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Physiological aspects of the halophilic and halotolerant fungi, and their potential applications

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Abstract

Extremophiles are organisms that can thrive under extreme environmental conditions. There are many types of extremophiles, which require different growth conditions and habitats to grow; among them are the halophilic and the halotolerant microbes. These microbes are reported to grow in habitats of high salinity regions including the sea, sediments, lakes, mines, plant and the soil. They need high carbon source and salt concentration to achieve maximum tolerable condition for their survival. High salinity survival and tolerance of these microbes are mechanized due to their osmotic and ionic stress, which are regulated through their genetic expression of enzymes, proteins, cell wall compositions and transporters. Thus, due to their robustness; the halophiles and halotolerant fungi showed high potential in health care; antimicrobial and anticancer activity, nanoparticle synthesis, enzyme production, genetics, bioremediation and other aspects. The aim of the current study was to explore the halophilic and halotolerant fungi, which are least explored for their habitats, growth requirements, and mechanism for salt resistance and tolerance. This will be followed by their biotechnological applications focusing on the biomedical industry, due to the emergence of the new multi-drug resistant pathogenic microbes.

Keywords: Extremophiles, Fungi, Halophiles, Halotolerant, Physiology

1. Introduction

Extremophilic microbes survive under extreme ecosystems such as hot; cold, salty, sandy, highly acidic and alkaline habitats, due to their physiological and metabolic activities. Because of their robustness, the extremophilic microbes not only have more attention as sources of novel bioactive compounds, but also for understanding the basis of evolution of life (Chung *et al*., 2019). It is observed that halophilic microorganisms were studied for their stress adaptation mechanisms and biotechnological applications (Chamekh *et al*., 2019). Halophilic fungi had been previously isolated from different habitats including terrestrial; aquatic, decaying matter and dried foods (González-Abradelo *et al*., 2019; Tafer *et al*., 2019; Pérez-Llano *et al*., 2020). High salt tolerating groups are more diverse and all types of microorganisms such as bacteria; algae, fungi and protozoa have been studied from different environmental and geographical samples (Chamekh *et al*., 2019). Halophilic bacteria are the most dominantly studied halophiles, compared to the halophilic fungi. The literatures and available reports showed that halophilic fungi have greater potential in terms of exploration of novel species with new bioactivities. Thus, the objective of the current study was to exploit the halophilic and halotolerant fungi; with a special focus on their physiological and biotechnological applications.

2. Habitats

A previous study of Ali *et al*., (2019) revealed that salt concentration makes categorization of the halophiles as slight halophiles (2-5 %), moderate halophiles (5-20 %) and extreme halophiles (20-30 %). Fungal diversity is very important, and the physiological behavior as well as metabolic secretions varies according to the geographical locations. The solar salterns; dead sea, arid desert, sebkha, soil, terrestrial habitats mud had been explored for their biodiversity studies (Moubasher *et al*., 2018; Chamekh *et al*., 2019). The biodiversity studies explored *Aspergillus* sp. strain A4, *Chaetomium* sp. strain H1, *Penicillium vinaceum*, *Gymnoascus halophilus*, *Wallemia* sp. and *Ustilago cynodontis* fungi from the great Sebkha of Oran, Algeria (Chamekh *et al*., 2019). Recently, *Aspergillus glaucus* is known to be 'China Changchun halophilic *Aspergillus* (CCHA)', which was isolated from the surface of plants growing near a salt mine in Jilin, China (Qiu *et al*., 2020). Fungi isolated from Miani-Hor Mangrove Forest Soil from Pakistan were recorded to be *Aspergillus chevalieri*; *Pleosporaceae* spp., *Alternaria tenuissima* and *A. alternata* (Khan *et al*., 2020). *G. halophilus* and *Wallemia* spp. were isolated from the Lake soil located in Algeria (Chamekh *et al*., 2019). A previous study conducted by González-Martínez *et al*., (2017) reported that sediment samples are sources of the halophilic fungi. *Scopulariopsis* spp.; *Aspergillus* spp., *Peniophora* spp. and *Cladosporium* spp. have been isolated from the Gulf sediment located in North America (González-Martínez *et al*., 2017). Similarly, Corral *et al*., (2018) highlighted that *P. rubens* and *A. protuberus* were isolated from Bonna sediment located in New England. Since the halophiles are known for their salt tolerance; exploration of salt mine and saltern has resulted in the discovery of diversified species including; *A. salisburgensis* isolated from a salt mine (Tafer *et al*., 2019), *Wallemia ichthyophaga* and *Paranerita triangularis* from solar saltern (Primožič *et al*., 2019) and *Yarrowia lipolytica* recovered from solar saltern saline (Alamillo *et al*., 2017). Other habitats include plants such as *A. glaucus* isolated from leave surface (Qiu *et al*., 2020) and *A. montevidensis* ZYD4 from *Medicago sativa* L. Plant (Liu *et al*., 2017a). Sugarcane bagasse is also recorded to be the habitat for halotolerant fungi such as *A. sydowii* (González-Abradelo *et al*., 2019). Results presented in Table. (1) demonstrate habitats of the halophilic and the halotolerant fungi, where it can be noticed that *Aspergillus* spp. are more dominant and located at every regional habitat.

Table 1: Different habitats of the halophilic fungi around the world (2017-2021)

Halophilic\ Halotolerant fungi	**Habitat**	**Country**	**Reference**
A. chevalieri, Pleosporaceae spp., *Alternaria tenuissima, A. alternata*	Miani-Hor Mangrove Forest Soil	Pakistan	(Khan *et al*., 2020)
Gymnoascus halophilus, Wallemia sp.	Great Sebkha (Lake) Soil	Algeria	(Chamekh *et al*., 2019)
A. glaucus	Plant surface	China	(Qiu *et al*., 2020)
A. destruens	Canvass of an oil painting	Slovenia	(González-Abradelo *et al*., 2019)
Wallemiai chthyophaga *Paranerita triangularis*	Solar saltern	Slovenia	(Primožič *et al*., 2019)
A. sydowii	Sugarcane Bagasse	Slovenia	(González-Abradelo *et al*., 2019)
Scopulariopsis sp.; *Aspergillus* sp.; *Peniophora* sp. and *Cladosporium* sp.	Gulf Sediments	North America	(González-Martínez *et al*., 2017)
Magnuscella marinae	Sponge sample	Europe	(Anteneh *et al*., 2019)
A. loretoensis	marine sediment of Loreto Bay	California	(González-Martínez *et al*., 2019)
A. atacamensis, A. salisburgensis	Old wooden staircase in a salt mine	Austria	(Martinelli *et al*., 2017)
A. loretoensis	Marine sediment of Loreto Bay	México	(González-Martínez *et al*., 2019)
A. salisburgensis, A. sclerotialis	Salt Mines	Austria	(Tafer *et al*., 2019)

A. montevidensis ZYD4	*Medicago sativa* L. plant	China	(Liu *et al.*, 2017a)
Yarrowia lipolytica	Solar salter saline	Maxico	(Alamillo *et al.*, 2017)
Penicillium rubens, P. chrysogenum	Goliat oil field	-	(Corral *et al.*, 2018)
P. chrysogenum	Repparfjord coastal	Norway	(Corral *et al.*, 2018)
P. rubens, A. protuberus	Bonna sediment	New England	(Corral *et al.*, 2018)
A. sydowii, Microascus trigonosporus	Sea	Kansas	(Corral *et al.*, 2018)

3. Isolation and nutritional requirements of the halophilic fungi

Isolation of the halophilic fungi from the microbial communities of high salt contents is challenging, and mainly depends on the enrichment followed by cultivation using different nutritional parameters (Anteneh *et al*., 2019). Diversities among the halophilic or the halotolerant fungi depend on their habitats and physiological requirements. Ruginescu *et al*., (2020) reported that the mechanisms used by these types of microorganisms to handle the osmotic pressure exerted with the high salt concentration of the surrounding medium are extremely diverse. Ability of the halophilic microorganisms to adapt to wide range of environments is attributed to the physicochemical conditions including overall salinity; temperature and nutrientional status, which is reflected in their heterogeneity within the different communities (Menasria *et al*., 2019). Many salt habitats have been described as suitable for the survival of halophiles such as; the lakes and rivers, salterns, soils, salted foods, leaves of some plants and wall paintings (Ruginescu *et al*., 2020).

The nutritional and cultivation parameters of the halophilic fungi includes carbon source; pH of medium, temperature and salt concentration. The most commonly used media for isolation of halophilic fungi include potato dextrose agar (Chamekh *et al*., 2019; Qiu *et al*., 2020), yeast extract peptone dextrose agar (González-Martínez *et al*., 2017) and malt extract agar (Pérez-Llano *et al*., 2020); with the reported incubation period of 7 days (González-Martínez *et al*., 2019). The media ingredients contain carbon sources with high concentration of sugars, which support the growth of fungi. The study conducted by Anteneh *et al*., (2019) highlighted that the lower acid pH produced during fermentation helps in bacterial inhibition; sometimes antibiotics may be supplemented in the medium for bacterial inhibition. Table. (2) shows isolation of the different halophilic fungi at different locations; based on their cultivational and nutritional parameters. González-Martínez *et al*., (2017) found that the majority of halophilic fungi are growing within 7-15 days; with two contradictory reports from the Gulf Sediments, Mexico, reporting the requirement of lower growth period of 48 h for *Scopulariopsis* sp., *Aspergillus* sp., *Peniophora* sp., *Cladosporium* sp., whereas a longer growth period of 2 months is required for *Cladosporium* spp.; *Aspergillus* sp. and

Talaromyces spp. Other study of Anteneh *et al*., (2019) revealed that *Magnuscella marinae* which was isolated from marine sponge samples of Australia required two months to be cultivated in different media supplemented with higher salt concentrations. Therefore, the geographical locations have different cultivation and nutritional requirements, but hold the main functions for the individual fungal physiology.

Table 2: Isolation of halophilic fungal spp. based on different cultivation and nutritional parameters (2017-2021)

Halophilic fungi	Source	Cultivation parameters	Nutritional parameters	References
A. sydowii BMH-0004	Sugarcane bagasse, Mexico	7 days at 30-37°C	Malt extract agar (MEA), Czapek yeast extract agar (CYA), Creatine-sucrose agar (CREA) with 5 % NaCl	(Pérez-Llano *et al*., 2020)
Magnus cellamarinae	Sponge sample, Marine, Australia	27°C in dark for 2 months	Starch yeast extract peptone agar (SYP), Asparagine peptone agar (APA), Natural seawater agar (SWA), Humic acid vitamin agar (HV), Nutrient agar (NA), Marine agar (MA), Tryptone soya agar (TSA with different concentrations of NaCl (0- 30 %)	(Anteneh *et al*., 2019)
Scopulariopsis sp., *Aspergillus* sp., *Peniophora* sp., *Cladosporium* sp.	Gulf Sediments, Loreto Bay, California, Baja Mexico.	18-20^{0}C in dark for 48 h	Yeast extract peptone dextrose (YEPD) agar with 100 % seawater	(González-Martínez *et al*., 2017)
Aspergillus sp., *G. halophilus*, *Fusarium* sp., *Chaetomium* sp., *Microascusmanginii, Cladosporium sp.*	Soil sample, Great Sebkha of Oran, Northwestern of Algeria	25^{0}C for 10 days	Potato dextrose agar with NaCl conc. 0- to 20 %; with an interval of 2.5 %	(Chamekh *et al*., 2019)
A. glaucus 'CCHA'	Solar salt field, Northeast China	6 days at 30^{0}C	Potato extract + 20 g\l · glucose, supplemented with 250 g\l NaCl	(Qiu *et al*., 2020)

M. marinae	Sponge samples, South Australian marine environments	27°C for 3 weeks	1, 2, 3, 4, 5, 10, 15, 25, and 30 % NaCl + Potato dextrose media	(Anteneh *et al*., 2019)
Cladosporium sp., *Aspergillus* sp., *Talaromyces* sp.	Gulf Sediments, Loreto-bay, Maxico	2 months, at room temperature (RT)	YEPD agar (yeast extract peptone dextrose agar + ampicillin 50 µg\ ml) + 50 % natural filtered (0.45 µm) sea water	(González-Martínez *et al*., 2017)
A. sydowii, A. destruens	Sugarcane bagasse, canvass of an oil painting, Slovenia	15 days at 28°C	Synthetic saline medium (SM) and MEA agar plates with added NaCl (MEA-SM), benzo-α-pyrene and phenanthrene (1:1)	(González-Abradelo *et al*., 2019)
Trimatostroma salinum, Wallemia ichthyophaga, Hortaea werneckii, Phaeotheca triangularis	Solar salterns, Slovenian	5-7 days, RT	Malt extract agar + 17 % NaCl	(Primožič *et al*., 2019)
A. protuberus MUT 3638	Sub-sea sediments, Barents Sea	7 to 14 days, RT	Artificial seawater media \Seawater minimal medium\ Malt extract agar\ Luria bertani + 3, 5, 10, 15, 20 and 25 % NaCl	(Corral *et al*., 2018)

4. Salt tolerance mechanisms of the halophilic fungal spp.

Fugal species that tolerate high salinity are known as halo tolerant fungi, which can withstand the high osmotic pressure (water loss from the fungal cells and built up of solutes in the cytosol), and the ionic stress (rise in the level of Na^+). According to Gunde-Cimerman *et al*., (2018), fungal adaptation necessitates their ability to tolerate fluctuating salinities and higher salt concentration. The use of compatible solutes is the most representative technique for salt adaptation, as presented in *Hortaea werneckii* and *Wallemia ichthyophaga* by Plemenitas *et al*., (2014). A previous study conducted by Chung *et al*., (2019) highlighted those fungi that are grown in saline containing media; accumulate compatible solutes in the cytosol in order to keep the intracellular Na^+ below the toxic levels. *A. sydowii* had been studied extensively due to its osmo protective strategies during the optimal and extreme saline conditions. Modification in the thickness of the cell wall and the lamellar structure; along with decrease in the chitin content and rise in the content of α and β-glucan were observed. Furthermore, a change in the hydrophobin gene expression under high salinity was also reported (Pérez-Llano *et al*., 2020). The proteome of *A. sclerotialis* showed increased proportion of alanine; glycine and proline, compared to the proteome of the non-halophilic species (Tafer *et al*., 2019). The hypersaline conditions have lower water activities and higher salt concentrations, and cause the halophilic microorganisms to produce the essential industrial enzymes. Several studies on the halophilic hydrolases produced by the halophilic fungi such as the amylases; cellulases, lipases and proteases have been reported; however, fewer studies focused on the enzymes recovered from the obligate halophilic fungi (Chamekh *et al*., 2019; Ruginescu *et al*., 2020). *Aspergillus* sp. strain A4, *Chaetomium* sp. strain H1, *P. vinaceum*, *Gracilibacillus halophilus*, *Wallemia* sp. and *Ustilago cynodontis* demonstrated the highest enzymatic indexes (Chamekh *et al*., 2019). Different transporters were identified in the halophilic fungi to achieve ion gradient, including K^+ efflux; K^+ uptake, P-type ATPase and Na^+ efflux (Gunde-Cimerman *et al*., 2018). This is the reason for survival of the halophilic fungi under the extreme salty conditions. Survival of the halophilic fungi under high salinity is mechanized at the cellular, genetic, enzyme and\or metabolic pathways, and is schematically presented in Fig. (1). In addition, list of the different halophilic fungi that were isolated from different extreme habitats and their salt tolerance concentrations are summarized in Table (3).

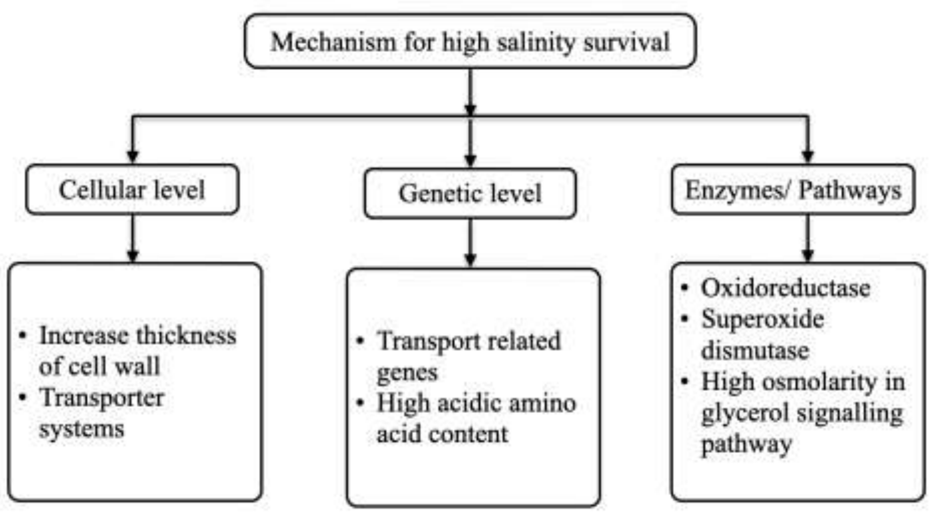

Fig. 1. Mechanisms of survival of the halophilic fungi under high salinity (Gunde-Cimerman *et al*., 2018; Pérez-Llano *et al*., 2020; Ruginescu *et al*., 2020)

Table 3: The halophilic and halotolerant fungi recovered from different sources based on their NaCl requirements

S. No	Name of the halophilic\ halotolerant fungi	Source	NaCl (%)	Reference
1	*Gymnoascus halophilus*, *Wallemia* sp.	Great Sebkha of Oran, Algeria	10 % 2.5-7.0 %	(Chamekh *et al*., 2019)
2	*A. salisburgensis*	Salt Mine, Austria	20 %	(Tafer *et al*., 2019)
4	*A. glaucus,* CCHA	Plant surface, China	25 %	(Qiu *et al*., 2020)
5	*A. sydowii, A. caesiellus*	Sugarcane bagasse	6 % 3 %	(González-Abradelo *et al*., 2019)
6	*A. destruens*	Canvass of an oil painting, Slovenia	12 %	(González-Abradelo *et al*., 2019)
7	*Wallemia ichthyophaga*, *Paranerita triangularis*	Slovenian Sečovlje solar salterns	10-25 %	(Primožič *et al*., 2019)
8	*Trimatostroma salinum*, *Wallemia ichthyophaga*, *Hortaea werneckii*, *Phaeotheca triangularis*	Solar salterns, Slovenia	17 %	(Primožič *et al*., 2019)

5. Applications of the halophilic and halotolerant fungi, and their future aspects

The different applications and future aspects of the halophilic and halotolerant fungi in the different sectors (i.e. health care, antimicrobial and anticancer activity, nanoparticle synthesis, enzyme production, genetics, bioremediation and other aspects) are show in Fig. (2).

5.1. Healthcare

Nowadays humans are creating lots of innovations in all the fields, which make the human's life better and\or enhance the quality of their health. Humans are fighting against different kinds of diseases (Stansberry *et al*., 2019). Traditionally, human diseases were treated based on the ancient healthcare systems of Ayurveda; Siddha, Unani and Chinese medicine; however, their modern medication system include; homeopathy, naturopathy and allopathy (Dhingra, 2020). Nevertheless, the current ways of living; eating habits and changes in ecosystem have created lot of destructions in the human lives, and allowed invasion of the pathogenic microbes as well. The previous study of Flandroy *et al*., (2018) revealed that the multidrug resistant pathogens are often heard and common ones to be observed now, which caused the human lives to be at greater risk and prone to diseases.

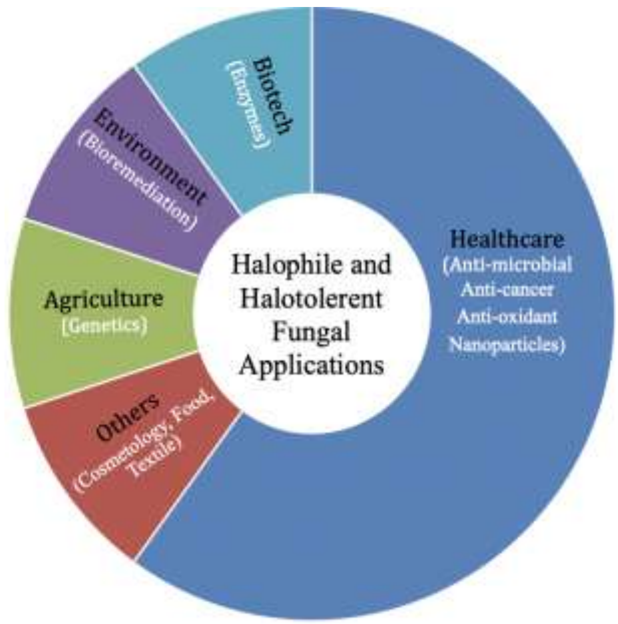

Fig. 2. Sector-wise applications of the halophilic and halotolerant fungi (Rajput, 2017; Corral *et al*., 2018; Ali *et al*., 2019; Namnuch *et al*., 2021)

This has created difficulties among the researchers concerning detailed studies of the pathogenic microorganisms up to the genetic level. Accordingly, it has become very crucial to formulate new drugs that can change the scenario of drug resistance. It is to be noted that most of the drugs approved by the Food and Drug Administration (FDA) are made from microbes; including fungi and bacteria (Andrei *et al*., 2019). This provides insight for more exploration of the halophilic fungi that have wider applications in the field of health sector.

5.1.1. Anti-microbial activity

The exploitation of extremophiles is particularly important for the development of new molecules with potential applications in biomedicine (Giordano, 2020). Efforts are being primarily aimed at meeting the urgent health needs; particularly to those associated with two of the most serious global risks mainly; cancer and resistant bacteria (Aslam *et al*., 2018). Antibiotic resistance propagation is creating world threat towards the public health (Ben *et al*., 2019). During the continuous research on natural products; fungi provided the wider foundation for antimicrobials discovery. Ruginescu *et al*., (2020) reported that the halophilic and halotolerant fungal spp. that live in natural hypersaline environments do not require salt, as they can grow and adapt to wide range of salinities; ranging from freshwater to infused NaCl solutions. The halophilic fungi as sources of bioactive compounds with antimicrobial activities are presented in Table (4).

Table. 4. The bioactive compounds produced by the halophilic fungi and their antimicrobial activities

Source	Fungi	Affected pathogens	Bioactive compound	Reference
Abyssal marine sediment, Barents Sea.	*A. protuberus* MUT 3638	*S. aureus*, *K. pneumoniae*, *A. baumanii* and *B. metallica*	Bisvertinolone	(Corral *et al*., 2018)
Putian saltern of Fujian, China	*A. flocculosus* PT05-1	*E. aerogenes, P. aeruginosa,* and *C. albicans*	Ergosteroids Pyrrole derivate	(Corral *et al*., 2019)
Putian saltern of Fujian, China	*A. terreus* PT06-2	*E. aerogenes, P. aeruginosa,* and *C. albicans*	Terremide A, B Terrelactone A	(Briard *et al*., 2019)
Decay leaves of *Avicennia marina*, Red Sea Coast of Saudi Arabia	*Hortaea werneckii*	Methicillin-resistant *Staphylococcus aureus* (MRSA), *Campylobacter jejuni* and *Salmonella typhimurium*	4-Acetoxy-2-azetidinone, sec-Butyl nitrite and Fatty Acid Methyl Ester (FAME)	(Hodhod *et al*., 2020)
Soil Sample	*Streptomyces cuspidosporus* strain SA4	*Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, S. typhi, Bacillus subtilis, Proteus vulgaris, Shigella flexineri, Candida albicans, and Fusarium* sp.	1,2-Benzenedicarboxylic acid, bis(2-Methylpropyl) ester compound	(Sholkamy *et al*., 2020)

5.1.2. Anticancer potential

A recent study conducted by Abdel-Razek *et al*., (2020) revealed that natural products are called as bioactive molecules, which include anticancer drugs produced by microorganisms. According to Pham *et al*., (2019), most of the well-established anticancer natural products have been obtained from plant cells, but microorganisms are also excellent alternatives because of these facts; 1) diversity of the microbial world, 2) ease of manipulation, and 3) ease of physiological screening to discover new natural products with antitumor properties. In spite of the fact that bacterial cells communicate with the tumor cells in ways other than the metabolites do in laboratory; however, bacterial metabolites are believed to be the most reliable way to prevent cancer cells from surviving (Sedighi *et al*., 2019). Recently, more emphasis is focused on the extremophiles as new sources of the novel biomolecules (Corral *et al*., 2019). The halophilic and halotolerant microorganisms that live in hypersaline environments are thought to be reliable sources of antitumor metabolites. Several studies have reported the roles of metabolites of the halophilic microorganisms in treating cancer disease Rani and Kalaiselvam, 2013; Corral *et al*., 2018; Ali *et al*., 2019; Ruginescu *et al*., 2020).

5.1.3. Role in nanoparticle synthesis

Nanotechnology has spread its roots in almost all the application fields. One of the innovations is nanoparticle (NP) synthesis, which are the smallest particles; whose size range from 1-100 nm (Rajput, 2017). These NP are synthesized through three methods namely; physical, chemical and green synthesis, depending on their fields of application as demonstrated in Fig. (3).

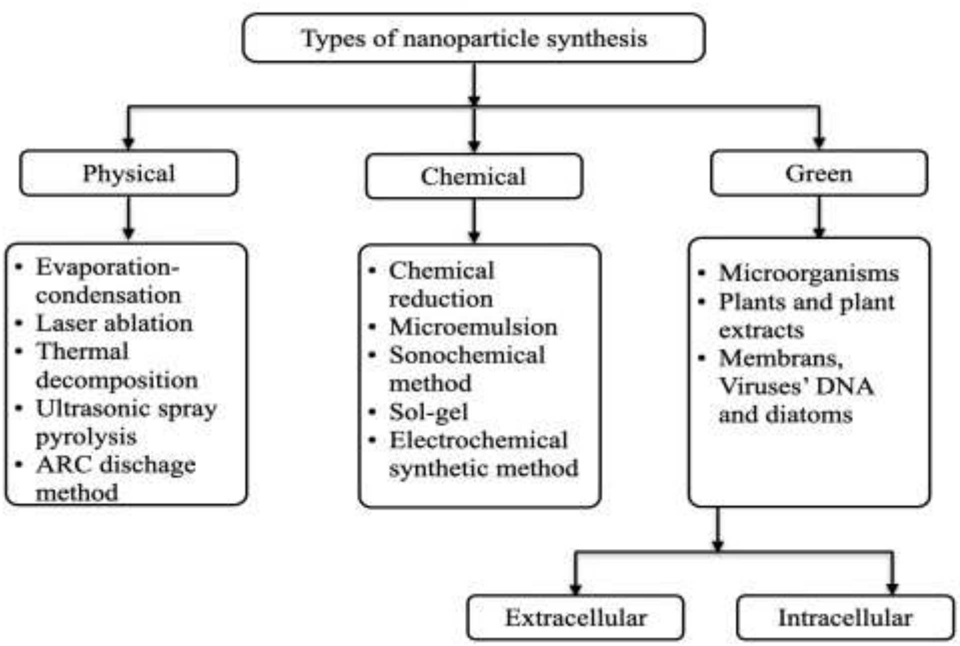

Fig. 3. Different methods used for synthesis of the nanoparticles (NPs) (Ijaz *et al*., 2020; Salem and Fouda, 2021)

Green synthesis refers to the production of NPs from microbes (Salem and Fouda, 2021). Nanoparticles are widely used in different fields including; textile, healthcare, food, agriculture, electronics, environment, renewable energy and various manufacturing processes (Jeevanandam *et al*., 2018). With respect to healthcare, many applications primarily drug delivery systems; are being reported for the NPs, as this method does not harm any tissue or organ while delivering the drug to the body (Chauhan *et al*., 2020). The NPs produced from the halophilic fungi also act as inhibitory agents against wide range of microbes, and are known also to have potent antimicrobial activities (Wang *et al*., 2017). The process for green synthesis of the NPs is shown in Fig. (4).

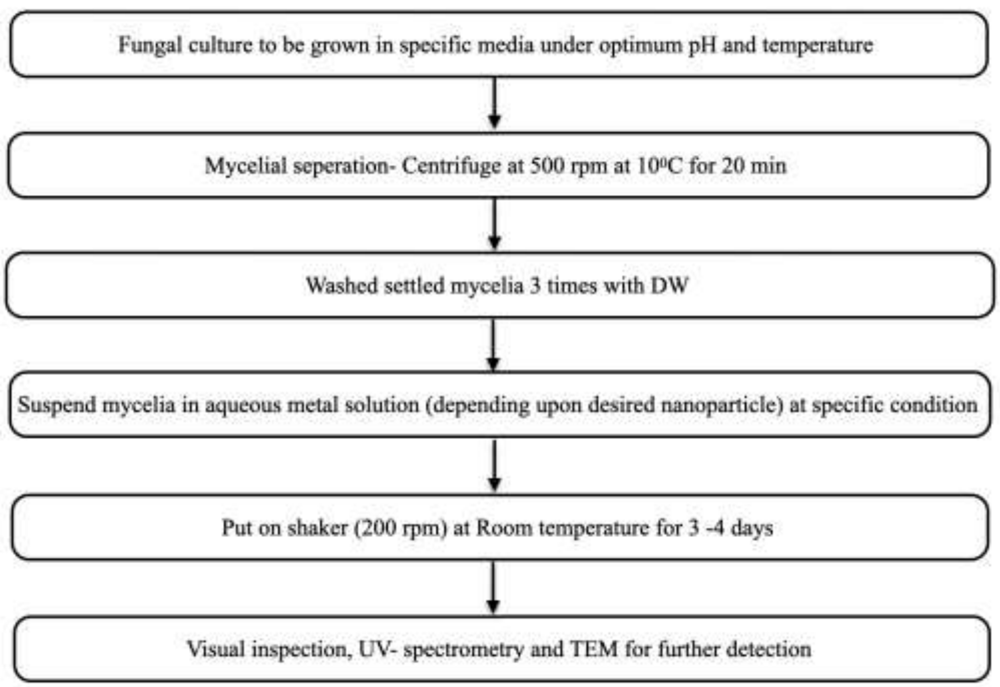

Fig. 4. Green synthesis of the NPs using the halophilic fungi (Huston *et al*., 2021)

5.2. Biotechnological applications (Enzymes production)

The extremophilic fungi are diverse groups of microbes with wide ranges of adaptation properties; genetic diversities and metabolic mechanisms that allow them to survive under high-salt containing environments. These fungi have numerous applications in the field of biotechnology; medicine, agriculture, genetics and others. Different applications of the halophilic and\or the halotolerant fungi have been developed (Satyanarayana *et al*., 2005); mainly the ability of these fungi to produce numerous enzymes. During the study of Chamekh *et al*., (2019), the halophilic fungi were isolated from Sebkha in Oran, Algeria, and their enzymatic activities were investigated. It was recorded that they could produce different types of enzymes including; lipases, amylases, proteases and cellulases; in presence of NaCl-rich medium. Production of the halotolerant protease by the halophilic fungus *A. flavus* can be applied in several industrial processes; as in normal cases, the salty solutions are used to inhibit activity of the normal proteases (Razzaq *et al*., 2019). Enzyme activity of α-amylase produced by the halophilic fungus *Engyodontium album* is found to increase with increasing NaCl concentration, and it has lot of applications in food; pharmaceutical and the detergent industries (Elyasi Far *et al*., 2020). *A. flavus* KUB2 produces the halophilic cellulases which have wide commercial applications (Namnuch *et al*., 2021). The different species of halophilic fungi associated with the production of specific enzymes, and their fields of applications are summarized in Table. (5).

Table 5. The different species of halophilic fungi characterized by the production of various enzymes

Halophilic fungi	**Source**	**Enzymatic activity**	**References**
A. subramanianii A2	Great Sebkha of Oran	Lipase, Amylase, Protease, Cellulase	(Chamekh *et al*., 2019)
A. terreus S11	Great Sebkha of Oran	Lipase, Cellulase	(Chamekh *et al*., 2019)
P. mariaecrucis S19	Great Sebkha of Oran	Amylase, Protease, Cellulase	(Chamekh *et al*., 2019)
A. flavus KUB2	Soil with decomposed plant materials and wood decayed samples	Cellulase, xylanase	(Namnuch *et al*., 2021)
Trimatostroma salinum EXF-295, *Wallemia ichthyophaga* EXF-5676, *Hortaea werneckii* EXF- 225, *Phaeotheca triangularis* EXF-206	Solar salterns	α-amylase, Protease, β-glucosidase	(Primožič *et al*., 2019)
A. flavus	Suez Gulf	Chitinase	(Beltagy *et al*., 2018)

5.3. Agriculture (Genetic)

The halophilic fungi help the humans to understand how survival is possible at extreme conditions by studying their biogeochemical cycles, which includes sulfur; nitrogen, carbon, and phosphorous that operate under extreme conditions (Martínez-Espinosa, 2020). Transcriptomics research is extremely beneficial in understanding gene expression and repression in the living organism. *A. salisburgensis*, which is a halophilic fungus compared to the halotolerant fungus *A. sclerotialis* showed difference in the transport-related genes (Tafer *et al*., 2019). Moreover, studying of *A. sydowii* under different salinity conditions showed expression profiles on the basis of stress-related genes; with an increase in the expression of the solute transporter coding gene (Pérez-Llano *et al*., 2020). The comparative studies conducted among *Wallemia ichthyophaga*, *Hortaea werneckii* and *Aureobasidium pullulans* demonstrated higher salinity tolerance, which was correlated with the superoxide dismutase, catalase and peroxiredoxin coding genes, also known as the oxidative stress response genes; responsible for both antioxidant activity and salt tolerance (Gostinčar and Gunde-Cimerman, 2018).

The increasing global problem of the agricultural salinization has put forward the halotolerant and halophilic fungi as emerging sources of target genes, which can be used to increase salt tolerance in plants at the genetic level (Egamberdieva *et al*., 2019). Salt tolerance mechanism in plants is beneficial; as it can protects the plants from being destroyed with the increasing soil pollution (Kamran *et al*., 2019). Recently, Gupta *et al*., (2021) reported that modifications in the model microorganisms can also be carried out, which show symbiotic association with the plants and indirectly help them to resist high salt concentrations.

5.4. Environment (Bioremediation)

Bioremediation is the process of removing pollutants from the environment through the use of living organisms; primarily the microbes (Abatenh *et al*., 2017). Although the halophilic microorganisms have been studied as promising bioscience agents used for the degradation of pollutants at high salt concentrations, however their bioremediation potentials still remain unclear (González-Abradelo *et al*., 2019). Pollutants are present in almost every eco-system (air, water and land), and their presence is becoming harmful to the communities that live in these systems. It is necessary to remove the harmful pollutants from the environment, which can be accomplished through bioremediation (Liu *et al*., 2017b). Due to robustness of the extremophilic halophilic and halotolerant fungi, they have important roles in bioremediation applications even under harsh conditions.

According to Briffa *et al*., (2020), heavy metals are part of the pollution in the marine environment and they become difficult to remove. Fungi; with their potentials to remediate the soil polluted by heavy metals are generally adaptive to the polluted environment. Jin *et al*., (2021) proposed that these fungi might have evolved mechanisms to escape the damage that heavy metals have created to them. *A. flavus*, *A. restrictus* and *Sterigmatomyces halophilus* are halophilic fungi that have metal degradation potencies; with their abilities to ingest Copper (Cu) metal (Bhattacharjee and Goswami, 2018). Meanwhile, *A. flavus* and *S. halophilus* have the abilities to degrade cadmium and Zinc; those chemicals are also degraded by *A. gracilis* and *S. halophilus* (Kalpana *et al*., 2018).

Agricultural lands have become polluted due to the excessive usage of pesticides; herbicides and the other harmful chemicals. These pollutants have completely reduced the ability of soil to provide beneficial components for growth of the plants, due to accumulation of the chemicals inland (Meena *et al*., 2020). Huge quantities of petroleum pollutants enter the environment causing serious degradations of the land and the water ecosystems (Fowzia and Fakhruddin, 2018). Microbial biodegradation of petroleum hydrocarbon pollutants has long been considered as eco-friendly; cost-effective and efficient biological treatment; however, their functionalities are reduced at extreme environments. So, there is a great need for enzymes and\or compounds which can operate under extreme conditions (Li *et al*., 2019). Enzymes such as lipase; amylase, protease, cellulase, β-glucosidase and chitinase are produced by the different halophilic fungi, which thus have greater applications during the process of bioremediation (Beltagy *et al*., 2018; Chamekh *et al*., 2019; Primožič *et al*., 2019; Namnuch *et al*., 2021). The halophilic fungi with their sources and produced enzymes are presented in Table (5).

5.5. Other applications (Cosmetology/ Food/ Textile)

Colors are having high demands in the fields of biotechnology related to food; textiles, medicine and cosmetics (Sajid and Akbar, 2018). Fungi are microbes that can create powerful pigments, which can be used as dyes or food colorants in the form of secondary metabolites. This application is possible with the help of pigments extracted from the halophilic and the halotolerant fungi. These pigments are compounds which absorb the light of specific wavelength at the visible region (Heer and Sharma, 2017).

Fungi are known to produce diverse range of pigments, including melanin; anthraquinones, hydroxyanthraquinones, azaphilones, carotenoids, oxopolyene, quinones and naphthoquinone (Kalra *et al*., 2020). Melanin pigment isolated from the halophilic fungus *Hortaea wernecki* has a cosmetic role (Sajid and Akbar, 2018), and is used also in the textile as well as in the food industries (Heer and Sharma, 2017). *Talaromyces verruculosus* produces red pigment (Chadni *et al*., 2017), whereas *Trypethelium eluteriae* produces Trypethelonamide A as red pigment, and 5-hydroxytrypethelone; (–)-trypethelone, (+)-trypethelone, (+)-8-hydroxy-7-methoxytrypethelone as dark violet-red pigments (Basnet *et al*., 2019). The marine fungus *Talaromyces albobiverticillius* 30548 also produces a red pigment (Venkatachalam *et al*., 2019). Isolation of the bioactive molecule Funiculosone from the endolichenic fungus named *Talaromyces funiculosus* yielded three compounds, one of them is ravenelin; a yellow colored homogeneous powder with good antimicrobial activity, thus making it beneficial in the pharmaceutical and food industries (Padhi *et al*., 2019). *Penicillium* sp. (GBPI_P155) isolated from the Himalayan region is found to produce an orange pigment, which is a derivative of the carotenoids (Pandey *et al*., 2018). Similarly, the fungus *Monascus ruber* M7 has the ability to produce Azaphilone pigment, which is orange; red or yellow in color (Chen *et al*., 2017). In considering the overall benefits of fungal diversity; fungi are regarded as the cell factories for pigments production, where researchers can experiment with their functionalities (Kalra *et al*., 2020).

Conclusion

This study discussed living of the halophilic and the halotolerant fungi under the harsh environmental conditions, and began with the basic understanding of the fungal habitats. Based on these fungal nutrient requirements, they are considered to be extremophiles. They are halophilic in nature, and require NaCl for their growth and survival. They exhibit different mechanisms to survive under extreme conditions. Furthermore, the enzymes isolated from these fungi have higher activities under high salt concentrations, and have wide range of industrial applications. Synthesis of the bioactive compounds and their inhibitory activities make the halophilic fungi blessing to the health care industry in fighting against the multidrug-resistant pathogens. Synthesis of nanoparticle is also the greatest breakthrough; because they have wide variety of applications, and play important roles in the drug delivery systems. In addition, the halophilic fungi are also very essential in the field of cosmetic industry. In conclusion, many fungi exist in different environments, but still remain unexplored. Accordingly, there is a need for further researches to discover and isolate the novel halophilic and halotolerant fungi, which have more potential in helping the mankind with their diverse products; beneficial mainly toward the human health.

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Conflict of interest

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6. References

Abatenh, E.; Gizaw, B.; Tsegaye, Z. and Wassie, M. (2017). The role of microorganisms in bioremediation- a review. Open Journal of Environmental Biology. 2(1): 038-046. https://doi.org/10.17352/OJEB.000007.

Abdel-Razek, A.S.; El-Naggar, M.E.; Allam, A.; Morsy, O.M. and Othman, S.I. (2020). Microbial natural products in drug discovery. Processes. 8(4): 1-19. https://doi.org/10.3390/pr8040470

Alamillo, E.; Reyes-Becerril, M.; Cuesta, A. and Angulo, C. (2017). Marine yeast *Yarrowia lipolytica* improves the immune responses in Pacific red snapper (*Lutjanus peru*) leukocytes. Fish and Shellfish Immunology. 70: 48-56. https://doi.org/10.1016/j.fsi.2017.08.036.

Ali, I.; Khaliq, S.; Sajid, S. and Akbar, A. (2019). Biotechnological applications of halophilic fungi: past, present, and future. In: Tiquia-Arashiro S. and Grube M. (Eds); Fungi in Extreme Environments: Ecological Role and Biotechnological Significance. Springer Nature Switzerland AG, Cham, Switzerland. 291-306. https://doi.org/10.1007/978-3-030-19030-9_15

Andrei, S.; Droc, G. and Stefan, G. (2019). FDA approved antibacterial drugs: 2018-2019. Discoveries. 7(4): 1-11. https://doi.org/10.15190/d.2019.15

Anteneh, Y. S.; Brown, M. H. and Franco, C.M.M. (2019). Characterization of a halotolerant fungus from a marine sponge. BioMed Research International. 2019(3456164): 1-9. https://doi.org/10.1155/2019/3456164.

Aslam, B.; Wang, W.; Arshad, M.I.; Khurshid, M.; Muzammil, S.; Rasool, M.H. et al. (2018). Antibiotic resistance: a rundown of a global crisis. Infection and Drug Resistance. 11: 1645-1658. https://doi.org/10.2147/IDR.S173867

Basnet, B.B.; Liu, L.; Zhao, W.; Liu, R.; Ma, K.; Bao, L. et al. (2019). New 1, 2-naphthoquinone-derived pigments from the mycobiont of lichen *Trypethelium eluteriae* Sprengel. Natural Product Research. 33(14): 2044-2050. https://doi.org/10.1080/14786419.2018.1484458.

Beltagy, E.A.; Rawway, M.; Abdul-Raouf, U.M.; Elshenawy, M.A.; and Kelany, M.S. (2018). Purification and characterization of theromohalophilic chitinase producing by halophilic *Aspergillus flavus* isolated from Suez Gulf. The Egyptian Journal of Aquatic Research. 44(3): 227–232. https://doi.org/10.1016/j.ejar.2018.08.002

Ben, Y.; Fu, C.; Hu, M.; Liu, L.; Wong, M.H. and Zheng, C. (2019). Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review. Environmental Research. 169: 483-493. https://doi.org/10.1016/j.envres.2018.11.040

Bhattacharjee, T. and Goswami, M. (2018). Heavy Metals (As, Cd & Pb) Toxicity and detection of these metals in ground water sample: a review on different techniques. International Journal of Engineering Science Invention. 7(1): 12-21.

Briard, B.; Mislin, G.L.A.; Latgé, J.P. and Beauvais, A. (2019). Interactions between *Aspergillus fumigatus* and pulmonary bacteria: current state of the field, new data, and future perspective. Journal of Fungi. 5(2): 48-68. https://doi.org/10.3390/jof5020048.

Briffa, J.; Sinagra, E. and Blundell, R. (2020). Heavy metal pollution in the environment and their toxicological effects on humans. Heliyon. 6(e04691): 1-26. https://doi.org/10.1016/j.heliyon.2020.e04691

Chadni, Z.; Rahaman, M.H.; Jerin, I.; Hoque, K.M. and Reza, M.A. (2017). Extraction and optimisation of red pigment production as secondary metabolites from *Talaromyces verruculosus* and its potential use in textile industries. Mycology. 8(1): 48-57. https://doi.org/10.1080/21501203.2017.1302013

Chamekh, R.; Deniel, F.; Donot, C.; Jany, J.L.; Nodet, P. and Belabid, L. (2019). Isolation, identification and enzymatic activity of halotolerant and halophilic fungi from the great Sebkha of Oran in Northwestern of Algeria. Mycobiology. 47(2): 230-241. https://doi.org/10.1080/12298093.2019.1623979

Chauhan, G.; Madou, M.J.; Kalra, S.; Chopra, V.; Ghosh, D. and Martinez-Chapa, S.O. (2020). Nanotechnology for COVID-19: Therapeutics and Vaccine Research. ACS Nano. 14(7): 7760-7782. https://doi.org/10.1021/acsnano.0c04006

Chen, W.; Chen, R.; Liu, Q.; He, Y.; He, K.; Ding, X. et al. (2017). Orange, red, yellow: biosynthesis of azaphilone pigments in *Monascus* fungi. Chemical Science. 8(7): 4917-4925. https://doi.org/10.1039/C7SC00475C

Chung, D.; Kim, H. and Choi, H.S. (2019). Fungi in salterns. Journal of Microbiology. 57(9): 717-724. https://doi.org/10.1007/s12275-019-9195-3

Corral, P.; Amoozegar, M.A. and Ventosa, A. (2019). Halophiles and their biomolecules: recent advances and future applications in biomedicine. Marine Drugs. 18(1): 33-67. https://doi.org/10.3390/md18010033

Corral, P.; Esposito, F.P.; Tedesco, P.; Falco, A.; Tortorella, E.; Tartaglione, L. et al., (2018). Identification of a sorbicillinoid-producing *Aspergillus* strain with antimicrobial activity against *Staphylococcus aureus*: a new polyextremophilic marine fungus from Barents Sea. Marine Biotechnology. 20(4): 502-511. https://doi.org/10.1007/s10126-018-9821-9

Dhingra, S. (2020). Govt wants to merge allopathy, homoeopathy, Ayurveda into one health system, plans 2030 launch. https://theprint.in/health/govt-wants-to-merge-allopathy-homoeopathy-ayurveda-into-one-health-system-plans-2030-launch/509983/

Egamberdieva, D.; Wirth, S.; Bellingrath-Kimura, S.D.; Mishra, J. and Arora, N.K. (2019). Salt-tolerant plant growth promoting *Rhizobacteria* for enhancing crop productivity of saline soils. Frontiers in Microbiology.10(2791): 1-18. https://doi.org/10.3389/fmicb.2019.02791.

Elyasi Far, B.; Ahmadi, Y.; Yari Khosroshahi, A. and Dilmaghani, A. (2020). Microbial alpha-amylase production: progress, challenges and perspectives. Advanced Pharmaceutical Bulletin. 10(3): 350-358. https://doi.org/10.34172/apb.2020.043

Flandroy, L.; Poutahidis, T.; Berg, G.; Clarke, G.; Dao, M.C.; Decaestecker, E. et al. (2018). The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems. The Science of the Total Environment. 627: 1018-1038. https://doi.org/10.1016/j.scitotenv.2018.01.288

Fowzia, A. and Fakhruddin, A. (2018). A Review on environmental contamination of petroleum hydrocarbons and its biodegradation. International Journal of Environmental Sciences and Natural Resources. 11(2): 63-69. https://doi.org/10.19080/IJESNR.2018.11.555811

Giordano, D. (2020). Bioactive molecules from extreme environments. Marine Drugs. 18(12): 640-646. https://doi.org/10.3390/md18120640

González-Abradelo, D.; Pérez-Llano, Y.; Peidro-Guzmán, H.; Sánchez-Carbente, M. del R.; Folch-Mallol, J.L.; Aranda, E. et al. (2019). First demonstration that ascomycetous halophilic fungi (*Aspergillus sydowii* and *Aspergillus destruens*) are useful in xenobiotic mycoremediation under high salinity conditions. Bioresource Technology. 279: 287-296. https://doi.org/10.1016/j.biortech.2019.02.002

González-Martínez, S.; Galindo-Sánchez, C.; López-Landavery, E.; Paniagua-Chávez, C. and Portillo-López, A. (2019). Correction to: *Aspergillus loretoensis*, a single isolate from marine sediment of Loreto Bay, Baja California Sur, México resulting as a new obligate halophile species. Extremophiles. 23(5): 569-571. https://doi.org/10.1007/s00792-019-01114-7

González-Martínez, S.; Soria, I.; Ayala, N. and Portillo-López, A. (2017). Culturable halotolerant fungal isolates from Southern California Gulf sediments. Open Agriculture. 2(1): 292-299. https://doi.org/10.1515/opag-2017-0033

Gostinčar, C. and Gunde-Cimerman, N. (2018). Overview of Oxidative Stress Response Genes in Selected Halophilic Fungi. Genes. 9(3): 143-156. https://doi.org/10.3390/genes9030143

Gunde-Cimerman, N.; Plemenitaš, A. and Oren, A. (2018). Strategies of adaptation of microorganisms of the three domains of life to high salt concentrations. FEMS Microbiology Reviews. 42(3): 353-375. https://doi.org/ 10.1093/femsre/fuy009

Gupta, S.; Schillaci, M.; Walker, R.; Smith, P.M.C; Watt, M. and Roessner, U. (2021) Alleviation of salinity stress in plants by endophytic plant-fungal symbiosis: Current knowledge, perspectives and future directions. Plant and Soil. 461: 219-244. https://doi.org/10.1007/s11104-020-04618-w

Heer, K. and Sharma, S. (2017). Microbial pigments as a natural color: A review. International Journal of Pharmaceutical Sciences and Research. 8(5): 1913-1922. https://doi.org/10.13040/IJPSR.0975-8232.8

Hodhod, M.S.E.D.; Gaafar, A.R.Z.; Alshameri, A.; Qahtan, A.A.; Noor, A. and Abdel-Wahab, M. (2020). Molecular characterization and bioactive potential of newly identified strains of the extremophilic black yeast *Hortaea werneckii* isolated from Red Sea mangrove. Biotechnology and Biotechnological Equipment. 34(1): 1288-1298. https://doi.org/10.1080/13102818.2020.1835535

Huston, M.; DeBella, M.; DiBella, M. and Gupta, A. (2021). Green synthesis of nanomaterials. Nanomaterials 11(8): 2130-2159. https://doi.org/10.3390/nano11082130

Ijaz, I.; Gilani, E.; Nazir, A. and Bukhari, A. (2020). Detail review on chemical, physical and green synthesis, classification, characterizations and applications of nanoparticles. Green Chemistry Letters and Reviews. 13(3): 223-245. https://doi.org/10.1080/17518253.2020.1802517

Jeevanandam, J.; Barhoum, A.; Chan, Y.S.; Dufresne, A. and Danquah, M.K. (2018). Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein Journal of Nanotechnology. 9: 1050-1074. https://doi.org/10.3762/bjnano.9.98

Jin, T.; Shi, C.; Wang, P.; Liu, J. and Zhan, L. (2021). A review of bioremediation techniques for heavy metals pollution in soil. IOP Conference Series: Earth and Environmental Science. 687(012012): 1-7. https://doi.org/10.1088/1755-1315/687/1/012012

Kalpana, V.N.; Kataru, B.A.S.; Sravani, N.; Vigneshwari, T.; Panneerselvam, A. and Devi Rajeswari, V. (2018). Biosynthesis of zinc oxide nanoparticles using culture filtrates of *Aspergillus niger*: Antimicrobial textiles and dye degradation studies. OpenNano. 3: 48-55. https://doi.org/10.1016/j.onano.2018.06.001

Kalra, R.; Conlan, X.A. and Goel, M. (2020). Fungi as a potential source of pigments: harnessing filamentous fungi. Frontiers in Chemistry. 8(369):1-23. https://doi.org/10.3389/fchem.2020.00369

Kamran, M.; Parveen, A.; Ahmar, S.; Malik, Z.; Hussain, S.; Chattha, M.S. et al. (2019). An overview of hazardous impacts of soil salinity in crops, tolerance mechanisms, and amelioration through selenium supplementation. International Journal of Molecular Sciences. 21(1): 148-175. https://doi.org/10.3390/ijms21010148

Khan, S.A.; Akbar, A.; Permpornsakul, P.; Yanwisetpakdee, B.; Chen, X.; Anwar, M. et al. (2020). Molecular diversity of halophilic fungi isolated from mangroves ecosystem of Miani Hor, Balochistan, Pakistan. Pakistan Journal of Botany. 52(5): 1823-1829. https://doi.org/10.30848/PJB2020-5(34)

Li, H., Li, X., Yu, T., Wang, F. and Qu, C. (2019). Study on extreme microbial degradation of petroleum hydrocarbons. IOP Conference Series: Materials Science and Engineering. 484: (012040): 1-6. https://doi.org/10.1088/1757-899X/484/1/012040

Liu, K.H.; Ding, X.W.; Narsing Rao, M.P.; Zhang, B.; Zhang, Y.G.; Liu, F.H. et al. (2017a). Morphological and transcriptomic analysis reveals the osmoadaptive response of endophytic fungus *Aspergillus montevidensis* ZYD4 to high salt stress. Frontiers in Microbiology. 8(1789): 1-12. https://doi.org/10.3389/fmicb.2017.01789

Liu, S.H.; Zeng, G.; Niu, Q.; Liu, Y.; Zhou, L.; Jiang, L.U., et al. (2017b). Bioremediation mechanisms of combined pollution of PAHs and heavy metals by bacteria and fungi: a mini review. Bioresource Technology. 224: 25-33. https://doi.org/10.1016/j.biortech.2016.11.095

Martinelli, L.; Zalar, P.; Gunde-Cimerman, N.; Azua-Bustos, A.; Sterflinger, K. and Piñar, G. (2017). *Aspergillus atacamensis* and *A. salisburgensis*: two new halophilic species from hypersaline/arid habitats with a phialosimplex-like morphology. Extremophiles. 21(4): 755-773. https://doi.org/10.1007/s00792-017-0941-3

Martínez-Espinosa, R.M. (2020). Microorganisms and their metabolic capabilities in the context of the biogeochemical nitrogen cycle at extreme environments. International Journal of Molecular Sciences. 21(12): 4228-4247. https://doi.org/10.3390/ijms21124228

Meena, R.; Kumar, S.; Datta, R.; Lal, R.; Vijayakumar, V.; Brtnicky, M. et al. (2020). Impact of agrochemicals on soil microbiota and management: a review. Land. 9(2): 34-56. https://doi.org/10.3390/land9020034

Menasria, T.; Monteoliva-Sánchez, M.; Benammar, L.; Benhadj, M.; Ayachi, A.; Hacène, H. et al. (2019). Culturable halophilic bacteria inhabiting Algerian saline ecosystems: A source of promising features and potentialities. World Journal of Microbiology and Biotechnology. 35(9): 132-148. https://doi.org/10.1007/s11274-019-2705-y

Moubasher, A.A.H.; Abdel-Sater, M.A. and Soliman, Z.S.M. (2018). Diversity of yeasts and filamentous fungi in mud from hypersaline and freshwater bodies in Egypt. Czech Mycology. 70(1): 1-32.

Namnuch, N.; Thammasittirong, A. and Thammasittirong, S.N.R. (2021). Lignocellulose hydrolytic enzymes production by *Aspergillus flavus* KUB2 using submerged fermentation of sugarcane bagasse waste. Mycology. 12(2): 119-127. https://doi.org/10.1080/21501203.2020.1806938

Padhi, S.; Masi, M.; Cimmino, A.; Tuzi, A.; Jena, S.; Tayung, K. et al. (2019). Funiculosone, a substituted dihydroxanthene-1,9-dione with two of its analogues produced by an endolichenic fungus *Talaromyces funiculosus* and their antimicrobial activity. Phytochemistry. 157: 175-183. https://doi.org/10.1016/j.phytochem.2018.10.031

Pandey, N.; Jain, R.; Pandey, A. and Tamta, S. (2018). Optimisation and characterisation of the orange pigment produced by a cold adapted strain of *Penicillium* sp. (GBPI_P155) isolated from mountain ecosystem. Mycology. 9(2): 81-92. https://doi.org/10.1080/21501203.2017.1423127

Pérez-Llano, Y.; Rodríguez-Pupo, E.C.; Druzhinina, I.S.; Chenthamara, K.; Cai, F.; Gunde-Cimerman, N. et al. (2020). Stress reshapes the physiological response of halophile fungi to salinity. Cells. 9(3): 525-546. https://doi.org/10.3390/cells9030525

Pham, J.V.; Yilma, M.A.; Feliz, A.; Majid, M.T.; Maffetone, N.; Walker, J.R. et al. (2019). A review of the microbial production of bioactive natural products and biologics. Frontiers in Microbiology. 10(1404): 1-27. https://doi.org/10.3389/fmicb.2019.01404

Plemenitas, A.; Lenassi, M.; Konte, T.; Kejzar, A.; Zajc, J.; Gostinacar, C. et al. (2014). Adaptation to high salt concentrations in halotolerant/halophilic fungi: a molecular perspective. Frontiers in Microbiology. 5(199): 1-13. https://doi.org/10.3389/fmicb.2014.00199

Primožič, M.; Čolnik, M.; Knez, Ž.; and Leitgeb, M. (2019). Release of halophilic extremozymes by mechanical cell disruption. Acta Chimica Slovenica. 66: 217-228. https://doi.org/10.17344/acsi.2018.4799

Qiu, W.; Li, J.; Wei, Y.; Fan, F.; Jiang, J.; Liu, M. et al. (2020). Genome sequencing of *Aspergillus glaucus*‘ CCHA ’provides insights into salt-stress adaptation. Peer Journal. 8 (e8609): 1-21. https://doi.org/10.7717/peerj.8609

Rajput, N. (2017). Development of nanotechnology in India: A review. IOSR Journal of Applied Physics. 9(3): 45-50. https://doi.org/10.9790/4861-0903034550

Rani, M.H.S. and Kalaiselvam, M. (2013). Antibacterial activity of halophilic fungi isolated from solar from solar saltern at tuticorin. World Journal of Pharmacy and Pharmaceutical Sciences. 2(2): 536-545.

Razzaq, A.; Shamsi, S.; Ali, A.; Ali, Q.; Sajjad, M.; Malik, A. and Ashraf, M. (2019). Microbial Proteases Applications. Frontiers in Bioengineering and Biotechnology. 2(2): 536-545. https://doi.org/10.3389/fbioe.2019.00110

Ruginescu, R.; Gomoiu, I.; Popescu, O.; Cojoc, R.; Neagu, S.; Lucaci, I. et al. (2020). Bioprospecting for novel halophilic and halotolerant sources of hydrolytic enzymes in brackish, saline and hypersaline lakes of Romania. Microorganisms. 8(12):1903-1924. https://doi.org/10.3390/microorganisms8121903

Sajid, S. and Akbar, N. (2018). Applications of fungal pigments in Biotechnology. Pure and Applied Biology. 7(2): 922-930. https://doi.org/10.19045/bspab.2018.700111

Salem, S.S., and Fouda, A. (2021). Green Synthesis of metallic nanoparticles and their prospective biotechnological applications: An overview. Biological Trace Element Research. 199(1): 344-370. https://doi.org/10.1007/s12011-020-02138-3

Satyanarayana, T.; Raghukumar, C. and Shivaji, S. (2005). Extremophilic microbes: diversity and perspectives. Current Science. 89(1): 78-90. https://doi.org/10.31080/ASMI.2020.03.0466

Sedighi, M.; Zahedi Bialvaei, A.; Hamblin, M.R.; Ohadi, E.; Asadi, A.; Halajzadeh, M. et al. (2019). Therapeutic bacteria to combat cancer; current advances, challenges, and opportunities. Cancer Medicine. 8(6): 3167-3181. https://doi.org/10.1002/cam4.2148

Sholkamy, E.N.; Muthukrishnan, P.; Abdel-Raouf, N.; Nandhini, X.; Ibraheem, I.B.M. and Mostafa, A.A. (2020). Antimicrobial and antinematicidal metabolites from *Streptomyces cuspidosporus* strain SA4 against selected pathogenic bacteria, fungi and nematode. Saudi Journal of Biological Sciences.

27(12): 3208-3220. https://doi.org/10.1016/j.sjbs.2020.08.043

Stansberry, K.; Anderson, J. and Rainie, L. (2019). The internet will continue to make life better. Pew Research Center-Internet and Technology. https://www.pewresearch.org/internet/2019/10/28/4-the-internet-will-continue-to-make-life-better/

Tafer, H.; Poyntner, C.; Lopandic, K.; Sterflinger, K. and Piñar, G. (2019). Back to the salt mines: genome and transcriptome comparisons of the halophilic fungus *Aspergillus salisburgensis* and its halotolerant relative *Aspergillus sclerotialis*. Genes. 10(5): 381: 1-21. https://doi.org/10.3390/genes10050381

Venkatachalam, M.; Gérard, L.; Milhau, C.; Vinale, F.; Dufossé, L. and Fouillaud, M. (2019). Salinity and temperature influence growth and pigment production in the marine-derived fungal strain *Talaromyces albobiverticillius* 30548. Microorganisms. 7(1): 10. https://doi.org/10.3390/microorganisms7010010

Wang, L.; Hu, C. and Shao, L. (2017). The antimicrobial activity of nanoparticles: present situation and prospects for the future. International Journal of Nanomedicine. 12: 1227-1249. https://doi.org/10.2147/IJN.S121956