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Review Article

# The Extremes of Life and Extremozymes: Diversity and Perspectives

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## Abstract

In mid 60's and 70's the discovery of *Thermus aquaticus* from Yellowstone National park in USA which could survive at extremely high temperatures of 80°C, opened gates towards exploration of extremophiles that emerged as a new field of microbiology. The microorganisms that can thrive at extreme environmental conditions where normal organisms fail to sustain are known as extremophiles. These microorganisms are found mainly in hot water springs, deep ocean vents, volcano pits, deep ice zones, deserts, saline lakes, mines, rocks beds and radiation zones etc. Since last two decades, the research data on extremophiles has increased exponentially as the enzymes extracted from the extremophilic microorganisms have shown potency in various industries like paper and pulp, leather, detergent, diary textiles, food and beverages, pharma, medicines and biotech industries. The current review encapsulates the knowledge about various extremophiles and their potential therapeutic and biotechnological applications.

**Keywords:** Extremophiles; Extremozymes; Adaptations and Industrial Applications

## Introduction

Microorganisms have the capability to survive in all extremity's environments. The most preferred range of environmental conditions for microorganisms are temperature (20 - 40°C), pH (nearly neutral), pressure (1atm), adequate amount of oxygen, water supply, nutrients and salts concentration. But there are a few organisms which survive in extremely harsh conditions where normal life fails to flourish these organisms are known as "Extremophiles". In order to differentiate different forms of microorganism there is still optimal range where most of the organism grows they are the termed as mesophiles [1]. The name "Extremophiles" term was coined by R D Mac Elroy in 1971 after the discovery of the first extremophile discovered was *Thermus aquaticus* in Yellow stone park by microbiologist.

Extensive studies on thermophiles has shown similarity with the last universal common ancestor (LUCA) found in hot water or hot springs. This has drawn the conclusion that life on earth may have been originated from hot water springs and its surrounding environments with geological chemical compositions [2].

A previous report released from NASA, reflects the existence of these extremophiles in virtually every corner of this planet, celestial bodies and extra-terrestrial space. This supports the speculations that these invaluable creature extremophiles have on life, evolution and their presence beyond this planet [3].

Extremophile term is derived from Latin word 'Extremus' meaning 'extreme' and Greek word 'philia' meaning 'love'. Extremophiles are characterized in all three domains of life archaea, prokaryotes and eukaryotes. Most of the known extremophiles are microorganism.

Extremophiles were previously unknown, but the exploitation of extremozymes at an industrial scale emerged as promising field that had various industrial application [4]. After development in the field of extremophiles number of societies and forum were established. The first International Congress on Extremophiles was convened in Portugal (1996) and establishment of scientific journal on "extremophiles" in 1997. An International society for extremophiles (ISE) was also formed (2002) to share the ideas, information and development in the field of extremophiles all over the world.

At the global level, since the discovery of extremophiles, many societies and union have been formed to investigate extremophiles and their role in various industries as well as their mechanisms, which may provide therapeutic insights in the field. Alkaline proteases isolated from Turkey and Malaysia have shown enormous potential in detergent industry such as bleach and thermal stability [5]. In addition, novel thermoalkalophilic such as *Anoxybacillus* sp strain KB4 from Turkey have been identified in [6], Zimbabwe [7], Antarctica and Mexico [8] that have an application in protein processing [9] and bioenergetics of ATP synthesis [10]. At genome level, transcriptional mechanisms regulating gene expression in most proteases are unknown, some specific protease are of great relevance for human disease, such as *Yersinia pestis* and *Legionella pneumophila* or in the malaria parasite *Plasmodium falciparum* [11].

Many natural environments pose two or more extremities such as acidic hot springs, alkaline hypersaline lakes and dry sandy deserts. These environments harbour acidothermophiles, halo thermophiles, haloalkaliphilic, and UV/radiation resistant oligotrophs, respectively [12]. Many halophiles are also alkaliphiles and thermophiles which are studied in different species of bacteria at different temperature, pH and salt concentration. Polyextremophiles from *Bacillus* sp produce various industrially important enzymes such as alkaline and serine proteases, amylases, pectinases, cellulases, lipases and xylanases [13]. A psychrophilic and slightly halophilic methanogen *Methanococcoides burtonii* was isolated from perennially cold, anoxic hypolimnion of Ace Lake, Antarctica. Furthermore, several new species in known genera of Sulfolobales (*Acidianus, Metallosphaera*) have also been reported, as well as a new member of the Thermoplasmatales, *Thermogymnomonas acidicola* have been reported [14]. In the last decade, an extracellular thermostable acid protease from a thermoacidophilic archaeon *Thermoplasma volcanium* was discovered.

As we know extremophiles are very difficult to culture in laboratory but by using metagenomics tool it can reveal the different aspects of extremophilic organisms [15].

Humans have been continuously exploiting enzymes for their use. Since long they are evolving regularly from their old and traditional processes to trending new process and ideas that are more robust. From the discoveries of novel enzymes and their properties it can be screened and give desired product for the biotechnological and industrial purpose.

By following old and traditional ways to stabilize enzymes to adapt in harsh conditions by using basic and biotechnological approaches [16].

The chemical reactions carried out in these processes are not optimized because enzymes from mesophiles are using at different extreme conditions like salt concentration, pH, temperature and pressure etc.

These processes suffer various drawbacks like being more cost affecting and less efficient. But the use of readily available forms of enzymes extracted from extremophiles are more promising and efficient because they are already stable under extreme environments. Each microorganism is different and they have their own mechanisms to adapt in extremes of environments [17].

The organisms which survive in extreme environments are called as 'extremophiles' and the enzymes produced by extremophiles are known as 'extremozymes' due to presence of these enzymes extremophiles can withstand extreme environments (high temperature, high salt concentration and high pressure) where normal enzymes begin to degrade even without consumed in the biochemical or physio-chemical reactions. The chemical, genetic and immobilization modification can be made to improve the effectiveness of enzymes in order to obtain upgraded biocatalysts with higher stability and activity in various industrial processes. After discovery of various enzymes which has been engineered and isolated from different sources to get desired product, which has advantages in various biotechnological industries like paper and pulp industry, textiles industry, soap and detergents industry, leather processing industry, dairy industry, food and beverages, dairy industry, baking industry, meat industry, pharmacology and drug manufacturers, biofuel production, biomining, medicines, bioremediation, anti-inflammatory, antimicrobial, anti-cancer and also exploitation for different therapeutic applications [18].

## Isolation, characterization and industrial applications

Contribution towards isolation, characterization and industrial application of novel enzymes derived from extremophiles and polyextremophiles has gained momentum since last decade which is shown in table 1. Some of the most significant studies are mentioned here in this review [19].

Novel bacterial species such as Bacillus alkalitelluris twi3 was reported to produce a metalloprotease from leather waste [20]. Extremophiles act as bio factories for novel antimicrobial agents and cytotoxins [21].

Multifactorial level of extreme stability of proteins can be exploited for protein engineering potentials [22]. Alkaline proteases from Bacillus sp were reported to be important in leather, textile and food industries [23]. Cold active alkaline proteases that are screened and characterized have a potential use in the various industries like detergents, textiles and leather. Production of xylanase using polyextremophilic Bacillus HX-6 strain which is optimized with respect to carbon and nitrogen source. It can optimally grow on high temperature and high pH high which make them good product for industries. Proteolytic enzyme is isolated from polyextremophiles which have potential in industrial sector [24]. Further application of these proteases was exploited following rigorous standardization procedures in bioreactor to produce at an industrial scale. Proteases have been used extensively in formulation of efficient detergents that offer an advantage for a safer environment in the polluted cities [25]. In addition to proteases, xylanase isolated from geothermal spring in Maharashtra, India was reported to be important for pulp industry. Thus, the study of micro-organism

| S.No. | Types of Extremophiles | Enzymes | Applications | References |
|---|---|---|---|---|
| 1 | Thermophiles | Amylases, α-Amylases, glucoamylase, α-glucosidase, pullulanase, amylopullulanase and xylose/glucose isomerases | Glucose and fructose for sweeteners, Starch processing. | (55) |
| | | Alkaline phosphatase | Detergents, stereo-specific reactions, dairy products | (56) |
| | | Alcohol dehydrogenase | Chemical synthesis | (57) |
| | | Antibiotics | Pharmaceutical | (58) |
| | | DNA ligase | Ligase chain reaction (LCR) Diagnostics | (59) |
| | | DNA polymerases | Genetic engineering | (59) |
| | | Dehydrogenases, | Oxidation reactions | (60) |
| | | Glycosyl hydrolases (amylases, pullulanase, glucoamylases, glucosidases, cellulases, xylanases), | Diagnostics Starch, cellulose, chitin, pectin processing, textiles Hydrolysis of starch, Cellulose and related poly- and oligosaccharides | (55) |
| | | Oil degrading microorganisms | Surfactants for oil recovery | (61) |
| | | Proteases and lipases<br><br>Lipases, pullulanase, amylopullulanase, and proteases, esterases | Baking and brewing and amino acid production from keratin, Detergents, Hydrolysis in food and feed | (58) |
| | | S-layer proteins and lipids | Molecular sieves | (62) |
| | | Sulphur oxidizing microorganisms | Bioleaching, coal, and waste gas desulfurization | (63) |
| | | Thermophilic consortia | Waste treatment and methane production | (64) |
| | | Xylanases | Paper bleaching | (65) |
| 2 | Psychrophile | Alkaline phosphatase | Molecular biology | (66) |
| | | Amylases | Detergents, | (67) |
| | | Cellulases, Hemi cellulases | Detergents, formation of ethanol, feed, textiles | (68) |
| | | β-galactosidase | Lactose hydrolysis | (69, 70) |
| | | Lipases | Detergents, food, cosmetics | (71) |
| | | Methanogens | Methane production | (72) |
| | | Proteases, Renin, Lipases Dehydrogenases | Cheese maturation, dairy production, detergents Biotransformation's, biosensors | (59) |
| 3 | Acidophile | Amylases, Glucoamylases | Starch processing | (55, 73) |
| | | Chalcopyrite concentrate | Valuable metals recovery | (74, 75) |
| | | Proteases, Cellulases | Feed component | (66) |
| | | Sulfur oxidation | Desulfurization of coal | (64, 76) |
| 4 | Alkaliphile | Alkaliphilic halophiles | Oil recovery | (77) |
| | | Cellulases, proteases | Polymer degradation in detergents, food and feed | (55, 78-81) |
| | | Cyclodextrins, Collagenase | Hide dehairing | (82) (83) |
| | | Pectinases | Pulp bleaching<br>Fine papers and degumming | (55, 65, 84)<br>(85) (86) |
| | | Proteases, cellulases, xylanases, lipases and pullulanases | Detergents | (87) |
| | | Proteases, Elastases, keratinases | Gelatin removal on X-ray film | (88) |
| | | Various microorganisms | Antibiotics | (89) |
| | | Xylanases | Foodstuffs, chemicals and pharmaceuticals | (22, 90) |

| | | | | |
|---|---|---|---|---|
| 5 | Halophile | Proteases | Peptide synthesis | (91) |
| | | Dehydrogenases | Biocatalysts in organic media | (92) |
| | | Polyhydroxy alkanoates | Medical plastics | (93) |
| | | Rheological polymers | Oil recovery | (94) |
| | | Compatible solutes | Protein and cell protectants in a variety of industrial uses, e.g. freezing, heating | (95) |
| | | Whole microorganism | Hypersaline waste transformation and degradation.<br><br>Ion exchange resin regenerate disposal, producing poly (β -glutamic acid; PGA) & poly (β-hydroxy butyric acid; PHB) | (96) |
| | | Bacteriorhodopsin | Optical switches and photocurrent generators in bioelectronics | (97) |
| | | Eukaryotic homologues (e.g. myc oncogene product) | Cancer detection, screening antitumor drugs | (98) |
| | | Lipids | Liposomes for drug delivery and cosmetic packaging | (99) |
| | | Lipids | Heating oil | (100) |
| | | Compatible solutes | Protein and cell protectants in a variety of industrial uses (e.g. freezing, heating) | (101)<br><br>(102) |
| | | Various enzymes (e.g. nucleases, amylases, proteases) γ-Linoleic acid, β-carotene and cell extracts (e.g. *Spirulina* and *Dunaliella*) | Various industrial uses (e.g. flavourings agents) | (103) (104) |
| | | Microorganisms | Health foods, dietary supplements, food colouring, and feedstock | (105) |
| | | Microorganisms<br><br>Membranes | Fermenting fish sauces and modifying food textures and flavours<br><br>Waste transformation and degradation (e.g. hypersaline waste brines contaminated with a wide range or organics) | (106) (83) (80) (81) |
| | | | | |
| 6. | Piezophile | Whole microorganism | Formation of gels and starch granules. Food processing and antibiotic production<br><br>Microbially enhanced oil recovery process | (58) |
| | | | | |
| 7. | Metalophule | Whole microorganism | Ore-bioleaching, bioremediation, biomineralization | (29) |
| | | | | |
| 8. | Radiophiles | Whole microorganism | Bioremediation of radio-nuclide contaminated sites | (107) |

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|---|---|---|---|---|
| | | | Degradation of organo-pollutants in radioactive mixed-waste environments | (108) |
| 9. | Toxitolerant | Proteases Lipases | Peptide synthesis, enzymatic catalysis in non-aqueous solvents Esterification/ transesterification | (80) |
| | | Cyclodextrin glucanotransferase | Synthesis of non-reducing cyclodextrins<br><br>from starch, utilized in food, pharmaceutical, and chemical industries | (109) |
| | | Whole microorganism | Solvent bioremediation and biotransformation | (103) |
| 10. | Micro-aerophile | Catalase, Superoxide dismutase | Produce toxic substances like superoxide free radicals and peroxides | (110) |
| 11. | Oligotrophs/oligophiles | | Bioassay of assimilable organic carbon in drinking water | (68) |
| 12. | Organic solvent tolerant microbes | | Bioconversion of water insoluble compounds (e.g. Sterols), bioremediation, biosurfactants | (103) |

**Table 1:** Different types of Extremophiles, Enzymes and their Applications.

from extreme conditions offers huge technical and economic advantages [26]. These organisms are also exploited in production of antimicrobials which have an impact on health sector [27]. Exploration and characterization of agriculturally and industrially important halo alkalophilic bacteria from hyper saline Sambhar lake, India [28]. Recently, alkaline proteases were discovered in *Bacillus circulans* which is compatible with many detergent, thus have high potential in detergent industries. Moreover, recent studies are directed towards production of more powerful and precise novel enzymes using computational biology [29]. Studies carried out on phylogenetic profiling of niche-specific Bacilli from extreme environments of India, have also shown diversity among the species [30].

On the basis of different parameters like pH, temperature, salt concentration, pressure and water availability etc. Extremophiles are divided into many categories like alkaliphiles, acidophiles, thermophiles, psychrophiles, barophiles, xerophiles, radiophiles and halophiles etc [31].

### Thermophiles

Thermophiles are the microorganism having optimal growth temperatures ranging from 45°C to 60°C [32]. Thermophiles are found mostly in hot spring and deep ocean hydrothermal vents [1]. Thermophiles grows in the high temperatures and this property to stand in high temperatures make them more important and the enzymes extracted from these organisms are more stable at higher temperature. Due to their thermostable activity (ability to oppose thermal inactivation which is irreversible and indicates half - life of enzyme at particular temperature), these are widely used in many biochemical and biotechnological processes in various industries. They can increase the rate of reactions and lower the risk of contamination and other modifications due to rise in temperatures [33]. Therefore, it is the most explored class of extremophiles due their thermostable enzymes.

### Classification of thermophiles

They are further classified into three sub classes: 1. Simple thermophile which thrive in the temperature range of 45°C to 60°C. 2. Extreme thermophiles capable to survive in the temperature of 60°C to 80°C. 3. Hyperthermophiles in which temperature adaptive range is from 80°C to 120°C [34].

### Halophiles

Halophiles are the microorganisms which can grow in higher salt concentration (> 0.3 M) of NaCl. Halophiles are divided into sub-classes based on their survival in different salt concentration [35]. Extreme halophiles which can survive at a salt concentration of 1.5 to 5.2 M; Moderate halophiles can grow at 0.2 to 0.5 M salt concentration whereas non-halophiles shows best growth at a lower concentration (<0.2 M NaCl). Halophiles have different mechanism to survive in different saline environments. It is found in all three domains archaea, bacteria and eukaryotes Halophiles play an important role in biotech industries like detergent, textile and pulp and paper industries [36].

### pH dependent

The microbes majorly grow at neutral pH but there are many microorganisms which can grow at low or high pH [37]. They are classified as acidophiles (low pH) and alkalophiles (high pH) [38] depending on their survival at acidic and basic pH conditions.

Alkalophiles are the organisms that shows optimal growth at pH 8 or more and show slow growth at a pH of 6.5. Alkalophiles are mostly found in soda lakes and in marshy areas [39].

### Acidophiles

Acidophiles are the microorganisms, which grow at a pH of 3.0 or less. Acidophiles can also adapt themselves in different environments like high temperatures, hyper saline plains and in the environments with heavy toxic metal concentrations [40]. The enzymes that are produced by acidophilic microorganism like proteases, amylases, cellulose ligases, esterase etc. these enzymes have the ability to survive in very low pH by maintaining the pH inside the cell [41].

### Metallophiles

Metallophiles are the organism that grows in the environment possessing high metal concentration. The increasing pollution level on land and in water produce immense threat to every living being. In order to remove heavy metal toxicity from soil and water we need to exploit more metallophiles [42]. Metallophiles can be helpful in different processes like biomining, bioleaching, bioaccumulation, biomineralization, bioremediation etc. to lower down the concentration of heavy toxic metals [43].

### Metallotolerants

These microorganisms can thrive in high concentrations of heavy metals [44]. Today by use of heavy metals (Cu, Cr, Zn, Cd, Co, Pb, Ag, Hg) in various industries causing contamination of soil air and water which is consumed by wild life as well as humans can cause serious health hazards. In order to reduce the toxicity of the environment. Metallotolerant microbes can be used as they have great potential to use these heavy metals in their metabolism and convert them to less toxic or completely into new compounds which are harmless. Metallophiles are highly potent in extracting expensive metals from waste effluents of industries by use of biomining. Heavy metals presence inhibits growth of microorganisms. But some of the microorganisms can tolerate high metal concentrations by accumulation of heavy metals or either develops some efflux pumps which can remove heavy metals outside the cells.

### Barophiles

Barophiles grows at very high-pressure conditions found in deep ocean beds [45]. These organisms produce enzymes that are stable at very high pressure and temperature [46]. Deep oceans and sea are best place for these microorganisms to flourish and commonly found species are *Pyrococcus, Moritella, Methanococcus* and *Shewanella*. Barophiles have main applications in food industries. Enzymes from barophiles adapt at high pressures which can be used in sterilization process for packed food products. The research on barophiles is mainly focusing on correlation between the pressure, temperature, growth of barophiles and their molecular mechanisms of adaptation [47].

### Psychrophiles

Psychrophiles are those microorganisms which can grows at temperature of 15°C and below where other microbes cannot survive [48]. They are mainly found in deep ice zones like Arctic and Antarctica ice beds, polar zones, glaciers etc.

The family of microorganism showing traits of psychrophiles are mainly *Bacillus, Arthrobacter, Pseudomonas, Pseudoalteromonas, Vibrio, Penicillium Halorubrum, Methanogenium, Cladosporium Crystococcus* and *Candida* etc. Proteases and keratinases from psychrophiles have good use in dehairing of skin as well as in reducing the toxicity during the process. The enzymes extracted from psychrophiles are also used in detergents and food industries. The psychrophilic proteases can be used in textiles industries for stone washing, meat tenderizing and processing of fruit juice processing using pectinase [49]. These extremozymes can also be used for waste management [50].

### Xerophiles

Water is important for every living being, if it insufficient then it is extreme environment to particular organism. The organisms which adapt in desiccation develop anhydrobiosis (ability to survive from very less intercellular water and they are metabolically inactive) and these organisms are known as Xerophiles. Xerophiles grow in dry environmental conditions where water availability is very less and enzyme from these organisms are used in agriculture industry to improve the water management in desert plants [51].

### Radiophiles

Radiophiles are those microbes which can tolerate to high radiation dosage. These microorganisms can be used in treatment of nuclear wastes. They have ability to survive in high radiations, stress and even with regular DNA damage [52]. These organisms have great potential in nuclear waste remediation. *Deinococcus radiodurans* is the toughest microorganism which can withstand high radiations, high temperature, high pressure and other extreme conditions. Radiophiles are mostly found in bacteria as well as in some of the cyanobacteria [53].

### Microaerophiles

These microorganisms grown best where oxygen concentration is approximately 2 to 10% in environment it is approximately 20%. They do not require more oxygen for their growth.

### Polyextremophiles

The microorganisms which possess more than one extreme or harsh conditions are known as poly extremophiles [54]. Example, halophiles which can thrive in alkaline rich soil as well as in high temperatures like *Halonatronum saccharophilum* and *Natranaerobius thermophilus* high temperature as well as in high salt concentration called as halo-thermophile [12]. High pH and high temperatures found in hot spring water are called as acid-thermophiles.

### Adaptation of important extremophiles

### Thermophilic proteins

Thermophilic microorganism has big issue to adapt in higher temperatures without disrupting their biomolecules. Due to this ability thermophilic microbes possess many adaptive proteins which elevate their stability and function. The adaptation of thermophilic proteins is due to elevated number of hydrophobic cores, disulfide bonds, ionic bonds, co-factors, prosthetic group and their interactions. These factors help to confine the flexibility of thermostable proteins even without the denaturation at higher temperature [111].

### Halophilic proteins

Halophilic microorganisms thrive themselves under high concentration of many ions like sodium and potassium. To survive in these types of hyper ionic concentration they assimilate amino acids, sugars and other biomolecules until osmolarity inside the cell will be equal to ionic concentration outside. Protein produced by halophiles completely depends on salt to fold properly. In order to get properly fold they have some adaptations like large number of acidic residues on surface, a smaller number of hydrophobic residues and many amino acids which enhance flexibility of an enzyme [112-115].

### Psychrophilic proteins

Psychrophilic protein has many problems because of confined motion among molecules. So, in this situation psychrophiles have to increase their kinetic energy in order to finish reaction in low energy state. To adapt themselves in low energy they need to possess large hydrophobic interface, less hydrogen bonds, disulfide bonds, salt bridges. So, they can get negative charge and hence it increases stability of proteins and flexibility. In addition, they also possess some surface loops and few prolines which inhibit the movement of protein backbone [116-122].

### Piezophilic proteins

In piezophilic microorganisms adapt in high pressure environment by reducing the molecular dynamics as well as cellular structures. They also possess few glycine and prolines which inhibit the flexibility of proteins by lowering the conformational space [123-125].

### Acidophilic proteins

These microorganisms thrive in highly acidic conditions. There are many adaptation strategies to sustain in such environments such as impermeable plasma membrane which resists any change in pH. It is mainly due to fixed nature, large isoprenoid core, membrane channels internal buffers and ether linkages [126-134].

### Alkalophilic proteins

Alkalophiles are microorganisms that show growth at pH 8 or above. These microbes have special adaptive feature that they use their proton pump to maintain internal neutral pH. They thrive in extreme condition by active and passive mechanisms. In addition to polyamines, peptidoglycan (positive charge), they have polymers of cell wall (negative charge) which support strengthen the cell membranes. There are many researches going on to find out the mechanisms of protein adaptation in high pH. They had concluded that in catalytic residues they modify their hydrogen bonds which results in providing shield to catalytic residues and hence resist change in total protein charge [39,135,136].

### Other extremophilic proteins

There are many microorganisms which are included in extremophiles like radioresistant which adapt themselves in very high radiations by modifying their DNA repair mechanisms. Some extremophiles are able to survive in presence of heavy metals which has caught attention due to its important role in bioremediation either by consuming the heavy metals or converting them into less toxic compounds.

Overall, we can conclude that for adaptation in extreme environments, extremophiles have their specific proteins, enzymes and different mechanisms respective to their category, which helps them to sustain the extremities [137-140].

## Conclusion

The new class of microorganisms, called as extremophiles has emerged in the recent past. As the name suggests these microorganisms live in extreme conditions. These extreme parameters are mainly high or low temperatures, pH, high salt concentrations, low nutrient availability, low water content, heavy metals, high radiations and other conditions etc. The enzymes extracted from extremophiles are called extremozymes and are highly stable as compared to the other enzymes which are either inactive or unstable when met with extreme conditions. Extremozymes have high potential in many industries like paper and pulp, leather, food and beverages, detergents and soap, textiles, pharma, medicine and many biotech industries. Due to stable nature of extremozymes in natural form they can be exploited for betterment of humans. The study of extremophiles and their potential in different industries will be advantageous for bio-based economy and the research in this field has lot of potential.

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### Compliance with the ethical standards

### Ethical approval

This review article does not contain any studies which include human participants or animals by any author.

## Conflict of Interest

The authors declare no conflict of interest.

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