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Review

Halophytes as Medicinal Plants against Human Infectious Diseases

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Abstract: Halophytes have long been used for medicinal purposes. However, for many decades, their use was entirely empirical, with virtually no knowledge of the bioactive compounds underlying the different applications. In recent decades, the growing problem of antibiotic resistance triggered the research on alternative antimicrobial approaches, and halophytes, along with other medicinal plants, regained attention as an underexplored pharmacological vein. Furthermore, the high nutritional/nutraceutical/pharmacological value of some halophytic species may represent added value to the emerging activity of saline agriculture and targeted modification of the rhizosphere, with plant-growth-promoting bacteria being attempted to be used as a tool to modulate the plant metabolome and enhance the expression of interesting metabolites. The objective of this review is to highlight the potential of halophytes as a valuable, and still unexplored, source of antimicrobial compounds for clinical applications. For that, we provide a critical perspective on the empirical use of halophytes in traditional medicine and a state-or-the-art overview of the most relevant plant species and metabolites related with antiviral, antifungal and antibacterial activities.

Keywords: antimicrobials; bioactive compounds; ethnobotany; plant extracts

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1. Introduction

Halophytes are ecologically, physiologically and biochemically specialized plants that are able to grow and reproduce under salinities >200 mM NaCl. Although representing only 1% of terrestrial angiosperms, approximately 3000 species in the world are considered as halophytes, corresponding to 550 genera and 120 families [1]. Halophytes have an extremely broad distribution, occurring over a wide range in mostly costal and wetlands habitats [2] that are directly or indirectly influenced by ocean waters, such as salt marshes/mangroves and sand dunes, and the significant fraction of once arable soils are now threatened by salinization as a consequence of irrigation practices or climate change [3].

A first line of physiological adaptation involves salt-induced signaling pathways of osmotic adjustment that trigger the removal of Na^+ and Cl^- from sap and sequestration in intracellular compartments known as vacuoles [4,5], whereas small organic molecules, such as soluble carbohydrates, polyols, amino acids and betaines, accumulate in the cytoplasm to further ensure osmotic balance [4,6,7]. Insufficient adjustment leads to osmotic and oxidative stress, ion toxicity and nutrient deficiency [4]. High concentrations of NaCl in soil reduce water availability to the roots, reduce the water potential of leaves and, ultimately, limit nutrient uptake [8]. Net photosynthesis is reduced because of stomatal closure, and the balance between the production and the scavenging of reactive oxidative species (ROS) is disrupted [9,10]. Energy is diverted from biosynthetic pathways associated with growth to the expression of enzymes and phytohormones involved in stress responses and homeostasis [11] with an overall reduction of productivity.

The multifactorial adaptive responses of halophytes involve a complex network of biochemical mechanisms and a plethora of bioactive molecules, such as phenolic compounds

(e.g., phenolic acids, flavonoids and tannins), polysaccharides, glycosides and related compounds, lipids (e.g., fats and fatty acids, phytosterols and tocopherols, essential oils, acetylenic lipids, carotenoids) and alkaloids [12]. The ethnobotanical literature provides evidence that, because of their phytochemical richness, halophytic medicinal plants have long been used to treat various infectious diseases, particularly in developing countries where traditional medicine remains the first approach to minor ailments [12,13]. In recent decades, little has been investigated about the utilization of halophytes for medicinal purposes as a way to validate their use in traditional medicine or as a source of pharmacological compounds and only recently, with the building up of antibiotic resistance and the perspective of a post-antibiotic era, has the screening of halophytes for antimicrobial compounds regained interest [12,14–17]. Furthermore, the high nutritional/nutraceutical/pharmacological value of some halophytic species may represent added value to the emerging activity of saline agriculture [12,14,18,19].

The present review intends to provide a critical perspective on the empirical use of halophytes in traditional medicine and on the recently produced scientific evidence of the antiviral, antibacterial and antifungal activities underlying ethnopharmacological applications, highlighting the importance of halophytes as a valuable and still unexplored source of antimicrobial compounds for clinical applications.

2. Halophytes in Traditional Medicine and Ethnopharmacology

Traditional medicine (TM) is the mainstay of health care delivery in many developing countries. In the 2019 WHO Global Report [20], 34 countries included TM in their national essential medicines list and 107 member states have acknowledged the use of traditional and complementary medicine. In some countries, such as India, China, South Africa, Ghana, Mexico and Russia, TM is actually the major source of health care, or is at least a very important health care resource for the poorer, less educated and rural communities [21].

Many halophytes have been used for centuries in TM [12,22,23]. Leaves, roots, seeds, fruits, barks, latex or whole plants are used as juices, decoctions, or infusions, macerated, grounded to powder, crumpled into pastes or poultices, or incinerated to ashes (Figure 1).

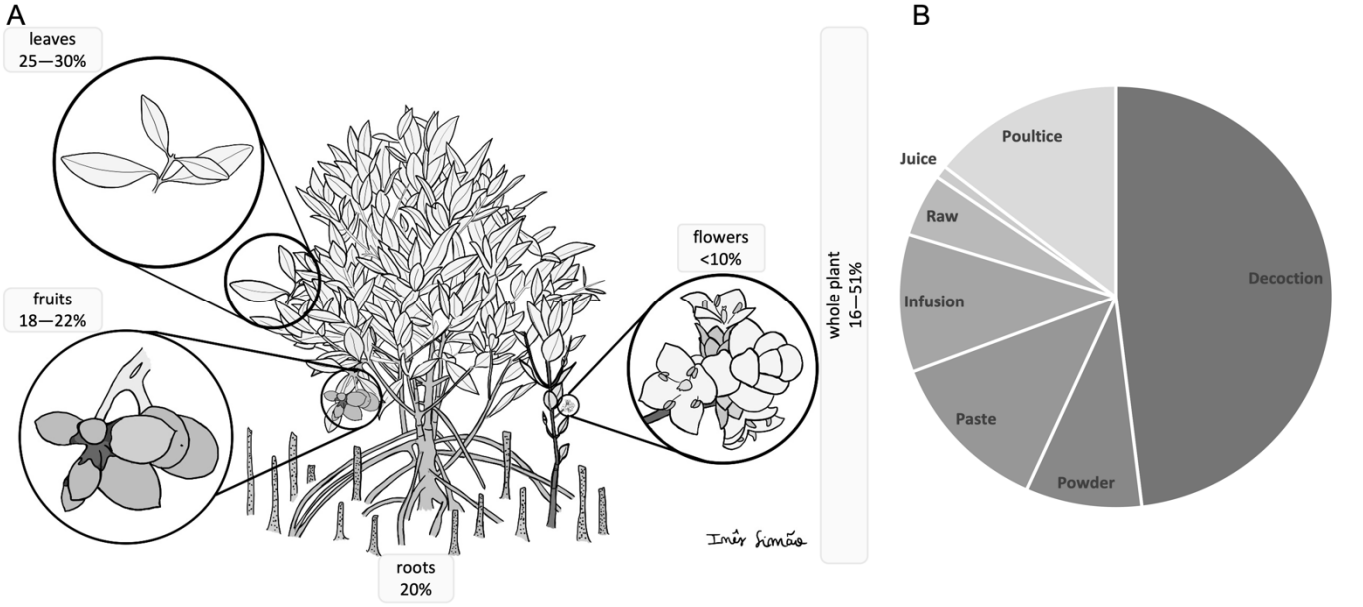

Figure 1. Most widely used parts of the plants (**A**) and most common preparations (**B**) in traditional medicine. *Avicennia marina* was illustrated by Inês Simão.

Halophytes thrive in diverse saline habitats, whether coastal, such as in salt marshes, or inland, such as in salt deserts and salt flats [12,24]. Therefore, the therapeutic use of halophytes is more common in populations established in these areas (Figure 2).

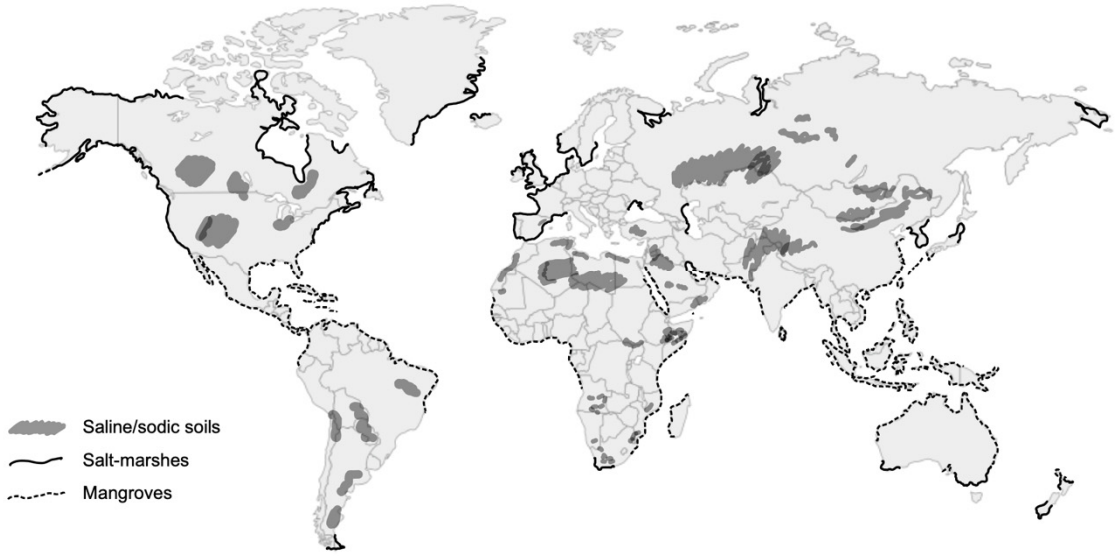

Figure 2. World distribution of halophyte habitats according to soil type (based on [25,26]).

Mediterranean regions of Africa and Europe, the Arabian Peninsula, southwest Asian countries such as Pakistan, India and Afghanistan, and east Asian countries such as China and Thailand have a millennial history of using halophyte species as traditional medicines to treat or relieve symptoms of infectious and noninfectious diseases (Table 1).

Table 1. Most common taxa of halophyte families used in traditional medicine and most frequent applications.

Familiy	Species	Plant Part	Application	Region	Reference
Aizoaceae	*Mesembryanthemum* spp.	aerial parts	fungal and bacterial infections, diarrhea, tuberculosis, antiseptic to treat infections of the mouth and throat	Europe, Africa, Australia and California	[27,28]
Amaranthaceae	*Aerva javanica*	roots, leaves, flowers and seeds	infected wounds, malaria	Saudi Arabia	[29]
Apiaceae	*Foeniculum vulgare*	root and seeds	gastrointestinal, urological, gynecological infections	Saudi Arabia	[30]
Apocynaceae	*Calotropis procera*	leaves and latex	skin infection (antifungal)	Morocco	[31]
	Calotropis procera	latex	skin infections	Saudi Arabia	[29]
Asteraceae	*Blumea lacera*	roots	antiseptic, dysentery	Pakistan	[32,33]
	Xanthium sibiricum	fruits	rhinitis, nasal sinusitis, headache, gastric ulcer, urticaria, rheumatism, bacterial and fungal infections, arthritis and eye diseases	China	[22]
Chenopodiaceae	*Kochia scoparia*	fruits	dysuria, skin, urinary tract and eye diseases, pruritus and thermal skin lesions	China, Japan and Korea	[34]
	Beta vulgaris	leaves and stems	digestive disorders, throat inflammation, digestive, diuretic and laxative properties	Mediterranean basin	[23]

Table 1. *Cont.*

Familiy	Species	Plant Part	Application	Region	Reference
Cucurbitaceae	*Citrullus colocynthis*	fruits and roots	bronchitis, tuberculosis, glands of the neck, throat infection	India and Pakistan, Arabia, West Asia, Tropical Africa and the Mediterranean region	[35]
Ephedraceae	*Ephedra sinica* *Ephedra major*		treatment of cold, bronchial asthma, cough, fever, flu, headache, edema, allergies, bacterial infections	China, India	[36]
Myrtaceae	*Eucalyptus camaldulensis*	leaves	infected wounds	Nigeria	[37]
Solanaceae	*Lycium barbarum* *L. chinense*	Fruits, leaves, root bark	lung function and eye diseases, cough	China	[38] [39] [40]
Tamaricaceae	*Tamarix aphylla*	leaves and roots	infected wounds	Saudi Arabia	[29]
Zygophyllaceae	*Tetraena alba*	leaves, stems, fruits	antiviral and antifungal	semiarid areas of Saudi Arabia, Africa	[41]
Liliaceae	*Aloe vera*	leaves and roots	fever, constipation, sunstroke, malaria, eczema, psoriasis, hair loss, gastric ulcer, liver pain, diabetes, menstrual troubles, gonorrhea, spleen disorders, nerve pain, rheumatism		[42]
Plumbaginaceae	*Limonium* spp.	leaves and roots	microbial and viral infections	Tunisia	[43]
Fabaceae	*Glycyrrhiza* spp.	underground unpeeled or peeled stems and roots	upper respiratory tract ailments including coughs, hoarseness, sore throat and bronchitis	China, Japan	[44]
Zygophyllaceae	*Nitraria* spp.	fruits	hypertension, menstrual disorders and gastroenteritis	China	[45]

In the Mediterranean basin, rural communities use halophytes both as food and a source of health-promoting compounds, consumed them fresh or cooked [23,46]. Leaves, fruits and seeds of species of Amaranthaceae, Asteraceae, Chenopodiaceae, Apiaceae, Brassicaceae, Capparaceae, Plantaginaceae, Portulacaceae and Zygophyllaceae are the most important families among more than 50 plant families with medicinal properties known in East Mediterranean regions (Turkey, Syria, Lebanon, Palestine, Jordan and Israel) [11]. These plants are mostly for the treatment of urinary system and internal diseases, as well as skin and respiratory conditions [46].

In Saudi Arabia, halophytes from the families of Asteraceae, Fabaceae and Apocynaceae are the most represented in traditional medicine, with the leaves, fruits or the whole plant being used. The species *Ziziphus spina-christi* (Mill.) Georgi and *Calotropis procera* (Aiton) Dryand have the largest range of therapeutic uses, but *Datura stramonium* L., *Withania somnifera* (L.) Dunal, and *Aloe vera* (L.) Burm.f. are also extensively applied [47]. Some species widely used in the Arabian Sea are also popular for traditional medicine applications in other regions. That is the case for *Zygophyllum album* L.f, which belongs to the Zygophyllaceae family [41], and *Citrullus colocynthis* (L.) Shrader (Cucurbitaceae),

which is used in Tropical Africa, India and Pakistan for the treatment of a wide range of infectious diseases [48]. In fact, countries in the Arabian Sea region, especially Pakistan, have a long and rich tradition in terms of medicinal applications of halophytes. On the Arabian Sea coast, Chenopodiaceae, Capparidaceae, Amaranthaceae, Zygophyllaceae, Poaceae and Boraginaceae are the most represented families. The whole plants are used, or only the leaves, fruits or roots [24]. *Solanum virginianum* L. and *Citrullus colocynthis* (L.) Shrader have the widest range of applications, but many more halophyte species are used in this region to treat digestive problems (*Acacia nilotica* L., *Citrullus colocynthis* and *Ipomoea pes-caprae* (L.) R.Br.), skin conditions (*Suaeda monoica* Forssk.), respiratory, liver and kidney problems, genito-urinary infections, piles, toothache, chronical pain and fever. *Ziziphus mauritiana* Lam., *Withania coagulans* (Stocks) Dunal, *Rhazya stricta* Decne., *Fagonia cretica* L., *Kochia prostrata* L., *Peganum harmala* L. and *Solanum surattense* are used for multiple purposes, particularly their leaves and fruits [32]. Some species are also used as alexipharmics and blood purifiers [49].

In China, *Apocynum venetum* L., *Astragalus membranaceus* Moench, *Glycyrrhiza uralensis* Fisch. ex.DC., *Lycium chinense* Mill. and *Nitraria tangutorum* Bobrov are extensively used in traditional medicine [50]. However, these species represent only a small fraction of the more than 100 species of halophytes used as Chinese medicines and some of them have even been domesticated [50]. In Thailand, mostly herbs, especially of the Fabaceae family, are used as traditional medicines against fever, skin diseases and gastrointestinal tract problems [51].

Ethnobotanical studies referring to the use of halophytes in traditional medicine usually identify general effects of plants or plant products. In most cases, what is intended is a relief of symptoms, and medicines are empirically used without attempting to establish the cause. As the infectious nature of the disease is not always confirmed, in most cases antimicrobial effects of halophyte-based medicines can only be indirectly inferred. There may be a significant overlapping of symptoms between infectious and noninfectious diseases and the effects of plant products, namely, in terms of antimicrobial, anti-inflammatory and antipyretic effects [52,53]; therefore, recent studies addressing the potential of halophytes as sources of antimicrobial compounds have set the focus on the demonstration of effects on defined infectious agents and on the purification and identification of the active molecules.

3. Halophytes as a Source of Antimicrobial Compounds

Plants accumulate bioactive compounds as a consequence of both phylogeny and the functional response to different environmental conditions [12]. Along with the abiotic conditions, plant species, genotype, physiology and the developmental stage also influence the type and concentration of these molecules produced by a plant [54,55]. The concentration and diversity of bioactive compounds in halophytes are higher compared to salt-sensitive species, and some compounds are exclusive to halophytes [14]. Moreover, there seems to exist a positive correlation between salt content in the medium and the production of secondary metabolites [56].

Primary metabolites of halophytes, such as carbohydrates and lipids, are regarded with interest as supplements or nutraceutics. Secondary metabolites, such as terpenes and phenols, have antioxidant and anti-inflammatory antitumoral and antimicrobial activities [35] and underlie many of the applications of halophytes in traditional medicine [57]. Some compounds modulate and stimulate the immune system, lower the risk of heart diseases, control body weight and blood sugar levels, and can even act as antiaging agents [58–63]. Antimicrobial activity is most commonly associated with phenolic acids, flavonoids and tannins (Figure 3). Terpenoids are the second most abundant group of bioactive molecules, followed by alkaloids, essential oils, glycosides and steroids.

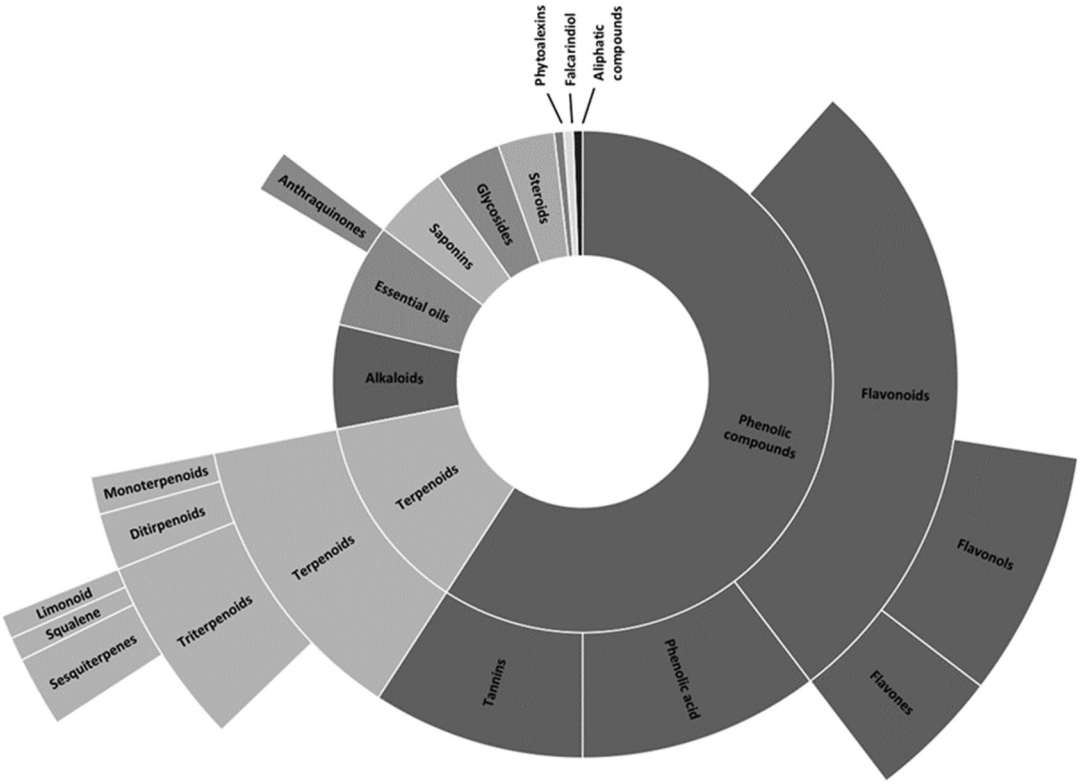

Figure 3. Diversity of bioactive compounds (secondary metabolites) with antimicrobial activity produced by halophyte plants.

In spite of the accumulation of evidence on the pharmacological potential of halophytes, only a few species have been subjected to systematic phytochemical characterization and screening for biological activities. Sixty-three species are reported in TM in Rwanda to treat diarrheal-like symptoms [64]. In fact, the same plants are used to treat different diseases with similar symptomatology, such as diarrhea, dysentery, cholera and gastroenteritis in general, but different aetiology (helminths, bacteria and viruses). Some studies have found that only some plants have antimicrobial properties in in vitro and in vivo studies. Additionally, only a few studies have researched the bioactive phytocompounds of some of these plants [64]. This situation is not exclusive to plants with antimicrobial effects. A pharmacological investigation conducted over a pool of plants used in TM to treat cancer patients found only 30% had a significant cytotoxic effect. Additionally, only 6 out of 77 bioactive compounds isolated from those plants exhibited beneficial effects with few side effects in clinical trials [65]. Ethnopharmacological and phytochemistry studies are essential for the pharmacological industry to look for and produce new antimicrobial drugs [66]. Even though some tests may be inconclusive or even show adverse effects, the ethnopharmacological approach is desirable as a selection method for screening potential new drugs. However, the phytochemistry of the plants, in vitro tests to determine the potential effect on the targeted microorganisms and clinical trials to determine toxicity and possible side effects are inherent parts of the process.

The development of new antimicrobial, anticancer or anti-inflammatory drugs has been the subject of rising interest. The emergence of various drug-resistant microbes has directed attention to the need for new drugs and evaluating methods [67]. A wide variety of methods are available to evaluate and detect in vitro antimicrobial activity of plant extracts and purified compounds. Diffusion methods (disk-diffusion, well diffusion or agar plug diffusion) are commonly used bioassay methods that are officially used as routine antimicrobial susceptibility tests. These are simple, standardized and low-cost methods and allow multiple testing. However, some of these techniques are not quantifiable and

do not allow for determining the minimum inhibitory concentration. Dilution methods can overcome this difficulty. However, none of these methods allow the evaluation of the clinical relevance of results.

Other methods, such as cytofluorometric and bioluminescent methods, require specified equipment and are not yet used as standard testing methods. These are quantifiable techniques and provide results within a short time window [67,68].

3.1. Antiviral Effects

Viral diseases represent major threats to human health and a global challenge in terms of disease prevention and treatment [69]. They are caused by a large diversity of agents that also display a high rate of mutation and are easily spread by water, air, inert materials and person-to-person contacts, and therefore, are prone to pandemics in a world where people and products rapidly circulate between continents [68].

Viral diseases can be treated with antiviral drugs. However, because of the intimate relationship between the virus and the host cells, the design of antiviral medicines that block the replication of the virus without causing unacceptable damage in the host represents a significant constraint in the progress of antiviral chemotherapy [70]. Moreover, vaccines and antiviral drugs are neither affordable nor readily accessible for general use in many developing countries. These circumstances lead to regaining interest in medicinal halophytes as sources of antiviral compounds.

Although in vitro tests are, in most cases, conducted with extracts containing mixtures of compounds and it is not possible to associate antiviral effects with specific bioactive molecules, there are now several halophytic plants for which antiviral effects have been demonstrated (Table 2). An extensive study of the antiviral potential of water:ethanol extracts of different plant parts of several halophyte species allowed the detection of anti-hepatitis B virus (HBV) activity in *Acanthus ilicifolius* L., *Aegiceras corniculatum* (L.) Blanco, *Avicennia marina* (Forssk.) Vierh., *Bruguiera cylindrica* L., *Ceriops decandra* (Griff.) Ding Hou, *Rhizophora apiculata* Blume, *R. lamarckii* Montrouz., *R. mucronata* Rathbun, *Salicornia brachiata* Sessé & Moc. and *Sesuvium portulacastrum* L. and anti-human immunodeficiency virus (HIV) activity in *Aegiceras corniculatum*, *Ceriops decandra*, *Excoecaria agallocha* L., *Rhizophora apiculata*, *R. lamarckii* and *R. mucronata* [71]. A leaf extract of *Suaeda maritima* Torr. containing polyphenols, flavonoids and tannins caused the inhibition of the HBV reverse transcriptase [72]. Extracts of *Limonium densiflorum* (Guss.) Kuntze shoots, also rich in phenolic compounds, caused direct inhibition of herpes simplex virus type 1 (HSV-1) [73], and ferulic acid and caffeic acids extracted from *Plantago major* L. exhibited activity against herpes simplex virus 2 (HSV-2) [12,27]. Extracts of *P. major* also demonstrated activity against adenoviruses (ADV-3, ADV-8, ADV-11), and among the classes of bioactive compounds identified, caffeic acid was associated with the strongest antiviral activity [74]. Activity against influenza A viruses (H1N1 strain) was also detected in *L. densiflorum* extracts [55]. Extracts of halophytes have also demonstrated activity against the Newcastle disease virus (NDV), vaccinia virus (VV), encephalomyocarditis virus (EMCV) and Semliki Forest virus (SFV) [71].

Table 2. Antiviral effects associated with extracts of halophyte plants.

Virus	Plants Species	Reference
Newcastle disease virus (NDV)	*Acanthus ilicifolius* *Aegiceras corniculatum* *Bruguiera cylindrica* *Excoecaria agallocha* *Lumnitzera racemosa* *Rhizophora mucronata*	[71]

Table 2. *Cont.*

Virus	Plants Species	Reference
Vaccinia virus (VV)	*Bruguiera cylindrica* *Lumnitzera racemosa* *Rhizophora mucronata* *Ceriops decandra*	
Encephalomyocarditis virus (EMCV)	*Avicennia marina* *Bruguiera cylindrica* *Excoecaria agallocha* *Lumnitzera racemosa* *Rhizophora apiculata* *Rhizophora lamarckii* *Rhizophora mucronata* *Salicornia brachiata*	
Semliki Forest virus (SFV)	*Bruguiera cylindrica* *Ceriops decandra* *Aegiceras corniculatum* *Rhizophora lamarckii* *Rhizophora mucronata*	
Hepatitis B virus (HBV)	*Acanthus ilicifolius* *Aegiceras corniculatum* *Avicennia marina* *Bruguiera cylindrica* *Ceriops decandra* *Rhizophora apiculata* *Rhizophora lamarckii* *Rhizophora mucronata* *Salicornia brachiata* *Sesuvium portulacastrum*	
	Suaeda maritima	[72]
Human immunodeficiency virus (HIV)	*Aegiceras corniculatum* *Ceriops decandra* *Excoecaria agallocha* *Rhizophora apiculata* *Rhizophora lamarckii* *Rhizophora mucronata*	[71]
Herpesviruses (HSV-1, HSV-2)	*Plantago major*	[75]
	Limonium densiflorum	[73]
Adenoviruses (ADV-3, ADV-8, ADV-11)	*Plantago major*	[74]
Influenza A viruses (H1N1 strain)	*Limonium densiflorum*	[73]
Human norovirus (HuNoV GII.4)	*Glehnia littoralis* *Mesembryanthemum crystallinum* *Salicornia europaea* *Spergularia marina* *Suaeda japonica*	[76]

3.2. Antibacterial Effects

Many halophytes have been screened for antibacterial effects (Table 3). Extracts obtained with various solvents from different plant parts have been tested against a variety of Gram-positive and Gram-negative bacteria commonly associated with urinary, intestinal, respiratory and skin infections in humans.

Persistent infections are commonly associated with bacterial biofilms, which normally exhibit enhanced resistant to antibiotics. Molecules that interfere with quorum-sensing communication (anti-quorum sensing, anti-QS) reduce biofilm development and make bacteria more susceptible to antimicrobials, being therefore used as coadjutants in antimicrobial chemotherapy [77]. Some halophytes (e.g., *Rhizophora annamalayana* Kathiresan) express metabolites with anti-QS activity against the biological models of *Chromobacterium violaceum* and *Vibrio harveyi* [78]. Ethanol extracts of the fruits of the facultative halophyte *Salvadora persica* L., containing gallic, chlorogenic and caffeic acids, inhibited biofilm development in oral *Staphylococcus* strains [79].

Ether extracts of *Salicornia europaea* L. inhibited *Bacillus cereus*, *Enterococcus faecalis*, *Escherichia coli*, *Micrococcus luteus*, *Salmonella typhimurium*, *Serratia marcescens* and *Staphylococcus epidermidis*. Interestingly, the water and acetone extracts had no significant antibacterial activity [80]. A study of the antibacterial properties of *Excoecaria agallocha* L. confirmed the influence of the solvent on the efficiency of the extract. Methanol extracts of leaves exhibited the highest activity, whereas hexane and chloroform extracts had no activity at all [81]. This indicates that antibacterial effects are closely related to specific metabolites that are selectively extracted.

Regardless of the solvent, extracts are mixtures of different metabolites that may interact to attain higher inactivation yields than equivalent concentrations of pure compounds. Extracts of *Citrullus colocynthis*, used to treat tuberculosis in traditional medicine, were successfully tested against *Mycobacterium tuberculosis* and the minimum inhibitory concentration (MIC) of a methanolic extract of ripe deseeded fruits (63 µg/mL) was lower than the MIC of cucurbitacin acid (25 mg/mL), an antibacterial membrane disruptor present in the extracts [82]. Additionally, there is a strong relation between the antibacterial efficiency of the extracts and the plant part from which they are obtained. Extracts from *E. agallocha* roots had higher activity against the Gram-negative *Salmonella typhi,* but leaf extracts were much less effective against this bacterium and, in contrast, highly effective against *Enterobacter* species and *Staphylococcus aureus* [81].

Table 3. Antibacterial effects associated with extracts of halophyte plants.

Bacteria	Plant Species	Reference
Bacillus cereus	*Salicornia europaea*	[80]
	Mesembryanthemum edulis *Suaeda monoica* *Cressa cretica* *Tamarix gallica*	[62,83–86]
Enterobacter sp.	*Exoecaria agallocha*	[59]
Enterococcus faecalis	*Salicornia europaea*	[80]
	Mesembryanthemum edulis *Suaeda monoica* *Tamarix gallica*	[86] [87] [86]
Escherichia coli	*Arthrocnemum macrostachyum*	[88]
	Salicornia europaea	[80]
	Cressa cretica *Mesembryanthemum edulis* *Suaeda monoica* *Tamarix gallica*	[89] [83] [84] [86]
Listeria monocytogenes	*Mesembryanthemum edulis* *Tamarix gallica*	[83] [86]

Table 3. *Cont.*

Bacteria	Plant Species	Reference
Micrococcus luteus	*Salicornia europaea*	[80]
	Cressa cretica	[89]
	Mesembryanthemum edulis	[90]
	Retama raetam	[91]
	Retama sphaerocarpa	[91]
	Tamarix gallica	[86]
Mycobacterium tuberculosis	*Citrullus colocynthis*	[82]
	Mesembryanthemum edulis	[88]
	Ziziphus spina-christi	[92]
Proteus sp.	*Exoecaria agallocha*	[34]
Pseudomonas sp.	*Cressa cretica*	[89]
	Mesembryanthemum edulis	[90]
	Suaeda monoica	[84]
	Tamarix gallica	[86]
Pseudomonas aeruginosa	*Arthrocnemum macrostachyum*	[88]
Multi-Resistant *Pseudomonas aeruginosa*	*Eryngium barrelieri* *Eryngium glomeratum*	[93]
Salmonella sp.	*Cressa cretica*	[89]
	Mesembryanthemum edulis	[88]
	Suaeda monoica	[84]
	Tamarix gallica	[86]
Salmonella typhi	*Exoecaria agallocha*	[81]
Salmonella typhimurium	*Salicornia europaea*	[80]
Serratia marcescens	*Salicornia europaea*	[80]
Staphylococcus aureus	*Arthrocnemum macrostachyum*	[88]
	Exoecaria agallocha	[81]
	Cressa cretica	[89]
	Mesembryanthemum edulis	[88]
	Suaeda monoica	[84]
	Tamarix gallica	[86]
Methicillin-Resistant *Staphylococcus aureus* (MRSA)	*Acanthus ilicifolius*	[94]
	Exoecaria agallocha	[95]
	Rhizophora mucronata	[96]
	Sonneratia caseolaris	[94]
	Aegiceras corniculatum	[97]
	Avicennia marina	[98]
	Ceriops decandra	[97]
	Eryngium thoraefolium	[99]
	Kochia scoparia	[34]
	Lumnitzera racemosa	[97]
	Rhizophora mucronata	[96]
	Tamarix gallica	[86]
Staphylococcus epidermidis	*Salicornia europaea*	[80]
Vibrio cholerae	*Exoecaria agallocha*	[81]

3.3. Antifungal Effects

Many plants produce antifungal compounds as a strategy of defense against phytopathogenic agents [100]. Facing the emergence of resistance to antifungal drugs among human pathogenic fungi, there is a regaining interest in plants as an alternative source of fungicidals [101].

Evidence of the activity of halophyte metabolites against pathogenic fungi is less documented in the literature than antibacterial effects, although in many studies, bacterial and fungal strains are included in the panel of microbial targets of bioactive compounds. Often, extracts that are active against bacteria are ineffective against fungi [102]. There are, however, encouraging reports of the antifungal activity of halophytes (Table 4), which are mainly associated with essential oils and phenolic-rich extracts [102,103], although there is a strong variability in the antifungal activity of different extracts, depending on the solvents used. The cell wall, the cytoplasmic membrane and the cytoplasm are considered as the main targets of the phenol attack that underlies antifungal activity of plant extracts [104]. Efficiency of extraction of phenolic compounds increases with the polarity of the solvents; hence, the strongest antifungal activity of water: methanol extracts and the correlation with antioxidant activities [105].

Candida species are normally represented in the human commensal microbiota, but some species are also among the most threatening fungal pathogens. *C. albicans* accounts for the vast majority of skin, urinary system and blood infections [106]. *C. auris* is an emergent pathogen that imposes concern because it is extremely invasive, multi-resistant to antifungal drugs, causes high mortality and has triggered research on plant-derived antifungals. Therefore, *Candida* species are the most frequent fungal models for the testing of antifungal activity of halophyte metabolites [107,108].

There is evidence that *C. albicans*, *C. glabrata*, *C. holmii*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* can be inactivated in vitro by extracts of many different halophytes, including *Avicennia marina*, *Eryngium* sp., *Rhizophora* sp. and *Xanthium sibiricum* Widd. [105]. Extracts of the facultative halophyte *Salsola kali* L. were also effective on *C. albicans*, *C. glabrata* and *C. holmii*, and the fungicidal activity was attributed to phenolic compounds such as syringic acid and kaempferol [109]. Essential oils of *Salsola vermiculata* L. and *S. cyclophylla* Gand. strongly inhibited *C. albicans* [110]. Extracts of *Arthrocnemum macrostachyum* Torr. and *Salicornia europaea* inhibited *C. albicans* [105] and *C. albicans*, *C. glabrata*, *C. utilis* and *C. tropicalis* [80], respectively.

There are also reports of the inhibition of pathogenic molds. Extracts of *Cressa cretica* L. inhibited several pathogenic fungi. The effect on the molds *Aspergillus fumigatus* and *A. niger* was even stronger than on the yeasts *Candida albicans* and *C. tropicalis* [89]. Aqueous extracts and the essential oil of *Myrtus communis* Blanco caused inhibition of the pathogenic mold *Aspergillus fumigatus*, and the effect was within the same order of magnitude as on *Candida albicans* [104].

Table 4. Antifungal effects associated with extracts of halophyte plants.

Fungi	Plant Species	Reference
Aspergillus fumigatus	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda maritima* *Suaeda monoica*	[111] [84]
	Cressa cretica	[89]
	Myrtus communis	[104]
	Eryngium maritimum	[112]
Aspergillus niger	*Cakile maritima* *Crithmum maritimum* *Eryngium maritimum*	[17]

Table 4. *Cont.*

Fungi	Plant Species	Reference
Candida albicans	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda maritima* *Suaeda monoica*	[111] [84]
	Salicornia europaea	[80]
	Cressa cretica	[89]
	Limoniastrum monopetalum *Limoniastrum guyonianum*	[113]
	Puccinellia maritima *Spartina maritima* *Spartina patens*	[114]
	Salsola kali	[109]
	Salsola cyclophylla *Suaeda vermiculata*	[110]
	Myrtus communis *Tetraena alba*	[104]
Candida glabrata	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda maritima* *Suaeda monoica*	[111]
	Tamarix gallica	[86]
	Salicornia europaea	[80]
	Cressa cretica	[89]
	Limoniastrum monopetalum *Limoniastrum guyonianum*	[113]
	Salsola kali	[109]
Candida holmii	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda marítima* *Suaeda monoica*	[111]
	Salsola kali	[109]
Candida krusei	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda marítima* *Suaeda monoica*	[111]
	Salicornia europaea	[80]
	Limoniastrum monopetalum *Limoniastrum guyonianum*	[113]
Candida parapsilosis	*Arthrocnemum indicum* *Salicornia brachiata* *Suaeda maritima* *Suaeda monoica*	[111]
	Limoniastrum monopetalum *Limoniastrum guyonianum*	[113]
Candida tropicalis	*Salicornia europaea*	[80]
Candida utilis		

4. Current Limitations and Future Prospects

There is a generalized consensus around the potential of plant metabolites as novel antimicrobials or coadjutants for antimicrobial chemotherapy. Being well represented in costal and arid regions, halophytes have been long used in traditional medicine and are, therefore, immediate candidates for the screening of new bioactive metabolites. There are, in fact, several studies that establish the link between the empiric use of these plants to treat infections with the photochemistry evidence of the compounds that underlie antimicrobial effects. However, efforts in the investigation of new antimicrobial compounds and the demonstration of their effect in vitro have not yet resulted in an antibiotic sufficiently effective to be clinically advantageous and economically profitable.

The concern around drug-resistant microbes has drawn attention to plant-derived, effective antimicrobial compounds. A new life is waiting for plants that have been used for centuries in infectious disease treatment. The detection and quantification of known, and even the discovery of new, small bioactive molecules produced by plants as secondary metabolites will provide new forms of therapy for numerous infectious and noninfectious illnesses. Appropriate and optimized extraction methods, susceptibility tests and clinical trials are still required. The prospects of the outcomes of further investigations seem promising and may lead to significant advances with the potential discovery of new and effective treatments [115,116].

Mass-spectrometry-based plant metabolomics is an extremely powerful approach, likely to provide comprehensive metabolite profiles of medicinal halophytes in the near future. In vitro tests represent the first approach to screen promising metabolites, either purified or as mixtures, for antimicrobial effects. The complexity and diverse chemical properties of plant metabolites demands a combined use of analytical platforms to increase the detection coverage of these compounds in biological samples. To detect volatile and nonvolatile metabolites, it is essential to use GC and HPLC coupled with mass spectrometry, as well as other techniques such as UPLC or NMR to ensure that all or at least the majority of compounds are separated, detected, identified, quantified and characterized. Each method should also cover several extraction solvents to ensure the detection of both polar and nonpolar compounds. The isolation and chemical characterization of each compound, by NMR technologies and testing them in bioassays, is crucial to move towards the assessment of the biological activity of each compound. The methodological approaches for in vitro tests must, however, be carefully adjusted to the chemical nature of the metabolites or extracts. Protocols need to be standardized and validated against representative biological models so that comparisons between products are reliable and meaningful.

Many bioactive metabolites are expressed by plants in response to stress or induced by environmental conditions or microbial symbionts colonizing plant tissues [117]. Examples of the most characteristic biologically active metabolites found in halophytes are the phenolic acids, sterols and terpenoids, among others (Figure 4).

The targeted manipulation on the plant microbiome is, therefore, regarded as a strategy to modulate the metabolome and to induce the expression of high added-value metabolites, such as antimicrobial compounds. Considering that the root is an important gateway for bacteria that are able to establish stable, mutually beneficial relations with the plant hosts (plant-growth-promoting bacteria), the modification of the rhizosphere microbiome with selected inoculants (rhizosphere engineering) represents an all-new line of research towards the general objective of plant-derived, effective antimicrobial compounds.

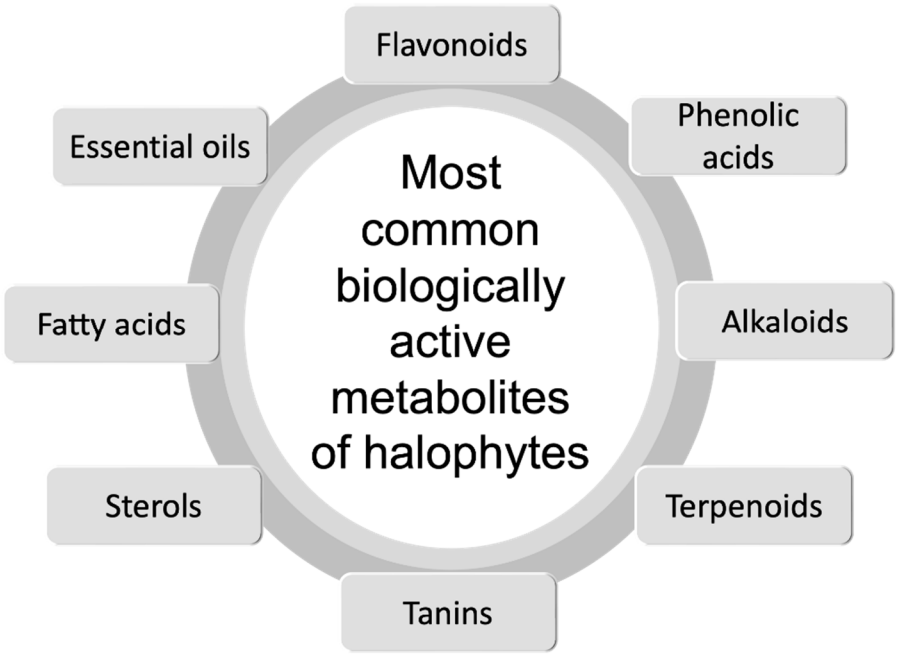

Figure 4. Most common bioactive compounds produced by halophyte plants.

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