Review paper

Study of Antimicrobial Peptides (AMPs) of Micro-organisms from Extreme and Unusual Environment to combat Multiple Drug Resistant Microbes and Cancer

Monish Bisen, Shruti Agrawal

Abstract

Antimicrobial peptides (AMPs) are naturally occurring antibiotics found in a variety of species, including arthropods, plants, mammals, and bacteria. Apart from antibacterial action, AMPs have been shown to stimulate chemokine synthesis, expedite angiogenesis and tissue repair, and regulate apoptotic in complex organisms. As a result, AMPs may be used to fight many drug-resistant microbes and cancer development. Initially, it was believed that their antibacterial mechanism was exclusively based on an increment in pathogenic cell membrane permeability, however it's been shown that many AMPs do not alter membrane permeability at fatal concentrations. Rather than that, they exert their influence through blocking a variety of activities, including protein and cell wall production, as well as enzymatic activities. Whereas resistance to these compounds is rare, many pathogens have evolved a variety of methods to evade their toxicity, including surface modification, development of efflux pumps, and protease secretion. This review discusses the different mechanism of action of AMPs and the evolution of pathogen resistance to drug-resistant bacteria and cancer.

Key Words: AMP; Antimicrobial compounds; Anticancer compounds; Biocompatibility.

1. Introduction

Antimicrobial peptides (AMPs) are physiologically active compounds generated through a diverse range of organisms as part of their immunity. The main function of AMPs is to protect the host by inflicting cytotoxic on entering pathogenic bacteria; however, they also function as immunological modulators in higher species [1]. Due to their wide spectrum of action, low toxicity, and reduced resistance growth by target cells, AMPs are regarded a potential and prospective therapeutic option for the future [2]. Variety secondary structure has been discovered of AMPs, which includes helices, α-strands with one or even more disulphide bridges, loops, and expanded structures [3]. The diversity of structural configuration of AMPs is critical for their wide range antibacterial action. Apart from these characteristics' hydrophobicity, charge, size, and peptide self-consortium to the cell membranes all contribute to their wide range antibacterial action [4]. The compact size of AMPs enables fast diffusion and release of peptides outside the cell, that is necessary for triggering an early defence response against harmful microorganisms. The variations in the lipid makeup of bacterial and eukaryotic cell membranes provide AMPs with their targets [5]. The antibacterial characteristic of AMPs against target cells was largely reliant to the preferred engagement of peptides with contagious cells, that enables them to kill particular target cells while causing no harm to host cells. Additionally, the net charge and hydrophobicity of AMPs are critical for their cellular interaction with certain cellular membranes in order to exhibit antimicrobial properties [6]. AMPs have been found in a range of organisms, including plants, environmental libraries, animals & insects (Table 1). Presently, the peptide database of antimicrobial has about two thousand AMPs.

Table 1: Diverse sources of AMPs.

AMPs	Source	References
Thionins, plant defensins	Plants	**[7]**
Nigrocin 1 & 2, Japonicin-1 & 2, temporin-1Od, tigerin-1, maximin-1	Amphibians	**[8]**
Callinectin, penaeidin, crustin, stylicin, astacidin 2, armadillidin, homarin, scygonadin, hyastatin, arasin	Crustaceans	**[9]**
Syringomycin, syringostatins iturin, bacillomycin	Bacteria	**[10]**
Histatin, protegrin, indolicidin, lactoferricin	Mammals	**[11]**
Strongylocins, filamin A, centrocins	Echinoderms	**[12]**

Echinocandins, aculeacins, leucinostatins, helioferins, aureobasidin	Fungi	**[13]**

2. Antimicrobial Peptides: A Quick Overview

Antimicrobial peptides are evolutionarily conserved compounds that are involved in the defence systems of a wide variety of species [14], towards prokaryotes organism to multicellular mammals like humans. They are first line defence towards pathogenic microorganisms in higher vertebrates; they are the sole line of defence towards saprophytic germs and pathogenic in several lower forms of life [15]. The preferential cytotoxicity of these peptide, in which they target harmful bacteria and yeasts but leave host cells alone, is owing to elemental change in the assemblage and structure of cells of the host and pathogenic bacteria and yeasts [16, 17]. Despite the fact that certain AMPs have immunomodulatory and/or chemotactic properties, these antimicrobial peptides are always amphipathic but have a finally positive charge.

1. **Antimicrobial Peptides with Predominant α-Helical Structures**: Nearly 30percentage points to 50percentage points of all antimicrobial peptides discovered and investigated to far have a predominance of α-helical structures. These peptides typically comprise between 12 and 40 amino acids and are abundant in helix-stabilizing amino acids like leucine, alanine, and lysine, but just never cysteine [18].
2. **β-Sheet Antimicrobial Peptides:** The second main class of antimicrobial peptides consists of those with 2–10 residues which create one to five disulphide links between the chains. Defensins are usually composed of 2 to 3 antiparallel α-sheets stabilised by 3 to 4 intramolecular disulphide bridges; however, in rare instances, nor C-terminus has a α-helical or unstructured region [19].
3. **Versatile:** Antimicrobial Peptides Containing Specific Amino Acids Certain amino acids like arginine, proline, histidine, tryptophan, and glycine are abundant in a minority of antimicrobial peptides. These peptides have extremely varied secondary structures as a result of their unique amino acid makeup. For example, in the presence of zwitterionic micelles made of dodecyl phosphocholine or anionic sodium-dodecyl sulphate.

3. History and Diversity of AMP

Antimicrobial peptides (AMPs), more lately referred to as host defence peptides residue, are present in almost every form of existence of life. All species, from prokaryotes to eukaryotes, vertebrates, and invertebrates, generate antimicrobial peptides (Figure 1). Individual bacteria profit from AMPs by eliminating other bacteria which contend for resources and same environmental niche. Bacteriocins, or bacterial AMPs, are divided into 2 groups: non-lantibiotics and lantibiotics. Several bacteriocins, like mersacidin, have also been investigated for their potential antimicrobial activity towards antibiotic-resistant Gram-positive bacteria [20, 21]. Lantibiotics are antimicrobial peptides (AMPs) that include the non-natural polymer of amino acid lanthionine residue. Nisin, a lantibiotic, was the first AMPs notified and described in 1947 from bacteria (*Lactococcus lactis*) [22].

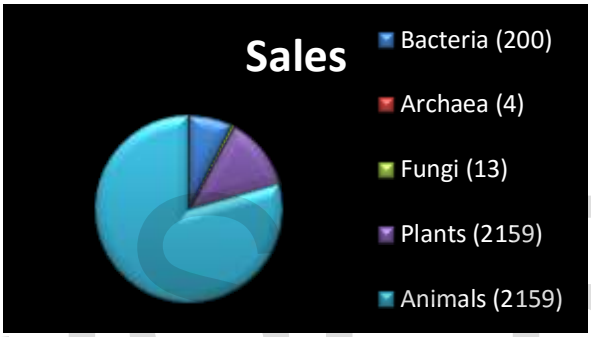

Figure: 1 Sources of antimicrobial peptides (number 2818) retrieved from the antimicrobial peptide database in September 2017.

4. Mechanism of Action of AMP

Antimicrobial peptides are novel compounds whose mode of action (MOA) has been intensively researched from their discovery. It is critical to understand the mechanism of action of these AMPs in order to assist their future development as medicinal medicines. Initially, it was believed that AMPs had just one method of action: membrane targeting [23]. (Figure 2). MOAs are classified into two broad categories: direct killing and immunological regulation. The mode of action of direct killing may be afore classified into membrane targeted and non-membrane targeting, the latter of that will be the focus of the next section.

Numerous studies have reported a high correlation among an AMP's cationic charge and its antimicrobial significance, with enhanced antimicrobial function of various AMPs towards fungal and bacterial pathogens being associated with an increment in cationic charge [24, 25] therefore, enhanced haemolytic pursuit has been omitted. Second, hydrophobicity is a critical

property of all AMPs and is attributable to a significant percentage of hydrophobic polymer in peptide sequences, including alanine, isoleucine, tyrosine, leucine, valine, tryptophan, methionine, and phenylalanine. Hydrophobicity is critical for peptide membrane selectivity, and higher hydrophobicity is associated with enhanced haemolytic activity.

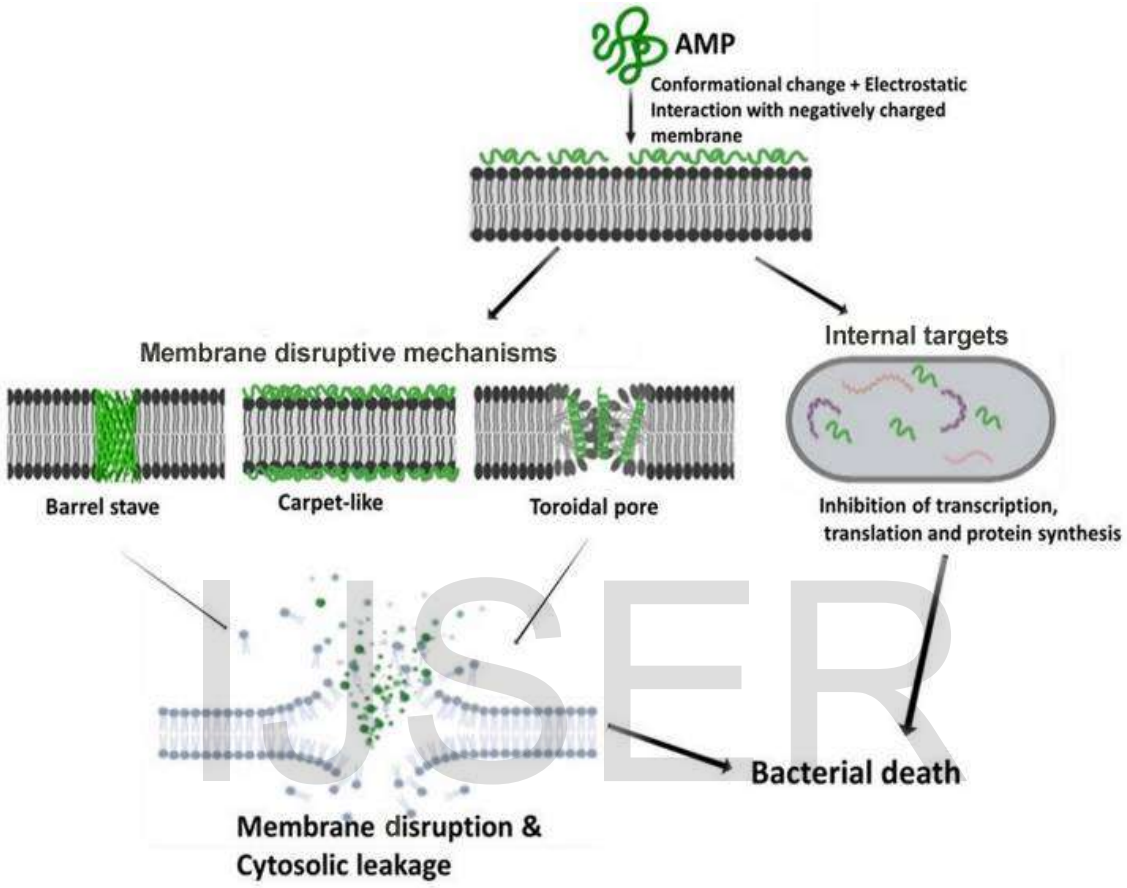

Figure: 2 The membrane-disr1upting and non-membrane-disrupting bacterial death methods of AMPs are shown schematically.

5. Advantages of AMPs

Catalytic AMPs are a class of peptides. In contrast to conventional antibiotics, these AMPs react with biological membranes by neutralising their charge. They then permeate bacterial membranes and kill bacteria, thus decreasing the likelihood of bacterial drug resistance [26].

- Additionally, these peptides are more effective than standard antibiotics.
- They outperform traditional antibiotics in terms of broad-spectrum antibacterial, antifungal, and antiviral activity [27]. Additionally, they are powerful, with fast germ-killing capacity and a minimal bactericidal level, are efficacious against conventional

antibiotic-resistant strains, and work synergistically with conventional antibiotics in neutralising endotoxin.

- Additionally, these AMPs are safer than traditional antibiotics, with no or few dangerous side effects, and are difficult to develop bacterial drug resistance.
- Apart from their wide range of antibacterial activity, they have excellent thermal stability and solubility in water [28].
- They are tiny compounds with a cheap cost of synthesising, a straightforward structure-activity connection, and a minimal or no sensitization [29].
- Numerous studies have shown that cancerous cells are more susceptible to AMPs than healthy cells are. Cancerous cells lack a well-developed cytoskeleton in contrast to normal cells. Catalytic AMPs colocalize with the very acidic phospholipids seen on the external surface of these cancerous cells. Cancer cells' rapid metabolism may result in alterations to their membrane, cytoskeleton, or extracellular matrix [30].

6. Halophilic Microorganisms

Halophiles are a class of organisms comprised of bacteria, archaea and eukarya that are defined by their salinity need, extremophilic "salt-loving." extremophilic microorganisms are found in the native microbial populations of environments found worldwide [31]. They need sodium ions to grow and metabolically function. Therefore, halophiles are categorised into three distinct groups depending on their optimum NaCl requirements for development: mild (1–3 percent); moderate (3–15 percent); and severe (15–30 percent) [32,33]. In comparison to halotolerant species, obligatory halophiles need NaCl concentrations more than 3percentage NaCl or greater than those found in seawater, which contains about 3.5 percent NaCl [34]. pH, temperature, and growth media all influence the tolerance criteria and salt needs. Thus, halophiles adapt to and are constrained by particular environmental conditions. Polyextremophiles are microorganisms that have been engineered to live and flourish under a broad range of severe environmental conditions [35]. Indeed, a halophilic microbe may also be an alkaliphile, referred to as a haloalkaliphile, thriving optimum or very well at pH 9.0 but not at the conditions while waiting pH value of 6.5. The basic characteristics of extremophilic bacteria include fewer nutritional needs and tolerance to high salt concentrations, as well as the ability to regulate the environment's osmotic pressure [36].

6.1 Antimicrobial Compounds

Rodriguez-Valera et al. discovered the first antibacterial chemicals produced by halophilic microbes in 1982. Halocin was created to describe chemicals produced by many species of the genus Halobacterium that are capable of killing and lysing the surrounding microbiota. Haloarchaea produces halocins compounds, which are antimicrobial peptides (AMPs) & proteins [37].

In the race of time, the extremophilic microorganisms' clinical significance is rarely reported, and antimicrobial activity towards the most essential human pathogen risk group, ESKAPE: Acinetobacter, *Klebsiella pneumoniae*, Baumannii, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterococcus faecium*, remains a possibility.

6.2 AMPs from extremophiles that combat multidrug resistant microbes

The quinolone exhibits antibacterial action towards S. aureus, E. coli, B. subtilis; it also has antifungal activity towards pathogenic fungi, as shown on *Pyricularia oryzae*. Additional five known substances were synthesised through N. terrae YIM 90022 [43]; novel p-terphenyls: p-terphenyl 1 and a novel p-terphenyl derivative containing a benzothiazole functional group were synthesised by the extremophilic actinomycete *Nocardiopsis gilva* YIM 90087, which was extracted from a hypersaline soil in Xinjiang, Additionally, these compounds show antifungal action against Fusarium, Candida, Trichophyton, Aspergillus and Pyricularia species. N. gilva YIM 90087 also produces well-known compounds such as novobiocin, p-terphenyl 2, cyclodipeptides and aromatic acids, and is deemed a novel source of novobiocin [38]. A comprehensive list of microbes and their antibiotic chemical is included in Table 2.

Members of the genus, on the other hand, are often extracted from marine deep or coastal sediments with salinities greater than those of saltwater. Among the compounds discovered are I 1-hydroxy-1-norresistomycin, a quinone-related antibiotic obtained from *Streptomyces chibaensis* marine sediment samples from India's Bay of Bengal. This drug showed antibacterial activity on Gram-negative bacteria and Gram-positive, as well as a high level of cytotoxicity in vitro towards the gastric adenocarcinoma and hepatocarcinoma cell lines HMO2 and HePG2 [39].

Table 2. Antimicrobial action of halophilic bacteria and their compounds against human infections.

Genus	Molecule	Isolation Source	Antimicrobial

			Activity
Vibrio sp. A1SM3–36-8	13-cis-docosenamide	Brine and sediments	B. subtilis S. aureus Methicillin-resistant
Nocardiopsis sp. HYJ128	Borrelidin C Borrelidin D	Topsoil saltern in Republic of Korea	Salmonella enterica
Pseudonocardia endophytica VUK-10	hexahydropyrrolo [1,2-a] pyrazine-1,4-dione 3-((1H-indol-6-yl) methyl)	Bay of Bengal, Andhra Pradesh, India,	E. coli, S. epidermis, B. subtilis,
Nocardiopsis sp. HR-4	Angucyclines and angucyclinones: Compound 1: (−)-8-O-methyltetrangomycin	Salt lake soil, Algeria	S. aureus, S. aureus, M. luteus, E. faecalis
Nocardiopsis sp. AJ1	hexahydro-3-(2-methylpropyl)-), Actinomycin C2	Saline soil of Kovalam solar salterns India	E. coli, S. aureus, A. hydrophila, P. aeruginosa
Paludifilum halophilum SMBg3	Cyclic lipopeptide: Gramicidin S	Sfax solar saltern, Tunisia	positive M. luteus LB, E. coli, S. henoxaz, Gram-S. aureus,

Although the frequency of new families of pathogens is substantial, the pace of discovery of novel biomolecules is modest in comparison to non-extremophilic bacteria. Despite frequent reports of unique species and efforts to grow hidden microbiota, no substantial research has been conducted on the identification of novel bioactive compounds generated by microbes in hypersaline environments. At the moment, genome-guided research provides the greatest assistance for developing new drug development methods. The antimicrobial chemicals reported in this article are all generated from extremophilic bacteria for that the molecule has been identified, and the strains' ability of suppressing infections in primary tests.

6.3 AMPs from Archea that combat multidrug resistant microbes

Since about the finding of extreme and associated antimicrobial activity over with the microbiota in particular habitats [40], no novel or previously unknown antimicrobial substances produced from archaea susceptible of suppressing human infections have been described in the literature [41]. Members of the genera Halorubrum and Haloferax were find as the major halocin producers, and antibacterial activity against bacteria belonging to the genera Rhodovibrio, Salisaeta, Halomonas or Pontibacillus was found in hypersaline samples [42].

6.4 AMPs from Fungi that combat multidrug resistant microbe

Over the course of decades of study on natural products, fungi have served as the foundation for antibacterial discoveries. The halotolerant and halophilic fungal communities seen in naturally hypersaline settings are not salt required, since they may grow and adapt to a wide range of upwelling, from freshwater to almost saturated sodium chloride aqueous solution [43]. Despite this flexibility, the overwhelming majority of antimicrobial compounds generated by extremophilic fungi have been synthesised at low or modest salinity, while screening targeting SKAPE bacteria is simpler without NaCl. The hypersaline mycobiota is dominated by Aspergillus and Penicillium species, as well as other genera like Debaryomyces, Scopulariopsis, Cladosporium, Fusarium, Chaetomium, Alternaria that are highly represented in ecological and biodiversity research [44]. *Phaeotheca triangularis*, *Aureobasidium pullulans*, *Aspergillus penicillioides*, *Hortaea werneckii* and several species of the genus such as W. ichthyophaga, are all recognised as obligately halophilic, or requiring concentrations of salt greater than those found in seawater However, these species have not been found to produce antibacterial chemicals.

The extremophilic bacterial species of Aspergillus are the most numerous, and many strains of Aspergillus sp. have been identified from Arctic subsea sediments in the Barents Sea. Bisvertinolone is a member of the Sorbicillinoid family of compounds [45]. Most *Aspergillus terreus* PT06-2 and *Aspergillus flocculosus* PT05-1 isolates from the Putian sea saltern in Fujian, China, shown antibiotic activity towards *Enterobacter aerogenes*, *Candida albicans* and *Pseudomonas aeruginosa*.

Table 3. Antimicrobial action of extremophilic fungus.

Species	Molecule	Isolation Source	Antimicrobial Activity
Aspergillus flocculosus PT05-1	16b-tetrahydroxyergosta-5, 7-dien-12-one, Ergosteroids: (22R,23S)-epoxy-3b	Putian saltern of Fujian, China	P. aeruginosa, C. albicans, E. aerogenes,
Aspergillus protuberus MUT 3638	Bisvertinolone	Barents Sea. Abyssal marine sediment and Arctic Ocean	K. pneumoniae, B. metallica, S. aureus,
Aspergillus terreus Tsp22	Crude extracellular substance	Semiarid saltpans in Botwana	S. aureus
Aspergillus gracilis, Aspergillus flavus and Aspergillus penicillioids	Crude extracellular compounds	Phetchaburi, Solar saltern, Thailand	Antibacterial and antioxidant

6.5 Anticancer Compounds

Pure products are important anticancer agents, also known as bioactive chemicals, that are generated by organisms [46]. Although the majority of previously discovered the plant cells, microorganisms are the excellent alternative source for pure product for anticancer due to their diversity, ease of manipulation, and ability to be physiologically scanned for the discovery of new products with antitumor action. While bacterial cells communicate with tumour cells through ways other than metabolites in the laboratory, bacterial metabolite have been regarded the most traditional technique of inhibiting cancer cell viability [47]. Especially extremophiles, halotolerant and halophilic microorganisms that thrive in hypersaline settings are regarded as dependable sources of anticancer metabolites with fewer adverse impacts. Numerous researches have been conducted in recent years to demonstrate the significance of metabolites produced by halophilic bacteria in cancer therapy. Table 4 summarises the extremophilic archaea, bacteria, and fungi responsible for the synthesis of anti-cancer compounds.

6.6 Cancer activity of AMPs isolated from extremophiles

Halophilic bacteria have piqued researchers' attention over the past two decades owing to their tolerance to a broad variety of salinities. Numerous researches have been conducted to ascertain the function of bacteria in the treatment of cancer. Tubercidin, an anticancer antibiotic derived from the extremophilic actinobacterium, actinopolyspora, erythraea YIM 90600, has the capacity to maintain the tumour suppressor Programmed Cell Death Protein 4 [48]. In one of these findings, Chen et al. (2010) determined that 14 crude extracts from 45 strains of bacteria exhibited cytotoxic activity against the human liver cancer cell line Bel at a 50 % inhibitory range of 500 g/mL, with five of them demonstrating remarkable activity at IC50 values less than 40 g/mL [49].

Sagar et al. (2013) [50] conducted two research on different extracts of extremophilic and halotolerant bacteria extracted from the Red Sea's brine-seawater interface. A total of twenty hydrophilic and lipophilic (chloroform) (70 percent ethanol) extracts from 12 distinct strains were evaluated in one of their experiments. After 24 hours of treatment, 12 extracts were determined to be very active, and their cytotoxic and apoptotic impacts were assessed after 48 hours [51].

The other research examined ethyl acetate isolates of 25 variants and found that the majority of extracts were cytotoxic to one or more tumour cell lines. 6 of the 13 most active microbial extracts substantially increased apoptosis (>70%) in cancer cells.

Table 4. The role of extremophilic bacteria in cancer care.

Anticancer Activity of Metabolites	Cancer Cell Lines	Molecule	Isolation Source	Halophilic Strain
	Bacteria			
	Stomach and Leukemia carcinoma	Borrelidin D and C	Republic of Korea, Topsoil saltern in Jeungdo	Nocardiopsis sp.
	Cervical carcinoma Myeloid leukemia	Iturin A8 Iturin F1 Iturin A9	Saltern in Incheon in South Korea	Bacillus sp.
	Cervical carcinoma	Methyl hexadeconate	Pichavaram mangroveForest in India and Marakkanam saltern	Bacillus sp.
	Colorectal cancer Gastric cancer	Salternamide A	A saltern on Shinui Island in Korea	Streptomyces sp.

Table 5. Extremophilic archaea and fungi and their relation in cancer care.

Anticancer Activity of:	Molecules	Cancer Cell Lines	Halophilic Strain	Isolation Source
Archaea				
Carotenoid	Bacterioruberin	Liver hepatocellular adenocarcinoma	Halobacterium halobium	Tunisian solar saltern
Carotenoid	Bacterioruberin	Liver carcinoma	Halogeometricum limi strain	Marine solar saltern in eastern China
Supernatant metabolite	Crude extract	Prostate carcinoma	Halobacterium salinarum IBRC-M 10715	Aran Bidgol hypersaline lake in Iran
Exopolysaccharide	Glucosamine, alacturonic acid, arabinose & glucuronic acid	Gastric adenocarcinoma	Halorubrum sp. TBZ112	Urmia Lake in Iran
Fungi				
Metabolite	Cytochalasin E Ergosterol Rosellichalasin	Lung adenocarcinoma adenocarcinoma Cervical carcinoma Colorectal cancer, Liver hepatocellular	Aspergillus sp. F1	Weihai Solar Saltern in China

6.7 Anti-cancer activity of AMPs isolated from Fungi

In contrast to halophilic fungus, halophilic bacteria have much fewer biotechnological uses. Only one research has been conducted on the cytotoxic impact of metabolites isolated from a psychrophilic fungal strain, Aspergillus sp. F1 [52]. According to this article, this strain generated 3 anticancer chemicals, like rosellichalasin, E, ergosterol, cytochalasin and enhanced synthesis of these compounds with increasing salt

concentrations. All extracted chemicals reduced the survival of BEL-7402, Hela, A549, and RKO human tumour cell lines, with ergosterol exhibiting the most powerful cytotoxic impact on the human colon carcinoma cells RKO. Table 5 summarises all the studies that discuss the anticancer properties of extremophilic fungi, bacteria and archaea isolated from various saline and hypersaline habitats throughout the globe.

6.7 Anti-cancer activity of AMPs isolated from Archea

While the majority of research in this area has been on bacteria, several studies have examined the possibilities of haloarchaea. In one of these investigations, supernatant metabolites from bacterium Salinarum were shown to have the most powerful cytotoxic impact on prostate cancer cell lines while having no impact on normal fibroblast cells [53]. The haloarchaeal species Halorubrum sp., was reported to be capable of producing EPSs. The isolated EPSs have a low molecular weight in contrast to those isolated from other severe settings, and their structure lacks sulphate functional groups, and no significant difference in the viability of gastric cancer cells or normal human dermal fibroblast cells was observed after 24 and 48 hours of treatment at concentrations of 1000, 500 250 and 100 g/mL [54].

7. Discussion

At the moment, research is focused on creating methods to boost the effectiveness of AMPs in vivo, to maximize their selection for microbes whilst minimising cytotoxicity, to increase their stability, and to reduce proteolytic breakdown. Its acetylation are critical methods for increasing the stability and susceptibility of AMPs to proteolytic degradation [55, 56]. In this regard, AMPs and their derivatives warrant further investigation not only as true antimicrobial agents but also as broadeners of the therapeutic range of already available medicines. Combining AMPs with conventional antibiotics may offer a method for overcoming resistance induced by outer membrane permeability limitations or drug efflux, as well as extending the useful life of both older and novel compounds. This vast area of study provides many opportunities for future investigation.

8. Conclusion and future prospect

With the growing incidence of multidrug-resistant bacteria (MDR), antimicrobial peptides (AMPs) have garnered considerable attention for their potential use in the treatment of these illnesses. Their benefits include the delayed selection of resistant strains and their novel methods of action. AMPs are very flexible molecules that allow for many chemical

modifications, resulting in new medicines with enhanced therapeutic and safety properties. As a result, a large number of these medicines are presently through various phases of development. We concentrated on all anticancer compounds discovered in microorganisms in this study. Primary screenings are targeted at the most common cancer forms that afflict the worldwide population based on the cellular lines utilised. Further screens, meanwhile, must include cellular populations with inherent cell survival, such as sarcoma and glioblastoma, which are characterised by persistent over proliferation. The direction of anticancer drug discovery appears to be a mix of high-throughput screenings and prediction biomarker analysis.

Numerous labs engaged in microbial bioprospecting maintain a personal collection of anticancer, antibiotic, antifungal, and other antibacterial compounds after anticancer, antifungal, antimicrobial and other antimicrobial compounds are discovered. Often, positive specimens identified after initial screens are not further investigated using dereplication and genome sequencing. Our aim sought to emphasise the critical nature of AMPs as possible next-generation antibiotics for the treatment of a broad variety of microbial illnesses, such as those caused by MDR strains. AMPs, both synthetic and natural, are unmatched in their medicinal potential.

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