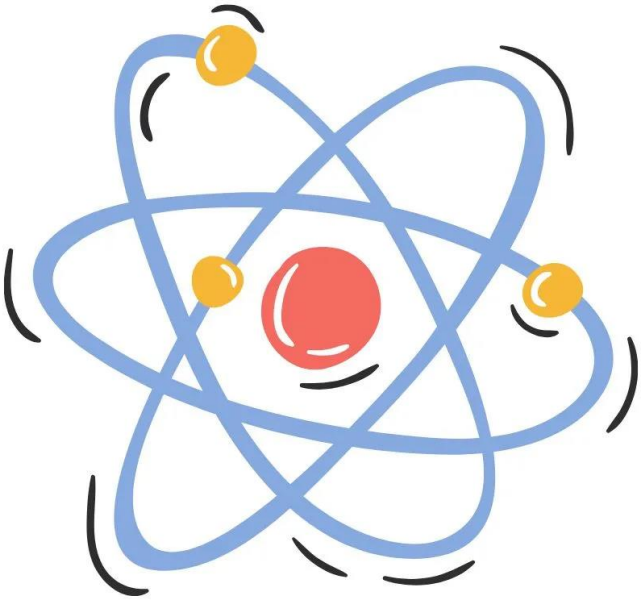

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STUDIES ON INDUSTRIAL APPLICATIONS OF EXTREMOPHILIC HALOPHILIC FUNGI

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Abstract: *Marine ecosystems, covering 71% of Earth's surface, harbor diverse life forms, including extremophilic halophilic fungi that thrive in hypersaline environments. Despite their ecological significance and biotechnological potential, halophilic fungi remain understudied. These organisms inhabit high-salt habitats like salt deserts, salterns, and certain foods, exhibiting unique adaptations to survive extreme salt, pH, and temperature conditions. Halophilic fungi produce stable enzymes, including xylanases, cellulases, amylases, and proteases, which maintain activity under stress. These enzymes hold immense potential for industries like bioremediation, wastewater treatment, and biofuel production. Their stability stems from distinct molecular features, such as acidic amino acids and hydrophobic side chains, which facilitate protective solvation and hydration shells, preventing enzyme aggregation at high salt concentrations. Elucidating these mechanisms can inform the development of sustainable industrial processes and environmental applications. By isolating and optimizing halophilic fungal enzymes, researchers can unlock cost-effective solutions to environmental and industrial challenges. Halophilic fungi thus represent a valuable resource for future biotechnology. This review provides enzymes production and applications of halophilic extremozymes and impact of halophilic extremophiles on the industrial biotechnology.*

Keywords: *Halophilic fungi, extremophiles, Hypersaline environments, stable enzymes, biotechnology, environment applications.*

1.0 Introduction

Earth is home to an immense variety of life, out of which marine environments account for most of the planet's surface 71%. Marine ecosystems sustain a wide range of microorganisms and serve as a repository for diversity. In the depths of the oceans, microorganisms that thrive in extreme conditions, particularly high salinity, are classified as halophiles. These extremophilic organisms exhibit specialized adaptations that enable them to survive and proliferate in hypersaline environments. Such habitats include salterns, saline soils, oceans, brines, high-salt foods, and salt deserts. Halophiles are present across all domains of life, yet fungi remain largely unexplored in hypersaline environments. This gap in research presents a unique opportunity to investigate the diversity and ecological roles of halophilic fungi under extreme conditions. Fungi are ubiquitous organisms capable of degrading complex substances,

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and there have been instances of their isolation from various inhospitable habitats. This resilience and adaptability in challenging environments highlight the ecological significance of fungi in biogeochemical processes Gunde-Cimerman, N. et al. (2000): Chamekh, Z. et al. (2019); Lee, H. S. (2013).

1.1 Sources of Halophilic Fungi

Halophilic extremophiles are known to have been isolated from a variety of habitats residing mostly in natural saline environments. Majority of the halophilic fungi like *Aspergillus flavus, Aspergillus gracilis, Aureobasidium pullulans, Hortaea werneckii, Sterigmatomyces halophilus, Aspergillus restrictus,* and *Aspergillus tubingensis* inhabiting salterns are reported to have been isolated from active solar saltern (Ali et al., 2014). Other notable halophilic extremophilic fungi are known to have been isolated from hypersaline environments are *Wallemia ichthyophaga, Verticillium dahliae, Scopulariopsis candida,* and *Scopulariopsis brevicaulis* (Lenassi et al., 2011; Mudau & Setati 2006).

Ascocratera manglicola, Aspergillus destruens, Aspergillus sydowii, Astrosphaeriella striatispora, Cryptovalsa halosarceicola, Linocarpon bipolaris, Phaeotheca triangularis, Rhizophila marina, and Trimmatostroma salinum are the halophilic fungi which are widely regarded to be present in the contaminated and polluted waters and soils (Bucher et al., 2004; Gonzalez-Abradelo et al., 2019; Primozic et al., 2019). Mangrove habitats accommodate fungal species like *Savoryella longispora,* and *Hypoxylon sp.*, whereas Flavodon flavus is investigated to inhabit sea grasses (Luo et al., 2005; Mtui & Nakamura 2008) see table 08

2.0 Halophilic Enzymes

The classification by Kushner and Kamekura (1988); and Ventosa, A. (1994) describes various halophilic life forms, categorizing them into four types based on their optimal growth at specific salt concentrations. Among these, moderate halophiles thrive best in sodium chloride (NaCl) concentrations of 1-3%. In contrast, extreme halophiles can grow at NaCl concentrations ranging from 15-30%. Lastly, microbes that can thrive in environments with less than 1% NaCl are classified as non-halophiles.

Research on halophilic fungi has garnered significant attention due to their remarkable ability to thrive in extreme environments, facilitating the discovery of novel biomolecules with vast industrial potential. These fungi have been found to produce a diverse array of enzymes,

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including xylanases, lipases, cellulases, proteases, and amylases, which have been extensively studied (Ali et al., 2014; Kumar et al., 2017). The economic benefits of halophilic fungi are multifaceted. Their high salt content reduces microbial contamination, minimizing the need for constant sanitation, and thereby decreasing production costs (Chen et al., 2012; Yin et al., 2015). Furthermore, halophilic fungi-derived biocontrol agents have emerged as a pressing requirement, offering a sustainable solution for environmental applications (Ali et al., 2014). In recent times the utilization of halophiles has been immensely increased due to their significant ability in the production of novel biological and ecofriendly products inclusive of enzymes.

Halophilic fungi-derived enzymes, due to their stability at elevated salt concentrations, are reported to have the ability to produce economically useful products. These fungi can also exhibit traits such as resistance to various parameters such as the ability to withstand pH of broad range and to endure temperature changes apart from being able to combat salinity (Yin et al., 2015; Zain et al., 2018). Despite the halophilic bacteria-producing enzymes, halophilic fungi are regarded as the most productive in the production of halophilic enzymes due to the labour-saving isolation of the enzymes in the industrial sector, which is the most prominent feature of halophilic fungi. On the surface of the halophilic enzymes, there is a presence of small amounts of residues that are hydrophobic, and a high number of amino acids are acidic (Flores-Gallegos et al., 2019; Madern et al., 2000; Schrek S.D & Grunden A.M 2014).

The composition of amino acids, particularly those with hydrophobic side chains like leucine, phenylalanine, and isoleucine, significantly influences protein properties. These bulky residues, in contrast to less hydrophobic and basic amino acids (e.g., threonine, arginine, serine, glycine, alanine, lysine), contribute to a net negative charge on the protein surface. The prevalence of negatively charged amino acids reduces hydrophobicity, enhancing solubility and minimizing aggregation at high salt concentrations. This feature is vital for maintaining the functional conformation of halophilic proteins (Ma et al., 2010; Karan et al., 2012). Additionally, this amino acid composition can promote the formation of random coil structures rather than α-helices, impacting protein stability and functionality (Siglioccolo et al., 2011).
Halophilic proteins employ the solvation-stabilization model to enhance solubility and maintain functionality at elevated salt concentrations (Flores-Gallegos et al., 2019; Zaccai, 2013). This mechanism involves the formation of a solvation shell, comprising solvent ions,

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around the protein. The localized regions of high ion concentrations prevent protein precipitation, ensuring stability and activity.

Furthermore, halophilic proteins form hydration shells to counteract reduced water activity. Interactions between acidic amino acids and hydrated ions generate a negatively charged surface, which aids in maintaining protein solubility (Graziano et al., 2014). At high salt concentrations, this mechanism enables halophilic enzymes to preserve their activity, stability, and solubility. Notably, halophilic enzymes are predominantly classified into two enzyme commission (EC) categories: oxidoreductases (EC 1) and hydrolases (EC 3) (Sánchez-Porro et al., 2017). These enzymes have garnered significant attention for their potential applications in industrial biotechnology.

2.1 Halophilic Hydrolases

Enzymes extracted from halophilic fungi predominantly belong to this category due to their significant applications in industrial biotechnology, which require enzyme activity and enhanced stability at elevated salt concentrations and under stress conditions (Flores-Gallegos et al., 2019; Primozic et al., 2019). Notable enzymes produced by halophilic fungi include cellulases, xylanases, amylases, pectinases, proteases, and lipases. These enzymes have extensive applications across various sectors, including biotechnological processes, the food industry, detergents, pharmaceuticals, biofuel production, and cosmetics (Ali et al., 2014; González-Abradelo et al., 2019; Mudau & Setati, 2006; Chi et al., 2007).

2.2 Halophilic Oxidoreductases

In addition to hydrolases, other enzyme classes that are widely recognized for their roles in lignin degradation include manganese peroxidases, laccases, and lignin peroxidases. These lignin lytic enzymes have significant potential in the treatment of coloured effluents, dye de-colorization, and bioremediation due to their ability to degrade alkaline and saline pollutants, as well as organic contaminants. Their effectiveness in these applications highlights their importance in environmental management and pollution mitigation(Zain et al., 2018).

2.3 Industrial Importance of Halophilic Enzymes

The application of enzymes of the classes' oxidoreductases and hydrolases in the treatment of wastewater and bioremediation is due to their ability to withstand low water activity and presence of excessive salt content. Several lignocellulosic enzymes are known to have been derived from fungi of marine habitats having potential in the conversion of lignocellulosic

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biomass, which can be utilized for the solubilization of lignin materials (Batista-García et al., 2017).

2.4 Other Classes of Enzymes

Singh et al., 2012 reported an extracellular lyase (EC 4.2.2) derived from the fungal species Aspergillus oryzae, isolated from the brown alga Dictyota dichotoma, exhibits enhanced enzyme activity when the halophilic fungi are grown in a medium supplemented with 0.2% KCl and 3% NaCl, along with additional NaCl up to 150 mM. This lyase has potential applications in the biomedical industry.

2.5 Amylases from marine halophiles

Higher plants predominantly contain the natural polymer starch, which is the most accessible form of energy. Starch comprises tightly chained amylose units, formed from compact glucose molecules linked by α-1, 4 glycosidic bonds. Additionally, amylopectin is characterized by its structure, which incorporates both α-1,4 and α-1,6 branching types, constituting the larger portion of the starch molecule (Zeeman & Kossmann et al., 2010; see Table 1). The enzyme amylase catalyzes the hydrolysis of starch molecules, which breaks them down into glucose monomers. Amylases can be further classified based on their mechanism of action and substrate specificity.

Table 01 Classification of amylases

		Enzyme	Classification	Cleavage	Product
Amylases	Exoamylase	Glucoamylase	EC 3.2.1.3	Outer regions of α-1,4	β-Cyclodextrin and glucose
		α-glucosidase	EC 3.2.1.20		
		β-amylase or maltase	EC 3.2.1.2		Maltose
	Debranching	Dextrinases	EC 3.2.1.142	α-1,6 linkages.	Maltose
		Isoamylases	EC 3.2.1.68	Pullulan.	Malto-oligosaccharides
		Pullulanases	EC 3.2.1.41	α-1,6 linkages	Maltotriose
	Endoamylases	α-amylases	EC 3.2.1.1	Internal α-1,4	Dextrins

Ali, A at el., 2014 investigated on the *Aspergillus gracilis* TISTR 3638-derived α-amylase, extracted from a solar salter, has been reported to exhibit enhanced enzyme activity at elevated

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salt concentrations. This enzyme can be utilized for mitigating metal ion contamination in industrial effluents and in the treatment of wastewater.

Chi, Y et al., 2007 one of the most fascinating enzymes in commercial processes is amylolytic enzymes. Protease and α-amylase derived from the halophilic fungi *Aureobasidium pullulans*, *Wallemia ichthyophaga*, and *Trimmatostroma salinum* are well known for their applications in industrial biotechnology, particularly in laundry detergents. Feller, G. & Gerday, C. 2003 due to the intriguing characteristics of halophilic enzymes, research has broadened industrial horizons in recent years. Various amylases from different origins, including alkaliphiles, thermophiles, acidophiles, and halophiles, have been investigated (Kuddus et al., 2011; Niehaus et al., 1999; Sharma & Satyanarayana, 2013).

3.0 Halophile derived cell wall degrading hydrolases

While starch is the primary energy reserve in higher plants, the cell wall also plays a crucial role in energy storage and structural integrity, though it is less frequently utilized and more challenging to extract. The plant cell wall is primarily composed of several polysaccharides, including cellulose, hemicellulose, and lignin. Among these, cellulose is the most abundant organic polymer on Earth and serves as a critical structural component in plant cells. Its crystalline and compact structure contributes to its high resistance to degradation and hydrolysis, making it a significant factor in plant durability and resilience (Somerville et al., 2004).

Hemicellulose, a heterogeneous group of non-cellulosic polysaccharides, includes carbohydrate polymers such as glucomannan and xylan. Lignin, another key component of the cell wall, serves to bridge cellulose fibers and works synergistically with pectin and hemicellulose to provide structural support and rigidity (Tomme et al., 1995). This complex interplay of polymers in the cell wall contributes to the overall mechanical properties and functionality of plant tissues.

Cellulases, which are critical enzymes in the breakdown of lignocellulosic biomass into fermentable sugars, are essential for biofuel production. The increasing demand for sustainable energy sources has prompted a growing interest in the production and application of these enzymes. The anticipated rise in cellulase production is driven by advances in biotechnology and genetic engineering (Wilson, 2009; Zhang et al., 2010). Additionally, the hydrolysis of xylan necessitates a variety of enzymes, each exhibiting distinct modes of action and substrate specificities, underscoring the complexity of biomass conversion processes (Li et al., 2016).

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Cellulose fibrils can be efficiently hydrolyzed by cellulolytic microorganisms that possess advanced cellulolytic systems. These microorganisms utilize organized multiprotein complexes, such as cellulosomes and xylanosomes, to enhance cellulose degradation (Ratanakhanokchai et al., 2013; Maki et al., 2009). The development of technologies for the production of second-generation ethanol from lignocellulosic biomass is crucial for advancing sustainable biofuel strategies, leveraging the inherent properties of plant materials (Chiaramonti et al., 2013; Xu et al., 2014) see table 02.

Table 02 Hydrolases capable of degrading cell wall

		Enzyme	Classification	Cleavage	Product
Xylanases		α-D-xylosidase	EC 3.2.1.177	Xylobiose and small xylo-oligosaccharides	Xylose
		β-1,4- endoxylanase	EC 3.2.1.8	Heteroxylan main skeleton along with Internal glycosidic linkages.	Polymerization degree of substrate.
Cellulases	Endoglucanases	Endo β-1,4- glucanase	EC 3.2.1.4	Intra molecular bonds of β-1,4-glucosides	New chains end.
	Exoglucanases	Exo-β-1,4-glucancellobiohydrolase	EC 3.2.1.91	Glycosidic terminals	Cellobiose
		β Glucosidase	EC 3.2.1.21	Ends of cellulose	Soluble cellulose or Glucose.

3.0 Halophilic marine proteases

Proteolytic enzymes that catalyze the hydrolysis of peptide bonds in proteins and peptides are known as proteases or peptidases. These enzymes can be classified based on several criteria:

(i) Reaction Catalyzed: Endopeptidases (EC 3.4.21-99) catalyze the hydrolysis of peptide bonds within the polypeptide chain. Exopeptidases (EC 3.4.11-19) cleave peptide bonds at the terminal amino acids.

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(ii) Molecular Structure and Homology: Proteases are grouped based on their structural features and evolutionary relationships.

(iii) Catalytic Mechanism: Peptidases are further categorized by the type of catalytic residues involved, such as serine, threonine, and aspartic acid.

Recent advances in 3D structural analysis and amino acid sequencing have led to the establishment of a refined classification system for peptidases, grouping them into clans and families. According to the MEROPS database Release 9, there are currently 251 families of peptidases documented, with over 4,000 distinct enzymes reported (Rawlings et al., 2018).

Peptidases are integral to a variety of biological processes, including modulation, regulation, protein interactions, and localization (Lopez-Otin & Matrisian, 2007). They play a crucial role in post-translational processing, contributing to both the inactivation and activation of enzymes and proteins (Rawlings & Bateman, 2009). Additionally, peptidases are involved in the inactivation of host defense mediators and can influence pathogenicity, making them attractive targets for drug development. Their unique capabilities render peptidases valuable assets in the pharmaceutical industry (Vermelho et al., 2013).

3.1 Marine derived Lipases and Esterases

The cleavage and formation of ester bonds (EC 3.1) are catalyzed by hydrolases, specifically esterases and lipases. These enzymes belong to the carboxylic ester hydrolase group (EC 3.1.1) and are classified as serine hydrolases, sharing both functional and structural characteristics. Their core structure typically features an α/β fold, which is a hallmark of hydrolases.

Esterases generally hydrolyze triglycerides and simple esters composed of short-chain fatty acids, typically those shorter than C8. In contrast, lipases are primarily active against triglycerides and are more effective with water-soluble substrates containing long-chain fatty acids (greater than C8) see the table-03.

Table 03 Esterases and Lipases nomenclature in accordance with NC-IUBMB. (ExplorEnz)

Lipases	Systematic name	EC	Reaction Catalyzed
Triacylglycerol lipase (other names- triglyceride lipase, lipase etc.)	Triacylglycerol acyl hydrolase	EC 3.1.1.3	Carboxylicester+H_2O=alcohol +carboxylate.

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Carboxylesterase (other names- serine Esterases, Esterases etc.)	Carboxylesterases	EC 3.1.1.1	Triacylglycerol+H_2O=diacylglycerol +carboxylate.

Aspergillus destruens EXF-10411 and Aspergillus sydowii EXF-12860 are halophilic fungi that can be utilized in downstream processing within industrial biotechnology, particularly for the treatment of wastewater. These organisms have demonstrated remarkable efficacy in the complete eradication of xenobiotics from saline wastewaters (greater than 1 M NaCl) (González-Abradelo et al., 2019). Other halophilic fungi, such as Marasmiellus sp. CBMAI 1062, Tinctoporellus sp. CBMAI 1061, and Peniophora sp. CBMAI 1063, are also important in the purification of colored effluents and the decolorization of dyes. Under both saline and non-saline conditions, these fungi have achieved 100% decolorization of Remazol Brilliant Blue R dye (Bonugli-Santos et al., 2010).

For instance, the extracellular halophilic enzyme β-glucosidase derived from Aspergillus sydowii BTMFS 55 has shown promising applications in biofuel production, yielding favorable outcomes (Madhu et al., 2009). Additionally, Aspergillus niger is recognized for its role in the processing of wines and juices (Sudeep et al., 2020). In the production of granular detergents, sodium chloride (NaCl) is a crucial ingredient, as it stabilizes the enzymes involved. Consequently, amylases and proteases derived from halophilic fungi are widely employed in detergent formulations (Mokashe et al., 2018; Patel and Saraf, 2015).

Despite the current underutilization of enzymes derived from these fungi, recent investigations have increased interest in enzyme-based products from extremophilic fungi. Beyond enzyme production, extremophilic fungi are known for generating a variety of other valuable products, such as carotenoids, biopolymers, and bioactive compounds, which exhibit immunostimulatory, antioxidant, antimicrobial, and cytotoxic properties (Zheng et al., 2013; Wang et al., 2007b, 2009, 2011a, 2011b; Alamillo et al., 2017; Xiao et al., 2013).

Additionally, other halophilic fungi, including Acremonium sclerotigenum, Wallemia ichthyophaga, Aspergillus sydowii, and Penicillium chrysogenum, have been identified as drug carriers through the utilization of the bio-compound hydrophobin (Pérez-Llano et al., 2020; Cicatiello et al., 2016; Zajc et al., 2013; Zhao et al., 2016).

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In summary, halophilic fungi offer immense advantages across various fields, including biotechnology and biopharmaceutics. They are extensively used as biocatalysts in both organic and non-conventional solvents, either in immobilized or free forms. Maintaining the catalytic activity of these halophilic extremophiles is crucial to overcoming significant challenges in large-scale applications, particularly through the reversal of micelles (Singh and Singh, 2017) see table 04.

3.2 Mechanism of Salt Tolerance in Halophilic Fungi: Hortea werneckii

Hortea werneckii, commonly known as the cosmopolitan black yeast, has long been recognized as a microorganism found on salty human skin, particularly on feet and hands. Its primary ecological niche is the brine of eutrophic solar salterns, although it is also isolated from various marine environments, including deep-sea habitats (Gunde-Cimerman and Zalar, 2014; Butinar et al., 2005). Notably, *H. werneckii* constitutes approximately 80% of fungal isolates from salterns.

This organism demonstrates remarkable salt tolerance, being able to withstand a wide range of NaCl concentrations, from 0% to 32%, with an optimal range between 6% and 14%. In addition to its ability to tolerate high NaCl levels, *H. werneckii* can also resist elevated concentrations of other salts, such as $MgCl_2$ and $CaCl_2$. These unique characteristics position *H. werneckii* as a potential model organism for studying eukaryotic halotolerance and the underlying mechanisms of salt adaptation see table 04 and 05.

An extreme phenotype is observed in *Hortea werneckii* under extreme halophilic conditions, characterized by increased meristematic growth, alterations in colony appearance and size, and enhanced melanization. These changes are linked to the successive synthesis of compatible solutes, which result from significant alterations in gene expression at the molecular level. Consequently, this also leads to changes in the morphology and structure of the cell wall.
The High Osmolarity Glycerol (HOG) signaling transduction pathway, part of the Mitogen-Activated Protein Kinase (MAPK) signal transduction system, is utilized by yeasts to detect increased osmolarity in the environment. This pathway is essential for cellular adaptations to temperature, oxidative stress, heavy metal exposure, and hypersaline conditions. Within this pathway, the SHO1 and SLN1 branches are structurally distinct yet functionally redundant, intersecting at Pbs2 MAPK, which acts as an activator of HOG1 MAPK (Bahn, 2008; Hohmann, 2002, 2009).

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In *H. werneckii*, components of the HOG pathway have been extensively studied (Plemenitas et al., 2014; Fettich et al., 2011; Kejzar et al., 2015). At high concentrations of NaCl, the robustness of the HOG signaling pathway is critical for the survival of H. werneckii. Key elements of the HOG pathway are involved in detecting elevated NaCl levels and regulating the transcription of osmo-responsive genes, all of which are present in the genome of *H. werneckii*.

Hortea werneckii exhibits an extreme phenotype under highly halophilic conditions, characterized by increased meristematic growth, changes in colony size and appearance, and heightened melanization. These adaptations are associated with the synthesis of osmolytes and significant changes in gene expression at the molecular level, leading to alterations in the morphology and structure of the cell wall. The HOG (High Osmolarity Glycerol) signaling transduction pathway, a component of the Mitogen-Activated Protein Kinase (MAPK) system, is critical for yeasts in sensing elevated osmolarity in their environment. This pathway is essential for adaptations to various stresses, including temperature fluctuations, oxidative stress, heavy metals, and hypersaline conditions. The branches of this pathway, SHO1 and SLN1, can both activate the Hog1 MAPK (Fettich et al., 2011). *H. werneckii* contains the cytoplasmic group VII histidine kinase HwHhk7B, which functions alongside members of the SLN1 branch to sense osmotic changes (Lenassi et al., 2007).

Table 4. Bioactive compounds from various Halophilic fungi

Source	Fungi	Affected pathogens	Bioactive compound	References
Putian Saltern of Fujian, China.	*flocculosus PT05-1*	*P. aeruginosa, C. albicans and E. aerogenes*	Pyrrole derivate Ergo steroids	Corral et al., 2018
Red sea coast of Saudi Arabia, Decay leaves of Avicennia marina.	*Hortea werneckii*	*Campylobacter jejuni and Salmonella typhimurium, Methicillin-resistant Staphylococcus aureus (MRSA).*	Fatty acid Methyl Ester (FAME) and 4-Acetoxy-2-azetidinone, sec-Butyl nitrite	Hodhod et al., 2020
Putian saltern of Fujian, China.	*Terreus PT06-02*	*P. aeruginosa, C. albicans and E. aerogenes.*	Terre lactone A Terremide A, B	Briard et al., 2019

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Soil sample	*Streptomyces cuspidosporus strain SA4*	*P. vulgaris, Shigella flexineri, Fusarium sp., S. aureus, Bacillus subtilis, E. coli, Klebsiella pneumonia, and S. typhi*	Bis(2-Methylpropyl) ester compound, 1,2- Benzene dicarboxylic acid	Sholkamy et al., 2020
Abyssal marine sediment, Barents Sea.	*Protuberus MUT 3638*	*Baumannii, S. aureus, K. pneumoniae and B. metallica.*	Bisvertinolone	Corral et al., 2018

Table 05 : Changes in plasma membrane fluidity and composition due to increased salinity in halotolerant and halophilic microorganisms, with Saccharomyces cerevisiae included for comparison as a salt-sensitive organism.

Micro organism	Fatty acids	Sterols	Fluidity	References
Debaryomyces hansenii	A substantial increase in PG and no great effect on PC, PE or anionic GPL, a decrease in PI and PS, a slight decrease in fatty acid unsaturation.	Increased sterol to GPL ratio and notable increase in ergosterol content.	No notable change in fluidity.	Turk et al., 2007, Michan et al., 2012, Russel 1993.
Saccharomyces cerevisiae		Significantly higher sterol-to-phospholipid ratio than in halophilic fungi; Almost unchanged total sterol content.	Elevated levels of fluidity at salinities that surpass optimal range.	Simonin et al., 2008, Plemenitas & Gunde-Cimerman 2011, Turk et al., 2004.
Wallemia ichthyophaga			Decreased levels of fluidity at suboptimal concentrations of NaCl and elevated at optimal concentrations.	Gunde-Cimerman.

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Hortea werneckii	Elevated levels of fatty acid saturation.	Significantly lower sterol-to -phospholipid ratio than in salt sensitive fungi; Almost unchanged total sterol content.	Highest fluidity at optimal salinities , Decreased levels of fluidity at above optimal (>15%) and suboptimal at (<5%) concentrations of NaCl.	Turk et al., 2004, 2007a, 2011.
Rhodotorula mucilaginosa			Increased fluidity at above optimal salinities.	Turk et al., 2004, 2011.
Phaeotheca triangularis	Decrease in PE and Moderate decrease in unsaturation of fatty acids.	Almost no significant change in total sterol content.	Elevated levels of fluidity than that of salt-sensitive fungi.	Turk et al., 2004.
Yarrowia lipolytica		Decreased levels of sterols.		Tunblad-Johansson et al., 1987.
Aureobasidium pullulans	Elevated levels of fatty acid unsaturation.	Significantly higher sterol-to -phospholipid ratio than in halophilic fungi; Almost unchanged total sterol content	Elevated levels of fluidity at salinities above the optimal range; decreased levels of fluidity than in halophilic fungi.	Turk et al., 2004, 2011.

Phosphatidyl glycerol (PG), Phosphatidyl serine (PS), Phosphatidyl ethanolamine (PE), Phosphatidylcholine (PC), Phosphatidyl inositol (PI), Glycerophospholipids (GPL).

H. werneckii can differentiate between various osmolytes: sorbitol and potassium chloride induce transient phosphorylation of HwHog1, while NaCl triggers continuous phosphorylation. This pattern is also reflected at the level of HOG-responsive gene transcription, where potassium chloride shows no effect, and sorbitol induces early responses (Kejzar et al., 2015). Genes associated with mitochondrial function demonstrate osmolyte-specific responses, enhancing oxidative damage protection and energy production at elevated NaCl concentrations, as confirmed by mitochondrial proteome studies. Non-ionic osmolytes promote the assembly of protein chaperones and metabolism-related enzymes in the presence of high NaCl concentrations (Vaupotic et al., 2008).

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Global transcriptomic analyses have identified several osmo-responsive genes in *H. werneckii* that are not commonly associated with other fungi or moderately salt-resistant species like *Saccharomyces cerevisiae*. The genes that are significantly represented include those related to energy supply under high NaCl conditions (up to 4.5 M NaCl) (Vaupotic & Plemenitas, 2007; Gostincar et al., 2011; Petrovic et al., 2002). More than one-third of the salt-responsive genes have demonstrated direct interaction with MAP kinase HwHog1 (Vaupotic & Plemenitas, 2007).

Proteome analysis of *H. werneckii* cell lysates reveals that its proteins are more acidic than those of the halotolerant *Debaryomyces hansenii* and the salt-sensitive *S. cerevisiae*. However, further investigation indicated that cytosolic proteins do not significantly differ from those of other studied fungal species (Gostincar et al., 2011). The primary compatible solute utilized by *H. werneckii* is glycerol (Kogej et al., 2007; Petrovic et al., 2002). The key regulatory enzyme for glycerol biosynthesis, glycerol-3-phosphate dehydrogenase, is encoded by two isoforms. The expression of these genes is upregulated by the HOG pathway in response to elevated salt concentrations (Vaupotic & Plemenitas, 2007). *H. werneckii* also produces other solutes such as mannitol, erythritol, and arabitol (Kogej et al., 2007).

In *H. werneckii*, intracellular concentrations of potassium and sodium cations are low, leading to its classification as a Na^+ excluder that prevents Na^+ influx through extrusion mechanisms (Kogej et al., 2005). The P-type ATPase (ENA-like) functions as a sodium-potassium pump, which is crucial for Na^+ extrusion. Ena-type pumps and their salt-dependent activities have been identified in *H. werneckii* (Gostincar et al., 2011). Subsequent genomic analyses revealed an enrichment of genes coding for alkali metal cation transporters, often found in multiple copies. This genetic diversity is essential for maintaining proper Na^+/K^+ ratios in fluctuating NaCl environments (Sinha et al., 2017; Lenassi et al., 2013; Plemenitas et al., 2016).

Notable biochemical features of halophily in *H. werneckii* include HMG-CoA reductase and the HAL2 gene, which encodes 3-phosphoadenosine 5-phosphatase, a key regulatory enzyme in the mevalonate pathway. HAL2 is associated with halotolerance in yeast; in *S. cerevisiae*, it encodes a lithium-sodium-sensitive protein (Glaser et al., 1993). Overexpression of DHAL2 in the halotolerant yeast *D. hansenii* enhances halotolerance (Aggarwal et al., 2005).

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The adaptations of *H. werneckii* to fluctuating saline environments involve unique roles for Hal2 proteins, which exhibit a distinctive META sequence motif linked to salt tolerance in the HwHal2B isoform (Vaupotic et al., 2008). Regulation of HMG-CoA reductase in *H. werneckii* is salinity-dependent at both protein and enzyme activity levels. Similar salinity-dependent regulation of HMG-CoA reductase has been observed in other halotolerant fungi, such as *Trimmatostroma salinum*, *Aureobasidium pullulans*, and *Eurotium amstelodami* (Vaupotic et al., 2008).

In *H. werneckii*, membrane integrity is maintained to prevent glycerol leakage, which is supported by a higher proportion of unsaturated fatty acids in the plasma membrane. This adaptation allows the membrane to retain fluidity across a wide salinity range (Turk et al., 2004, 2011). Precise regulation of membrane fluidity is facilitated by the expression of fatty acid-modifying enzymes, including elongases and desaturases (Gostincar et al., 2011). Glycerol retention is further enhanced by the melanin granules present in the cell wall, forming a continuous outer layer (Kogej et al., 2007). The genome sequencing of *H. werneckii* has revealed approximately 50 Mb of genetic material, containing around 16,000 genes, with 90% being duplicates, not due to repetitive DNA. This extensive genome is enriched with metallocation transporters and halotolerance-related genes, present in multiple copies (Sinha et al., 2017; Lenassi et al., 2013) see table 06.

Table 06: Mechanism of high survival under salt stress in halophilic/halotolerant fungi

High salinity survival mechanism		
Cellular level	Genetic level	Enzymes/Pathways
Transporter mechanism	Higher content of amino acids	Superoxide dismutase
Increase in cell wall thickness.	Gene related transport	High osmolarity in glycerol signaling pathway
		Oxidoreductase

(Perez-Llano et al., 2020, Gunde-Cimerman et al., 2018, Ruginescu et al., 2020)

4.0 Wallemia ichthyophaga: A *Basidiomycetous* Fungus

Wallemia ichthyophaga is a powdery, cosmopolitan, xerophilic filamentous fungus characterized by its brown colonies (Zalar et al., 2005). As one of the few known halophilic

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fungi within the Basidiomycota, it notably lacks a discernible mating-type (MAT) locus and teleomorph (Zajc et al., 2013). This organism thrives optimally at NaCl concentrations of 15-20%, requiring a minimum of 10% NaCl for growth, and remains metabolically active at up to 32% NaCl (Zajc et al., 2014). W. ichthyophaga has been isolated from various sources, including solar salterns, salted meats, hypersaline waters, and bitterns, with only 24 strains documented (Jancic et al., 2016; Zalar et al., 2005).

The ability of W. ichthyophaga to detect environmental changes is facilitated by its adaptations through the High Osmolarity Glycerol (HOG) signaling pathway. The components of the HOG pathway are predominantly represented in a single form, with the upstream kinase WiPbs2 interacting optimally with the functionally active MAP kinase, WiHog1B. Notably, the transcript levels of WiHog1 are dependent on salt concentration (Konte & Plemenitas, 2013). The SHO1 branch does not play a role in activating WiHog1, as evidenced by the absence of the membrane anchor Opy2 and mucins Msb2 and Hkr1, which are critical for osmosensing in other yeast species. Additionally, the poor interactions between the MAPKK Pbs2 and the Sho1 protein indicate a divergence in the osmosensing mechanism in W. ichthyophaga (Konte et al., 2016). The cytosolic group III histidine kinase WiNik1 also contributes to osmoregulation through HAMP domain repeats (Konte et al., 2016). Under optimal osmotic conditions, WiHog1 is constitutively phosphorylated, whereas it is dephosphorylated in both hypersaline and hyposaline conditions, revealing a unique salt-dependent modulation of the HOG signaling pathway.

In addition to the HOG pathway, HMG-CoA reductase in W. ichthyophaga exhibits a salt-dependent U-shaped activity pattern, acting as a salt-sensing protein in both hypersaline and hyposaline environments (Vaupotic et al., 2008). The primary compatible solutes for this fungus are glycerol and, to a lesser extent, arabitol (Zajc et al., 2014). Expression studies indicate slower responses to hyperosmotic shock and lower levels of glycerol 3-phosphate dehydrogenase (WiGPD1) (Lenassi et al., 2011). The regulation of GPD1 expression by WiHog1 further emphasizes the role of this MAP kinase in osmotic stress response (Konte & Plemenitas, 2013). Despite maintaining low intracellular levels of Na^+ and K^+ under constant salinity conditions, W. ichthyophaga shows a significant increase in these cations during hyperosmotic shock, indicating its limited adaptability to changing environments. Notably, the expression of genes coding for metal cation transporters is relatively low, with neither Na^+/H^+

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antiporters nor Na^+-exporting P-type ATPases present among the 2000 most expressed genes at high salinity (Zajc et al., 2013).

Morphological analyses of W. ichthyophaga reveal that changes in cell wall thickness and aggregation are critical for survival. The cell wall can thicken up to three-fold, while cell aggregates can enhance resilience to osmotic stress (Zajc et al., 2014). The genome of W. ichthyophaga is unusually small at only 9.6 Mb, characterized by high gene density (514 genes/Mb scaffold) and compactness (1.67%). Coding sequences comprise approximately three-quarters of the genome, predicting 4884 proteins (Zajc et al., 2013). Notably, while some orthologs in the osmosensing apparatus of the SHO1 branch of the HOG pathway are missing, homologs of the cytosolic group III histidine kinase WiNik1 are present. The genome contains genes associated with compatible solute management; however, those coding for cation transporters are limited. Some genes, such as FPS1, which encodes the aquaglyceroporin channel Fps1, and SLT1 for the plasma membrane, are found in multiple copies. Differential expression of hydrophobins—cell wall proteins—demonstrates their pivotal role in salinity adaptation, as their surface-exposed amino acids indicate adaptation to salt stress (Zajc et al., 2013) see table 07.

Table 07: Eukaryotic Halophilic and Halotolerant Fungal Proteins Involved in Sensing Increased Salinity via Signal Transduction Pathways

HOG (High Osmolarity Glycerol pathway)	*Wallemia ichthyophaga*	*Dunaliella viridis*	*Debaryomyces hansenii*	*Saccharomyces cerevisiae*	*Aureobasidium pullulans*	*Dunaliella tertiolecta*	*Hortea werneckii*
Transmembrane Osmo sensor				Sho1			HwSho1A/B
MAP Kinase Kinase Kinase	WiSte11			Ste11			HwSte11A/B
Hybrid histidine kinase	WiNik1		DhNik1	Sln1			HwHhk7A/B
Phosphorelay response regulator	WiSsk1			Ssk1			HwSsk1A/B

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MAPKKK	WiSsk2			Ssk2			HwSsk2A/B
MAP Kinase Kinase kinase	WiPbs2		DhPbs2	Pbs2			HwPbs2A/B
MAP Kinase	WiHog1A/B	DvHog1 like MAPK	DhHog1	Hog1	ApHog1	DtMaAPK-Hog1 like function.	HwHog1A/B

4.1 Anti-microbial activity of halophilic/halotolerant fungi

For the development of novel molecules with significant applications in biomedicine, the exploitation of extremophiles is essential (Giordano 2020). To meet the constant demands of the health care sector, especially with those of the global risks as resistant bacteria and cancer (Aslam et al., 2018). Fungi provided wide range of applications in antimicrobial discovery0. Ruginescu et al., 2020 presented that halophilic/halotolerant fungi do not require salt as they grow in saline environments. The table below represents the bioactive compounds with antimicrobial activities.

Figure 1. Applications of halophilic/halotolerant fungi in various fields

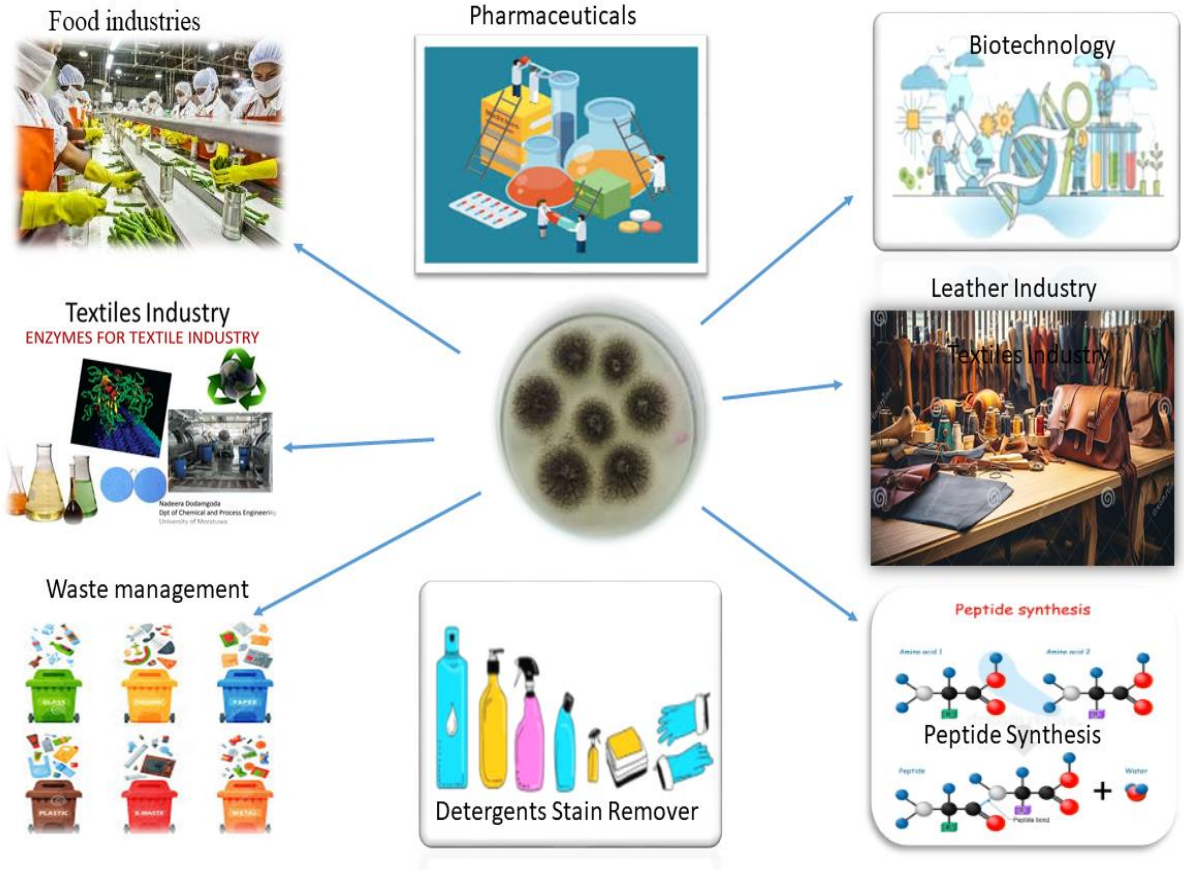

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Table 08 Industrial Applications of Halophilic and Halotolerant Fungi

S. No	Species	Habitat	Enzyme	Salinity growth conditions	Application	References
1.	*Ascocratera manglicola*	Soil, polluted water.	Xylanase, Cellulase.	1.5% (w/v) marine salts	Degradation of lignocellulosic biomass.	Bucher et al., (2004)
2.	*Aspergillus destruens*	Saline waste waters.	Peroxidase, laccase, Esterase.	1.9 M NaCl	biotechnological downstream processing of various industrial wastewaters	Gonzalez-Abradelo et al., (2019)
3.	*Aspergillus flavus*	Saltern	Cellulase	2.5 M NaCl	Bioethanol production	Ali et al., (2014)
4.	*Aspergillus gracilis*	Saltern	Xylanase, Amylase, lipase.	2.5 M NaCl	Bioremediation, Wastewater purification, Bioethanol production	Ali et al., (2014)
5.	*Aspergillus niger*	Soil	Pectinase, Xylanase,	0.5 M to 4.0 M NaCl	Processing of juices and wines	Kukateladze et al., (2009), Sudeep et al., (2020)
6.	*Aspergillus penicillioides*	Saltern	Amylase, xylanase	2.5 M NaCl	Wastewater purification, Bioethanol production	Ali et al., (2014), Bonugli-Santos et al., (2010)
7.	*Aspergillus restrictus*	Saltern	Cellulase, lipase, protease	2.5 M NaCl	Bioremediation, Bioethanol production, Fish sauce production	Ali et al., (2014), Bonugli-Santos et al., (2010)
8.	*Aspergillus sclerotiorum*	Marine environments.	Lignin peroxidase, manganese peroxidases	0.5 M NaCl	colored industrial effluent treatment.	Bonugli-Santos et al., (2010),

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9.	*Aspergillus sydowii*	Saline waste waters.	Peroxidase, laccase, Esterase	1.0 M NaCl	Bioethanol production, Biodiesel production, Flavour enhancement, Pharmaceutical Additives, Drug carriers	Gonzalez-Abradelo et al., (2019), Primozic et al., (2019)
10.	*Aspergillus tubingensis*	Saltern	β-galactosidase	1.2 M NaCl	Hydrolysis of lactose	Raol et al., (2015)
11.	*Aspergillus versicolor*	water	Xylanases, L-Glutaminase	--	Anti-cancer, Antioxidant activities.	Awad et al., (2021)
12.	*Astrosphaeriella striatispora*	Soil, contaminated water	Xylanase, Cellulase.	1.5% (w/v) marine salts	Lignin degradation	Bucher et al., (2004)
13.	*Aureobasidium pullulans*	Soil, water, sediment of saltern	Protease	Sea water	Anti-aging ingredients, UV-absorbing agents, laundry detergents, Leather tanning	Chi et al., (2007), Kogej et al., (2006)
14.	*Chaetomium indicum*	Marine habitat	Beta -1,3-Glucanase	0.2 M NaCl	Conversion of lignocellulosic biomass for bioethanol production.	Bursera et al., (2003)
15.	*Cladosporium cladosporioides*	Marine habitats	Lignin peroxidase, manganese peroxidases, Laccases	0.5 M NaCl	Anti-aging ingredients, UV-absorbing agents	Bonugli-Santos et al., (2010),
16.	*Cryptovalsa halosarceicola*	Soil, contaminated water	Xylanase, Cellulase.	1.5% (w/v) marine salts	Degradation of Lignocellulosic biomass.	Bucher et al., (2004)
17.	*Flavodon flavus*	Sea grass	Lignin peroxidase, manganese peroxidase, laccase	Diluted seawater (1:1)	Wastewater purification, Dye decolorization	Mtui & Nakamura (2008)

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18.	*Hortaea werneckii*	Salterns	Protease	1.0 and 3.0 M NaCl	Biodiesel production, Fish sauce production, Anti-aging ingredients, UV-absorbing agents	Ali et al., (2014),
19.	*Hypoxylon sp.*	Mangrove, marine habitats	Endoglucanase, cellulose, xylanase	50% (v/v) artificial seawater	Lignin breakdown.	Luo et al., (2005)
20.	*Linocarpon bipolaris*	Soil, polluted waters	Xylanase, Cellulase.	1.5% (w/v) marine salts	Degradation of lignocellulosic biomass.	Bucher et al., (2004)
21.	*Marasmiellus sp.*	Marine habitats.	Laccase	Artificial seawater	Degradation of xenobiotics	Bonugli-Santos et al., (2010)
22.	*Mucor racemosus*	Marine habitats.	Lignin peroxidase, manganese peroxidases, laccases, Phytases, Aspartic Proteases	0.5 M NaCl	Anti-cancer activity, production of cheese	Bonugli-Santos et al., (2010), Qasim et al., (2022)
23.	*Penicillium chrysogenum*	Soil	Xylanase, Cellulase.	2.0 mM NaCl	degradation of lignin, winery-derived biomass waste	Terrone et al., (2018), Azzaz et al., (2021)
24.	*Peniophora sp.*	Marine environments.	Laccase	Artificial seawater	Degradation of xenobiotics	Bonugli-Santos et al., (2010), Wesenberg et al., (2003)
25.	*Phaeotheca triangularis*	Saline waste waters.	Beta - glucosidase	3-30% NaCl	Bioethanol production, Flavour	Primozic et al., (2019), Kageyama

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					enhancement, Anti-aging ingredients, UV-absorbing agents	& Waditee (2019)
26.	*Phanerochaete chrysosporium*	Marine environments.	Lignin peroxidases, manganese peroxidases and laccases, β-Glucosidase, Mannanase, xylanase.	--	Dye decolorization, Lignin deconstruction	Wesenberg et al., (2003),
27.	*Rhizophila marina*	Soil, contaminated waters.	Cellulase, xylanase	1.5% (w/v) marine salts	Degradation of lignocellulosic biomass.	Bucher et al., (2004)
28.	*Savoryella longispora*	Mangrove, marine habitats	Xylanase, Cellulase.	50% (v/v) artificial seawater	Pulp bleaching in paper production	Luo et al., (2005), Beg et al., (2001)
29.	*Scopulariopsis brevicaulis*	Hypersaline environments	Endomannanase	1.7 M NaCl	Feed additives	Mudau & Setati (2006)
30.	*Scopulariopsis candida*	Hypersaline environments	Endomannanase	1.7 M NaCl	Feed additives	Mudau & Setati (2006)
31.	*Sterigmatomyces halophilus*	Salterns	Lipase	2.5 M NaCl	Bioremediation	Ali et al., (2014),
32.	*Tinctoporellus sp.*	Marine environments	Lignin peroxidase, Laccases	Artificial seawater	Degradation of xenobiotics	Bonugli-Santos et al., (2010), Wesenberg et al., (2003)
33.	*Trametes versicolor*	Marine environments	Lignin peroxidases, manganese peroxidases and laccases	--	Dye decolorization, Antioxidant property	Wesenberg et al., (2003)
34.	*Trimmatostroma salinum*	Saline waste waters.	Alpha-amylase	3-30% NaCl	Anti-aging ingredients, UV-absorbing	Primozic et al., (2019),

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					agents, laundry detergents	
35.	*Verticillium dahliae*	Hypersaline environments	Endomannanase endoxylanase, cellulase	1.7 M NaCl	Feed additives	Mudau & Setati (2006)
36.	*Wallemia ichthyophaga*	Hyper saline waters.	α-Amylase	1.8 and 4.5 M NaCl	Biodiesel production, laundry detergents	Lenassi et al., (2011), Primozic et al., (2019).

6.0 Conclusion

Halophilic extremophiles have garnered significant attention for their diverse biotechnological applications, particularly due to their exceptional ability to thrive under extreme conditions. This resilience is attributed to specific physicochemical properties and adaptive mechanisms that distinguish them from organisms in more moderate environments. Their stability and functional efficacy in environments characterized by low water activity and high salt concentrations render halophilic enzymes particularly valuable for industrial processes.

In addition to enzymatic applications, halophilic extremophiles produce biomolecules recognized for their antioxidant, antimicrobial, and anticancer properties, as well as pigments and biosurfactants. These halophilic extremozymes are pivotal in microbial biocatalysis, exhibiting enhanced specificity under stringent industrial conditions. However, several challenges persist in industrial biotechnology, including the limited recycling of biocatalysts, microbial contamination, and the instability of enzymes during harsh processing conditions (Chen and Jiang, 2018).

Despite their myriad applications and significant potential, halophilic extremozymes remain underexplored. There is a compelling possibility that these extremozymes harbor additional compounds with unique properties, which could contribute to environmentally friendly and sustainable practices in biotechnology.

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