicted (Acheampong et al., 2017; Coker, 2016). Besides that, there are fourth-generation biofuels obtained as electro fuel and solar fuel (Balwan and Kour, 2021).

Extremozymes used in the synthesis of various biofuels

Extremozymes from thermophilic organisms play a valuable role in biotechnology and are widely used in industrial applications due to their characteristics of remaining active under harsh processing conditions. Moreover, their use has been reported in countless applications of industry (Dumorné et al., 2017).

Lipases: Lipases have great potential in biotechnological applications and they contribute to the production of biofuels such as biodiesel (Bibra et al., 2015). The identification of cold-active lipases from psychrophilic extremophiles is currently applied in the industrial production of biodiesel as they help catalyze reactions at very low temperatures (Mukhtar and Aslam, 2020; Barnard et al., 2010).

Lignocellulose-degrading enzymes: Lignocellulose, derived from grass, agricultural and municipal wastes, and industrial by-products, is recalcitrant biomass composed of 35–50% cellulose, 20–35% hemicellulose, and 5–30% lignin (Berger et al., 2014; Wang et al., 2018). Hydrolytic enzymes break down the cellulose into fermentable sugars and lastly, the sugars are converted into ethanol (Berger et al., 2014). Thermophilic microbes like Geobacillus sp. R7, Phanerochaete chrysosporium, and Sporotrichum thermophile have been identified to produce lignocellulase degrading enzymes like cellulases, xylanases, lignases, lignin peroxidases, and manganese peroxidases (Barnard et al., 2010). Thermophilic, anaerobic bacterium Caldicellulosiruptor bescii efficiently degrades untreated biomass as well as crystalline cellulose and shows promising results for bioconversion of lignocellulose to ethanol without pretreatment, also shown in Table 2 (Berger et al., 2014).

α-Amylases: The degradation of starch through enzymes requires optimally high temperatures which make extremozymes from thermophilic organisms the ideal choice for isolation of α-amylase (Jin et al., 2013). Though conventional ethanol production through fermentation utilizes acid hydrolyzed starch and derived glucose as a starting material, new advancements favor the use of microbial enzymes for ethanol production (Chilakamary et al., 2021). α-amylase derived from thermotolerant bacteria like Bacillus licheniformis is a prime choice in this regard. The production of ethanol includes the processes of liquefaction (starch degradation), saccharification (glucose solution and dextrin subjected to microbial glucoamylase), and fermentation. Pyrococcus furiosus, B. acidocaldarius, B. thermophiloicus, and Alteromonas sp. also produce α-amylase as shown in Table 2 (Barnard et al., 2010).

Biorefinery

Biorefinery is a refinery process that allows complete and integrated conversion of organic substrates into a variety of bio-products, biofuels, and bioenergy (Awasthi et al., 2020; Zhu et al., 2020). Lignocellulose is the best candidate for biofuel production with its high mass availability, cheaper price, lack of competition to food crops, and less land utilization (Arevalo-Gallegos et al., 2017; Zhu et al., 2020). The market needs an enhanced refinery with high catalytic efficiency, high-temperature stability, pH stability, and resistance to inhibition by end-product. Since commercial enzymes cannot withstand high temperatures, extreme changes in pH, and oxygen availability, biorefinery units prefer utilizing extremozymes over them. Pretreatment of lignocellulose is important as it improves the availability of sugars for biodegradation by lignin degradation, expands the usable surface area of biomass, and reduces the crystallinity of cellulose (Zhu et al., 2020).

Recent Advancements in Extremozymes Discovery With Multi-Omics Approaches: New enzymes in extremophiles are identified with the help of “omics” technology. Meta-genomics, meta-transcriptomics, metabolomics, and meta-proteomics help in discovering and developing applications of extremophiles in biorefinery and thus achieving sustainable biofuel production (Chettri et al., 2021; Krüger et al., 2018; Zhu et al., 2020). In-situ mutagenesis and gene shuffling techniques that modify the stability of proteins are designed using bioinformatics and algorithms. Genomic study of thermophilic bacteria like Thermotoga, Thermoplasma, Pyrococcus, and Thermus has provided suitable enzymes for biorefinery (Zhu et al., 2020).

Target utilization of enzymes is difficult as 99% of the microorganisms are uncultured and therefore, the study of the survival and adapting strategies of extremophiles through genomics provides insights into metabolic pathways, transport mechanisms, substrate biotransformation, and enzymatic mechanisms. Modifying proteins through gene-recombinant techniques and proteomics helps enhance the thermal stability, pH tolerance, solvent tolerance, higher specificity, and activity of many enzymes (Zhu et al., 2020).

Extremophiles and Lignin Valorization: Lignin, the most abundant aromatic organic polymer constituting 15 to 40% of the dry weight of lignocellulosic biomass, helps in renewable organic resources for value-added products. Lignin separation involves the cleavage of bonds between cellulose and lignin through steam explosion under high temperature and pressure. Lignin valorization can produce various aromatics, carbon materials, and bio-oil through thermochemical methods (Cao et al., 2018). “Biological Funneling” with the help of extremozymes in refineries allows high utilization of lignin. The alkanolic bacteria Bacillus licheniihphus L1 and other halotolerant bacteria can degrade lignin and produce aromatic compounds and bio-oil (Zhu et al., 2020).

Biosurfactants in oil industry

Biosurfactants are selective, needed in small quantities, and are efficient under a wide range of oil and reservoir conditions. They increase mobility, solubility, lubrication, and remove soil and therefore, can be used in different industries (Shekhar et al., 2015). They strengthen the interaction between pollutants and microbes, increase the solubility of hydrophobic organic compounds and remove the pollutants by reducing the surface and interfacial tension, creating emulsions, and altering hydrophilic/hydrophobic properties of microbial surfaces. Biosurfactants help microbes overcome the high toxicity of compounds and increase remediation efficiency under extreme conditions in cases of environmental contamination (Schultz and Rosado, 2020; Rath and Srivastava, 2021).

Biosurfactants are used in the oil industry because of their high potential to enhance the recovery of crude oil through microbial-enhanced oil recovery (MEOR) (Markande et al., 2021; Saha and Rao, 2017). Microorganisms and their metabolic side-products are infused into the biofuel production process.
Significance of extremophiles in the biofuel industry

Extremophiles are ideal organisms in the production of biofuels as they are tolerant to high temperature and extreme pH e.g. ethanol can be produced by Thermoanaerobacterium saccharolyticum (Krüger et al., 2018; Coker, 2016). The genetic engineering of S. cerevisiae and E. coli allows them to commercially produce biofuels (Mukhtar and Aslam, 2020).

Biodiesel: Vegetable oils are processed into mono-alkyl esters of the plant fatty acids by transesterification (Kamil et al., 2019). However, these oleaginous plants produce only 5% of fatty acids out of their whole biomass which results in the production of very small quantities of biodiesel (Martinez-Silveira et al., 2019). Microalgae convert sunlight, water, and CO₂ to algal biomass through photosynthesis (Malavasi et al., 2020). However, under stressful conditions, some extremophilic microalgae such as Botryococcus braunii produce very long-chain hydrocarbons which can even exceed 80% of their dry cell weight and thus, can be hugely applicable in the production of biodiesel. Cyanidium caldarium and Galdieria sulfuraria, with their high lipid content help in biodiesel production (Vidyashankar and Ravishankar, 2016; Barnard et al., 2010). Higher accumulation of oils and lipids, rapid growth, production of bipolymer & polysaccharides, minimum contamination in the bioreactor, and biogas production are some of the advantages of utilizing microalgae over traditional methods for biofuel production (Varshney et al., 2015; Barnard et al., 2010).

Biobutanol: Butanol hinders the growth of microorganisms and therefore, most microbes cannot tolerate more than 2% of butanol (Benninghoff et al., 2021). A few species of Bacillus can tolerate 2.5–7% of butanol concentration. Extremophiles can also be genetically modified to produce butanol and increase tolerance like Pseudomonas putida. Green Biologics, a UK-based company, is using corn stock, waste biomass, and thermophilic Clostridium to produce biobutanol (Karthick and Nanthagopal, 2021; Barnard et al., 2010).

Biohydrogen: At present hydrogen is produced at a small scale and used for heat, electrical, and transportation power (Sazali, 2020). The most preferred method for hydrogen production is via anaerobic fermentations (Baeyens et al., 2020). Thermophiles have a wider utilization range of organic wastes than mesophiles and produce few fermentation byproducts and are vastly applicable in the production of hydrogen. The bacterial genus Thermoanaerobacterium comprises efficient hydrogen producers (An et al., 2018). The thermophile Caldi- cellulosiorputor saccharolyticus, and archaeal genera Thermostroccus and Pyrococcus also convert organic compounds to hydrogen (Berger et al., 2014).

Biogas: Biogas comprises mainly methane (CH₄) and carbon dioxide (CO₂) produced by extremophiles, also known as methanogens (Coker, 2016). Organic substrates like manure from farm animals, household waste, municipal solid waste, fat from slaughter waste are used for the production of biogas (Tyagi et al., 2016). Thermophilic extremophiles like Methanococcus maripaludis, Methanococcus jannaschii, and Methanothermobacterthermoautotrophicus are shown to produce methane and thus can be used in industries eventually reducing operational costs (Barnard et al., 2010). They have a higher growth rate and show accelerated reactions making the process faster and efficient (Berger et al., 2014).

Biomining

The extraction of minerals through bioleaching and bio-oxidation is called biomining. It is an economical and eco-friendly process. Bioleaching, done by thermophiles and sulfur-oxidizing chemolithotrophs, involves the oxidation of metal sulfides into sulfur compounds or metal ions in an acidic environment (Pattanaik et al., 2020). Biooxidation is the breakdown of the mineral matrix surrounding the target metal with microorganisms so that the target metal is exposed to the oxidation lag (Jerez, 2012). High salt concentration, high and low temperature, and organic solvents along with low pH and high metal concentrations (due to acid mine drainage) have been recorded in bio-mining so polyextremophiles like Acidithiobacillus ferrooxidans, Sulfolobacillus sp., and Ferroplasma sp. are used in the bio-mining of metals (copper, nickel, uranium, etc.). Some acidophiles (Acidithiobacillus prosperus and Acidibacter ferrooxidans) can be used in bio-metalurgy (Li and Wen, 2021). At very high temperatures, archaeaacteria such as Metallosphaera and Sulfolobus are useful in biomining. Microorganisms utilized in biomining can fix carbon dioxide and grow in aerated conditions (Deshpande et al., 2018). Roasting and smelting in biomining are more energy-efficient processes than traditional mining processes. It does not produce toxic gases (e.g. sulfur dioxide) and is advantageous since both low and high-grade ores can be leached economically. Environmental pollution, via dumping or leakage, can be avoided by curbing acid mine drainage (Jerez, 2012).

There are several techniques to extract metals from their ore; bio-reactors, heaps and dumps being the most common for commercial-scale extraction, in-situ mining, and vats for low-grade ores, etc. (Kaksonen et al., 2017). Acidophilic iron-oxidizing extremophiles can be used for the generation and reuse of reagents used as lixiviants since they can remove excess iron, sulfate, and other contaminants from the hydro-metallurgical solvents. Genetically Modified (GM) microorganisms are beneficial in the extraction process and make biomining more efficient and controlled since they increase resistance to fluctuating conditions (Gumulya et al., 2018; Jerez, 2017). OMICs (genomics, proteomics, transcriptomics, metabolomics) have increased our knowledge about the internal growth mechanisms which help extremophiles adapt (Krüger et al., 2018). Research to find higher metal tolerances, better attachment to minerals, and high growth rates at high metal concentrations should be done. Bioleaching and biomining for asteroid and planetary deployment can be explored using synthetic biology (Jerez, 2017).

Extremophiles and astrobiology

The last common ancestor of all life forms, LUCA, is considered to be hyperthermophilic due to heat resistant and anaerobic respiration features (Thombre et al., 2020). Extremophiles live under conditions of desiccation, radiation, extreme pH and might be capable of travelling in space, enased in salt crystals further being protected from damaging radiation (Nicholson, 2020, 2018; Feshangaz et al., 2020). They can metabolically and biochemically operate and survive under stressful conditions (Das Sarma et al., 2020). The halophile Haloarcula strain G, survived for several weeks without protection in deep space. Hence conducting more lithopanspermic experiments to understand the conditions for life existence in outer space is important (P. DasSarma et al., 2020). Extremophiles like Bacillus subtilis, Chroococcidiopsis, Euglena gracilis, and Deinococcus radiodurans are tested for their survival capability, tolerance to UV radiation and prevailing stressful environment conditions of Mars (Nandhini et al., 2021). Study of extremophiles for their capacity to adapt and survive and their limitations is helpful for the assumption and search for life in outer space (Hegner, 2020). Studying extremophiles found in inhospitable regions (hot springs, hot and arid deserts, glaciers, saline marshes) broadens our knowledge of their adaptations and novel bio-signatures that they use to survive. Though these sites do not entirely resemble the extra-terrestrial bodies,
they imitate their certain environmental parameters (Foucher et al., 2021). Planetary Field Analogue sites, PFA sites help in understanding planetary processes, examining technologies, methods and operations of instruments used in Mars missions and predicting the habitat for extant/ extinct life to exist (Thombre et al., 2020; Foucher et al., 2021). A model PFA site should imitate most of the compositional (organic and mineral content, elemental constituents), environmental (aridity, temperature), electrochemical (pH, magnetism) and physical analogues (thermal inertia, particle porosity and size) of an extra terrestrial site under investigation (Martins et al., 2017). Extremophiles and microbial diversity from these sites are used as model organisms for studying the survival of life in outer space, LEO (Low Earth Orbit) and in the International Space Station (ISS), provide knowledge on evolution of life and habitability beyond our planet (Thambre et al., 2020). Rio Tinto (Spain), Lonar lake (India), Ibn Battuta Center’s (Morocco), and regoliths, rocky desert, sand dunes, volcanoes, evaporitic deposits are the best examples of these PFA sites (Thombre et al., 2020; Moelling and Broecker, 2019).

Yeasts are found to survive in the stratosphere under UV radiations by experiments conducted in chambers stimulating the stratosphere (Lin, 2020; Pulchen et al., 2018). Mycobacterium luteum, Aspergillus niger and Penicillium notatum are extremophiles detected in the upper mesosphere (Thombre et al., 2020). Extremophiles survive under harsh ranges of temperature, pressure, space vacuum, UV radiations, solar cosmic radiations (SCR), galactic cosmic radiation (GCR) and hence, their survival in Earth’s upper atmosphere (EUA), Low Earth Orbit (LEO) and Outer Space is pivotal in determining the boundaries of life (DasSarma, 2018; Thombre et al., 2020; Omaiari, 2017).

Planetary Protection (PP) includes the policies, methods and practices employed to safeguard scientific objectives of the missions to other planetary bodies from unintentional contamination by Earth’s microorganisms and protection of Earth from possible life from outer space (Persson, 2017). COSPAR (Committee for space research) maintains PP policy by designing space missions and regulating guidelines that prevent contamination of microorganisms to other planetary bodies and help researchers explore the natural habitat of extra-terrestrial bodies and the possible life present there (Coutenis et al., 2019). Despite sanitizing spacecraft assembly rooms, many extremophiles grow in the harsh nutrient deficient cleanrooms (Rettberg et al., 2019). Certain extremophiles (Tersicoccus phoenicis, Acinetobacter johnsonii, Brevundimonas diminuta, and Bacillus safensis sp. nov.) have been isolated from cleanrooms (Thambre et al., 2020). The study of clean room microbial diversity is necessary for conserving the integrity of further space exploration (Mohan et al., 2017).

Conclusion and future perspectives

Extremophiles and their products have already proven to be more beneficial than conventional methods. Moreover, they have immense potential to extend their uses into industries which haven’t been explored. They can be used to attain global food security (Sustainable agriculture and Food industry), as alternatives for gene delivery and in the development of vaccines as immunological adjuvants (pharmaceutical industry), etc. Current and future research should concentrate on enhancing their specificity and availability. Increasing their specificity using nanotechnology would lead to advancement in the bioremediation sector, nuclear power industry, textile industry, etc. MAA products and the amount of MAAs used in sunscreen and already existing products are low; hence production on a larger scale and new technologies for high soluble protein expression of the extremophiles host microorganisms is needed. This would remove roadblocks in several industries other than cosmetics; production of more radiophiles so that they can be used for radioactive waste disposal. Research into genetic modification of extremophiles that are used in the production of biofuels can help overcome the limitations on the productivity of the conventional methods. More PFA sites need to be located for the advancement of the astrobiology sector. The biochemical properties and structure of known extremophiles should also be studied further. Extremophiles have a very high economic potential; though they are used in some industries, their applications can extend into more varied fields. Extremophiles and their products are immensely beneficial to several industries and their market will only grow further. What we need is more research on extremophiles in areas unexplored. For this, we need fundings and co-ordination between government and institutions. Currently extremophiles are used in the field of biotechnology, but we need to focus mainly on industries such as bio remediation, bioenergy, etc. keeping in mind the current climate crisis. We need to consider extremophiles for the replacement of current/conventional methods as they are more sustainable, efficient and cheaper. One of the major roadblocks in the advancement of the nuclear power industry is the disposal of nuclear waste, radiophiles can be used for its bioremediation. Large scale supply of extremophiles and their products along with any possible side effects are issues that need to be studied further. For supply on a larger scale, genetic modification of the currently known extremophiles for a better yield of the required metabolites and study of long-term effects of using extremophiles and their products should be done.

Credit author statement

All authors have equal contribution and share equal authorship.

Declaration of Competing Interest

None of the authors show any kind of conflict of interest.

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